A Randomized Trial of a Long-Acting Depot Corticosteroid Versus Dexamethasone to Prevent Headache Recurrence Among Patients With Acute Migraine Who Are Discharged From an Emergency Department

Alexander Latev, MD*; Benjamin W. Friedman, MD, MS; Eddie Irizarry, MD; Clemencia Solorzano, PharmD; Andrew Restivo, MD; Andrew Chertoff, MD; Eleftheria Zias, RPh; E. John Gallagher, MD

*Corresponding Author. E-mail: Alatev@montefiore.org, Twitter: @AlexLatev.

Study objective: Migraine patients continue to report headache during the days and weeks after emergency department (ED) discharge. Dexamethasone is an evidence-based treatment of acute migraine that decreases the frequency of moderate or severe headache within 72 hours of ED discharge. We hypothesize that intramuscular methylprednisolone acetate, a long-acting steroid that remains biologically active for 14 days, will decrease the number of days with headache during the week after ED discharge by at least 1 day compared with intramuscular dexamethasone.

Methods: We conducted a randomized, blinded clinical trial comparing intravenous metoclopramide at 10 mg+intramuscular dexamethasone at 10 mg with intravenous metoclopramide at 10 mg+intramuscular methylprednisolone acetate at a dose of 160 mg for patients presenting to 2 different EDs with moderate or severe migraine. Outcomes were assessed by telephone with a standardized instrument. The primary outcome was number of days with headache during the week after ED discharge. Secondary outcomes were complete freedom from headache, without the necessity of additional headache medication for the entire week after ED discharge, and medication preference, as determined by asking the patient whether he or she would want to receive the same medication again.

Results: One hundred nine patients received dexamethasone and 111 received methylprednisolone acetate. We obtained primary outcome data from 101 dexamethasone patients and 106 methylprednisolone acetate patients. Dexamethasone patients reported 3.0 headache days and methylprednisolone acetate 3.3 headache days (95% confidence interval for rounded mean difference of 0.4 days: −0.4 to 1.1). Of 107 dexamethasone patients with analyzable data, 10 (9%) reported complete freedom from headache at 1 week versus 6 of 110 (5%) methylprednisolone acetate patients (95% confidence interval for difference of 4%: −3% to 11%). In the dexamethasone group, 76 of 101 (75%) patients would want the same medication again versus 75 of 106 (71%) of methylprednisolone acetate patients (95% confidence interval for difference of 4%: −8% to 17%). Other than injection site reactions, which were more common in the methylprednisolone acetate group, there were no substantial differences in frequency of adverse events.

Conclusion: Methylprednisolone acetate does not decrease the frequency of post-ED discharge headache days compared with dexamethasone. Most migraine patients are likely to continue to experience headache during the week after ED discharge. [Ann Emerg Med. 2019;73:141-149.]

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INTRODUCTION

Migraine, a chronic, episodic headache disorder characterized by recurrent exacerbations, is responsible for 1.2 million visits to US emergency departments (EDs) annually.[1] Nearly two thirds of migraine patients who are successfully treated in the ED experience worsening or recurrence of headache within 48 hours of ED discharge.[2] Approximately half of discharged ED migraine patients experience more than 2 days of headache during the week after ED discharge.[3] Dexamethasone, a corticosteroid medication, is an evidence-based treatment for migraine. When administered in combination with a first-line migraine-abortive medication, it decreases the frequency of moderate or severe headache within 72 hours of ED discharge.[4] However, the optimal dose and

Editor's Capsule Summary

What is already known on this topic

Dexamethasone decreases moderate to severe headache frequency during the first 72 hours after emergency department (ED) discharge of migraine patients.

What question this study addressed

The authors investigated the effectiveness of a longer-acting steroid in decreasing the number of days with headache during the week after ED discharge.

What this study adds to our knowledge

In this 207-patient randomized trial of intramuscular metoclopramide plus either dexamethasone or methylprednisolone acetate, there was little difference in days with headache during the first week after ED discharge.

How this is relevant to clinical practice

This study failed to establish that the longer-acting agent, methylprednisolone, was superior to dexamethasone for preventing post–ED visit headaches in patients with migraines.

duration of therapy with corticosteroids are unknown. We wished to test the hypothesis that a steroid with a longer duration of action would result in better outcomes. Therefore, we designed a clinical trial in which half of the study participants would receive methylprednisolone acetate, a long-acting version of the corticosteroid methylprednisolone, and the other half would receive dexamethasone, the currently recommended adjuvant treatment.[4] Dexamethasone has a half-life of 36 to 72 hours. Methylprednisolone acetate peaks in the serum 2 days after intramuscular injection and maintains an appreciable serum level for 14 days.[5] When administered intramuscularly, methylprednisolone acetate is comparable in efficacy to a 1-week steroid taper. We hypothesized that a single intramuscular injection of methylprednisolone acetate would decrease the number of headache days experienced by migraine patients during the week after discharge from an ED by at least 1 day compared with a single intramuscular injection of dexamethasone.

MATERIALS AND METHODS

Study Design and Setting

We conducted a randomized, blinded study of 2 different parenteral corticosteroid treatments for ED patients with moderate or severe acute migraine. This study was conducted in 2 EDs of Montefiore Medical Center, an urban teaching institution in Bronx, NY, with an annual visit volume exceeding 170,000 visits. Both EDs are staffed by bilingual (Spanish and English), salaried research associates 24 hours per day, 7 days per week. All participants in this study received intravenous metoclopramide, a first-line migraine abortive. Research personnel assessed outcomes during the research subjects' ED course and by telephone 48 hours and 7 days after the ED index visit, using a standardized data collection instrument. The study was reviewed and approved by the Albert Einstein College of Medicine institutional review board. Written consent was obtained from all participants.

Selection of Participants

Eligible patients were adults older than 18 years and presenting to the ED for treatment of an acute migraine headache, as defined by *International Classification of Headache Disorders Third Edition (Beta Version)* criteria (1.1, migraine without aura; or 1.5.1, probable migraine without aura).[6] To be included, probable migraine patients were required to have had a similar headache at least once previously. There was no limitation on duration of symptoms. Using a headache rating scale of severe, moderate, mild, or none, patients had to describe their headache as moderate or severe in intensity. Research associates screened patients for eligibility 24 hours per day, 7 days per week. Once patients were deemed eligible, research associates confirmed eligibility with the treating attending physician. Patients were excluded for signs of secondary headaches including fever or for objective neurologic findings on physical examination, or if their attending physician intended to order a computed tomography scan of the head. Patients were also excluded if already receiving corticosteroids, for contraindications or allergies to any of the investigational medications, or if pregnant or breastfeeding.

Interventions

All participants received metoclopramide 10 mg as an intravenous drip during 15 minutes. Participants were concurrently randomized to either dexamethasone 10 mg or methylprednisolone acetate 160 mg, both given by intramuscular injection.

Dexamethasone is an evidence-based,[4,7] guideline-supported[8] treatment of acute migraine. Dexamethasone is more effective than placebo at reducing migraine relapse during the 24 to 72 hours after ED treatment (number needed to treat versus placebo=9).[4] The optimal dose of dexamethasone is not known; various published studies have

used intramuscular or intravenous doses ranging from 4 to 24 mg. We selected the most commonly used dose of 10 mg.[4]

Methylprednisolone acetate, a long-acting depot formulation of methylprednisolone, is often dosed 40 to 120 mg weekly. We could not identify published dose-finding studies, so we selected an above-average intramuscular dose of 160 mg.

Research pharmacists prepared investigational medication packets after randomization in blocks of 4 by using a random-number generator (http://www.randomization.com). This was done at a location distant from and inaccessible to all ED personnel. Assignment was concealed by using opaque packaging. Patients were not told which treatment they received. However, because methylprednisolone acetate is a milky solution and dexamethasone is clear, an observant, motivated patient could have deduced which steroid was administered. Research staff, outcome assessors, and the investigators blinded themselves to treatment by removing themselves from the immediate patient care area when the injection was administered. Patients were stratified by study site.

Rescue medication, both in the ED and during the follow-up period, was administered at the discretion of the treating physician.

Methods of Measurement

The primary endpoint, the number of headache days during the week after ED discharge, was assessed by asking how many days the patient had any headache since ED discharge. For the purpose of this tabulation, a new day began when the patient awoke to begin activities for the day and ended when the patient went to sleep after ceasing all activities for the day. We also asked participants how often during their awake hours they experienced any headache, using the following scale: "always," "often," "sometimes," "rarely," or "never." We assessed headache intensity in the ED, at 48 hours, and at 1 week, using the recommended 4-item descriptive scale commonly used in headache clinical trials, in which the headache is described as "severe," "moderate," "mild," or "none."[9] At each of the follow-up points, research personnel asked patients to recall their worst headache since ED discharge. Medication preference for a specific medication is a highly patient-centered outcome that has been used in multiple ED-based trials, and is evaluated by the question "The next time you come to the ED for treatment of migraine, do you want to receive the same medication again?"[10] Patients chose among "yes," "no," and "not sure." We assessed adverse outcomes with an open-ended format in the ED and at 48 hours. Baseline data, including sex, age, duration and severity of headache, the presence of aura symptoms, and use of medication before ED presentation, were assessed while the patient was in the ED.

Outcome Measures

The primary outcome for this study was the mean number of days with headache during the 7 days immediately after ED discharge.

Secondary outcomes included sustained freedom from headache, defined as achieving a headache intensity of "none" within 2 hours of treatment in the ED and maintaining this level, without requirement of additional headache medication, for the entire follow-up period; patient preference for receiving the same medication for a subsequent headache, measured at the 7-day follow-up telephone call; headache frequency at each follow-up period; pain intensity in the ED; and frequency of use of additional medication for headache in the ED.

Primary Data Analysis

We analyzed all data with Stata (version 14.2; StataCorp, College Station, TX). For the primary analysis, we compared the number of headache days among patients randomized to dexamethasone versus methylprednisolone acetate. The difference between the 2 arms is reported with 95% confidence interval (CI). Secondary outcomes are reported as n/N (%). Between-group differences are reported with 95% CI. As planned a priori, we addressed asymmetry in regard to baseline variables, using multivariable regression techniques, in which discrepant baseline variables were included in the model along with the primary outcome and the study arm assignment. The results of this regression analysis are reported as beta coefficients and B coefficients with 95% CI.

Sample size was estimated according to data we collected previously. The mean number of headache days during the week after ED discharge in this previous work was 3.2 (SD 2.5). We estimated that the long-acting corticosteroid would change the mean number of headache days by at least 1.0 day compared with dexamethasone as the minimum criterion for declaration of a clinically meaningful difference. Assuming a 2-tailed α=.05 and β=.20, we calculated the need for 100 patients in each group. We added to this 10% for participants lost to follow-up and protocol violations, and thus determined the need for 220 patients.

RESULTS

Enrollment commenced in September 2016 and continued for 13 months. During this period, 1,292

patients with headache were screened and 220 met eligibility criteria and consented to participate (Figure 1). Of these 220 participants, 109 were randomized to receive dexamethasone and 111 methylprednisolone acetate. Baseline characteristics were similar among the 2 study arms, with the exception of duration of headache before presentation (Table 1).

The primary outcome was mean number of headache days during the week after ED discharge. This was 3.0 days among patients receiving dexamethasone and 3.3 days among patients receiving methylprednisolone acetate (95% CI for rounded mean difference of 0.4: –0.4 to 1.1) (Figure 2). Secondary outcomes assessed at 1 week are presented in Table 2. There were no substantial differences among these outcomes. Sustained freedom from headache throughout the week after discharge was achieved by 10 of 107 patients (9%) in the dexamethasone arm and 6 of 110 (5%) in the methylprednisolone acetate arm (95% CI for a difference of 4%: –3% to 11%).

At 48-hour follow-up, 64 of 104 dexamethasone patients (62%) reported any headache since ED discharge versus 84 of 108 methylprednisolone acetate patients (78%; 95% CI for difference of 16%: 4% to 28%). Other 48-hour outcomes are presented in Table 3.

During the ED visit, 13 of 109 dexamethasone patients (12%) required additional medication to treat their headache, as did 29 of 111 methylprednisolone acetate patients (26%; 95% CI for difference of 14%: 4% to 24%). Other in-ED outcomes are reported in Table 4.

Adverse medication effects were reported by 18 of 109 patients (17%) in the dexamethasone group and 28 of 111 methylprednisolone patients (25%; 95% CI for difference of 9%: –2% to 19%). Injection site reactions occurred more frequently in the methylprednisolone group (Table 5). No patient required admission to the hospital for medication-related adverse events.

As planned a priori, because of between-group differences in duration of headache at baseline, we built a multivariable linear regression model, in which the dependent variable was the primary outcome and the independent variables were investigational medication and duration of headache. Duration of headache was associated

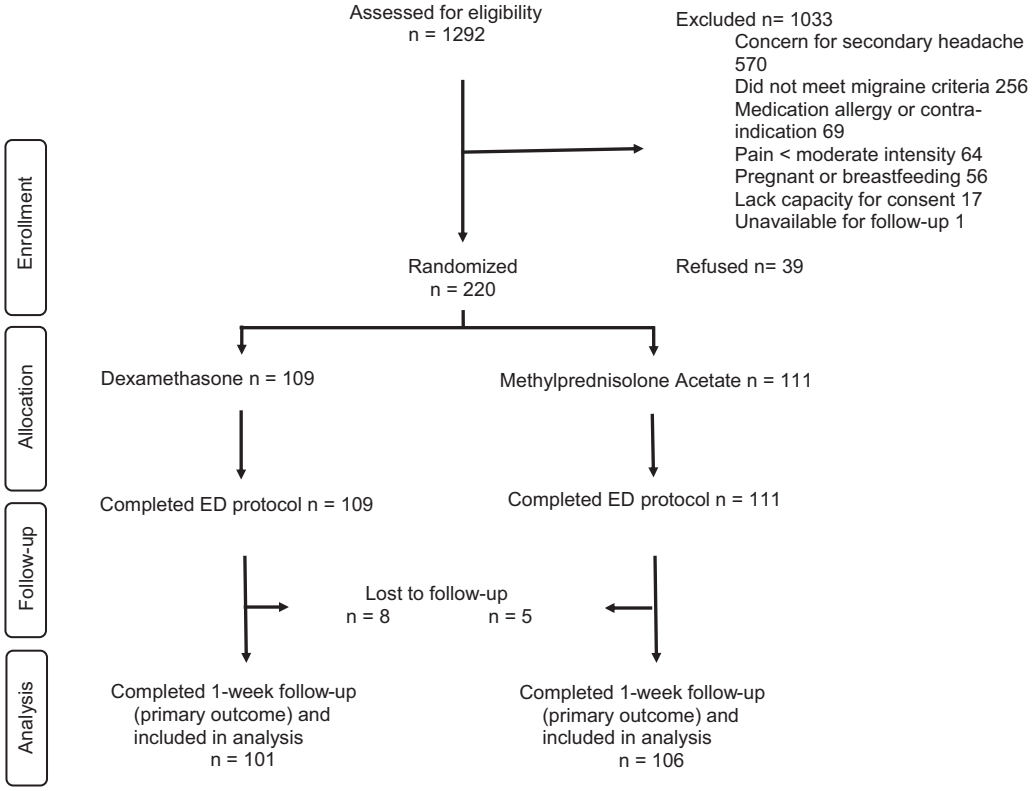

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. Of the 207 patients who provided primary outcome data, 83% did so 7 days after ED discharge (Appendix E1, available online at http://www.annemergmed.com).

Table 1. Baseline characteristics.

Variable	Dexamethasone (n=109)	Methylprednisolone Acetate (n=111)
Women	93 (85)	94 (85)
Age, mean (SD), y	36 (13)	39 (16)
Duration of headache, median (IQR), h	48 (24–96)	72 (24–120)
Baseline pain intensity		
Moderate	20 (18)	21 (19)
Severe	89 (82)	90 (81)
Aura symptoms		
No	69 (64)	59 (54)
Yes	39 (36)	51 (46)
Missing	1	1
Took headache medication on day of ED presentation		
No	37 (34)	42 (38)
Yes	72 (66)	69 (62)

IQR, Interquartile range.
Data are presented as No. (%) unless otherwise indicated.

with the primary outcome (beta coefficient=0.2; B coefficient=0.004 days, 95% CI 0.002 to 0.007), but its effect on investigational medication was minimal: with duration of headache in the model, the beta coefficient of investigational medication was 0.1 and B coefficient was 0.3 days (95% CI –0.4 to 1.0); without duration of headache in the model, the beta coefficient of investigational medication was 0.1 and the B coefficient was 0.4 days (95% CI –0.4 to 1.1).

A sensitivity analysis, which used extreme assumptions to account for missing data, did not result in a meaningfully different conclusion (Appendix E1, available online at http://www.annemergmed.com).

LIMITATIONS

Limitations of the study are as follows: Because methylprednisolone acetate and dexamethasone have different appearances, there was no pragmatic mechanism to blind patients to study medication received. An observant, motivated patient could have deduced which medication he or she received with a simple Internet search. Research personnel, including the outcomes assessors and the investigators, remained blinded because they removed themselves from the patient's vicinity during the injection.

Also, in an effort to maximize adherence, both medications were administered intramuscularly rather than orally. However, we did not limit the type and amount of rescue medication administered to participants during ED treatment or self-administered in the week after discharge. The use of rescue medication among participants experiencing more severe or frequent headaches may have mitigated reporting of extreme outcomes during the follow-up interviews, which would skew results toward the null hypothesis. However (as reported in Table 2), the frequency of use of rescue medication during the week after discharge was comparable between the groups.

Additionally, 6% of primary outcome data were missing. To ensure these missing data did not bias the primary outcome, we repeated the primary analysis, using extreme assumptions (Appendix E1, available online at http://www.annemergmed.com). This analysis did not alter the study results meaningfully.

Finally, it is possible that we underdosed the steroids used in this study. Several meta-analyses have demonstrated a benefit of dexamethasone compared with placebo independent of dose (dose ranges 4 to 24 mg), but it is not known whether larger doses would have resulted in more prolonged efficacy.[4,7,11] To our knowledge, methylprednisolone acetate has never been studied in migraine. It is therefore unknown whether larger doses of it would have conferred more benefit or produced more adverse effects.

DISCUSSION

Among ED patients with acute migraine headache, intravenous metoclopramide+intramuscular methylprednisolone acetate did not decrease the number of headache days during the week after ED discharge compared with intravenous metoclopramide+intramuscular dexamethasone. Our findings suggest that an above-average dose of a long-acting depot corticosteroid formulation provides no more headache relief than a 10-mg dose of dexamethasone and caused substantially more injection site reactions. Despite receiving corticosteroids, patients in this study experienced, on average, more than 3 days with headache during the week after ED discharge. Additionally, less than 10% of patients in either group achieved complete freedom from headache without the need for additional medication during this same week. Nearly two thirds of subjects in both groups experienced a headache sometimes, often, or always. Clearly, most migraineurs presenting to the ED with acute headache continue to experience headache after discharge despite initially successful treatment with intravenous metoclopramide.

Poor pain outcomes among discharged ED migraine patients have been described previously. In ED-based cohort studies, between half and two thirds of patients

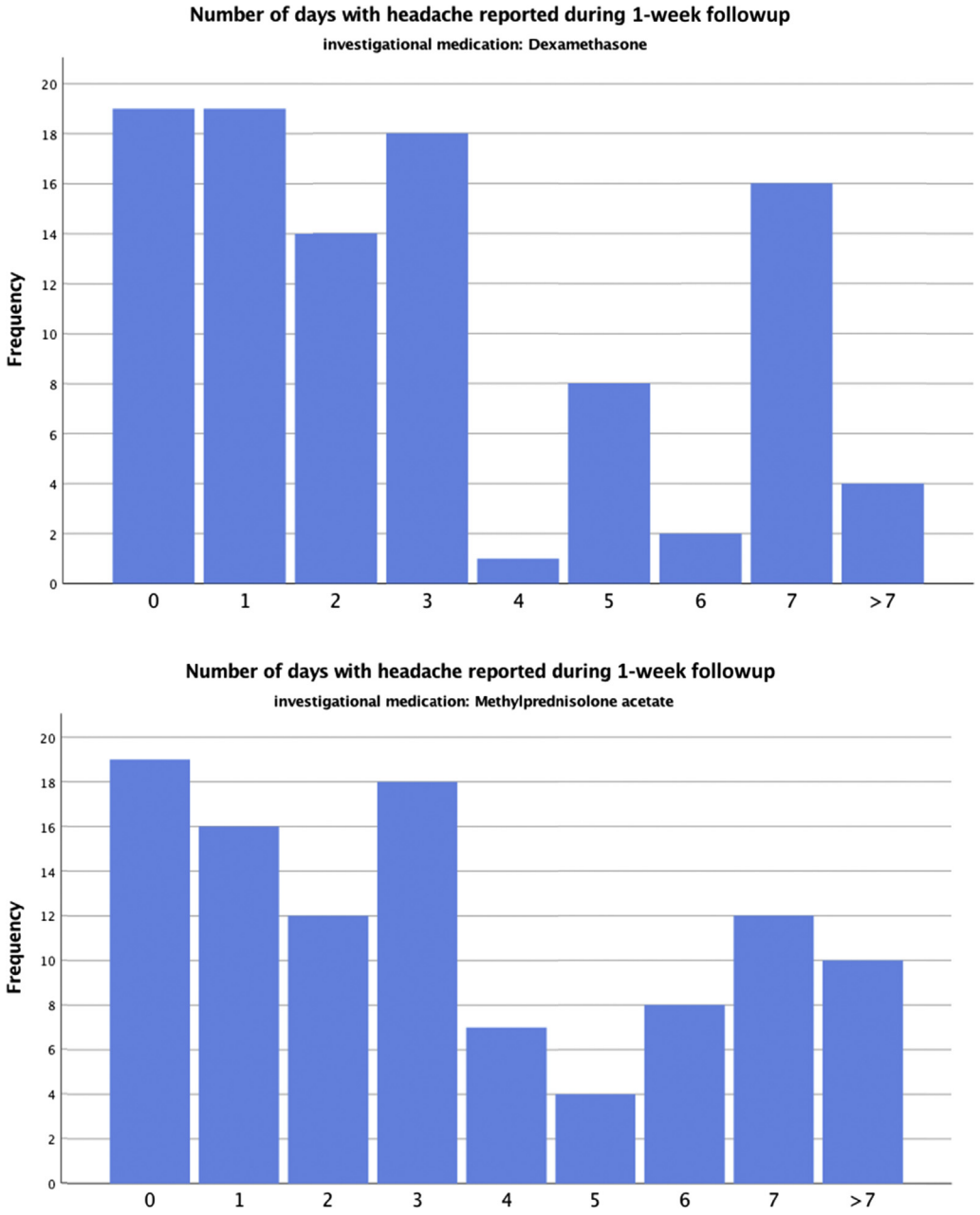

Figure 2. Primary outcome data. Number of days with headache since ED discharge, as reported by patients during the follow-up telephone call 1 week after discharge. Some patients could not be contacted until after day 7 (Appendix E1, available online at http://www.annemergmed.com) and reported greater than 7 days of headache.

report headache during the first days after ED discharge, whereas nearly 50% report functional impairment.[2,12] Approximately 75% of discharged migraine patients continue to use headache medication, and, on average, patients experience headache for 2 to 3 days in the week after discharge.[3] Dexamethasone is an evidence-based treatment that, when administered as adjuvant therapy and compared with placebo, can decrease the frequency of moderate or severe headache recurrence (number needed to treat=9). Frequency of postdischarge headache among patients who received dexamethasone in clinical trials ranged from 13% to 62%.[4] We hypothesized that methylprednisolone acetate would improve these outcomes, although the findings from this study suggest that this is not the case. Emergency physicians should be aware of the high probability of postdischarge headache, even among patients administered corticosteroids, and provide their patients with anticipatory guidance.[13]

The optimal dose of corticosteroids for migraine is not known. Aggregated data do not suggest an association

Table 2. Outcomes reported at 1 week.

Outcome	Dexamethasone, No. (%) (n=109)	Methylprednisolone Acetate, No. (%) (n=111)	Difference (95% CI), %
Sustained freedom from headache for 1 wk*			
Yes	10 (9)	6 (5)	4 (−3 to 11)
No	97 (91)	104 (95)	
Missing	2	1	
Medication preference†			
Yes	76 (75)	75 (71)	4 (−8 to 17)
No	14 (14)	20 (19)	
Not sure	11 (11)	11 (10)	
Missing	8	5	
Headache frequency since ED discharge			
Never/rarely	47 (47)	45 (42)	5 (−9 to 19)
Sometimes	27 (27)	21 (20)	
Often/always	25 (25)	40 (38)	
Missing	10	5	
No. of days with headache during the week since ED visit‡			
0	19 (19)	19 (18)	1 (−10 to 11)
1–3	51 (50)	46 (43)	
≥4	31 (31)	41 (39)	
Missing	8	5	
Headache or pain medication use during the week after discharge			
Used medication	56 (55)	60 (57)	1 (−12 to 15)
Did not use medication	45 (45)	46 (43)	
Missing	8	5	

*To meet this endpoint, participants were required to report a headache level of none in the ED and maintain this level, without the use of any additional headache medication, throughout the entire follow-up period.
†Study participants were asked whether they would want to receive the same combination of medication during a subsequent visit to the ED for headache.
‡Also see Figure 2.

Table 3. Outcomes reported at 48 hours.

Outcome	Dexamethasone, No. (%) (n=109)	Methylprednisolone Acetate, No. (%) (n=111)	Difference, %
Sustained freedom from headache for 48 h*			
Yes	22 (20)	13 (12)	8 (−1 to 18)
No	86 (80)	96 (88)	
Missing	1	2	
Headache frequency since ED discharge			
Never/rarely	58 (56)	46 (43)	13 (0 to 27)
Sometimes	18 (17)	25 (23)	
Often/always	28 (27)	37 (34)	
Missing	5	3	

*To meet this endpoint, participants were required to report a headache level of none in the ED and maintain this level, without the use of any additional headache or pain medication, throughout the entire follow-up period.

between dose of dexamethasone and efficacy,[4] but these data are far from conclusive and do not apply to methylprednisolone acetate, which to our knowledge has not previously been studied in migraine. By choosing methylprednisolone acetate, a long-acting corticosteroid, as the comparator in this study, we hoped to extend the

Table 4. In-ED outcomes.

Outcome	Dexamethasone, No. (%) (n=109)	Methylprednisolone Acetate, No. (%) (n=111)
Pain intensity 1 h after medication administration		
Severe	5 (5)	9 (8)
Moderate	16 (15)	25 (23)
Mild	52 (49)	46 (42)
None	34 (32)	29 (27)
Missing	2	2
Pain intensity at ED discharge		
Severe	1 (1)	1 (1)
Moderate	8 (7)	11 (10)
Mild	47 (44)	52 (47)
None	52 (48)	46 (42)
Missing	1	1

Table 5. Number of individuals reporting specific adverse events.

Outcome	Dexamethasone (n=109)	Methylprednisolone Acetate (n=111)
Akathisia	2	7
Injection site reaction	1	9
Drowsy	2	5
Dizzy	3	4
Nausea	3	2
Palpitations	4	0
Insomnia	3	0

corticosteroid efficacy to days 4 to 7 after ED discharge. Because this study had negative results, we do not know whether methylprednisolone acetate was efficacious in this regard. It may be that both dexamethasone and methylprednisolone acetate were highly efficacious, and had we not administered these medications, study participants would have experienced even more headaches during the week after ED discharge. Alternatively, corticosteroids may play only a modest role in the early postdischarge period and may lack any sustained efficacy. We anticipated that methylprednisolone acetate patients would continue to experience corticosteroid effects for several days longer than dexamethasone patients. It may be that dexamethasone continued to have biologic activity longer than we anticipated, or that methylprednisolone acetate was relatively underdosed. With the goal of improving the quality of life of discharged ED migraine patients and with an eye to the demonstrated tolerability of these investigational medications in this patient population, a reasonable next step would be to increase the steroid dose in future clinical trials. Alternatively, pharmacodynamic studies could be conducted to determine the optimal dose of corticosteroids.

As initial treatment of migraine, we used metoclopramide, a guideline-supported treatment known to be effective in the acute setting.[14] In previous work at our institution, 30% to 38% of migraine patients receiving intravenous metoclopramide required additional medication for headache in the ED,[15,16] which is substantially more than the 12% of patients who required rescue medication in this study after receiving metoclopramide+dexamethasone. This finding, combined with the difference in the use of rescue medication in this study between dexamethasone (12% of patients required rescue medications) and methylprednisolone acetate (26% of patients required rescue medications), made us wonder whether dexamethasone is acting more quickly against migraine than is generally recognized. Some[11] but not all[4] placebo-controlled data suggest that dexamethasone may begin to have efficacy within 2 hours of parenteral administration. To help answer this question, we reviewed the several migraine clinical trials in which monotherapy with dexamethasone was compared with an analgesic or antimigraine treatment known to have short-term efficacy. In one study of 190 patients with acute migraine, patients who received dexamethasone 8 mg intravenously had clinically indistinguishable pain scores 10 and 60 minutes after medication administration compared with those who received morphine dosed at 0.1 mg/kg.[17] (Pain scores were also clinically indistinguishable 24 hours after medication administration.) A randomized study of dexamethasone 8 mg intravenously versus dihydroergotamine 1 mg demonstrated nearly 67% improvement in both groups 30 minutes later, although the dihydroergotamine patients slightly outperformed the dexamethasone patients.[18] In a randomized study of haloperidol 5 mg intravenously versus dexamethasone 4 mg intravenously, the haloperidol patients substantially outperformed the dexamethasone patients, although 47% of the dexamethasone patients were asymptomatic 2 hours after medication administration.[19] In a randomized study of oral dexamethasone 4 mg versus rizatriptan 10 mg, rizatriptan substantially outperformed dexamethasone.[20] In sum, dexamethasone appears to be insufficient as monotherapy but, especially when administered intravenously in conjunction with migraine-abortive medications such as the dopamine antagonists, may provide additional therapeutic benefit while the patient is still in the ED.

In conclusion, during the week after ED discharge, we found no difference in number of headache days experienced by migraine patients randomized to metoclopramide+dexamethasone 10 mg intramuscularly versus metoclopramide+methylprednisolone acetate 160 mg intramuscularly.

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Author affiliations: From the Department of Emergency Medicine (Latev, Friedman, Irizarry, Chertoff, Gallagher), Albert Einstein College of Medicine, Bronx, NY (Restivo); and the Pharmacy Department (Solorzano, Zias), Montefiore Health, Bronx, NY (Latev, Friedman, Irizarry, Chertoff, Gallagher).

Author contributions: AL and BWF designed the study and created the study protocol. CS and EZ conducted randomization and blinding. EI AC, and AR conducted study recruitment and data management. AL, BWF, and EJG drafted the article and completed the statistical analysis. All authors significantly contributed to article revisions. AL takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the

work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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