A randomized placebo-controlled trial of greater occipital nerve injections for chronic migraine in pediatric patients

Investigators: [redacted]

Research question: Does a greater occipital nerve injection result in fewer migraine/migrainous days than a placebo injection in the first 30 days following injection in pediatric patients with chronic migraine?

Type of randomized trial design: Placebo-controlled, parallel-group, double-blind randomized trial.

Randomization scheme: Block randomization (blocks of n=4) to be done using a computer-generated scheme. Given this is a relatively small study (n=64) , we will stratify randomization based on the presence or absence of medication overuse. Though in our open-label adult and pediatric studies of greater occipital nerve injections' efficacy this variable did not predict efficacy, we may have been underpowered to detect it and it has been significant in other chronic migraine treatment studies hence it is worth ensuring that an equal number of patients with and without medication overuse get randomized to each arm of the study.

Subjects:
Target population: Children and adolescents with chronic migraine
Accessible population: Children and adolescents with chronic migraine who attend the UCSF Headache Center clinic

Inclusion Criteria:
1. Age <18 years**;**
2. Patient has been given a diagnosis of **chronic migraine** by a headache neurologist at the UCSF Headache Center using International Classification for Headache Disorders, Second Edition(3), criteria for chronic migraine in pediatric patients. The phenotype can be with or without aura, and medication overuse can be present;
3. There is tenderness to palpation over at least one greater occipital nerve. This is a predictor of response to greater occipital nerve injections(10) and therefore a prerequisite to offering the injection as a treatment in our clinic;

Exclusion Criteria:
1. Allergy or contra-indication to any of the study medications: Lidocaine, Depo-medrol, or propranolol;
2. Previous ineffective adequate trial of propranolol as a migraine preventive (or intolerance due to side effects)**;**
3. Contra-indication to greater occipital nerve injection due to history of suboccipital craniotomy or history of occipital skull fracture

4. Previously received a greater occipital nerve injection at our clinic—as therefore response, or lack of response, to nerve injection is already thought be known in that person so not ethical to randomize. Those who have received greater occipital nerve injections done at other clinics will still be eligible as often these injections used different techniques/sites of injection and/or different medications.

Control group: Those pediatric patients with chronic migraine randomized to receive placebo-injection over the greater occipital nerve.

Intervention group: Those pediatric patients with chronic migraine randomized to receive active medications injected over the greater occipital nerve.

Primary outcome measure: Mean number of migraine/migrainous days in the saline injection group vs. the active injection group in the 30 days following the injection. A migraine day will be defined as one on which the patient met International Headache Society criteria for pediatric migraine (according to the headache diary), AND/OR they were symptomatic enough to take their usual migraine acute treatment. A migrainous day will be a day where (according to the headache diary) they had moderate/severe headache for at least one hour and one migrainous feature: unilateral pain or pain worse on 1 side of the head, pulsatile pain, photophobia and/or phonophobia, nausea and/or vomiting, or pain made worse by physical activity.

Secondary outcome measures:

1. Mean number of headache days (i.e. days the patient had any headache at all)
2. Mean number of days of moderate/severe headache of any duration
3. Mean number of hours of headache on headache days
4. Mean number of days acute migraine medication was used
5. Mean modified PedMIDAS score, a measure of disability from headache
6. Side effect rates in the saline injection group vs. the active injection group
7. Percent of patients and percent of parents who perceived the injection as beneficial; and significantly beneficial
8. Percent of patients and percent of parents who perceived the propranolol as beneficial; and significantly beneficial
9. Mean number of unscheduled medical visits for migraine
10. Percent of patients who are ultimately admitted to UCSF for a course of IV dihydroergotamine for treatment of chronic migraine in the 6 weeks following study completion, or who existed the study early to be admitted.

Blinding:

1. **Blinding the provider who is doing the injection:** Placebo (normal saline) is a clear fluid, as is lidocaine. However Depo-medrol is white. Hence the syringes will be masked so that the provider can not see the color of the injected materials. The study medications will be drawn up in a separate room by a clinical nurse (or a study pharmacist if funds allow), out of the provider's view. The person drawing up the medications will need to be able

to see inside the syringe in order to draw up the correct amount. They will then place the masking sticker over the syringe so that the contents are no longer viewable. They will then take care to remove the air from the syringe as some fluid can come out when this is done so it would break the provider's blinding. They will check a box on a safety sheet next to the syringe indicating that the air has been removed so the provider can feel comfortable giving the injection without personally checking this. The nurse (or pharmacist) will then leave the room and the provider will come and pick up the syringe and bring it back to the exam room and give the injection. The provider will not interact with the person who drew up the study medications so that there is no opportunity for verbal or non-verbal communication.

2. **Blinding the patients (and their parents/caregivers):** The patients generally do not know the appearance of the medications, but nonetheless they will only potential see a syringe that has already been masked. Once the injection is given there is no way for them to see what was given as it is now sub-cutaneous. Known possible side effects from greater occipital nerve injections include:
    a. Soreness at the site: Can result from just the needle stick and the injection of 3 ml of fluid, so it will not break the blind.
    b. Transient light-headedness: Thought to be vasovagal in origin just from the needle-stick and injection of fluid, should not break the blind
    c. Tingling/decreased sensation in the distribution of the injected greater occipital nerve: This is from the lidocaine and potentially could break the blind. However, surprisingly few patients spontaneously note this—many more will note it if a sensory examination is performed comparing sensation in the two sides a few minutes after the injection. Such an exam will not be performed by the provider, and the patients will be counseled not to touch the area for several hours (a good infection prevention measure anyway) to avoid inadvertently noting this.
    d. Focal alopecia at the site: A rare side effect of the steroid that occurs in <1% of cases so is unlikely to happen in a trial of n=64. It is also a late finding so unlikely to occur during the time of active data collection.

Ways to maximize adherence: The intervention is a one-time injection done in the office so we will not need to maximize adherence with that. However, the patients will need to keep a detailed headache diary for 30 days following. To encourage subjects to do this, our study coordinator will call weekly to reinforce the need to keep the diary and answer any questions about the diary. There will also be a gift card at the end for successfully completing the diary.

Adverse event and side effect measures:
There are several known adverse events/side effects from greater occipital nerve injections that we will specifically look for among participants.

At the time of the injection:

1) We will explicitly ask about the presence or absence of lightheadedness. If present, we will record the duration (usually minutes).
2) Bleeding at the site: Significant bleeding at the site has not been reported, however the investigator will check a box on the study form indicating whether significant bleeding was present or absent.

At the follow-up visit:

1) Soreness at the injection site: We will explicitly ask about this side effect and its duration if present.
2) Infection at the site: Is not reported, however could be potentially serious so we will ask about it.
3) Local alopecia at the site: Rare; occurs <1% of the time. We will explicitly ask about it and examine the site for it.
4) Open-ended question: We will ask the participant whether there were any other side effects they experienced that they attributed to the injection, and we will let them list them. The investigator will also make an indication as to whether she/he thinks the side effect is likely injection related.

For each side effect/adverse event, the investigator will indicate whether it was "serious"---defined as requiring hospitalization (for the side effect, not for headache) or potentially life-threatening.

Plans for Interim Monitoring:

This is a relatively small trial. Power calculation indicates we will need approximately 64 participants, or about 32 per arm. Conservatively estimating we can enroll three participants per month, we anticipate the trial will take about 22 months to fully enroll. When we have enrolled half-way and have follow-up data on that half, we will do a blinded interim analysis. We will compare the rate of serious side effects only, as only a difference in the rate of serious side effects would be significant enough to consider stopping the trial early. We will compare the mean number of migraine/migrainous days between groups as well. To stop the trial early, there would have to be a statistically significant difference between groups that is ≥100% larger than the 3day/month difference we anticipate between groups, (i.e. at least a 6 day/month difference that is statistically significant) as this is how significant a change it would have to be to justify stopping early as stopping early may prevent us from having adequate data to answer some of the secondary endpoints.

Ethics:

One potential ethical issue with this study is that these injections are currently offered "open label" in our clinic, hence one might wonder about the ethics of randomizing some patients not to receive it. The way we are addressing this is as follows: Our standard current practice is that when the treating clinician thinks a GON is indicated after doing an initial consultation visit for a pediatric patient, the patient is scheduled for a follow-up visit for the GON. On average, the wait time for

these follow-up visits is 16 days. For this trial, we will build "same day" research GON time slots into the clinic day so that for those who wish to enroll, they can get a study injection done on the same day. Hence, families will have the choice of either 1) getting an open-label clinical injection but having a likely waiting period of 16 days to get that (on average), or 2) getting a study injection that same day with no wait at all, but with a chance of getting a placebo injection. We think this is ethical as it allows the family access to both possible choices, and as there is to date no RCT evidence that injections work (just open-label evidence), randomizing to placebo is ethical.