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The importance of aspirin, catheterization accuracy, and catheter design in external ventricular drainage-related hemorrhage: a multicenter study of 1002 procedures

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Abstract

Background External ventricular drainage (EVD) is the commonest neurosurgical procedure performed in daily neurosurgical practice, but relatively few studies have investigated the incidence and risk factors of its related hemorrhagic complications.
Methods This was a multicenter retrospective review of consecutive EVD procedures. Patients 18 years or older who underwent EVD and had a routine postoperative computed tomography (CT) scan performed within 24 hours were included. EVD-related hemorrhage was defined as new intracranial hemorrhage immediately adjacent or within the ventricular catheter trajectory. The volume of hemorrhage and the position of the catheter tip were assessed. A review of patient-, disease-, and surgery-related factors including the ventricular catheter design utilized was conducted. The Bonferroni correction was applied to the alpha level of significance (0.05) for multivariable analysis.
Results Nine hundred sixty-two patients underwent 1002 EVD performed by neurosurgeons in the operating theater. Sixteen percent (154) of patients were on aspirin before the procedure. Thirty-four percent (333) of patients had intracerebral hemorrhage, 25% (251) had aneurysmal subarachnoid hemorrhage and 16% (158) had traumatic brain injury. The mean duration from EVD to the first postoperative CT scan was 20 ± 4 h. EVD-related hematomas were detected after 81 procedures with a per-catheter risk of 8.1%. Mean hematoma volume was 1.2 ± 3.3 ml. Most were less than 1 ml (grade I, 79%, 64), 1 to 15 ml (grade II) in 20% (16) and a single clot larger than 15 ml (grade III, 1%) were detected. Clinically significant hemorrhage that resulted in catheter occlusion occurred in 1.7% (17) of procedures. Most catheters (62%, 625) were optimally placed, i.e., its tip being within the ipsilateral frontal horn or third ventricle. Three non-antibiotic-impregnated ventricular catheter designs were used with 55% (550) being the 2.2-mm Integra™ catheter, 14% (137) being the 2.8-mm Medtronic™ catheter, and 31% (315) being the 3.1-mm Codman™ catheter. Independent significant predictors for EVD-related hemorrhage were the preoperative prescription of aspirin (adjusted OR 1.94; 95% CI 1.10–3.44), catheter malposition (aOR 1.99; 95% CI 1.22–3.23), and use of the 2.8-mm Medtronic™ catheter (aOR 4.22; 95% CI 2.39–7.41).
Conclusions The per-catheter risk of hemorrhage was 8.1%, but the incidence of symptomatic hemorrhage was low. The only patient risk factor was aspirin intake. This is the first study to evaluate and establish an association between catheter malposition and catheter design with EVD-related hemorrhage.

Keywords External ventricular drainage · Ventricular catheter · Hemorrhage · Tract hematoma

Abbreviations

CI	Confidence interval
CSF	Cerebrospinal fluid
CT	Computed tomography
DICOM	Digital images for communications in medicine
EVD	External ventricular drainage
ICH	Intracerebral hematoma
OD	Outer diameter
OR	Odds ratio

Introduction

External ventricular drainage (EVD) is the commonest operative procedure performed in daily neurosurgical practice. Although several modifications have been made since Claude-Nicolas Le Cat first performed the procedure in 1744, the therapeutic principles of cerebrospinal fluid (CSF) drainage for the management of intracranial hypertension have remained unchanged [27, 33].

The two major complications of EVD are infection and hemorrhage [29]. The abundance of literature devoted to the incidence and risk factors for ventriculostomy-related infection is in stark contrast to the number of studies reviewing EVD-related hemorrhage as the primary endpoint of enquiry. Hemorrhagic complications of this time-honored procedure have been reported to occur between 1 and 41% of cases [2, 3, 29]. The reasons for the wide disparity in post-procedural hemorrhage rates are likely due to study methodology heterogeneity. For example, a number of studies were performed in a single-center setting, ventriculostomies were conducted by non-neurosurgeons outside the operating theater, a rigorous definition for EVD-related hemorrhage was lacking and few attempts were made to quantify the degree of hemorrhage with post-procedural imaging at fixed time points [1, 3]. Furthermore, comprehensive evaluations of possible surgical risk factors such as EVD approach, operator experience, and the type of catheter utilized are limited [16, 17, 25, 36].

We therefore embarked on a multicenter study to determine the incidence and severity of EVD-associated hemorrhage, performed exclusively by neurosurgeons in the operating theater, with the systematic assessment of routine postoperative computed tomography (CT) scans. In addition, we also analyzed a comprehensive inventory of patient-, disease-, and surgery-related variables to identify predictors for this complication.

Methods

This was a multicenter retrospective study of consecutive adult (18 years or older) patients who underwent EVD from five Hong Kong Hospital Authority neurosurgical units from January 1, 2012, to December 31, 2014. The Hospital Authority is a public health service highly subsidized by the Hong Kong Special Administrative Region Government and is responsible for 90% of inpatient bed days in the city. Clinical research ethics committee approval was obtained from the participating centers (Institutional Review Board number, KW/EX-16-128 (102-02)). Data from clinical records, operation notes, laboratory, and medication records as well as from a central digital imaging repository was collected. It is standard practice in Hong Kong for patients to undergo a postoperative CT brain scan within 24 h after a cranial neurosurgical procedure such as EVD. Potential predictors for postoperative hemorrhage were classified into patient-, disease-, and surgery-related factors. Patient-risk stratification was performed by using the Charlson comorbidity index (CCI), an age-adjusted weighted score of 17 comorbidities, with a maximum score of 24, based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes [4].

Surgical technique

All EVD procedures were performed by neurosurgeons in the operating theater. For catheters placed via a frontal burr hole, Kocher's point was utilized as the entry site. This point was localized by the intersection of the midpupillary line and a line 2.5 cm anterior to the coronal suture. A high-speed drill or Hudson brace was subsequently used to create a 14-mm burr hole. After dural incision, catheters were inserted and advanced to a maximal length of 6.5 cm until CSF drainage was observed. The frontal trajectory target was towards the ipsilateral medial canthus and the external auditory meatus. For catheters placed via a parietal burr hole, the entry site was determined either by Keen's point (3 cm superior and posterior to the helix of the ear), a point one-third of the distance between the parietal eminence and the inion or by image guidance where the parenchymal mantle was thinnest in order to enter the atrium of the lateral ventricle. Occipital catheters were either placed via a burr hole positioned at Frazier's point (4 cm lateral to the midline and 6 cm above the inion) or by image guidance where the parenchymal mantle was thinnest allowing entry into the occipital horn of the lateral ventricle.

Three types of plain, i.e. non-antibiotic-impregnated, silicone polymer ventricular catheters produced by three manufacturers were used in accordance with each institution's usual practice (Fig. 1). One catheter type had an outer diameter (OD) of 3.1 mm with 20 inlet holes located within 27 mm from its tip (catalog number, 82-1735, Codman Neuro™, Depuy Synthes, Raynham [MA], USA); another had an OD of 2.8 mm with 16 holes situated within 24 mm from the tip (catalog number, 46118, Medtronic, Minneapolis [MN], USA); and the third catheter had the narrowest OD of 2.2 mm with 40 flow holes situated within 17 mm from the tip (catalog number, NL850-1504, Integra Neurosciences™,
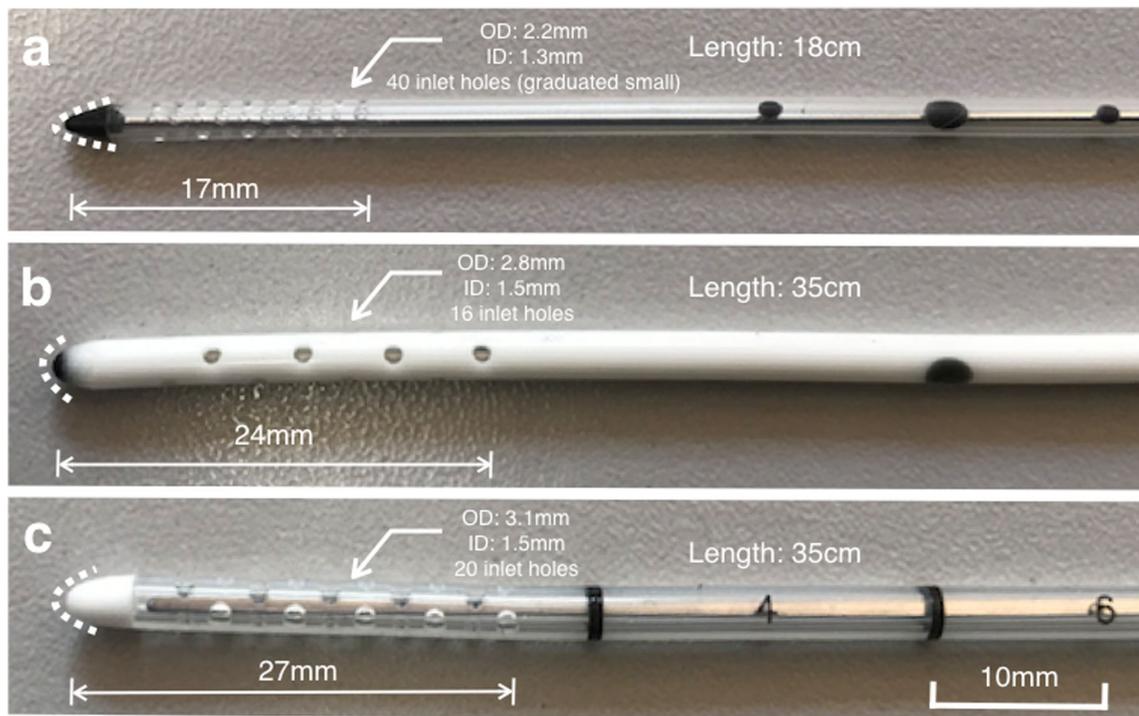
Fig. 1 Photograph showing the design features of the three plain silicone polymer ventricular catheters utilized. The 2.2-mm Integra™ catheter (**a**, catalog number, NL850-1504, Integra Neurosciences™, Integra LifeSciences, Plainsboro [NJ], USA). The 2.8-mm Medtronic™ catheter (**b**, catalog number, 46118, Medtronic, Minneapolis [MN], USA). The 3.1-mm Codman™ catheter (**c**, catalog number, 82-1735, Codman Neuro™, Depuy Synthes, Raynham, [MA], USA). The dashed white line indicates the contour of the catheter tip. OD, outer diameter; ID, inner diameter

Integra LifeSciences, Plainsboro [NJ], USA). All catheters were then tunneled out, anchored with sutures, and connected to a closed drainage system.

Radiological evaluation and grading of EVD-related hemorrhage

Radiological evaluations were independently analyzed by clinicians with at least six months of neurosurgical training and blinded to the clinical characteristics of each subject. Scans were conducting according to each institution's standard protocol using a 64-detector scanner with 5 mm axial sections. Digital images for communications in medicine (DICOM) were then uploaded to workstations installed with Centricity Enterprise Web (General Electric Medical Systems, Barrington, Illinois, USA) image viewers. The primary endpoint was the detection of EVD-related hemorrhage defined as new intracranial hemorrhage immediately adjacent or within the ventricular catheter trajectory on the first postoperative scan performed within 24 hours. A further CT assessment for EVD-related hemorrhage was also performed at a 1-week time point. The volumes (ml) of new intracerebral hematomas (ICH) were measured by adopting the validated ABC/2 formula [32]. ICH volumes were then classified into three grades: grade I, < 1 ml; grade II, 1–15 ml; and grade III, >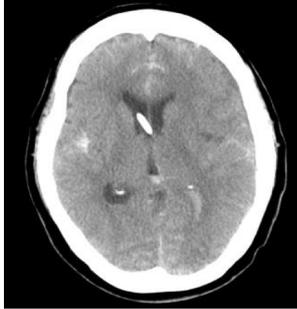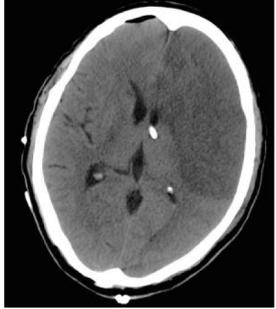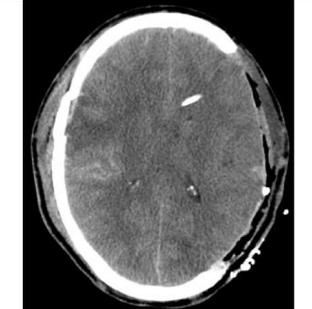 15 ml according to Wiesmann et al., one of the first groups that investigated this surgical complication [34]. EVD catheter position was also assessed and categorized according to Kakarla et al. into the following: grade I, optimal placement of the catheter tip into the ipsilateral frontal horn or third ventricle; grade II, functional placement in the contralateral lateral ventricle or non-eloquent cortex; and grade III, suboptimal placement in eloquent cortex or non-target CSF space (Table 1) [11]. The Kakarla grading system has been proven to have a high degree of intra- and interobserver agreement and is frequently adopted in studies investigating EVD catheter placement accuracy [11, 22]. Clinically significant EVD-related hemorrhage was identified when either: the patient required a subsequent neurosurgical procedure directly as a result of the hematoma, such as EVD revision or clot evacuation, or developed attributable neurological deficits as a consequence of this complication.

Statistical analysis

Statistical analysis was carried out using the Pearson's chi-squared test, linear, and binary logistic regression to identify risk factors for EVD-related hemorrhage. Patient, disease, and surgical factors were covariables and a stepwise regression strategy was adopted. Significant factors identified by univariable analysis were subject to multivariable logistic regression and the Bonferroni correction was applied to the α-

Table 1 Grading systems for EVD-related hemorrhage and ventricular catheter tip position

Grading System	I	II	III
EVD-related ICH Grade			
	< 1cc (volume: 0.4cc; white dotted line encircled area)	1-15cc (volume: 4cc)	>15cc (volume: 17cc)
Kakarla EVD Position Grade			
	Optimal: Catheter tip in ipsilateral frontal horn / 3rd ventricle	Functional: Contralateral ventricle / non-eloquent cortex	Suboptimal: Eloquent cortex or non-target CSF space

EVD, external ventricular drain; *ICH*, intracerebral hemorrhage; *CSF*, cerebrospinal fluid

level of significance (0.05) according to the number of group comparisons conducted. If x number of factors were determined to be significant for EVD-related hemorrhage from univariable analysis, an adjusted α-level of $0.05/x$ was used in order iden-tify significant factors after multivariable analysis. All tests were performed using the Statistical Package for the Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

During the 3-year period, a total of 1155 EVD procedures were performed. Nine hundred sixty-two patients fulfilled study criteria comprising a total of 1002 (87%) operations. Of the 153 procedures that were excluded, 42 (27%) were due to de-layed CT scanning beyond 24 hours and the remainder was attributed to the patient being younger than 18 years. The clin-ical and surgical characteristics are summarized in Table 2. The mean age (± standard deviation) was 55 ± 14 years (range 18 to 88 years) and the female-to-male ratio was 1:1. The mean CCI

was 1.6 ± 1.6 (range 0 to 13) indicating that most patients had few comorbidities before admission. Four percent of patients had liver cirrhosis ($n = 40$) and 2% ($n = 19$) had moderate to severe chronic renal disease, defined as a serum creatine of > 265 μmol/L. Sixteen percent of patients ($n = 154$) had a preced-ing history of aspirin intake within 48 h of the procedure, 4% received clopidogrel ($n = 36$), 4% had both antiplatelet medica-tions ($n = 35$), 4% were on warfarin ($n = 35$), and 3% receieved low molecular weight heparin ($n = 26$). One percent of patients ($n = 10$) was prescribed postoperative unfractionated heparin due to the need for endovascular stenting of a ruptured intracranial aneurysm.

Overall, primary EVD was performed for spontaneous in-tracerebral hemorrhage (ICH) in a third of patients (333, 34%), aneurysmal subarachnoid hemorrhage (SAH) in a quar-ter of patients (251, 25%) followed by 158 patients (16%) with traumatic brain injury (TBI) and 141 (14%) with neoplastic lesions.

For operations where only a single EVD catheter was inserted ($n = 399$, 40% of procedures), the mean operating

Table 2 Per procedure clinical characteristics of adult patients with primary EVD and univariable logistic regression analysis for EVD-related hemorrhage

Characteristics	Overall $n = 1002$ (%)	EVD-related hemorrhage* $n = 81$ (%)	No hemorrhage $n = 921$ (%)	Univariable analysis OR 95% CI
Patient factors				
Age, years, mean ± SD	55 ± 14	55 ± 15	55 ± 14	NS
> 75 years	61 (6)	3 (4)	58 (6)	NS
Male	510 (51)	44 (55)	466 (51)	NS
Charlson Comorbidity Index, mean ± SD	1.6 ± 1.6	1.7 ± 1.5	1.6 ± 1.6	NS
Moderate to severe renal disease	19 (2)	0	19 (2.1)	NS
Moderate to severe liver disease with portal hypertension	1 (0.1)	0	1 (0.1)	NS
Chronic liver disease without portal hypertension	40 (4)	3 (4)	37 (4)	NS
Medication				
Antiplatelet medication	162 (16)	21 (26)	141 (15)	1.94 (1.14-3.28)
Aspirin	156 (16)	21 (26)	135 (15)	2.04 (1.20–3.46)
Clopidogrel	36 (4)	4 (5)	32 (4)	NS
Dipyridamole	6 (0.6)	0	6 (0.7)	NS
Double antiplatelet medication	35 (4)	4 (5)	31 (3)	NS
Anticoagulant medication	64 (6)	8 (10)	56 (6)	NS
Warfarin	36 (4)	3 (4)	33 (4)	NS
Unfractionated heparin	10 (1)	3 (4)	7 (0.8)	5.02 (1.27–19.81)
LMWH	26 (3)	3 (4)	23 (3)	NS
Dabigatran	3 (0.3)	0	3 (0.3)	NS
Antiplatelet and anticoagulant medication	29 (3)	2 (3)	27 (3)	NS
Platelet level ($\times 10^9$/L), mean ± SD	233 ± 79	219 ± 65	234 ± 80	NS
Platelet level < 100×10^9/L	29 (3)	2 (3)	27 (3)	NS
Platelet level < 50×10^9/L	1 (0.1)	0	1 (0.1)	NS
INR				
Mean ± SD	1.2 ± 0.3	1.1 ± 0.3	1.0 ± 0.3	NS
≥ 1.4	45 (5)	6 (7)	39 (4)	NS
≥ 2.0	19 (2)	1 (1)	18 (2)	NS
≥ 2.5	13 (1)	1 (1)	12 (1)	NS
Disease etiology				
Spontaneous intracerebral hemorrhage	344 (34)	29 (36)	315 (34)	NS
Aneurysmal SAH	251 (25)	16 (20)	235 (26)	NS
Traumatic brain injury	158 (16)	13 (16)	145 (16)	NS
Tumor	141 (14)	11 (14)	130 (14)	NS
Ischemic stroke	82 (8)	8 (10)	74 (8)	NS
Surgical factors				
Operation duration, minutes, mean ± SD				
EVD insertion only	45 ± 60	65 ± 99	43 ± 57	NS
EVD with additional procedure	222 ± 160	211 ± 174	224 ± 159	NS
Additional procedure	603 (60)	54 (67)	549 (60)	NS
Bilateral EVD only	104 (10)	7 (9)	97 (11)	NS
Emergency procedure	899 (90)	71 (88)	828 (90)	NS
Time of day				
08:00–17:59	544 (54)	45 (55)	499 (54)	NS
18:00–23:59	262 (26)	20 (25)	242 (26)	NS
00:00–07:59	196 (20)	16 (20)	180 (20)	NS

Table 2 (continued)

Characteristics	Overall $n = 1002$ (%)	EVD-related hemorrhage* $n = 81$ (%)	No hemorrhage $n = 921$ (%)	Univariable analysis OR 95% CI
Burr hole location				
Frontal	856 (86)	69 (86)	787 (86)	NS
Parietal	103 (10)	9 (11)	94 (10)	NS
Occipital	35 (4)	2 (3)	33 (4)	NS
Temporal	7 (0.7)	0	7 (0.8)	NS
EVD insertion via dedicated burr hole	731 (73)	62 (77)	669 (73)	NS
Number of surgeons per procedure, median	2	2	2	NS
Residents (i.e., less than 5 years of neurosurgical experience)	779 (78)	58 (72)	721 (78)	NS
EVD design (OD)				
Codman Neuro™ (3.1 mm)	315 (31)	24 (30)	291 (32)	NS
Medtronic™ (2.8 mm)	137 (14)	40 (49)	97 (10)	7.14 (4.40–11.60)
Integra Neurosciences™ (2.2 mm)	550 (55)	17 (21)	533 (58)	0.19 (0.11–0.34)
Kakarla EVD position				
I (optimal)	625 (62)	40 (49)	585 (63)	0.56 (0.36–0.88)
II (functional)	297 (30)	32 (40)	265 (29)	1.62 (1.01–2.58)
III (suboptimal)	80 (8)	9 (11)	71 (8)	NS
Not optimal position (II and III)	377 (38)	41 (51)	336 (37)	1.79 (1.13–2.82)

EVD, external ventricular drain; *OR*, odds ratio; *CI*, confidence interval; *SD*, standard deviation; *NS*, not significant; *LMWH*, low molecular weight heparin; *INR*, international normalized ratio; *SAH*, subarachnoid hemorrhage; *OD*, outer diameter

*Data are shown in No., No. (%), or mean ± standard deviation, unless otherwise specified

time was 45 ± 60 min. The mean duration for procedures performed in conjunction with EVD, for example, a craniotomy, was 222 ± 160 min. The majority of patients underwent the procedure as an emergency ($n = 899$, 90%) with most performed during daytime from 08:00 to 17:59 ($n = 544$, 54%). The most frequent approach for catheter insertion was via the frontal lobe in 86% of procedures ($n = 856$) and through a dedicated burr hole in 73% ($n = 731$). The operation records of only 48 (4.7%) procedures described the number of attempted passes for catheterization. The median number of neurosurgeons performing the procedure was two and the majority of catheters ($n = 779$, 78%) was placed by residents with fewer than 5 years of neurosurgical experience. Most catheters were optimally placed (62%, 625 were Kakarla grade I) and 8% (80) were inserted in suboptimal locations (Kakarla grade III). Apart from one neurosurgical center that switched from using the Medtronic™ ventricular catheter design (from January 2012 to July 2013) to the Codman™ design (from July 2013 to December 2014), the remaining centers used only one specific EVD catheter during the entire study period. Half of the total number of ventricular catheters utilized was of the Integra™ design (55%, 550), a third were of the Codman™ design (31%, 315) and 14% (137) were from Medtronic™. The mean duration from EVD and the first postoperative CT scan performed within 24 hours was 20 ± 4 hours.

EVD-related tract hematomas were detected after 81 procedures (74 patients) with a per-catheter risk of 8.1%. The mean tract hematoma volume was 1.2 ± 3.3 ml (range, 0.5 to 27.4 ml). Most hematomas were less than 1 ml (grade I, 79%, $n = 64$), 1 to 15 ml (grade II) in 20% ($n = 16$) and a single case where a clot greater than 15 ml (grade III, 1%) was recorded. The mean duration from EVD insertion to the 1-week scan was 6 ± 18 days and the occurrence of tract hematomas at this time point increased to 15.5% ($n = 129$) of procedures. The mean hematoma volume at 1-week was 1.0 ± 2.2 ml (range, 0.2 to 20.5 ml) and was not considerably different from the initial postoperative scan (p value = 0.13). One-fifth of EVD-related tract hematomas (21%, 17), or 1.7% of procedures, was clinically significant with all leading to catheter occlusion. As a result, the provoking catheter was either replaced (13, 76% of cases), instilled with urokinase to re-establish its patency (1, 6%), required a craniotomy for clot evacuation (1, 6%) or was simply removed (2, 12%). The mean duration from EVD to the performance of an additional operative procedure to address catheter blockage as a result of hemorrhage was 4.6 ± 3.6 days.

Univariable logistic regression analysis revealed that the only patient-related predictors for EVD-tract hematoma formation were the preoperative administration of aspirin (OR 2.02; 95% CI 1.20–3.46) and unfractionated heparin (OR 5.02; 1.27–19.81) (Table 1). Patients with underlying

moderate to severe renal or liver disease were not particularly prone to experiencing this complication. Preoperative platelet levels and international normalized ratio (INR) values were also not associated with hemorrhage. No elevated risk was detected even for patients with preoperative platelet levels < 50×10^9/L or INR levels ≥ 2.5. There was also no association detected with presenting disease etiology. For surgery-related factors, the type of EVD catheter utilized and its final position were significant determinants for tract hematomas. The EVD catheter with the narrowest OD of 2.2 mm (Integra™) had the lowest risk of inducing a hematoma (OR 0.19; 95% CI 0.11–0.34) with 17 (3%) procedures utilizing this device resulting in this complication. EVD with the Codman™ catheter, having the widest OD of 3.1 mm, resulted in tract hemorrhage in 8% (24) of procedures that used this design and was not associated with bleeding (OR 1.01; 95% CI 0.67–1.80). However, the Medtronic™ catheter, with an OD of 2.8mm, was associated with a significantly increased risk of hemorrhage (OR 7.14; 95% CI 4.40–11.60) and was detected in more than a quarter of operations (27%, 37) utilizing this design. Catheters that were placed at an optimal Kakarla grade I location were least likely to result in hemorrhage (OR 0.56; 95% CI 0.36–0.88) and those that were not, namely Kakarla grades II and III, were associated with this complication (OR 1.79; 95% CI 1.13–2.82). Significant factors identified during univariable analysis were subsequently included in a multivariable binary logistic regression model (Table 3). Since a total of five factors were identified, by applying the Bonferroni correction, the alpha level of significance was adjusted to 0.01 (0.05/5). The only independent patient-related predictor for developing EVD-related hemorrhage was the preoperative prescription of aspirin (p value, 0.009; adjusted OR 1.94; 95% CI 1.10–3.44). The two previously identified surgery-related factors continued to be significant independent predictors for hemorrhage.

Table 3 Per procedure clinical characteristics of adult patients with primary EVD and multivariable logistic regression analysis for EVD-related hemorrhage

Predictor	Multivariable analysis Adjusted OR (95% CI)	p value†
Patient factors		
Aspirin	1.94 (1.10–3.44)	0.009
Unfractionated heparin	2.08 (0.47–9.17)	0.311
Surgical factors		
EVD design		
Medtronic™ (OD 2.8 mm)	4.22 (2.39–7.41)	< 0.001
Integra™ (OD 2.2 mm)	0.34 (0.18–0.65)	0.001
Kakarla EVD position		
Not optimal (II and III)	1.99 (1.22–3.23)	0.006

OR, odds ratio; *CI*, confidence interval; *OD*, outer diameter; *EVD*, external ventricular drain

†Bonferroni-corrected α-level for significance: 0.01 (0.05/5)

Namely, use of the Medtronic™ catheter (p value, < 0.001; adjusted OR 4.22; 95% CI 2.39–7.41) and EVD catheters that were not optimally placed (p value 0.006; adjusted 1.99; 95% CI 1.22–3.23). Catheter placement approach, whether it was placed through a dedicated burr hole, overall procedure duration, the addition of another operative intervention in the same setting, the nature of the EVD (as an emergency or otherwise) and neurosurgical experience were not associated with hemorrhage. A similar analysis was performed for clinically significant EVD-related hemorrhage, but due to its rarity no significant predictors could be identified.

Since the catheter models utilized were institution-specific, a review of factors that could contribute to center bias was performed. Patient age (p value = 0.88), disease etiology (p value = 0.76), antiplatelet medication intake (p value = 0.94), surgical experience (p value = 0.81), and neurosurgical procedure caseload (p value = 0.81) were not significantly different between centers.

Discussion

External ventricular drainage is arguably one of the most important lifesaving interventions that can be offered in neurocritical care. During a 3-year period, a total of 2 575 EVD procedures were performed in Hong Kong's public health system and in the USA alone a total of 108 167 catheters were placed over three decades from 1988 to 2010 [24, 35]. The wide range in the incidence of EVD-related hemorrhage of 1 to 41% has been observed and suggests considerable heterogeneity in study methodology prohibiting the drawing of meaningful conclusions [2, 3, 29]. Several studies only reported the presence of symptomatic hemorrhage without routine post-procedural scanning [3], but a meta-analysis confirmed higher rates of EVD-related hemorrhage (12.1%) when regular scanning was conducted compared with those where only ad hoc imaging was arranged [2]. To our knowledge, this is the first analysis of a multi-center patient cohort of this scale comprehensively reviewing risk factors for EVD-related hemorrhage, including the type of catheter design utilized, with volumetric assessment of routine postoperative imaging.

We identified a per-catheter hemorrhage rate of 8.1% in 74 patients (7.7%). Clinically significant hemorrhage was low (1.7% of procedures) and was comparable to the frequency of symptomatic hematomas occurring in 0 to 2.5% of cases documented in the literature [2]. The only independent significant patient-related predictor for EVD-related hemorrhage was aspirin intake. Due to its irreversible qualitative inhibitory effect on platelet function, it is reasonable to expect that such patients would be at risk [5, 25]. Our findings support those of a recent study that adopted a point-of-care platelet function test for patients on preoperative antiplatelet medication that

concluded that assay-guided platelet transfusions did not reduce the incidence of EVD-related hemorrhage [15]. In contrast, patients with thrombocytopenia or with clotting factor deficiencies were not susceptible. These quantitative bleeding tendencies were likely to have been sufficiently reversed with perioperative blood product transfusion and the resulting risk for hemorrhage was noted to be minimal [1]. The deleterious effects of antiplatelet medications are well known and represent a unique clinical challenge for patients undergoing subsequent neurosurgical interventions necessitating its administration [8, 9, 12, 13, 25]. The rising popularity of endovascular therapy for the treatment of aneurysmal SAH with the placement of intracranial arterial stenting or flow-diverters is one such example where a consequent increase in EVD-related hemorrhage has been observed [8, 13, 37]. However, since few patients in our cohort required such interventions, we were unable to arrive at similar conclusions for this subgroup of patients.

Two novel findings were noted among the surgery-related factors reviewed. Ventricular catheterization accuracy and catheter design were the only independent surgical predictors for hemorrhage. Adopting the Kakarla grading system, 62% (625) of catheters were at an optimal position. Prior studies adopting this system noted that accurate placement in between 40 and 88% of procedures [10, 11, 22, 26, 31]. The present study is the first to evaluate and establish a relationship between catheter position and EVD-related hemorrhage. Malpositioned catheters are naturally predisposed to this complication either as a result of multiple insertion attempts or due to the increased distance of traversed brain parenchyma required to breach a CSF space for drainage. Although an investigation of the determinants of catheter placement accuracy was beyond the scope of this study, we noted that several surgical factors were not associated with hemorrhage including the approach, whether a dedicated burr hole was used, the urgency of the procedure, or the level of neurosurgical experience. Strategies to improve accuracy have been proposed including the adoption of a Ghajar guide or image-guidance systems [7, 18, 19]. But the benefits of Ghajar guides are limited when mass lesions distort ventricular anatomy, when the calvarial slope surrounding the burr hole is significant and when catheters are inserted through a craniotomy or craniectomy site [21]. As for image-guided catheter placement, a survey of EVD practices revealed that neurosurgeons were reluctant to embrace technologies that increased procedure time especially when emergency CSF drainage was required [20]. Assistive devices such as the Ghajar guide are not available in Hong Kong and there was inadequate documentation in the operation records on the use of image-guidance to conclude its merits in this study.

Our large multi-center cohort allowed for the analysis of three ventricular catheter designs with regard to EVD-related hemorrhage. The Integra™ catheter design was associated with the lowest per-catheter hemorrhage rate of 3% compared with the Codman™ catheters with a rate of 8% and both were substantially lower than the Medtronic™ catheters that had a rate of 27%. The considerable difference in hemorrhage risk is unclear, but could be due to several distinguishing design features. Only three studies evaluated the significance of catheter OD among smaller patient cohorts and unexpectedly concluded that catheters with a wider gauge had a reduced risk of tract hematoma formation [15, 16, 28]. It was suggested that increased catheter sizes exerted a greater outer radial force upon the surrounding brain parenchyma that allowed for improved tamponade of injured blood vessels, but this theory has yet to be corroborated with preclinical experimental data [28]. We also noted that the Codman™ ventricular catheter with the widest largest OD of 3.1 mm was not associated with hemorrhage. But contrary to previous observations, the narrower 2.2-mm Integra™ design had the lowest hemorrhagic risk. It is therefore reasonable to presume that narrower gauge catheters induce less traumatic parenchymal injury. An interesting finding from this study is that ventricular catheter OD may only partially account for hemorrhage risk. The Medtronic™ 2.8-mm ventricular catheter was of intermediate diameter, but was the only design model that was significantly associated with tract hematomas. The results of an ongoing randomized clinical trial comparing the hemorrhagic complications of two antibiotic impregnated catheters, with differing ODs of 3 mm and 3.4 mm, will likely contribute to our understanding of the importance of this design feature [NCT03248739].

We therefore performed a further comparative qualitative appraisal of the three catheter designs (Fig. 1) and propose additional features that could contribute to tract hematoma formation. First, with regard to the catheter tip, the Medtronic™ design has a distinctly spherical shape compared with the conical configuration of its counterparts. We theorize that not only a wider pial opening would be required to penetrate brain tissue, but also the larger leading edge surface area could increase the probability of encountering blood vessels along its trajectory. Second, Medtronic™ catheters have the fewest inlet side-holes with 16 compared with the Integra™ catheter's 40. Computational fluid dynamic studies have documented that under normal circumstances CSF flow is highest through the proximal holes and that catheters with fewer holes have elevated fluid wall shear stress to reduce blockage risk [6, 30]. We hypothesize that although Medtronic™ catheters may have superior CSF flow dynamics, in the event of bleeding with proximal side-hole clot occlusion, the ensuing elevated distal wall shear stress could contribute to tract hematoma expansion [14]. Another distinctive design element concerns the catheter length. The Integra™ catheter was considerably shorter (18 cm) than the other designs (35 cm). We believe that the shorter catheter allowed for enhanced tactile feedback for the neurosurgeon particularly during the moment of ventricular puncture. This give-way sensation may be diminished with

the longer catheters and mislead the surgeon to attempt multiple passes that in turn could increase hemorrhage risk. Finally, two other features that were noticeably different with the Medtronic™ catheter were its complete barium impregnated opaque coating and the reduced number of depth indicator markings (at 5-cm intervals) from its tip. The other two catheter designs were translucent and had 1-cm interval markers starting from 4-cm from the tip. Confirmation of successful ventricular drainage by observing CSF backflow within these translucent catheters as well as clear markers for the depth of catheter insertion would have assisted surgeon in verifying their positioning reducing the need for reinsertion. The EVD catheter has undergone an extensive design evolution with priorities based on preventing infection and blockage [33]. For the latter, apart from the aforementioned features, studies have highlighted the importance of side-hole size, shape, and orientation in improving CSF flow [6, 33]. Since we were unable to obtain this information from the manufacturer's device information insert that accompanied the ventricular catheters, comments on their relationship with EVD-related hemorrhage could not be made.

A number of study limitations require addressing. The decision for a neurosurgical center to utilize a particular catheter design was largely influenced by historical reasons. This could be a potential source of center bias, but given that factors such as disease etiology, level of training and surgical management practices for such a commonplace procedure were not significantly different between institutions, its effect was believed to be minimal. The retrospective nature of this study meant that data on other potential surgery-related factors for EVD-related hemorrhage was not available. For example, most operation records did not include information on the number of catheterization attempts. One study noted a threefold increase in the risk of hemorrhage with each additional pass, but another failed to detect an association with multiple passes [17, 23]. There was also inadequate documentation on the use of image-guidance, for example intraoperative ultrasound, to better position catheters and thereby reduce hemorrhage risk. Finally, postulations on the design differences between catheters could not be verified by a study of this nature and further research in a laboratory setting simulating conditions in animal models would be required.

Conclusions

This is the largest study reviewing EVD-related hemorrhage with routine CT imaging at a defined post-procedural time interval. Although the per-catheter risk of hemorrhage was 8.1%, the incidence of symptomatic hemorrhage was low. We identify aspirin treatment, catheter design, and catheter malposition as risk factors for EVD-related hemorrhage.

Compliance with ethical standards

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