A randomized trial of greater occipital nerve block with bupivacaine versus intravenous metoclopramide for acute migraine. Version date 02042020

Overview and hypothesis

More than one million patients present to US emergency departments (ED) annually to obtain relief from 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 TCC, 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.Clinical evidence supporting this hypothesis, however, 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.

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, bilateral greater occipital nerve blocks with bupivicaine will provide non-inferior rates of headache relief as compared to intravenous metoclopramide, a guideline-endorsed treatment of acute migraine.

Methods

Study Overview: This will be a randomized, double-dummy clinical trial comparing greater occipital nerve block with an evidence-based treatment of acute migraine. The Albert Einstein College of Medicine IRB will provide ethical oversight. The trial has been 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-3β (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 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, allergy to the investigational medications, pheochromocytoma, seizure disorder, Parkinson's disease, use of MAO inhibitors, and use of anti-rejection transplant medications. Pregnant patients will be excluded. Women of child-bearing age will be asked if they are pregnant. As both of the investigational medications are commonly used during pregnancy, pregnancy testing is not warranted. Patients will be identified by the attending emergency physician or database review and referred to research personnel.

Intervention:
Nerve bock arm: 6ml bupivacaine 0.5%, injected adjacent to the greater occipital nerve bilaterally (3ml each side) + 2ml normal saline, administered as an intravenous drip over 15 minutes

Metoclopramide arm: 6ml normal saline, injected into the greater occipital nerve bilaterally (3ml each side) + 10mg in 2ml metoclopramide, administered as an intravenous drip over 15 minutes

The intravenous drip will be administered as follows. A clinical nurse, blinded to assignment, will retrieve a vial from the pharmacy containing either metoclopramide 10mg or normal saline. The contents of this vial will be inserted into a 100ml bag of normal saline, shaken, and administered as an intravenous drip over 15 minutes.

Step-by-step procedure for performing bilateral occipital nerve block
1. Eligible patient identified.
2. Consent obtained.
3. Research associate hands clinician a bottle from pharmacy containing either 10ml of 0.5% bupivacaine or normal saline, a 3 cc syringe, a 27 gauge needle, and 2 alcohol swabs
4. Clinician confirms correct patient using name and MRN
5. Clincian draws 3cc of the blinded solution into syringe
6. Clinician performs GONB as follows: a) identify occipital protuberance and mastoid process b) identify occipital groove 1/3 of the distance medial from occipital prominence c) swab identified area with alcohol pad d) Insert 3 cc of blinded solution within occipital groove using fan technique e) Clinician repeats procedure on contralateral side f)Local pressure applied if required for hemostasis
Formal training sessions will be conducted for those who will inject for research purposes.

Randomization and Blinding: Study participants, clinicians, and outcome assessors will be blinded. A randomization list will be generated using an online generator at http://www.randomization.com. Participants will be assigned to metoclopramide or GONB in a 1:1 ratio. Assignment will be stratified on baseline pain intensity (moderate or severe) and study site. Based on the randomization schema, the pharmacist will place either metoclopramide or normal saline into vial 1 (for intravenous administration) and either bupivacaine or normal saline into vial 2 (for subcutaneous injection). These solutions are all clear; they appear identical. The research packets provided by the pharmacy will be used in sequential order.

Methods of Measurement: As a primary measure of headache intensity, we will assess pain using an 11-point numerical rating scale (NRS). This 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. We will also utilize a commonly-used ordinal headache intensity scale, in which subjects describe their headache as "severe", "moderate", "mild", or "none". 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 study medications?) followed by an open ended question (Please tell us about the side effects you experienced). Restlessness, a common side effect of metoclopramide, will be assessed specifically. We will also perform an assessment of light touch and allodynia before and after the procedure (Appendix). Research associates will contact subjects by telephone 48 hours after ED discharge to ascertain headache status, satisfaction with treatment, and presence of adverse events.

Outcomes: The primary outcome will be improvement in 0 – 10 pain scale between baseline and one hour.

Important secondary outcomes will be the frequency of sustained headache relief, defined as obtaining a headache level of mild or none in the ED within two hours of medication administration, not requiring additional analgesic medication, and not relapsing to a headache level worse than mild during the 48 hours after medication administration; sustained headache freedom (achieving a pain level of none within two hours of medication administration and maintaining a level of none without the use of additional analgesic 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 frequency of adverse events, and ED dwell time, defined as elapsed time between medication administration and ED discharge.

One hour after medication administration, participants will be asked if they need more medication for pain. Those who reply affirmatively will be offered rescue medication. The specific agent to be used will be decided by the attending physician and may include metoclopramide (possibly a second dose), ketorolac, or an opioid.

Sample size calculation: We intend to test the null hypothesis that metoclopramide is more efficacious than the greater occipital nerve block (GONB) with regard to improvement in pain between baseline and one hour later, as measured by change in 0-10 pain score (improvement = baseline score- one hour score). The minimum clinically important difference on the 0-10 pain score is 1.3. Based on a standard deviation of 3.1, a sample size of 97 will allow us to reject the null hypothesis if the between-group difference (Improvement in GONB- improvement in metoclopramide) $\geq$ -0.6.

Analysis: We will compare improvement in pain score (baseline score- one hour score) between the two groups. If the lower bound of the 95% CI of the between-group difference (Improvement in GONB- improvement in metoclopramide) is > -1.3, we will conclude GONB is non-inferior. All dichotomous secondary outcomes will be reported as frequencies with 95%CI.

Data safety and monitoring: The goal of the data safety committee will be to review 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. 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 allow the patient to provide details. All SAEs will be communicated to the IRB after review for causality by the PI. Other AEs will be communicated during annual review. The data monitoring committee will be staffed by local faculty. This committee will be headed by Dr. Polly Bijur, PhD, an epidemiologist and include Dr. Esses, MD, the director of the Moses ED. The committee will meet every month with the PI to monitor: 1) adverse events; and 2) recruitment and enrollment.

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.

Consent. Informed consent will be obtained when patients present to the ED and are experiencing the pain of acute migraine. However, there is no other practical way to perform this study as a large majority of Montefiore ED migraine patients do not see outpatient clinicians for management of headaches. As part of our consent process, we will offer to help patients call a family member or friend and discuss the study with them.

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 2015;35:301-9.
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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.
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Appendix . 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?

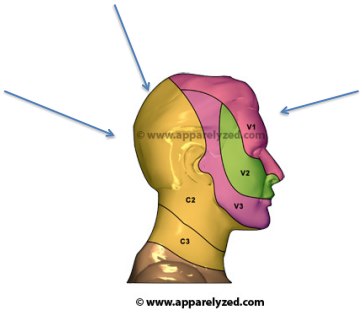

Figure: Locations at which allodynia and light touch will be assessed before and after intervention