ORIGINAL ARTICLE

The Incidence of Catheter Tract Hemorrhage and Catheter Placement Accuracy in the CLEAR III Trial

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Abstract

Background Incidence of catheter tract hemorrhage (CTH) after initial ventriculostomy placement ranges from 10 to 34%. We investigated CTH incidence in the Clot Lysis: Evaluation of Accelerated Resolution of Intraventricular Hemorrhage Phase III trial.

Methods Prospective observational analysis of 1000 computer tomography (CT) scans from all 500 patients enrolled in the trial. All catheters were evaluated on first CT post-placement and on last CT prior to randomization for placement location and CTH size, location, and severity. Clinical variables were assessed for association with CTH with multivariable logistic regression.

Results Of 563 catheters, CTH was detected in 14 and 21% of patients on first and last CT (median 3.7 and 43.4 h after catheter placement, respectively). All, but one were asymptomatic. Majority of CTH (86%) occurred within 24 h after placement, were located within 1 cm of the skull, and had at least one diameter > 5 mm. Most catheters (71%) terminated in the third or lateral ventricle ipsilateral to insertion site. Factors significantly associated with CTH were pre-admission use of antiplatelet drugs, accuracy of catheter placement, non-operating room catheter placement, Asian race, and intraventricular hemorrhage expansion.

Conclusions CTH incidence on initial catheter placement and during stabilization was relatively low, despite emergent placement in a high-risk population. Catheter placement accuracy was similar or better than convenience samples from the published literature. Decreasing risk of CTH may be achieved with attention to catheter placement accuracy and placement in the operating room. Antiplatelet agent use was an independent risk factor for CTH.

Keywords Intracerebral hemorrhage · Intraventricular hemorrhage · External ventricular drain · Catheter tract hemorrhage · Computed tomography · Intraventricular fibrinolysis

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Introduction

Since the initial presentation of ventriculography by Dandy et al. [1], the technique of external ventricular drain (EVD) placement has evolved significantly. The most frequent indications for EVD placement are for measurement and control of intracranial pressure in patients with traumatic brain injury (TBI) [2], acute hydrocephalus [3], intraventricular hemorrhage (IVH) [4], and subarachnoid hemorrhage (SAH) [5]. The two most common complications of EVD placement are hemorrhage and infection. In contrast to infection, catheter tract hemorrhage (CTH) has received significantly less attention in the literature. Reported rates of new or expanded hemorrhage after ventriculostomy range from 0.7 to 41% [6–9]. Dey et al. [6] in a systematic review of bleeding and hemorrhage risks with EVD use attributed the wide variation to lack of standard definitions for ascertaining the presence of CTH. Age > 75 years, international normalized ratio (INR) > 1.4, and use of antithrombotic agents have been identified as risk factors for CTH [10–12].

The CLEAR III trial was a randomized, double-blind, multicenter phase III clinical trial with 500 enrolled patients assessing efficacy of intraventricular alteplase administered through an EVD versus saline for clearance of IVH. The trial benefitted from systematic surveillance and independent adjudication of all CTHs. We analyzed occurrence of CTH immediately after EVD placement and pre-randomization in all 500 patients enrolled in the CLEAR III trial. This is the first study with protocolized imaging, masked assessment of multiple time points post-placement, and protocolized definition of bleeding on image review after EVD placement to investigate incidence and characteristics of CTH in a multicenter phase III clinical trial.

Methods

CLEAR III Patient Population

CLEAR III enrolled patients 18–80 years of age with spontaneous intracerebral hemorrhage (ICH) volume ≤ 30 mL and IVH obstructing the third and/or fourth ventricle, verified by computed tomography (CT) scan performed within 24 h of symptom onset, and requiring EVD placement per institutional standard of care. Exclusion criteria were: infratentorial hemorrhage, ruptured aneurysms, tumors, TBI, and other structural causes of ICH, and clotting disorders (platelet count < 100,000, INR > 1.4, prothrombin time [PT], or partial thrombo-plastin time [PTT] outside of normal range). Reversal of

coagulopathy was permitted. Stability of the primary bleeding site and the EVD region was the main safety requirement for alteplase administration [7]. The CLEAR III trial was performed at 73 sites in Brazil, Canada, Germany, Hungary, Israel, Spain, the UK and the USA following local institutional review board and country ethics approval. Written informed consent for research was obtained from all participants (or legal representatives or surrogates) in the study.

Pre-randomization Imaging Schedule in the CLEAR III Trial

The screening protocol included the diagnostic CT scan and a subsequent stability CT scan 6 h or more after EVD placement. If more than 2 EVD passes were required for placement, additional stabilization of EVD site was determined with a CT performed at 24 h after placement. The investigator could continue to screen up to 72 h for initial bleeding to stabilize. If clot sizes stabilized between two sequential CT scans at least 12 h apart (≤ 5 mL increase in volume by ABC/2 method), the patient was eligible for enrollment.

Catheter Placement and Catheter-Related Hemorrhage Definitions

Because placement of the catheter was a clinical decision preceding trial eligibility, the initial EVD target and method were not governed by trial protocol. All included catheters were evaluated for CTH on the first CT scan taken after EVD placement (T1) and on the last CT scan taken before the start of treatment (T2). EVDs placed after T1 were placed with consultation between the site and the central, core surgical laboratory. If a patient had more than one catheter placed before the first CT scan, these were included as well. All subsequently placed catheters (N = 182) were excluded from this analysis. On both scans, the occurrence of CTH was defined as any new blood (HU ≥ 40 units) along the tract after initial EVD placement and was characterized using a severity grading system along with location, diameter, and edema criteria, as well as likely etiology (Table 1; Fig. 1).

EVD Placement Location

EVD placement location was evaluated using a modified version of the score described by Kakarla et al. [8], in which grade 1 was split into two groups 0 and 1 (Fig. 2). The tip of the EVD was assigned to one of 4 graded locations defined as either "optimal": (grade 0)—frontal horn ipsilateral to the skull entry point with tip ending in the third ventricle, or "acceptable" (grade 1) with tip in

Table 1 Computed tomography scan assessment of catheter tract hemorrhage

Criteria	Definition
CTH severity (modified from Jackson et al. [22])	0: No CTH
	1: Trace of blood along the tract
	2: Intracerebral hematoma without edema
	3: Intracerebral hematoma with edema and a largest diameter ≥ 5 mm
CTH Localization	Superficial: within 1 cm of the skull
	Middle: between superficial and deep
	Deep: within 1 cm of the ventricle wall
CTH Diameter	First measurement: largest visible diameter on any CT slice (mm)
	Second measurement: diameter perpendicular to largest diameter on the same CT slice (mm)
Apparent Peri-CTH Edema	Yes or no
Possible origin of the CTH (mutually exclusive categories)	
Spontaneous CTH within 24 h after placement	Blood visible within the first 24 h after EVD placement, without evidence of any other of the listed origins
Spontaneous new late onset CTH (> 24 h)	Blood visible later than 24 h after EVD placement, after a negative initial CT within 24 h, and, without evidence of any other of the listed origins. Time between placement and occurrence was recorded
CTH after EVD exchange	Blood visible after EVD exchange
CTH after EVD	
Manipulation	Blood visible after any kind of accidental/intentional movement of the EVD
Reposition	≥ 1 repositioning attempts (EVD passes) were recorded and blood visible along the presumed prior cannulation tract
CTH after EVD removal	Blood visible after EVD removal

CTH catheter tract hemorrhage, *EVD* external ventricular drain
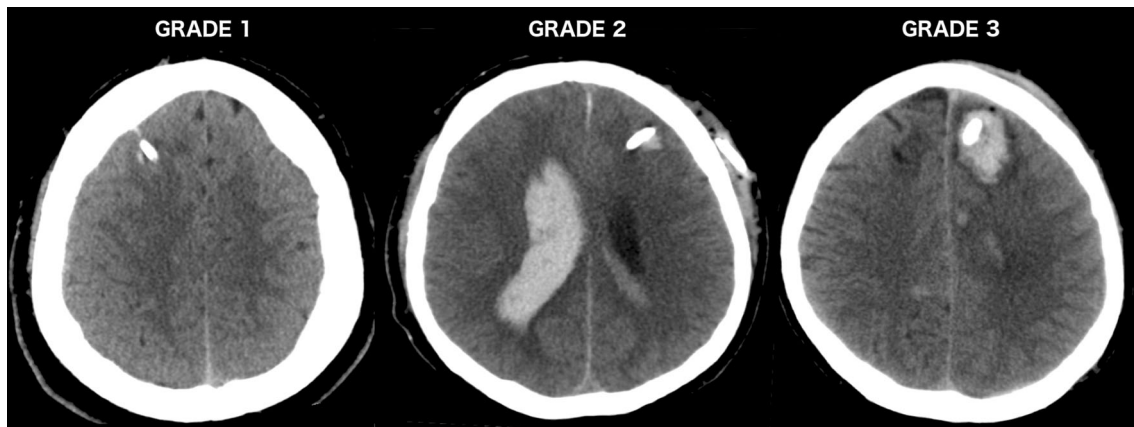
Fig. 1 Modified CTH severity score

lateral ventricle or foramen of Munro; or (grade 2) "suboptimal in non-eloquent tissue": EVD tip in contralateral frontal horn, corpus callosum, or interhemispheric fissure; or (grade 3) "suboptimal in eloquent tissue": EVD in thalamus, brainstem, or basal ganglia. Positioning of the EVD tip in the third ventricle was scored separately because it may more successfully deliver thrombolytic to the third ventricle and potentially remove the obstructing blood clot faster. This hypothesis not yet been tested.

Demographic and Clinical Data

The following demographic and clinical data were assessed for association with CTH incidence: patient age, sex, race, median ICH and IVH volume on diagnostic CT, time from EVD placement to first CT, ICH, or IVH enlargement (> 5 mL) during the pre-randomization phase, EVD placement side relative to ICH location and largest IVH volume, use of anticoagulant and antiplatelet drugs at
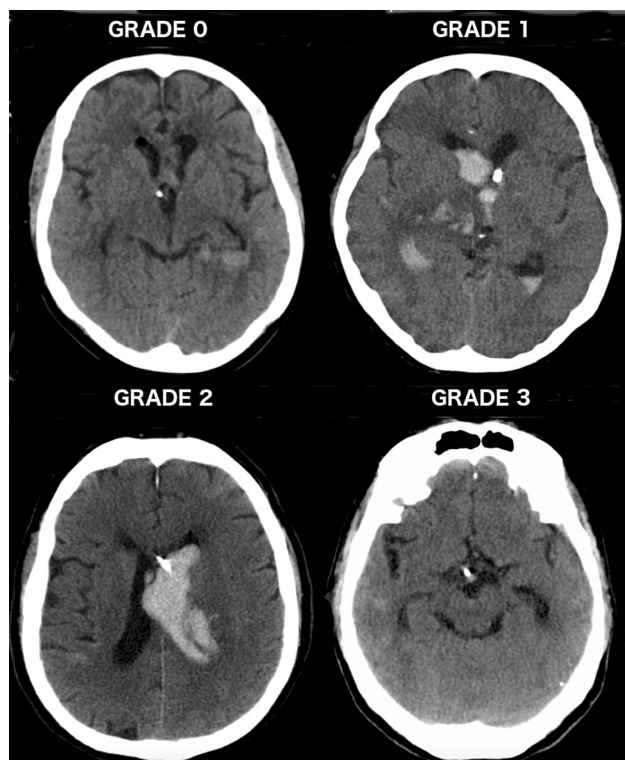
Fig. 2 EVD placement location score: modified Kakarla score. Grade 0: EVD placed in the targeted ipsilateral lateral ventricle of the EVD access side with the tip ending in the third ventricle (optimal EVD placement). Grade 1: EVD tip ends in the targeted ipsilateral lateral ventricle or foramen of Monroe ipsilateral to the EVD access side but not in the third ventricle (acceptable EVD placement). Grade 2: EVD tip ends in the nontargeted contralateral lateral ventricle of the EVD access side or just outside the ventricular system; e.g., corpus callosum or interhemispheric fissure (suboptimal EVD placement in non-eloquent brain tissue). Grade 3: EVD tip ends in eloquent brain tissue; e.g., basal cisterns, brainstem, basal ganglia, thalamus (suboptimal EVD placement in eloquent brain tissue)

admission, platelet transfusion on admission, use of pharmacologic prophylaxis for venous thromboembolism prior to day 3, baseline INR, PT, PTT, and platelet count, requirement for nicardipine in the pre-randomization phase (typically administered intravenously indicating clinically significant hypertension), and EVD factors: hospital location (intensive care unit [ICU], operating room [OR], or emergency department [ED]) and CT location of first EVD placement, number of EVD passes, and EVD placement accuracy (modified Kakarla score).

Statistics

We identified factors associated with CTH risk of T1 and T2 CTs before start of treatment. We used the Wilcoxon rank sum test or Student's t test for continuous variables depending on the normality of distribution. Categorical variables were analyzed using Pearson's Chi-square test (Fisher exact test when appropriate). Candidate

independent variables for multivariable modeling included all those with $p < 0.20$ for association with CTH in univariable analyses. After variable selection, a minimal logistic regression model was generated by backward elimination of nonsignificant variables ($p > 0.05$). All analyses were performed with STATA v.13 software (STATA corp. College Station, TX).

Results

One thousand CT scans were analyzed (500 at T1 and 500 at T2). Demographic and clinical characteristics of interest are presented in Table 2. Initial EVDs were placed in the ICU in 363 (72.6%), in the operating room in 127 (25.4%), and in the emergency department in 10 (2.0%). On T1 CT scan obtained at a median (IQR) of 3.7 (1.3, 9.6) hours after EVD placement, 563 EVD's were identified, 438 patients had 1 EVD, 61 patients had 2, and 1 patient had 3 EVDs in place simultaneously. "Optimal" catheter placement (Table 3) occurred in 21% (grade 0) and was acceptable in 49% (grade 1). "Suboptimal" placement occurred in 20% (grade 2) and 10% (grade 3). The grade 3 accuracy catheters were mostly located in the basal cisterns (38%), caudate nucleus (27%), and contralateral thalamus (16%) (Fig. 3). A total of 73 CTHs were found in 70 of 500 patients (14%) detected at median 4.7 [1.5–10.2] hours after EVD placement. CTH severity, location, and diameters are reported in Table 3. The majority of CTHs ($n = 63/73$; 86%) occurred within 24 h after placement after a single pass; 9 (12%) occurred after > 1 EVD pass; and 1 (1%) occurred on a T1 CT scan more than 24 h (37.5) after placement.

From these initial catheters, 529 (94%) were still present on the T2 CT at a median of 43.4 (28.3, 55.9) hours after EVD placement. At this time, from only the initial catheters evaluated on T1 CT, a total of 112 CTHs were detected in 107 patients (21%); 6 of the 73 CTHs from the T1 CT had resolved; and 45 new "delayed" CTHs were detected in 40 subjects (3 patients with 2 CTHs, 1 patient with 3 CTHs) yielding a delayed CTH incidence of 8.0% (40/500) at median 39.5 (32.3–57.7) hours after EVD placement. Of the delayed CTHs, 9/45 (20%) occurred within the first 24 h after EVD placement (in these cases, more than 1 CT was obtained during the first day), 5 (11.1%) occurred after > 1 EVD pass or catheter manipulation, and 28 (62.2%) occurred spontaneously more than 24 h after EVD placement (median 37.5 [27.3, 45.4] hours) and 3 (6.7%) after EVD removal. The diameters were not different compared to T1 CT CTHs, but CTH-associated edema occurred significantly more often on T2 scans (42% vs. 27%; $p = 0.04$). Only one CTH was reported as symptomatic by the study site. Between the T1 and T2 scan, a

Table 2 Demographics and baseline characteristics	Characteristics	$N = 500$
	Age (years), (SD)	58.6 (11.2)
	Male, N (%)	278 (55.6%)
	Race, N (%)	
	Caucasian	252 (50.4%)
	African-American	168 (33.6%)
	Hispanic	60 (12.0%)
	Asian	18 (3.6%)
	Other	2 (0.4%)
	Catheter data (median [range])	
	Number of catheter passes on first EVD placement	1 [1–5]
	Number of catheters placed before start of treatment	1 [1–8]
	Anticoagulated on admission, N (%)	49 (9.8%)
	Antiplatelet use on admission, N (%)	128 (25.6%)
	Laboratory data at baseline (median [IQR])	
	Platelet count	206 [168, 249]
	PTT	28 [25.7, 30]
	INR	1.1 [1, 1.2]
	Fibrinogen	424 [342, 516]
	Use of nicardipine to treat high blood pressure PR, N (%)	291 (58.2)
	Radiology (median [IQR])	
	Time from symptom onset to catheter placement (h)	7.5 [5, 12]
	Time from EVD placement to first CT (h)	4.0 [1.4, 9.7]
	ICH volume (mL)	8.5 [4.2, 14.2]
	IVH volume (mL)	35.2 [22.7, 49.4]

CT computer tomography, *ED* emergency department, *ICH* intracerebral hemorrhage, *INR* international normalized ratio, *IVH* intraventricular hemorrhage, *PR* pre-randomization, *PTT* partial thromboplastin time, *SD* standard deviation

significant increase in grade 2 ($p = 0.04$) and decrease in grade 3 ($p = 0.049$) catheter placement was observed (Table 3).

Factors Associated with Catheter Tract Hemorrhage

Tables 4 and 5 show demographic, clinical, and catheter data associations with CTH incidence on T1 and T2 CT. Variables significantly associated with CTH at both time points were race, non-operating room placement of first EVD, modified Kakarla score (MKS), use of antiplatelet agents pre-admission, and any IVH enlargement > 5 mL in the pre-randomization period. The association with race/ethnicity was significant for Asians and Native Hawaiian/Pacific Islanders (PI) with relatively higher rates of CTH versus all other races with lower rates. CTH rates were significantly higher for ICU-/ED-placed catheters (16.1 and 23.9% on first and last CT, respectively) versus 7.9 and 14.2% for OR-placed catheters ($p = 0.02$ for both). Number of EVD passes was nonsignificantly higher for CTH versus no CTH at both T1 CT ($p = 0.12$) and T2 CT

($p = 0.14$). Non-operating room (non-OR) placement of first catheters was nonsignificantly associated with higher proportion of MKS grade 3 compared to OR-placed catheters (11 vs. 8%; $p = 0.4$) (Fig. 3). There were significantly more catheters requiring more than 1 pass in non-OR- versus OR-placed catheters (18.2 vs. 7.9%; $p = 0.005$). Requirement for nicardipine in PR phase was associated with higher frequency of CTH on T2 compared to no requirement (24.7 vs. 16.8%; $p = 0.03$). In the multivariable analysis, independent predictors of CTH on first CT were non-OR placement of first catheter (OR 2.91, CI 1.35–6.24; $p = 0.01$), MKS (per point increase) (OR 1.57, CI 1.12–2.21; $p = 0.01$.), pre-admission use of antiplatelet agents (OR 2.57, CI 1.42–4.65; $p = 0.002$), Asian/PI race (OR 7.91, CI 2.11–29.72; $p = -0.002$), and IVH enlargement > 5 mL during the pre-randomization period (OR 2.29, CI 1.18–4.47; $p = 0.01$). Analysis was adjusted for time from EVD placement to first CT and number of EVD passes. The same factors were significantly associated with CTH on last CT. Of 128 patients on antiplatelet agents prior to admission, 39 (30.5%) received at least one platelet transfusion. The rate of CTH on T1 CT (and T2

Table 3 Catheter placement accuracy and catheter tract hemorrhage incidence and grading

CTH number and grading criteria	First CT after EVD placement [T1]	Last CT before study treatment [T2]
Number of catheters evaluated	563	529
Catheter placement location, N (%)		
Grade 0	117 (21%)	106 (20%)
1	276 (49%)	251 (48%)
2	111 (20%)	131 (25%)
3	56 (10%0	35 (7%)
Number of CTHs, N (%)	73 (13%)	112 (21%)
CTH severity, N (%):		
Grade 1	22 (30%)	30 (27%)
Grade 2	22 (30%)	27 (24%)
Grade 3	29 (40%)	55 (49%)
CTH location, N (%)		
Superficial	6 (8%)	4 (4%)
Middle	9 (12%)	15 (13%)
Deep	2 (3%)	7 (6%)
Superficial and middle	35 (48%)	44 (39%)
Middle and deep	7 (10%)	12 (11%)
All regions	14 (19%)	30 (27%)
CTH diameter (mm)		
Largest (median [range])	9.4 [2.9–31.4]	9.9 [2.4–36.3]
Perpendicular (median [range])	4 [1.5–26]	4.7 [1.3–22.6]
No. < 5 mm largest diameter, N (%)	8 (11%)	14 (12%)
Edema, N (%)	20 (27%)	47 (42%)
Etiology, N (%)		
Spontaneous CTH within 24 h after placement	63 (88%)	68 (60%)
Spontaneous new late onset (> 24 h)[a] CTH	1 (1%)	29 (26%)
CTH after EVD exchange	0	0
CTH after EVD manipulation/reposition (> 1 pass)	9 (12%)	12 (11%)
CTH after EVD removal	0	3 (3%)

CT computer tomography, CTH catheter tract hemorrhage, EVD external ventricular drain, mm millimeters

[a] CT performed > 24 h after EVD placement

CT) was not different between those transfused and not transfused (23.1 vs. 21.4%; $p = 0.83$).

Discussion

This study represents the largest and only multicenter prospective evaluation of incidence of hemorrhagic complications of emergent EVD placement in routine clinical practice. With rigorous validated scoring of CTH including trace hemorrhage, the incidence of early (within 24 h of EVD placement) and delayed (up to 72 h after EVD placement) CTH was 14 and 8%, respectively. The vast majority of hemorrhages were < 5 mL in volume and were of uncertain clinical significance. We confirmed several potentially modifiable clinical factors related to CTH

which may have future practice implications and could decrease additional risk associated with EVD placement. The data presented highlight that EVD placement and attendant CTH are well-defined targets for future improvement.

Risk Factors for CTH

Independent risk factors for CTH identified in this study were pre-admission use of antiplatelet agents, higher modified Kakarla score, ICU or ED placement (vs. OR), Asian/Pacific Islander ethnicity, and IVH expansion > 5 mL in the pre-randomization phase. Only the first of these has been previously reported. Sussman et al. [11] prospectively studied 69 patients with ICH and reported a post-ventriculostomy hemorrhage rate of 31.9% with only
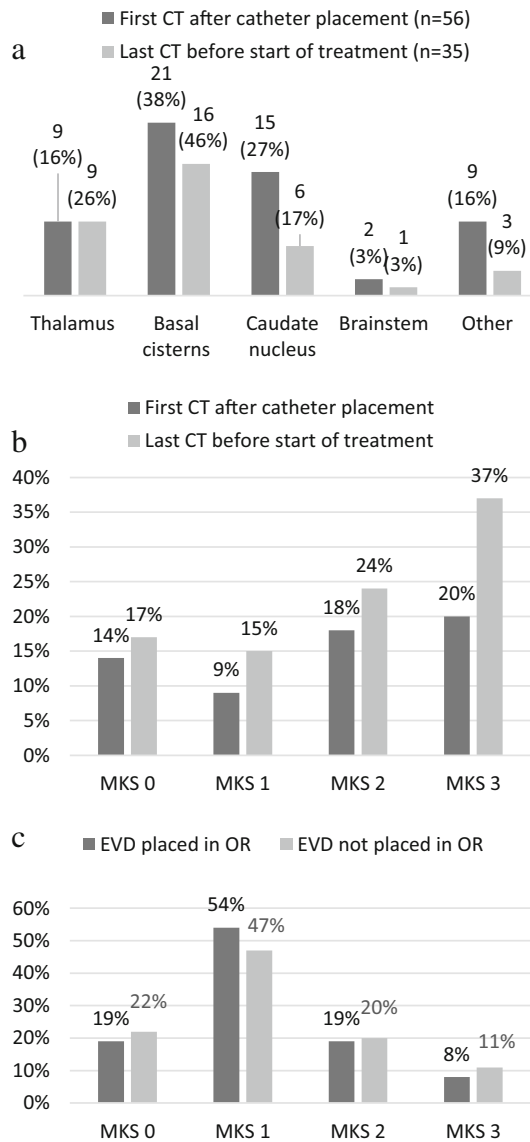
Fig. 3 **a** MKS grade 3 tip location, **b** CTH incidence by MKS grade, **c** MKS by OR versus non-OR catheter placement on last CT before start of treatment. *Significant at $p < 0.05$

1 event considered clinically significant (1.4%). Age > 75 years was the only independent predictor of post-ventriculostomy hemorrhage. Ko et al. retrospectively studied 370 patients with various indications for EVD placement. They reported a hemorrhage rate of 20.5% ($n = 76$) of which 5 patients had clinically symptomatic bleeds resulting in 2 deaths and of which 64.5% were delayed, occurring up to 2 weeks after placement and not visible on the first CT scan post-EVD placement. Preoperative antiplatelet medication was the only significant risk factor for CTH [12]. We also found that pre-admission use of antiplatelet agents was an independent risk factor for CTH. We did not find a significant association between occurrence of CTH and platelet transfusion in patients on antiplatelet agents or in the full cohort. We could not confirm, however, whether platelet transfusion occurred prior to EVD placement or in response to CTH.

In CLEAR III, as is true for most earlier studies, catheters were more often placed freehanded in the ICU, without image guidance. Some (25.4% of them), however, were placed in the OR and were associated with lower incidence of CTH, fewer placement attempts, and lower proportion of MKS grade 3 location with the EVD tip in eloquent tissue. Foreman et al. [10] also reported lower CTH rates in EVDs placed in the OR compared to ICU (4.4 vs. 15.1%), respectively, in a study of 138 patients. Huyette et al. [13] reported that freehand ventricular catheterization typically required two passes per successful placement, and 22.4% of catheter tips were in non-ventricular spaces. Although the number of catheter positioning attempts reported in CLEAR III was low, even a small number of misplacements create a safety issue in terms of additional risk of CTH, infection, or non-functional drains which can be reduced by placement in the OR and ideally with stereotactic guidance [10].

Other factors which may be associated with CTH incidence, but were not assessed in this study include operator experience, burr-hole location (distance to superior sagittal sinus), and choice of landmarks for EVD placement.

CTH Incidence

Dey et al. [6] reported a pooled incidence of hemorrhagic complications after EVD placement of 8.4% (range from < 1 to 41%). This review included a heterogeneous population with SAH, TBI, IVH, and brain tumors as indications for EVD placement [8, 9, 13–17]. Most studies included only one post-procedural CT scan, usually within the first 24 h [13, 14, 18, 19], although in one study after an average of 6.2 ± 5.4 days post-ventriculostomy [16]. Gardner et al. [9] assessed either CT or magnetic resonance imaging within 48 h post-procedure and after EVD removal and reported the highest rate (41%). Naff et al. [15] included daily CT scans during treatment with fibrinolytic and a scan at day 28–32 after enrollment. One study included all CT scans obtained during hospitalization [8] and two used radiology reports [20, 21]. Most studies defined CTH as any hemorrhage/hyperdense lesion along the catheter tract after placement [9, 14, 16, 18, 19, 21] similar to our definition. Planar and volume measures were not performed in most studies, and Patil et al. [20] did not include trace blood along the tract. In the pooled study of Dey et al., from EVD placement to first CT, CTH rates ranged from 1.8 [20] to 34% [9]. Based on the heterogeneity of patient subtypes and imaging surveillance reported, our CTH incidence does not appear to be excessive given the high-risk condition of ICH with IVH,

Table 4 Associations between demographic and clinical variables and CTH incidence

Characteristics	CTH—first CT (N = 70)	No CTH—first CT (N = 430)	CTH—last CT (N = 107)	No CTH—last CT (N = 393)
Age (years), (SD)	58.6 (9.6)	58.6 (11.5)	59.7 (9.7)	58.3 (11.6)
Male, N (%)	36 (51.4)	242 (56.3)	56 (52.3)	222 (56.5)
Race, N (%)[b]				
Caucasian	31 (44.3)	221 (51.4)	47 (43.9)	205 (52.2)
African-American	22 (31.4)	146 (33.9)	37 (34.6)	131 (33.3)
Hispanic	8 (11.4)	52 (12.1)	13 (12.2)	47 (12.0)
Asian	9 (12.9)	9 (2.1)	9 (8.4)	9 (2.3)
Other	0	2 (0.5)	1 (0.9)	1 (0.2)
Anticoagulated on admission, N (%)	4 (5.7)	45 (10.5)	7 (6.5)	42 (10.7)
Antiplatelet use on admission, N (%)[b]	28 (40)	100 (23.3)	38 (35.5)	90 (22.9)
Platelet transfusion	10 (14.3)	39 (9.1)	15 (14.0)	34 (8.7)
Chemoprophylaxis for DVT before day 3, N (%)	26 (42.6)	136 (39)	38 (40.9)	124 (39.1)
Laboratory data at baseline (median [IQR])				
Platelet count	210 [163, 246]	203 [169, 250]	209 [163, 250]	204 [169, 249]
PTT	28 [26, 30.6]	28 [25.6, 30]	28.3 [26, 30.6]	27.9 [25.5, 30]
INR	1.1 [1, 1.2]	1.1 [1, 1.2]	1.1 [1, 1.2]	1.1 [1, 1.1]
Fibrinogen	448 [377, 547]	418 [341, 511]	434 [359, 531]	419 [341, 510]
Use of nicardipine to treat high blood pressure PR, N (%)	48 (68.6)	243 (56.5)	72 (67.3)	219 (55.7)
Radiology (median [IQR])				
Time from symptom onset to catheter placement (h)	7.7 [5, 13.1]	7.5 [5, 11.9]	7.9 [5, 12.8]	7.5 [4.7, 11.8]
Time from EVD placement to first CT (h)	4.7 [1.5, 10]	3.9 [1.4, 9.5]	3.6 [1.5, 9.3]	4.2 [1.4, 9.7]
ICH volume (mL)	8.7 [3.9, 16.2]	8.5 [4.3, 13.9]	9.1 [3.8, 16.2]	8.5 [4.3, 14.0]
IVH volume (mL)	34.2 [27, 49.2]	35.8 [22.2, 49.4]	35.0 [27, 52]	35.3 [22, 49.2]
Any ICH expansion, N (%)[c]	12 (17.1)	36 (8.4)	13 (12.2)	35 (8.9)
Any IVH expansion, N (%)[b]	28 (40)	93 (21.6)	36 (33.6)	85 (21.6)

CT computer tomography, DVT deep venous thrombosis, ED emergency department, EVD external ventricular drain, GCS glasgow coma scale, ICH intracerebral hemorrhage, INR international normalized ratio, IQR interquartile range, mL milliliters, OR operating room, PR pre-randomization, PTT partial thromboplastin time, SD standard deviation

[a]Highest grade on first CT if > 1 EVD

[b]Significant at $p < 0.05$ for both first and last CT

[c]Significant at $p < 0.05$ for only first CT

use of the most stringent definition of CTH, emergent placement, rigorous CT imaging protocol, and multicenter international nature of the CLEAR III study (vs. all single-center comparison studies).

The pooled incidence of symptomatic catheter-related hemorrhage of 0.7% (range 0–14.6%) reported by Dey [6] compares with our finding of 0.2% (n = 1) in the pre-randomization phase of CLEAR III. Definitions of symptomatic hemorrhage are limited, however, with retrospective reports lacking a standard definition of deterioration. There is also little information about potential interventions to correct coagulopathy that may have been deployed to prevent conversion of asymptomatic to symptomatic hemorrhages.

CTH Description

We evaluated CTH using a severity grading score adapted from Jackson et al. [22]. In their two-center study with 27 patients and 30 EVDs, CTH incidence was 47.7% (n = 14). As in our study, the majority of CTHs had severity grade 1 (35.7%), or grade 2 (50%) with only 2 CTHs graded 3 (14.3%). We made a slight modification to this severity score to reduce apparent subjectivity between

Table 5 Associations between catheter variables and CTH incidence

Characteristics (median [range])	Patients with CTH—first CT ($N = 70$)	Patients without CTH—first CT ($N = 430$)	Patients with CTH—last CT ($N = 107$)	Patients without CTH—last CT ($N = 393$)
Non-OR placement, N (%)[b]	60 (85.7)	313 (72.8)	89 (83.2)	284 (72.3)
Number of catheter passes on first catheter placement	1 [1–5]	1 [1–5]	1 [1–5]	1 [1–5]
Number of catheters placed before start of treatment	1 [1–4]	1 [1–8]	1 [1–8]	1 [1–5]
First catheter side ipsilateral to dominant IVH, N (%)	20 (36.4)	116 (32.9)	33 (38.8)	103 (31.9)
Dual catheters, N (%)	24 (34.3)	113 (26.3)	36 (33.6)	101 (25.7)
Kakarla score, N (%)[ab]				
Number of catheters	73 (100)	490 (100)	106 (100)	423 (100)
Not gradeable	0	3 (0.6)	4 (3.8)	2 (0.5)
0	16 (21.9)	101 (20.6)	19 (17.9)	87 (20.6)
1	26 (35.6)	250 (51)	39 (36.8)	212 (50.1)
2	20 (27.4)	91 (18.6)	31 (29.2)	100 (23.6)
3	11 (15.1)	45 (9.2)	13 (12.3)	22 (5)
Kakarla score > 1, N (%)[ab]	31 (42.5)	136 (27.8)	43 (40.7)	122 (28.8)

CTH catheter tract hemorrhage, *IVH* intraventricular hemorrhage, *OR* operating room

[a]Highest grade on first CT if > 1 EVD

[b]Significant at $p < 0.05$ for both first and last CT

grades 2 and 3. Our severity score results were similar (Table 3) with a few more grade 3 CTHs. Using three CTH "distance from skull" strata (superficial, middle, and deep), we found that most CTHs occurred in the superficial and middle regions of the catheter (48% T1 CT; 39% T2 CT) rather than deep at the brain–ventricle interface. This likely reflects the high density of arteries and veins on and close to the brain surface. Conversely, only 3 and 6% of CTHs, on T1 and T2 CTs, respectively, were in the deep location only.

Catheter Placement Location

Two studies report the original Kakarla score for catheter placement accuracy. Kakarla et al. [8] reported grade 1, 2, and 3 accuracy of 77, 10, and 13%, respectively. Foreman et al. [10] investigated placement accuracy for catheters placed in the OR and in the ICU and reported grade 1, 2, and 3 accuracy of 67.7, 25.8, and 6.5% in ICU-placed catheters and 55.6, 42.2, and 2.2%, respectively, in OR-placed catheters. Our results are similar to both studies (combining grades 0 and 1 as "1" from the original Kakarla). For OR-placed catheters, we also found slightly better accuracy (grades 1, 2, 3 = 72.2, 19.3, 8.4 vs. 69.3, 20.1, 11%, respectively, for ICU- or ED-placed catheters). Patil et al. modified the original Kakarla score with addition of a category 4 for failed procedure. They

found 79% of catheters had grade 1 accuracy, while 14, 5, and 2% were grade 2, 3, and 4, respectively [20]. We observed an increase in grade 2 and decrease in grade 3 placed catheters between T1 and T2 scans, likely due to repositioning or removal of initial grade 3 catheters or different head angles between scans.

Limitations

There are several limitations to this study. Despite imaging protocols, image acquisition post-EVD placement was not consistently performed at specified time points since patients were not yet enrolled in the CLEAR III trial at time of first CT. However, all patients acquired both initial and follow-up CT scans allowing determination of early and delayed CTH incidence and almost all patients (87.4%) had at least one CT on each day prior to randomization. The association of several potentially important factors with CTH incidence could not be analyzed with these data including surgeon experience in catheter placement, technical aspects of EVD placement, and timing of platelet transfusion (prior to or following EVD placement). This study was not powered to assess association between platelet transfusion and CTH in patients taking antiplatelet agents. Another limitation is our inability to address catheter accuracy and CTH in cases excluded from the trial. Moreover, results of this study are not necessarily

generalizable to EVD placement in other conditions requiring urgent EVD placement (for example, subarachnoid hemorrhage or traumatic brain injury). Finally, our definition for symptomatic CTH as associated with a glasgow coma scale drop by 2 or more points may be insensitive to relevant clinical sequelae, particularly among patients in poor neurologic condition.

Conclusions

The accuracy of emergent EVD placement in 73 sites in the CLEAR III trial is equal to or better than convenience samples from the published literature. The initial CTH incidence was low and remained low during stabilization. Symptomatic hemorrhage associated with emergent EVD placement was uncommon (0.2%). CTH appears to be associated with several potentially modifiable risk factors including hospital location of EVD placement (OR vs. ICU/ED), accuracy of placement, and prior use of antiplatelet agents. CTH may be an index of occult or overt coagulopathy given the association of CTH with unstable IVH.

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