Endovascular Infusion of Lidocaine and Steroids in the Middle Meningeal Artery for Pain Management in Spontaneous Subarachnoid Hemorrhage Patients

(MISSY)

IRB Number: 25-0010

NCT07294118

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1. Introduction and Purpose:

This is a **three-arm prospective cohort study**. Participants will be placed into one of three treatment arms: (1) bilateral infusion of lidocaine plus dexamethasone; (2) bilateral infusion of lidocaine; or (3) no infusion. All patients enrolled in arms 1 and 2 will receive the middle meningeal artery (MMA) infusion intervention, and outcomes will be assessed through pre- and post-intervention comparisons.

We hypothesize that the targeted infusion of local anesthetics, with or without steroids, into the MMA will provide direct therapeutic action on the sensory terminals innervating the dura mater, effectively mitigating pain and inflammation. The dura mater's dense sensory innervation, primarily via the first division of the trigeminal nerve, makes it a critical site for pain modulation in headache disorders. Local anesthetics can inhibit nociceptive signaling by blocking sodium channels in peripheral nerve terminals, thereby halting the transmission of pain signals. Concurrently, the addition of steroids could suppress local neuroinflammation by inhibiting the release of pro-inflammatory cytokines, such as interleukin-6 (IL-6), which is known to contribute to hyperalgesia and nociception. By targeting the MMA during angiographic procedures, this approach could leverage its proximity to dural nociceptors, offering a dual benefit: direct pain relief via anesthetic action and potential long-term reduction in inflammatory processes depending on the agent used. This integrated strategy may provide a novel, efficient avenue for managing refractory headaches associated with meningeal nociception and inflammation, particularly in conditions such as post-subarachnoid hemorrhage headaches.

Primary Objective: To assess changes in Visual Analog Scale (VAS) scores pre- and post-MMA infusion of lidocaine alone, lidocaine + dexamethasone, and no infusion groups.
Secondary Objective: To measure analgetic use by category and total quantity in the case of non-opiates, or morphine equivalents in the case of opiates, pre- and post-intervention.

Safety outcomes: These will be events related to the procedure itself and will include new stroke, vessel dissection, brain bleeding, cranial nerve palsy, cardiac depression, arrythmias, respiratory depression, seizures, and any other events that will be attributed to the MMA catheterization and infusion of lidocaine, steroids or both.

2. Background:

Pain and opiate consumption

Spontaneous subarachnoid hemorrhage (sSAH) is a critical condition often accompanied by severe headaches and postoperative pain, necessitating effective pain management strategies.

In the intensive care unit (ICU), up to 90% of patients experience severe headaches immediately following subarachnoid hemorrhage (SAH). In a study, 41% of patients experienced burdensome headaches that significantly reduced their quality of life and limited daily activities at long-term follow-up (mean 32.6 months). [1]

Opioids are frequently employed to palliate these headaches due to their potent analgesic properties. However, their use is fraught with significant challenges and adverse effects. Patients with post-SAH headaches often require higher morphine-equivalent opioid doses during hospitalization and continued pain management long-term, raising concerns about the potential for long-term opioid dependency and associated risks of addiction. [2] Additionally, these patients are exposed to common opiate side effects including nausea, vomiting, ileus, hemodynamic instability, and respiratory depression, which complicate their clinical management. [3] Finally, prolonged opioid use can lead to tolerance, necessitating higher doses and potentially resulting in altered mental status and delirium, which can obscure neurological assessments.[3]

Despite efforts to reduce opioid prescriptions in light of the opioid crisis, studies have shown that opioid use during hospitalization for sSAH has not significantly decreased over time, highlighting the persistent need for effective pain relief. [4] Moreover, high opioid consumption during the initial hospitalization is associated with longer hospital stays and continued headache issues post-discharge. [5] The complexity of managing pain in sSAH patients underscores the urgent need for alternative analgesic strategies that minimize opioid use while effectively controlling pain. [4]

The pathophysiology of headaches in SAH

The mechanisms of pain in SAH are complex. The cranial meninges consist of three layers: the dura mater, arachnoid, and pia mater. The dura mater, the outermost layer, is composed of a dense collagen network produced by connective tissue fibroblasts and is divided into an outer periosteal/endosteal layer and an inner dural border cell layer, which borders the arachnoid. The dura possesses a massive innervation by sensory and autonomic nerves, particularly near its large blood vessels, including venous sinuses, veins, and arteries, making it a very probable source of headaches in pathological conditions. [6,7]

The first division of the trigeminal nerve primarily innervates the dura, with contributions from the second and third divisions. Specific branches, such as the tentorial nerve, supply areas including the supratentorial dura, superior sagittal and transverse sinuses, and parietal branches of the middle meningeal artery. Additionally, trigeminal meningeal afferents form collateral branches that terminate in the calvarial bone marrow or external periosteal layer. These complex networks highlight the anatomical basis of the meninges' sensory functions. [6,7]

The meninges are the only pain-sensitive structures within the cranium, making them pivotal in headache mechanisms. Meningeal inflammation leads to classic headache symptoms such as throbbing pain, nausea, vomiting, and sensitivity to light and sound, resembling meningitis. Mechanical or electrical stimulation of the meninges results in referred head pain patterns typical of migraines. Notably, the dura mater's innervation and blood supply lie outside the blood-brain barrier. This distinction is crucial in understanding pain mechanisms, as it allows for the use of CGRP-targeting medications. These drugs act directly on the dura mater without crossing the blood-brain barrier yet are highly effective in alleviating migraine pain. These insights highlight the meninges as a critical interface in pain perception and a key target for headache treatments. [8]

During the acute phase, blood in the subarachnoid space irritates the meninges, triggering inflammatory responses and activating nociceptors in the dura mater, which results in a pattern similar to aseptic meningitis. [9] Additionally, elevated levels of inflammatory cytokines in the cerebrospinal fluid (CSF) are related to headache severity. [10] The increase in interleukin-6 (IL-6) following subarachnoid hemorrhage (SAH) plays a role in hyperalgesia and nociception, further supporting the notion of an inflammatory mechanism driving these headaches. [11]

In the chronic phase, persistent meningeal inflammation is sustained by ongoing neuroinflammation and changes in vascular permeability, which contribute to prolonged activation of meningeal nociceptors. Additionally, the role of cortical spreading depression (CSD) in inducing meningeal inflammation and linking trigeminal-dural interactions with central pain sensitization underscores the significance of meningeal processes in the evolution of chronic headaches post-SAH. These findings elucidate the dual-phase involvement of the meninges in both acute and chronic headache pathophysiology after SAH. [12]

Utilization of Lidocaine and Steroids injected into the MMA by previous authors

The potential for lidocaine and steroid injection into the middle meningeal artery (MMA) to alleviate headaches has been explored in contexts other than subarachnoid hemorrhage (SAH), with promising results. While this approach has not yet been studied specifically for SAH-related headaches, the concept is supported by findings from related applications.

For instance, a study involving four patients with severe headaches—two with intractable headaches and two experiencing status migrainosus—demonstrated the efficacy of intra-arterial lidocaine injections in the MMA. Patients reported immediate pain relief, with intensity dropping from 8–10/10 to 0/10, lasting up to two days, and partial relief extending to seven days. For those with status migrainosus, disability scores significantly improved over three months, suggesting prolonged benefits likely due to central desensitization effects. [13]

In a broader study, 32 patients with cSDH undergoing middle meningeal artery embolization (MMAE) with ethylene vinyl alcohol (EVOH) received intra-arterial lidocaine on one side before embolization to mitigate procedure-related headaches. Lidocaine was administered through a microcatheter distal to the petrous-squamous branch, followed by EVOH injection into target MMA branches. This protocol resulted in pain reduction from a median VAS score of 7 to 3, with lidocaine's effect lasting several hours, greatly enhancing patient comfort and compliance without notable side effects. [14]

In a study by Qureshi et al. (2017), intra-arterial lidocaine was administered in the middle meningeal artery to

modulate trigeminal nerve ganglion function in patients with refractory trigeminal neuralgia. Using electrophysiologic monitoring, the study observed latency prolongation and amplitude reduction in blink reflex responses (R1 and R2) after incremental doses of lidocaine. Three patients showed short-term clinical improvement, with two experiencing pain reduction and pain-free intervals of 3–5 days. However, symptoms returned to baseline within a month, highlighting the potential yet transient effects of this approach in modulating trigeminal nerve activity. [15]

In a report by Qureshi et al., the intra-arterial injection of lidocaine and methylprednisolone into the middle meningeal artery was examined for its impact on severe headaches unresponsive to conventional therapies. Two patients, each with distinct headache etiologies, received a 40 mg dose of lidocaine followed by 20 mg of methylprednisolone. Both experienced rapid headache relief within 5 minutes, although the effect lasted only 5–8 hours initially. However, 24 hours post-procedure, both patients reported improved headache intensity. This method presents a promising alternative for managing refractory headaches, adding to the expanding therapeutic approaches targeting the middle meningeal artery for headache relief. [16]

These findings suggest that the middle meningeal artery (MMA) may also be a viable target for managing subarachnoid hemorrhage (SAH)-related headaches. The involvement of dural pain receptors in SAH pathophysiology aligns with the mechanisms observed in other conditions, such as chronic subdural hematomas and migraines, where MMA interventions provided significant headache relief. This supports the hypothesis that targeting the MMA with lidocaine and steroid injections could similarly alleviate SAH-related headaches.

The integration of our intervention in the modern SAH work-flow

Angiography remains a crucial diagnostic tool for all cases of sSAH due to its unparalleled ability to identify underlying vascular lesions that may not be detected by other imaging modalities. Despite advancements in computed tomography (CT) angiography, studies have shown that it can still yield false-negative results, missing critical diagnoses such as small aneurysms that are better visualized with digital subtraction angiography (DSA). [17] The necessity of angiography is further underscored by the fact that a significant proportion of spontaneous SAH cases are caused by ruptured aneurysms, which require prompt and accurate identification for effective treatment. [18,19] Additionally, repeat angiography has been shown to uncover vascular abnormalities in cases where initial imaging was negative, highlighting its importance in comprehensive patient evaluation. [20,21] Therefore, to ensure no underlying pathology is overlooked, angiography should be performed in all patients presenting with spontaneous subarachnoid bleeding. [17–21]

Our institutional guidelines already involve the performance of angiography in cases of sSAH to ensure accurate detection of vascular lesions. In parallel, we can capitalize on this existing setup for the administration of our treatment.

3. Concise Summary of Project:

This protocol outlines a three-arm prospective cohort study evaluating the efficacy of endovascular infusion of lidocaine and steroids into the MMA for managing post-SAH pain (i.e., headaches) in patients with SAH with Hunt and Hess Grades 1-2. We will enroll 15 patients into three groups of treatment (N=5 patients per Treatment Arm): (1) bilateral lidocaine infusion, (2) bilateral lidocaine plus dexamethasone infusion, and (3) no infusion. Pain outcomes will be evaluated using VAS at 5 timepoints, including during neurochecks postoperatively, to calculate a cumulative "total VAS score." Morphine equivalents will also be tracked to assess opioid needs over time.

Selection of Lidocaine and Dexamethasone

The choice of lidocaine and dexamethasone for this study is grounded in their distinct yet complementary mechanisms in managing pain and inflammation, particularly targeting the dura mater's nociceptive pathways.

Lidocaine is an amide anesthetic that works by blocking sodium channels, which inhibits the initiation and conduction of nerve impulses, providing pain relief. [22] [23] The meninges, which are protective membranes covering the brain and spinal cord, play a significant role in headaches. In particular, post-subarachnoid hemorrhage headaches occur due to irritation and inflammation of the meninges following bleeding into the subarachnoid space [9] [24] Lidocaine may improve headaches in SAH patients by selectively anesthetizing the

afferent neural supply of the dura, reducing pain transmission from the trigeminal nerve, and suppressing trigeminal ganglion activity. Intra-arterial lidocaine, injected into the middle meningeal artery, delays nerve depolarization and diminishes ectopic discharges, leading to prolonged sensory blockade. Additionally, lidocaine appears to induce paradoxical vasoconstriction in the middle meningeal artery, counteracting vasodilation caused by neuropeptides like CGRP and substance P, which are implicated in SAH-related headaches. The analgesic effects of intra-arterial lidocaine extend beyond its elimination half-life, likely due to interruption of central sensitization and modulation of pain pathways, resulting in long-lasting relief of headaches and reduced headache-related disability. [25]

Lidocaine infusion through the MMA has been used successfully for headaches related to migraines, CSDH and trigeminal neuralgia, without negative side effects. [15] [14] [13] Lidocaine in the realm of SAH has been scarcely explored. The paper by Navia, titled *"Lidocaine Infusion for the Treatment of Headache Associated With Subarachnoid Hemorrhage: A Case Report,"* presents two cases where intravenous lidocaine was used to manage severe headaches following subarachnoid hemorrhage and craniotomy with aneurysm clipping. Both patients exhibited hyperalgesia resistant to conventional analgesics, but during lidocaine infusion, their opioid use dropped to zero without signs of toxicity. After discontinuation, they maintained adequate pain control with standard oral medications, suggesting that lidocaine infusion could be a viable adjunct for managing refractory headaches in this context. [9]

Qureshi and colleagues, in their study *"Intra-arterial lidocaine administration in the middle meningeal artery for short-term treatment of subarachnoid hemorrhage-related headaches,"* explored the effects of intra-arterial lidocaine injections for severe headaches following subarachnoid hemorrhage. Seven patients received up to 50 mg of lidocaine bilaterally (except one), for a maximum of 100 mg administered via microcatheters. All patients reported headache improvement, with four achieving immediate and complete resolution. Angiographic analysis showed consistent narrowing of the middle meningeal arteries post-administration, suggesting that the therapeutic benefit may stem from reversing prior vasodilation through vasoconstriction. [26]

Dexamethasone, as a potent corticosteroid, suppresses neuroinflammation by inhibiting the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6), which are implicated in nociceptive sensitization following subarachnoid hemorrhage (SAH). By reducing inflammation in the dura mater, dexamethasone may contribute to sustained pain relief. Steroids have only been studied in combination with lidocaine in this context. In their study titled "*Effect of intra-arterial injection of lidocaine and methyl-prednisolone into middle meningeal artery on intractable headaches*," Qureshi et.al. investigated the impact of administering 40 mg of lidocaine and 20 mg of methylprednisolone directly into the MMA of two patients experiencing severe headaches unresponsive to standard treatments. Both patients reported significant pain relief within 5 minutes post-injection, with effects lasting between 5 to 8 hours. Notably, both individuals experienced sustained improvement in headache intensity 24 hours after the procedure. [27] Even though the previous author used methyl-prednisolone, we consider dexamethasone to be a better choice for the following reasons:

- **Potency**: Dexamethasone is generally considered more potent than methylprednisolone. This increased potency allows for lower doses to achieve similar anti-inflammatory effects, which can be beneficial in reducing potential side effects associated with higher steroid doses. [28]
- **Glucocorticoid and Mineralocorticoid Differences**: Dexamethasone has a higher glucocorticoid activity and negligible mineralocorticoid activity compared to methylprednisolone. This difference is significant because it reduces the risk of fluid retention and electrolyte imbalances, which are common side effects associated with mineralocorticoid activity. The reduced mineralocorticoid activity of dexamethasone makes it a preferable choice in conditions where fluid retention is a concern, [29] such as SAH where fluid imbalances are common.
- **Half-life**: Dexamethasone has a longer half-life than methylprednisolone, which allows for less frequent dosing. This can improve patient compliance and convenience, as well as maintain more stable blood levels of the medication, potentially enhancing its therapeutic effects. [30]

In summary, dexamethasone's higher potency, reduced risk of fluid retention due to lower mineralocorticoid activity, and longer half-life make it a favorable option over methylprednisolone for managing inflammatory conditions.

4. Study Procedures:

4.1. Endovascular Access

This will be performed according to our standard-of-care diagnostic brain angiography protocol routinely performed for spontaneous subarachnoid hemorrhage. No added elements, modifications or steps are added.

4.2. Drug Administration

- **Target vessel selection:** During the diagnostic angiography part involving the external carotid arteries, and after having evaluated the images carefully, the middle meningeal artery will be selected with a microcatheter and microwire system.
- **Lidocaine and Steroid Infusion**:
  - On the first 5 consecutive patients, Lidocaine and Dexamethasone will be administered directly into the MMA bilaterally. Lidocaine dose will be 50mg bilaterally (100mg total) and the Dexamethasone dose will be 5mg bilaterally (10mg total).
- **Lidocaine Infusion**:
  - On the second 5 consecutive patients (Patients 6-10), Lidocaine will be administered directly into the MMA bilaterally. Lidocaine dose will be 50mg bilaterally (100mg total).
- **No Infusion**:
  - On the third 5 consecutive patients, no infusion will be performed into the MMA bilaterally.
- **Infusion Protocol**: Infusion will be conducted slowly to ensure optimal delivery and tissue saturation, with continuous monitoring for immediate side effects. Each medication will be administered over 10 minutes. In the case of Lidocaine + Dexamethasone, they will be administered sequentially.
- **Dosage Rationale**

  The selected dosages—50 mg of lidocaine bilaterally and 5 mg of dexamethasone bilaterally—are informed by prior research indicating both safety and efficacy.

  Regarding lidocaine 50 mg bilaterally (100 mg in total), studies involving MMA injections for migraines, CSDH, trigeminal neuralgia and SAH have utilized doses ranging from 40 to 50 mg, demonstrating good tolerability and no local or systemic complications, with rapid and substantial headache relief in most cases. [14,15]

  Most recently, Zhang et al. conducted a prospective pilot study of 9 patients with aneurysmal subarachnoid hemorrhage (aSAH), utilizing bilateral MMA infusion of lidocaine at 50 mg per side, identical to our protocol. No complications were observed and all treated patients demonstrated meaningful pain reduction, further validating this dose as both safe and effective. [32]

  Dexamethasone 5 mg bilaterally (10 mg in total), aligns with amounts used in intra-arterial steroid injections for neuroinflammatory conditions and is consistent with protocols for peripheral nerve and epidural steroid injections, aiming to achieve effective anti-inflammatory effects without inducing systemic immunosuppression and demonstrating safety and efficacy. In the context of postoperative care, a study found that intravenous dexamethasone at doses ranging from 8 mg to 10 mg effectively reduced postoperative nausea and vomiting (PONV) without significant adverse effects, suggesting that this dosage is well-tolerated when used systemically. [16] Additionally, research on perioperative administration of dexamethasone in orthopedic surgeries, such as total knee and hip arthroplasty, has shown that a 10 mg dose can effectively manage pain and inflammation, reduce the need for additional analgesics, and improve recovery outcomes without increasing the risk of infections or gastrointestinal complications.[17] [18] Furthermore, in the context of nerve blocks, a 10 mg dose of

intravenous dexamethasone was found to prolong the duration of analgesia without adverse events, indicating its safety in enhancing postoperative pain management. [19] These findings collectively support the notion that high dose dexamethasone is a safe and effective systemic dose for various medical applications when used in very sporadic doses.

Zhang et al. utilized dexamethasone at 10 mg per side (20 mg total) in their pilot study, demonstrating safety and efficacy at that dose. [32] We have elected to reduce our dexamethasone dose to 5 mg per side (10 mg total) based on the reasoning that a lower dose can be just as efficacious.

Finally, administering these medications over a 10-minute period is intended to optimize tissue saturation and minimize potential adverse effects. Additionally, we believe that administration into the MMA will improve local effectiveness of the medication and limit systemic spread.

4.3 Outcome Measures and Follow-up

4.3.1. Primary Outcome

VAS Score:

- **Baseline**: Record prior to MMA infusion.
- **Postoperative Period**: Record VAS score at each neurocheck (typically every 4 hours post-intervention) to calculate a cumulative **Total VAS Score**.

4.3.2. Secondary Outcome

- To measure analgetic use by category and total quantity in the case of non-opiates, or morphine equivalents in the case of opiates, pre- and post-intervention.

4.3.3. Follow-up Timeline

Post-Discharge Follow-up:

- **1-Month Follow-up**: VAS score, morphine equivalent, analgetic consumption and adverse events assessment.
- **3-Month Follow-up**: VAS score, morphine equivalent, analgetic consumption and adverse events assessment.
- **6-Month Follow-up:** VAS score, morphine equivalent, analgetic consumption and adverse events assessment.
- We have added visit windows to each visit to allow flexibility for the participant. These windows are as displayed in Section 5 “Schedule of Events”.

Some of the visit data collection may be done through a combination of visit EMR abstraction and a phone call. Visits will be done by PI and/or appropriately licensed IRB-approved personnel.

5. Schedule of Events

Procedures	**Screening & Enrollment** Visit 1 (Day 0)	**Intervention & post-op period (every 4 hours)** Visit 2 (Day 1)	**1-Month Follow-Up** Visit 3 (Day 31 ± 7)	**3-Month Follow-Up** Visit 4 (Day 91 ± 7)	**6-Month Follow-Up** Visit 5 (Day 181 ± 14)
Informed Consent	X				
Demographics	X				
Medical History	X				
Endovascular Access		X			
Drug Administration[a]		X			
VAS Scoring[b,c]	X	X	X	X	X
Morphine Equivalents Calculation[c]		X	X	X	X
Analgetic Consumption Calculation[c]		X	X	X	X
Neurochecks (every 4 hrs post-op up to 24 hrs)		X			
Adverse event assessment (neurological exam, complications, patient-reported outcomes)[c]			X	X	X

[a] Arm 1: Lidocaine (50 mg) + Dexamethasone (5 mg bilaterally) – 5 patients total
Arm 2: Lidocaine (50 mg bilaterally) – 5 patients total
Arm 3: No Infusion (Control group) – 5 patients total

[b] VAS score may also be listed in patient chart under "pain" or "pain score"

[c] This data collection may be done through a phone call.

6. Criteria for Inclusion of Subjects:

- Age ≥18 years.
- Diagnosed with aneurysmal SAH, Hunt and Hess Grades 1-2.
- Consent to study procedures and follow-up evaluations.

7. Criteria for Exclusion of Subjects:

- Known allergies to lidocaine or steroids.
- Arteriovenous malformations.
- Dural Arteriovenous Fistulas.
- Other significant intracranial pathologies.
- Hemodynamic instability preventing safe intervention
    - *Defined as MAP <65 mmHg or SBP <90 mmHg despite resuscitation, clinically significant arrhythmias with hypoperfusion, elevated/rising lactate (≥3-4 mmol/L), oliguria, or oxygen desaturations on room air.*
- Previous MMA interventions.
- Previous craniotomies or need for craniotomy.
- Inability to provide a baseline VAS score.

8. Sources of Research Material:

Approved personnel and/or PI will identify their patients through surgical case logs, chart review (i.e. EPIC or physical charts), ER visits, clinic visits by the neurology, interventional neuroradiology, and neurosurgery departments. Data from existing sources will be collected from February 1, 2025 to February 28, 2029. To determine eligibility, approved study personnel may review existing medical records

and data sources (such as EMR, surgical case logs, and chart reviews) prior to approaching a patient for consent. This pre-consent review is limited to screening purposes only. Once a patient provides written informed consent, all research data collection will formally begin. Enrolled participants' data will be collected from the time of consent through the end of the study period. All patients thus identified who meet criteria will be included in the study.

9. Recruitment Methods and Consenting Process:

If the patient /legally authorized representative (LAR) agrees to the procedure, then the PI and/or IRB-approved personnel will commence the informed consent process. The patient will be presented with the procedures of the study, risks and benefits, etc. To prevent undue influence and assess the subject's/LAR (if needed) understanding of the study, the study team will engage the potential participant in a dialogue, using open-ended questions about the nature of the study, the risks and benefits of participating, and the voluntary nature of participation. Interested patients will be enrolled in the study, otherwise the patient will continue with the standard of care with no effect. Informed consent forms will be kept in a locked/secured room with study coordinators. No non-English speaking patients will be enrolled until IRB-approved translated consent documents are available in the participant's language.

10. Potential Risks & Benefits:

Risks:

Standard-of-care Risks:

The risks of this study are primarily those associated with standard endovascular procedures. Thus, potential minor adverse events associated with angiography include access site bleeding, bruising or hematoma, vascular damage or spasms or allergic response to use of iodinated radiographic contrasts. Serious adverse effects include death, clots forming in the leg, post-procedure bleeding, renal failure, blood vessel perforation, and vessel occlusion from clots. Furthermore, microcatheters and microwires are routinely placed in the MMA for established interventions such as refractory headache treatment, embolization of chronic subdural hematomas, dural arteriovenous fistulas, and preoperative tumor devascularization. Thus, vascular access complications, including hematoma, arterial dissection, stroke, or vessel injury, are consistent with known risks of neuroendovascular procedures.

Research-Related Risks:

<u>Infusion Medication-Related Risk</u>

Lidocaine: The doses used in this study are within the safe range for local or regional anesthesia, but if inadvertently injected intravascularly, it could still cause mild systemic effects like dizziness, lightheadedness, and perioral numbness, especially in sensitive individuals. While unlikely to cause severe cardiotoxicity or seizures, rapid administration into the bloodstream may still trigger low blood pressure or low heart rate due to sodium channel blockade.

Dexamethasone: The doses used in this study are commonly used for anti-inflammatory or anti-edema purposes, but if injected intravascularly, it may cause temporary high blood sugar, mild high blood pressure, or flushing. While systemic toxicity at this dose is minimal, repeated high-dose exposure could contribute to lower cortisol level (hormone produce by the adrenal glands) or immunosuppression over time.

<u>Privacy Risk</u>

A confidentiality breach is a risk associated with any research that collects data. Every effort will be performed by study personnel to ensure this risk is minimized. Several measures will be taken to reduce random and systematic error as discussed in section 12.

Benefits:

The subjects who participate may alleviate SAH-related headaches with lidocaine or steroid injections. Society and investigators may benefit from the knowledge gained from the research developed from this protocol. This study will provide key information on SAH-related headaches to gain significant novel insights that can advance the treatment plan of this disease. This knowledge could not be gained using a safer approach compared to this study that has minimal risk of loss of confidentiality.

11. Subject Safety:

Potential risks and adverse events that could occur through participation in the study are listed above in section 10. In the event that an Adverse Event (AE)/Serious Adverse Event (SAE)/Unanticipated Problem Involving Risks to Subjects or Others (UPIRSO) occurs, it will be handled as described in the table below:

	Definition	**UTMB IRB Reporting Procedures**
AE Adverse Event	Any physical, psychological, or social harm to participants during the course of research.	1. Document on AE log. 2. Provide to UTMB IRB during continuing review, *if requested*
SAE Serious Adverse Event	An event that results in any one of the 6 categories*	Report **if possibly related to study:** within **10 days** of study staff awareness ⇒ If **unexpected death/life-threatening & related to study**, report within **2 days** of study staff awareness.
UPIRSO Unanticipated Problem Involving Risks to Subjects or Others	Any event that is (i) unexpected, (ii) related or possibly related to the study, and (iii) potentially increases risk.	Report within **10 days** ⇒ If **unexpected death/life-threatening & related to study**, report within **2 days** of study staff awareness. ⇒ Report to **UTMB Risk Management**
*Death, Life-threatening, Hospitalization, Persistent Disability, Congenital Anomaly, Other Important Medical Event		

AEs, SAEs, and UPIRSOs will be assessed for clinical significance and reasonable relationship to the study intervention or procedures. Laboratory abnormalities, vital sign changes, or clinical findings that are pre-existing, incidental, or expected for the subject's underlying condition, will not be considered reportable adverse events unless, in the judgment of the PI, they are new, worsening, clinically meaningful, or reasonably related to the study intervention or procedures. Our patient population is not suspected to have any abnormal laboratory values, vital sign changes, and clinical findings at baseline.

Some of these events that are incidental or expected for the underlying condition include worsening or persistent headache, rebleeding of the aneurysm, worsening of SAH, cerebral vasospasm and other vascular complications, delayed cerebral ischemia (DCI), hyponatremia, fever or infection, nausea and vomiting, elevated blood pressure or hypertensive episodes, seizures related to the hemorrhage, deep vein thrombosis, pulmonary embolism, and cardiac arrhythmias or EKG changes. These events would be considered reportable if they were to result in the patient being readmitted to the hospital, an extended stay at the hospital, or being shown to have a considerate effect on the patient's daily life, with all of these being determined at the judgement of the PI.

12. Study Withdrawal/Discontinuation

Reasons for Withdrawal

The PI and/or IRB-approved personnel can discontinue the study intervention(s) and/or discontinue a patient from participation in the study based on their clinical judgement and patient's best interest.

The study intervention may be discontinued, or a study subject may be discontinued from participation in the study if any of the following occur:

- Intercurrent illness, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject in the opinion of the treating investigator
- Subjects withdraws consent to continue in the research for any reason

Handling of Withdrawals

If a subject chooses to withdraw from participation, every effort will be made to continue collecting safety data and outcome measures. Specifically:

- Safety Follow-Up: Subjects who discontinue early will be encouraged to complete protocol-specified safety assessments, including at least one final evaluation (neurological exam, vital signs, and documentation of adverse events). If an AE or SAE prompted withdrawal, participants will be monitored until resolution or stabilization of the event.
- End-of-Study Evaluation: With consent, withdrawn participants will be asked to complete an abbreviated end-of-study visit (in-person or by phone) to capture final safety outcomes.
- Ongoing Care: All subjects who withdraw will continue to receive appropriate standard-of-care treatment for their underlying condition under the supervision of their treating physician.

Efforts to Continue Follow-Up

- The study team will attempt at least three follow-up contacts (phone, in-person, or through email) after withdrawal (or if patient Is lost to follow-up) to collect safety and outcome data.
- Participants will be reminded that their withdrawal will not affect their access to clinical care.
- Data collected up to the point of withdrawal will be retained for safety analysis, unless the subject specifically revokes permission.

Termination of Study

The study may be suspended or terminated early by the PI, IRB, or sponsor for any of the following reasons:

- **Safety concerns:** Emergence of unanticipated serious adverse events (SAEs) or an unfavorable risk–benefit profile based on cumulative data.
- **Feasibility/futility:** Inability to achieve study objectives (e.g., insufficient evaluable data, no measurable physiologic/clinical response) or clear evidence the intervention is not feasible.
- **Insufficient enrollment/retention:** Persistent failure to enroll or retain participants to meet the sample size/timeline necessary for meaningful analysis.
- **Protocol noncompliance:** Systematic or significant deviations that compromise participant safety, data integrity, or scientific validity.
- **Regulatory/IRB action:** Suspension or withdrawal of IRB approval; new regulatory requirements that cannot be met; request from oversight bodies (e.g., FDA, OHRP).
- **Data integrity issues:** Evidence of fabrication, loss, or compromise of essential study records or source data.
- **Product/equipment issues:** Unavailability, malfunction, or recall of required devices/equipment (e.g., stimulators, catheters) without timely remediation.
- **Funding/sponsor changes:** Loss of funding, withdrawal by sponsor, or institutional prioritization that precludes continuation.
- **New external information:** Publication or advisory indicating unacceptable risk or lack of rationale to continue.
- **Operational/force majeure:** Site closure, staff unavailability, natural disaster, cyber incident, or other events preventing safe conduct of the study.

- **Administrative close-out:** Completion of all protocol activities or replacement by a superseding protocol.

If early termination occurs, the PI/IRB-approved personnel will: (1) notify the IRB and applicable regulatory bodies per policy; (2) inform participants; (3) ensure appropriate clinical follow-up and safety monitoring; and (4) document and secure all data collected to date for safety reporting and final accounting.

13. Data Collection Procedures to Maintain Confidentiality:

Data collection will be completed by the PI and/or IRB-approved personnel. Data will be collected and stored in REDCap (Research Electronic Data Capture), and on secure, password-protected computers to ensure confidentiality. Access to REDCap will be limited to authorized study personnel only. The de-identified version of the REDCap data will be created before analysis.

As the initial collected variables will include PHI (e.g., MRN) the following system has been implemented to automate censoring of PHI, thereby ensuring patient confidentiality is maintained while errors are minimized:

1. Data will be collected and stored in REDCap (Research Electronic Data Capture), and on secure, password-protected computers to ensure confidentiality. Access to REDCap will be limited to authorized study personnel only. The de-identified version of the REDCap data will be created before analysis.
2. Data limitation will be utilized where necessary to ensure that only correctly formatted values can be entered into REDCap.
3. Auto-population of certain values in REDCap will be used to reduce reviewer fatigue.
4. If multiple reviewers will extract data at a center to split the workload, we ask that they first duplicate their work for the first 10 subjects and then compare values. This will allow reviewers to clarify any definitions and compare their values to ensure data are correctly entered.

When finished with data collection, we will verify censorship of PHI before data analysis. Thus, the final data sent will have randomly assigned patient numbers. Essential/Source Documents may be maintained in electronic form or via paper records. Digital data, aside from REDCap, will be stored securely on UTMB servers or UTMB cloud-based OneDrive or SharePoint with access limited to the study team. Paper records will be maintained in a lockable room or cabinet accessed only by authorized research staff.

14. Ethics and the Protection of Human Subjects

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

The investigator must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate independent ethics committee (IEC) or IRB registered with the OHRP. Any amendments to the protocol or consent materials must also be approved before they are placed into use. In the United States and in other countries, only institutions holding a current US Federalwide Assurance issued by OHRP may participate. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Privacy/Confidentiality Issues

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal investigator.

Individuals authorized to view study records will be identified to the study subject on the informed consent but may include a study monitor or other authorized representatives of the sponsor or funding agency or federal or local agencies that regulate research including representatives from the Food and Drug Administration, Office of Human Research Protections, or the Institutional Review Board. Study records may also be made available for internal compliance reviews and quality assurance representatives.

These individuals may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

Record Retention

At completion of the study, the records will be kept for at least 15 years after completion of research. After this period, the data files will be destroyed (i.e., overwrite or shredding). Periodic review by research team will be performed to ensure appropriate storage and use of data.

Disclosure of any records will be in accordance with federal law, including the Federal Privacy Act, 5 U.S.C. 552a, and its implementing regulations.

If a research study accesses protected health information (PHI) and is covered under the Health Insurance Portability Accountability Act (HIPAA), consent forms that include the HIPAA Authorization are to be retained for a minimum of 6 years from the date of the authorization.

Research records will be maintained in accordance with the current version of the Texas Health Records Table 17-III. Record Retention Schedule, Human Subject Research Records and Documents).

15. Statistical Considerations

Primary Analysis

- **VAS Score Changes**:
    - VAS pain scores will be analyzed using repeated measures ANOVA to assess within subject changes over time and between-group differences across five time points (baseline, discharge, 1-month, 3-month, and 6-month follow-ups).
    - The **Total VAS Score**, calculated as the sum of all recorded neurocheck scores, will be compared across groups using ANOVA or a non-parametric test if needed.

Secondary Analysis

- **Opioid Consumption (Morphine Equivalent)**:
    - Compare the total morphine equivalents used pre-intervention and post-intervention using paired t-tests (or Wilcoxon signed-rank test for non-normal data).
    - Summarize opioid usage during the hospital stay and at each follow-up using means or medians.

Correlational Analysis

- **VAS Scores and Opioid Use**: Calculate the correlation between total VAS score and total morphine equivalents.

Subgroup Analysis

- If feasible, conduct subgroup analyses by simple categories (e.g., age groups or Hunt and Hess grade) to compare VAS scores or opioid use between these groups.

Significance Level

- A p-value of <0.05 will be considered statistically significant for all tests.

Power Analysis

- This study is designed with a total sample size of 15 participants, distributed across three treatment groups (n = 5 per group). The primary goal is to evaluate practicality and estimate treatment effects. Based on previous studies showing large pain reductions with lidocaine, we believe the sample is enough to detect large effects.
- A repeated measures ANOVA with a within-between interaction (time x treatment group) was selected as the appropriate model, as the study involves 5 repeated measurements of VAS pain scores per participant over time and aims to evaluate whether treatment groups differ in their trajectories of pain reduction.
- An a priori power analysis was conducted using G*Power 3.1, under the F tests family, specifically the ANOVA: Repeated measures, within-between interaction test. The parameters used were:
    - Effect size (f) = 0.35
    - Alpha (Type I error rate) = 0.05
    - Power = 0.80
    - Number of groups = 3
    - Number of repeated measures = 5
    - Correlation among repeated measures = 0.5
    - Nonsphericity correlation = 1
- Under these parameters, the model is sufficiently powered (80%) to detect a medium-to-large time-by-group interaction effect, which is the primary statistical target of interest.

Treatment Arms

To ensure methodological rigor, participants will be placed into three treatment arms:

- Arm 1: Lidocaine (50 mg bilaterally) + Dexamethasone (5 mg bilaterally) – 5 patients total
    - First 5 consecutive patients
- Arm 2: Lidocaine (50 mg bilaterally) – 5 patients total
    - Second 5 consecutive patients
- Arm 3: No Infusion (Control group) – 5 patients total
    - Third 5 consecutive patients

Statistical Analysis: Repeated Measures ANOVA

A repeated measures ANOVA is appropriate for analyzing changes in Visual Analog Scale (VAS) pain scores across multiple time points (baseline, post-intervention, and follow-ups). This statistical approach will allow for:

- Between-group comparisons: Assessing differences in pain reduction efficacy among the three treatment groups.
- Within-subject analyses: Evaluating individual changes over time to determine the sustainability of treatment effects.
- Time-by-group interaction: Determining whether the pattern of pain reduction over time differs significantly across treatment groups, with a specific interest in whether the combination therapy yields enhanced or prolonged analgesic effects.

16. Summary of Rationale for The Study

While large-scale clinical trials specifically investigating MMA infusions for SAH-related headaches are lacking, the proposed study is supported by several considerations.

a) Pathophysiological basis: The pathophysiological basis to think that the meningeal system is heavily involved in post-SAH pain is detailed at the beginning of this protocol. In that part we explain that following a subarachnoid hemorrhage (SAH), blood in the subarachnoid space irritates the meninges, triggering inflammatory responses and activating nociceptors in the dura mater, leading to severe headaches. Elevated

levels of inflammatory cytokines, such as interleukin-6 (IL-6), in the cerebrospinal fluid are associated with increased headache severity. In the chronic phase, ongoing meningeal inflammation, sustained by neuroinflammation and changes in vascular permeability, contributes to prolonged activation of meningeal nociceptors. Additionally, cortical spreading depression (CSD) may induce meningeal inflammation, linking trigeminal-dural interactions with central pain sensitization, underscoring the role of meningeal processes in chronic headaches post-SAH.

b) Precedent in Other Conditions: Please refer to the introduction of this project for detailed information on this section. Intra-arterial lidocaine and steroid injections into the MMA have been effective in alleviating headaches related to cSDH, intractable headaches, migraines and trigeminal neuralgia, suggesting potential applicability to SAH-related headaches, since several pain mechanisms are shared between these conditions.

c) Precedent in this condition: A recent study by Bhogal et.al explored the mechanisms by which intra-arterial lidocaine alleviated severe headaches. One proposed mechanism was vasoconstriction of the middle meningeal artery, which was consistently observed after administration and may have reduced headache symptoms by decreasing local blood flow and pressure, mitigating the effects of vasodilation-related pain. Another key mechanism involved the blockade of nociceptive transmission. Lidocaine, a sodium channel blocker, prevented the initiation and propagation of action potentials in pain-transmitting neurons. By directly delivering lidocaine into the middle meningeal artery, the drug effectively targeted nociceptive fibers in the dura mater, blocking pain perception at its source. Additionally, intra-arterial administration allowed for concentrated drug delivery at the site of action while minimizing systemic exposure and associated risks.

However, the study noted that the analgesic effects were short-lived, lasting only a few hours, highlighting the need for further investigation into dosing strategies and potential combination therapies for more sustained pain relief, such as the combination with Steroids that we are proposing. Moreover, while these findings provided valuable insight into the effect of intra-arterial lidocaine for SAH headaches, further research is needed to fully establish its efficacy and safety as a clinical intervention with appropriate control groups, as well as isolated agent groups as we are proposing.

Existing Safety Data: In North America, diagnostic cerebral angiography is the standard of care for evaluating patients with spontaneous subarachnoid hemorrhage (SAH). This procedure routinely involves catheterization of the external carotid artery (ECA) to assess the size of the superficial temporal artery (STA) for potential bypass procedures and to identify other possible causes of SAH, such as dural arteriovenous fistulas (DAVFs).

Given that ECA catheterization is a standard component of cerebral angiography, this step does not add any risks to the standard procedure. Multiple studies have demonstrated the safety and efficacy of intra-arterial lidocaine and steroid infusions for treating various headache disorders, including chronic subdural hematoma (CSDH) headaches, intractable headaches, migraines, and SAH-related pain.

One important consideration is the potential risk of seizures if lidocaine crosses the blood-brain barrier. However, this has typically been reported at doses exceeding 5–7 mg/kg (e.g., 350 mg in a 70 kg patient), which is significantly higher than our total lidocaine dose of 100 mg per patient. Given this, the doses we administer would only pose a theoretical risk for patients weighing approximately 15 kg—a scenario that does not apply in our study.

It is essential to emphasize that our procedure exclusively targets the dural branches of the external carotid artery, rather than the pial vessels supplying the brain, thereby minimizing any risk of significant intracranial leakage during injection.

Risk-Benefit Analysis: The proposed endovascular infusion of lidocaine and steroids into the middle meningeal artery (MMA) for spontaneous subarachnoid hemorrhage (sSAH)-related headaches presents several compelling advantages, aligning with the urgent need for improved pain control in this population. SAH headaches are severe, often resistant to conventional management, and driven by meningeal inflammation and trigeminal activation. A key advantage of this approach is its potential to significantly reduce opioid consumption, which remains persistently high in SAH patients despite efforts to curb overprescription. Opioids introduce numerous complications, including sedation, respiratory depression, ileus, and delirium, which complicate neurological assessments and prolong hospitalization. By providing targeted pain relief, this

intervention could mitigate opioid-related risks, improving both short- and long-term patient outcomes. Importantly, this strategy integrates seamlessly into routine SAH management without additional procedural risks. Diagnostic cerebral angiography is already the gold standard for identifying aneurysmal and non-aneurysmal SAH causes, with external carotid artery (ECA) catheterization performed in every case to assess the MMA's caliber for potential STA-MCA bypass or to rule out dural arteriovenous fistulas (DAVFs). As MMA catheterization is a routine part of SAH angiographic workups, adding lidocaine and steroids incurs no additional risk beyond the medication infusion, which has been shown to be safe in multiple studies. Furthermore, the potential to prevent the progression of acute to chronic SAH-related headaches is a major advantage, given that post-SAH headaches can persist for months or years due to ongoing meningeal inflammation and cortical spreading depression (CSD). By interrupting early inflammatory cascades, this technique may provide sustained headache relief and prevent chronic pain syndromes. Additionally, the favorable safety profile of intra-arterial lidocaine and steroids suggests broader applications in other conditions involving meningeal pain and inflammation, such as post-dural puncture headaches (PDPH), traumatic SAH, refractory cluster headaches, and post-craniotomy headaches. This intervention represents a paradigm shift in SAH pain management by providing rapid, targeted pain relief, reducing opioid dependence, integrating seamlessly into standard workflows, and potentially preventing chronic headache development, ultimately improving patient outcomes in neurovascular care.

In conclusion, we believe that the study's design is grounded in robust pathophysiological rationale, supported by existing clinical evidence, and employs rigorous randomization and statistical methodologies to evaluate the efficacy and safety of MMA infusions of lidocaine and dexamethasone for managing SAH-related headaches.

17. References

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