STUDY PROTOCOL

Title:	Occipital Nerve Blocks for Acute Treatment of Pediatric Migraine
Short Title	Occipital Blocks for Acute Migraine
Drug or Device Name(s):	Occipital Nerve Block with Lidocaine vs Saline Injection after Lidocaine Cream run-in
FDA IND	N/A
Regulatory Sponsor:	National Institutes of Neurological Disorders & Stroke (NINDS)
eIRB Number	18-014939
Protocol Date:	April 20, 2018

Amendment 1 Date: July 23, 2018	Amendment 2 Date: October 04, 2018
Amendment 3 Date: March 25, 2019	Amendment 4 Date: April 16, 2019
Amendment 5 Date: January 22, 2021	Amendment 6 Date: October 18, 2021
Amendment 7 Date: July 29, 2022	

Sponsor: NINDS

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ABBREVIATIONS AND DEFINITIONS OF TERMS

°C	Degrees centigrade
AE	Adverse event
GON	Greater Occipital Nerve
CHOP	Children's Hospital of Philadelphia
VAS	Visual Analog Scale
PNB	Peripheral Nerve Blocks
IV	Intravenous
ATN	Auriculotemporal Nerve
STN	Supratrochlear Nerve
SON	Supraorbital Nerve
LON	Lesser Occipital Nerve
PedMIDAS	Pediatric Migraine Disability Assessment
PROMIS	Patient-Reported Outcomes Measurement Information System

ABSTRACT

Context:

Migraine is a common and disabling headache disorder in children and adolescents, yet few treatment options are available, and these are often ineffective. More invasive treatments such as nerve blocks could be helpful, but must be tested with a trial design which addresses known challenges.

Objectives:

1. To test the efficacy of lidocaine vs saline greater occipital nerve (GON) injections to treat pediatric acute migraine.
2. To test whether lidocaine cream leads to successful blinding of injected medication.
3. To characterize how perceived treatment affects expectation of benefit, and how expectation affects change in pain score.

Study Design: Randomized controlled trial

Setting/Participants: Up to 97 subjects, ages 7 to 21, will be recruited from CHOP Neurology, Emergency Department and referrals. Patients with a diagnosis of episodic or chronic migraine who require escalation of care for acute headache flare (lasting up to 3 months and unresponsive to acute medications) will later be offered an outpatient study visit (if eligible). One parent or guardian per child/adolescent will also be enrolled in the study.

Study Interventions and Measures:

Lidocaine cream will be applied over subjects' bilateral greater occipital nerves (GON). After about 30 minutes, subjects who continue to have significant headache will proceed to randomized, blinded injections of lidocaine or saline over the bilateral GON. The primary outcome will be difference in mean change in pain score (pre- to ~ 30 minutes post-injection) between injection groups.

PROTOCOL SYNOPSIS

Study Title	Occipital Nerve Blocks for Acute Treatment of Pediatric Migraine
Funder	NINDS
Clinical Phase	Phase 3
Study Rationale	• Migraine affects 10-28% of children and adolescents, yet 20-30% of patients are ineffectively treated with current oral and nasal options. • Peripheral nerve blocks (PNBs), injections of local anesthetics over branches of the occipital and/or trigeminal nerves, have been associated with possible benefit for pediatric headaches in case series, and may be useful for both acute and preventive treatment of migraine for children who fail less invasive treatments. PNBs are used by 80% of pediatric headache specialists and carry low risk of serious side effects, but have never been formally tested in a randomized pediatric trial. • There are two substantial hurdles which must be overcome in designing a trial to test the efficacy of PNBs – high placebo response rate and possible unblinding. • In order to test the efficacy of this commonly used treatment for children and adolescents with difficult-to-treat headache, we need utilize a trial design which will address the high placebo response rate and the potential lack of blinding. • This study will examine the efficacy of the most commonly used PNB, greater occipital nerve (GON) blocks, as an acute treatment for pediatric migraine using a run-in study design, starting with lidocaine cream and proceeding to randomized injection only for subjects who are not pain free. Lidocaine cream is an appropriate run-in step because it is non-invasive, has some evidence of efficacy as a headache treatment, and causes superficial numbness which should facilitate blinding to the injection medication.
Study Objective(s)	**Primary** • To test the efficacy of lidocaine vs saline GON injections to treat pediatric acute migraine. **Secondary** • To test whether lidocaine cream leads to successful blinding of saline versus lidocaine injection • To characterize how perceived treatment affects expectation of benefit, and how expectation affects change in pain score.
Test Article(s)	Occipital nerve block performed with 2% lidocaine

Study Design	Randomized, double-blind greater occipital nerve injection of lidocaine versus saline after open-label lidocaine cream run-in
Subject Population key criteria for Inclusion and Exclusion:	**Inclusion Criteria** **Childrens/adolescents** 1. Subjects, ages 7 - 21, any gender, race, or ethnicity 2. Diagnosis of episodic or chronic migraine with an acute headache flare lasting up to 3 months and unresponsive to medications 3. Informed parental consent and subject assent **Parents or Guardians** 1. Parents or guardians of children enrolled, who speak either English or Spanish, and provide parental/guardian permission (informed consent) for their participation 2. Subject (child) assent **Exclusion Criteria** **Childrens/adolescent** 1. Subjects who have previously received a nerve block less than 3 months ago or more than 2 previous nerve blocks 2. Allergy to local anesthetics 3. Skull defect **Parents or Guardians** 1. Parents or guardians of children enrolled who do not speak English or Spanish 2. Parental/guardian permission and/or subject (child) assent has been declined 3. Parents/guardians, who in the opinion of the investigator, may be non-compliant or unable to complete the questionnaires
Number Of Subjects	Anticipating that up to 42% of subjects will respond to the lidocaine cream run-in, in order to achieve the goal of 29 subjects per injection arm who receive the randomized nerve block intervention, up to 97 subjects will be enrolled in the study. One parent or guardian per child/adolescent will also be enrolled in the study. This will be a single site study at CHOP.
Study Duration	Each subject's participation will last 29 days. The entire study is expected to last 3.5 years.
Study Phases	

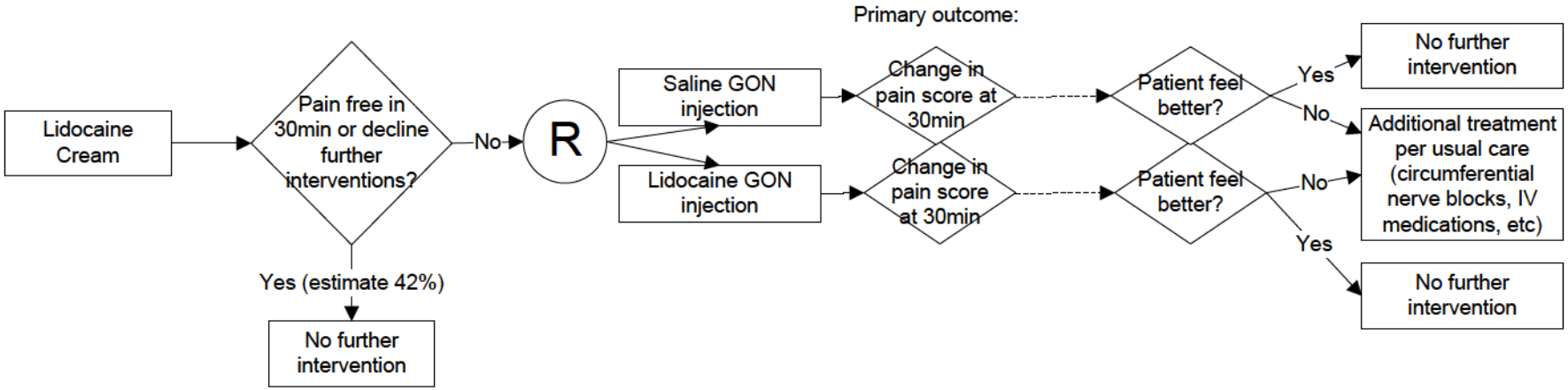
Screening **Study Treatment** **Follow-Up**	(1) Screening: Initial screening will be done on the phone (after obtaining verbal consent), which will be as soon as possible. Eligibility criteria will be further confirmed and consent obtained at the in-person study visit. (2) Intervention: Study visit will be done on a single day. (3) Follow-up will be via text messaging/phone call for an additional 28 days.
Efficacy Evaluations	The study is powered to detect a 2-point difference in the mean change in pain score (immediately pre- to ~ 30 minutes post-injection) between the lidocaine and saline injection groups.
Safety Evaluations	Lidocaine and saline are both widely used medications for injection. Several case series of injection procedures for headache in children and adults have been published, and none have reported serious adverse events (SAEs). However, minor side effects including injection-related pain are a significant concern for children and adolescents, so these will be recorded.
Statistical And Analytic Plan	The average drop in pain score in our retrospective study of nerve blocks in children with acute flare of both episodic and chronic migraine was 4 points (pre- to post-injection, on a numeric 0-10 scale). Given that the minimal clinically significant change in pain score across multiple chronic pain conditions is 2 points[40], we will estimate that the saline injection group will drop an average of 4-2 = 2 points. Assuming that lidocaine injections lead to a mean change of 4 points, and saline injections lead to a mean change of 2 points, with a standard deviation of 2.7, with α=0.05 and β=0.8, we will need to 29 subjects per injection arm to demonstrate efficacy using an unpaired t-test.
DATA AND SAFETY MONITORING PLAN	An Independent Medical Monitor will review enrollment, protocol deviations, and adverse events about every 6 months, and as needed if any serious adverse events (SAEs) occur. These will also be reported to the CHOP IRB per usual protocol.

TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	Screening (Telephone)	Screening/Intervention	Follow-up		
Visit Number		**1**			
Study Days	**~ -3**	**0**	**1 - 6**	**7**	**8 - 28**
Informed Consent / Assent (Main Study)		X			
Informed Consent (Screening)	X				
Review Inclusion / Exclusion Criteria	X	X			
Demographics / Medical History	X	X			
Physical Examination		X			
Neurological Examination (including a fundoscopic exam)		X			
Vital Signs: BP, HR		X			
Height, Weight, Head Circumference		X			
Pregnancy Test		X			
Prior/Concomitant Medications		X			
Study Interventions: Lidocaine Cream and Randomized Nerve Block Injections		X			
Adverse Event Assessment		X	X	X	X
Headache Diary (pain, nausea, photophobia, etc)			X	X	X
PedMIDAS		X			X[1]
PROMIS Pain Interference		X		X	X[1]
Patient Global Impression of Change		X	X		X

[1] Day 28 only

FIGURE 1: STUDY DIAGRAM[2]



[2] The randomized notation (R) refers to subjects proceeding to **receive** the randomized nerve block injection. This does not represent the act of carrying out the Randomization step in RedCap. This operation takes place immediately after the study team has obtained informed consent for the Main Study.

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Relevant Literature and Data

Migraine Prevalence & Disability
Migraine is the second leading cause of disability worldwide according to the Global Burden of Disease Study 2016[1]. The prevalence of migraine within the pediatric population is a function of age, increasing from 10.6% of children ages 5-15 years to 28% of adolescents ages 15-19[2, 3]. Children with migraine miss more school than their peers[4], and have impaired quality of life, similar to that of children with rheumatoid arthritis or cancer[5]. In addition to the problems of disability in childhood, up to three-quarters of children with migraine will continue to have symptoms into adulthood [6-8].

Migraine Treatment & Lessons from Prior Trials
To mitigate this disability we need acute treatments which can stop headache flares, and preventive treatments which can control the frequency and severity of headaches. While several treatments have level A evidence of benefit in the acute and preventive treatment of episodic migraine in adults[9-11], evidence is lacking for children. Though the rate of response to active therapy in pediatric and adult trials has been similar (60-85%), the high pediatric placebo group response (50-60%) makes it difficult to prove a significant difference in this age group[12-14]. Approximately 30 randomized trials have been performed to evaluate the effect of acute migraine treatments in children[15]. After several failed studies with parallel design, triptan studies which utilized crossover design and placebo challenge prior to randomization[16-18] demonstrated a significant differential between placebo and active treatments[19]. Utilizing a run-in treatment prior to randomization is appealing because that treatment, whether placebo or active, could be one with low risk of side effects, thus exposing children/adolescents to the higher risk experimental treatment only if needed. Taken together, an ideal trial design would enable demonstration of benefit in those with difficult-to-treat headache, and would also utilize lower risk interventions for those who are easily treated.

Nerve blocks
Peripheral nerve blocks (PNBs), in which local anesthetic medications are injected over branches of the occipital and trigeminal nerves, may be effective in refractory headache[20]. Retrospective, uncontrolled pediatric case series have described benefit from PNBs as both acute and preventive treatment for chronic migraine and post-traumatic headache[21-23]. *Our own retrospective study of nerve blocks, in which injections were tailored to the individual response of teenagers with headaches unresponsive to prior treatments, found that 86% of those with acute headache flare had at least transient improvement in pain severity* [24]. Despite the lack of controlled trials, nerve blocks are used commonly among pediatric headache specialists. Our recent survey of the Pediatric & Adolescent Section of the American Headache Society found that 80% of respondents either perform or refer patients for PNBs[25]. Consistent with the variability demonstrated in adult headache care[26], PNBs are used for multiple different headache conditions in children, and there is wide variability in the medication used, site(s) injected, and use of repeated injections[12]. Respondents expressed interest in conducting a multi-site trial to determine efficacy and clarify injection technique. The studies in this proposal will utilize the run-in design which was effective for triptan studies to study nerve blocks. Our primary objective is to determine the efficacy of occipital nerve blocks for the treatment of acute migraine unresponsive to prior therapies.

Blinding

Saline injections will be used as the comparator to lidocaine injections in this study. However, lidocaine injections cause immediate pain followed by local numbness, whereas saline injections do not cause local numbness. This difference may have caused unblinding in some of the adult nerve block trials, which could explain their contradictory outcomes[27-30]. Local anesthetic cream should maintain blinding, since these creams cause local numbness, and one has been shown to decrease the pain of lumbar puncture[31]. Bang's blinding index will be used because it permits assessment of blinding of each treatment arm separately[32]. A secondary objective is to assess whether lidocaine cream can blind subjects to lidocaine versus saline injection.

Subject characteristics which affect placebo group response

In planning future trials of nerve blocks and other treatments, it will be helpful to know patient characteristics which predict response. Post-hoc analyses of data from efficacy trials in pediatric migraine have shown that characteristics such as age, sex, and natural history of disease do not consistently affect response to treatment[5, 12-15]. Neurobehavioral characteristics such as expectation of benefit may play a role. A study of correctly and incorrectly labeled rizatriptan and placebo for acute migraine treatment in adults demonstrated differential pain freedom response to rizatriptan but not placebo based on labeling, indicating importance of both treatment and expectation of benefit[33]. In contrast, scripted language designed to alter expectation of benefit did not influence response to intravenous saline in children with migraine in the emergency department[34]. We will measure expectation of benefit using a modified version of the Stanford Expectations of Treatment Scale, a 6-item scale measuring positive and negative treatment expectancies[35]. To accomplish our secondary objectives, we will examine how expectation is affected by perceived treatment, and how it influences outcome in pediatric and adolescent acute migraine.

In conclusion, in these studies we will test the efficacy of occipital nerve blocks utilizing a run-in design. We will simultaneously test whether lidocaine cream will blind subjects to injected medication, and examine the relationship between perceived treatment, expectation, and outcome.

1.2 Name and Description of Investigational Product or Intervention

Randomized Occipital Nerve Block with injection of 2% Lidocaine vs Saline

1.3 Findings from Clinical Studies

1.3.1.1 Human Pharmacokinetics

Onset of Action of Lidocaine:

-Cream 3-5 minutes, with recommended 30 minute application time[36, 37]

-Injection 1-5 minutes[36, 38]

Duration of Action:

-Cream: 60min after removal[37]

-Intradermal Injection: 10-200 minutes[36, 39]

Dose: Total amount of lidocaine (combined cream and injection) used should not exceed 4.5mg/kg, max 300mg[36]

1.3.1.2 Clinical Studies in Adults

Nerve blocks can be used as an acute headache treatment, and repeated nerve blocks may also be used for preventive headache treatment. Nerve blocks have been described in the treatment of many headache types in adults including Migraine, Cluster headache, Chronic Daily Headache (including Chronic Migraine), Hemicrania Continua, Cervicogenic Headache, Post-Traumatic Headache, Post-Dural Puncture Headache, and Cranial Neuralgias[38]. Greater occipital nerve injections have been studied most commonly, but the lesser occipital nerve and several branches of the trigeminal nerve (auriculotemporal, supraorbital, supratrochlear) are sometimes included[26].

1.3.1.3 Clinical Studies in Children

Retrospective, uncontrolled pediatric case series have described benefit from PNBs as treatment for chronic migraine and post-traumatic headache[21-23]. Our own retrospective study of nerve blocks, in which injections were tailored to the individual response of teenagers with headaches unresponsive to prior treatments, found that 86% of those with acute headache flare had at least transient improvement in pain severity [24].

Both the literature, and the experience of the Headache Program clinicians who have performed hundreds of nerve block procedures over the past few years have demonstrated excellent safety. In our retrospective study, 19.5% of subjects experienced minor side effects with first nerve block[24]. Side effects, typically mild (grade 1 and grade 2), fall into three main groups – pain, numbness, and anxiety:

> *Pain*: Injection-related discomfort is relatively common, but very brief in duration. Clinically, headache clinicians sometimes use lidocaine cream or ice to try to reduce this immediate discomfort, and that experience contributed to the study design here. Injection site discomfort after the procedure occurred in ~8% of subjects in our retrospective study. In most cases no intervention is required for this. If intervention is required, it is usually limited to use of topical ice at the site, and/or use of an anti-inflammatory medication such as ibuprofen. While rare patients from our clinic have been hospitalized after nerve block, they have been hospitalized for escalation of headache treatment because the nerve block was ineffective in preventing the hospitalization, not because it was causative.
>
> *Numbness*: Many patients do report altered sensorium, including feelings of numbness. This resolves with time. Very rarely patients who are numb develop dizziness. In these cases the patients are observed until they are able to ambulate safely.
>
> *Anxiety*: Feelings of both anxiety and giddiness are common, likely related to anxiety and relief from anxiety associated with the procedure. Panic attacks and syncope related to procedural anxiety are very rare (1 case of syncope in our retrospective study of 125 first nerve blocks[24]), and resolve with cessation of procedures, time, and reassurance.

Despite the lack of controlled trials, nerve blocks are used commonly among pediatric headache specialists. Our recent survey of the Pediatric & Adolescent Section of the American Headache Society found that 80% of respondents either perform or refer patients for PNBs[25]. However, health insurance does not always cover nerve blocks because they are considered experimental due to the absence of controlled trials in children and adolescents. The study described here will address that gap of knowledge.

1.4 Selection of Drugs and Dosages

Lead-in lidocaine 4% cream:

Selection of Drug: Lidocaine cream is an appropriate run-in step. It is non-invasive, has some evidence of efficacy as a headache treatment, and causes superficial numbness which should decrease injection-related discomfort and facilitate blinding to the injection medication. A small study of lidocaine cream as treatment for migraine headache demonstrated that 7 of 30 subjects (23%, 95% CI 9-42%) were pain-free at 2 hours[40, 41], and lidocaine cream has been used to reduce the pain of nerve block injections[42]. Lidocaine cream has a fast onset of action, can be used on hairy skin, and does not require occlusion with an airtight dressing. Furthermore, lidocaine cream causes numbness, which should mimic the local numbness caused by lidocaine injection, and permit blinding of lidocaine versus saline injection. In this study we will apply the lidocaine cream over the GON distribution for 30 minutes, which is sufficient time to achieve local numbness and reduce the discomfort of injections. In the PI's clinical experience that duration can also reduce headache pain, whereas longer duration of application can cause a burning sensation. We will use the lidocaine cream open-label to maximize expectation of pain relief and numbness. Lidocaine cream is FDA-approved in children >2years[37].

Dosage: 4cm ribbon of cream = 32mg lidocaine

Randomized GON injection with 2% lidocaine or saline:

Selection of Drug:
-Lidocaine 2%: Our practice pattern survey demonstrated that lidocaine and bupivacaine are the most commonly used local anesthetics in nerve blocks performed in children[25, 43]. Until 2014 at CHOP we used a combination of both until our pharmacy raised concerns that bupivacaine carries a higher risk of causing Local Anesthetic Systemic Toxicity. Since then, our retrospective case series did not demonstrate any difference in outcome with lidocaine vs lidocaine + bupivacaine[24], so we have continued to use lidocaine only. While many case series have also included corticosteroid[21, 44], there was no clear benefit to adding corticosteroid to lidocaine + bupivacaine in chronic migraine[45]. For these reasons lidocaine will be the active agent.
-Saline: Saline injections will be used as a comparator in this trial, recognizing that they may be placebo or an active treatment.

Dosage:
-Lidocaine 2%: will use 2mL lidocaine over each right and left Greater Occipital Nerve x 20mg/mL = 80mg lidocaine
-Saline: will use 2mL of saline over each right and left Greater Occipital Nerve for blinded comparator

Selection of Injection Site

The clinical practice in our headache group has been to tailor injection sites to patient response, with most patients in our retrospective study receiving both occipital and trigeminal injections[24]. However, other studies have demonstrated efficacy with greater occipital nerve block alone. Since fewer injections are clearly less invasive, and would be more desirable if sufficient, we will test efficacy of GON injections in this study (see pictures below). However, for subjects who do not obtain sufficient relief from study procedures we will offer additional nerve blocks per usual clinical practice as one option for rescue treatment, and we will collect observational data from those subjects.

1.5 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46 and 21 CFR 50, 56 , and the HIPAA Privacy Rule. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

This study will examine the efficacy of the most commonly used peripheral nerve blocks, greater occipital nerve (GON) blocks, as an acute treatment for pediatric migraine using a run-in study design, starting with lidocaine cream and proceeding to randomized injection only for subjects who are not pain free or nearly so. We will utilize this design to test whether lidocaine cream run-in blinds subjects to injected medication, and to study the relationship between perceived treatment, expectation, and outcome.

2.1 Primary Objectives (or Aim)

To test the efficacy of lidocaine versus saline GON injections to treat pediatric acute migraine.

2.2 Secondary Objectives (or Aim)

To test whether lidocaine cream leads to successful blinding of saline versus lidocaine injection

To characterize how perceived treatment affects expectation of benefit, and how expectation affects change in pain score.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

The study schema is a run-in design (lidocaine cream) followed by double-blind randomized injection of active treatment (lidocaine) versus comparator (saline) in subjects who continue to have significant headache after run-in.

3.1.1 Screening Phase

Patients with episodic or chronic migraine who contact the Neurology clinic requesting escalation of care for acute headache flare refractory to home treatment will be invited by clinical staff to receive additional information about this clinical trial option. Subjects may also be recruited from the Emergency Department. Interested patients will then be contacted and described the study, using the main consent form to guide the conversation. A member of the study team (via telephone) will then screen potential families, with a continued interest. Screening will not occur ***until*** after obtaining verbal parental/guardian informed consent and HIPAA authorization. Initial screening procedures include a medical chart review and questions about health history that will help determine eligibility based on protocol inclusion / exclusion criteria. Those who are interested will be offered a study visit as soon as possible. Patients who decline participation will be directed back to clinical care.

On the day of the visit, parental/guardian informed consent and child assent, will be obtained prior to any study related procedures being performed for the main study. Potential subjects will be further screened using the protocol inclusion and exclusion criteria. Females, who have reached menarche, will have a urine pregnancy test. One parent or guardian per child/adolescent will also be enrolled in the study.

3.1.2 Study Treatment Phase

Study treatment will involve two steps:

-lidocaine cream run-in for all subjects

-subjects who are not pain free or sufficiently improved that they decline further procedures will receive randomized injection of lidocaine or saline over the Greater Occipital Nerves.

Subjects who report insufficient improvement (per their determination) ~ 30 minutes after GON injections will be offered additional treatments per usual clinical care, outside the study, but their immediate outcomes and follow-up data will be recorded.

3.1.3 Follow-up Phase

The follow-up phase will continue for 28 days.

3.2 Allocation to Treatment Groups and Blinding

Lidocaine cream lead-in will be used open-label for all subjects.

Injection medication (lidocaine versus saline) - Randomization will be done using REDCap, stratified based on diagnosis of episodic versus chronic migraine. The investigator who

performs the injection and the subject will be blinded to medication. The study team will use research pharmacy (IDS) to dispense injectable medications. Research pharmacy (IDS) will be unblinded in order to manage and prepare the randomized injectable medications.

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Study Participation

The study duration per subject will be up to 29 days, with a single visit for screening, enrollment, and study procedures, and 28 days follow-up.

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted only at the Children's Hospital of Philadelphia. Per discussion with research pharmacy in September of 2016, because all of the medications (lidocaine cream, injectable lidocaine, saline) are already stored in neurology clinic and used clinically, no IND will be required and the study medications do not necessarily need to be dispensed by research pharmacy. However, the study team will be using research pharmacy (IDS) and we do not expect this to limit enrollment to our main campus.

Recruitment will stop when approximately 58 subjects have received the randomized to lidocaine versus saline injection. It is expected that approximately 97 primary child subjects will be enrolled to produce 58 evaluable subjects for the primary objective (though data from all enrolled subjects will be used for other objectives). 97 parent/guardian subjects, one per child/adolescent, will also be enrolled in the study.

3.4 Study Population

3.4.1 Inclusion Criteria

Children/Adolescents

1) Males or females, ages 7 - 21, of any gender, race, or ethnicity.

2) Diagnosis of episodic or chronic migraine with acute headache flare lasting up to 3 months unresponsive to acute medications. Patients who report that acute medications were not used during this headache flare because those medications have been ineffective for several prior headache flares will be included.

3) Informed parental consent and subject assent.

4) Girls who have reached menarche must have a negative urine/serum pregnancy test because lidocaine is Pregnancy Class B.

5) Weight >25kg

To maximize applicability of the results, we will include any patients ages 7 through 21, as long as the child is old enough to understand the study and provide assent. Based on clinical experience, it is rare for a child younger than 11 years to assent to injections. However, there is no inherent safety concern below a specific age, and no reason to specifically exclude children if they are willing to undergo the procedure and understand the study well enough to give assent.

Parents or Guardians

1) Parents or guardians of children enrolled, who speak either English or Spanish, and provide parental/guardian permission (informed consent) for their participation

2) Subject (child) assent

3.4.2 Exclusion Criteria

Children/Adolescents

1) Previous nerve block less than 3 months ago or more than 2 previous nerve blocks
2) Allergy to local anesthetics
3) Skull defect or break in the skin at the planned site of cream application or GON injection
4) Any investigational drug use within 30 days prior to enrollment, or 90 days prior to enrollment for medications targeted at Calcitonin Gene-Related Peptide.
5) Pregnant or lactating females.
6) Parents/guardians or subjects who, in the opinion of the Investigator, may be non-compliant with study schedules or procedures.
7) Significant adverse event with prior injection or procedure.
8) New abnormalities on physical or neurological examination.
9) Newly reported red flags in headache history which prompt investigation for secondary headache.
10) Non-English and Non-Spanish speaking
11) Non-English speaking with no Spanish interpreter available. This is unlikely since CHOP Interpreter Services provides assistance with research visits.

Parents

1) Parents or guardians of children enrolled who do not speak English or Spanish

2) Parental/guardian permission and/or subject (child) assent has been declined

3) Parents/guardians, who in the opinion of the investigator, may be non-compliant or unable to complete the questionnaires

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

4 STUDY PROCEDURES

4.1 Initial Recruitment and Screening for the Study on the Phone

- Study team member provides a description of study to potential subjects and/or parents (Recruitment)
- Verbal Informed Consent for Screening, if still interested
- Screening Questions, involving medical history, to preliminary assess eligibility (based on Inclusion/Exclusion Criteria)
- Interested candidates are offered study visit, contingent on initial confirmation of eligibility based on investigator review of inclusion/exclusion criteria and medical record review

4.2 Screening[3]

4.2.1 In-person Study Visit

- Informed Consent and Assent
- Pregnancy Test (females of age of menarche only)
    - If meeting this criteria and the study team has already obtained consent to this procedure during the telephone screening, then a urine sample can be collected as early as the beginning of the study visit.
    - If subject is enrolled while admitted to the inpatient unit, the results from the clinically performed pregnancy test will be used for the research visit. No additional pregnancy test will be performed.
    - If subject is female sex assigned at birth but identifies as gender non-conforming, we will give the subject the option to skip the pregnancy test. Urinary pregnancy test is typically done in this study as pregnancy would change differential diagnosis of headache. Both lidocaine and saline can be used in pregnancy safely.
- Review Inclusion/Exclusion Criteria and confirm eligibility
- If subject is not naïve to nerve block or has received IV medications, information on treatment benefit, side effects and nerve procedure used will be collected.
- Demographics/Medical History

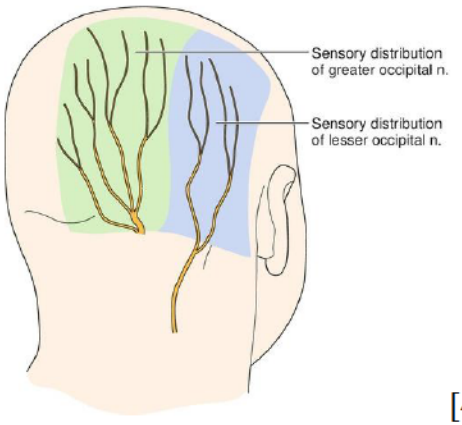
[3] If historical data points (e.g. vital signs, height, weight, head circumference, etc.) are available from earlier that day, then the study team does not have to repeat these procedures for screening and enrollment.

- Report of headache disability using PedMIDAS and child PROMIS Pain Interference
- Physical Exam
- Neurological examination including fundoscopic exam
- Vital Signs
- Height, Weight, Head Circumference
- Review of Prior/Concomitant Medications

4.3 Study Treatment Phase

4.3.1 In-person Study Visit

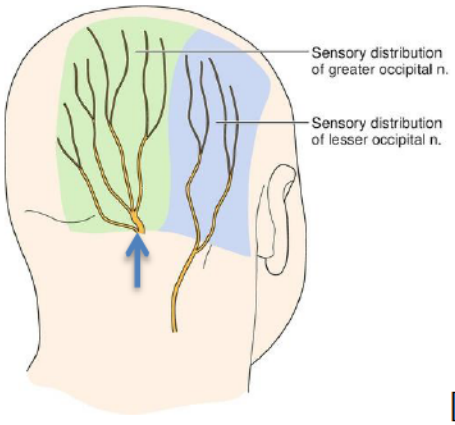
- Assess pain using Visual Analog Scale representing 0-10 and Numeric Rating Scale (NRS)
- Investigator will apply 4 cm ribbon (32mg) of lidocaine cream over the bilateral greater occipital nerve and its distribution (green area of figure):



[46]

- In addition to Zheng's expectation question, subject, parent, and injector complete modified Stanford Expectations of Treatment Scale (SETS) to report expected benefit of lidocaine cream
- After lidocaine cream has been in place for ~ 30 minutes, assess pain using Visual Analog Scale representing 0-10 and Numeric Rating Scale (NRS)
- If pain is 0, or sufficiently better such that subject/parent decline further interventions then no additional procedures at Study Visit, proceed to Follow-Up Phase
- For non-responders, the investigator will perform injection with randomized lidocaine or saline over the bilateral greater occipital nerve at the location demonstrated on the figure below. The injection site location will be determined by

palpation, 1/3 of the distance laterally from the occipital protuberance toward the mastoid process, at the site of maximal tenderness. The needle will be inserted at that location, pointing toward the vertex of the head. 1cc will be injected directly. The needle will be slightly withdrawn and reinserted 45 degrees each direction from the initial site, injecting an additional 0.5cc each laterally and medially. Because the occipital artery usually courses lateral to the greater occipital nerve, after needle insertion and before injection of saline or lidocaine each time the investigator will draw back on the syringe to confirm that the needle is not intra-arterial. If the needle is intra-arterial it will be repositioned.



[46]

- Subject, parent, and injector will report perceived medication and complete modified Stanford Expectations of Treatment Scale (SETS) to report expected benefit of injection (will be done immediately before numbness sets in).
- About 30 minutes after injection subject, parent, and injector again report perceived medication and the subject will also complete the PGIC scale
- Assess pain using Visual Analog Scale representing 0-10 and Numeric Rating Scale (NRS)
- Adverse Event Assessment

4.4 Follow-up Phase

Subjects will be asked to maintain electronic headache diary to report pain, disability, use of rescue medications, and other migraine symptoms for 28 days. They will also be asked about adverse events, use of other medications, and about satisfaction with treatment. On day 7 and day 28, subjects will be asked to complete the PROMIS Pain Interference scale. The PedMIDAS will be administered at day 28 while the PGIC will be weekly. Links to Redcap surveys will be sent via text message.

Paper versions of these forms and the headache diary will also be at hand in case access to the require technology to fill these forms on-line is not available or families decline to use electronic platforms.

4.5 Unscheduled Visits

Additional visits will be scheduled as needed for any subjects who reports unexpected adverse events.

4.6 Concomitant Medication

All prior and concomitant headache preventive medications used within 30 days prior to the Visit 1 and through the end of the study will be recorded. All prior and concomitant acute headache medications and non-headache medications used within 7 days prior to the Visit 1 and through the end of the study will be recorded. The dates of administration, dosage, and reason for use will be included.

4.7 Rescue Medication Administration

Subjects who report inadequate relief from study treatments ~ 30 minutes after injection will be offered additional treatment per usual clinical care. These options could include:

-intravenous medications

-no additional treatment

-open-label circumferential nerve block injections of lidocaine. In order to limit the maximum possible dose of lidocaine to 4.5mg/kg, including the cream, randomized injection, and open-label injections, the amount of lidocaine used will be weight-based:

Weight	Volume of 2% lidocaine	Dose of lidocaine	Total dose lidocaine from all procedures
64kg+	8.8mL: 2mL over each GON 1mL over each LON 1mL over each ATN 0.2mL over each SON 0.2mL over each STN	176mg	288mg
59.5kg-63.9kg	7.8mL: 1.5mL over each GON 1mL over each LON 1mL over each ATN 0.2mL over each SON 0.2mL over each STN	156mg	268mg
55.1kg-59.4kg	6.8mL: 1mL over each GON 1mL over each LON 1mL over each ATN	136mg	248mg

	0.2mL over each SON 0.2mL over each STN		
50.6kg-55kg	5.8mL: 1mL over each GON 1 mL over each LON 0.5 mL over each ATN 0.2mL over each SON 0.2mL over each STN	116mg	228mg
46.2kg-50.5kg	4.8mL: 1mL over each GON 0.5 mL over each LON 0.5 mL over each ATN 0.2mL over each SON 0.2mL over each STN	96mg	208mg
41.7kg-46.1kg	3.8mL: 0.5mL over each GON 0.5 mL over each LON 0.5 mL over each ATN 0.2mL over each SON 0.2mL over each STN	76mg	188mg
25-41.7kg	TBD based on headache location	TBD	TBD, max 4.5mg/kg

4.8 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for AEs. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Medical Record Review

The following variables will be abstracted from the medical chart:

- Date of birth
- Weight
- Allergies
- Headache features and diagnosis, prior physical exam findings
- Prior headache treatments including nerve block and other procedures, as well as adverse events
- Surgical history
- Record of recent investigational drug study participation

5.1.2 Medical History

Medical history will be gathered in a semi-structured interview based on patient answers provided in our Headache Questionnaire. Because a very similar Questionnaire is used for clinical care, the answers provided for clinical care will be used if available, and confirmed in the interview.

Demographics including age, gender, race, and ethnicity will be collected.

5.1.3 Vital Signs & Physical Exam

Vital signs will be measured following the same standard of care for all neurology patients seen clinically. This includes measurement of height and weight, head circumference, pulse, and blood pressure. Blood pressure will be measured using an automated device in a seated position, using either left or right arm, with recheck done with sphygmomanometer if the automated reading is outside the age-appropriate normal range.

Full general medical and neurological examination will be performed, including funduscopic examination and headache-specific examination (palpation for allodynia, tenderness over nerves, tightness and tenderness of muscles of neck and back, auscultation for bruits). These examinations are identical to the examination that the Principal Investigator performs as part of usual clinical care.

5.1.4 Pregnancy Testing

A urine pregnancy test will be performed for female subjects who have reached menarche.

5.1.5 Other Evaluations, Measures

- **Headache Questionnaire (HQ)**
    - Because a similar questionnaire is used for clinical care, the answers provided for clinical care will be used (if available) and confirmed during the study visit.
    - These questions are based on the NINDS Common Data Elements for headache. The "Headache Questionnaire" will include the following:
        - Current Headache Condition and Headache History
            - Includes questions related to durations and timing of headaches, severity or intensity, triggers, failed and current treatments, non-medication treatments, use of supplements or vitamins, age of onset, frequency and pattern of headache pain, characterization of pain, red flags for secondary headache (i.e. recent injury or trauma, stressors), alleviating or aggravating factors, aura and/or premonitory symptoms, characterization of headache flare, diagnosis
        - Current and Past Medical History
            - Includes questions related to birth and developmental history, surgeries, immunizations, family history, previous or current health problems, previous or current medications
        - Social History and School Life
            - Includes questions such as who lives with the subject, any recent changes or stressors to home life, subject grade level and schooling environment, any concerns with academic performance
- **PedMIDAS**
- **PROMIS Pediatric SF v2.0 - Pain Interference**
- **Zheng's expectation question**: a single question about expectation as done in Zheng's acupuncture study in migraine[53]
- **Modified SETS**
- **Patient Global Impression of Change (PGIC) Scale**[54]: A single-item response measure in which patients use a 7-point numerical rating scale to self-report their degree of overall change or their perceived improvement with treatment. This tool has been used widely in pain research as a standard measure of outcome. In consideration of our targeted patient population, the scale includes slight revisions to wording: "my headaches are" replaces "my overall status is"; "a little" replaces "minimally"; "better" replaces "improved."
- **Blinding questions**: Based on the approach of Byington[47], subjects will be asked: "What treatment do you think you received in this study? (A) I am certain lidocaine was used; (B) I think lidocaine was probably used; (C) I have absolutely no idea which medication was used; (D) I think saline was probably used; (E) I am certain saline was used.

Subjects who answer choice (C) will be asked, which medication would you guess? (A) lidocaine; (B) saline.

5.2 Efficacy Evaluations

5.2.1 Diagnostic Tests, Scales, Measures, etc.

Pain score will be assessed using a Visual Analog Scale with anchors at 0 and 10 and a Numeric Rating Scale (NRS). Pain will be assessed with this at the following times:

- Prior to application of lidocaine cream

- About 30 minutes after application of lidocaine cream/just prior to injection

- About every 5 minutes after the injection, *if performed* (i.e. ~ 5, 10, 15, 20, 25, and 30 minutes)

Headache diary, based on the NINDS Headache Common Data Elements, will be used to collect outcomes for 28 days of follow-up. This will be a daily, prospective tool used to capture the presence or absence of headache. If present, then additional questions will be asked to collect information that further characterizes it, such as headache intensity, use of rescue medications on each day, disability associated with headache pain, and other symptoms. If not present, then additional questions will be asked to collect information about the use of preventative medications and the use of medications for any other pain.

5.3 Safety Evaluation

Subject safety will be monitored by adverse events and physical examinations.

6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

Change in pain scores, measured by subtracting the 30min post-injection score from the pre-injection score, both measured by the Visual Analog Scale[48] and Numeric Rating Scale (NRS), will be used as the primary outcome measure. A continuous outcome measure enables us to examine the variability of the outcome, and a change of 2 points has been previously shown to be clinically relevant.

6.2 Secondary Endpoints

Per the guidelines of controlled trials of drugs in migraine, secondary outcome measures will include pain freedom, pain relief (improvement of pain from moderate/severe to none/mild), 24-hour sustained pain freedom and relief, freedom from all symptoms of migraine (including photophobia, nausea), use of rescue treatments, and disability[49].

6.3 Statistical Methods

6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).

6.3.2 Efficacy Analysis

The primary analysis will be based on an intention to treat approach. For Objective 1 this will include all subjects who receive the randomized lidocaine versus saline injection at the Study Visit. Difference in mean change in pain score in the lidocaine injection and saline injection groups will be compared using an independent t-test.

6.3.3 Safety Analysis

All subjects who have lidocaine cream applied at the Study Visit will be included in the safety analysis. The frequencies of AEs by type, body system, severity and relationship to study drug will be summarized. SAEs (if any) will be described in detail.

AE incidence will be summarized along with the corresponding exact binomial 95% two-sided confidence intervals.

6.4 Sample Size and Power

Sample size for randomized step: The mean drop in pain score in our retrospective study of nerve blocks in children with acute flare of both episodic and chronic migraine was 4 points (immediately pre- to a few minutes post-injection, as measured on a numeric 0-10 scale). Similarly, Dr. Young & Oshinsky's study of the effects of GON block in the first five minutes found an average drop of 3.3 points on a Visual Analog Scale[50], and with the timing of action of local anesthetics, it is reasonable to estimate that continued time would have led to a drop of ~4 points. Given that the minimal clinically significant change in pain score across multiple chronic pain conditions is 2 points[51], we will estimate that the saline injection group will drop an average of 4-2 = 2 points. The standard deviation of change in pain score in our observational study was 2.5, and in Dr. Young's smaller study was 2.7, so we will use the latter to estimate sample size. Assuming that lidocaine injections lead to a mean change of 4 points, and saline injections lead to a mean change of 2 points, with a standard deviation of 2.7, two-sided α=0.05 and 80% power, we will need 29 primary child/adolescent subjects to receive the randomized nerve block treatment, per injection arm, for a total of 58.

7 *EFFECT OF LIDOCAINE CREAM RUN-IN ON OVERALL SAMPLE SIZE*: A SMALL STUDY OF LIDOCAINE CREAM AS TREATMENT FOR MIGRAINE HEADACHE DEMONSTRATED THAT 7 OF 30 SUBJECTS, OR 23% (95% CONFIDENCE INTERVAL: 9-42%), WERE PAIN-FREE AT 2 HOURS[40, 41]. WE WILL PLAN THAT THE UPPER END OF THIS CONFIDENCE INTERVAL, 42% OF SUBJECTS WILL DROP-OUT DUE TO PAIN FREEDOM WITH LIDOCAINE CREAM (OR SUFFICIENT IMPROVEMENT SUCH THAT THEY DECLINE FURTHER INTERVENTIONS). AS A RESULT, WE ESTIMATE

THAT WE WILL NEED TO ENROLL UP TO 97 PRIMARY CHILD/ADOLESCENT SUBJECTS IN ORDER TO ACHIEVE THE GOAL OF PRIMARY CHILD ADOLESCENT 58 SUBJECTS RECEIVING THE RANDOMIZED NERVE BLOCK INJECTION. STUDY MEDICATION (STUDY DEVICE OR OTHER STUDY INTERVENTION)

7.1 Description

Study medications will include lidocaine cream, injectable 2% lidocaine solution, and saline. Per discussion with research pharmacy in July 2018, the study team can manage the lidocaine cream. This study medication will be kept separate from the clinical supply in a locked closet in clinic. The study team will use research pharmacy (IDS) to prepare and dispense the injectable medications. Research pharmacy will remain unblinded.

7.1.1 Drug Accountability

Adequate records of study drug receipt and disposition for the lidocaine cream will be maintained by the study team. Research pharmacy (IDS) will manage accountability of the injectable study medications.

8 SAFETY MANAGEMENT

Based on clinical experience and prior studies, we consider this study to be a mild increase above minimal risk and do not anticipate any SAEs.

- Lidocaine cream is approved by the Food & Drug Administration as a safe and effective drug for minor skin irritation over 2 years of age[37].
- Saline nerve blocks have been used in multiple prior studies with some benefit and without report of harm. Subjects will be exposed to a maximum of 2 saline injections in this study.
- In our retrospective study of nerve blocks with lidocaine and bupivacaine, 86% of those with acute headache flare had at least transient improvement in pain severity [24], and there were no serious adverse events. There were cases in which nerve block was used unsuccessfully to prevent hospitalization, but it was the headache, not the nerve block, that led to hospitalization. A small portion of subjects reported increased pain, numbness, or anxiety usually during and immediately following injection, but these symptoms were self-resolved.

8.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study directly by the PI and study team,

8.2 Adverse Event Reporting

Unanticipated problems related to the research involving risks to subjects or others that occur during the course of this study (including SAEs) will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

8.3 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

8.4 Definition of a Serious Adverse Event (SAE)

An SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death,
- a life-threatening event (at risk of death at the time of the event),
- requires unexpected inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/incapacity, or
- a congenital anomaly/birth defect in the offspring of a subject.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Because the current standard of care for patients with acute, severe headache is intravenous medications, it is expected that some subjects in this study will be treated in the Emergency Department or hospitalized. This represents a failure of benefit of the study treatment, rather than an adverse effect of the study treatment. These hospitalizations will not be treated as Serious Adverse Events because they are expected in the course of the headache flare in a small portion of patients, even when appropriate treatments are used to try to prevent hospitalization.

Similarly, many children with severe, refractory headaches have multiple medical and psychiatric comorbidities. Hospitalizations which are not related to the study interventions will not be considered SAEs.

8.4.1 Relationship of SAE to study drug or other intervention

The relationship of each SAE to the study intervention should be characterized using one of the following terms in accordance with CHOP IRB Guidelines: definitely, probably, possibly, unlikely or unrelated.

8.5 IRB/IEC Notification of SAEs and Other Unanticipated Problems

The Investigator will promptly notify the IRB of all unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the eIRB system and in accordance with the timeline below.

Type of Unanticipated Problem	Initial Notification (Phone, Email, Fax)	Written Report
Internal (on-site) SAEs Death or Life Threatening	24 hours	Within 2 calendar days
Internal (on-site) SAEs	7 days	Within 7 business days

All other SAEs		
Unanticipated Problems Related to Research	7 days	Within 7 business days
All other AEs	N/A	Brief Summary of important AEs may be reported at time of continuing review

8.5.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

9 STUDY ADMINISTRATION

9.1 Treatment Assignment Methods

9.1.1 Randomization

Randomization will be done using REDCap, which can stratify the randomization. That information will be kept separately from other subject records in REDCap.

9.1.2 Blinding

The investigator who performs the injection, the subject and his/her parent(s) will be blinded to medication. Research pharmacy will be unblinded and will prepare and dispense the injectable study medications.

9.1.3 Unblinding

In the event of a serious SAE in which there is a concern for participant safety and it is imperative to know whether the participant received lidocaine or saline , we will unblind the treatment for the specific participant without breaking the blind for other participants.

For that, the Principal Investigator will contact the Research Pharmacy to request the unblinded treatment information for the specific subject.

9.2 Data Collection and Management

Data will be managed and stored using the research-focused electronic web-based data capture system REDCap, under an agreement with the software's development consortium, led by Vanderbilt University. Identifiable information of subjects will be entered into REDCap, which will be accessible only to the investigators, research coordinator, and Independent Medical Monitor. Identifier fields will be removed when exporting data for analysis.

Data backup is performed nightly via a dedicated backup system. The backup environment is maintained by a dedicated staff using dedicated resources. Access to the backup environment is restricted to Research Information Systems staff.

REDCap has the capability to send SMS text messages to survey respondents by using a third-party web service named Twilio (www.twilio.com). Twilio provides specific HTTP headers that are encoded and are verifiable to ensure that they are truly coming from the Twilio server. REDCap utilizes these headers to authenticate to the request to REDCap from Twilio. REDCap uses a technical methodology enabling near-instantaneous removal of the minimal transaction logging – essentially removing contacts and duration logs within seconds of the SMS or phone transaction occurring. All logs are scrubbed; nothing else is captured on Twilio, and the REDCap implementation ensures significant controls to warrant authority to operate. The would like to utilize the REDCap-Twilio integration tool for sending a survey link via SMS (text message) to a REDCap survey.

In consideration of the mandatory retention policies for research records set forth by CHOP, our team would like to scan and store the written paper consent and other paper source

documents electronically, which would not require the study team to retain the physical paper copies.

9.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy. The Investigator and other site personnel will not use such data and records for any purpose other than conducting the study.

No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between the provider (the PI) of the data and any recipient researchers (including others at CHOP) before sharing a limited dataset (PHI limited to dates and zip codes).

9.4 Regulatory and Ethical Considerations

9.4.1 Data and Safety Monitoring Plan

The Office of Research Compliance (ORC) provides qualified and trained staff to support the monitoring plan. The ORC takes a risk-based approach to monitoring. The purposes of trial monitoring are to verify the protection of the rights, safety and well-being of human subjects are protected, as well as, to ensure the quality and integrity of data resulting from this investigation. Additionally, monitoring will be conducted to verify the conduct of the trial is in compliance with the currently approved protocol/amendment(s), and with the applicable regulatory requirement(s).

Prior to initiation of recruitment activities, the ORC will conduct a review of regulatory documents to confirm clinical trial readiness. Thereafter, the ORC will perform the first monitoring visit after the first subject is enrolled and completes administration of the investigational product. Thereafter, the Investigator will contact ORC to arrange a monitoring visit. Subsequent monitoring activities will consist of 100% review of regulatory records and consent documentation, and review of a subset of subject data after an additional 6-months of research activity. At that time, a recommendation for the continued monitoring frequency will be determined based upon the observations and/or findings noted. Monitoring may continue at 6-month intervals, or may be tapered.

The study will be monitored by an Independent Medical Monitor (IMM) because it involves only a minor increase above minimal risk with direct possibility of benefit, and will be conducted at a single site. Dr. Amy Gelfand, who has published on the use of nerve blocks in children, has agreed to serve as IMM. She will have access to all data in REDCap, including patient identifiers, which will be noted in the informed consent document. Consistent with the responsibilities of an IMM outlined by NINDS, about every 6 months she will review the research protocol and ongoing study activities with emphasis on data integrity, protocol adherence, and study participant safety issues. The IMM's review will focus on adverse events and reasons for losses to follow up, raising any concerns or issues with the NINDS and the PI, and recommending to the NINDS and PI the continuation, modification, or conclusion of the trial, while protecting the confidentiality of the trial data

and the results of monitoring. In addition, both Dr. Gelfand and the IRB will be notified if any serious adverse events (SAEs) occur per the timeline outlined in the protocol.

Because the planned study includes a relatively small number of subjects, and the interventions involve only a minor increase above minimal risk with direct possibility of benefit, there is no plan for interim analysis or premature stopping based on efficacy.

9.4.2 Risk Assessment

The study procedures will be performed in neurology clinic, with the same safeguards we observe as part of usual clinical care. The medications are kept in a locked storage closet, and a 2-staff person "time out" is performed prior to all injection procedures.

Completion of study surveys are not greater than minimal risk. Most of the surveys are used commonly in routine medical care, and none ask uncomfortable or private questions.

Application of lidocaine cream is not greater than minimal risk. The lidocaine cream is actually an over-the-counter cream sold for treatment of hemorrhoids and minor skin irritation, so can be used in everyday life.

Saline injection over the greater occipital nerves is also minimal risk, similar to a blood draw. A small volume (2cc) of saline will be injected over each nerve, using a 30gauge needle, which is smaller than needles typically used for phlebotomy. The needle will be inserted only superficially into the skin. There is no known risk to small injections of saline, and this has been used as the placebo comparator in numerous trials of nerve blocks in adults[27-30]. Multiple saline injections were used as the placebo treatment in the recently-completed trial on a botulinum toxin for chronic migraine in adolescents[52].

Lidocaine greater occipital nerve injection involves a minor increase above minimal risk with direct prospect of benefit. We commonly perform nerve blocks with lidocaine in our headache clinic, and nerve blocks elsewhere on the body are performed prior to painful procedures very commonly in medical care (catheter placement, stitches, etc). Based on our retrospective clinical data, 85% of patients who received nerve blocks with local anesthetic for headache derived some benefit. The most frequently reported negative outcome was minor discomfort. No subjects experiences serious harm or reported what would be considered a serious negative outcome. In addition, in this study we are seeking to utilize the lidocaine cream run-in to minimize the injection discomfort. A large portion of patients in our retrospective study and in another published pediatric study elected to receive repeated nerve blocks, indicating that benefit outweighed risks in the opinion of the patient.

9.4.3 Potential Benefits of Trial Participation

Direct benefits: Subjects who participate in the study may have improvement in their headache treatment. As described above, a prior study demonstrated that that 7 of 30 subjects (23%, 95% CI 9-42%) treated with lidocaine cream had resolution of headache [40, 41]. All subjects will be treated with lidocaine cream as the first study treatment. Those who do not derive sufficient benefit from the lidocaine cream will receive randomized, blinded saline or lidocaine GON injections. Based on our retrospective clinical data, 85% of patients who received nerve blocks with local anesthetic derived some benefit. If subjects continue to have significant headache at the end of study procedures they will be offered

additional treatments per usual clinical care (IV medications, open-label nerve blocks with lidocaine, etc).

Indirect benefits: The current standard of care for acute, severe headache refractory to oral/nasal medications is intravenous medications. The administration of IV medications comes with significant burden to the individual and the medical system. If we demonstrate that occipital nerve blocks are an effective method of treating acute, severe headache then we will add another treatment option which is more convenient for patients and less costly for the medical system.

9.4.4 Risk-Benefit Assessment

Based on clinical experience, the potential benefits of this treatment substantially outweigh the minor risks.

9.5 Recruitment Strategy

Patients with episodic or chronic migraine who require escalation of care for disabling acute migraine headache refractory to home treatment will be invited to receive additional information about this clinical trial option. Our preliminary data indicate that we will primarily recruit teenage girls, consistent with the distribution of migraine in children and adolescents, with rising incidence in girls after puberty.

Additionally, to enhance recruitment efforts, as needed we will:

1. The Recruitment Enhancement Center will email patients who have been seen in Neurology or the ED for treatment of migraine within the past year. In addition, patients who have been seen recently for acute treatment may be contacted by telephone to offer the option to enroll in the nerve block study for their next prolonged migraine flare.
2. We will hand out recruitment materials to potentially eligible patients in Neurology clinic, in the ED, and at Headache Education events.
3. We will also discuss this study with patients (both CHOP and non-CHOP) who contact us asking about potential studies.
4. We will reach out to the potential subjects through my CHOP to ask if they're interested to hear about the study and we'll follow up with a phone call if they are.
5. We will post information about the study in CHOP website and general CHOP Facebook.
6. We will use the Recruitment Enhancement Core Services to help us increase our recruitment numbers.
7. In order to alleviate the ED load, the division of Neurology will send Neurology patients a communication with alternative treatments for headache flares that don't involve a visit to the ED. Participation in this study will be one of the options listed.

9.6 Informed Consent/Assent and HIPAA Authorization

An approved study team member will obtain verbal consent and HIPAA authorization prior to soliciting information from interested potential families during the initial telephone call. The Investigator will obtain written informed consent/assent and HIPAA authorization for the main study at the in-person study visit. The subject and parent will be given approximately 30 minutes to make a decision about participation on the study.

9.7 Payment to Subjects/Families

9.7.1 Reimbursement for travel, parking and meals

Reimbursement of parking/travel cost per subject, including screen failures = $20

9.7.2 Payments to parent for time and inconvenience (i.e. compensation)

None

9.7.3 Payments to subject for time, effort and inconvenience (i.e. compensation)

$25 for study visit + $25 for 28-day headache diary

9.7.4 Gifts

None

10 PUBLICATION

We anticipate several publications from these studies. We plan to publish the efficacy of nerve blocks, effectiveness of lidocaine cream lead-in, and subject predictors of response to lidocaine injection and cream within 6-12 months of study completion. Studies of blinding and expectation will be published in the following year.

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