Assessing Outcomes of Coil Embolization for Unilateral vs Bilateral Chronic Subdural Hematomas: A Randomized Controlled Trial. (COAST)

CLINICAL STUDY PROTOCOL

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Investigator's Signature Page

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Study Center: BILH Lahey Hospital & Medical Center

I, the undersigned, have read and understand the protocol specified above and agree on its content. I agree to perform and conduct the study as described in the protocol. In addition, when applicable, I agree to enlist sub-investigators who also agree to perform and conduct the study as described in the protocol.

_____ _____

Principal Investigator (Signature) **Date**

Print Name: Jonathan Pace, MD

Introduction

Chronic Subdural hematoma (cSDH) is the neurosurgical condition characterized by slow accumulation of blood between the dura mater and arachnoid membrane. It evolves over weeks or months, generally due to minor head trauma or spontaneous bleeding. While an acute subdural hematoma is almost invariably associated with severe head injury, cSDH may result from less apparent causes, and symptoms may manifest insidiously. These symptoms include headache, confusion, cognitive decline, and focal neurological deficits and often present like other diseases, especially among the elderly. In light of this, the diagnosis of cSDH is usually late (1).

Delayed identification may cause a risk of significant morbidity. The Pathophysiology of cSDH is multifaceted to say the least; it begins with trauma leading to hemorrhage into the subdural space. Over time, the clot undergoes a process of fibrinolysis, resulting in the formation of a hypervascular likely inflamed neomembrane, which may continue to leak and exacerbate the hematoma (2). This pathological cascade contributes to the progressive nature of cSDH.

The incidence of cSDH is significantly higher in the elderly population, with rates as high as 80 per 100,000 individuals aged 65 and older (3). Risk factors for cSDH include chronic alcohol consumption, anticoagulant therapy, coagulopathies, and the use of antiplatelet drugs, which increase the risk of bleeding and hematoma formation (4). Moreover, age-related changes, such as brain atrophy and expansion of subdural space, create a predisposition to this condition. Besides, anticoagulant medications, prescribed for numerous cardiovascular conditions, considerably increase the risk of bleeding and hematoma progression (5). The aging of the population worldwide is going to contribute to an increase in the prevalence of cSDH and, therefore, be a growing concern for healthcare systems worldwide. The rise in cases is also accompanied by increasing healthcare costs, with national estimates for the treatment of all subdural hematomas in the U.S. reaching $1.6 billion in 2007, a 60% increase from the previous decade (6). Diagnosis of cSDH typically involves imaging studies, with computed tomography (CT) and magnetic resonance imaging (MRI) being the gold standards.

On CT, cSDH appears as a hypodense mass, and MRI can provide additional detail in terms of hematoma size, membrane formation, and the presence of complications such as mass effect or midline shift (7). Treatment strategies primarily involve surgical intervention to evacuate the hematoma and relieve intracranial pressure. The most common procedure is burr hole drainage, though craniotomy may be required in more complicated cases (8). More recently, Middle Meningeal Artery (MMA) embolization has emerged as an alternative or adjunctive treatment option. This technique involves

selectively embolizing the MMA to reduce the blood supply to the hematoma and has shown promise in reducing recurrence rates, particularly in patients at high surgical risk (9). While surgery generally improves outcomes, recurrence rates remain a significant concern, with up to 20% of patients experiencing rebleeding or the development of acute-on-chronic subdural hematoma, which further complicates management (2). Other adjuvant therapies besides surgery, such as minimal have been studied to reduce the inflammation and inhibit further hematoma expansion with corticosteroids and antifibrinolytic agents, although they have been used with very inconclusive efficacy (5). Given the high recurrence rates and complexity of cSDH, research into the disease is continuously being pursued for more effective treatment regimens that would provide better long-term outcomes.

Recent open- label trials have explored the use of liquid embolic agents as adjunctive treatments in MMA embolization. This approach addresses the concern of potential anastomoses between meningeal arteries that may cross the midline and contribute to the blood supply of cSDH. Studies such as EMBOLISE, MEMBRANE, and MAGIC-MT have shown that embolizing the middle meningeal artery can reduce recurrence or progression compared to standard management alone. However, the use of liquid embolic materials carries a higher risk of adverse events, including unintended involvement of the ophthalmic artery, the need for general anesthesia, and higher procedural costs. In contrast, coil embolization is associated with fewer complications, a lower stroke risk, reduced radiation exposure, and can be performed with local anesthesia, making it a more cost-effective option. (10)

Current treatment Options

There are two primary approaches of treatment: conservative medical management and surgical intervention.

Conservative management is typically used for patients with mild symptoms or significant comorbidities, involving close observation and supportive care, including the use of corticosteroids or antifibrinolytic agents, through their effectiveness is inconclusive. (18, 19)

Surgical intervention is recommended for more severe cases, with the most common procedure being burr hole drainage to remove the hematoma. While surgery often results in quicker symptom resolution, recurrence rates can be as high as 20%, making cSDH a challenging condition to treat long-term. (20)

The standard of care for of Chronic Subdural Hematoma involves Surgery + Middle meningeal artery embolization or Medical management + Middle meningeal artery embolization. The decision to proceed with unilateral or bilateral treatment will be based on the patient's anatomy and the physician's clinical judgment.

CT scans and visits within the proposed time frame are part of the standard of care for patients undergoing **both** conservative management and Surgical intervention.

If the patient chooses not to participate in the trial, they would still be eligible for the procedure as part of the standard of care.

Study Objective

The objective of this study is to compare the efficacy of unilateral MMA Embolization using coils versus bilateral MMA Embolization using coils in reducing the size and volume of unilateral cSDH.

Primary end point

- Trial Conduct: 1:1 Randomization of patients with unilateral CSDH to bilateral or unilateral Coil embolization.
- Primary Endpoint: To analyze the Size-reduction of the cSDH after 1 month and
- 3 months of the Embolization procedure.
- To analyze the progression of cSDH
- Need for additional surgical intervention, including initial surgical management for the medical management arm and repeat evacuation in the surgical treatment arm
- Secondary Endpoints:
    - Measure the total Radiation of the procedure
    - Measure the Time of Procedure
    - Change in the Modified Rankin Scale in the first 1 Month and 3 months compared to baseline.

Study Design and Consent Process

This study is a pragmatic, prospective, multicenter, randomized controlled trial with intent-to-treat analysis. Up to 400 subjects will be enrolled and randomized to either the Surgical or Medical cohort. Participants in each cohort will be randomized to receive either Uni or Bi- lateral Middle Meningeal artery Embolization. Investigators participating in this study are expected to follow their normal clinical practice in enrolling, treating and following patients with neurovascular diseases and conditions that are amenable to endovascular treatment in the neuro-angiography suite.

Enrollment

Chronic Unilateral or bilateral subdural hematoma patients that are potential study subject will go through standard of care work up upon arrival at the hospital. If the patient requires surgical intervention as deemed appropriate by the neurosurgery service, they will then undergo surgical evacuation of hematoma with either burr hole, SEPS (Subdural Evacuation Port System), or craniotomy. Subdural Evacucation Port System is a bedside procedure, for minimally invasive burrhole drainage of subdural hematoma. If the patient is not requiring surgical evacuation as deemed appropriate by the neurosurgery service, they will then be managed medically. Following this determination, these patients will be screened to determine if they are potential candidates for this study and to determine if they meet all of the inclusion/exclusion criteria. Informed consent will be obtained from the patient or their legally designated representative. If a surgical procedure is planned, MMA embolization may be performed prior to, in conjunction with, or following surgical treatment of the SDH.

The study will enroll a minimum of 50 subjects in total.

Inclusion criteria

Candidates for this study must meet **ALL** of the following criteria:

1. Subject is 18 years of age or older

2. Subject has a diagnosis of chronic subdural hematoma with mass effect Determined by brain imaging (CT or MRI) and correlated clinical symptoms

3. Pre-randomization modified Rankin Score (mRS) ≤3
    a. Surgical Cohort: Assessment should reflect the subject's condition just prior to undergoing surgery. Assessment may be performed post-surgery using pre-surgical data.

4. Subdural Hematoma Size

Medical Management Cohort:

• Midline shift < 10mm and hematoma thickness > 10 mm as measured on coronal imaging perpendicular to the skull

• No focal deficit related to the chronic subdural hematoma requiring surgical intervention

Surgical Cohort:

• No requirement

5. A CT performed prior to randomization demonstrating stability of the hematoma. Stability is defined as no worsening of midline shift or increase in the size of the cSDH from the screening image that results in new or worsening clinical symptoms.

6. Patient or designated Legal Authorized Representative, confirms the patient has the mental capacity, willingness and ability to comply with protocol and follow-up requirements

7. In the opinion of the treating physician, MMA embolization is technically feasible, including evaluation of preoperative CTA, if available, or presence of a foramen spinosum bilaterally.

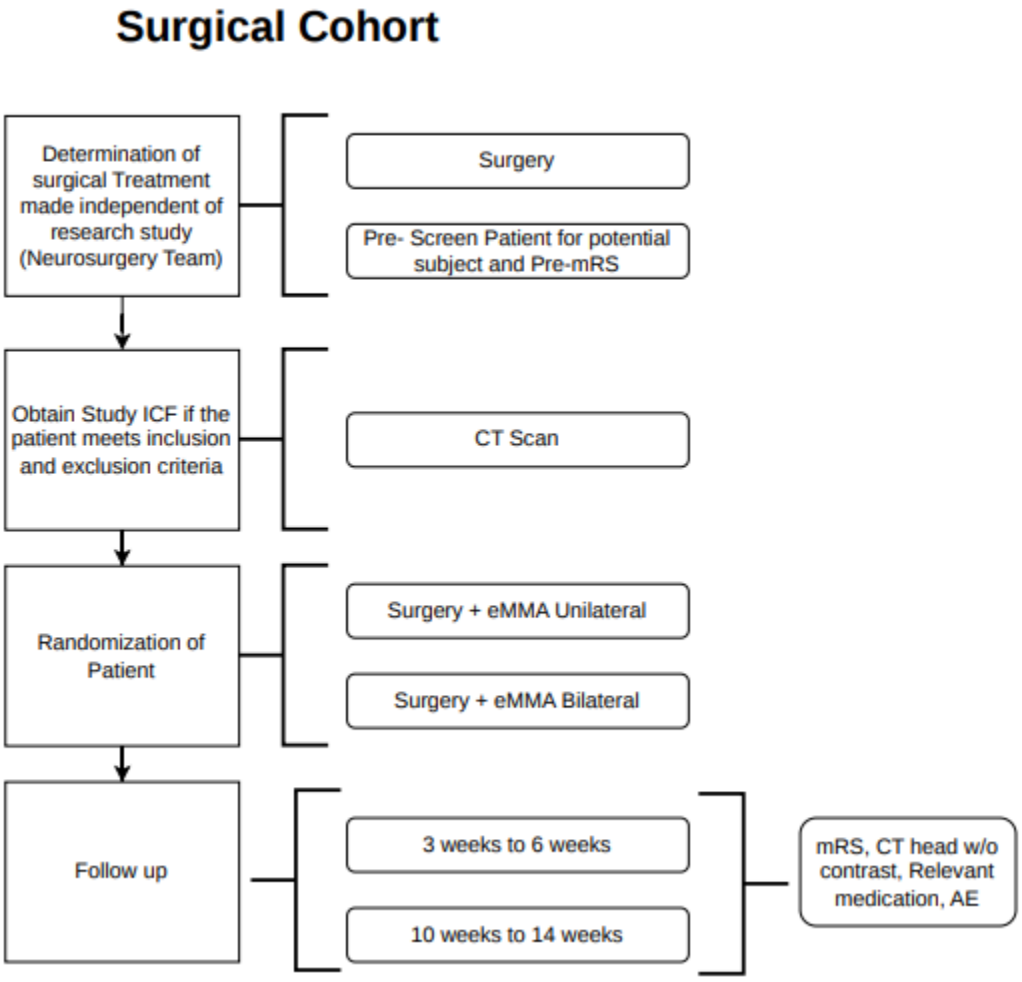
Exclusion Criteria

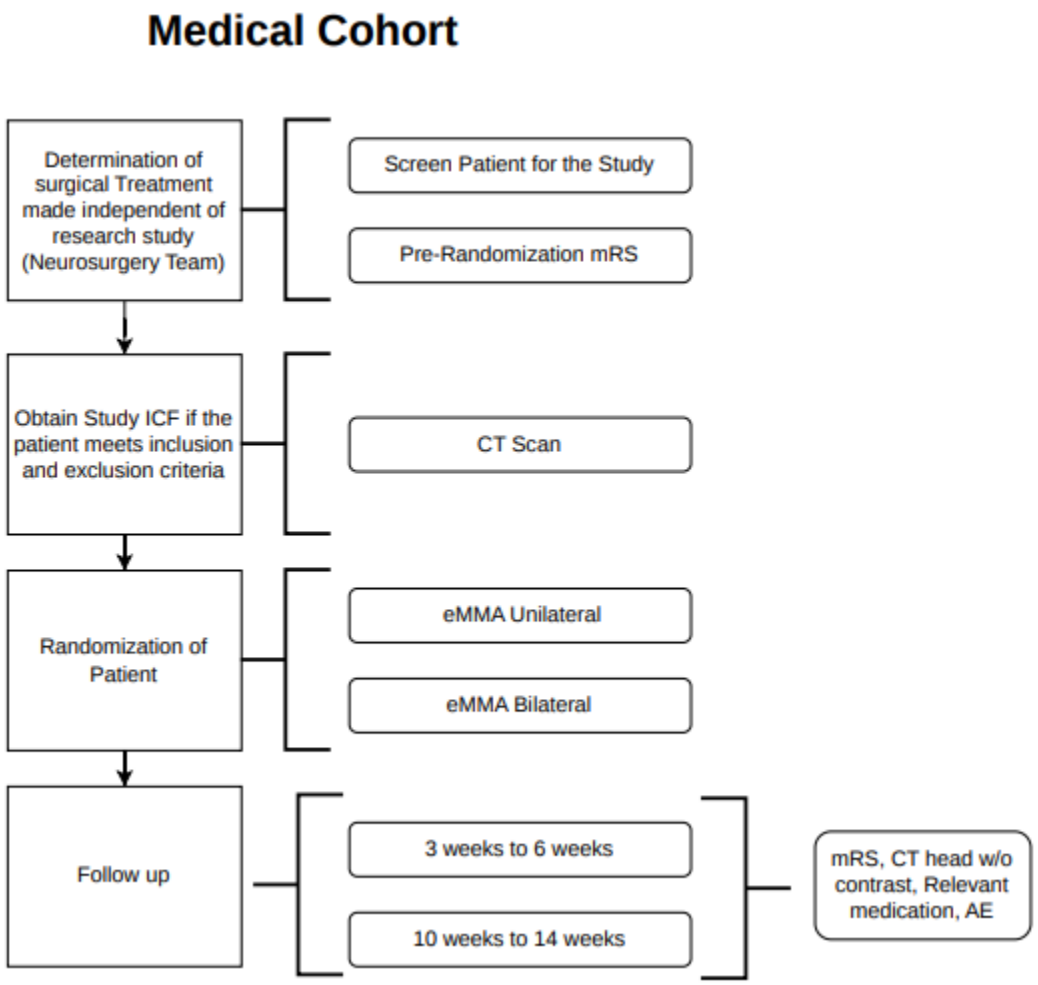
Candidates will be excluded from participation if **ANY** of the following apply:

1. Patients presenting with an acute SDH (e.g. patient with presenting with a SDH due to trauma); mixed density is permitted.
2. Subject presents with bilateral cSDHs requiring treatment (contralateral cSDH <5mm and not requiring treatment is permitted.
3. Subject presents with Glasgow Coma Scale < 9
4. Markwalder assessment >4

5. cSDH that developed with underlying conditions such as vascular lesions, brain tumor, arachnoid cyst, spontaneous intracranial hypotension, end stage renal disease (ESRD) on hemodialysis, end stage liver disease or other comorbidities causing a coagulopathy
6. Prior carotid stent placement that crosses the origin of the External Carotid Artery (ECA) ipsilateral to the subdural hematoma
7. Presumed septic embolus, or suspicion of microbial superinfection
8. CT or MRI evidence of intra-cranial tumor or mass lesion
9. Significant contraindication to angiography (eg. kidney failure).
10. Life expectancy of less than 1-year
11. Women who are pregnant, lactating, plan on becoming pregnant during the course of the clinical investigation. We routinely do pregnancy tests prior to this procedure, to avoid radiation exposure to the fetus including radiation on follow up CT scans
12. Current involvement in an investigational (drug, device, etc.) clinical trial that may confound study endpoints. Subjects in observational, natural history, and/or epidemiological studies not involving intervention are eligible
13. Patient unwilling to follow SOC recommendations (e.g. refuses surgery or lifestyle modifications)

Schematic of Study Design.




Medical Cohort
Determination of surgical Treatment made independent of research study (Neurosurgery Team)
Screen Patient for the Study
Pre-Randomization mRS
Obtain Study ICF if the patient meets inclusion and exclusion criteria
CT Scan
Randomization of Patient
eMMA Unilateral
eMMA Bilateral
Follow up
3 weeks to 6 weeks
10 weeks to 14 weeks
mRS, CT head w/o contrast, Relevant medication, AE

Procedure

Patients will be fully informed and consented before being enrolled in the trial. Following consent, they will be randomly assigned to receive either unilateral or bilateral coil embolization based on the BILH REDCap not FDA part 11 HIPPA compliant tool, with 200 patients in each group. It is important to note that this is a multicenter, pragmatic, randomized trial. Based on prior trials (MEMBRANE, EMBOLIZE), this sample size is anticipated to clearly delineate the primary outcome. The embolization procedure will be carried out according to standard care protocols as outlined in existing literature, ensuring that all steps are in line with established best practices (11, 12). For this procedure, any commercially available coils systems available in the angio suite will be utilized to occlude the middle meningeal artery.

Upon enrollment, the treating physician will evaluate the patient's baseline neurological function using modified Rankin scale (mRS). This scale will provide an initial measurement of the patients' functional status and serve as a reference for comparison throughout the trial.

The Procedure is performed via a catheter inserted into the femoral artery or the radial artery and guided to the MMA through an angiographic approach. Once the artery is located, a Coil System will be introduced to occlude the vessel. This is done under fluoroscopic guidance to ensure precise placement of the coils. The coils are deployed sequentially starting distally and working proximally, to achieve complete occlusion of the target vessel. The size and type of coils used are selected based on the diameter and tortuosity of the MMA and treatment physician preference. After coil deployment, angiography is often repeated to confirm successful embolization and to ensure there is no residual flow in the vessel. The catheter is then removed, and hemostasis is achieved at the access site. Patients will be monitored post procedure for any complications, and the treating physician or study nurse will conduct the mRS assessment 24 hours after the procedure to evaluate the patients' functional outcome and neurological status, which may be performed via telemedicine visit, if the patient is discharged. Per physician preference, this procedure may be performed on an outpatient basis.

For all embolizations, bilateral external carotid artery injections will be performed. The order of catheterization and embolization will be as follows:

1) Ipsilateral CCA or ICA per treating physician preference, ECA angiogram
2) Ipsilateral MMA embolization
3) Ipsilateral ECA, CCA or ICA post embolization angiogram
4) Contralateral CCA or ICA (if randomized to bilateral embolization), ECA angiogram (to evaluate for collateral circulation
5) Contralateral MMA embolization (if randomized to bilateral embolization)
6) Contralateral ECA, ICA or CCA post embolization (if bilateral embolization is performed)

Follow-up assessments will be conducted by the Neurosurgeon physician who will perform the 3 weeks to 6 weeks (1 month), 10 weeks to 14 weeks (3 months), depending of standard of care, using the mRS scale, detailed clinical history, and evaluated with a new head CT scan without contrast to measure the size and volume of the cSDH. Additional imaging may be obtained if clinically indicated.

Randomization

The randomization process for this study will be conducted using the BILH REDCap tool at each site. This approach ensures unbiased and equitable allocation of patients into the two study arms: unilateral MMA embolization with coils and bilateral MMA embolization with coils.

Data analysis and management

For this randomized clinical trial, data management and statistical evaluation will be conducted for 400 enrolled patients. Key variables such as:

- Sex
- Age
- MRN
  Unilateral cSDH
- Measurement of cSDH pre-procedure (Maximum width, volume, midline shift)
- Identification of collateral circulation to the ipsilateral MMA territory before or after coil embolization (i.e. from intracranial circulation, ophthalmic artery, contralateral MMA, or contralateral ophthalmic artery

- cSDH measurement of cSDH 3 weeks to 6 weeks, 10 weeks to 14 weeks post procedure(Maximum width, volume, midline shift)
- Pre- mRS
- mRS 3 weeks to 6 weeks, 10 weeks to 14 weeks, depending of standard of care
- Surgical treatment (Burr hole, SEPS or Craniotomy)
- Complications

Statistical Analysis Plan

The data from this study will be systematically recorded in a standardized sheet using BILH REDCap not FDA part 11 HIPPA compliant to ensure consistency across all measurements. To maintain data security and confidentiality, all information will be accessible only to authorized members of the study team and research administration at the primary site (Lahey). Study teams will have access only to their own assigned data and will not have access to data from other teams. Images will be stored in a secure OneDrive environment, with access provided through restricted links shared only with the appropriate study team. Once data collection is complete, the study team will perform a detailed statistical analysis to compare the outcomes of the two treatment groups. The primary focus of the analysis will be on assessing efficacy, safety, and patient recovery, using the following key metrics:

1. **Treatment Success Rates**: The proportion of patients in each group who achieve successful outcomes, as defined by predefined clinical criteria.

2. **Adverse Events (AEs):** The frequency, type, and severity of adverse events encountered in both treatment groups will be compared. This will include a descriptive analysis of AEs, followed by inferential statistical tests (e.g., chi-square or Fisher's exact test) to assess whether there is a significant difference in the incidence of AEs between the groups.

3. **Time to Full Recovery**: The time (in days or weeks) required for patients to achieve full recovery will be analyzed using survival analysis techniques to compare the median recovery times between the treatment groups. A Cox

proportional hazards regression may be employed to control for potential confounders.

Additional secondary analyses may include subgroup analysis based on demographic factors (e.g., age, sex), comorbidities, presence of anastomoses, proximal or distal embolization, and baseline disease severity, which will be used to explore potential modifiers of treatment effects.

Descriptive statistics will be used to summarize the data, with means and standard deviations (SD) reported for continuous variables, and frequencies and percentages for categorical variables.

All statistical tests will be two-tailed, and significance will be defined as a p-value of <0.05. The results will be meticulously documented, and the findings will be prepared for publication in a peer-reviewed journal. This will contribute valuable data to the growing evidence base for chronic subdural hematoma (cSDH) management and may influence future clinical practices.

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The ultimate goal is to improve clinical outcomes for patients with cSDH by providing evidence-based guidance for treatment strategies.

An interim analysis for efficacy and futility will be conducted after approximately 25%, 50%, 60%, 75% and 90% of subjects have been enrolled. Early termination criteria will be based on pre-specified statistical boundaries to control the overall type I error rate. Or completed primary endpoint assessment is completed

Potential Risks of Middle Meningeal Artery Embolization

- Access site injury (including bleeding, bruising, infection, pain)
- Allergic reaction / anaphylactic shock
- Cerebral infarction (ischemic stroke due to reduced blood flow)
- Death
- Embolism (including pulmonary embolism and thromboembolism)
- Headache
- Hematoma (post-procedure bleeding or collection of blood)
- Hemorrhage (uncontrolled bleeding, potentially leading to rebleeding of the subdural hematoma)

- Infection / inflammation (infection at the access site or in the embolized area)
- Nausea / vomiting
- Neurological deficits (e.g., seizures, cognitive impairment, weakness, or sensory changes)
- Occluded catheter (blocked catheter, which can impede the procedure)
- Renal failure (due to contrast-induced nephropathy or other factors)
- Seizure
- Stroke (ischemic or hemorrhagic)
- Subdural hematoma recurrence (reappearance of cSDH after embolization)
- Vasospasm (constriction of blood vessels, potentially leading to ischemia)
- Vessel dissection, perforation, and injury (damage to blood vessels during the procedure)

Patients will sign a separate procedure consent for the MMA embolization, as would be routinely done for standard of care treatment.

Randomization to bilateral embolization as compared with unilateral embolization adds very slight, but not zero, risk to the patient from embolization of the contralateral MMA. This risk is mainly due to microcatheterization of the MMA, which may cause vessel injury, a very low risk possibility. Embolization of MMA with coils is universally well tolerated with near zero risk.

All study patients will undergo bilateral cerebral angiograms; therefore the risk difference from unilateral as compared to bilateral embolization is minimal.

Benefit

MMA embolization is a minimal invasive procedure which can effectively reduce the risk of hematoma recurrence by targeting one/both sides, ensuring comprehensive treatment for cSDH cases. It is currently unknown whether unilateral embolization alone is sufficient, or if additional benefit to the patient may be had through bilateral embolization. By occluding the MMA bilaterally, the procedure addresses the underlying pathophysiology of cSDH, such as abnormal neovascularization and recurrent bleeding, therefore leading to improved patient outcomes. This study aims to help answer the question and determine whether bilateral embolization is more effective than unilateral embolization. The procedure is performed under fluoroscopic guidance, ensuring precision and safety, and is associated with a low complication rate. Overall, MMA embolization has been shown to decrease recurrence and retreatment rates of cSDH. (21)

Data safety Monitoring

There is no DSM/quality group for this study.

Adverse Events (AE) will be monitored and recorded for each participant at the time of follow ups. An AE will be considered mild or severe depending on the standard of care and potential risk.

Future Research

Personal health information and/or scans collected for this research study may be stored and used in future research. This future research may or may not be related to the cSDH condition. If the information is utilized, then personal identifiers will be removed and personal health information and images will be coded. The consent could be withdrawn at any time in order for this information not to be stored.

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