Acute headache treatment in pregnancy:

Occipital Nerve Block compared to Acetaminophen/caffeine PO

A Randomized Controlled Trial

(ON ACT TRIAL)

Protocol

April 15, 2019

Version 1

Protocol Table of Contents

Study Title: Acute headache treatment in pregnancy: Occipital Nerve Block compared to Acetaminophen/caffeine PO, A Randomized Controlled Trial (ACT ON Trial)

Author: Elisa T. Bushman, MD
Mentor: Rachel Sinkey, MD
Neurology: Khurram Bashir, MD

1. Introduction

1.1 Study Abstract

Headache is a common complaint in the reproductive population with 16% of women suffering from migraine and 88% from tension headache. **In the University of Alabama Birmingham (UAB) Maternal Emergency Unit (MEU)** (analogous to obstetric triage units at other centers), **19-26 patients from September-November 2018 presented monthly with the chief complaint of headache.** During pregnancy the treatment of headache is delayed due to concern for potential fetal exposure limiting treatment and appropriate workup. **Delaying treatment places women at increased risk for worsening of headache disorders and developing more refractory headaches.** Improving the treatment of headaches has both the potential to improve patient care and satisfaction, and to reduce progression of headache disorders.

Occipital nerve blocks (ONB) are a well-established treatment for tension and migraine headaches with both abortive and prophylactic treatment benefits. The use in pregnancy currently is limited to expert opinion and retrospective studies which show efficacy and safety in the pregnant population in the setting of refractory headache. A MEDLINE review using search terms “occipital nerve block” and “pregnancy” yielded 5 results, confirming that there are no randomized trials evaluating ONB in pregnancy. Furthermore, clinicaltrials.gov has no registered trials on the topic of occipital nerve block and pregnancy as of March 2019.

In light of the paucity of data, we propose a single center open label randomized controlled trial to test the central hypothesis that use of occipital nerve block results in greater resolution of pain score when compared to Acetaminophen/ Caffeine cocktail for treatment of headache in pregnancy. By expanding the use of evidence-based treatment options for headache in pregnancy, our objective is to provide this at risk population with improved access to treatment. **To our knowledge, this study will be the first randomized control trial addressing the use of occipital nerve block in pregnancy.**

1.2 Primary Hypothesis

Bupivacaine occipital nerve block as compared to Acetaminophen/Caffeine PO cocktail results in a greater proportion of pregnant women with response to treatment, defined as resolution or headache or improvement to mild severity (VSR ≤3) at 1 hour after treatment.

1.3 Secondary Hypotheses

Compared to women receiving the PO cocktail treatment, women who receive ONB will:

a) Have improved headache pain at 2 hours following treatment
b) Have a shortened interval to response to treatment
c) Have improved satisfaction with treatment
d) Have decreased headache frequency for the 7 days following treatment
e) Experience no difference in the development of hypertensive disease of pregnancy at 7 days following treatment
f) Have less utilization of crossover treatment
g) have no difference in the development of hypertensive disease of pregnancy at 28 days following treatment
h) Have decreased utilization of MEU services in the next 28 days
i) Have a greater improvement in pain scores

1.4 Purpose of the Study Protocol

The purpose of our study is to determine if ONB is a beneficial first line treatment of acute headache in pregnancy.

2. Background

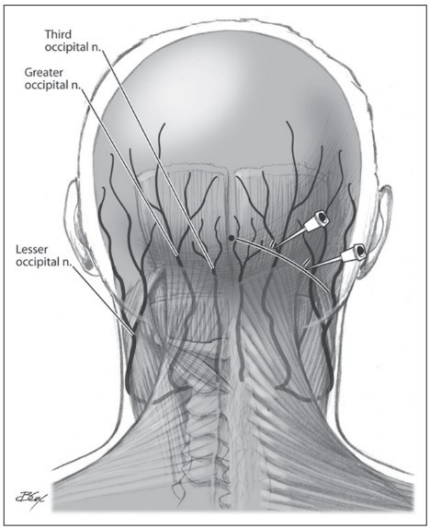
2.1 Introduction

Headache is a common complaint in the reproductive population. Primary headache disorders include migraine, cluster, and tension headache. Of reproductive age women, 1/6 suffer from migraine and 88% meet criteria for tension headache at some point in their life.[1,2] Despite an anticipated improvement in primary headache disorders with pregnancy, primary headache disorders can initially present, worsen, or be diagnosed during pregnancy.[3] **The diagnosis and treatment of acute headache in pregnancy is of great importance as it can dictate delivery and early maternal/fetal interventions.**

During pregnancy the treatment of headache is made more difficult due to an increase in secondary headaches, such as pre-eclampsia, and concern for potential fetal exposure limiting treatment.[4] As a result treatment of headache disorders is delayed during pregnancy.[5] Delaying treatment of headache disorders places women at increased risk for worsening of primary headache disorders and developing more refractory headaches.[6] **The improved treatment of headache has both the potential to improve patient care, satisfaction, and disease progression of headache disorders.**

Occipital nerve blocks (ONB) are a well-established treatment for tension and migraine headache in the non-pregnant population with both abortive and prophylactic treatment benefits.[7-13] ONBs are a safe procedure that involves a subcutaneous injection of local anesthetic with or without a steroid component bilaterally into the area around the occipital nerves.[14] The local anesthetic used is typically lidocaine or bupivacaine both of which are routinely used with epidural placement. The use in pregnancy currently is limited to expert opinion and retrospective studies which suggest efficacy and safety in the pregnant population.[15] Complications of occipital nerve blocks are limited to rare injection site infections. A MEDLINE review using search terms “occipital nerve block” and “pregnancy” yielded 5 results, confirming that there are no randomized trials evaluating ONB in pregnancy. Furthermore, clinicaltrials.gov has no registered trials on the topic of occipital nerve block and pregnancy. **By expanding the use of evidence-based treatment options for headache in pregnancy this at risk population may have improved access to treatment.**

Figure 1: Site of injection of occipital nerve block[13]



2.2 Current Recommendations for treatment of acute headache in pregnancy

There are many good treatment options for acute headache in pregnancy however these treatments are underutilized due to provider discomfort. This innate discomfort is likely due to a lack of evidence based treatment protocols for headache in pregnancy. As a result first line treatment varies widely by institution and provider.

There is level A evidence for the use of acetaminophen, acetaminophen/aspirin/caffeine (Excedrin Migraine®), and butorphanol for treatment of acute headache that are all safe for use during pregnancy.[16,17] Due to the concern for blood thinning and a theoretical risk of closure of the fetal ductus arteriosus, regular-dose aspirin is avoided by many providers in the 3rd trimester.[18] As a result many providers favor the use of acetaminophen/butalbital/caffeine (Fioricet®) despite there being no Level A or Level B evidence for the use of butalbital containing medications for treatment of headache. Despite butorphanol being a Level A treatment for acute headache use in pregnancy is again limited by provider comfort. Ketoralac, naproxen and ibuprofen are also FDA level A and can be safely used prior to 28 weeks for 48-72 hours. However, the potential risk of premature closure of the ductus arteriosus, platelet dysfunction, and/or fetal and maternal renal dysfunction limit NSAIDS use for treatment of headache in pregnancy, particularly in the third trimester.[17]

Level B medications that can be used for the treatment of acute headache in pregnancy are the dopamine blockers: chlorpromazine, promethazine, metoclopramide, and prochloperazine.[17] The exact mechanism of dopamine blockade on headache is unknown but is felt to be safe in pregnancy and have the added benefit of treatment of nausea. There is also Level B evidence for the use of Codeine in combination with acetaminophen and tramadol in combination with acetaminophen, but these are used more rarely due to increasing awareness of their potential for maternal opioid use disorder and the potential for neonatal withdrawal syndrome with chronic maternal opioid use.

Despite headache being a common complaint in pregnancy there is no obstetric or neurologic society that has standardized recommendations for treatment of headache in pregnancy leaving treatment provider dependent.

2.3 Safety and efficacy of occipital nerve blocks

Injection of local anesthesia into the greater or lesser occipital nerve, known as occipital nerve block (ONB), is an acute and prophylactic treatment of headache commonly used outside of pregnancy. Five – ten cc of local anesthetic with or without steroid is injected into the greater occipital nerve and/or lesser occipital nerve every 6-9 weeks as desired for prophylactic benefit. ONB has been studied extensively in both randomized controlled trails and prospective cohort studies. Randomized controlled trials show therapeutic benefit with clinically significant reduction in headache (HA) days in the 1st week, and 2 and 3 months following ONB.[7,9] Retrospective studies has shown benefit of occipital nerve block in all primary headache disorders (cluster, migraine and tension).[8] While reducing the number of headache days ONB has also been shown to decreased use of oral medication consumption over the month following injection.[10,11] Due to the acute benefit of ONB the use in emergency department settings is becoming an area of increasing interest. Current evidence shows that the use of ONB in acute care settings is safe with risk of complication being similar to that of any subcutaneous injection.[14] Response of acute headache to ONB ranges from a 50% pain reduction in pain to 90% resolution at 45 minutes after treatment.[19,20]

2.4 Use of occipital nerve block in pregnancy

Although use of ONB has not been studied extensively in pregnancy a case series has been published with a population of 13 pregnancies who failed oral and IV treatment of migraine. Of these women, 38% suffered from chronic migraines with 51% suffering from status migrainosis (migraine lasting >72hrs) at the time of injection. Eleven patients had acute pain relief and resolution. Two patients had no pain relief and went on to be diagnosed with preeclampsia and no patients suffered from minor or major complications.[15]

The American Headache Society distributed a member survey 2010 with 161 responses questioning the use of ONB in pregnancy. Greater than one half of members surveyed preformed ONB in pregnancy and felt it was safe. The majority of practitioners usually waited until 2nd trimester to give injections and used lidocaine only although there is no evidence that ONB in the first trimester or use of other types of local anesthetic is unsafe.[13]

2.5 Rationale for a Clinical Trial

Few studies exist which have examined the treatment of acute headache in pregnancy. Treatment of headache in pregnancy is currently based on extrapolated treatment of headache in the non-pregnant population. Specifically, no published data exists involving the use of ONB in the acute setting. Our study would provide evidence on the potential benefits of ONB for treatment of headache in pregnancy providing an additional treatment tool in this at risk population.

2.6 Innovation

There is a paucity of data regarding treatment of headache in pregnancy with most research addressing the natural course of headache in pregnancy rather than treatment of headache in pregnancy. [21,22] There is scant literature addressing the use of ONB in an emergency department setting but the few published studies are promising showing efficacy and safety. [14,15] A MEDLINE review using search terms “occipital nerve block” and “pregnancy” yielded 5 results, confirming that there are no randomized trials evaluating ONB in pregnancy. Furthermore, clinicaltrials.gov has zero registered trials on the topic of occipital nerve block and pregnancy. **This innovative randomized controlled trail will expand the use of evidence-based treatment options for headache in pregnancy leading to improved access to evidence based treatment of acute and chronic headache in pregnancy.**

3. Study Design

This is an open label randomized controlled trial evaluating response to bupivacaine occipital nerve block compared to Tylenol/Caffeine cocktail in treatment of pregnant patients seeking headache treatment.

3.1 Primary Research Question: Is occipital nerve block more efficacious than Tylenol/ Caffeine cocktail in the treatment of headache in pregnancy? Benefit of occipital nerve block will be defined as a resolution or improvement of headache pain to mild range (VRS ≤ 3) at 1 hours by visual/verbal rating score (VRS).

3.2 Secondary Research Aims:

a) To assess the difference in response to treatment at 2 hours following treatment.

b) To assess the difference in time to resolution of pain after treatment of acute headache between groups.
c) To assess patient satisfaction with treatment at time of discharge and at 7 days.
d) To assess headache free duration within 7 days after treatment.
e) To assess the development of hypertensive disease of pregnancy without 7 days after treatment.
f) To assess the need for crossover treatment.
g) To assess development of hypertensive disease of pregnancy within 28 days of treatment.
h) To assess the need of MEU services for treatment of headache within 28 days of treatment.
i) To assess the change in VSR before and after treatment.

3.3 Design Summary: This is an open label randomized controlled trial. Women who present to the MEU with headache will be assessed by trained nurse practitioners and/or OB/GYN residents. If the woman meets criteria for the study she will be enrolled by an MEU provider doing the primary assessment.

See Figure 2 for the flow diagram depicting the patient's course through MEU. If eligible for inclusion, women will be randomly assigned to ONB or headache cocktail. Randomization will occur at time of enrollment. Prior to headache treatment 10-point visual/verbal rating scale (VRS) will be obtained. Treatment time is defined as time the patient takes the medication or the time that the needle is inserted into the greater occipital notch. At 60 min after treatment VRS will again be obtained by nursing staff or primary provider. If headache pain is resolved, defined as a VRS 0, the patient will be discharged to home (at the discretion of the managing team provided there are no other indications for further observation or admission). If pain continues to be present VRS will again be assessed at 120 min after treatment. If pain is not improved to mild range, defined as a VRS ≤ 3, or resolved, crossover treatment will be given. VRS will be obtained at 60 min after cross over treatment; if pain is resolved patient will be discharge to home. If pain continues to be present VRS will be obtained at 120 min after cross over treatment. If pain is not improved to mild pain or resolved; second line treatment of Promethazine 25mg/Benadryl 25mg will be given. VRS will again be obtained 60 min after second line treatment. If pain is not improved to mild pain (VRS ≤3) or resolved neurology consult will be considered. If at any point during treatment the patient develops new neurological symptoms study protocol will be stopped and neurology will be consulted.

Patients will be called 7 days after discharge to access short term outcomes (headache frequency since MEU visit, injection site complications, and satisfaction with treatment.) Patients will again be called at 28 days and a chart abstraction will be done to assess long-term outcomes (recurrent presentation for headache to the MEU, maternal complications including preeclampsia, or fetal complications).

3.4 Study Population and Eligibility Criteria:

Inclusion criteria:
a) Women presenting to Maternal Evaluation Unit at UAB hospital
b) Confirmed live intrauterine pregnancy (previous ultrasound, bedside ultrasound, or fetal monitoring)
c) Complaint of headache
d) Minimal pain level of 4 on VRS

Exclusion criteria:
a) Systolic BP >= 140 or diastolic BP>=90 with 1+ protein on urine dip

b) Systolic BP >=160 or diastolic BP>=105
c) Focal neurological symptoms
d) Altered level of consciousness defined as not being oriented to person, place, situation, and/or year
e) Complaint of seizure
f) Known under lying brain abnormality
g) Fever
h) Use of >3 grams of acetaminophen in past 24hrs
i) ONB in the past 3 months
j) Reported allergy to study medications (Bupivacaine, acetaminophen, or caffeine)

Table 1. Inclusion and Exclusion Criteria

Inclusion	Exclusion
• Women presenting to Maternal Evaluation Unit at UAB hospital • Pregnancy confirmed on bedside US or with fetal monitoring • Complaint of headache • Pain level of ≥4on VRS	• BP >140/90 with 1+ protein on urine dip • BP >160/105 • Focal neurological symptoms • Altered level of consciousness defined as not being oriented to person, place, situation, and/or year • Complaint of seizure • Known under lying brain abnormality • Fever • Use of >3g of acetaminophen in past 24hrs • ONB in the past 3 months • Reported allergy to study medications (Bupivacaine, acetaminophen, or caffeine) • VRS score <4 • No transportation • Non English speaking

3.5 Study Groups:

There will be two intervention groups:

a) Occipital Nerve block Group (Treatment): [8,11]
    a. Trained OB/GYN providers will perform a physical exam to access location of occipital nerve injection based on palpation of bony landmarks.
    b. Site of injection will be cleaned with an alcohol swab.
    c. 5cc of 0.5% bupivacaine will be injected into both right and left occipital nerves using a 2.5 inch 25 gauge needle. The needle will be changed between injecting sites.
    d. After injection is completed sterile gauze will be held on injection sites for 2-3 min or until bleeding is resolved.
b) Oral Tylenol/Caffeine Group (Control):
    a. Tylenol 650mg PO and Caffeine 100mg PO (both Level A treatments for acute headache)[16,17,23]

3.7 Informed Consent

Institutional Review Board (IRB) approved informed consent forms will be presented to the patient, and informed consent must be obtained prior to enrolling the patient in this randomized controlled trial. The full list of potential risks to the patient and her neonate will be listed in the informed consent. The nature and purpose of the study will also be detailed in the informed consent. The patient will be provided a copy of the signed informed consent. The informed consent will only be in English, and thus, only English-speaking individuals may participate in the study.

4. Provider Training

4.1 Procedure Education

All MEU providers will be trained in ONB prior to initiation of study. Procedure methods used will be those recommended by the expert consensus on performance of nerve blocks published by the American Headache Society in 2013.[13] All teaching will be done in a single 30min session during resident didactics. Teaching will be done by a neurology trained provider with extensive experience in ONB. MEU providers will practice injections on models with supervision during the teaching session and will be signed off on procedural technique at the end of the session.

4.2 Procedure Technique

1. Supply Preparation:
    a. 10 cc of 0.5% bupivacaine will be drawn up into a 10 cc syringe using a draw up needle.
    b. A 1.5-2 inch 27 gag needle will be placed on the 10 cc syringe.
    c. A second 1.5-2 inch 27 gag needle will be opened and ready for exchange of needles between injection sites.
    d. Two alcohol swabs
    e. Two 2x2 gauze or 2 cotton balls
2. Positioning: The patient will be positioned in a sitting position leaning forward with forehead resting on crossed arms over a table.
3. Location: Bilateral greater and lesser occipital notches will then be palpated with gloved non sterile hands. After boney landmarks have been identified, one finger pressure will be placed on a unilateral greater occipital notch. Pressure will then be released. Then, on the same side using one finger the lesser occipital notch will be palpated. The patient will be asked which results in more pain. Based the patient response the site of greatest pain will be chosen as the site of injection. Attention will then be turned to the opposite side and testing will be repeated. After bilateral sites of injection has been identified based on physical exam. Injection site will be recorded.

4. Injection: Bilateral sites will be cleaned with an alcohol swab. 5cc of bupivacaine will then be injected after the needle has been inserted until boney land mark is hit. If a boney landmark is not hit the needle will be withdrawn and inserted superiorly to ensure injection in to supra-ostia area. Prior to injection the plunger will be drawing back to assess for vascular structure. If there is return of blood the needle we removed and reinserted. The injection will not be given until there is no return of blood suggesting vascular penetration. After injection into unilateral occipital nerve the needle will be exchanged and 5cc of 0.5% bupivacaine will be injected into contralateral site previously identified using the same technique.

5. Post-injection care: After injections have been completed the patient will hold gauze or cotton balls on bilateral injection site for 2-3 mins. The site will then be examined for continued bleeding. If bleeding is present pressure will be held until bleeding is resolved.

5. Study Procedures

5.1 Screening for Eligibility and Consent

All patients who present to the MEU will be screened for inclusion in the study. If the patient meets eligibility criteria, the MEU provider will present the study, which includes risks, benefits, procedures, and alternatives. The informed consent will be signed after all questions have been answered.

5.2 Randomization

After the treating provider has consented the patient, she will be randomized. Randomization will occur by a predetermined computer-generated block randomization scheme prepared by a study statistician with further stratification by trimester to account for anticipated decrease in headache frequency through pregnancy.

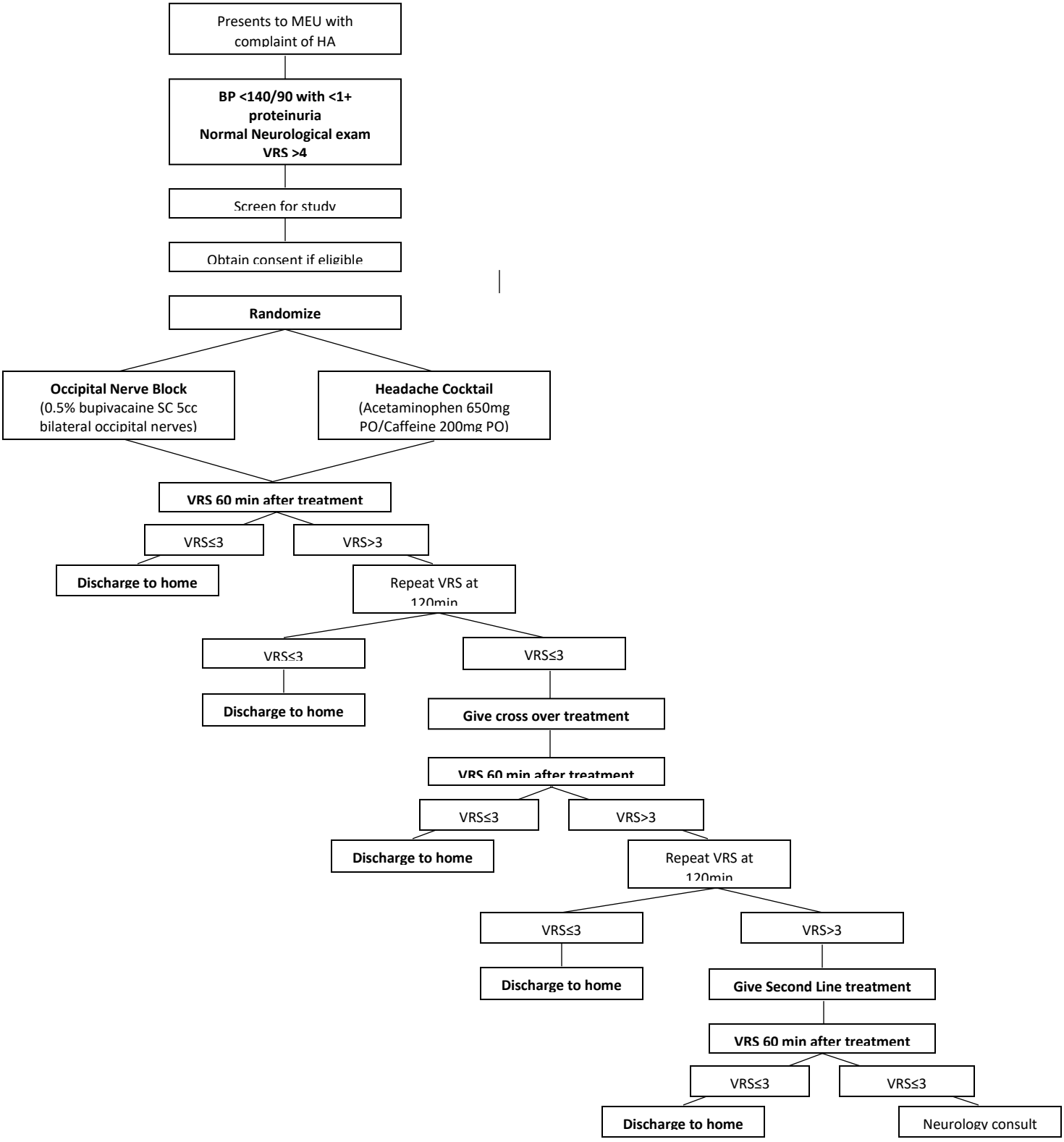
5.3 Flow of patients

All Patients (both treatment and control groups):

a. Blood pressure and urine assessment will be performed in the MEU
b. Fetal viability will be confirmed with ultrasound or fetal heart monitoring
c. Gestational age will be verified by review of early ultrasound of fetal biometry on admission
d. All women with the compliant of headache will have pain accessed with VRS
e. Brief neurological exam will be done on all patients to access for gross deficits (Strength, Sensory, and cranial nerve assessment)
f. Women meeting inclusion and exclusion criteria will be enrolled by MEU provider performing primary assessment
g. Women will be randomized at time of enrollment
h. 60 minutes after treatment VRS score will be obtained if headache is resolved patient will be discharge to home. If pain is not resolved VRS will be repeated at 120 minutes. If pain is mild (VRS ≤ 3) or resolved patient will be discharged to home. If moderate or unimproved patient will be given cross over treatment.

i. 60 minutes after crossover treatment VRS score will be obtained if headache is resolved patient will be discharge to home. If pain is not resolved VRS will be repeated at 120 minutes. If pain is mild or resolved patient will be discharged to home. If moderate or unimproved patient will be given second line treatment of Promethazine 25mg/Benadryl 25mg PO (Level B treatment for headache)[17].
j. 60 minutes after second line treatment VRS score will be obtained if headache is resolved or mild patient will be discharge to home. If pain is not improved neurology consult will be placed.
k. It at any point during study protocol new neurological deficit develops study protocol will be stopped and neurology consult will be placed.

Figure 2. Flow of Patients through Study



5.4 Participant Follow-Up

Patients will be called by investigators at 7 days and 28 days after treatment to access satisfaction with treatment. Patients will be asked if on a scale of 1-10 if they would recommend treatment to a friend; with 10 being recommended and 1 being advise against. Headache free duration will be assessed at 7 days and will be record and days headache free following treatment. At 7 days development of local injection site reaction will also be assessed. At 7 and 28 days need for representation for headache treatment and development of hypertensive disease of pregnancy will be assessed.

In addition investigators experienced in abstracting obstetrical outcomes will review the patient's chart at 28 days to assess for recurrent headache, representation for treatment of headache, and development of hypertensive disease of pregnancy.

5.5 Adverse Event Reporting

A Data Safety Monitoring Board (DSMB) will be formed and consist of three individuals within the Division of Maternal-Fetal Medicine and Department of Pediatrics who have no ties to the study design, evaluation of results or potential authorship of the manuscript. The primary purpose of the DSMB will be to monitor patient safety. The members of this board will be Brian Smins, Janeen Arbuckle, and Rhiannon Reed.

The purpose of the study is to determine whether ONB is a beneficial treatment for headache in pregnancy in an acute care setting. In pregnancy treatment of headache is delayed due to concern for fetal exposure and provider experience. As a result headache treatment is not standardized in pregnancy and varies widely based on provider comfort and experience. Expanding the use of ONB in this population may lead to improved access to treatment.

Potential risks of ONB are injection site infection, development of hematoma and ecchymosis. The risk of infection is the same as any subcutaneous infection. Risk will be minimized by cleaning the injection site with alcohol prior to injection. Sterile tips will be used and injecting needs will be changed between injections to further minimize risk of injection site infection. To reduce the risk of hematoma and ecchymosis pressure will be held on injection site for 2-3 min following injection.

We define an adverse event as an undesirable experience or outcome occurring in a research participant, regardless of whether participation in the research study caused the event to occur. For example, maternal death and/or fetal demise are known risks of pregnancy, and while not known to be related to occipital nerve block, would be considered an adverse event if it occurred during the study. All serious adverse events will be reported to the DSMB and IRB. A serious adverse event will include the following events, if occurring within 28 days of treatment:

a. Injection site complications:
    a. Infection
    b. Hematoma
b. Development of hypertensive disease of pregnancy

c. Death
    a. Maternal
    b. Fetal (stillbirth)
    c. Neonatal
d. Life-threatening event
e. Prolonged maternal hospitalization >5 days
f. Any other event not listed that the investigators believe may have been caused by the intervention.

5.6 Study Outcome Measures and Ascertainment

5.6.1 Primary Outcome

Based on guidelines from the International Headache Society the primary outcome is the portion of women who experience resolution of headache or improvement of headache to mild range (VRS ≤ 3) at 2 hours following treatment with Occipital nerve block as compared to acetaminophen/caffeine cocktail.[24]

5.6.2 Secondary Outcomes

a. Response to treatment within 2 hours
b. Need for crossover treatment
c. Response to cross over treatment at 60 or 120 min
d. Need for second line treatment
e. Response to second line treatment at 60 min
f. Need for neurology consult
g. Need for admission for treatment of headache
h. Need for representation for treatment of headache with 28 days
i. Development of hypertensive disease of pregnancy within 28 days
j. Satisfaction with treatment at 7 days
k. Duration of headache free period at 7 days
l. Development of hypertensive disease of pregnancy within 7 days
m. Response for headache treatment will be adjusted for by primary headache disorder
n. Need for neuroimaging within 28 days
o. Injection site complication (infection, hematoma, and ecchymosis)

5.6.3 Data Collection and Data Management

We will collect data at 7 and 28 days from study participants. Relevant data will be collected initially to assess eligibility. Complete baseline information and outcome data will be collected by trained MEU providers by direct interview and chart review. The study statistician and the primary investigator will be responsible for coordinating the overall data management of the trial. Data management includes: development and maintenance of study case report forms and the electronic database, procedures for

data entry, data editing, and compilation; procedures for quality control, data verification, confidentiality, and security. Data will be collected and managed with REDCap (Research Electronic Data Capture), an established, secure, web-based data capture and management tool developed at Vanderbilit University and supported by the bioinformatics team at UAB. Missing data rates and patterns will be assessed monthly by the primary investigator, and remedial measures, including re-abstraction of data and retraining of staff, will be used as needed to minimize missing data.

Figure 3. Visual Pain Scale to be used

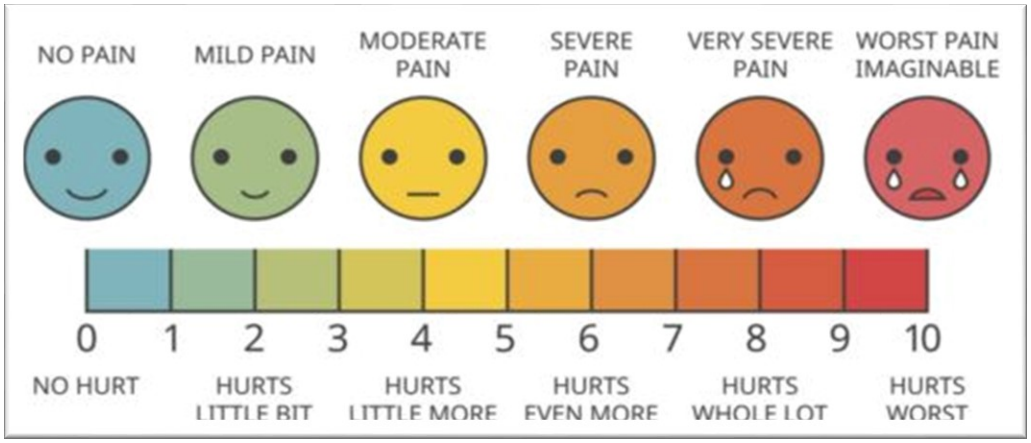


Table 2. Outline of Data to be Collected

Prior To Treatment	Treatment	7 days Following treatment	28 days following treatment
○ Demographics (age, race, ethnicity, marital status, insurance status) ○ Obstetric history (prior cesarean, number of deliveries) ○ 5 point headache history (family, life, attack, general, and medication) ○ Maternal BMI ○ Gestational age ○ Pregnancy comorbidities ○ Assessment for hypertensive disease of pregnancy ○ Basic neurological exam	**After primary treatment** ○ VRS score at 60 min ○ VRS score at 120 min if VRS ≥3 at 60 min **After crossover treatment** ○ VRS score at 60 min ○ VRS score at 120 min if VRS ≥3 at 60 min **After 2nd line treatment** ○ VRS score at 60 min ○ **Need for admission** ○ **Need for Neurology consult**	**Telephone Call:** ○ Timing to return to headache in days ○ Satisfaction with headache treatment, likeliness of recommending treatment ○ Complication of hematoma, ecchymosis, or site infection ○ Need for return to EU for treatment of HA ○ Development of hypertensive disease of pregnancy ○ Maternal or fetal complication	**Telephone Call:** ○ Need for return to EU for treatment of HA ○ Development of hypertensive disease of pregnancy ○ Maternal or fetal complication **Chart Review:** ○ Need for return to MEU for treatment of HA ○ Development of hypertensive disease of pregnancy ○ Maternal or fetal complication

5.6.4 Follow-up and Outcome Ascertainment Periods

Response to treatment will be ascertained by VRS prior to treatment and again at 60 min after treatment and 120 minutes after treatment if headache is not resolved or mild at 60 min. VRS score will again be obtained 60 min after crossover treatment and 120 min after crossover treatment if headache is not resolved or is mild. If second line treatment is given VRS will be obtained 60 min after crossover treatment. Maternal outcomes (e.g. injection site infection or development of pre-eclampsia) are delayed outcomes which will require review after discharge. These outcomes will be assessed at 7 and 28 days after treatment by telephone call and chart review.

5.7 Telephone scripts:

5.7.1 Telephone script at 7 days:

Introduce yourself

Hello, my name is _____ from the department of maternal fetal medicine at UAB hospital.

Tell the person why you are calling

I am calling to follow up on treatment you received for a headache at the UAB Maternity Evaluation Unit. Is now a good time to discuss your treatment?

If person says "No," thank the person for her time and ask if there is a better time to call back.

If person says "Yes," inform them about use of their private health information (PHI) that will be collected during the phone call.

> Use the following language: We will be collecting information about you during this phone call. You taking part in this phone call is completely voluntary. The information you provide will only be seen by researchers at UAB hospital. We try to make sure that the information we collect from you is kept private and used only for the headache research study you were enrolled in. If you do not agree to continue to phone call, it will not affect your care at UAB Hospital.

Begin questionnaire

1. How satisfied were you with the treatment you received? Zero being strongly dissatisfied, 2 being neutral, and 4 being very satisfied.
2. How likely are you to recommend the treatment you received to a friend? Zero Very unlikely, 2 no opinion, 4 very likely
3. Have you had a return of headache since your treatment? If yes how long was it until your headache returned?
4. If your headache has returned is it the more, the same, or less severe than it was prior to treatment?

5. For patients that received ONB: Did you develop any signs of infection or swelling at the site of your injection? If so can you describe them to me?

6. Since your treatment have you represented to any provider (ER, MEU, or clinic) for treatment of headache?

7. Since being treated has your doctor diagnosed you with any blood pressure problems in pregnancy such as gestational hypertension or pre-eclampsia?

8. Since being treated have you developed any new complications in your pregnancy?

9. Are there any other aspects of your headache treatment you would like to discuss with me?

Thank the person for participating is the study

Thank you for taking time to discuss your experience with me and for participating in the study. You will be contacted again in 3 weeks to readdress your experience.

5.7.2 Telephone script at 28 days:

Introduce yourself

Hello, my name is _____ from the department of maternal fetal medicine at UAB hospital.

Tell the person why you are calling

I am calling to follow up on treatment you received for a headache at the UAB Maternity Evaluation Unit. Is now a good time to discuss your treatment?

If person says "No," thank the person for her time and ask if there is a better time to call back.

If person says "Yes," inform them about use of their private health information (PHI) that will be collected during the phone call.

> Use the following language: We will be collecting information about you during this phone call. You taking part in this phone call is completely voluntary. The information you provide will only be seen by researchers at UAB hospital. We try to make sure that the information we collect from you is kept private and used only for the headache research study you were enrolled in. If you do not agree to continue to phone call, it will not affect your care at UAB Hospital.

Begin questionnaire

1. How satisfied were you with the treatment you received? Zero being strongly dissatisfied, 2 being neutral, and 4 being very satisfied.

2. How likely are you to recommend the treatment you received to a friend? Zero Very unlikely, 2 no opinion, 4 very likely

3. Since your treatment have you represented to any provider (ER, MEU, or clinic) for treatment of headache?

4. Since being treated has your doctor diagnosed you with any blood pressure problems in pregnancy such as gestational hypertension or pre-eclampsia?

5. Since being treated have you developed any new complications in your pregnancy?

6. Are there any other aspects of your headache treatment you would like to discuss with me?

Thank the person for participating is the study

Thank you for taking time to discuss your experience with me and for participating in the study. You will not be contacted further regarding this study.

6. Statistical Considerations

6.1 Sample Size for Primary Outcome

The total sample size is estimated based on the analysis for the primary outcome. From this we estimate our ability to detect a difference in secondary outcomes. All sample size and power estimates are based on *treating a pain improvement as a dichotomous outcome with the endpoint being resolution of pain or improvement in pain to mild severity (VRS ≤3).* The improvement of headache with acetaminophen 500mg/Aspirin 500mg/Caffeine 130mg PO is 50% pain reduction to mild headache at 65min.[23] Given Aspirin is not felt to be a potent anti-headache medication we have assumed the same or similar response to Acetaminophen 650mg/Caffeine 100mg PO cocktail to reduce exposure to aspirin given theoretical fetal risk of early closure of ductus arteriosus. We anticipate a 58-90% reduction following occipital nerve block.[19,20] Given recent randomized controlled trails evaluating treatment of acute headache with ONB showing a response of 90% at 45 min and retrospective studies evaluating the use of ONB in the setting of headache prophylaxis showing a 82% with mild or significant response and 58% showing significant response at 1 month, we have chosen an 85% response rate to account for this variation in results. We estimate that a total of 62 women (31 ONB and 31 Acetaminophen/Caffeine) will be sufficient to detect a difference in headache resolution at 1 hour, with 80% power and a 5% significance level. To account for a 5% loss to follow up, we will aim to enroll 86 women. On average there are 750 evaluations in the MEU each month with 19-26 of these patients presenting with the chief complaint of headache. Based on a 25% enrollment rate we have calculated it will take 16 months to complete enrolment.

Table 3: Sample Size*

Headache resolution at 2 hours		**Sample Size per Group**	**Total Sample Size**
ONB	**Acetaminophen/Caffeine**		
90%	50%	19	38
85%	50%	28	56
80%	50%	38	76

70%	50%	93	186
60%	50%	387	774

*Based upon 80% power and significance of 0.05

Table 4: Enrollment Time

Enrollment rate per month	Enrollment goal per month	Total study time in month
10%	2	31
25%	5	12
50%	10	6.2
75%	15	4.1

6.2 Power for Other Outcomes

The sample size of 86 for the primary aim will be sufficient to provide 80% power to detect an absolute difference of 30% between ONB and acetaminophen/caffeine headache cocktail (odds ratio of 4, risk ratio of 1.6) at significance level of 5%. While this study will not be definitive regarding the potential benefits associated with ONB for specific headache disorders when compared to acetaminophen/caffeine, it will provide important baseline information to power a future randomized study evaluating the benefits of ONB for treatment of specific headache disorder in pregnancy. In addition we anticipate we will be underpowered to detect differences between individual components concerning prophylactic benefit of ONB.

6.3 Analysis Plan

Data analyses will adhere closely to those recommended by the International Headache Society Guidelines for controlled trial on treatment of acute migraine attacks.[24] Analyses will follow the intention to treat principle in which participants will be analyzed in the group to which they were randomized, regardless of whether or not they received the assigned intervention.[25]

6.3.1 Primary analysis: Descriptive statistics will characterize the group of individuals recruited and investigate comparability of the two groups at baseline. Formal statistical testing will be limited to selected baseline characteristics considered to be prognostic factors for the primary outcome such as known diagnosis of primary headache disorder and baseline headache severity. The categorical prognostic factors will be compared between trial groups by using the Chi-square test of association or Fisher's exact tests as appropriate. The two-group independent t-test and the Mann-Whitney U test, as appropriate, will be used to compare quantitative characteristics between the trial groups.

The primary outcome and other categorical secondary outcomes will be compared between intervention groups by using the Chi-square test. We will use the Breslow-Day test to assess homogeneity of the odds ratios across the gestational age categories. Multivariable logistic regression

models will be used to estimate treatment effects while adjusting for potential confounders. Characteristics that are imbalanced at baseline will be considered as covariates in multivariable models. Adjusted odds ratios and 95% confidence intervals will be estimated. Multivariable modified Poisson regression models will be considered to estimated adjusted risk ratios and 95% confidence intervals.

6.3.2 Secondary Analysis.

Secondary outcomes will be evaluated using the approaches for categorical variables described above. Quantitative secondary outcomes will be compared using the two-sample t-test or Mann-Whitney U tests (as appropriate) as described above. Multivariable regression models including imbalanced baseline characteristics will be explored to determine estimated treatment differences while accounting for potential covariates. Estimated beta coefficients and 95% confidence intervals will be generated.

6.4 Interim Monitoring

Given the small sample size we do not plan an interim analysis. The interventions compared in this trial are both currently used in clinical obstetric practice and there is no defined standard of care. Therefore, no serious or life threatening adverse events are expected. Nonetheless, the following measures will be taken to monitor and investigate adverse events:

1. Independent Data and Safety Monitoring Board (DSMB): We have assembled an independent, study-specific DSMB composed of three distinguished individuals Brian Smins, Janeen Arbuckle, and Rhiannon Reed who represent appropriate expertise (maternal health, neonatology, clinical trials, and biostatistics). They will provide oversight to assure that the trial accrues at a sufficient rate and that the safety and privacy of all study participants is assured. Members of the DSMB are not involved in any aspect of the trial operation. The DSMB will be provided progress reports and adverse event reports on a monthly basis to review study progress and monitor adverse events.
2. Adverse events reporting: Detailed information concerning adverse events will be collected and evaluated throughout the trial. The DSMB will review all Adverse Event Report forms and other safety data.

7 Future Studies

8 References

1. Rasmussen BK, Jensen R, Schroll M, Olesen J. Epidemiology of headache in a general population--a prevalence study. Journal of clinical epidemiology 1991;44:1147-57.
2. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 2007;68:343-9.
3. Marcus DA, Scharff L, Turk D. Longitudinal prospective study of headache during pregnancy and postpartum. Headache 1999;39:625-32.
4. Bushman ET, Varner MW, Digre KB. Headaches Through a Woman's Life. Obstetrical & gynecological survey 2018;73:161-73.
5. Robbins MS, Farmakidis C, Dayal AK, Lipton RB. Acute headache diagnosis in pregnant women: a hospital-based study. Neurology 2015;85:1024-30.
6. Loder E, Biondi D. General principles of migraine management: the changing role of prevention. Headache 2005;45 Suppl 1:S33-47.
7. Cuadrado ML, Aledo-Serrano A, Navarro P, et al. Short-term effects of greater occipital nerve blocks in chronic migraine: A double-blind, randomised, placebo-controlled clinical trial. Cephalalgia : an international journal of headache 2017;37:864-72.
8. Dach F, Eckeli AL, Ferreira Kdos S, Speciali JG. Nerve block for the treatment of headaches and cranial neuralgias - a practical approach. Headache 2015;55 Suppl 1:59-71.
9. Gul HL, Ozon AO, Karadas O, Koc G, Inan LE. The efficacy of greater occipital nerve blockade in chronic migraine: A placebo-controlled study. Acta neurologica Scandinavica 2017;136:138-44.
10. Hascalovici JR, Robbins MS. Peripheral Nerve Blocks for the Treatment of Headache in Older Adults: A Retrospective Study. Headache 2017;57:80-6.
11. Tang Y, Kang J, Zhang Y, Zhang X. Influence of greater occipital nerve block on pain severity in migraine patients: A systematic review and meta-analysis. The American journal of emergency medicine 2017;35:1750-4.
12. Tobin J, Flitman S. Occipital nerve blocks: when and what to inject? Headache 2009;49:1521-33.
13. Blumenfeld A, Ashkenazi A, Napchan U, et al. Expert consensus recommendations for the performance of peripheral nerve blocks for headaches--a narrative review. Headache 2013;53:437-46.
14. Voigt CL, Murphy MO. Occipital nerve blocks in the treatment of headaches: safety and efficacy. The Journal of emergency medicine 2015;48:115-29.
15. Govindappagari S, Grossman TB, Dayal AK, Grosberg BM, Vollbracht S, Robbins MS. Peripheral nerve blocks in the treatment of migraine in pregnancy. Obstetrics and gynecology 2014;124:1169-74.
16. Lipton RB, Baggish JS, Stewart WF, Codispoti JR, Fu M. Efficacy and safety of acetaminophen in the treatment of migraine: results of a randomized, double-blind, placebo-controlled, population-based study. Archives of internal medicine 2000;160:3486-92.
17. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the american headache society evidence assessment of migraine pharmacotherapies. Headache 2015;55:3-20.
18. James AH, Brancazio LR, Price T. Aspirin and reproductive outcomes. Obstetrical & gynecological survey 2008;63:49-57.
19. Korucu O, Dagar S, Corbacioglu SK, Emektar E, Cevik Y. The effectiveness of greater occipital nerve blockade in treating acute migraine-related headaches in emergency departments. Acta neurologica Scandinavica 2018;138:212-8.
20. Allen SM, Mookadam F, Cha SS, Freeman JA, Starling AJ, Mookadam M. Greater Occipital Nerve Block for Acute Treatment of Migraine Headache: A Large Retrospective Cohort Study. Journal of the American Board of Family Medicine : JABFM 2018;31:211-8.

21. Negro A, Delaruelle Z, Ivanova TA, et al. Headache and pregnancy: a systematic review. The journal of headache and pain 2017;18:106.
22. Schoen JC, Campbell RL, Sadosty AT. Headache in pregnancy: an approach to emergency department evaluation and management. The western journal of emergency medicine 2015;16:291-301.
23. Lipton RB, Diener HC, Robbins MS, Garas SY, Patel K. Caffeine in the management of patients with headache. The journal of headache and pain 2017;18:107.
24. Diener HC, Tassorelli C, Dodick DW, et al. Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults: Fourth edition. Cephalalgia : an international journal of headache 2019:333102419828967.
25. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. International journal of surgery (London, England) 2012;10:28-55.