Gabapentin for headache in aneurysmal subarachnoid hemorrhage

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Study Title: Gabapentin for headache in aneurysmal subarachnoid hemorrhage.

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1. Abstract

Aneurysmal subarachnoid hemorrhage (aSAH) is a form of hemorrhagic stroke that affects up to 30,000 individuals per year in the United States. It is a devastating disease, with one-month mortality of approximately 40% with less than 60% of survivors regaining functional independence. All SAH patients experience the "worst headache of their life", that lasts for weeks. Narcotics along with nonsteroidal anti-inflammatory (NSAID) and steroid agents have been used in order to help reduce headache symptoms. Narcotics and steroids have serious side effects however, including potential obtundation or overdose, and gastrointestinal side effects.

We plan to use gabapentin (GBP), an FDA approved non-narcotic pain medication for neuropathic pain, which is also an alpha-2-delta (A2DR) receptor analogue to reduce the pain and decrease the need for narcotics. GBP has been shown to decrease neuropathic and non-neuropathic pain in variety of perioperative and postoperative conditions. A2DR affinity also has some neuroprotective effect in animal data. Research at Mayo Clinic has shown initial safety and tolerability of GBP for aSAH headache. We plan to conduct a prospective, double-blinded randomized trial to further assess GBP-associated reductions in narcotic use and pain scores compared to the non-GBP arm. To accomplish this aim, we plan to randomize 20 aSAH patients with headache to either GBP with standard of care pain treatment versus standard of care treatment without GBP.

Our primary aim is evaluate the efficacy of GBP in reducing the headache and narcotic requirement in aSAH compared with the non-interventional arm. We will conduct the study in Mayo clinic NeuroICU in Jacksonville, FL.

2. Specific Aims

Stroke is a leading cause of death & disability. Subarachnoid hemorrhage is 6-8% of all strokes. Aneurysmal subarachnoid hemorrhage (aSAH) is a form of hemorrhagic stroke that affects up to 30,000 individuals per year in the United States. It is a devastating disease, with mortality approaching 50% and less than 60% of survivors returning to functional independence[1]. Lifetime cost of SAH per patient is $228,030. Aggregate yearly economic burden is estimated to be $5.6 billion.[2]

Headache after aSAH is very common (97-100%), and often described as the "worst" headache imaginable[3]. Aseptic inflammation of meninges (aseptic meningitis) caused by the breakdown of blood products, aggravates head, neck and back pain [4]. SAH-headache can persist for days to weeks and is traditionally treated with narcotics. However narcotics have significant side effects and include narcotic-related ileus, constipation (20-60%), pruritus (0-30%), urinary retention (40-45%), hypoventilation, acute withdrawal syndromes during drug weaning, delirium.[5-9] Many study have shown use of high doses of narcotics causes delirium and prolongs the length of the ICU stay for up to 8 days and the length of the postoperative hospital stay for up to 24 days [8,10] On an average of 5 days added in ICU would cost US hospitals an estimated US$17, 000 among the brain injury patient.[11] ICU length of stay is among the first three areas of high cost that accounted for almost 50% of the total cost of treating patients with acute SAH [12].

Gabapentin is alpha2 delta receptor (A2DR) analogue and decrease calcium influx decreasing the neurotransmitter release. First approved for partial seizure it is usually started with low dose

and slowly titrated up to maintenance dose. Gabapentin has been used successfully to treat neuropathic pain and perioperative pain [13]. It has been shown to reduce stroke size, decrease the cortical spreading depression (CSD), which in turn can cause vasospasm and delayed ischemic neurologic deficit (DIND) [14]. Mayo Clinic Jacksonville has been using gabapentin in order to reduce the narcotic requirement and complication. In our retrospective chart review in neurocritical care ICU (NICU) from January 2011 till February 2013, study (53 patients) there was 6% nausea (intolerable in 1.9%) but no major adverse effects of gabapentin maintenance dose (1800-2700mg /day). We also found a decrease in mean use of opioids with the use of gabapentin within the first 4 days post SAH compared to after 5 days (P = 0.01) . There was no fall, dizziness and abnormal liver function associated with the use of gabapentin. Aseptic meningitis was detected with the analysis of cerebrospinal fluid (CSF) during the second half of the ICU stay. The cost of 300mg of gabapentin was average of 30 times less than intravenous fentanyl 100 mcg. We did not find any other study looking at the use of gabapentin in aSAH patients.
The plan is to conduct a randomized control trial with a total of 20 aSAH patients. 10 aSAH patients admitted in NICU will be assigned to receive gabapentin, and 10 will receive placebo. Both of the groups will receive standard of care for pain control for 7 days.

Hypothesis: "Gabapentin will reduce the pain score and narcotics requirement among hospitalized aSAH patients compared to placebo alone."

The primary specific aims and hypothesis of this study are:

1. To compare the narcotic requirements among SAH patients experiencing headache treated with gabapentin or placebo for 7 days.
2. To compare efficacy of gabapentin in reducing the headache numeric pain score (NPS) compared to the non-GBP arm among hospitalized aSAH patients. Both groups are treated by an existing standard of care algorithm with narcotics and NSAIDSs.

The secondary aims of this study are:

1. To evaluate the initial dose, escalation and side effects of gabapentin (nausea, vomiting, fall, lightheadedness, dizziness, vertigo, confusion).
2. To evaluate the incidence of delirium, vasospasm, delayed ischemic neurologic deficit (DIND) and seizure among hospitalized aSAH patients.
3. To evaluate the incidence of aseptic meningitis with cerebrospinal fluid (white blood cell and red blood cell ratio).
4. To evaluate the pain control satisfaction among patients treated with or without gabapentin.

If gabapentin reduces the pain and/or improves pain control satisfaction without major side effects it will be drug of choice for headache among patients with SAH with lower cost benefit ratio by decreasing the narcotic requirement.

3. Research Strategy a. Significance

A.1. Subarachnoid hemorrhage

Subarachnoid hemorrhage is mainly due to rupture of saccular aneurysm. This is often a devastating clinical event with mortality rates that approach 40 percent by one month, as well as substantial neurologic morbidity in SAH survivors. The lifetime cost per person of first strokes occurring in 1990 is estimated to be $228,030 for SAH. Indirect costs accounted for 58.0% of lifetime costs. Aggregate lifetime cost associated with SAH is estimated to be about $5.6 billion in the U.S. Acute-care costs incurred in the 2 years following a first stroke accounted for 45.0% of these costs, while long-term ambulatory care accounted for 35.0%, and nursing home costs

accounted for 17.5%. Inpatient hospital costs comprise the majority of first-year cost, which accounted for over 70% of first-year direct cost[1]. SAH patients also may have complicated medical and neurological hospital stay. Complications include delirium and drug-related side effects by the same medication that is routinely given to them to control their headache. GBP has been shown to reduce pain and narcotic requirements[13].Delayed cerebral ischemia (DCI) is a frequent complication of SAH that occurs in up to 33% of SAH patients, and one that contributes substantial morbidity to SAH[15]disease. The most common cause of DCI after SAH is assumed to be vasospasm [16] (VSP) Vasospasm causes symptomatic ischemia and infarction in approximately 20 to 30 percent of patients with aneurysmal SAH [17,18] the severity of symptoms depends upon the artery affected and the degree of collateral circulation. VSP typically begins after the third day after hemorrhage, and peaks around seven to eight[19] days post SAH. GBP has been shown to decrease electrical depolarization that lead to DCI in neurons called cortical spreading depression (CSD). CSD are noted to occur prior to the onset of angiographically defined vasospasm, subsequent DIND and stroke[14]. Further, acute seizures complicate SAH patients in about 6 - 18 percent of SAH patients[20]. Seizures at the onset of SAH are also an independent risk factor for subsequent seizures (ie, epilepsy) and predict poor outcome [21]. GBP is also a FDA-approved adjunctive antiepileptic drug that can potentially be additionally neuroprotective in this vulnerable patient population. Finally, the SAH breakdown of blood products causes an aseptic meningitis [22] and pain, of which GBP has FDA- label indication for neuropathic pain. The meninges are the membranes that encircle and protect the brain and are innervated by nerves themselves. Therefore, GBP is a logical medication given its pleiotropic actions on 1) reducing neuropathic headache pain, 2) reducing risk of seizures, and 3) potentially reduce the risk of CSD-mediated DIND (neuroprotective effects).

A.2.Pain

Adequate pain control is critical in reducing human suffering and a national benchmark for quality-patient care[23]. The primary symptom of aneurysmal SAH is a sudden, severe headache in 97 -100% of SAH patients. SAH headache is classically described as the "worst headache of ones life", this is followed by meningismus (neck and backache) and aseptic meningitis [24] which can mimic bacterial meningitis which causes severe pain. Aseptic meningitis is the term for sterile inflammation of the meninges, which can also be associated with fever and severe headache, neck and backache similar to bacterial meningitis. The blood leaked from aSAH causes a delayed inflammation as the body's white cells try to absorb the abnormal red cells around the meninges. We plan to utilize a numeric pain score (NPS) which range from 0-10, in which 0= no pain and 10 being the worst pain. We will calculate a daily total NPS score for each patient from nursing assessments of pain which are standard of care measurements. Only headache and neck pain will be included in the study to calculate the pain score. Pain from other causes or body parts will be excluded from analysis since our hypothesis is in assessing GBP on meningitic pain after SAH.

A.3. Gabapentin (GBP)

GBP is a structural analog of γ-aminobutyric acid (GABA) [25]. Despite GBP having structural homology to GABA there is no conclusive evidence yet that GBP blocks GABA. The history of GBP clinical use began in 1993 after FDA approval for the treatment of partial seizures and was secondarily approved for postherpetic neuralgia in 2002. GBP is also used as an effective analgesic in different types of neuropathic pain syndromes such as diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, and painful neuropathy resulting from HIV infection, cancer, fibromyalgia, and complex regional pain syndromes[26]. Meningeal irritation due to the breakdown of SAH blood products relates to the sudden onset and persistent headache after aSAH. Therefore, we hypothesize that at least one component of SAH pain is neuropathic in origin, which another component being inflammatory in nature. GBP is thought to exert its beneficial effects on neuropathic pain by binding to the α-2-delta subunit (A2DR) of voltage-dependent calcium channels. This leads to reduction of the influx of calcium into neurons

throughout the central nervous system (CNS). This in turn may decrease the release of glutamate, norepinephrine, and substance P[27]. Substance P is an inflammatory substance and invoked in central sensitization of pain pathways. Thus, GBP would seem to be a logical medication to potentially reduce narcotic requirements in SAH patients, and potentially provide neuroprotective and anti-inflammatory effects against vasospasm and DIND. The initial starting dose of GBP per FDA package insert is 100 to 300 mg at bedtime or 100 to 300 mg orally three times daily. GBP is then titrated by 100 to 300 mg every 3 to 7 days as tolerated to a maximum dose of 3600 mg per day in patients with normal kidney function. An effective maintenance dose is 1800 mg to 3600 mg per day. GBP is adjusted based on renal function and has minimal risk for drug-drug interactions and minimal hepatic metabolism. Sedation is the most common side effects with initial use, is dose-dependent (higher initial doses cause more sedation) and typically transient after the patient tolerates the dose. Elderly patients may describe worsening cognitive function in dose-dependent escalation and may pose a risk of falls if the dose is not reduced.

A.4. Opioid and Its side effects

Opioid (mu and kappa) receptors are located in the central and peripheral nervous system. Activation of mu receptors in the central nervous system results in responses such as respiratory depression, analgesia, euphoria, and miosis. Stimulation of peripheral mu opioid receptors, in smooth muscle of the bronchi and intestines, results in cough suppression and opioid-induced constipation[28]. Allergy, arrhythmias, CNS and respiratory depression, constipation, cough depression, dry mouth, histamine release, immunomodulation, myoclonus, nausea and vomiting, pruritus, rigidity, serotonin syndrome, urinary retention, and withdrawal are known side effects of opioids [29,30.] Respiratory depression is a feature common to all narcotics. Most narcotics and their metabolites accumulate in patients receiving prolonged treatment, especially those with hepatic or renal failure or both. All narcotics eventually depend upon hepatic biotransformation before renal. Commonly used synthetic opiates (fentanyl, sufentanil) are highly lipid-soluble. Therefore, the action of isolated doses of these drugs is not terminated by drug metabolism but by redistribution of the drug out of brain to other body compartments (predominately skeletal muscle) [31]. Opioid used at doses high enough to cause sedation may increase the risk of delirium. [32]. Delirium is common among hospitalized patients, particularly in the ICU setting, where it has been reported to occur in up to 70% of patients[33-34.] In the neurocritical care population, delirium occurs acutely (within the first 3–4 days) in 13–28% of patients with ischemic stroke, subarachnoid hemorrhage or intracerebral hemorrhage [35].Delirium can cause devastating consequences. In a prospective study of ICH, SAH, and ischemic stroke patients, 76% of patients with delirium had moderate disability or death (modified Rankin Score 3-6) compared to 33% of those without delirium. [36]

A.5. Rationale of Gabapentin Use

Abdel et al has shown GBP exerted anti-nociceptive (ie., anti-pain) effects to thermal and electrical hypersensensitivity and additional gastric-protective effects[26]. The A2DR receptor effect also has potential for possible neuroprotection against delayed cerebral ischemia (DCI) after SAH. Regarding its pain-reducing effects, the 2013 Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit has recommended enterally administered GBP, in addition to IV opioids, for treatment of neuropathic pain (+1A) [37]. A randomized, double-blinded, placebo-controlled, crossover study in 18 Guillain-Barre Syndrome (GBS) patients treated with GBP showed decreased numeric pain score, decreased need of fentanyl, minimal sedation and rapid titration of GBP is safe[38]. GBP has been used and shown helpful in nonneuropathic pain and especially in anesthesia during perioperative period and has been shown to reduces analgesic, particularly opiate, consumption and associated adverse effects. Patients benefited from GBP's anxiolytic, anti-emetic, and antipruritic effects[39]. The meta-analysis of 12 randomized controlled trials done on GBP uses in perioperative surgical patients by Hurley RW et al showed significantly less pooled VAS among

GBP patients. Decrease in opioid usage GBP group (odds ratio [OR] = -17.84; CI, -23.50 to -12.18). GBP was associated with sedation and anxiolysis (OR = 3.28; CI, 1.21-8.87) but not lightheadedness, dizziness, nausea, or vomiting[40]. Also as mentioned above, GBP has FDA-adjunctive approval for seizures and reduces the seizure threshold, of which SAH patients are particularly vulnerable.

B. Innovation

In the present study, we are proposing to use GBP among aSAH headache that are able to verbalize their numeric pain score while they admitted in a neuro intensive care unit. Our study is directly inspired by the previous study of GBP in perioperative and neuropathic pain. To date GBP use in aSAH has not been published. This research would be a landmark study exploring the use of GBP in aSAH headache in a prospective fashion. If GBP reduces the SAH-mediated neuropathic and inflammatory pain without major side effects, it could lead to an orphan-drug development extra-murally funded NIH (RO1) or NINDS-funded award to study this drug since SAH disease occurs less than 200,000 cases per year. Therefore, this study would provide pivotal prospective safety and tolerability data as well as some exploratory data on its neuroprotective effects (albeit underpowered). The potential of this study is that if our hypothesis is confirmed that GBP reduces narcotic requirements after SAH, it may become (under FDA-IND development or orphan drug funding) the drug of choice this disease. Further, if the study is positive in terms of its findings for reduced pain and/or neuroprotective effects, this could lead to further drug-discovery for the use of GBP or similar drug design for neuroprotection.

C. Approach

C.1. Preliminary Studies

C.1.a. Subarachnoid Research: Mayo Clinic Florida (MCF) is a high-volume SAH referral center with an average of about 90 SAH patients a year making this an ideal study population and site to conduct the research study. MCF has a prospective cerebrovascular database of SAH patients that is kept by 3 full -time Neuroscience research coordinators. MCF would be an ideal place to start the GBP study since our center has an existing IRB approval and retrospective study that has shown safety and tolerability of this agent as part of standard management (IRB 13-003673) [41].The purpose of this study is to provide more prospective scientific study to see if the results fit the retrospective data, and possibly help with a larger extra-murally funded trial examining this drug. MCF has a team of experienced neurologists, and intensivists, as well as research coordinator in order to conduct this project. Other trials conducted at MCF in the NeuroICU include CLEAR3 (NCT00784134), ATACH2 (NCT01176565) that are NIH/NINDS funded national/international trials. Dr. Freeman as the mentor of this study has extensive clinical experience in SAH patients, and has significant research experience in SAH and neurocritical care. He has served as site principal investigator of the aforementioned multicenter research trials at MCF, and is a productive mentor with mentees being academically productive with research abstracts and full-length publications. Dr. Freeman also holds a FDA-investigational new drug (IND) for nicardipine for SAH, and has experience with this process with the FDA. Similarly Dr. Meschia has been involved in multiple NIH/NINDS. He have received CREST-2, The National Institute of Neurological Disorders and Stroke which will begin enrolling 2,480 patients in 120 centers in the United States and Canada with carotid disease.

C.1.b. Gabapentin for headache in SAH Research: Our research group at MCF conducted a retrospective study of a consecutive series of SAH patient from January 2011 till February of 2013 in the neurointensive care unit [41]. The study had 53 aSAH patients who were treated with GBP along with standard of care analgesics, NSAIDs and sometimes dexamethasone for severe headache. Severe headache was observed in all aSAH patients, with average maximal

intensity on day 5 of aSAH. GBP dosing was rapidly escalated within days of SAH up to a median of 1200 mg/day, with a range of 300 mg three times a day to 900 mg three times a day which was overall well-tolerated. Approximately 6% of patients treated with GBP had nausea (95% CI, 1-16%) that is also associated with SAH disease. Only 1 patient (1.8%) had to discontinue GBP due to nausea and vomiting. GBP dose was rapidly weaned similar to its tiered dose escalation or stopped after discharge in most of the patients. There were no major reported GBP withdrawal side effects such as seizure. However approximately, 4 patients had return of headaches observed after they weaned off the medication within a 30 day period in which case, GBP was resumed until headaches resolved. In 2 of these cases GBP was used for their outpatient management of baseline migraines or postoperative craniotomy headaches. In the Mayo Clinic study, visual analog scale (VAS) was used which is similar to NPS and was charted on a daily basis to document pain severity. VAS in these patients showed a slow rise from day one of aSAH until a maximum intensity around day 5. Two different peaks on day 11 and day 16 after aSAH were also noted subsequently. These peaks in VAS score also interestingly correlated with high CSF WBC/ RBC ratio and there were no culture proven bacterial or viral infection. This data suggests the inflammatory delayed headache pathophysiology of SAH headache and separate from the initial headache onset. These headaches also were more responsive to corticosteroids apparently since steroid use for breakthrough pain was noted during this time period. This data provides important insight that this period of time of post-SAH headache and meningismus may be a form or inflammatory or steroid- responsive aseptic meningitis.
Overall, the Mayo Clinic study demonstrated that GBP is safe and tolerable in aSAH patients with headache. No major adverse events (AE) were noted. A small portion of patients reported nausea that is inherent to SAH disease, and was managed conservatively with typical anti-nausea medications and did not require GBP discontinuation. The escalation of GBP in this population also appeared feasible and without major side effects. We saw decrease trends in use of opioid and steroids requirements with upward titrated and therapeutic doses of GBP.

C.2. Current Proposal Overview

This study will be a randomized, placebo-controlled clinical trial enrolling 20 subjects at MCF to either GBP + standard of care (SOC) vs placebo + SOC arm. While enrolling the patients we will stratify patients via numerical pain score (NPS) to either <5 or ≥ 5. Patients with an NPS ≥5 will be randomly assigned to either GBP or placebo group within 72 hours of SAH admission and after informed consent. The SOC pain regimen is comprised of intravenous (IV) fentanyl 25mcg to 50mcg q1hr PRN for head and neck pain as the first-line agent. If SAH pain remains >5 on NPS after the next nursing pain assessment, the next tier of pain agents will be utilized consisting of the following tier:
2nd line- enteral /PO oxycodone 5mg PRN q4hrs pain, and if still in pain after next assessment, then 10mg q4hrs PRN,
3rd line (if 2nd line failed to reduce NPS < 5)- IV 15mg ketorolac q6hrs PRN x 24hrs, unless serum creatinine > 1.3, or GFR < 30, or concern for gastrointestinal bleed risk, or history of bleeding peptic ulcer.
4th line (if 3rd line failed to reduce NPS < 5)- dexamethasone 2mg IV BID x 24hrs.
The patient will be enrolled within 72 hours of admission and meeting inclusion criteria by investigator and coinvestigators. Documentation of numeric pain score will be done by standard of care per nursing and hospital policies in the medical record. After consent and enrollment, a data collection sheet will be recorded by nursing to summate the NPS scores every 24 hours along with the SOC pain management plan. The SOC pain management plan will be implemented by the NeuroICU team of residents, attending, and nurse practitioners/PA's who are available on a 24/7 basis. A decrease in pain score equal or more than 50% will be defined as meeting the goal of the study, and as headache pain being under control. Patients will begin study medication (gabapentin or placebo) at approximately 9:00 AM on the morning following randomization into the trial to allow for documentation of the baseline average NPS. The

baseline NPS will be used to determine if the patient has had a 50% or more decrease in pain score.
In patients with a normal creatinine clearance (CrCl) ≥ 60 ml/min the study medication will be started at 100 mg three times a day and if headache is not controlled by study day #2, it will be increased to 300mg three times a day. For headaches that are still not controlled by day 3, study medication will be increased to 600 mg three times a day and by day 4, 900 mg three times a day. For the purposes of this study, a maximal dose of 900 mg tid in patients with normal kidney function (2700mg/day) even though the package insert describes 3600mg/day as maximal. For patients with a CrCl of 30 -59 ml/min, we will use an initial dose of 100mg tid day #1, then 200 mg tid by day #2 if pain uncontrolled, and 400mg tid if by day #3 if pain still uncontrolled. This dose of 1200mg/day would be the maximal dose used for these patients if CrCl remains within the 30-59ml/min range. We will exclude any patients who have CrCl <30 ml/min. When patients have achieved a 50% reduction of NPS, this will be defined as the maintenance dose and no escalation of GBP will be done after that, unless there is headache worsening. Placebo pills will be given three times a day and SOC pain management performed as indicated above in the control arm. The pharmacist or nurse will dispense the study drug. The bedside nurse will record the numeric pain score (NPS) 0-10, 0 being no pain and 10 being worst pain every 4 hours per hospital policy but done on a bedside data collection form as well for the purposes of the study. Total score over 24 hours will be averaged as daily score. Decision to increase the GBP will be based on 24 hour score communicated by the treating team as part of morning rounds by calling the central pharmacy.
After the 7 day study period, patients will be unblinded to either arm and those on gabapentin may remain on the medication if pain is controlled. However patients in the placebo arm-- if still in pain-- after 7 days may be treated with gabapentin up-titration similar to the treatment arm but used as standard of care. Patient's pain scores will also be recorded after the 7 day randomized period for observational purposes to examine for crossover effect (the proportion of those within the placebo arm who are placed on gabapentin). Analysis of these groups will be based on intention to treat principle.

C.3. Participants

Inclusion Criteria:
1. .18 years of age or older
2. Have aneurysmal SAH diagnosed by CT scan of the brain and/or angiogram evidence of intracranial aneurysm (CTA or digital subtraction angiogram or MRA)
3. Have symptomatic headache
4. Able to swallow and verbalize pain score
5. No known allergy to GBP or fentanyl
6. Numeric pain score ≥5
7. Ability to provide written personal consent

Exclusion Criteria:
1. GBP use prior to SAH admission
2. Renal failure with creatinine clearance less than 30 ml/min
3. Unable to receive standard of care pain medications
4. Pregnant patients
5. History of severe depression defined by DSM IV

C.4. Study Procedures & Schedule
All study medication will be labeled and dispensed according to subject number ensuring that treatment assignment remains concealed to the subject, investigator, and all study personnel who have subject contact. Data collection will be done in case report form at the bedside and

later will be enter in spread sheet. We will issue unique ID for each study patients. 20 preprinted study ID labels will be used to randomly select study patients.
Subject selection: All aneurysmal SAH admitted will be screened by the Mayo Cerebrovascular laboratory for eligibility and the NeuroICU attending and/or fellow will be contacted about potential enrollment in the study. Subjects who are able to provide written consent will be approached for enrollment. Based on prior volumes, we expect to have 20 subjects enrolled within 6-9 months.
Pain assessment: We will use numeric pain scale (NPS) that is been validated in many studies and is easy to use. Nurse and medical staff are familiar with this scale in our institute as it has been commonly used as standard of care. We plan to perform this pain scale every 4 hours in the study patients. The scale range from 0-10, 0 being the no pain and 10 being the worst pain ever. We will calculate daily total score for each patient. Only headache and neck pain will be included in the study to calculate the pain score. We will not include the score for other pain like back and abdominal pain.
Narcotic Requirement: We will use intravenous fentanyl as a pain medication. The dose range of fentanyl will be from 25 micrograms to 50 micrograms, which could be repeated hourly. Total daily requirement of fentanyl for head and neck pain will be calculated every day. The side effects of the fentanyl will be prospectively charted. We plan to use subsequent line of pain management as describe in the text above if not controlled by fentanyl or have side effects with it.
Laboratory variables: Whenever cerebrospinal fluid (CSF) is collected by standard of care via an external ventricular drain or lumbar specimen. We will review this data for white blood cell (WBC), red blood cell (RBC) counts, as well as the CSF WBC/RBC ratio and culture and sensitivity. We will also review values of kidney function (creatinine and BUN), in the medical record performed as standard of care by the treating team.
Radiological variables: We will review patient CT or CT angiography done by standard of care by the treating team. We plan to get SAH severity using the Fisher grade, aneurysm location, follow up CT angiography and/ or transcranial Doppler for detection of vasospasm.
Aseptic Meningitis Screening: In order to screen that meningitic pain after aSAH was not due to from frank bacterial (septic) meningitis, CSF data will be reviewed from existing external ventricular drain (EVD) or CSF samples especially when there is fever and headaches documented in the electronic health record. The CSF culture result will also be analyzed to rule out any bacterial meningitis or ventriculitis. When CSF WBC is elevated and culture is negative for microorganisms, with persisting headache, these groups will be defined as 'aseptic' or inflammatory meningitis. Any patient who develops bacterial meningitis will be excluded from final headache analysis since the pathology will be different. The incidence of bacterial meningitis in SAH patients with EVD is < 1.0% and unlikely given the small sample size of this study. Also GBP medication is not expected to in any way increase the risk of bacterial meningitis based on our retrospective study and existing FDA safety data on GBP.
Vasospasm detection and treatment: We will review the presence or absence of vasospasm (VSP) based on transcranial Doppler (TCD) mean flow velocity (MFV) of the middle cerebral artery, which is done by standard of care to monitor for this condition. VSP will be graded as mild to moderate based on MFV between 120 - 199 cm/s and/or a hemispheric ratio of carotid to MCA MFV (i.e., Lindegaard ratio ≥ 3.0). Severe VSP will be classified as MFV ≥ 200 and/or a Lindegaard ratio ≥ 6.0.[42] CT angiography data will be also reviewed for the presence or absence of VSP and defined as mild, moderate or severe by the neuroradiologist attendings report. We will review the treatment received for VSP including induced hypertension, intrathecal nicardipine, intraarterial verapamil, or balloon angioplasty. DCI will be defined as cerebral infarction identified on CT or MRI after exclusion of procedure-related or other etiologic vascular infarctions [43].
Gabapentin dosing evaluation and side effects: A thorough daily documentation of GBP vs. placebo will be done for each patient including side effects and tolerability and safety. Full table of adverse event and side effects is listed in Table 2 at Appendix. We will follow NIH AE

classification for reporting these events in both groups. The total daily dose of GBP will be tabulated in each patient for every hospital day. Laboratory values will be reviewed for any abnormality in hepatic or renal function while receiving these drugs.
Patient pain satisfaction score: We will use modified Brigham and Women's Hospital Management of Post-operative Pain Patients discharge questionnaire (Table 3 Appendix). This test has average of the test-retest reliability r = .86, with a range of coefficients from .76 to .92. Interexaminer reliability of r = .98[44]. We plan to use this score at day 7 after completion of primary endpoint of our study. This will be conducted by study investigators or trained nurse, prior to unblinding the patient.

C.5. Medication Intervention: Gabapentin
Gabapentin escalation dosing will be modeled after our retrospective safety study. We will start with 100 mg orally three times a day then every 24 hours increase to 300 mg tid as tolerated, then 600 mg tid and to a maximum of 900 mg tid. We plan to use 100mg tid then 200 mg tid and 400mg tid if creatinine clearance of 30 -59. We will exclude any patients who have CrCl <30. We will define maintenance dose of GBP as a dose in which after being on it for 24 hours there is 50% reduction of daily average NPS. We will continue maintenance dose throughout hospital stay. aSAH patients will be in observation in NICU for median of 15 days. The placebo will be escalated in the same manner as GBP. A Mayo pharmacist would dispense the study drug (ie., GBP or placebo). Every patients discharged with aSAH will be followed by Mayo neurologist as a SOC and they will plan to reduce or stop GBP.

C.6. Data Analysis
Unless otherwise specified, analyses will be performed using an intention-to-treat approach whereby subjects are analyzed according to randomized treatment arm. The primary endpoint for this trial will be the 7 days of treatment with or without GBP and best medical therapy. For this endpoint the treatment groups will be compared using a two-tailed test with a p-value ≤ 0.05.
Categorical variables will be summarized as percentages, and continuous factors will be described using means or medians to best describe the distributions. Adverse events will be described as rates, and 95% confidence intervals estimated for those rates. The calculated total daily NPS score; opioid requirement and GBP dose will be analyzed. CSF WBC/RBC ratio will be calculated from the available sample and trended on days of SAH. All the plotted data will be projected with a 95% confidence interval.
We will compare the NPS, patient satisfaction score and the fentanyl requirement among the GBP and placebo group. We will use 2 sample t test or Wilcoxon rank sum test. The data will be analyzed to see if there is difference in incidence of aseptic meningitis, vasospasm and DIND between the GBP and placebo group. If there is difference more than 5 %, we will use regression modeling to analyze the data.

C.7. Sample Size Considerations
The null hypothesis is that there is less than a 25 % difference between the NPS daily score and patient satisfaction score between GBP and placebo group. For sample-size purposes, we assume that the mean percentage difference will be 25%. From our retrospective study we have found the standard deviation of pain score was 5.84. Assuming alpha is kept at 0.05 and power at 80 %, the sample size is less than 10. We propose to get 10 in each arm with total of 20 patients.

4. Literature Cited

Reference

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Appendix 1

Table 1.Gabapentin Dosage based on Renal function

Renal function Creatinine Clearance (mL/min)	Maximum Total Daily Dose (mg/day)
≥60	2700
>30–59	1200

Table 2. Side effects and adverse effects

Systems	Side/ Adverse effects GBP group.	Side/ Adverse effects Placebo group	Comments / Measures taken
Body as whole			
Fatigue			
Weight Increase			
Back Pain			
Peripheral Edema			
Digestive System			
Dyspepsia/Nausea			
Vomiting			
Nervous System			
Suicide/ Depression			
Somnolence			
Dizziness			
Ataxia			
Nystagmus			
Tremor			
Dysarthria			
Skin and Appendages			
Rash			

Table 3 Modified Brigham and Women's Hospital Pain management Satisfaction Score
Name:
Study ID:
MRN:

A. Questions	0 No pain	1 Mild pain	2 Moderate	3 Severe	4 Very Severe	5 Unbearable	Comments
1.How much pain do you have right now ?							
2. How much pain have you had in past 24 hrs.							
B. Questions	1 Strongly agree	2 Agree	3 Neutral	4 Disagree	5 Strongly disagree	Comments	
1.I am satisfied with the way the nurse and physician treated my pain.							
2. I am dissatisfied with the care I received during my hospitalization.							
3. The physician and nurse were concerned with how much pain I might be experiencing.							
C. Questions	0 Not at all	1 Barely	3 Slightly	4 Moderately	5 Quite a bit	6 Extremely	
1. How helpful were the medication and other treatments in relieving your pain.							