Protocol Title: Endovascular Embolization for Chronic Subdural Hematomas Following Surgical Evacuation

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1. Objectives

Describe the purpose, specific aims, and hypothesis:

Evaluate the effectiveness of endovascular embolization of the middle meningeal artery following surgical evacuation of subdural hematomas (SDH) to assess rate of recurrence of SDHs.

2. Background

Describe the background and rationale for the study:

The historical standard for treatment of chronic subdural hematomas (SDH) has been through surgical evacuation through burr holes or craniotomies. Many of these patients are elderly patients who are high risk surgical candidates. Unfortunately given the pathophysiology of SDHs there is a high rate of recurrence ranging 5-30% in the literature necessitation frequent imaging, increased length of hospital stay, increased morbidity, and increased rate of reoperations. A more novel and less invasive approach has been used to treat SDHs in this patient population. There are increasing reports of endovascular embolization of the middle meningeal artery using a less invasive endovascular approach for SDHs. The reported outcomes in literature have been very positive when endovascular embolization has been used without surgery or as an adjuvant to surgery. These reports include case series and retrospective reviews. There have been no studies directly comparing endovascular embolization following surgical evacuation to assess if this technique can actually benefit patients with chronic SDHs. We propose to study this treatment process by randomly assigning patients who have undergone surgical evacuation of SDHs through burr holes into a control and treatment group. The control group (surgery) would only receive surgical evacuation of a hematoma using current standard of care. The treatment group (surgery plus) would receive surgical evacuation followed by endovascular embolization of the middle meningeal vessels using current standard of care. We will directly compare these two treatment modalities to obtain class I evidence on the efficacy of embolization for treatment of chronic subdural hematomas.

References:

Ronald S, Goshtasbi K, Mahmoodi A, Tran D. Chen J. Chronic Subdural Hematoma: A Historical and Clinical Perspective. World Neurosurgery. 2017; 108:948-953

Link TW, Boddu S, Paine SM, Kamel H, Knopman, J. Middle Meningeal Artery Embolization for Chronic Subdural Hematoma: A series of 60 Cases. Neurosurgery. December 2019; 85(6) 801-807

Ban SP, Hwang G, Soo Byoun H, Kim T, Lee SU, Bang J, Han JH, Kim C, Kwon O, Oh CW. Middle Meningeal Artery Embolizatino for Chronic Subdural Hematomas. Radioly. March 2018; 286(3) 992-999.

Arthur AS, Fiorella D. Middle Meningeal Artry Embolization for the Management of Chronic Subdural Hematoma. Journal of Neurointerventional Surgery. 2019; 11:912-915

3. Inclusion and Exclusion Criteria

List the inclusion/exclusion criteria:
Inclusion criteria:
Patients 18-90 with chronic SDH
Patients that require surgical evacuation of SDH following assessment by a neurosurgeon
Glasgow Coma Scale (GCS) >6; this may be evaluated from exam results if not present in medical records

Exclusion criteria:
Patients < 18 or >90 years of age
Pregnancy
Patients with extensive multisystem trauma requiring multidisciplinary surgical interventions
Chronic renal insufficiency with creatinine >1.8, unless undergoing hemodialysis
GCS <6
Genetic bleeding disorder
Liver failure
Coagulopathy
Patients unable to consent who do not have an LAR available

4. Number of Subjects/Records/Samples Collected

Indicate the total number of subjects to be accrued/records reviewed/samples collected across all sites:
30 patients in control group. 30 patients in treatment group.

5. Recruitment Methods

Describe when, where, and how potential subjects will be recruited:

Subjects meeting the inclusion/exclusion criteria will be recruited after they are hospitalized and determined by the clinical staff to require surgical evacuation of SDH. Subjects will be approached in a private hospital setting by one of the study investigators who will explain the study and review the consent with the patient.

6. Multiple Site ☒ N/A

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7. Reliance Agreements/Single IRB ☒ N/A

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8. Procedures Involved

a. *Describe the procedures involved to include those procedures that are standard evaluation and/or care and those that are solely for research purposes:*

All procedures done during the course of this study are standard treatments for SDH. Patients with SDH that require surgical evacuation who agree to participate, will be randomly assigned either to a surgery group who will continue their course of care after surgery with no further intervention (unless needed as determined by standard of care) and a surgery plus group who, after surgery, will undergo endovascular embolization using standard of care embolization procedures (unless embolization is not indicated for the patient as determined by standard of care). Embolization includes cerebral angiogram with polyvinyl alcohol particle or onyx glue embolization via a catheter inserted in the groin while under general anesthesia. Patients undergoing SDH surgical evacuation are hospitalized on average 2-5 days; randomization and the embolization procedure will take place during the same hospitalization period within 72 hours after surgery. Embolization is a minimally invasive procedure and patients are typically discharged on post procedure Day 1, so the hospital stay will not be increased due to the embolization procedure. . Patients will undergo a CT scan within 24 hours after surgery. This scan is standard care and will occur prior to the embolization. Approximately 4-6 weeks after the hospitalization, the patients will undergo a standard follow-up CT scan. Further scans will be done thereafter if clinically indicated. All patients will have the same follow-up care during the course of their hospitalization unless there is a complication.

These procedures, surgery and embolization, are done routinely separately and in combination for treatment of SDH. The research procedure will be the collection of data from these patients to assess whether endovascular embolization following surgical evacuation can reduce the complications of SDH.

b. *Describe and explain the study design:*
If the study involves multiple conditions where each condition involves different procedures, please provide a table that breaks down the procedures by condition and in chronological order. Include when and where they are performed.

The study design will include a surgery group and a surgery plus group. All patients will have been scheduled to undergo surgical evacuation of SDH as standard treatment. These patients will be approached by one of the investigators with information about the study. After consent, the patient will be randomly assigned to either the surgery or the surgery plus group. A random number list will be provided to the investigators to use for assignment of patients to the surgery or surgery plus group. Patients randomized in the surgery plus group will subsequently undergo endovascular embolization within 72 hours after surgery and during their hospital stay. Patients in the surgery group will not undergo

the embolization procedure. CT scans will be performed as described above as standard care for this population. Follow-up care during their hospitalization will be the same for both groups barring a complication. All procedures (surgical evacuation and endovascular embolization) performed are standard treatment options for SDH that are used at our institution and facilities across the country

c. *Data Types and Source Records:*

Data will be collected from medical records and will include the following: name, medical record number, age, sex, GCS at admission, IPH volume, whether the patient had surgery, length of stay in the ICU and hospital, IPH volume post-operatively from CT scans, anticoagulant use, history of brain trauma, and any complications (AEs or SAEs).

The study information will be entered into spreadsheets and stored on the secure drive provided by Information Technology specifically for the study.

d. *Describe the procedures performed to lessen the probability or magnitude of risks*

All data will be managed in a secure format and according to all applicable regulatory guidelines. All medical records information will be entered into the secure drive by the PI or designated study team members. There will be a separate key to link the entries on the data collection form using an assigned study ID# and the patient medical records. The key will be stored on the secure drive. Only the approved investigator or study team members with username/password access will review medical records and the study information that is collected and stored on the secure drive. Women of child-bearing potential are routinely assessed for pregnancy during the pre-operative workup; any with a positive pregnancy test will not be considered for the study, either as treatment or control subjects. Endovascular embolization and imaging are approved and widely used standard treatment options for SDH but carries the risks of groin hematoma, infection, and embolic stroke. In the event of groin hematoma, pressure is applied to the site, evidence of infection would be treated with appropriate antibiotics, and the AU acute stroke protocol would be implemented in the event of an embolic stroke. Study investigators are experienced in performing the procedure and caring for the patients.

If the patient's clinical picture indicates that the embolization procedure is necessary, the patient would not participate in the study. If this determination is made following consent, the patient would be considered a screen failure.

e. *Describe the duration of an individual subject's participation in the study and the time involved also include the overall duration of the project:*

The duration of subject participation may range from 2 weeks to 3 months following surgical intervention. These are typical follow-up timelines for patients undergoing treatment for SDH. Study information collected from medical records will extend from the time of diagnosis until the completion of follow-up visits.

9. Data and Specimen Management

a. Describe the data analysis plan, including any statistical procedures: ☐ N/A

Data analysis will include patient age and sex, GCS score, need for redo surgery for surgical decompression of SDHs, complication rates of procedures, length of hospital stay, and follow up CT imaging findings, anticoagulant use, and history of brain trauma. All statistical analysis will be performed using SAS 9,4 and statistical significance will be assessed using an alpha level of 0.05. Descriptive statistics will be determined within surgical group (treatment or control) and will include frequencies and percentages for categorical variables, means and standard deviations for continuous variables, and medians and interquartile ranges for ordinal data.

To examine differences in the need for additional surgical decompression of SDH, demographic variables, CGS scores, complication rates of procedures, length of hospital stay, and follow up CT image findings a variety of statistical tests will be performed. For categorical data (additional surgical decompression of SDH, sex, complication rates of procedures, and follow up CT image findings), chi-square tests will be used to examine differences in proportions between control and treatment groups. For continuous data (age, GCS score, and length of hospital stay) two-sample t-tests will be used to examine differences in means between control and treatment groups. For the mRS score, a non-parametric Wilcoxon Rank Sum test will be used to examine differences in medians between control and treatment groups.

b. When applicable, provide a power analysis: N/A

The sample size needed to examine differences in percent needing additional surgical decompression of SDH using a chi-square test at an alpha level of 0.05 was determined assuming a power of 0.80, 0.85 and0.90. The percent needing additional surgical decompression of SDH in the control group was assumed to be 35% . The percent needing additional surgical decompression of SDH in the treatment group was assumed to be 5% and 10%. The table below shows the required sample size per group to detect differences in the percent needing additional surgical decompression of SDH between the treatment and control groups.

Recurrence per Group		Sample Size per Group by Power		
Control	Treatment	Power=0.80	Power=0.85	Power=0.90
35%	5%	27	31	36
35%	10%	43	49	57

The expected percent needing additional surgical decompression of SDH in the treatment group is expected to be 5% or lower. A sample size of 30 per group, for a total of 60 patients, will provide adequate power to show differences between these two groups.

c. Describe how data and specimens will be handled: ☐ N/A

i.	*What information will be included in that data or associated with the specimens?* Data to be assessed include: name, medical record number, age, sex, GCS at admission, IPH volume, whether the patient had surgery, length of stay in the ICU and hospital, IPH volume post-operatively from CT scans, anticoagulant use, recent brain trauma, and any complications (AEs and SAEs).
ii.	*Where and how data and/or specimens will be stored?* The data will be stored on a secure website provided by AU Information Technology specifically for this study that is accessible by approved team members using username/password access. The data collection form and the key to link the records will be stored separately on the secure drive.
iii.	*How long will the data and/or specimens be stored?* Data will be maintained according to AU and University System Board of Regents policies.
iv.	*Who will have access to the data or specimens?* Data access will be restricted to the research team
i.	*Who is responsible for receipt or transmission of the data and/or specimens?* The study investigators
ii.	*How will data and/or specimens be transported?* N/A

10. Provisions to Monitor the Data to Ensure the Safety of Subjects ☐ N/A

The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.

a.	*Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.* A Data Safety Monitoring Board will be established to assess harms and benefits to subjects. The DSMB will evaluate safety data every 6 months during the trial and at the reporting of any serious adverse event.
b.	*Describe what data are reviewed, including safety data, untoward events, and efficacy data.* The data collection form and all AEs and SAEs will be reviewed, including whether repeat surgery is needed, length of ICU stay and hospitalizations, and any complications/adverse events that occur.
c.	*Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).*

	The information will be collected from medical records and entered into the data collection form and/or AE/SAE form.
d.	*Describe the frequency of data collection, including when safety data collection starts.* Data collection, including safety information, will begin as soon as patients are enrolled and will last up to three months post-procedure.
e.	*Describe who will review the data.* Members of the DSMB will include Samuel Macomson, MD and John Vender, MD. Both are board-certified neurosurgeons who have completed CITI training.
f.	*Describe the frequency or periodicity of review of cumulative data.* Every 6 months and at the report of any SAE.
g.	*Describe any conditions that trigger an immediate suspension of the research.* If the embolization procedure is associated with statistically significant increased risks to the subject

11. Withdrawal of Subjects ☐ N/A

a.	*If applicable, describe anticipated circumstances under which subjects will be withdrawn from the research without their consent.* Physicians may determine that it is not in the best interest of the patient to undergo the embolization procedure; the patient would be removed for their safety. The patient may also be removed from the study if the physicians determine that another type of treatment would be more beneficial.	☐ N/A
b.	*If applicable, describe any procedures for orderly termination.* The procedure would not be done.	☐ N/A
c.	*If applicable, describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.* Subjects may choose to discontinue their participation in the study at any time by notifying the PI. To withdraw from the study individuals are asked to send a written letter to the PI. Data collection for the subject will stop, but data already collected will continue to be used. Subjects may, at any time, change their mind and decide not to have the embolization procedure by letting the study doctors know their wishes. If the embolization procedure is not done, the patient will be included in the analysis as they were randomized.	☐ N/A

12. Risks to Subjects

a. List the reasonably foreseeable risks. There is a potential risk in breach of confidentiality. Endovascular embolization is an accepted standard of care treatment for subdural hematoma but carries the additional risk of groin hematoma, infection, and embolic stroke. The risks of the procedure will be addressed with subjects randomized to the procedure. Control subjects will have no further risks associated with participation.	
b. If applicable, describe any costs that subjects may be responsible for because of participation in the research. The patient's insurance will be billed for the endovascular embolization procedure that is standard clinical care. The patient will be responsible for paying for the care they would normally receive for their condition, as well as for all co-pays, deductibles and denied claims. The embolization procedure and the surgery-embolization procedure combination have been standard practice for the last three years and insurance companies typically pay when both procedures are done in a single hospitalization.	☐ N/A
c. If applicable, describe risks to others who are not subjects. Click here to enter text.	X N/A

13. Potential Benefits to Subjects

Describe the potential benefits that individual subjects may experience from taking part in the research

There is no benefit guaranteed to the subjects. It is hoped that the results of this study will benefit patients in the future.

14. Confidentiality

Describe the procedures for maintenance of confidentiality.

All investigators have undergone proper training for evaluation and handling patient information through the CITI program. Only the study investigator and research staff with username/password access to the system will collect data from medical records. Study data will be stored on the secure drive requiring username/password access and will be available to only the study investigator and staff. The data collection form will contain no identifiable information. The original signed informed consent documents will be secured in a locked cabinet that is accessible only to members of the study team. No identifiable patient information will be used in any publication materials. All study information will be kept confidential per HIPAA regulations.

15. Incomplete Disclosure, Authorized Deception, or Deception

☒ **N/A**

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16. Consent Process

The patient/legally authorized representative (LAR) will be approached in a private setting by an approved research team member to discuss the study. The study will be explained at a level they can understand. The patient/LAR will be given time to review the consent and it will be explained to them by the team member. The purpose of the study, nature of their involvement, risks, benefits, alternatives and confidentiality will be addressed. The subject/LAR will be told they do not have to participate in the study to have the embolization procedure done. Any questions will be addressed until the patient/LAR is satisfied. The consent/adult assent will be signed in the presence of the approved team member, a copy will be given to the patient/LAR and a copy will be filed in the subject's medical records. The patient/LAR will be given the opportunity to take the consent home to review with family or others if they wish.

Prior to the embolization procedure, cognitive capacity of the patient will have already been assessed by the neurosurgical service (third party not associated with the study) in an effort to obtain consent for surgical evacuation of the SDH. Based upon those findings, consent for the study will be obtained from the patient or the LAR, whichever is appropriate. The patient will be assessed for improvement or deterioration before study consent is obtained by means of a neurological exam.
In the event that a subject is deemed cognitively impaired or has impaired decision-making capacity, an LAR who will determine what is in the patient's best interest will be identified as follows:

- *An individual with durable power of attorney for health care*
- *Legal guardian*
  Next of kin 18 years of age or older:
- *Spouse*
- *Child*
- *Parent*
- *Sibling*
- *Grandparent*
- *Grandchild*
- *Close friend*

Based upon the investigator's assessment, the patient may be deemed able to provide meaningful assent, and every effort will be made by the investigators to review the assent document with the subject in a manner and language they can understand, explaining the purpose, procedures, risks and benefits, and assuring that the patients understands. If the patient provides assent, the LAR will also be used to provide consent. During the course of their participation, the subject will be re-assessed by the investigators to determine whether their decision-making capacity has changed and if consent/assent is possible. If a subject regains decision-making capacity and indicates they do not wish to participate, the subject will be withdrawn.

17. Compensation for Research-Related Injury

This section is not required when research involves no more than Minimal Risk to subjects. ☐ **N/A**

a. Describe the available compensation in the event of research related injury.

In the event that this research related activity results in an injury, treatment will be made available including first aid, emergency treatment, and follow-up care as needed. Cost for such care will be billed in the ordinary manner to the patient or the patient's insurance company. No reimbursement, compensation, or free medical care is offered by Augusta University.

18. Qualifications to Conduct Research and Resources Available

Describe the qualifications of you and your staff to conduct this research. The IRB is looking for information such as area(s) of expertise, past research experience, relevant certifications, etc.

For international research or research with vulnerable populations, describe the qualifications (e.g., training, experience, oversight) of you and your staff as required to conduct the research. When applicable describe the knowledge of the local study sites, culture, and society. Provide enough information so the IRB knows that you have qualified staff for the proposed research.

Note: If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify people by role (e.g., coordinator, research assistant, Sub-Investigator, or pharmacist), a change to that person will not require prior approval by the IRB, provided that person meets the qualifications described above to fulfill their roles.

The investigators of this study are board-certified physicians and have all been involved in extensive clinical and basic science research. We have been through multiple IRB reviews. Our training is up to date. We have shown the highest ethical standard as recognized by our peers and institution while performing research projects.

a. Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.

N/A

b. Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

Once we have IRB approval for this project, investigators will meet to discuss the details of starting the study. Specific roles and tasks will be assigned by the principal investigator at that time.

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