Metoclopramide for Post-Traumatic Headache
A Pilot Study

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A pilot study of IV metoclopramide for acute post-traumatic headache

Nearly 1.5 million patients present to US emergency departments 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.(2) Post-traumatic headaches are believed to respond to the same parenteral medications as primary headaches, but this hypothesis has never been tested experimentally. We propose a series of clinical investigations examining the role of IV metoclopramide for acute post-traumatic headache. Our hypothesis is that metoclopramide will improve headache pain more than placebo one hour, 48 hours and one week after medication administration. As a precursor to a definitive study, we intend to perform an open-label pilot study to determine the feasibility of this line of investigation.

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.

Methods

Overview. This will be a non-randomized, open-label study of IV metoclopramide for acute post-traumatic headache. Patients will be enrolled during a visit to one of two Montefiore EDs and followed by telephone 48 hours and 7 days after the ED visit.

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 parenteral metoclopramide. 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: Metoclopramide 20mg IV drip over 15 minutes + diphenhydramine 25mg IV drip over 15 minutes. Diphenhydramine is co-administered to prevent subjective restlessness.(5)

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
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 and 7 days

Details of protocol
Patients who present to either of the study 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. The research associate will perform a baseline pain assessment. The ED nurse will then administer the research medication as described above. 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 history. Contact information will be verified by calling the number given at the time of acquisition in the ED. A specific time to perform the first follow-up phone call will be scheduled.

Follow-up phone calls will be performed 48 hours and 7 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 this point, questionnaires will be sent by express courier, and failing this, the investigator will perform a home visit.

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.

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 one's fault, patient's fault, someone else's fault)

Sample size: We intend to enroll up to 20 patients. We will review data after each group of five patients to determine whether there is compelling data to proceed with a definitive study.

Analysis

The primary purpose of this study is to determine whether there is a compelling rationale to proceed with a definitive study. We will analyze the data after each group of five patients have been enrolled. If 0 of the initial five patients achieve the primary outcome, we will halt this line of investigation. After 10 patients have been enrolled, we will use the threshold of 40% response (48 hour sustained relief) to determine whether or not to proceed with the definitive study. We intend to continue enrollment until 10 patients have provided complete outcome data (may require up to 20 patients). We also intend to continue enrollment beyond 10 patients in this pilot study if study instruments require refinement or if there is discrepancy between primary and secondary outcomes.

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. Paper consent documents will be maintained in locked research cabinets.

Consent
Informed consent will be obtained when patients present to 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.

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 initially de-identifies patients, and is done only on password-protected computers behind an institutional firewall, protected with professionally maintained anti-viral software. 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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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.

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

(follow up symptoms only)
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
Other: _____ 0 1 2 3 4 5 6