Study Title: **Dexamethasone for Post Traumatic Headache**

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A randomized placebo controlled trial of IV metoclopramide + dexamethasone versus IV metoclopramide + placebo for acute post-traumatic headache

Nearly 1.5 million patients present to US EDs annually following head trauma.(1) Headache is a frequent symptom of victims of trauma. (2) For most patients, post-traumatic headaches will resolve after several months, though up to ¼ will develop a persistent headache syndrome.

Post-traumatic headaches are thought to be likely to respond to the same parenteral medications as primary headaches (eg migraine or tension type headache), but only scant data are available to support this hypothesis. We recently completed a randomized, placebo-controlled study of IV metoclopramide for acute post-traumatic headache. In this study, metoclopramide resulted in greater relief of headache and other post-concussive symptoms acutely, though this benefit was not sustained beyond the ED visit. The benefit was not dependent on whether or not the headache, phenotypically, resembled either migraine or tension-type headache. Despite this clear short-term benefit, nearly 40% of patients, regardless of study arm assignment, reported moderate or severe headache during the 48 hours after ED discharge, and on average, patients reported 3.3 days of headache during the week after discharge. Clearly, more needs to be done for these patients.

For patients with migraine, corticosteroids are known to improve outcomes during the 48 hours after ED discharge.(3) Case reports have indicated that corticosteroids may improve outcomes among children with post-traumatic headache.(4) Given the unmet need, the efficacy in other headache syndromes, and the suggestion of benefit from case reports, we propose a randomized, placebo-controlled study to determine whether corticosteroids are of benefit for patients with acute post-traumatic headache. Specifically, we will test the following hypothesis: Among patients who present to the ED with acute post-traumatic headache, the combination of IV metoclopramide + dexamethasone will result in less headache intensity during the 48 hours after ED discharge than the combination of IV metoclopramide + placebo.

Methods.
Overview. This will be a randomized, double blind, placebo-controlled study of IV dexamethasone for acute post-traumatic headache. All patients will be treated with IV metoclopramide. Outcomes will be assessed for up to two hours after medication administration in the ED and by telephone 48 hours, 7 days, and 30 days after ED discharge. This study will be conducted in two Montefiore EDs. This study will be reviewed by the Albert Einstein College of Medicine IRB and be registered online at http://clinicaltrials.gov.

Population of interest: Included patients will be ≥16 years and meet International Classification of Headache Disorders criteria for acute post-traumatic headache. These are as follows:
-Traumatic injury to the head has occurred
- Headache has developed within 7 days of injury to the head
-Headache is not better accounted for by another diagnosis (eg, migraine or tension-type headache)

The headache must be rated as moderate or severe in intensity at the time of initial evaluation. The plan of the attending emergency physician must include treatment with a parenteral medication. Patients will be excluded if more than ten days have elapsed since the head trauma, if the headache has already been treated with an anti-dopaminergic medication, or for medication allergies or contra-indications including pheochromocytoma, seizure disorder, Parkinson's disease, use of MAO inhibitors, and use of anti-rejection transplant medications. Patients will not be excluded for pregnancy because both investigational medications are commonly used in pregnancy.

Study setting: This study will be conducted in the Moses and Einstein EDs

Investigational medications: Interventions in each study arm are as follows:

1) Active arm: Metoclopramide 10mg + dexamethasone 10mg IV drip over 15 minutes.
2) Placebo: Metoclopramide 10mng + normal saline IV drip over 15 minutes

Assignment. Will be concealed. The research pharmacist will determine assignment based on a random number sequence at http://randomization.com. This random number sequence will be maintained in a secure location in the pharmacy, inaccessible to research staff or clinicians.
Randomization. Randomization will occur in a 1:1 ratio and blocks of four based on a random number generator.
Blinding. Patients, clinicians, and research personnel will be blinded. The pharmacist will stock the secured medication cabinet in the ED with sequentially numbered research packages. Each research package will contain two vials, one containing metoclopramide 10mg in solution with normal saline, the other containing dexamethasone 10mg in solution with normal saline or normal saline alone. The metoclopramide and dexamethasone solutions appear identical to normal saline. The research packages will be used in sequential order.

Stratification. Subjects will be stratified by study site

Measures:
International Headache Society pain scale. Headache is described as severe, moderate, mild, or none(5)
Numerical Rating Scale for pain. This is a 0 to 10 verbal rating scale on which 0 signifies no pain and 10 signifies the worst pain imaginable.
Satisfaction scale. Patients are asked if they would want to receive the same medication during a subsequent visit to the ED for post-traumatic headache
The Sport Concussion Assessment Tool (SCAT) Post Concussion Symptom Scale (PCSS). On this validated instrument, patients rate 22 symptoms on a 0 to 6 scale.(6) (Appendix)

Primary outcome. The primary outcome is frequency of moderate or severe headache during the 48 hour period after ED discharge, as rated using the International Headache Society severe, moderate, mild, or none scale. Patients who use any analgesic or abortive headache medication during this time period will be considered an outcome failure.

Secondary outcomes.
1) Sustained headache relief for 48 hours—Achieving a headache intensity of mild or none in the ED without use of rescue medication and maintaining that level for 48 hours without use of rescue medication.
2) SCAT PCSS scores at 48 hours and 7 days
3) Use of rescue medication in the ED, defined as any analgesic medication or headache abortive medication

Other outcomes.
1) Use of additional medication in the ED for associated symptoms
2) Achieving headache freedom in the ED without use of additional medication for headache
3) Satisfaction with the medication, measured at the 48 hour follow-up phone call
4) Number of days with headache during the week after ED discharge
5) Return visits to the ED over the week after discharge
6) SCAT PCSS at 30 days

Details of protocol. Patients who present to the Moses or Weiler EDs with an acute headache will be referred by the attending emergency physician to the research staff for enrollment. Capacity to consent to participate in this study will be assessed by the attending emergency physician and specifically documented. Masked medication will be obtained from the secured medication cabinet. The research associate will perform a baseline pain assessment. The ED nurse will then take the two vials containing metoclopramide and dexamethasone or normal saline, insert these vials into a 100cc bag of normal saline, and administer as an intravenous drip over 15 minutes. The research associates will return every 30 minutes to perform an assessment of headache, associated features, and adverse events. The use of rescue medications to treat persistent pain will also be recorded. Prior to discharge, research associates will ascertain key socio-

demographics and pertinent features of the headache and medical history. Contact information will be verified. A specific time to perform the first follow-up phone call will be scheduled. Research personnel will ensure that study subjects have a way home and do not have to drive themselves.

Follow-up phone calls will be performed 48 hours and 7 and 30 days after ED discharge. At the first call, the next follow-up phone call will be scheduled. Attempts to complete the follow-up calls successfully will be made every eight hours until deemed futile.

At the 48-hour phone call, the focus will be assessments of pain and associated symptoms, adverse events, satisfaction with the medication received, and use of rescue medication. The focus of the seven day phone call will be total number of days with headache and associated symptoms since ED discharge, the need for repeat ED visits, healthcare providers visited, days of work missed, and adverse medication effects.

The SCAT PCSS will be assessed at 48 hours, 7 days and 30 days.

Baseline co-variates
1. Severity of initial trauma, as measured by presence and duration of loss of consciousness and amnesia (missing time)
2. Anxiety, as measured by anxiety scale (GAD-7)
3. Concern about cause of headache (Four item Likert: I probably didn't need to see a doctor but I wanted to be sure; I'm not sure if I did or didn't need to see a doctor; I probably needed to see a doctor; I definitely needed to see a doctor)
4 Personal and family primary headache history
5. Patient's assessment of liability (no ones fault, patient's fault, someone else's fault)

Analysis.
Baseline characteristics will be reported as mean(SD), median (IQR), or n/N(%), as appropriate.

Primary outcome. We will report the frequency of moderate or severe headache after discharge in each group as n/N (%) with 95%CIs. We will calculate between-group difference (ARR) and report this with 95%CIs. If the 95%CI does not cross 0, the result will be considered statistically significant. If there is a difference in the frequency of rescue medication use in the ED, we will build a logistic regression model in which moderate/severe headache is the dependent variable, and investigational medication and use of rescue medication will be included as independent variables.
Other outcomes: Dichotomous outcomes will be reported as frequencies with 95%CI. Headache days and PCSS score will be reported as mean with 95%CI. Between group differences will be calculated as above.

Missing data will be managed by alternating worst case and best case scenarios for each study arm and determining the impact of these assumptions.

Subject treatment assignments will remain blinded until the final subject has completed follow up and all data has been recorded and validated. Urgent, immediate unblinding due to medical emergency may be authorized by the Investigator. When possible, the treatment assignment will be provided to the treating physician in order to maintain the blind for the Investigator and study staff.

We used the following assumptions for the sample size collection: alpha=0.05, beta= 0.20, a two-sided test, frequency of moderate or severe post discharge headache among those who receive metoclopramide + placebo= 35%, frequency of moderate or severe post-discharge headache among those who receive metoclopramide + dexamethasone= 15%. We intend to enroll an additional 10% to account for protocol violations and missing data, giving a total sample size of 162.

Data collection and processing. Data acquisition will be performed using REDCap (Research Electronic Data Capture), a secure, web-based application designed specifically to support data capture for research studies. The REDCap project (http://project-redcap.org/) is an international project, with more than 70 institutional partners from CTSA and GCRC funded institutions.

Data monitoring committee and interim analysis. This committee will be headed by Dr. Polly Bijur, PhD, an epidemiologist and include Dr. Esses, MD, the interim chair of Emergency Medicine. The committee will meet every month with the PI to monitor: 1) adverse events; and 2) recruitment and enrollment. We will perform two interim analyses with the goal of determining futility. The first interim analysis will occur after 54 patients have been enrolled. The second interim analysis will occur after 109 patients have occurred. The study will be halted after the first interim analysis if the point estimate of the control arm is superior to that of the experimental arm. No statistical test will be performed. The study will be halted after the second interim analysis if the point estimate of the experimental arm is < 10% better than the control arm because it is exceedingly unlikely that we would discover a statistically significant benefit by continuing the study if this were true. Again, no statistical test will be performed.

Registration. The study will be registered at http://www.clinicaltrials.gov.

Consent. Informed consent will be obtained after the patient is evaluated in the ED. As part of our consent process, we will offer to help patients call a family member or friend and discuss the study with them if they wish. We will also have the patient's attending physician confirm that the patient has the capacity to consent to participate in the study at the time they are asked to provide consent. Both research associates and health care providers will participate in the consent process. Both will document their participation with a note in Epic and by signing the consent document. Children 16 & 17 years old will be enrolled in the study only if they provide their consent and, along with one parent, sign the consent document.

Risks/Benefits

Anti-dopaminergics such as metoclopramide can cause extra-pyramidal side effects including tardive dyskinesia. Irreversible extra-pyramidal symptoms have never been reported after one intravenous dose of metoclopramide. The investigational medication can also cause a variety of nuisance side effects including dizziness, drowsiness, and palpitations. As with any clinical study, there is a risk that the patient's personal identifiers and private health data may be seen by non-study personnel. It is clear that a great many patients continue to suffer from headache after ED discharge. This protocol is specifically designed to inform the ED-based treatment of acute post-traumatic headache.

References

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Post Concussion Symptom Scale

All items are rated on a 0-6 scale, with 0= none and 6=severe

1.Headache 0 1 2 3 4 5 6
2. Pressure in head 0 1 2 3 4 5 6
3. Neck Pain 0 1 2 3 4 5 6
4. Nausea or vomiting 0 1 2 3 4 5 6
5. Dizziness 0 1 2 3 4 5 6
6. Blurred vision 0 1 2 3 4 5 6
7. Balance problems 0 1 2 3 4 5 6
8. Sensitivity to light 0 1 2 3 4 5 6
9. Sensitivity to noise 0 1 2 3 4 5 6
10. Feeling slowed down 0 1 2 3 4 5 6
11. Feeling like "in a fog" 0 1 2 3 4 5 6
12. Don't feel right 0 1 2 3 4 5 6
13. Difficulty concentrating 0 1 2 3 4 5 6
14. Difficulty remembering 0 1 2 3 4 5 6
15. Fatigue or low energy 0 1 2 3 4 5 6
16. Confusion 0 1 2 3 4 5 6
17. Drowsiness 0 1 2 3 4 5 6
18. Trouble falling asleep 0 1 2 3 4 5 6
19. More emotional than usual 0 1 2 3 4 5 6
20. Irritability 0 1 2 3 4 5 6
21. Sadness 0 1 2 3 4 5 6
22. Nervous or Anxious 0 1 2 3 4 5 6