Symptomatic Hemorrhagic Complications in Clot Lysis: Evaluation of Accelerated Resolution of Intraventricular Hemorrhage Phase III Clinical Trial (CLEAR III): A Posthoc Root-Cause Analysis

Maged D. Fam, MD*
Agnieszka Stadnik, MS*
Hussein A. Zeineddine, MD*
Romuald Girard, PhD*
Steven Mayo, PD‡
Rachel Dlugash, MSPH§
Nichol McBee, MPH§
Karen Lane, CMA§
W. Andrew Mould, MPH§
Wendy Ziai, MD§
Daniel Hanley, MD§
Issam A. Awad, MD*

*Neurovascular Surgery Program, Section of Neurosurgery, The University of Chicago Medicine, Chicago, Illinois; ‡Emissary International, LLC, Austin, Texas; §Brain Injury Outcomes Unit, Johns Hopkins University, Baltimore, Maryland

Correspondence:
Issam A. Awad, MD, MSc, MA (hon),
Section of Neurosurgery,
University of Chicago Medicine,
5841 S Maryland,
MC3026/Neurosurgery J341,
Chicago, IL 60637.
E-mail: iawad@uchicago.edu

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BACKGROUND: As intraventricular thrombolysis for intraventricular hemorrhage (IVH) has developed over the last 2 decades, hemorrhagic complications have remained a concern despite general validation of its safety in controlled trials in the Clot Lysis: Evaluation of Accelerated Resolution of Intraventricular Hemorrhage Phase III (CLEAR-IVH) program.
OBJECTIVE: To analyze factors associated with symptomatic bleeding following IVH with and without thrombolysis in conjunction with the recently completed CLEAR III trial.
METHODS: We reviewed safety reports on symptomatic bleeding events reported during the first year after randomization among subjects enrolled in the CLEAR III trial. Clinical and imaging data were retrieved through the trial database as part of ongoing quality and safety monitoring. A posthoc root-cause analysis was performed to identify potential factors predisposing to rebleeding in each case. Cases were classified according to onset of rebleeding (during dosing, early after dosing and delayed), the pattern of bleeding, and treatment rendered (alteplase vs saline).
RESULTS: Twenty subjects developed a secondary symptomatic intracranial hemorrhage constituting 4% of subjects. Symptomatic rebleeding events occurred during the dosing protocol (n = 9, 67% alteplase), early after the protocol (n = 5, 40% alteplase), and late (n = 6, 0% alteplase). Catheter-related hemorrhages were the most common (n = 7, 35%) followed by expansion or new intraventricular (n = 6, 30%) and intracerebral (n = 5, 25%) hemorrhages. Symptomatic hemorrhages during therapy resulted from a combination of treatment- and patient-related factors and were at most partially attributable to alteplase. Rebleeding after the dosing protocol primarily reflected patients' risk factors.
CONCLUSION: Intraventricular thrombolysis marginally increases the overall risk of symptomatic hemorrhagic complications after IVH, and only during the treatment phase.

KEY WORDS: Intraventricular hemorrhage, Thrombolysis, Rebleeding, Complications, Hemorrhage

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Intraventricular hemorrhage (IVH) results from intracranial bleeding gaining access to or, less commonly, arising within the ventricular system,[1] and is associated with high mortality and poor functional outcome.[2-4] The pathophysiology of the disorder involves complex mechanisms, including derangement of cerebrospinal fluid (CSF) circulation, trapping, mass effect and shifts, and thrombotoxicity.[1,5] For many years, treatment of IVH has included the placement of external ventricular drains (EVD) to relieve early obstructive hydrocephalus pending spontaneous resolution of the blood.[6-8] The EVDs have long been associated with complications of catheter tract hemorrhage, infection, and repetitive blockage by clotted blood necessitating frequent manipulation and/or replacement.[9]

ABBREVIATIONS: CLEAR, Clot Lysis: Evaluation of Accelerated Resolution; **CSF,** cerebrospinal fluid; **CT,** computed tomography; **CTA,** CT angiography; **EVD,** external ventricular drains; **GCS,** Glasgow Coma Scale; **ICH,** intracerebral hematoma; **IVH,** intraventricular hemorrhage; **MRI,** magnetic resonance imaging; **mRS,** modified Rankin Scale

Intraventricular thrombolysis is an emerging therapeutic modality intended to hasten clot resolution minimizing the pathological disturbances induced by IVH. But there remains a legitimate concern about hemorrhagic risk with intraventricular thrombolytic administration.[10] Factors associated with symptomatic hemorrhagic complications and delayed bleeding after thrombolytic therapy have never been formally queried. The "Clot Lysis: Evaluation of Accelerated Resolution of Intraventricular Hemorrhage Phase III" (CLEAR III) clinical trial is an international multicenter double-blinded randomized phase III clinical trial investigating the effect of an intraventricular recombinant tissue plasminogen activator (alteplase) on outcomes in patients with IVH. Seventy-three study centers across the United States, Europe, Israel, and Brazil participated in enrolling 500 subjects for the trial between April 2009 and January 2015. The methodology and primary results of the trial have been published.[11] With a small number of symptomatic hemorrhages documented in CLEAR III precluding statistical analyses of causative factors, we performed this observational study with the aim of describing symptomatic bleeding events, and assessing them using a surgical morbidity root-cause analysis methodology.

METHODS

The local institutional review board of each participating site approved the CLEAR III trial study. After determining eligibility by the enrolling site's principal investigator, standardized written informed consent was obtained in accordance with local institutional review boards.

The CLEAR III Trial

A total of 10 538 IVH patients were screened and 500 subjects were enrolled in the trial. Potential subjects underwent a detailed screening to exclude a structural vascular lesion as etiology of hemorrhage.[12] All cases required satisfactory placement of an EVD as part of their clinical management prior to randomization. All enrolled subjects underwent correction of any coagulopathy, and documented hemorrhage stability (including any bleeding caused by initial EVD placement) on 2 scans at least 6 h apart. Subjects were then randomized to receive alteplase or saline doses via the EVD (administered every 8 h with the drain remaining clamped for 1 h postdose). Dosing was continued until clearance of the third and fourth ventricles, and/or clearance of 80% of the ventricular blood, or a total of 12 doses. The trial protocol prearticulated adverse events and serious adverse events, to be reported by the site and adjudicated by the trial safety committee, including symptomatic bleeding. Symptomatic hemorrhagic expansion or de novo hemorrhages during dosing were defined as safety endpoints with study-stop thresholds prespecified in the trial protocol, in addition to 30-d mortality and brain infections.[11] These were reviewed by the trial's Surgical Committee during the course of the trial, and regularly presented to the trial's Executive Committee, utilizing a surgical morbidity root-cause analysis methodology, with an eye toward lessons learnt. The observational methodology was used, given the limited number of symptomatic hemorrhage, precluding statistical analyses of association or causation.

Patients and Methods

We here report a posthoc compilation of the root-cause analyses addressing 21 symptomatic bleeding events diagnosed and adjudicated in 20 subjects after enrollment in the CLEAR III trial and followed up for a minimum of 12 mo. Bleed expansions and hemorrhages caused by initial EVD placement prior to demonstrated stability and randomization were not considered herein, and have been addressed elsewhere.[13] While all hemorrhagic events noted on follow-up computed tomography (CT) scans were recorded, asymptomatic hemorrhages were not included in our analysis. Symptomatic rebleeding was predefined in the trial protocol as evidence of new intracranial hemorrhage or as expansion of original bleed on CT imaging, coinciding with new congruent focal neurological deficit or persistent drop in Glasgow Coma Scale (GCS) motor score of 2 or more points measured twice over at least 8 h, or other neurological signs and symptoms of similar severity. The treating sites diagnosed and reported all incidences of symptomatic hemorrhagic events or delayed rebleeding between enrollment and the last follow-up appointment at 1 yr from onset of IVH. In all incidences, case records were reviewed by the trial Safety Committee which verified hemorrhagic expansion and adjudicated the symptomatic associated. In 1 reported and adjudicated case, new bleeding was solely in the scalp and was excluded from our analysis herein.

Data were retrieved from the trial database (VISION EDC system, software from Prelude Dynamics Inc, Austin, Texas; study-specific implementation developed by Emissary International LLC, Austin, Texas). We queried patient-related risk factors that could predispose to rebleeding. We extracted demographic data (age, gender, ethnicity), clinical information (comorbidities, concomitant antiplatelet or anticoagulants, and presenting GCS), clotting profile and anticoagulation reversal if applicable, and radiological characteristics of index IVH. We also systematically appraised treatment-related factors that have the potential to cause or predispose to hemorrhagic complications or delayed rebleeding. We collected treatment assignment (alteplase or saline) following completion of the trial and unblinding, details of EVD(s) deployed (number of catheters, laterality, number of passes, quality of placement, and number of doses), bleeding pattern of the secondary event and concurrent clotting profile, and the use of prophylactic or therapeutic anticoagulation at the time of the bleed. Additionally, we collected the nature of all protocol deviations registered by the monitoring team for each of the included cases (eg, technical mishaps such as catheter pull-back, failure to comply with dosing or imaging protocol, etc.). Each protocol deviation was further appraised by the trial coprimary investigators (D.H. and I.A.A.) for its potential to predispose to the hemorrhagic complication, as well as its clinical and chronological relation to the rebleeding event in the same patient.

With input by the trial's Safety and Executive Committees, time of onset of rebleeding was retrospectively categorized per pragmatic clinical considerations as "dosing" (from randomization up to 72 h following the last dose of study agent), "early" (72 h to 30 d following the last dose), and delayed (after 30 d). Based on the distribution of acute blood relative to the EVD and index hemorrhage, patterns of rebleeding were categorized for the purpose of our analyses as catheter-related hemorrhage, IVH (new or expansion of index IVH), new lobar intracerebral hematoma (ICH), new deep ICH, or other categorization (subdural etc.).

TABLE 1. Demographic and Baseline Characteristics at Enrollment of 20 cases With Symptomatic Bleeding Within 1 yr of Enrollment in CLEAR III

Features[a]	Dosing	Early	Late	Total
N	9	5	6	20
Age: mean (range)	60.5 (40-79)	63 (42-78)	61.5 (50-81)	61.45 (40-81)
Gender				
Female (%)	2 (22)	2 (40)	1 (17)	5 (25)
Race				
African-American (%)	2 (22)	3 (60)	1 (17)	6 (30)
White-Caucasian (%)	6 (67)	2 (40)	5 (83)	13 (65)
Hawaiian-Islander (%)	1 (11)	–	–	1 (5)
Initial ICH location (%)				
Thalamic	4 (44)	3 (60)	3 (50)	10 (50)
Caudate	4 (44)	1 (20)	3 (50)	8 (40)
Putamen	1 (11)	1 (20)	–	2 (10)
Lobar	–	–	–	–
Primary IVH	–	–	–	–
Etiology Screening				
MRI/MRA	1	–	1	2
CTA	8	5	6	19
Formal catheter angiography	2	–	1	3
Comorbidities				
Cerebrovascular disease	1 (11)	–	1 (17)	2 (10)
Hypertension	9 (100)	5 (100)	6 (100)	20 (100)
Dyslipidemia	9 (100)	5 (100)	6 (100)	20 (100)
Diabetes mellitus	1 (11)	1 (20)	1 (17)	3 (15)
Atrial fibrillation	2 (22)	1 (20)	1 (17)	4 (20)
Neoplasia	2 (22)	1 (20)	–	3 (15)
Smoking	6 (67)	2 (40)	–	8 (40)
Alcohol	3 (33)	–	–	3 (15)
Coagulopathy				
Antiplatelet	–	–	4 (67)	4 (20)
Anticoagulant	2 (22)	–	1 (17)	3 (15)
Other[b]	2 (22)	–	1 (17)	3 (15)
Coagulation profile				
Platelet count: median (range)	209 (165-404)	210 (140-303)	232 (139-406)	222 (139-406)
INR > 1.2 (%)	2 (22)	–	1 (17)	3 (15)

[a]Time course of bleeding events during dosing (within 72 h of the last dose of study agent), early (from 72 h after completion of dosing to 30 d from randomization) or late (between 30 d and 1 yr after randomization).
[b]Medical disorders potentially associated with platelet or coagulation dysfunction.

RESULTS

General Characteristics

Twenty-one events in 20 subjects were recorded by the treating site and further adjudicated by the trial Safety Committee as symptomatic bleeding (Table 1). In 1 subject, an early symptomatic subdural hematoma was further complicated by reaccumulation after burr-hole drainage. Eight subjects had been randomized to receiving alteplase and 12 to saline (placebo) via EVD. Subjects had a mean age of 61.45 yr (range, 40-81). Demographic and baseline characteristics of these cases are summarized in Table 1. All subjects presented with IVH secondary to deep ICH, with none of the symptomatic rebleed cases, were associated with initial lobar ICH or primary IVH. In all but 1, screening for an underlying vascular etiology was undertaken before randomization using CT angiography (CTA) or formal catheter angiography. A magnetic resonance imaging was solely used for vascular etiology screening/angiography (MRI/MRA) in one case because of impaired renal function precluding vascular contrast. All subjects had a past medical history of hypertension and dyslipidemia. Other less common comorbidities included atrial fibrillation (20%), diabetes mellitus (15%), previous cerebrovascular disease (10%), and neoplasia (15%). Of the 20 subjects, 8 were smokers (40%) and 3 had a history of alcohol abuse (15%). Ten subjects were deemed potentially coagulopathic at initial presentation based on antiplatelet therapy (n = 4, 20%), oral anticoagulation (n = 3, 15%), or other medical disorders potentially associated with platelet or coagulation dysfunction (eg, liver failure, prior multiple myeloma, etc.; n = 3, 15%). None of these factors were

TABLE 2. Symptomatic Bleeding Events and Associated Factors

Features[a]	Dosing	Early	Late	Total
N	9	5	6	20
Alteplase (%)	6 (67)	2 (40)	–	8 (40)
Number of EVDs: median (range)	2 (1-3)	2 (1-3)	1 (1-2)	2 (1-3)
Number of passes: median (range)	1 (1-4)	1 (1-5)	1 (1-2)	1 (1-5)
Suboptimal EVD placement (%)	4 (44)	4 (80)	4 (67)	12 (60)
Number of doses: median (range)	6 (2-12)	9 (5-12)	11.5 (5-12)	9.5 (2-12)
Protocol deviations (%)	5 (56)	1 (17)	3 (50)	9 (45)
Related to rebleeding (%)	4 (44)	1 (17)	–	5 (25)
Anticoagulation[b]	5 (56)	3 (60)	5 (83)	14 (70)
Rebleeding				
Catheter related	5 (56)	2 (40)	–	7 (35)
IVH (new or expansion)	3 (33)	2 (40)	1 (17)	6 (30)
New deep ICH	–	–	2 (33)	2 (10)
New lobar ICH	–	1 (20)	1 (17)	2 (10)
Cerebellar ICH	–	–	1 (17)	1 (5)
Subdural	1 (11)	–	1 (17)	2 (10)

[a]Time course of bleeding events during dosing (within 72 h of the last dose of study agent), early (from 72 h after completion of dosing to 30 d from randomization) or late (between 30 d and 1 yr after randomization).
[b]Any dose, at time of rebleeding.

statistically more common in this cohort than in the remaining subjects enrolled in the trial, nor were the number of EVD catheters used, number of "passes" for EVD placement, nor doses administered.[11] Coagulation profiles assessed at presentation showed a median platelet count of 222 × 1000 (range, 139-406). There was increased INR (International Normalized Ratio >1.2) in 3 subjects (15%). All these were corrected to meet the trial enrollment criteria of platelet count >100 000 and INR < 1.4 before randomization, and were aimed to be maintained during dosing and duration of EVD drainage. Platelet transfusion was administered in all cases receiving clopidogrel (Plavix; Bristol-Myers Squib, New York, New York) at enrollment and, at the discretion of the site investigators, in cases receiving aspirin. Restarting antiplatelet agents and therapeutic anticoagulation was delayed per trial protocol for 30 d after enrollment, although low-dose thromboprophylaxis was allowed after 72 h of enrollment per local practice standards. Table 2 summarizes potentially associated factors with symptomatic bleeding events, and Table 3 outlines demographic and treatment differences between saline- and alteplase-treated participants who developed symptomatic hemorrhagic complications.

Symptomatic Hemorrhage During Dosing

Nine subjects developed symptomatic rebleeding after randomization and before 72 h from the last dose of study agent (thrombolytic or placebo irrigation of the EVD). Of these, 6 received alteplase (67%) and 3 received saline (33%) via EVD. Two of the 9 subjects (22%) had a malignancy in remission on presentation; another 2 had been on long-term anticoagulation for atrial fibrillation with therapeutic range INR, which was reversed prior to randomization (Table 1). At the time of hemorrhage, 5 subjects (56%) had been on thromboprophylactic dose anticoagulants but with no discernable abnormality of coagulation tests.

Patterns of rebleeding in this group were in the form of catheter-related hemorrhage (n = 5, 56%), IVH expansion (n = 3, 33%), and subdural hematoma (n = 1, 11%). Significant protocol deviations were encountered during management in 5 of these 9 subjects. These included administrations of double volume of test article, timing outside the dosing window and failure to obtain required daily follow-up imaging. In 4 of these, the protocol deviation was deemed potentially causative/contributive to the bleeding (Table 2).

Illustrative Case

A 67-yr-old female with history of smoking presented with IVH secondary to caudate ICH. The subject was treated with bilateral EVDs and randomized to intraventricular thrombolysis. Subject developed catheter tract hemorrhage with neurological decline following the third dose of thrombolytic agent and contemporaneous commencement of thromboprophylactic dose anticoagulation. *Bleeding was possibly due to combined effect of thromboprophylaxis and alteplase, although this was not a protocol deviation* (Figure 1).

Early Symptomatic Bleeding

Five subjects developed symptomatic rebleeding after 72 h and before 30 d of the dosing protocol. Only 2 subjects in this group received alteplase during the dosing protocol (40%). Symptomatic rebleeding events encountered in this group were

TABLE 3. Demographic and Treatment Differences Between Saline- and Alteplase-Treated Participants who Developed Symptomatic Hemorrhagic Complications

Features	Saline	Alteplase
n	12	8
Age: mean (range)	65.2 (49-79)	55.9 (40-78)
Gender		
Female (%)	4 (33)	1 (12.5)
Race		
African-American (%)	4 (33)	2 (25)
White-Caucasian (%)	8 (67)	5 (63)
Hawaiian-Islander (%)	0	1 (12.5)
Initial ICH location (%)		
Thalamic	4 (33)	6 (75)
Caudate	6 (50)	2 (25)
Putamen	2 (17)	0 (0)
Primary IVH	0 (0)	0 (0)
Etiology screening (%)		
MRI/MRA	1 (8)	1 (12.5)
CTA	12 (100)	7 (87.5)
Formal catheter angiography	1 (8)	2 (25)
Comorbidities		
Cerebrovascular disease	2 (17)	0 (0)
Hypertension	12 (100)	8 (100)
Dyslipidemia	12 (100)	8 (100)
Diabetes mellitus	2 (17)	1 (12.5)
Atrial fibrillation	3(25)	1 (12.5)
Neoplasia	2 (17)	1 (12.5)
Smoking	2 (17)	6 (75)
Alcohol	0 (0)	3 (37.5)
Coagulopathy		
Antiplatelet	4 (33)	0 (0)
Anticoagulant	2 (17)	1 (12.5)
Other[a]	2 (17)	1 (12.5)
Coagulation profile		
Platelet count: median (range)	200 (139-406)	170 (141-265)
INR > 1.2 (%)	3 (25)	1 (12.5)
Number of EVDs: median (range)	2 (1-3)	1 (1-2)
Number of passes: median (range)	1 (1-5)	1 (1-2)
Suboptimal EVD placement (%)	8 (67)	4 (50)
Number of doses: median (range)	11.5 (3-12)	5.5 (2-12)
Protocol deviations (%)	5	4
Related to rebleeding (%)	1	4
Anticoagulation[b]	8	6
Onset[c]		
Dosing	3 (25)	6 (75)
Early	3 (25)	2 (25)
Late	6 (50)	0 (0)
Rebleeding		
Catheter related	2 (17)	5 (62.5)
IVH (new or expansion)	4 (33)	2 (25)
New deep ICH	2 (17)	0 (0)
New lobar ICH	2 (17)	0 (0)
Cerebellar ICH	1 (8)	0 (0)
Subdural	1 (8)	1(12.5)

[a]Medical disorders potentially associated with platelet or coagulation dysfunction.
[b]Any dose, at time of rebleeding.
[c]Time course of bleeding events during dosing (within 72 h of the last dose of study agent), early (from 72 h after completion of dosing to 30 d from randomization) or late (between 30 d and 1 yr after randomization).

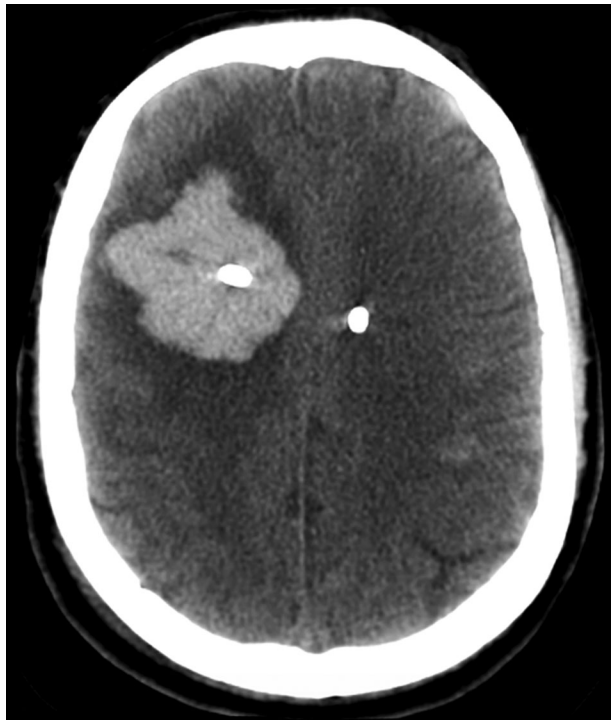

FIGURE 1. *Illustrative case 1. Symptomatic catheter-related hemorrhage during the dosing protocol in subject randomized to alteplase (treatment).*

in the form of catheter-tract hemorrhage (n = 2, 40%), IVH expansion (n = 2, 40%), and new lobar ICH (n = 1, 20%). At the time of hemorrhage, 2 subjects (40%) had been on a thromboprophylactic dose. One case (20%) was receiving a therapeutic dose of anticoagulation, a protocol deviation. Another serious protocol deviation involved administration of alteplase with elevated INR; although this occurred 5 d prior to the onset of bleeding, it could have been a contributive factor (Table 2).

Illustrative Case

A 66-yr-old African-American female presented with IVH secondary to a thalamic ICH. The subject was treated with bilateral EVDs and randomized to receiving saline (placebo) via EVD. Dosing endpoint was reached after 12 doses of saline. Subject developed recurrent IVH 23 d after the last dose of the protocol. Rebleeding followed delayed reinsertion of EVD for hydrocephalus without withholding thromboprophylactic anticoagulant dose. *Bleeding was likely due to repeated/multiple catheter placements and prophylactic anticoagulation* (Figure 2).

Late Symptomatic Bleeding

Six subjects developed symptomatic hemorrhage more than 1 mo after the last dose. Most subjects (5 out of 6) in this group had prior antiplatelet or anticoagulation therapy and/or other coagulopathy upon initial enrollment, although they all

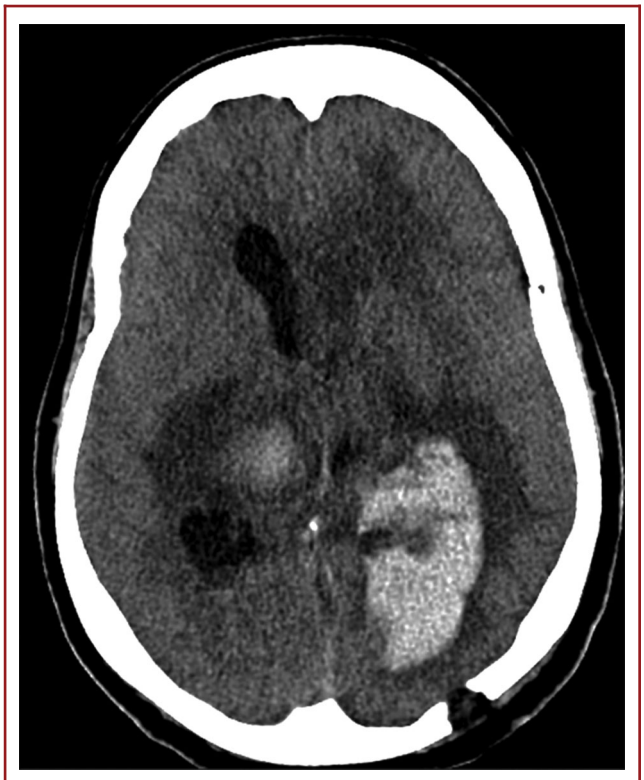

FIGURE 2. *Illustrative case 2. Early recurrence of IVH following the dosing protocol in subject randomized to saline (placebo).*

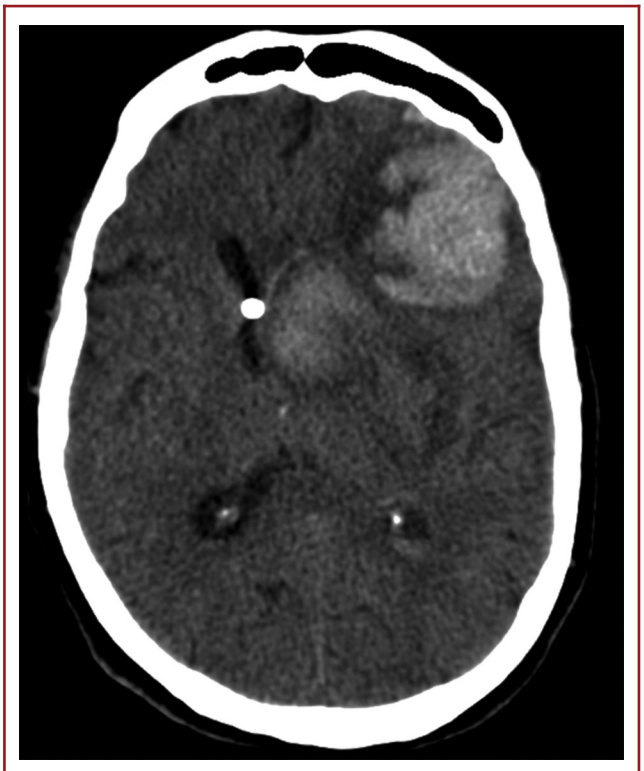

FIGURE 3. *Illustrative case 3. New lobar ICH developing late after the dosing protocol in subject randomized to saline (placebo).*

met protocol criteria of corrected coagulopathy. All subjects in this group had been randomized to placebo (saline). Symptomatic rebleeding events encountered in this group were in the form of new IVH (n = 1, 17%), deep ICH (n = 2, 33%), lobar ICH (n = 1, 17%), cerebellar hemorrhage (n = 1, 17%), and subdural hematoma (n = 1, 17%). At the time of hemorrhage, 5 subjects (83%) had been receiving anticoagulation (thromboprophylactic or therapeutic doses). Protocol deviations were encountered in 3 of the 6 subjects, all involved failure to obtain a required follow-up CT imaging earlier during the protocol. All took place in saline-treated subjects and were chronologically remote from the bleeding event and, hence, alteplase had not contributed to the bleeding.

Illustrative Case

A 71-yr-old white/Caucasian male presented with IVH secondary to a caudate ICH. The patient's medical history comprised hypertension, dyslipidemia, and hypothyroidism. After diagnosis, treatment was initiated with a 1-pass single EVD, and the patient was randomized to receive saline (placebo) and he received 12 doses. Subject developed new lobar ICH almost 4 mo after the last dose. *Bleeding was possibly due to underlying cerebral amyloid angiopathy* (Figure 3).

DISCUSSION

The CLEAR III trial results demonstrated benefits of intraventricular thrombolysis on mortality, but not on the prespecified primary outcome of cases achieving favorable modified Rankin Score (mRS 0-3). There was a significant benefit in mRS 0-3 in the subgroup of cases including nearly half the cases, with larger IVH volume (>20 mL), and in other outcome parameters (the Extended-Glasgow Outcome Score). And the trial confirmed the safety of the intervention, with lower prevalence of serious adverse events, and a similar prevalence of symptomatic hemorrhage.[11] These results did not analyze the patterns or specific associations of symptomatic bleeds during or after the dosing period, which are of interest to clinicians applying this intervention.

Recurrence of hemorrhagic stroke primarily depends on the cause of the primary event. Whereas recurrence rates in IVH have not been specifically studied previously, longitudinal follow-up of ICH has shown that a subsequent hemorrhage is not uncommon. A study by Passero et al[14] reported recurrence of primary ICH in 24% of subjects after a mean follow-up of 84 mo from the initial bleed, with 30% of recurrences occurring in the first year. With advances in medical practice and improved understanding and management guidelines, a substantial reduction in recurrence rates is appreciated in more recent series, mostly with prevention

of recurrent deep hemorrhages with judicious control of hypertension.[15] Recurrent hemorrhage is more common after lobar ICH as compared to deep ICH (cumulative 2-yr recurrence rate 15.7% vs 3.4%, $P = .011$).[16] This has been attributed to the lack of secondary prevention strategies in amyloid angiopathy, as well as varying practices and low levels and classes of evidence regarding resumption of anticoagulation in this setting.[17] It has also been consistently noted that ICH most commonly recurs within the first 2 yr after the index hemorrhage.[18,19]

The rates of asymptomatic hemorrhagic complications following IVH vary significantly, reported in as high as 30%.[19,20] Reports on the more clinically relevant symptomatic complications are much rarer, ranging between 0% and 2.5%.[21-24] A systematic review by our group identified 18 clinical studies comprising a total of 2829 cases of EVD placement. There was CT-verified hemorrhage in 8.4% of cases and symptomatic hemorrhage in 0.7%.[10] In all but the CLEAR-IVH phase II trial and the more recent CLEAR III, criteria of hemorrhage and symptomatic hemorrhage were not prospectively articulated, survey for hemorrhage was not standardized, nor were bleeds adjudicated by an imaging center, nor surgical or safety committees.

Prior to studies that thoroughly studied the drug pharmacokinetics and dose optimization for intraventricular route, there were case reports of hemorrhagic complications following the administration of high-dose thrombolytic agents (up to 4 mg of alteplase).[25] A thrombolytic dose escalation study by Naff et al,[21] reported a 23% incidence of symptomatic bleeding events when 3 mg dose of alteplase was administered, and this has guided dose optimization at no greater than 1 mg every 8 h in subsequent studies.[21] That study helped define the approximate half-life of intraventricular alteplase as 6 to 8 h, based on the assay of remaining alteplase antigen in the CSF at the time of subsequent dose. Retrospective analyses of patients receiving intraventricular fibrinolysis demonstrated relative safety given optimal placement of EVD,[26] including a pooled analysis of 24 studies on fibrinolysis in IVH.[27]

The period of dosing is intuitively expected to have the highest risk of treatment-related complications, particularly given the short half-life of intraventricular alteplase.[21] In our analysis, twice as many events taking place during dosing were in subjects receiving alteplase. Yet, the occurrence of hemorrhagic complication in saline-treated subjects during therapy denotes that other predisposing factors are also involved. Patient-related factors may have included prior history of coagulopathy (including that related to prior malignancy or liver disease), even when apparently corrected per protocol definitions. Examples of treatment-related factors potentially predisposing to hemorrhagic complications included protocol deviations in EVD management and drug administration (eg, double dosing, catheter manipulation/removal without withholding anticoagulation, etc.). These and the use of thromboprophylactic anticoagulation in 5 of 9 cases could have contributed to individual instances of symptomatic hemorrhages during dosing.

Most symptomatic bleeding after the dosing protocol was in subjects randomized to saline (placebo); hence, alteplase did not seem to increase the risk of subsequent bleeding following the dosing protocol. Most later symptomatic bleeds were associated with coagulopathy secondary to antiplatelet, anticoagulation therapy, or other systemic medical illnesses. We did not encounter rebleeding from occult underlying structural vascular lesion, and this could be attributed to the rigorous protocol of vascular imaging for etiology screening as implemented in the trial.[12] Screening for occult cerebral amyloid angiopathy, however, which requires MRI special sequences (Gradient Recoil Echo or susceptibility sequences), was not routinely performed in the CLEAR III cohort. A symptomatic new lobar ICH that is chronologically and anatomically remote from the index bleed, suggestive of amyloid etiology, was seen in 2 saline-treated subjects.

Limitations

The relative scarcity of symptomatic bleeds in our study precluded a meaningful statistical analysis of the potential causative or contributive risk factors. Similar protocol deviations also occurred, and thromboprophylaxis was routinely used per standard of practice throughout the CLEAR III trial, in the absence of symptomatic hemorrhage. The small numbers also precluded a potential correlation with various regimens of thromboprophylaxis (subcutaneous heparin, Lovenox [Sanofi SA, Paris, France], and different doses). By limiting our analysis to symptomatic cases, we may have missed significant associations with more frequent asymptomatic bleeds. The role of different thromboprophylactic regimens, and their impact on asymptomatic and symptomatic bleeds, venous thrombosis, and pulmonary embolism will be analyzed in a future separate report. Our root-cause analysis was also limited by the inconsistent access to subjects' healthcare records beyond the CLEAR III trial's follow-up framework.

CONCLUSION

Despite these limitations, observational data can be very useful in gleaning clinical patterns, and will form the basis of hypotheses for future studies. Our results indicate that recurrent symptomatic hemorrhage is generally uncommon within 1 yr following IVH, documented in only 4% of cases, with different patterns and association among early and later bleeds. Intraventricular thrombolysis seems to only marginally, and not significantly increase the overall risk of symptomatic hemorrhage, and only during the dosing period. Bleeding could not be directly attributed to 1 single factor in any of these cases, but more likely resulted from a constellation of treatment- or patient-related factors. An equal number of symptomatic hemorrhages occurred beyond the dosing period, unrelated to the use of thrombolysis. This highlights the importance of secondary prevention strategies, including blood pressure control and judicious management of anticoagulation or antiplatelet therapy during the year following IVH.

Disclosures

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COMMENTS

In the present study, the authors perform a careful, post-hoc evaluation of the recently published CLEAR III trial,[1] specifically assessing patients with symptomatic hemorrhage following intraventricular alteplase administration. In their root-cause analysis, they characterized several important observations.

First, patients with re-hemorrhage during the study protocol were more likely to have been treated with alteplase versus placebo. In contrast, patients with delayed re-hemorrhage were more likely to have been treated with saline. Furthermore, these delayed hemorrhages seemed to be unrelated to the initial hemorrhage, separated by both time and location. Thus, as concluded in the study, delayed symptomatic re-hemorrhage is most likely related to the underlying pathophysiology, rather than the administration of alteplase.

Second, in patients with symptomatic re-hemorrhage during study dosing, protocol deviation seemed to be associated with this adverse event (encountered in 5 of 9 patients in this subgroup). Importantly, this particular root-cause can be directly addressed with future clarifications to the study protocol.

As addressed by the study authors, the overall low rate of symptomatic re-hemorrhages in the CLEAR III study makes statistical analysis difficult. A post-hoc, root-cause analysis is appropriate in this setting; however the lack of statistical interpretation makes the observations less conclusive, and should be noted in this study.

Kurt Yaeger
J. Mocco
New York, New York

1. Hanley DF, Lane K, McBee N, Ziai W, Tuhrim 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. [published ahead of print Accessed 14 June 2017.] *Lancet (London, England)* 2017;389:603-611, Available: http://linkinghub.elsevier.com/retrieve/pii/S0140673616324102.

In this study, the authors perform a substudy of the CLEAR III data and perform a root cause analysis to explore symptomatic rehemorrhage after IVH with and without alteplase. There are 2 critical aspects to the study: the effect of aletplase on the incidence of symptomatic rehemorrhage after IVH, and the timing of such rehemorrhages (dosing, early, or late). Their findings support that most rehemorrhage occurs during dosing, and the rates do not differ significantly with the addition of atletplase. In addition, the majority of alteplase bleeding events were related to protocol deviations (double dosing, failure to obtain surveillance imaging).

There are several strengths of this study:

- As a substudy of a large, adjudicated trial, hemorrhage was specifically screened for in a prospective manner, and the criteria for symptomatic hemorrhages were clearly defined a priori. This limits selection bias.
- It's comforting for the clinician to know that the CLEAR III protocol is safe when followed as most symptomatic bleeds in the treatment group occurred from protocol deviations. It also supports the need of a strict protocol when transitioning the trial protocol into practice.
- All rebleeds occurred in patients with concurrent IPH, which allows for additional suspicion and caution in this group.

Despite the fact that this is an underpowered post-hoc analysis, this study makes important contributions to the literature in regards to the natural history of IVH with respect to rehemorrhage as well as the safety of intraventricular alteplase.

Abdulrahman Y. Alturki
Christopher S. Ogilvy
Boston, Massachusetts