Dexamethasone for Migraine - Dose Comparison
Protocol ID: **2019-10562**
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Aims

Migraine, a chronic, episodic headache disorder characterized by recurrent exacerbations, causes 1.2 million visits to US emergency departments (ED) annually.[1] Nearly 2/3rds of migraine patients experience worsening or recurrence of headache within 48 hours of ED discharge. About half of patients suffer more than two days of headache during the week following ED discharge.[2] Dexamethasone is an evidence-based treatment for migraine, with a number needed to treat of nine to decrease the frequency of moderate or severe headache within 72 hours of ED discharge.[3] The American Headache Society recommends dexamethasone for use in patients with acute migraine.[4] However, the optimal dose of dexamethasone is not known. Aggregated data do not reveal an association between dose of steroids and outcome. We therefore will perform a randomized dose-finding study to determine whether high-dose dexamethasone affords more relief for patients with an acute migraine who present to an ED than low-dose dexamethasone. We hypothesize that dose of dexamethasone will be directly associated with the rate of sustained headache relief.

Methods.

Study design. This will be a randomized, double blind, comparative efficacy study conducted among patients who present to an ED with acute migraine. All participants will receive standard-of-care acute treatment, consisting of metoclopramide 10mg IV as the primary abortive medication. Additionally, all participants will receive a dose of dexamethasone IV. Because dexamethasone is an evidence-based therapy in these patients, there will be no placebo arm. Outcomes will be assessed by telephone 48 hours and seven days after the ED visit using a standardized instrument with a closed-question format.

Population of interest. Eligible patients are those presenting to the ED for treatment of an acute migraine headache as defined by International Headache Society clinical criteria.[5] At the time of enrollment, the patient must rate the headache as moderate or severe in intensity and the ED treatment plan must include use of an intravenous medication. Adults aged at least 18 years will be eligible to participate. Patients are to be excluded for signs of secondary headaches including fever or objective neurologic findings on physical exam. Patients will also be excluded if already using corticosteroids, for contraindications or allergies to the investigational medications, or if pregnant or breastfeeding. Medication contra-indications are as follows: pheochromocytoma, seizure disorder, Parkinson's disease, use of MAO inhibitors, and use of anti-rejection transplant medications. Because patients will receive only one dose of dexamethasone, we will not exclude diabetics from participation.

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

Investigational medications. Medications in each study arm are as follows:

A. Metoclopramide 10mg IV drip over 15 minutes (for acute treatment)+ dexamethasone 4 mg IV
B. Metoclopramide 10mg IV drip over 15 minutes (for acute treatment)+ dexamethasone 16 mg IV

Assignment. Will be concealed. The research pharmacist will determine assignment based on a random number sequence.
Randomization. Randomization will occur in blocks of 4 based on a random number generator.
Blinding. Patients, clinicians, and research personnel will be blinded.
Stratification. Subjects will be stratified by study site (Moses or Weiler) and baseline pain intensity (moderate or severe).

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. Prior to enrollment, patients with diabetes will be cautioned that the study medications may cause loss of glycemic control and that they will need to be attentive to their blood sugar during the week following ED discharge. Masked medication will be obtained from the pharmacy. 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 60 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. A specific time to perform the first follow-up phone call will be scheduled. At the time of discharge, we will again caution diabetics to be attentive to their blood sugar.

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, functional status, migraine associated features, adverse events, satisfaction with the medication received, and use of rescue medication. The focus of the seven day phone call will be on the total number of days with headache since ED discharge, the need for repeat ED visits, healthcare providers visited, days of work missed, and adverse medication effects.

Measures and outcomes

Measures and outcomes used in this trial will utilize NINDS's common data elements for headache and adhere to the International Headache Society's clinical trials guidelines.[6] Exceptions to this will occur only for recommendations not relevant to ED-based studies.

Baseline variables of interest: Age, sex, duration of headache, use of medication prior to ED presentation (yes/no), aura symptoms

1) Headache intensity. We will assess headache intensity using the recommended four-item descriptive scale commonly used in headache clinical trials. Patients will be asked to describe their headache intensity as "severe," "moderate," "mild," or "none."[6]
2) Functional disability will be assessed using the recommended four-item scale: Severely impaired ("can't get out of bed"); Moderately impaired ("great deal of difficulty doing what I usually do"); Mildly impaired ("some difficulty doing what I usually do"); and Not impaired [6]
3) Headache days. We will ask how many days since ED discharge the patient had any headache, a moderate or severe headache, or an activity-impairing headache. For the purpose of this tabulation, a new day begins when the patient awakens to begin activities for the day and ends when the patient sleeps after ceasing all activities for the day. We will also ask patients to determine how often during their awake hours they experienced any headache using the following Likert scale: always, often, sometimes, rarely, never.
4) Medication preference. Preference for a specific medication is a highly patient centered outcome, in which an individual determines for herself the benefit of a particular drug versus the adverse effects experienced. We will include in this study a measure that has been used in multiple ED-based trials—"The next time you come to the

ER for treatment of migraine, do you want to receive the same medication again?"[7] Patients will be asked to choose among "Yes," "No," or "Not sure".
5) Adverse outcomes will be assessed using an open-ended format. Patients will be asked to grade the specific adverse events they list as "mild," "moderate," or "severe."

Outcomes.
Efficacy analysis. The primary outcome for this study will be sustained headache relief for 48 hours: achieving a headache intensity = "none" or "mild" within two hours of medication administration and maintaining this level, without requiring additional headache medication, for the entire 48 follow-up period

Secondary efficacy endpoints.
1) Two hours headache relief (achieving a headache level = mild or none within two hours of medication administration without requiring rescue medication 2) Number of headache days during the week after ED discharge 3) Patient preference for receiving the same medication for a subsequent headache, measured at the 48 follow-up phone call 4) Use of additional headache medication in the ED 5) Use of additional headache medical after ED discharge

Safety endpoints. 1) Frequency of adverse events in the ED; 2) Frequency of adverse events developing within 48 hours following ED discharge.

Both during the ED visit and at the 48 hour follow-up, we will ask the following question: Did any new symptoms begin after you received the study medication. An affirmative response will be followed with open-ended queries to categorize these symptoms. Affirmative responses will be tabulated. The open-ended queries will be used to categorize specific adverse events.

Analysis. Efficacy. For the primary analysis, we will report the rate of sustained headache freedom in each group as n/N (%, 95%CI). Random assignment will be stratified to ensure balance among the study arms with regard to study site and baseline pain intensity. Asymmetry with regard to the other important baseline variables discussed above will be addressed using multivariable regression techniques. We will address discrepant baseline variable by building a multivariate linear regression model in which the dependent variable in number of headache days, the primary predictor variable is investigational medication, and all discrepant important baseline variables are included in the model.

Dichotomous secondary outcomes will be reported as simple proportions, relative risk, and odds ratios with 95%CI. Absolute risk reduction will be calculated and reported with 95%CI.

Safety analysis. We will perform simple pairwise comparisons of specific adverse events.

Sample size calculation. In a recently completed study performed here at Montefiore, the rate of sustained headache relief after administration of metoclopramide 10mg IV +dexamethasone 10mg IV was 37%. In this type of research, a clinically important difference has been defined as an approximate 15% absolute risk reduction (between group difference). Assuming a primary outcome rate of 30% in the high dose group and 45% in the low dose group, we calculated the need for 163 patients in each arm, using an alpha =0.05 and beta= 0.20. To this we added a 10% margin to account for protocol violations and patients lost to follow-up. Therefore, we hope to enroll 360 patients.

We anticipate that we can enroll 250 patients/ year.

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.

Data monitoring committee and interim analysis. This committee will be headed by Dr. Carlo Lutz, MD MS, and include Dr. Esses, MD, the interim chair of the Department of Emergency Medicine. The committee will meet every month with the PI and co-investigators to monitor: 1) adverse events; and, 2) recruitment and enrollment.

We will perform an interim analysis after 200 patients have been enrolled, slightly past the halfway point. At this point, we will halt the study for futility, clear superiority, or a large discrepancy in adverse medication events. Futility will be defined as < 10% between-group difference, as continuing the study beyond this point would be unlikely to result in a statistically significant difference between the groups. Clear superiority will be defined as >20% between-group difference. A large discrepancy in adverse events will be defined as >20% between-group difference in the overall rate of participants who suffer any adverse event.

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

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. Corticosteroids can cause irreversible boney necrosis and short-term side effects including mood swings, nightmares, loss of glycemic control, and an increased propensity for infections. Of note, the irreversible side effects listed above have never been reported after a single standard dose of any of the investigational medications administered in this study. The investigational medications 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 migraine patients continue to suffer from headache after ED discharge. This protocol is specifically designed to inform the ED-based treatment of acute migraine.

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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4. Orr, S.L., 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): p. 911-40.
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7. Friedman, B.W., P.E. Bijur, and R.B. Lipton, *Standardizing emergency department-based migraine research: an analysis of commonly used clinical trial outcome measures.* Academic emergency medicine : official journal of the Society for Academic Emergency Medicine, 2010. **17**(1): p. 72-9.