Corticosteroids for Acute Migraine:
An ED-Based, Randomized, Comparative Effectiveness Trial

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Aims

Migraine is a chronic, episodic headache disorder characterized by recurrent exacerbations, responsible for 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] We wished to test the hypothesis that methylprednisolone acetate, a long-acting corticosteroid (comparable to a one week steroid taper when administered intramuscularly), would decrease the mean number of headache days experienced by migraineurs during the week following discharge from an ED when compared to dexamethasone.

Methods.

Study design. This will be a randomized, double blind, comparative efficacy study. All participants will receive active treatment. 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.[4] 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 any of 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.

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 10mg IM
B. Metoclopramide 10mg IV drip over 15 minutes (for acute treatment) + methylprednisolone acetate 160mg IM

Assignment. Will be concealed. The research pharmacist will determine assignment based on a random number sequence.
Randomization. Randomization will occur in blocks of four based on a random number generator.
Blinding. Patients, clinicians, and research personnel will be blinded.
Stratification. Subjects will be stratified by study site.

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. Contact information will be verified with at least two phone numbers, one of which – typically the mobile number - will be confirmed 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. At the time of discharge, we will again caution diabetics to be attentive to their blood sugar and encourage rapid follow-up with their primary care provider.

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 primary endpoint of 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.

Co-variates of interest. Because any of the following independent variables may influence the primary dependent outcome variable, they will each be measured at baseline to facilitate multivariate adjustment if indicated clinically or in the bivariate analysis.
-Baseline MIDAS score. This validated scale (**MI**graine **D**isability **A**ssessment **S**cale) measures the impact of the underlying migraine disorder on the individual's quality of life and is used to gauge its severity. For example, patients who suffer three days of functionally disabling headache per week will score substantially worse on this scale than those with only one disabling headache day every three months. Because participants with worse baseline migraine assessment scores may respond differently to acute treatment, we will assess and adjust for this variable at baseline as indicated.
-Aura. To facilitate a homogeneous study cohort, we will require all participants, at a minimum, to meet "migraine without aura" criteria. . Some of our participants may also meet criteria for the less common "migraine with aura," which may be more or less amenable to any of the investigational agents

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.[5] Exceptions to this will occur only for recommendations not relevant to ED-based studies.

1) Headache days. At the seven day follow-up, 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.

2) 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."[5]
3) 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 [5]
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?"[6] 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 number of days with headache during the 7 days immediately following ED discharge.

Secondary efficacy endpoints.
1) Sustained headache freedom (achieving a headache intensity = "none" within two hours and maintaining this level, without requiring additional headache medication, for the entire follow-up period) 2) Sustained headache relief (achieving a headache intensity = "none" or "mild" within two hours and maintaining this level, without requiring additional headache medication, for the entire follow-up period) 3) Patient preference for receiving the same medication for a subsequent headache, measured at the 7 day follow-up phone call 4) Number of days with a moderate/ severe or activity-impairing headache during the 7 day follow-up 5) How often during the seven day follow-up period the patient experienced headache (rarely/ never vs sometimes/ often/ always)

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.

Sample size calculation. We have previously collected data on outcomes of migraine patients after ED discharge. The mean number of headache days post ED discharge was 3.2 (SD-2.5). We estimate that the long-acting corticosteroid would have to decrease the mean number of headache days by at least 1.0 day compared to dexamethasone as the minimum criteria for declaration of clinically meaningful difference. Assuming a 2-tailed alpha =0.05 and a 1-tailed beta = 0.20, we calculated the need for 100 patients in each group. Adding to this 10% for lost-to-follow-up and protocol violations, we determined the need for 220 patients.

Analysis. Efficacy. For the primary analysis, we will compare the mean number of headache days (0- 7) between those randomized to dexamethasone and those randomized to methylprednisolone acetate. Point estimates and 95%CI will be reported. Although these data are likely to be skewed towards smaller numbers, our sample size is sufficient to allow a parametric analysis. We will report the difference between means with

95%CI. A statistically significant difference is one for which the 95%CI does not include zero. We will dichotomize the number of headache days at two and report the frequency with which subjects report fewer than two headache days post ED discharge. Random assignment will be stratified to ensure balance among the study arms with regard to study site. 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.

In conducting ED-based migraine research, there is often a small subset of patients who appeared to meet inclusion criteria at the time of enrollment but in whom it was determined later that the patient was not, in retrospect, appropriate for the study. For example, patients may develop a fever later in their ED course or subsequently develop objective neurologic findings. In keeping with the principles of an intention-to-treat analysis, these patients will be retained in the study and included in the primary analysis. A secondary analysis, if needed, will include only those determined by adjudication to have true migraine by International Headache Society criteria.

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

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. 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 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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