A randomized placebo controlled trial of IV metoclopramide for acute post-traumatic headache
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Nearly 1.5 million patients present to US EDs annually following head trauma.(1) Headache is a frequent symptom of victims of trauma and may take the form of either migraine or tension-type headache. (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, but this hypothesis has never been tested experimentally. We propose a randomized, double blind, placebo controlled study of metoclopramide for acute post-traumatic headache. Our primary hypothesis is that metoclopramide will improve headache pain more than placebo one hour after medication administration. Secondarily, we will determine whether metoclopramide is associated with persistent headache relief up to 48 hours, one week, and 30 days after medication administration.

It is not yet understood why anti-dopaminergic medications are effective treatment for acute headache, but there is a substantial evidence base supporting efficacy of this class of medication for headache, regardless of whether the headache is migraine,(3) or tension-type(4) headache. Also, when used for headache, this medication is generally well-tolerated; serious adverse events have not been reported in this population. Given this track record of successful use in primary headache disorders, we believe this medication is appropriate for use in this initial study of parenteral treatment for post-traumatic headache.

Pilot data.
In an open label study of patients with post-traumatic headache conducted in the Montefiore EDs, 9 patients with moderate or severe post-traumatic headache were administered the medication regimen described in this protocol. 8 of the 9 patients reported no headache within two hours of receiving the medication. The remaining patient reported mild headache. During the 48 hours after medication administration, three of the nine patients relapsed and had headaches worse than mild. The only adverse event patients reported was drowsiness. Eight of the nine patients reported that they would want to receive the same medication regimen during a subsequent ED visit for headache. The one patient who would not want the same medication again said so attributed this response to medication-induced drowsiness.

Methods.
Overview. This will be a randomized, double blind, placebo-controlled study of IV metoclopramide for acute post-traumatic headache. 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 adults who 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, previous history of 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 contra-indications including pheochromocytoma, seizure disorder, Parkinson's disease, use of MAO inhibitors, and use of anti-rejection transplant medications. Patients will be excluded for 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 20mg + diphenhydramine 25mg IV drip over 15 minutes. Diphenhydramine is co-administered to prevent subjective restlessness, a not infrequent side effect of higher doses of metoclopramide.(5)
2) Placebo: Normal saline IV drip over 15 minutes

Rationale for placebo. To the best of our knowledge, there are no published studies of treatment for acute post-traumatic headache. It is unknown if active intravenous treatment is more beneficial than normal saline alone. Therefore, there is a compelling rationale for a placebo-controlled study. Patients who have not experienced adequate headache relief one hour after treatment initiation will be offered rescue therapy.

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 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 20mg in solution with normal saline or normal saline alone, the other containing diphenhydramine 25mg in solution with normal saline or normal saline alone. The metoclopramide and diphenhydramine solutions appear identical to normal saline. The research packages will be used in sequential order.
Stratification. Subjects will be stratified by study site and baseline headache intensity.

Measures:
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.
International Headache Society pain scale. Headache is described as severe, moderate, mild, or none
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
Overall sense of wellbeing. Patients are asked to report their overall health since before their injury as better, same, or worse
The Sport Concussion Assessment Tool (SCAT) Post Concussion Symptom Scale (PCSS). On this validated instrument, patients rate 25 symptoms on a 0 to 6 scale. (Appendix)

Primary outcome. The primary outcome is improvement in 0 to 10 pain score between medication administration and one hour later
Secondary outcome. 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.
Other outcomes.
1) Use of additional medication in the ED for headache
2) Use of additional medication in the ED for associated symptoms
3) Achieving headache freedom in the ED without use of additional medication for headache
4) Satisfaction with the medication, measured at the 48 hour follow-up phone call
5) Number of days with headache during the week after ED discharge
6) Return visits to the ED over the week after discharge
7) SCAT PCSS at 48 hours, 7 days, and 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. Eligibility will be ascertained by research associates and verified by the site investigator. 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, diphenhydramine, or normal saline alone, 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 both 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.
Primary outcome. We will report mean one-hour improvement in each group with 95%CIs. We will calculate between-group difference in mean one-hour improvement and report this with 95%CIs. If the 95%CI does not cross 0, the result will be considered statistically significant.
Secondary outcome. We will report frequencies of sustained headache relief in each group with 95%CI. We will calculate the between group difference (absolute risk reduction) and report this with 95%CI. We will calculate the number needed to treat and report this with 95%CI.
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.

Sample size calculation: A review of a recent migraine trial involving metoclopramide revealed a mean improvement in 0 – 10 score of 5.1 and a standard deviation of 2.8.(6) Using these values and assuming a normal distribution, a two-sided α=0.05, and a minimum clinically important difference between groups of 1.3, we calculated the need for 74 patients in each group. 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 director of the Moses ED. The committee will meet every month with the PI to monitor: 1) adverse events; and 2) recruitment and enrollment. We will not perform an interim analysis as we wish to optimize the precision with which we report study results.

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.

Pyxis procedures. The healthcare provider will place an order in Epic for the study medication. The order will trigger a specific pocket in Pyxis to open. The research associate and the clinical nurse will then complete the RA/RN checklist (Appendix).

Description of orientation and education that providers receive about this study and about research procedures. This study in particular and research procedures in general are introduced during faculty meetings and reinforced with emails and Powerpoints. The PI then meets with providers in brief one-on-one sessions to describe these. Finally, the investigators and research associates discuss these during the in-shift briefs.

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.

Data Storage & Confidentiality

Data will be stored and maintained securely in REDCap. Data analysis will be performed on password-protected computers. Consent documents will be maintained in locked research cabinets in inaccessible areas. Only study personnel will have access to the data and consent documents.

References

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3. Orr SL, Friedman BW, Christie S, Minen MT, Bamford C, Kelley NE, et al. Management of Adults With Acute Migraine in the Emergency Department: The American Headache Society Evidence Assessment of Parenteral Pharmacotherapies. Headache. 2016;56(6):911-40.
4. Weinman D, Nicastro O, Akala O, Friedman BW**.** Parenteral treatment of episodic tension-type headache: a systematic review. Headache. 2014;54(2):260-8.
5. Friedman BW, Bender B, Davitt M, Solorzano C, Paternoster J, Esses D, et al. A randomized trial of diphenhydramine as prophylaxis against metoclopramide-induced akathisia in nauseated emergency department patients. Annals of emergency medicine. 2009;53(3):379-85.
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Post Concussion Symptom Scale

0=none, 6= severe

Headache 0 1 2 3 4 5 6
Pressure in head 0 1 2 3 4 5 6
Neck Pain 0 1 2 3 4 5 6
Balance problems or dizzy 0 1 2 3 4 5 6
Nausea or vomiting 0 1 2 3 4 5 6
Vision problems 0 1 2 3 4 5 6
Hearing problems / ringing 0 1 2 3 4 5 6
Don’t feel right 0 1 2 3 4 5 6
Feeling “dinged” or “dazed” 0 1 2 3 4 5 6
Confusion 0 1 2 3 4 5 6
Feeling slowed down 0 1 2 3 4 5 6
Feeling like "in a fog" 0 1 2 3 4 5 6
Drowsiness 0 1 2 3 4 5 6
Fatigue or low energy 0 1 2 3 4 5 6
More emotional than usual 0 1 2 3 4 5 6
Irritability 0 1 2 3 4 5 6
Difficulty concentrating 0 1 2 3 4 5 6
Difficulty remembering 0 1 2 3 4 5 6
Sadness 0 1 2 3 4 5 6
Nervous or Anxious 0 1 2 3 4 5 6
Trouble falling asleep 0 1 2 3 4 5 6
Sleeping more than usual 0 1 2 3 4 5 6
Sensitivity to light 0 1 2 3 4 5 6
Sensitivity to noise 0 1 2 3 4 5 6