Published in final edited form as:

Neurocrit Care. 2019 April ; 30(2): 380–386. doi:10.1007/s12028-018-0610-0.

Third Ventricle Obstruction by Thalamic Intracerebral Hemorrhage Predicts Poor Functional Outcome Among Patients Treated with Alteplase in the CLEAR III Trial

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Abstract

Introduction: The Clot Lysis: Evaluating Accelerated Resolution of IVH (CLEAR III) trial examined whether irrigating the ventricular system with Alteplase improved functional outcomes in patients with small intracerebral hemorrhage (ICH) and large intraventricular hemorrhage (IVH). Thalamic ICH location was common and was associated with poor outcome. One possible explanation is thalamic ICH-associated mass effect obstructing the 3rd ventricle. We hypothesized that patients with thalamic ICH obstructing the 3rd ventricle would have worse functional outcomes compared to patients without obstructing lesions.

Methods: ICH obstruction of 3rd ventricle was defined as 3rd ventricle compression on 1 or more axial computed tomography slices visually impeding cerebral spinal fluid flow. If the 3rd ventricle was casted with IVH it was scored as such. Multivariable logistic regression analyses were used to determine whether obstruction of the 3rd ventricle predicts poor functional outcomes defined as modified Rankin score (mRS) 4–6, higher mRS, and mortality at 180 days. Models were adjusted for thalamic ICH location, ICH volume, IVH volume, age, hydrocephalus, baseline Glasgow coma scale, and percentage of low cerebral perfusion pressures during treatment.

Results: Among saline-treated patients obstruction of the 3rd ventricle by IVH was a significant predictor of higher mRS at 180 days (OR = 1.87, CI: 1.01–3.47), and mortality at 180 days (OR = 2.73, CI: 1.27–5.87) while obstruction by ICH was not. In contrast, among Alteplase-treated patients, obstruction by ICH was a significant predictor of mRS 4–6 (OR = 3.20, CI: 1.30–7.88) and higher mRS at 180 days (OR = 2.33, CI: 1.24–4.35), while obstruction by IVH was not.

Conclusions: Poor outcomes were associated with mass-related obstruction of the 3rd ventricle from thalamic ICH in Alteplase-treated patients, and from IVH in saline-treated patients. Once the

ventricular system is cleared with Alteplase, obstruction of cerebral spinal fluid flow from thalamic ICH might become important in functional recovery.

Keywords

stroke; intracerebral hemorrhage; intraventricular hemorrhage; alteplase; thrombolytic; thalamus; functional outcomes; modified Rankin; ventricular system; neuroimaging; computed tomography

Introduction

Intracerebral hemorrhage (ICH) affects approximately 37,000 patients per year in the United States. (1) Extension into the ventricular system occurs in about 45% of spontaneous ICH (2) and dramatically increases the risk for a poor outcome. One study found that patients with intraventricular hemorrhage (IVH) were twice as likely to have poor outcomes, defined as mRS 4–6 at discharge from acute care hospital, when compared to those without IVH. (2) Epidemiologic data and small cohorts suggest that relieving obstructive hydrocephalus and reducing neurotoxicity from blood products can improve survival and long-term functional outcome in patients with IVH. (3–5) Based on these findings and preliminary studies showing safety, (6) the Clot Lysis: Evaluating Accelerated Resolution of IVH (CLEAR III) trial was designed to test the hypothesis that irrigating the ventricular system with Alteplase would result in improved functional outcomes in patients with small ICH and large IVH requiring extraventricular drain (EVD), compared to irrigation with normal saline. (7) The CLEAR III trial randomized 500 patients to receive up to 12 doses of either saline or Alteplase delivered via extraventricular drain. The primary endpoint of the study, good functional outcome defined as modified Rankin score (mRS) ≤ 3 at 180 days was not different between the Alteplase and saline groups. Interestingly, a large proportion of patients in the CLEAR III study (60% in the Alteplase arm and 57% in the saline arm) had ICH in the thalamus. Adjusting for IVH size and thalamic ICH location resulted in a 3.5% treatment effect, and although not significant, this raises the important question about patient selection for this therapy and special considerations for patients with thalamic ICH.

Simply categorizing a patient as having ICH in the thalamus, as was done in CLEAR III, does not necessarily characterize the significance of a lesion in this location, especially in a cohort where ICH ranged in size from 1–30cc. (16) Additionally, it was not documented whether that lesion resulted in mass effect and/or significant shift on the 3rd ventricle, influencing CSF flow, hydrocephalus, and clot resolution dynamics within the ventricular system. We sought to better characterize the relationship between thalamic hematomas and the ventricular system, specifically the 3rd ventricle, and to determine whether these features play a role in functional outcomes and ICP in patients with IVH. We hypothesized that patients with thalamic ICH causing mass effect and obstruction of the 3rd ventricle will experience worse functional outcomes, higher ICP, and greater number of adverse events, compared to patients without such obstructing lesions.

Methods

All 500 patients enrolled in the CLEAR III trial (7) were included. The CLEAR III trial was approved by the Johns Hopkins Institutional Review Board, Baltimore, MD, and by the local

Institutional Review Boards of participating enrolling study sites. Informed consent was obtained from all study participants at their respective enrolling sites. All data used in this secondary analysis were collected as part of the CLEAR III trial and deidentified prior to use in this investigation. The CLEAR III trial endpoints for stopping study drug administration were: 3rd and 4th ventricles open, IVH mass effect relieved, 80% of clot removed, or 12 doses given. Third ventricle obstruction was assessed on computed tomography (CT) scans acquired at 24 hours post-last dose of either Alteplase or saline by two independent readers (neurocritical care physician and CLEAR III central Reading Center grader). Both readers assessed all scans independently. Discrepant readings were then adjudicated to reach consensus. If no consensus could be reached, an expert reader (a second neurocritical care physician) was consulted for final assessment. Obstruction by ICH was defined as ventricular compression on 1 or more axial CT slices such that CSF flow could not occur. Scans demonstrating IVH present within the 3rd ventricle that was primarily responsible for CSF obstruction were scored as such (Fig 1). All other variables were collected as part of the CLEAR III trial protocol. (16)

To assess functional outcomes, multivariable logistic regression analyses were used to determine whether obstruction of the 3rd ventricle by ICH or IVH predicts poor functional outcome defined as mRS 4–6 and mortality at 180 days. An ordered logistic regression was used to examine the relationship between obstruction and mRS as an ordinal variable. Univariate regressions were performed to examine important potential confounders. Based on these results (not shown) the final analyses were adjusted for baseline ICH volume, baseline IVH volume, thalamic location, age, presence of hydrocephalus on the 24-hour post-last dose CT, baseline Glasgow coma scale (GCS), and percentage of cerebral perfusion pressure (CPP) readings below 60 mmHg. The calculation of CPP was standardized across all study sites based on the Brain Trauma Foundation Guidelines. (17)

The effect of obstruction on ICP was assessed using two different methods. First, a multivariable logistic regression was used to determine whether 3rd ventricle obstruction was associated with the occurrence of an intracranial hypertension adverse event (AE), defined as ICP greater than 20 mmHg for 2 or more consecutive hours despite maximal medical ICP management during the study protocol. Additionally, we used a multivariable regression of obstruction with percentage of ICP measurements above 30 mmHg from time of EVD placement to day 7-post-randomization (17). A multivariable regression was also used to assess whether obstruction resulted in an increased number of AEs of any type (not just ICP-related) during the study protocol. These analyses were adjusted for baseline ICH volume, baseline IVH volume, thalamic location, age, and presence of hydrocephalus on the 24-hour post-last dose CT. Saline and Alteplase treatment arms were analyzed separately. Fisher's exact test was used to assess relationship between obstruction on long-term shunt dependency and ventriculitis during the study protocol. All analyses were performed using STATA 11.0 (2009, STATA Corp, College Station, Texas).

Results

Inter-rater reliability for obstruction was good with agreement of 82.8%. After discussion and consensus, only 5 cases required expert review. There were 251 patients in the saline

treatment group and 249 randomized to receive Alteplase. Demographics for each group are shown in Table 1. Not surprisingly, IVH volume at baseline was larger in patients with obstruction of the 3rd ventricle from IVH compared to those with obstruction from ICH and no obstruction. Additionally, baseline ICH volume was largest in patients with obstruction from ICH. Obstruction of the 3rd ventricle from ICH occurred significantly more among patients with thalamic ICH compared to patients with ICH in locations other than the thalamus ($p < 0.001$).

Functional Outcomes

Five patients (4 in saline group and 1 in the Alteplase group) who were lost to follow-up at 180 days were excluded from the functional outcome analysis. As shown in Table 2, among saline-treated patients, obstruction of the 3rd ventricle by ICH was not a significant predictor of poor outcome, higher 180-day mRS, or mortality at 180 days when compared to patients without such obstructing lesions. However, among saline-treated patients obstruction of the 3rd ventricle by IVH did increase the odds of higher mRS at 180 days (OR = 1.87, CI: 1.01–3.47) and mortality at 180 days (OR = 2.73, CI: 1.27–5.87). Obstruction of the 3rd ventricle by IVH was not a significant predictor for poor outcome. In contrast, among Alteplase-treated patients, obstruction of the 3rd ventricle by ICH was a significant predictor of poor functional outcome (OR = 3.20 CI: 1.30–7.88) and higher mRS (OR = 2.33, CI: 1.24–4.35) but obstruction by IVH was not. Neither IVH nor ICH obstruction significantly predicted mortality at 180 days in the Alteplase group.

Intracranial Pressure

There was no association between the number of intracranial hypertension AEs and obstruction after adjusting for age, thalamic ICH location, baseline IVH volume, baseline ICH volume, and hydrocephalus at 24 hours-post-last dose. However, obstruction of the 3rd ventricle by ICH was associated with a higher percentage of ICP readings >30 mmHg in the saline (coefficient = 1.20, $p = 0.04$), but not in the Alteplase group. Obstruction of the 3rd ventricle by IVH was associated with a higher percentage of ICP readings >30 mmHg in both saline (coefficient = 1.24, $p = 0.02$) and Alteplase (coefficient 2.89, $p = 0.05$) groups (Table 3).

Obstruction with ICH was associated with more AEs of any type, coefficient 1.45 (0.44–2.46), $p=0.005$ in the Alteplase group, but not the saline group. Obstruction with IVH was not associated with more AEs in either treatment arm. Only five patients in the cohort had a ventriculitis AE during the study protocol, with only one of these patients also having obstruction of the 3rd ventricle by ICH. The placement of a permanent shunt was not significantly associated with obstruction of the 3rd ventricle by IVH, ICH, or both (any obstruction) in either the saline or Alteplase groups.

Discussion

It is well known that patients with ICH in the thalamus have poor outcomes. In the CLEAR III trial, adjustment for IVH size and thalamic ICH location resulted in a 3.5% treatment effect, (7) A secondary analysis of the INTERACT2 study (examining early intensive blood

pressure management in patients with spontaneous ICH) included 2,066 patients and also found that having ICH in the thalamus increased risk of death or major disability and death alone after adjustment for many baseline patient characteristics including baseline hematoma volume, IVH, study treatment arm, and NIH Stroke Scale score. (8,9) Classically, the proposed mechanism for the effect of thalamic ICH location on outcome has been destruction of the thalamic grey matter, an important relay center for many neurologic pathways. However, this secondary analysis of the CLEAR III trial supports a growing body of evidence suggesting a secondary mechanism behind poor outcomes among patients with thalamic ICH: CSF flow obstruction.

Thalamic ICH and elevated intracranial pressure (ICP) have been shown to be important predictors of long-term shunt dependence in patients with spontaneous ICH. (10,11) Zacharia et al. reported these effects to be independent of age, admission neurologic status, and IVH volume. The authors suggest that because of the anatomic relationship of the thalamus to the third ventricle and foramen of Monroe, hematoma in this location may more easily obstruct cerebral spinal fluid (CSF) flow, independent of IVH volume. (10) This theory is supported by other reports of hydrocephalus developing in patients with thalamic masses and thalamic hemorrhage without IVH. (12,13) A recent retrospective cohort study of patients with spontaneous ICH found that only hydrocephalus and ICH volume were associated with poor outcome, and the presence of IVH was not. (14) Diringer et al. reported that among patients with spontaneous ICH, hydrocephalus was more likely to occur in those with thalamic hemorrhage and was an independent predictor of mortality. (15)

This analysis found poor functional outcome, defined as mRS 4–6 and greater overall mRS, to be associated with mass-related obstruction of the 3rd ventricle from thalamic ICH in Alteplase-treated patients. In contrast, in the saline-treated patients, obstruction of the 3rd ventricle by IVH was associated with worsened clinical outcomes (greater mRS and mortality). We assessed obstruction at 24 hours after the last dose of study drug was given. Most patients (78%) in the Alteplase group discontinued dosing before the 12th dose due to clearance of blood from the 3rd and 4th ventricles, with the average number of doses of Alteplase being 5 (IQR 3–8) compared to 12 (IQR 9–12) doses of saline. (7) When the 3rd ventricle is cleared of IVH (as seen in the Alteplase-treated patients), mass effect from ICH in close proximity to the 3rd ventricle impairing CSF flow may have a more important role in functional recovery. These findings suggest that ICH in the thalamus obstructing CSF flow within the ventricular system may diminish the potential benefit of intraventricular thrombolytic therapy in patients with concomitant IVH, and raises an important consideration for patient selection in future intraventricular thrombolytic trials.

We also found that obstruction of the 3rd ventricle by IVH was associated with greater elevations of ICP >30 mmHg in both treatment groups. Interestingly, obstruction of the 3rd ventricle by ICH was also associated with more ICP elevations >30 mmHg in the saline-treated, but not Alteplase-treated patients. Additionally, obstruction with ICH was associated with a greater number of AEs among Alteplase-treated patients only, after adjusting for ICH and IVH volume, age, presence of hydrocephalus, and thalamic ICH location, suggesting that obstruction alone may place patients at a greater risk for complications from their stroke. Although one can hypothesize that obstruction and stasis of CSF flow may

predispose a patient to CSF infection, the low number of ventriculitis events in this dataset prohibited drawing conclusions about the relationship between obstruction and risk of ventriculitis.

This analysis includes a large number of patients from multiple hospitals around the world, with high-quality imaging and clinical data collected as part of a large phase III clinical trial. However, it is limited in that it is an analysis of clinical trial patients, who may not be representative of the general IVH patient population. (18) Another important consideration is that specifications about neurologic rehabilitation were not part of the trial protocol, and likely varied among patients, study sites, and geographic location. The type and frequency of rehabilitation has an important affect on outcomes and should be investigated prospectively in future studies. Finally, obstruction was assessed on axial CT scans which can capture a transient state of blood within the ventricular system or falsely miss obstruction depending on where the slices were acquired on that given scan. Additional investigations are needed to fully understand the role of thalamic ICH on 3rd ventricle compression and obstruction of CSF flow, but this secondary analysis of the CLEAR III cohort suggests that obstruction of the 3rd ventricle may be an important mechanism for the poor prognosis commonly associated with thalamic ICH, especially among patients treated with intraventricular Alteplase.

Acknowledgments

We wish to thank the CLEAR III patients and their families and the CLEAR III investigators and coordinators who provided and cared for them.

Financial Support: The CLEAR III study was funded by the National Institute of Neurological Disorders and Stroke; [ClinicalTrials.gov](https://clinicaltrials.gov) NCT00784134.

Source of support: Dr. Daniel F. Hanley was awarded significant research support of grants R01NS046309, 5U01 NS062851–05, and 5U01 NS080824–02.

References

- (1). Broderick JP, Brott T, Tomsick T, Miller R, Huster G. Intracerebral hemorrhage more than twice as common as subarachnoid hemorrhage. *J Neurosurg* 1993 2;78(2):188–191. [PubMed: 8421201]
- (2). Hallevi H, Albright KC, Aronowski J, Barreto AD, Martin-Schild S, Khaja AM, et al. Intraventricular hemorrhage: Anatomic relationships and clinical implications. *Neurology* 2008 3 11;70(11):848–852. [PubMed: 18332342]
- (3). Moradiya Y, Murthy SB, Newman-Toker DE, Hanley DF, Ziai WC. Intraventricular thrombolysis in intracerebral hemorrhage requiring ventriculostomy: a decade-long real-world experience. *Stroke* 2014 9;45(9):2629–2635. [PubMed: 25061080]
- (4). Gaberel T, Magheru C, Parienti JJ, Huttner HB, Vivien D, Emery E. Intraventricular fibrinolysis versus external ventricular drainage alone in intraventricular hemorrhage: a meta-analysis. *Stroke* 2011 10;42(10):2776–2781. [PubMed: 21817146]
- (5). Nieuwkamp DJ, de Gans K, Rinkel GJ, Algra A. Treatment and outcome of severe intraventricular extension in patients with subarachnoid or intracerebral hemorrhage: a systematic review of the literature. *J Neurol* 2000 2;247(2):117–121. [PubMed: 10751114]
- (6). Naff N, Williams MA, Keyl PM, Tuhim S, Bullock MR, Mayer SA, et al. Low-dose recombinant tissue-type plasminogen activator enhances clot resolution in brain hemorrhage: the intraventricular hemorrhage thrombolysis trial. *Stroke* 2011 11;42(11):3009–3016. [PubMed: 21868730]

- (7). Hanley DF, Lane K, McBee N, Ziai W, Tuhim S, Lees KR, et al. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. *Lancet* 2017 2 11;389(10069):603–611. [PubMed: 28081952]
- (8). Ziai WC, Tuhim S, Lane K, McBee N, Lees K, Dawson J, et al. A multicenter, randomized, double-blinded, placebo-controlled phase III study of Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III). *Int J Stroke* 2014 6;9(4):536–542. [PubMed: 24033910]
- (9). Ziai WC, Melnychuk E, Thompson CB, Awad I, Lane K, Hanley DF. Occurrence and impact of intracranial pressure elevation during treatment of severe intraventricular hemorrhage. *Crit Care Med* 2012 5;40(5):1601–1608. [PubMed: 22430237]
- (10). Delcourt C, Sato S, Zhang S, Sandset EC, Zheng D, Chen X, et al. Intracerebral hemorrhage location and outcome among INTERACT2 participants. *Neurology* 2017 4 11;88(15):1408–1414. [PubMed: 28235817]
- (11). Eslami V, Nekoobakht-Tak S, Tahsili-Fahadan P, Dlugash R, McBee N, Lane K, et al. Influence of intracerebral hemorrhage location in patients with spontaneous intraventricular hemorrhage results from the clot lysis: evaluating accelerated resolution of intraventricular hemorrhage (CLEAR) III trial. Annual Meeting of the Neurocritical Care Society 2016, National Harbor, MD.
- (12). Zacharia BE, Vaughan KA, Hickman ZL, Bruce SS, Carpenter AM, Petersen NH, et al. Predictors of long-term shunt-dependent hydrocephalus in patients with intracerebral hemorrhage requiring emergency cerebrospinal fluid diversion. *Neurosurg Focus* 2012 4;32(4):E5.
- (13). Miller C, Tsivgoulis G, Nakaji P. Predictors of ventriculoperitoneal shunting after spontaneous intraparenchymal hemorrhage. *Neurocrit Care* 2008;8(2):235–240. [PubMed: 17928961]
- (14). Ng LK, Schwarz G, Mishkin MM. Hematoma from arteriovenous malformation producing hydrocephalus and simulating a thalamic tumor. Report of two cases. *J Neurosurg* 1971 2;34(2 Pt 1):229–235. [PubMed: 14768692]
- (15). Tokumitsu N, Sako K, Kunimoto M, Nakai H, Yonemasu Y. Glial cyst in the thalamus with intracystic hemorrhage--case report. *Neurol Med Chir (Tokyo)* 1997 3;37(3):284–287. [PubMed: 9095631]
- (16). Mahta A, Katz PM, Kamel H, Azizi SA. Intracerebral hemorrhage with intraventricular extension and no hydrocephalus may not increase mortality or severe disability. *J Clin Neurosci* 2016 8;30:56–59. [PubMed: 26972705]
- (17). Diringer MN, Edwards DF, Zazulia AR. Hydrocephalus: a previously unrecognized predictor of poor outcome from supratentorial intracerebral hemorrhage. *Stroke* 1998 7;29(7):1352–1357. [PubMed: 9660386]
- (18). Hansen BM, Ullman N, Norrving B, Hanley DF, Lindgren A. Applicability of Clinical Trials in an Unselected Cohort of Patients With Intracerebral Hemorrhage. *Stroke* 2016 10;47(10):2634–2637. [PubMed: 27625384]

Fig 1. Non-contrast head CT examples of a) patient without obstruction of the 3rd ventricle b) patient with obstruction from a thalamic ICH, and c) patient with obstruction of the 3rd ventricle from IVH.

Table 1.

Patient demographics and baseline variables by group.

	Not Obstructed (n = 292)	Obstructed with ICH (n = 121)	Obstructed with IVH (n = 87)
Demographic Variables			
Age	59.5 (12.0)	56.8 (10.0)	58.1 (11.4)
Female	127 (43.5%)	55 (45.5%)	40 (46.0%)
Ethnic origin			
White	178 (61.0%)	76(62.8%)	51 (58.6%)
African American	95 (32.5%)	43 (35.5%)	32 (36.8%)
American Indian or Alaskan Native	1 (0.3%)	0	0
Other	18 (6.2%)	2 (1.7%)	4 (4.6%)
Hispanic	40 (13.7%)	9 (7.4%)	11(12.6%)
Baseline Variables			
Tobacco use	85 (29.1%)	25 (20.7%)	22 (25.3%)
Cocaine use	16 (5.5%)	8 (6.6%)	6 (6.9%)
Anticoagulated at registration	31 (10.6%)	10 (8.3%)	8 (9.2%)
On antiplatelet medications at registration	80 (27.4%)	26 (21.5%)	22 (25.3%)
Randomization MAP	95.2 (14.6)	97.8 (12.3)	96.2 (16.9)
Randomization GCS	10.0 (3.6)	8.6 (3.4)	8.1 (3.2)
Randomization NIHSS	18.1 (12.2)	24.3 (11.1)	25.4 (11.8)
Baseline IVH volume, mL	27.3 (21.5)	20.0 (12.8)	35.7 (22.5)
Baseline ICH volume, mL	7.5 (7.5)	14.3 (7.3)	9.4 (8.5)
Thalamic ICH location	127 (43.5%)	113 (93.4%)	53 (60.9%)
Time to EVD placement	12.1 (11.4)	9.9 (10.4)	8.7 (7.0)

Data are mean (SD) or n (%). MAP = mean arterial pressure, GCS = Glasgow coma scale, NIHSS = NIH Stroke Scale, EVD = extraventricular drain, ICH = intracerebral hemorrhage, IVH = intraventricular hemorrhage.

Table 2.

Functional outcomes at 180 days adjusted for ICH volume, IVH volume, thalamic location, age, hydrocephalus, baseline GCS, and percentage of CPP readings below 60 mmHg.

	Saline			Alteplase		
	Coefficient (CI)	p	n	Coefficient (CI)	p	n
3V obstruction by ICH						
Poor outcome (mRS 4-6)	1.30 (0.52-3.21)	0.57	242	3.20 (1.30-7.88)	0.01	246
mRS (ordinal)	1.02 (0.53-1.97)	0.94	242	2.33 (1.24-4.35)	>0.01	246
Mortality	1.29 (0.53-3.18)	0.58	244	2.11 (0.82-5.47)	0.12	248
3V obstruction by IVH						
Poor outcome (mRS 4-6)	2.34 (0.99-5.55)	0.05	242	1.25 (0.32-4.78)	0.75	246
mRS (ordinal)	1.87 (1.01-3.47)	0.05	242	2.24 (0.73-6.87)	0.16	246
Mortality	2.73 (1.27-5.87)	0.01	244	1.89 (0.46-7.77)	0.38	248

Table 3:

Multivariable regression of obstruction with percentage of intracranial pressure measurements above 30 mmHg from extraventricular drain placement to day 7 post-randomization, adjusted for ICH volume, IVH volume, thalamic location, age, and hydrocephalus.

	Saline			Alteplase		
	Coefficient (CI)	p	n	Coefficient (CI)	p	n
3V obstruction by ICH	1.20 (0.06-2.33)	0.04	63	0.73 (-0.99-2.45)	0.41	58
3V obstruction by IVH	1.24 (0.22-2.25)	0.02	74	2.89 (0.02-5.77)	0.05	13