Title: A Randomized, Sham-controlled Trial of Greater Occipital Nerve Block as second line therapy for ED patients with acute migraine

PI: Benjamin Friedman, MD

IRB Number: 2015-4654

NCT# 02665273

IRB Approval Date: 06/01/2015

Overview and hypothesis

More than one million patients present to US emergency departments (ED) annually to obtain relief from an acute migraine.[1] Nearly twenty different medications are commonly used to treat acute migraine in the ED, yet the goal of sustained headache relief remains elusive.[1,2] Fewer than 25% of ED migraine patients achieve freedom from their headache and remain headache free for 48 hours, regardless of which medication they receive.[2] Medications commonly used to treat acute migraine are burdened by a host of nuisance side effects including drowsiness, dizziness, and restlessness. There remains a need for an acute migraine intervention that can deliver rapid, complete, and sustained headache relief without causing side effects that prevent a patient from returning to work or usual activities.

Greater occipital nerve blocks are an emerging migraine treatment modality that are discussed increasingly in the headache and pain literature.[3]Excitement about this procedure is partially fueled by the continuing need for effective treatment. A greater occipital nerve block is a peripheral nerve block that provides regional anesthesia. Using a small gauge needle, a small volume of a topical anesthetic is injected into the subcutaneous tissues at the back of the skull, where the greater occipital nerve lies. Though neither efficacy nor mechanism have been well established for migraine, this procedure is hypothesized to work by decreasing transmission through the trigeminocervical complex (TCC)The TCC is believed to be an important way station in migraine pathogenesis. Within the TNC, nociceptive input arriving from the trigeminal nerve is relayed to second order nerves that terminate in the thalamus. As with the trigeminal nerve, upper cervical nerves, including the greater occipital nerve also terminate in the TCC. It is believed that nerve fibers originating from the upper cervical nerves converge on the same second order nerves as the trigeminal nerve fibers. Decreasing transmission of sensory input through the TCC by blocking the greater occipital nerve can relieve the pain of acute migraine by blocking transmission through the TCC.

Evidence supporting this hypothesis is limited.[3] For the most part, published studies on greater occipital nerve blocks for migraine patients use a non-experimental design and are rife with bias. The goal of this proposed study is to provide sufficient evidence to support or refute a claim of efficacy. We fear that patients who present to an ED with acute migraine may be reluctant to accept treatment with an injection to the scalp as a first-line therapy. Therefore, we will test this hypothesis among patients who have already received first-line treatment in the ED and who require additional medication for refractory pain.

While efficacy data supporting greater occipital nerve blocks is lacking, there is a large amount of data supporting safety. Adverse events include pain at the site of injection, numbness and tingling at site of injection, infection of the injection site, dizziness, and allergic reaction to local anesthetics. The major complication of any peripheral nerve block is intravascular injection into major vessels which can have systemic effects. These effects can be avoided by aspirating prior to injection to ensure no blood return.

Emergency clinicians are adept at performing peripheral nerve blocks. Digital, wrist, foot, penile, and facial nerve blocks are commonly performed in typical emergency care. As the technique for an occipital nerve block is identical, we believe this procedure, if efficacious, will be embraced by the emergency medicine community.

Hypothesis: In a population of patients who present to an ED with acute migraine and have been treated with parenteral metoclopramide unsuccessfully, bilateral greater occipital nerve blocks with bupivicaine will provide greater rates of short-term and sustained headache freedom than bupivacaine injected intradermally.

Methods.

Study Overview: This will be a randomized, double-blind clinical trial comparing an active treatment of acute migraine versus placebo in an emergency department after the standard of care for acute migraine has already been administered. The Albert Einstein College of Medicine IRB will provide ethical oversight. The trial will be registered at http:www.clinicaltrials.gov.

Setting: This study is to be performed in the emergency departments of Montefiore Medical Center. Salaried, trained, bilingual (English and Spanish) technician-level research associates, who execute research studies under the supervision of the principal investigators, staff the emergency department 24 hours per day/ seven days per week and will collect outcome data for this study.

Selection of Participants:Eligible patients are adults who present with an acute moderate or severe headache meeting migraine headache criteria, as defined by the International Classification of Headache Disorders-3**β** (1.1, migraine without aura).[4] Patients who meet criteria for Probable Migraine without Aura (1.5.1) will also be included, provided they have had at least one similar attack previously. Status migrainosus, prolonged duration of headache (>72 hours), or early presentation (<4 hours) do not preclude participation. Patients are to be enrolled if they fail first line parenteral migraine therapy. Specifically, we will require patients to have received metoclopramide for treatment of migraine during the ED visit and to request additional treatment for persistent moderate or severe headache. Patients will be excluded if informed consent cannot be obtained, if there is concern for a secondary cause of headache, if the maximum documented temperature is greater than 100.3 degrees, for a new objective neurologic abnormality, skull defect, suspected infection overlying injection site, known bleeding disorder, ongoing use of anti-platelet agents including P2Y12 platelet inhibitors (clopidogrel, prasugrel, ticagrelor), heparins, warfarin, or 10a inhibitors (rivaroxaban, apixaban, edoxaban, fondaparinux), prior treatment with a greater occipital nerve block, pregnancy, or allergy, intolerance,or contra-indication to the study medication. Patients will be identified by the attending emergency physician and referred to research personnel. Alternatively, research personnel may identify potential participants by searching the ED tracking board, and asking the attending emergency physician if patients are appropriate for the study.

Intervention:

Active arm) 3cc bupivacaine 0.5% to be injected into the greater occipital nerve region bilaterally
Sham arm) 0.5cc bupivacaine 0.5% to be injected intradermally in the posterior scalp bilaterally

Formal training sessions will be conducted for those who will inject for research purposes.

Step-by-step procedure for performing bilateral occipital nerve block or sham injection

1. Eligible patient identified.
2. Consent obtained.
3. Research associate hands provider assignment envelope, bottle of 0.5% bupivacaine, 10cc syringe, 27 gauge needle, 2 alcohol swabs and then goes away
4. Provider opens envelope, reads assignment, destroys paper containing assignment
5. Provider draws 3cc bupivacaine into syringe
6a. If patient is randomized to active intervention, provider performs GONB: 1) identify occipital protuberance and mastoid process 2) insert 3 cc bupivacaine 1/3 of distance lateral to occipital protuberance, within groove, using fan technique. Repeat procedure on opposite side.

6b. If patient is randomized to sham intervention, provider performs intradermal injection: 1) identify occipital protuberance and mastoid process 2) insert 0.5 ccc bupivacaine intradermally 1/3 of distance lateral to occipital protuberance
7. Provider discards all supplies and summons research associate.

Randomization and Blinding:Study participants and outcome assessors will be blinded. Because the technique will vary depending on assignment, the clinician performing the procedure will not be blinded. A randomization list will be generated using an online generator at http://www.randomization.com. Participants will be assigned to active or sham arm in a 1:1 ratio. Assignment will be stratified on baseline pain intensity. Assignment will be placed in an opaque, sealed envelope with sequential study IDs written on the outside. Research personnel will hand the next sequential envelope to the clinician, who will read the assignment and then shred the envelope and its contents. We will give active agent to both sudy groups to ensure subject blinding. We hope subjects are more likely to believe they got active agent if part of their scalp is numb.

Methods of Measurement:As a primary measure of headache intensity, this study will utilize a standard ordinal headache intensity scale, in which subjects describe their headache as "severe", "moderate", "mild", or "none". We will also assess pain using an 11-point numerical rating scale (NRS). This latter scale asks subjects to assign their pain a number between 0 and 10, with 0 representing no pain and ten representing the worst pain imaginable. Both of these measures are recommended for use in migraine research by the International Headache Society.[5] We will ascertain overall subject satisfaction with the experimental treatment by asking them if they want to receive the same treatment the next time they come to the ER with a migraine headache. Adverse events will be elicited using a dichotomous question (Did you have any side effects that were caused by the procedure?) followed by an open ended question (Please tell us about the side effects you experienced).Light touch will be assessed in the C2 dermatome. If done correctly, patients will be numb in GON distribution and hopefully migraine free. The number of previous GONB performed will be recorded.

Outcomes: The primary outcome will be the frequency of headache freedom (headache level = none) thirty minutes after completion of the procedure. Important secondary outcomes will be the frequency of sustained headache relief (achieving a pain level of mild or none within one hour of the procedure and maintaining a level of mild or none without the use of additional medication for 48 hours) and subject satisfaction, as evidenced by an affirmative response to the question, do you want to receive the same procedure the next time you come to the ER with migraine. We will also report the improvement in 0 – 10 pain scale between baseline and one hour and the frequency of adverse events.

Protocol: After obtaining informed consent, a brief pain assessment will be performed. A clinician will then inject bilateral GONs (Appendix 1). Research associates will ascertain the patient's headache level 15, 30, 60, and 120 minutes post-injection. We will ask about the frequency of adverse events 30 minutes after the injection. We will also perform an assessment of light touch and allodynia before and after the procedure (Appendix 2 and Figure). Research associates will contact subjects by telephone 48 hours after ED discharge to ascertain headache status, satisfaction with treatment, and presence of adverse events.

Sample Size calculation: We chose a frequency of headache freedom of 50% as the lowest frequency of success for which clinicians would be willing to perform this procedure. We hope to minimize the placebo effect on the primary outcome by requiring headache freedom rather than just headache improvement. It is unlikely that a patient would progress from moderate/ severe headache to headache freedom within 30 minutes without intervention. We estimated a placebo rate of headache freedom of 20%. Using an alpha of 0.05 and a beta of

0.20, we calculated the need for 39 subjects in each arm. The study will continue until 78 patients have provided primary outcome data.

Analysis: The primary outcome is the rate of headache freedom at 30 minutes. Absolute risk reduction and number needed to treat will be reported with 95%CI. All dichotomous secondary outcomes will be reported as frequencies with 95%CI. Improvement in numerical rating scale will be reported as mean with 95%CI. The primary goal of this analysis is to demonstrate efficacy. If we do not demonstrate statistically significant differences but do see a signal through the noise, we will use the point estimates to decide the feasibility of another study. We will determine the between-group difference (absolute risk reduction) in rates of headache freedom and report this with 95%CI.

Data safety and monitoring:The goal of the data safety committee will be to review study protocol and adverse events on an ongoing basis to determine if risk to subjects can be minimized further without compromising study integrity. Because the overall sample size is relatively small and it will be important to report our findings with sufficient precision, the study will not be halted early for efficacy or futility.

Data Safety and Monitoring Section

(i) A description of the types of data or events that will be captured by explaining:
- What safety information will be collected: *Adverse events will be collected in the ED and at 48 hour follow-up by asking a screening question: "Did you experience any side effects from the medication" followed by an open-ended query to have the patient explain.*
- How safety information will be collected: *Subject Interview*
- When data will be collected: *In ED, every 30 minutes, and by telephone 48 hours later*.

(ii) A plan for assuring data accuracy and protocol compliance. *Data will be reviewed by the PI after entry into REDCap.*

(iii) Timeframes for reporting adverse events and unanticipated problems to the monitoring entity. *The PI is the monitoring entity*

(iv) The frequency of monitoring entity's assessment of data or events. *After every enrollment*.

(v) The specific triggers or stopping rules: Conditions that would trigger an immediate suspension of the research. *No automatic triggers have ben established.*

(vi) The procedures for communicating the outcome of the reviews by the Monitoring Entity to the IRB, and other appropriate entities. *All SAEs will be communicated to the IRB after review for causality by the PI. Other AEs will be communicated during annual review.*

Data Storage &Confidentiality:Data will be stored and maintained in REDCap. Data analysis will occur on password-protected computers. Consent documents will be maintained in locked research cabinets. Only study personnel will have access to the data and consent documents.

References

1. Friedman BW, West J, Vinson DR, Minen MT, Restivo A, Gallagher EJ. Current management of migraine in US emergency departments: An analysis of the National Hospital Ambulatory Medical Care Survey. Cephalalgia 2014.
2. Friedman BW, Bijur PE, Lipton RB. Standardizing emergency department-based migraine research: an analysis of commonly used clinical trial outcome measures. Acad Emerg Med 2010;17:72-9.
3. 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.
4. Olesen J, Bendtsen L, Dodick D, et al. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33:629-808.
5. Tfelt-Hansen P, Pascual J, Ramadan N, et al. Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. Cephalalgia 2012;32:6-38.

Appendix 1. Step-by-step procedure for performing bilateral occipital nerve block or sham injection

1. Research associate identifies eligible patient.
2. Research associate obtains consent
3. Research associate hands provider assignment envelope (lowest available study ID), bottle of 0.5% bupivacaine, 10cc syringe, 27 gauge needle, 2 alcohol swabs. Research associate then returns to research desk.
4. Provider opens envelope, reads assignment, destroys paper containing assignment
5. Provider draws 6cc bupivacaine into syringe
6a. If patient is randomized to active intervention, provider performs GONB: 1) identify occipital protuberance and mastoid process 2) after negative aspiration insert 3 cc bupivacaine 1/3 of distance lateral to occipital protuberance, within groove, using fan technique. Repeat procedure on opposite side.
6b. If patient is randomized to sham intervention, provider performs intradermal injection: 1) identify occipital protuberance and mastoid process 2) insert 0.5 cc bupivacaine intradermally 1/3 of distance lateral to occipital protuberance
7. Provider discards all supplies and summons research associate.

Appendix 2. Assessment of light touch and allodynia

Prior to procedure and 15 minutes after the procedure, research associates will assess light touch sensation and allodynia in 6 locations around the scalp: bilateral forehead, bilateral upper posterior scalp, and bilateral lower posterior scalp overlying the injection site (see figure). Using a piece of gauze, research associates will gently stroke each area 4 times and ask two questions: 1) Did you feel that? 2) Did that hurt?

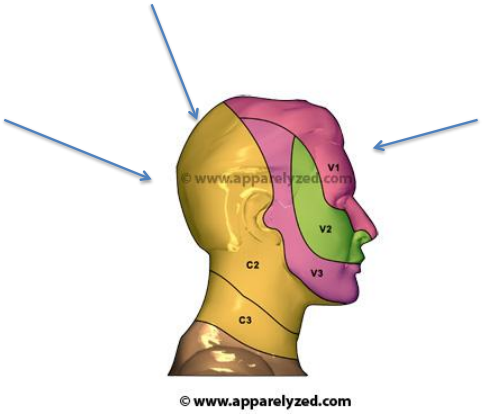

Figure: Locations at which allodynia and light touch will be assessed before and after intervention