PROTOCAL ADDENDUM

A Comparison of External Ventricular Drain Catheter Diameter on Occlusion and Replacement: A Multicenter Randomized Trial

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Background and Purpose:

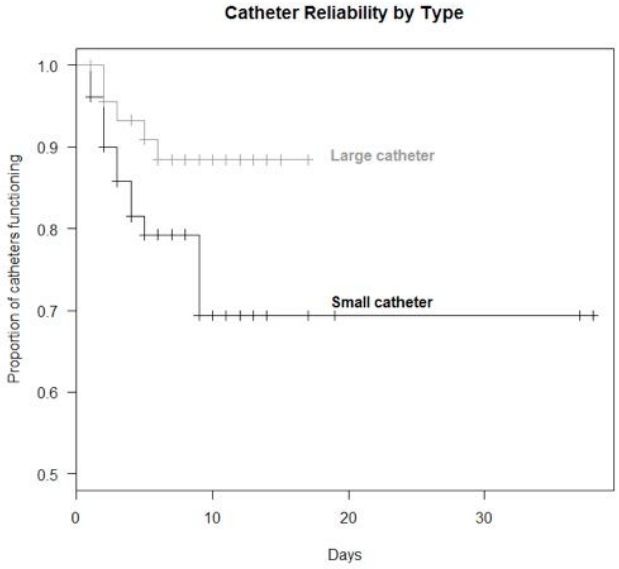
Ventriculostomy is a common neurosurgical procedure. A Nationwide Inpatient Sample (NIS) database study demonstrated a significant increase in ventriculostomy utilization from 1988-2010, with over 35,000 hospitalizations including a procedural code for ventriculostomy in 2010[1].

Ventriculostomy occlusion is a common complication after external ventricular drain (EVD) placement. A review of published prospective and retrospective studies indicates that approximately 1-7% of EVDs require replacement secondary to occlusion[2-8]. Furthermore, in the NIS database study of over 101,000 hospitalizations in which ventriculostomy was performed, nearly 6% of patients required at least one additional ventriculostomy procedure[1]. Studies have demonstrated non-patent EVD in 19-47% of patients[8-10], however these studies did not prospectively evaluate EVD occlusion as a primary endpoint, report on number of catheter irrigations performed, or identify risk factors for EVD occlusion.

Recently, we completed a retrospective review of a prospectively collected database of patients undergoing bedside EVD placement with the primary outcome of interest being catheter occlusion (published in *Journal of Neurosurgery*). This sample included 101 patients over a 1 year period. Two Codman (Codman & Shurtleff Inc., Raynham, MA) catheters were available for use (Clear Bactiseal 'large' catheter: outer diameter 3.4 mm, inner diameter 1.9 mm; and Orange Bactiseal 'small' catheter: outer diameter 3 mm, inner diameter 1.5 mm). The decision regarding which catheter to use was made at the time of the procedure based on resident preference and availability. Both temporary occlusion (requiring flushing but patency could be restored) and permanent catheter occlusion (requiring replacement) were common, occurring in 41% and 19% of patients, respectively. Over 25% of small catheters became occluded during the study period compared to 11% of large catheters. Small catheters were associated with a 3.4 times greater odds of occlusion than the larger diameter catheters on multivariable regression analysis (P= 0.04; Figure 1). This study suggests that the preferential use of larger diameter catheters may reduce the risk of ventriculostomy occlusion and need for replacement, however the study was not randomized and catheter selection may have been biased.

Recently, a smaller retrospective study of patients with intraventricular hemorrhage performed by Gilard and colleagues demonstrated a lower rate of occlusion and no increased risk of hemorrhage with larger bore catheters[11]. Otherwise, there is no data in the literature supporting the preferential use of catheters based on size (clinical equipoise). Therefore, a randomized trial comparing small versus large catheters in terms of occlusion and need for replacement will be beneficial in confirming differential occlusion risk based on catheter size.

Figure 1: Kaplan-Meier curve demonstrating catheter survival for large and small catheters.



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Study Design: Prospective, multicenter, randomized controlled trial.

Primary Coordinating Site: Wake Forest University, Winston-Salem, NC.

Participating Study Centers:

Wake Forest University, site PI: Kyle Fargen, MD MPH

Mount Sinai Hospital, New York, NY; site PI: Christopher Kellner, MD

Treatment Arms

Patients will be randomized 1:1 to receive either a small (ID 1.5 mm) antibiotic impregnated catheter or a large (ID 1.9 mm) antibiotic impregnated catheter.

Study Population

Detailed inclusion and exclusion criteria are shown in Table 1. All adult patients with spontaneous intracranial hemorrhage requiring placement of a frontal external ventricular drain at a study center will be potential candidates for inclusion. Patients may undergo placement of the EVD either at the bedside or in the operating room or angiography suite. Patient (if able to consent) or next of kin must be immediately available in person or by phone, if approved procedure for individual center's IRB, to consent for randomization for the patient to be included in the study.

Based on occlusion data from the previously referenced prospective study, as well as a P-value of 0.05 and power of 0.80, the study will need to include 90 patients to demonstrate statistical significance. To ensure that power is adequate, we will plan to enroll 120 patients (60 in each arm).

Randomization

Randomization will be performed through the use of real-time, internet-based randomization procedure contained within RedCap to achieve a distribution balance for age, sex, diagnosis, and intraventricular hemorrhage distribution.

Primary Outcome Measure

The primary outcome measure will be permanent catheter occlusion, defined by a non-functioning (non-patent) EVD where patency cannot be restored through catheter manipulation or flushing.

Table 1: Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion criteria
Adult patient (18-85 years) requiring frontal EVD placement	Patient cannot consent and next of kin cannot provide consent prior to procedure
Diagnosis of spontaneous subarachnoid hemorrhage, intraventricular hemorrhage, intraparenchymal (or cerebellar) hemorrhage due to aneurysm, vascular malformation (arteriovenous malformation or arteriovenous fistula), hypertension, or idiopathic etiology	Diagnosis of traumatic brain injury (EVD often times remain clamped for prolonged periods)
Attending neurosurgeon decides that frontal EVD indicated for patient treatment with planned CSF drainage for 72 hours or more	Anticoagulated prior to admission and not fully reversed with Coumadin (warfarin), Effient, Plavix, therapeutic heparin infusion, therapeutic subcutaneous Lovenox, therapeutic subcutaneous Arixtra, or other therapeutic anticoagulant or antiplatelet agent (ASA not included)
Glasgow Coma Score of 5 or higher within 12 hours of EVD insertion	Best Glasgow Coma Scale of 4 or less within 12 hours of EVD insertion
	Hunt and Hess subarachnoid hemorrhage grade of 5
	Age 86 or greater
	Plan for placement of EVD through non-frontal burr hole approach

Secondary Outcome Measures

1. Catheter replacement: defined by replacement of the ipsilateral EVD due to permanent occlusion, or placement of a contralateral EVD in the setting of a non-functioning ipsilateral catheter. Catheters placed contralaterally in the setting of a functioning ipsilateral catheter will not be considered replacements.
2. Temporary occlusion: defined by non-functioning (non-patent) catheter requiring neurosurgeon flushing or manipulation in order to restore patency. By definition, such maneuvers must restore patency of the EVD such that it is functioning normally afterwards. Multiple temporary occlusions may be possible.
3. Procedure-related hemorrhage: Presence of new catheter-related intraparenchymal hemorrhage, subdural hematoma, or intraventricular hemorrhage on CT scan after placement.
4. Symptomatic hemorrhage: Presence of new neurologic deficits as a result of EVD-related hemorrhage, or resulting in need for further procedures due to new EVD-related hemorrhage (craniotomy for hematoma evacuation, ICP monitoring, etc).
5. Administration of intraventricular tPA (Tissue Plasminogen Activator) regardless if catheter patency is restored.

Protocol

Once EVD is deemed indicated by the attending neurosurgeon, the patient becomes a candidate for enrollment. At this point, research staff will determine candidacy by reviewing inclusion and exclusion criteria. Patients that meet inclusion criteria, in the absence of exclusion criteria, will be consented and randomized by enrolling the patient in RedCap. Patients who meet inclusion criteria and have no exclusion criteria but cannot be consented before treatment will undergo placement of an EVD, with catheter size based on surgeon preference, and will be enrolled in an ongoing prospective database.

Procedural technique

All EVD will be placed by neurological surgeons in either the major operating suite or in an ICU setting using a previously published protocol[12]. This protocol includes using a burr hole entry point 1 cm anterior to the coronal suture in the mid-pupillary line, prep and sterile drape, pre-procedural antibiotic administration, and tunneling the catheter to an exit site at least 5 cm from the incision. Following EVD insertion, physicians will document procedural factors on the procedural data sheet (Appendix A)

Flushing technique

No formal published protocols exist for catheter irrigation. In general, physicians are instructed to first attempt distal irrigation of the drainage chamber using sterile techniques (rarely effective), followed by gentle aspiration of the proximal system and catheter if distal flushing is not effective. If these do not restore patency, a small volume of sterile saline, 3 ml or less, is flushed proximally into the catheter. Patency is checked by lowering the EVD drainage system and evaluating for spontaneous flow through the EVD. Each irrigation will be recorded on the daily record sheet (Appendix B).

Treatment Arms

Enrolled patients will be randomized to one of two catheters in a 1:1 randomization scheme. These include the antibiotic-impregnated 'large' catheter (outer diameter 3.4 mm, inner diameter 1.9 mm) and an antibiotic-impregnated 'small' catheter (outer diameter 3 mm, inner diameter 1.5 mm). After placement of the EVD catheter, all clinical and radiographic follow-up will be the same for both treatment arms.

Data collection

Data will be collected prospectively by the research team. Trial data will be reported via RedCap. Collected data will included a number of factors, such as: age, gender and underlying diagnosis; procedural data including faculty versus resident physician as primary proceduralist, number of passes, side of placement; radiographic data including ventricular size (based upon Evan's ratio: maximum bifrontal ventricular distance divided by maximal intracranial biparietal distance), pre-procedural midline shift, presence of intraventricular hemorrhage, catheter location, and presence of catheter-related hemorrhage; and clinical data including symptomatic hemorrhage, number and type of catheter irrigations, catheter

occlusion and replacement, number of catheter days, catheter endpoint, cerebrospinal fluid analysis and incidence of catheter-related infection (Appendices).

Imaging Review

A blinded physician at each treatment center will review brain imaging to document all radiographic data into RedCap, including: Evan's ratio, midline shift, presence of intraventricular hemorrhage, catheter location, and presence of catheter-related hemorrhage. At time of site activation for each center, the radiographic reviewer will undergo a training session via conference call, performed by the study PI (KF), which will ensure consistent interpretation of imaging across centers. The primary center may ask for select image series to be uploaded into RedCap for review by the PI.

Study Endpoint

Patients will have met the study endpoint when the EVD is intentionally removed by the supervising physician, in any of the following scenarios: 1) The EVD is removed due to resolution of hydrocephalus; 2) The EVD is removed because it is non-functional but not replaced; 3) The EVD is removed and is replaced with a shunt. Once the endpoint has been reached, no further data collection will occur for that study subject.

Adverse Events

Adverse events will be recorded. Adverse events include: symptomatic intracranial intraparenchymal or subdural hemorrhage (with new neurologic deficit or need for surgery), symptomatic intraventricular hemorrhage (defined as new neurologic deficit, need for surgery, or catheter occlusion within 2 hours of placement requiring contralateral EVD placement), meningitis (confirmed by positive CSF cultures and initiation of antibiotic therapy), catheter in extraventricular position on placement, and catheter malposition after confirmation of correct positioning requiring replacement (ie. catheter is unintentionally pulled out by nurse, patient, or due to loose sutures).

APPENDIX A:

EVD Insertion Procedure Datasheet

Subject No: _____

Date: _____

Side (Circle one): Right Left

Year of Physician Performing Procedure (Circle one):

PGY1 PGY2 PGY3 PGY4 PGY5 PGY6 PGY7 Faculty

Number of Passes Required (Circle one):

1 2 3 4 5 6 7 8 9 10 11 or more

Degree of Confidence Ventricular Catheter in Ipsilateral Lateral Ventricle, from 1-5 (Circle one):

1 2 3 4 5

(Poor Confidence) (Moderate Confidence) (Highly Confident)

APPENDIX B:

STUDY SUBJECT DAILY RECORD SHEET

Subject No: _____ **Date: _____**

Side (Circle one): R L

At time 00:00, EVD is (Circle one): Clamped Open to Drain

At time 00:00, Height of EVD (cm of water): _____

RECORD ANY EVD HEIGHT OR CLAMPING ORDER CHANGES:

Height Change #1: Changed to: _____ cm water Time:

Height Change #2: Changed to: _____ cm water Time:

Height Change #3: Changed to: _____ cm water Time:

Clamping/Unclamping #1: ☐Clamped ☐Unclamped Time:

Clamping/Unclamping #2: ☐Clamped ☐Unclamped Time:

Clamping/Unclamping #3: ☐Clamped ☐Unclamped Time:

RECORD ANY EVD FLUSHING EVENTS:

1. Time:	☐Distal system flushed only ☐Proximal system aspirated only ☐Proximal system flushed - number of times: _____ **RESULT:** ☐EVD functioning ☐EVD occluded
2. Time:	☐Distal system flushed only ☐Proximal system aspirated only ☐Proximal system flushed - number of times: _____ **RESULT:** ☐EVD functioning ☐EVD occluded
3. Time:	☐Distal system flushed only ☐Proximal system aspirated only ☐Proximal system flushed - number of times: _____ **RESULT:** ☐EVD functioning ☐EVD occluded
4. Time:	☐Distal system flushed only ☐Proximal system aspirated only ☐Proximal system flushed - number of times: _____ **RESULT:** ☐EVD functioning ☐EVD occluded
5. Time:	☐Distal system flushed only ☐Proximal system aspirated only ☐Proximal system flushed - number of times: _____ **RESULT:** ☐EVD functioning ☐EVD occluded

6. Time:	☐Distal system flushed only ☐Proximal system aspirated only ☐Proximal system flushed - number of times: _____ **RESULT:** ☐EVD functioning ☐EVD occluded
7. Time:	☐Distal system flushed only ☐Proximal system aspirated only ☐Proximal system flushed - number of times: _____ **RESULT:** ☐EVD functioning ☐EVD occluded
8. Time:	☐Distal system flushed only ☐Proximal system aspirated only ☐Proximal system flushed - number of times: _____ **RESULT:** ☐EVD functioning ☐EVD occluded
9. Time:	☐Distal system flushed only ☐Proximal system aspirated only ☐Proximal system flushed - number of times: _____ **RESULT:** ☐EVD functioning ☐EVD occluded
10. Time:	☐Distal system flushed only ☐Proximal system aspirated only ☐Proximal system flushed - number of times: _____ **RESULT:** ☐EVD functioning ☐EVD occluded
11. Time:	☐Distal system flushed only ☐Proximal system aspirated only ☐Proximal system flushed - number of times: _____ **RESULT:** ☐EVD functioning ☐EVD occluded
12. Time:	☐Distal system flushed only ☐Proximal system aspirated only ☐Proximal system flushed - number of times: _____ **RESULT:** ☐EVD functioning ☐EVD occluded
13. Time:	☐Distal system flushed only ☐Proximal system aspirated only ☐Proximal system flushed - number of times: _____ **RESULT:** ☐EVD functioning ☐EVD occluded
14. Time:	☐Distal system flushed only ☐Proximal system aspirated only ☐Proximal system flushed - number of times: _____ **RESULT:** ☐EVD functioning ☐EVD occluded
15. Time:	☐Distal system flushed only ☐Proximal system aspirated only ☐Proximal system flushed - number of times: _____ **RESULT:** ☐EVD functioning ☐EVD occluded