Protocol Title: A Prospective Controlled Treatment Trial for Post-Traumatic Headaches

NCT#: 03007420

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A. SPECIFIC AIMS AND HYPOTHESIS

1. **To compare the efficacy of Occipital Nerve Blocks (ONB) vs. Cervical Medial Branch Blocks (CMBB) in patients presenting with post-traumatic headache (PTH) who were non-responsive to previous interventional management.**

    - To examine differences in Numeric Rating Scale (NRS) pain measurements (> 50% or < 50% pain reduction)
    - To examine differences in Migraine Disability Assessment (MIDAS) and Pediatric Migraine Disability Assessment (PedMIDAS) scores
    - To describe differences in functional outcomes using the Functional Disability Inventory (FDI) and the Pain Disability Index (PDI).
    - To study differences in Quality of Life (QL) and Pediatric Quality of Life (PedsQL) scores

Hypothesis: Treatment with CMBB with steroids and lidocaine will be associated with a greater improvement in pain scores, functional and QL scores than the ONB.

2. **To describe the baseline socio-demographic characteristics of individuals with PTH and chronic axial neck pain.**

    - To study gender, BMI, age, school and work absences and disrupted sleep
    - To study psychological (anxiety, depression) and pain related comorbidities (whole body pain, gastrointestinal problems, small fiber neuropathy)
    - To study correlation to nature of injury (concussion vs. head injury and severity of injury based on 1997 AAN guidelines)
    - To study previous treatment methods and interventions

Hypothesis: Of the participants with PTH, the majority will exhibit school or work absences and disrupted sleep. The majority of participants will also have higher scores of anxiety and depression, more pain related comorbidities, history of prior injury, and previous treatment from other providers.

3. **To describe and understand how clinical features, physical exam characteristics, and radiologic findings among patients with PTH and axial neck pain associate with treatment response for each of the treatment options.**
    - To assess physical exam characteristics (axial neck pain which is extension related, myofascial spasms and occipital neuralgia)
    - To characterize the diagnosis given by the clinicians in their notes
    - To characterize the presence of radiologic or predictive clinical findings such as facet arthropathy, disc changes, spondylolysis, or spondylolisthesis

Hypothesis: Treatment response (improvement in pain) will be associated with features on the physical exam (neck pain with extension, headaches associated with cervicogenic causes) and with presumed anatomic diagnosis (facet arthropathy, spondyloysis, spondylolisthesis, axial and discogenic pain).

4. **To study the effects of socio-demographic, clinical, and psychosocial predictor variables on CMBB and ONB treatment outcomes.**

Hypothesis: The likelihood of improvement with CMBB or ONB is associated with a combination of socio-demographic, clinical/anatomic, and psychosocial variables. Improved responses following treatment with ONB and CMBB will be associated with a shorter duration of pain prior to intervention, normal weight, younger age and lack psychological comorbidities.

5. **To study the safety of the ONB and CMBB treatment.**
    - To study fluoroscopy time and amount of radiation exposure
    - To study sedation method if any including the use of propofol, benzodiazepine or fentanyl vs. awake procedure
    - To study anesthetic complications

Hypothesis: The time of fluoroscopy and radiation exposure will be low, and anesthetic complications or side effects will be minimal.

B. Background and Significance

PTH is the most common physical symptom following concussion[1, 2] with up to 36% of athletes reporting headaches throughout the first year after concussion. PTH is defined as a secondary headache disorder through ICDH-3 criteria[2]. There is an estimated 3.8 million sports related concussions in the US each year, and concussion has become an important global health issue in recent years[3]. PTH pathophysiology is predominantly migrainous and cervicogenic in nature[4]. Neurogenic inflammation after head injury can lead to activation of meningeal nociceptors and the trigeminovascular system leading to development of post-traumatic migraine. This can be secondary to direct injury of the trigeminal afferent nerves or to leptomeningeal or cerebrovascular structures innervated by trigeminal nerves. Activated glial cells, with increased production of pro-inflammatory substances have been implicated in the development and persistence of pain. The neuronal-glial signaling is suspected to play a role in sensitizing afferent trigeminal nociceptors. Prolonged inflammation and chronic hyper excitability are thought to predispose to a pathological pain state[5].

In addition, a common etiology of headache and neck pain in football related concussions is whiplash associated disorder (WAD)[6], secondary to acceleration-deceleration injuries. Pain may be generated by inflammation of the high cervical facet joints[7], traumatic neuralgias and myofascial injury[8]. Occipital headaches result from activation of the sensory branches of C2 and C3 peripherally, causing occipital neuralgia, with cervical facet inflammation and myofascial spasms resulting in cervicogenic headaches. The reported convergence of sensory C2 and the nucleus caudalis of the trigeminal nerve may result in exacerbation of post-traumatic migraines[9,10], and therefore treatment of cervicogenic headache etiologies could also improve post-traumatic migraines. The mechanism of overlap between the trigeminal nerve and the cervical nerves is known as convergence, whereby trigeminal nerve activation produces symptoms in the trigeminal and cervical territories and cervical activation produces symptoms in the cervical and trigeminal territory[11]. In addition, multiple lifetime concussions in older and retired football players with

subsequent chronic cervical facet inflammation increase the risk of degenerative cervical arthritis and, therefore, the risk of cervicogenic headaches, which due to convergence also increases the risk of post-traumatic migraines[11].

Headache and neck pain following concussion are potentially treatable and resolve over time. Nerve blockade may enhance the recovery of appropriate neural circuits involved in the pathophysiology of chronic headache. Currently, no evidence-based guidelines exist for treatment of PTH. Adoption of "brain rest" for 1-2 weeks, followed by gradual return to activity and avoiding "second-impact syndrome" are current practice. The use of medications controlling neuropathic pain is of partial benefit for some patients and requires several weeks to evaluate, and as many take 4-6 weeks to show effect.[10] Adverse effects like sedation, mood changes, cardiac side effects of pharmacologic agents are often not compatible with the demands of athletics. For those patients where sports performance is paramount, they may therefore not be able to tolerate typical medications. Incidence of chronic post-concussive headaches (> 3 months) at 1 year is 8.4% - 35% and at 4 years is up to 25%.[11] Therefore, patients can have significant disability from their post-traumatic headaches for many years after their injury. Without appropriate treatment, these headaches can remain as chronic headaches. Over-the-counter and other symptomatic medication overuse can exacerbate and prolong PTH significantly, secondary to rebound headaches[2]. Successful treatment is essential since PTH limits return to sports as well as more general activities of living, such as work and school. Most interventions currently in use partially help and take several weeks to months for noticeable benefit. Additionally, a multicenter, double-blind, placebo-controlled trial recently published in *The New England Journal of Medicine* showed no significant differences among amitriptyline, topiramate and placebo in reducing headache days or related disability after a 24-week period, and showed an increase in side effects (Powers et al, NEJM 2016). PTH interventions, including ONB and CMBB are used in the treatment of primary headache disorders and neck pain from cervical arthritis and may provide more improved, faster and more sustained pain relief in many patients[12]. In addition, given that most of the action of the nerve blocks is local, there are significantly fewer side effects than in more typical headache medications. Injections that use corticosteroids may be beneficial in post-traumatic headache by reducing inflammation and therefore mechanical allodynia[13]. Injection of corticosteroids in the cervical facet joint area has shown up to 13 months of pain relief [12]. This prolonged effect may be

secondary to central pain modulation[13]. Ultimately, nerve blocks may be a more effective and efficient post-traumatic headache given the onset of effect and the minimal side effects.

To date, there have been no prospective studies of procedural treatments for medically refractory PTH and none in the adolescent and young adult population in whom football injuries are common. Despite the frequent clinical practice of using ONB and CMBB for occipital neuralgia, cervical arthritis and cervicogenic headaches, there has been no adequate scientific investigation into the use of these interventions for PTH. Given that PTH is typically felt to be secondary to inflammatory reaction to trauma, the use of injection of corticosteroids may be more effective in PTH than in typical headache disorders. There is also no adequate comparison of these interventions to medications.

C. PRELIMINARY STUDIES

There are no preliminary studies comparing the effect of interventions and medications on PTH to date.

D. DESIGN AND METHODS

1. Study Design

We propose a randomized, controlled clinical trial and prospective follow up to evaluate the effect of invasive procedures in the management of PTH. Adolescents and young adults will be recruited from Boston Children's Hospital, Beth Israel Deaconess Medical Center, and Mass General Brigham Pain clinics, Concussion clinics and Headache clinics. Patients will be recruited beginning July 2017.

We propose to study the effect of CMBB versus ONB treatment with lidocaine and steroids. Patient demographics (e.g. age, sex, ethnicity, and race), disease characteristics (e.g. symptoms, duration of the disease, medications taken, etc.), and description of the intervention will be collected. As part of the standard of clinical care at the study sites, patients will complete the intake Standard Pain Questionnaire at baseline. During the first two months of the study, patients will be contacted by our research team via email on a weekly basis requesting them to complete a study questionnaires. After the initial 2 months on the study, we will continue to contact patients every 2 weeks over the next 10-months. Patients will remain in the study up to 12 months after enrollment.

2. Patient Selection and Inclusion/Exclusion Criteria

Patients who meet the criteria below will be recruited from Boston Children's Hospital, Beth Israel Deaconess Medical Center, and Mass General Brigham Pain clinics, Concussion clinics and Headache clinics.

Inclusion Criteria:

- Age 14 – 45 years.
- History of post-traumatic headache or neck pain following a concussion or head injury within the last 2 years.
- Self-reported lack of meaningful benefit with at least one previous treatment trial. Previous treatment could include a migraine prophylactic medication, a neuropathic pain medication, a physical intervention, or a cognitive-behavioral intervention.

Exclusion Criteria: Subjects will be excluded in the following circumstances:

- Significant underlying psychological concerns, as determined by study psychologist up on review of standardized assessment
- Lack of parental consent and child assent (if patient age <18 years) or lack of consent (if patient age >18 years). Unable to complete the questionnaire, based on parental or patient estimation of cognitive or language limitations

3. Description of Study Treatments or Exposures/Predictors

Patients enrolled in the study will be randomized to receive either an ONB (Figure 2, additional procedure details provided below) with dexamethasone 2mg each site with 3ml 1% lidocaine, for a total of two sites or a CMBB (Figure 3a & 3b, additional procedure details provided below) with dexamethasone 1.5mg each site with 2 ml 1% lidocaine, for a total of three sites on each side. The assignment of the procedure will be randomized however neither the patients nor the investigator will be blinded to the procedure. If patients exhibit a $\geq$50% pain reduction on receiving the block evaluated after four weeks, then they may continue to receive blocks as needed, but not more than one every three months. If patients exhibit < 50% pain reduction, the patient will be treated as per the clinician's judgment with the possibility of a cross over to the other treatment option in the protocol.

All patients will be followed for 12 months after enrollment and after the crossover of treatments they will continue to be treated and followed per clinical standard of care.

As part of this study, patients will need to complete 8 follow-up visits, of which the first and second will be in-person clinical visits and the other follow-ups could either be conducted in-person at the clinic or via teleconference - video:

a) Visit 1: in-person clinic visit

- At the first visit to the clinic, the physician or nurse will verify the patient's name and date of birth, and will collect information about pain, current and past medicines, and general health. The physician will perform a physical examination and measure heart rate, blood pressure and respiratory rate, and conduct a neurological exam.
- Baseline questionnaires will be taken, including Pain (NRS), Concussion Symptom Score, MIDAS/PedMIDAS, Anxiety, Depression, FDI, and QL.

At the end of the visit, all enrolled patients will be randomized to one of the two minimally invasive procedures, the ONB or the CMBB. Information from the patient's most recent clinical visit note (retrieved from the patient's medical record) may be used to obtain Visit 1 data.

b) Visit 2: Cervical and medial branch block procedures

The procedure will be performed at Boston Children's Hospital or Beth Israel Deaconess Medical Center or Mass General Brigham Operation Room. Patients may receive sedation as per clinical need, and procedures will be performed in a standardized manner. Neither the patient nor the investigator will be blinded to the type of procedure.

Patients will not be universally sedated however a particular subset of patients may receive sedation. Pediatric patients and some adults with extreme anxiety to procedures will receive mild IV sedation with fentanyl, midazolam and occasionally propofol. This is not general anesthesia but is Monitored Anesthesia Care (MAC). Patients will be awake enough to report any symptoms or discomfort. Anesthesia will be administered either in an Operating Room or Day Surgery Unit setting of the study sites and not in an outpatient setting. A separate anesthesia team consisting of an anesthesiologist and nurse anesthetist (CRNA) will be responsible for administration of anesthesia and airway maintenance. Vital signs will be monitored every 5 minutes and anesthesia adjusted based on patient discomfort.

Details on doses of dexamethasone and lidocaine to be used:

<u>Dexamethasone doses:</u>

Occipital nerve block: 2 mg / block

Cervical facet injections/medial branch block: 1.5 mg / facet joint

Lidocaine doses:

Occipital nerve block: 3 ml of 1% lidocaine / block

Cervical facet injections/medial branch block: 2 ml of 1% lidocaine / facet joint

DESCRIPTION OF OCCIPITAL NERVE BLOCK:

The patient will be in the seated position. The back of the head (occipital area) will be prepped with alcohol pads. Following this, the left or right greater occipital nerve will be accessed at the midpoint of the occipital protuberance and the mastoid process using a 25-gauge 1-1/2 inch needle. 1% lidocaine will be used for skin and subcutaneous analgesia. Following this, area of the left greater occipital nerve will be accessed and the injection fanned. A mixture of 2 mg of dexamethasone and 3 ml of 1% lidocaine will be injected into this area. Following this, the contralateral side will be addressed in a similar fashion (if patient needs bilateral injection). A total of 4 mg of dexamethasone and 6 mL of 1% lidocaine will be injected. The patient will be observed in recovery for complications of bleeding, worsening of symptoms, or paresthesias.

DESCRIPTION OF CERVICAL FACET / MEDIAL BRANCH BLOCK:

The patient will be placed in the prone position in the procedure room on a Steris table with fluoroscopy. The back of the neck will be prepped and draped in the usual sterile fashion with ChloraPrep. Under fluoroscopy guidance the high cervical facets will be visualized in AP, oblique and lateral views. Using a 22-gauge, 2-1/2-inch spinal needle, the left C 4-5 facet joint/medial branch area will accessed under fluoroscopy. 1% lidocaine will be used for the skin and subcutaneous analgesia. Contrast omnipaque 300 mg/ ml, 0.5 ml will be used to confirm the needle position. Similar procedures will be repeated at C2-3 and C 3-4 levels. Similar procedures will be done on the corresponding levels on the contralateral side. Dexamethasone 1.5 mg with 2 mL of 1% lidocaine will be injected at each of these levels. A maximum of 9 mg of dexamethasone will be used. The patient will be observed in recovery for complications of bleeding, worsening of symptoms or paresthesias.

After the procedure is completed, all patients will recover in the Post Anesthesia Care Unit (PACU). Patients will be examined and they will be required to complete questionnaires. Patients will be discharged from the hospital per hospital guidelines and standard of clinical practice.

c) Visit 3 to 8: in-person visit or tele-conference

At 1, 2, 3, 6, 9, and 12 months after enrollment, patients will be evaluated to determine how well they did after the procedures. This would include the same steps from previous appointments. If the study treatment has been helpful, the physician might decide to continue the treatment with the procedures as needed. Clinical criteria and patient – physician agreement would be used to determine next steps in the patient's treatment plan.

d) E-mail questionnaires:

During the first two months of the study, patients will be contacted by our research team via email on a weekly basis requesting them to complete a short questionnaire that includes questions about their pain scores (NRS), MIDAS/ PedMIDAS, QL, FDI, Anxiety, Depression, and Concussion Symptoms Score. After the initial 2 months on the study, we will continue to contact patients every 2 weeks over the next 10-months (follow-ups over a total of 12 months). See Table 1 below for REDCap survey schedule.

Table 1: Schedule of REDCap surveys

Follow-Up	**Questionnaire**
Week 0	Migraine disability
	Pain Assessment
	Concussion Score
	General functionality
	Quality of Life
	Anxiety
	Depression
Week 1	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Week 2	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Week 3	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Improvement Evaluation 1m	Pain Assessment
	Concussion Score
	General Functionality

	Side Effects Related to Invasive Treatment
	Improvement
	Additional Procedures
Week 5	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Week 6	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Week 7	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Improvement Evaluation 2m	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
	Quality of Life
	Anxiety
	Depression
	Improvement
	Additional Procedures
Week 10	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Improvement Evaluation 3m	Migraine disability
	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
	Quality of Life
	Anxiety
	Depression
	Improvement
	Additional Procedures
Week 14	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Week 16	Pain Assessment
	Concussion Score
	General Functionality

	Side Effects Related to Invasive Treatment
Week 18	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Week 20	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Week 22	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Improvement Evaluation 6m	Migraine disability
	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
	Quality of Life
	Anxiety
	Depression
	Improvement
	Additional Procedures
Week 26	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Week 28	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Week 30	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Week 32	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Week 34	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Improvement Evaluation 9m	Migraine disability
	Pain Assessment

	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
	Quality of Life
	Anxiety
	Depression
	Improvement
	Additional Procedures
Week 38	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Week 40	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Week 42	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Week 44	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Week 46	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
Improvement Evaluation 12m	Migraine disability
	Pain Assessment
	Concussion Score
	General Functionality
	Side Effects Related to Invasive Treatment
	Quality of Life
	Anxiety
	Depression
	Improvement
	Additional Procedures

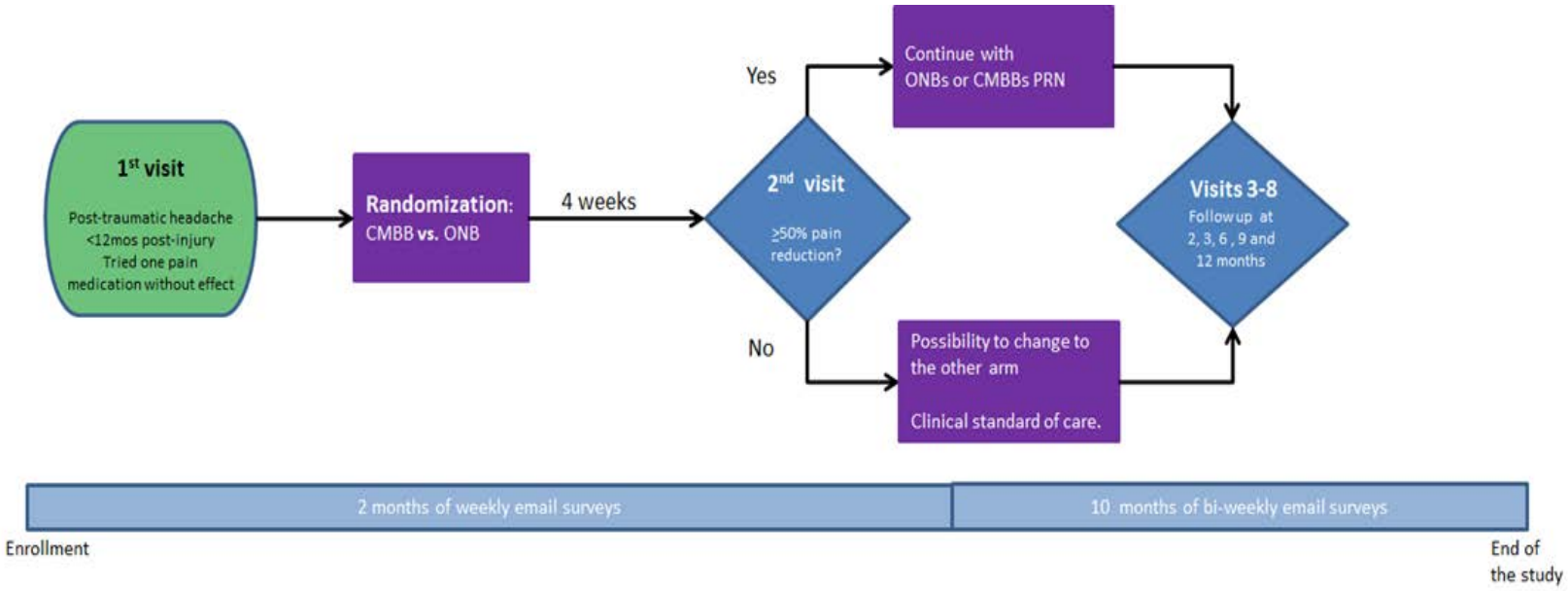

Figure 1: *Study design for a prospective controlled trial in posttraumatic headaches*

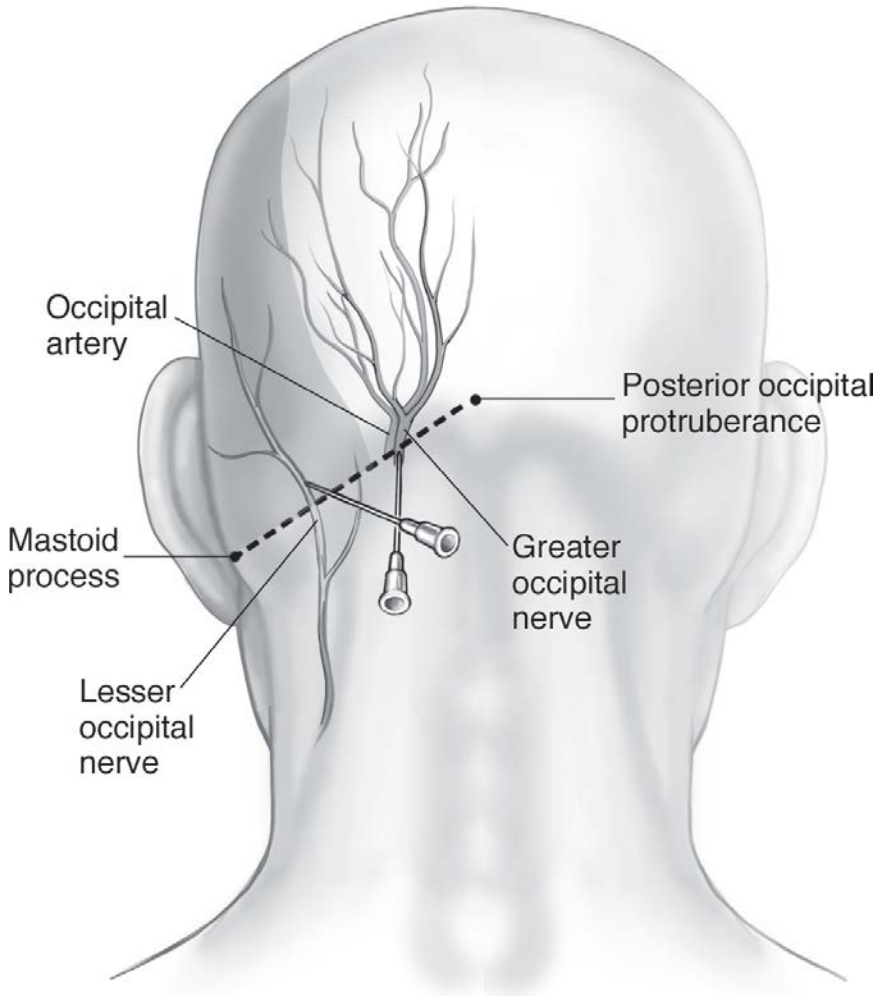

Figure 2: *Occipital nerve blocks (ONB). (Adapted from Waldman SD. Atlas of interventional Pain Management. 2nd ed. Philadelphia: Elsevier; 2004.) The ONB site of injection is determined at the midpoint of the line joining the mastoid process and external occipital protuberance.*

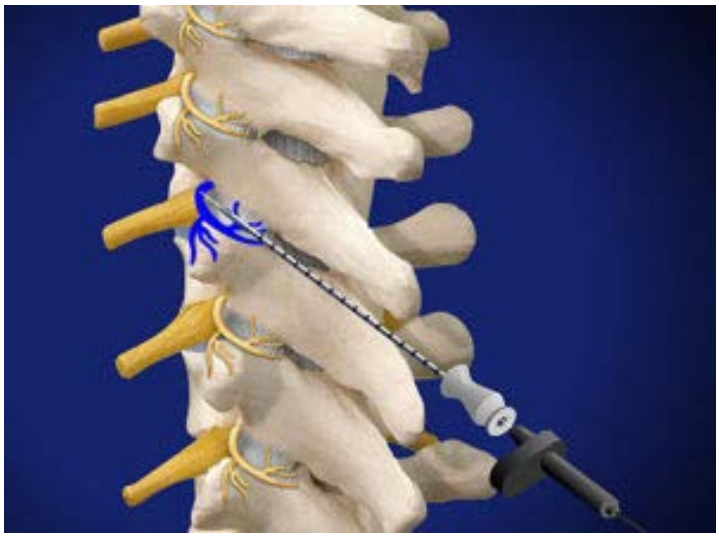

Figure 3a: *Cervical medial branch block (CMBB) posterior approach targeting the medial branch of the dorsal ramus of the spinal nerves*

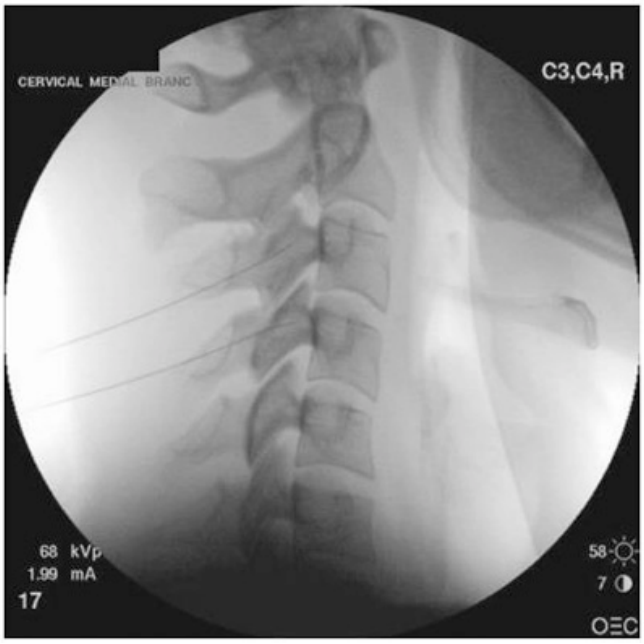

Figure 3b: *Cervical medial branch block (CMBB) posterior approach fluoroscopy view*

E. Definition of Primary and Secondary Outcomes / Endpoints:

Primary Outcome Measures

The overall goal of this study is to examine the change in PTH and / or axial neck pain in groups of patients receiving minimally invasive nerve block interventions (ONB with lidocaine and steroids vs. CMBB with lidocaine and steroids). The primary outcome is defined as change in pain

intensity scores (NRS), which will be collected at baseline, weekly for two months, and then bi-weekly throughout rest of the study.

Pain scales: The numerical rating scale (NRS) will be utilized in this study. Patients will rate their pain score on a scale of 0 to 10 with 0 being no pain and 10 being the worst pain imaginable.

Secondary Outcome Measure

The secondary outcome measures include data about associated pain and psychological comorbidities, and concomitant effects of intervention.

- Headache frequency and severity: The MIDAS[14] and PedMIDAS[15] are brief questionnaires, which are self-administered to quantify headache-related disability. The MIDAS score has been shown to have moderately high test-retest reliability in headache sufferers and is correlated with clinical judgment regarding the need for medical care.
- Functional Disability: The Functional Disability Inventory (FDI) [16, 17] is a valid and reliable measure consisting of 15 items concerning perceptions of physical and psychosocial functioning. Total scores range from 0 to 60 with higher scores indicating greater disability. The Pain Disability Index (PDI) is a simple and rapid instrument used to measure the impact that pain has on the ability of a person to participate in essential life activities. Participants will rate their disability using a scale of 0 to 10 where 0 indicates no disability and 10, total disability.
- QL Scores: QL (Quality of Life Questionnaire) and PedsQL[18] is a brief, standardized, generic assessment instrument that systematically assesses adult patients and pediatric patients / parent's perceptions of health-related quality of life (HRQOL) with chronic health conditions. The QL is based on a modular approach to measuring HRQOL and consists of a 15-item core measure of global HRQOL that includes physical, emotional, school and social domains of function
- Time to return to sports, school and/or work in weeks

Other Independent Variables

- Socio-demographic characteristics: Age and BMI, which will be reported as a continuous variable and sex, will be reported as a dichotomous variable.
- Physical exam characteristics will be described as a categorical variable and classified as: Headaches (migrainous, cervicogenic/tension type, neuralgic or mixed) and / or axial neck pain (with extension, flexion, or extension and flexion)

- Presence of headaches, neck pain, or whole body pain before the intervention, which will be reported as a continuous variable in number of months. Concussion symptom scores will be collected using the Concussion Symptom Inventory, a symptom scale designed for tracking recovery/improvement from concussion headache.
- Presence of psychological comorbidities such as anxiety and depression will be assessed over the course of the study using the Patient-Reported Outcomes Measurement Information System (PROMIS) Anxiety Symptoms Scale and the PROMIS Depressive Symptoms Scale Both scales have demonstrated reliability and validity, including internal consistency and convergent/divergent validity.
- Presence of pain related comorbidities such as whole body pain, gastrointestinal problems, fibromyalgia and small fiber neuropathy will be classified as a categorical variable.
- Presumed anatomic diagnosis will be described as a categorical variable and classified as: Facet arthropathy, occipital neuralgia, myofascial spams, spondyloysis, spondylolisthesis, axial, discogenic pain.

F. Data Collection Methods

All patients will be assigned a unique personal identifier that will not be linked to any patient identifying information. Data will be collected during the study in case report forms and then will be entered into an Excel database, data form the email follow ups will be collected in REDCap and extracted and merged into the master Excel database.

Research information collected during the study will be stored in locked cabinets with access limited to the Principal Investigator and research personnel affiliated with the study. All health information is protected by HIPAA (Health Insurance Portability and Accountability Act) and all health records will be kept confidential. Patients' birthdate, name, and all other identifying information will be removed when analyzing and reporting on the data. Any personal identifying information will be stored separately from the other information the patient gives us and no personal identifying information will be reported in any publications or presentations. Identifying information will be kept in a password protected, secure file with limited access by research personnel. Once data collection is complete, identifying information will be destroyed.

G. Data Management Methods

All relevant information retrieved from the electronic medical record, by the PI and/or a member of staff will be translated into an electronic form. Data collected in paper case report forms will be entered into a 21 CFR Part 11 compliant database, InForm Electronic Data Capture (EDC) Systems, for intake and checking, and will be protected by encryption and password. We will administer a baseline survey, followed by weekly or bi-weekly REDCap questionnaires that include information regarding post-procedure pain intensity scores, functional disability scores, anxiety and depression scores, and symptoms scores using REDCap questionnaires. The data obtained from these REDCap surveys will be maintained in the study's REDCap database. REDCap is a secure, web-based application designed to support electronic data capture for research. Only authorized users are permitted access to the data files, and daily server back-up activities are executed to ensure data recovery. All data will be stored on a password-secured research computer, and all data entered into the computers will be password protected. Procedures to ensure accurate and reliable data collection will include well designed data forms and training.

H. Quality Control Methods

Data quality control will be assured through automated and manual methods. The study database enhances data quality through required entry fields for critical data and automatic flags for missing or out-of-range data. Efforts will be made to minimize data entry error by the development of a user-friendly database and all data entry will be double-checked with the source files.

I. Data Analysis Plan and Sample Size

At the time of data analysis, datasets will be downloaded from both REDCap and InForm and merged into Statistical Analysis Systems 9.3 for purposes of analysis. Missing data will be accounted for when the data is coded into respective variables.

In order to detect a 30% difference between treatment groups, and with an α of 0.05 and β of 0.8, we will need a sample size of 24 subjects per group. Taking into consideration a 30% dropout rate during the study, we estimate a sample size of 63 subjects in the trial.

We will analyze pain scores (NRS), MIDAS/ PedMIDAS, FDI and QL scores as continuous variables. Differences of these parameters from baseline will be the outcomes variables. The differences in pain, functional, and QL scores will first be tested for normality. Assuming normality, T-Tests will be conducted to investigate the differences between the two randomized

groups. If data does not appear to be normal, Wilcoxon Rank Sum Tests will be performed in contrast to T-Tests.

Descriptive statistics will be generated in order to summarize socio-demographic characteristics of study participants. Frequency tables will be generated to describe gender, psychological and pain related comorbidities, history of injury, previous treatment methods and interventions. Similarly, frequency tables will be generated to depict physical exam characteristics, presumed anatomic diagnosis provided by clinicians, and presence of any predictive clinical findings. Continuous characteristics such as age and BMI will be tested for normality using the Shapiro-Wilk test. Continuous characteristics will be summarized using mean and standard deviation if the distribution appears normal, or will be summarized using median and interquartile range if the distribution does not appear normal. We will evaluate baseline differences between responders and non-responders, using chi-square and t-test for categorical and continuous variables, respectively.

Additionally, pain, functional, and QL scores will be assessed at multiple time points after treatment. Repeated measure analysis will be used to compare the pain, functional and QL scores over time between groups and compared with baseline values. We will also use multiple regression analysis where treatment, epidemiological, clinical, and psychosocial characteristics will be used as independent variables. Exploratory analysis comparing the two interventional groups will also be performed in order to generate future hypothesis of the best sequential treatment algorithm in PTH.

The fluoroscopy time and radiation exposure amount will be checked for normality using the Shapiro-Wilk Test. If data is assumed to be normal, an analysis of variance will be conducted to assess difference in mean fluoroscopy time and radiation exposure amount. If data does not appear normal, a Kruskal-Wallis test will be performed.

J. Adverse Event Criteria and Reporting Procedures

Adverse or unanticipated events will be reported as required to the Boston Children's Hospital and other site IRB's according to institutional reporting requirements. An adverse event log will be used to document adverse events.

An Adverse Event (AE) refers to any untoward medical occurrence associated with the use of Amitriptyline, whether or not considered drug related, as described in 21 CFR 312.32. We will monitor and report any AEs, as guided in 21 CFR 312.32.

The intensity (grade) of each AE will be assessed using the following scale:

i. Grade 1 (Mild): Experiences which are usually transient, requiring no special treatment, and do not interfere with the subject's daily activities.
ii. Grade 2 (Moderate): Experiences which introduce some level of inconvenience or concern the subject, and may somewhat interfere with daily activities, but are usually ameliorated by simple therapeutic measures (may include drug therapy).
iii. Grade 3 (Severe): Experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment.
iv. Grade 4 (Life-threatening): Experiences which cause the subject to be in imminent danger of death.
v. Grade 5 (Death): Subject fatality

If the intensity (grade) changes within a day, the maximum intensity (grade) should be recorded. If the intensity (grade) changes over a longer period of time, the changes should be recorded as separate events (having separate onset and stop dates for each grade).

Relationship to the medication or procedure administration will be determined by the Investigator according to the following criteria:

i. Unexpected/Expected Adverse Drug Events
    a. Unexpected: Any adverse experience, the nature, severity or frequency of which is not consistent with the the risk information described in the investigational plan or protocol or consent form. Unexpected refers to an experience that has not been previously observed. This includes events that are more serious than expected or occur more frequently than expected.
    b. Expected: Those experiences that have been identified in nature, severity, or frequency in the current investigator brochure, investigational plan/protocol and current consent form.
ii. Relatedness
    a. Unrelated: The adverse event is clearly not related to the investigational agent
    b. Unlikely: The adverse event is doubtfully related to the investigational agent
    c. Possible: The adverse event may be related to the agent

d. Probable: The adverse event is likely related to the investigational agent
e. Definite: The adverse event is clearly related to the investigational agent

For the purpose of safety analyses, all AEs that are classified as possible, probable or definite will be considered treatment-related events.

We regard the following as AEs for ONB and CMBB procedures:

- Neurotoxicity: The injection of anesthetics or steroids, or meningeal inflammation from the breech of the spinal canal during the procedure with or without direct neural injury can result in arachnoiditis or cauda equina syndrome. We regard these risks to be extremely low.
- Neurological injury: Direct mechanical injury to the spinal nerves or the spinal cord itself can occur during needle placement for injections. We regard these risks to be extremely low.
- Vascular injury: Unintentional vascular injection of the steroid and local anesthetic suspension will result in medications simply being carried away from the site of inflammation, thus reducing any local anti-inflammatory effect. In contrast, intra-arterial injection is far less common, but may cause catastrophic neurologic injury and seizures. We regard these risks to be extremely low.
- Pharmacologic effects of corticosteroids: The administration of exogenous corticosteroids can lead to both hypercortisolism and suppression of the adrenal cortex's normal production of endogenous glucocorticoids. The long-acting corticosteroid preparations used for injections slowly release the active steroid over 1 to 3 weeks. Fluid retention, weight gain, increased blood pressure and cushingoid side effects have been reported. Glucocorticoid administration reduces the effect of insulin and results in increased blood glucose levels and insulin requirements in diabetics for 48 to 72 hours. Although rare, allergic reaction to systemic administration of corticosteroid has also been documented. We regard these risks to be extremely low.
- Bleeding complications: Injections for pain treatment carries the risk of bleeding in patients without any apparent coagulopathy. Significant bleeding can cause compression of surrounding structures, potentially resulting neurological problems and worsening pain. We regard these risks to be extremely low.

- Infectious complications: Injection therapy for pain treatment carries a small risk of both superficial and deep infection, including neuraxial complications including sensory and motor deficits. Other complications include osteomyelitis and septic arthritis of the facet joints. We regard these risks to be extremely low.

In order to safeguard the privacy of patients, we have developed a mechanism for data and safety monitoring. A Data and Safety Monitoring Board (DSMB) will be established and will consist of 2 members (see DSMB Plan and Charter). The PI will not be members of this board. All members of the DSMB will pay special attention to occurrence of AEs and SAEs.

Reporting to the DSMB will occur if any 1 subject experiences a SAE as identified by the PI.

Data and safety monitoring will be performed once per year by the DSMB.

No individual care data will be reported unless there is a serious adverse effect. Reports will be done in an aggregated way.

K. Data and Safety Monitoring Plan

The Data and Safety Monitoring Plan will focus on adequacy of data collection, and occurrence of serious adverse events. In the event of a DSMB review, the research information stored electronically and paper records will be available for examination by the DSMB and IRB as required. Any serious adverse events that occur will be promptly reported to the Institutional Review Board according to IRB guidelines. A log will be used to document adverse events. The PI will review the safety and progress of this study on a regular basis. All data will be collected in the strictest confidential manner and no personal identifiers will be recorded or included into the possible publication. All data will be protected by HIPAA (Health Insurance Portability and Accountability Act) and be stored electronically and maintained on a private folder in a password protected laptop/computer with limited access to investigators and research personnel affiliated with the study. After data analysis is complete any possible link to participants will be destroyed. The potential risks are limited, though as with any research participation, risk of breach of confidentiality exists.

We have a licensed clinical psychologist included on this protocol that will review the anxiety and depression standard questionnaires of each participant and will contact those who score in the clinical range and provide referrals if necessary. It is important to note that we will not be asking

any self-harm questions. Subjects who are found to need further attention will be referred to the appropriate services.

L. Risks and Discomforts

The study treatments are part of the clinical standard of care for this patient population. Some patients may experience known drug side effects, or pain, bruising and anxiety from treatment. However, we expect the risks to be minimal. Patients will be removed from the study at any point if the attending physician feels that treatment may be inappropriate to that patient's care at that time or they develop any unexpected complications. The patient will be treated for any potential reactions. If a patient enrolled in the study should have an adverse event not typically associated with the study drug and the reaction is severe or life-threatening, then the investigator or the attending physician may choose to withdraw the patient from the study. If this occurs, the patient will be withdrawn and unblinded and the IRB notified of the occurrence.

For the interventional procedures such as the nerve block injections, the patient may receive sedation per physician's discretion. If the patient requires sedation for the procedure we will inject drugs into the bloodstream generally using the intravenous route. We aim to reduce anxiety and pain, and achieve partial or total amnesia. The risks associated with sedation are an unconscious state, depressed breathing, and injury to blood vessels. We regard the likelihood of any side effects occurring from this procedure to be extremely low.

M. Potential Benefits

There is direct individual benefit given that the treatments in the study are part of clinical standard of care. Potentially, the information generated will strengthen the evidence base of medication management and interventional approaches in post traumatic headaches.

Additionally, patients and families will be compensated for their time, possible expenses, and participation in the study in the form of a ClinCard Mastercard, a reloadable debit card. Patients could receive up to a maximum of $150 in compensation by the end of the study. Reimbursements will be distributed as follows:

- $15 after the screening visit and nerve block injection;
- $15 after the intitial two months, if patients complete more than 80% of the weekly follow-up visits they will receive an additional $10;

- $30 after completing 6 months on the study, if patients complete more than 80% of the by-weekly follow-up visits they will receive an additional $10;
- $50 at the end of the study, 12 months after enrollment, if patients complete more than 80% of the by-weekly follow-up visits they will receive an additional $20.

N. Privacy Provisions

All efforts will be made to ensure patient confidentiality. No patient identifiers will be used in the analysis or publications.

O. Confidentiality Provisions

All identifying information such as dates of birth, names, and medical record numbers will be removed from the study database. All patients will be assigned to an ID number that will not be linked to any patient identifying information. Data collected for research purposes will not be entered into patient's medical records. All data will be electronically secured in a password protected private folder. Only research investigators and personel affiliated with the study will have access to patient information.

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