A Randomized Trial of Intravenous Ketorolac Versus Intravenous Metoclopramide Plus Diphenhydramine for Tension-Type and All Nonmigraine, Noncluster Recurrent Headaches

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Study objective: We compare metoclopramide 20 mg intravenously, combined with diphenhydramine 25 mg intravenously, with ketorolac 30 mg intravenously in adults with tension-type headache and all nonmigraine, noncluster recurrent headaches.

Methods: In this emergency department (ED)–based randomized, double-blind study, we enrolled adults with nonmigraine, noncluster recurrent headaches. Patients with tension-type headache were a subgroup of special interest. Our primary outcome was a comparison of the improvement in pain score between baseline and 1 hour later, assessed on a 0 to 10 verbal scale. We defined a between-group difference of 2.0 as the minimum clinically significant difference. Secondary endpoints included need for rescue medication in the ED, achieving headache freedom in the ED and sustaining it for 24 hours, and patient’s desire to receive the same medication again.

Results: We included 120 patients in the analysis. The metoclopramide/diphenhydramine arm improved by a median of 5 (interquartile range 3, 7) scale units, whereas the ketorolac arm improved by a median of 3 (IQR 2, 6) (95% confidence interval [CI] for difference 0 to 3). Metoclopramide + diphenhydramine was superior to ketorolac for all 3 secondary outcomes: the number needed to treat for not requiring ED rescue medication was 3 (95% CI 2 to 6); for sustained headache freedom, 6 (95% CI 3 to 20); and for wish to receive the same medication again, 7 (95% CI 4 to 65). Tension-type headache subgroup results were similar.

Conclusion: For adults who presented to an ED with tension-type headache or with nonmigraine, noncluster recurrent headache, intravenous metoclopramide + diphenhydramine provided more headache relief than intravenous ketorolac. [Ann Emerg Med. 2013;xx:xxx.]

Please see page XX for the Editor’s Capsule Summary of this article.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs are commonly used to treat tension-type headache. Several studies have also demonstrated efficacy of parenteral dopaminergic antagonists such as chlorpromazine and metoclopramide for these headaches. Comparative efficacy studies of the dopamine antagonists versus the nonsteroidal have yet to be performed. One aim of this study was to compare the efficacy in tension-type headache of intravenous metoclopramide, a safe and well-tolerated dopamine receptor antagonist, with that of intravenous ketorolac, a parenteral nonsteroidal anti-inflammatory drug.

Patients who present to an emergency department (ED) for treatment of an acute exacerbation of a recurrent headache disorder at times cannot receive a formal headache diagnosis because of bland or conflicting headache features, prolonged headache duration, or a history of only infrequent recurrence of headache. These difficult-to-classify headaches will either continue to recur and ultimately meet criteria for one of the named headache disorders, such as tension-type, migraine, or cluster, or resolve and thus not require classification. In clinical practice, when these headaches present to our ED acutely, we treat them as presumptive tension-type headache with nonsteroidal anti-inflammatory drugs or as presumptive migraine, with dopamine antagonists.

In this study, we lumped nonmigraine, noncluster recurrent headaches together with tension-type headache because this reflects a clinical reality: once clinicians exclude a pathologic underlying cause of headache from the differential diagnosis, and when the headache lacks the requisite features to support the diagnosis of migraine or cluster, subtleties in headache nosology are of only marginal practical use to emergency clinicians. This approach has ample precedent in emergency medicine headache research, in which researchers often
Treatment for Recurrent Headaches

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MATERIALS AND METHODS

Study Design and Setting

This was a randomized, double-blind trial comparing 2 parenteral treatments among patients presenting to our ED with nonmigraine, noncluster recurrent headache and tension-type headache. The Montefiore Medical Center institutional review board approved this protocol. We registered it at http://clinicaltrials.gov (NCT01011673).

This study was performed in the ED of Montefiore Medical Center, an urban teaching hospital with more than 100,000 adult visits annually. Salaried, trained, fluently bilingual (English and Spanish) research associates staff the ED 24 hours per day, 7 days per week.

Selection of Participants

Research associates screened adult patients younger than 65 years who presented to our ED with headache. Those who had a recurrent episode of a headache experienced at least once before were eligible for participation, provided they did not meet migraine or cluster headache criteria as defined by the International Headache Society’s International Classification of Headache Disorders, 2nd Edition.9 We excluded patients if the attending physician was suspicious of a serious secondary cause of headache, for temperature greater than 100.4°F (38°C), a new objective neurologic abnormality, allergy, active gastritis or peptic ulcer disease, history of upper gastrointestinal bleeding, organ transplant, use of a monoamine oxidase inhibitor, pregnancy, lactation, or previous enrollment. We asked patients a series of close-ended questions about their current headache and their headache history, which allowed us to define the subgroup who met criteria for tension-type headache (International Classification of Headache Disorders 2.1, 2.2, or 2.3)9 (Figure 1).

Interventions

The research pharmacist performed randomization in blocks of 6, using an online random-number generator. The pharmacist filled medication vials and placed them into sequentially numbered research bags. Research associates then allocated the bags to patients in order. Only the pharmacist, whose records were maintained in a location distant from the ED and unavailable to the investigators, knew the assignment. Every research bag in the metoclopramide/diphenhydramine arm held 2 vials, one containing 20 mg of metoclopramide and one containing 25 mg of diphenhydramine. Every bag in the ketorolac arm also held 2 vials, one containing ketorolac 30 mg and one containing normal saline solution placebo. The contents of these vials were clear and indistinguishable. Normal saline solution was added to the ketorolac vial to make the volume in each vial identical. To maintain allocation

aggregate all benign headaches.5-7 It may also reflect a reality of headache nociception known as the “convergence hypothesis,” which posits that various distinct primary headaches are manifestations of the same underlying neuropathophysiology.8

In this study we tested 2 distinct hypotheses:

- Hypothesis 1: In a population of patients with an exacerbation of a recurrent headache meeting neither migraine nor cluster headache criteria, 20 mg of intravenous metoclopramide combined with 25 mg of intravenous diphenhydramine will produce greater relief of headache 60 minutes after medication administration than will 30 mg of intravenous ketorolac.

- Hypothesis 2: Within the subset of patients meeting International Headache Society criteria for tension-type headache, 20 mg of intravenous metoclopramide combined with 25 mg of intravenous diphenhydramine will also produce greater relief of headache 60 minutes after medication administration than will 30 mg of intravenous ketorolac.

Figure 1. Tension-type headache criteria. From the International Headache Society’s International Classification of Headache Disorders, 2nd Edition. Tension-type headaches can be further subdivided into infrequent episodic, frequent episodic, or chronic.

How this is relevant to clinical practice

In the doses used in this study, metoclopramide plus diphenhydramine was better than ketorolac for nonmigraine, noncluster recurrent headaches.

What question this study addressed

Which is better for nonmigraine, noncluster recurrent headaches: metoclopramide 20 mg plus diphenhydramine 25 mg intravenously or ketorolac 30 mg intravenously?

What this study adds to our knowledge

All measures of pain relief were superior in the metoclopramide plus diphenhydramine group in this randomized, blinded, controlled trial of 120 adults.

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Editor’s Capsule Summary

What is already known on this topic

The best nonopioid therapy for headaches remains unclear.

What question this study addressed

Which is better for nonmigraine, noncluster recurrent headaches: metoclopramide 20 mg plus diphenhydramine 25 mg intravenously or ketorolac 30 mg intravenously?

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How this is relevant to clinical practice

In the doses used in this study, metoclopramide plus diphenhydramine was better than ketorolac for nonmigraine, noncluster recurrent headaches.
concealment, a nurse, also blinded, placed the 2 vials from each bag in a 50-mL bag of normal saline solution for administration to the patient as an intravenous drip during 15 minutes (200 mL/hour). We chose to use 20 mg of metoclopramide rather than a more standard 10-mg dose to avoid failure to detect a benefit of the drug because of underdosing. Because akathisia is common among patients who receive higher doses of intravenous metoclopramide, we coadministered diphenhydramine to all patients who received it. 10

Methods of Measurement
After obtaining informed written consent, research associates performed a brief pain assessment, using a structured questionnaire (Appendix E1, available online at http://www.annemergmed.com). The nurse then administered the intravenous solution. The research associates returned every 30 minutes to ascertain the patient’s pain level. At 1 and 2 hours after medication administration, the research associates asked a more detailed series of questions. Patients who required additional analgesia after 1 hour had elapsed were administered medication at the discretion of the treating physician. We contacted patients by telephone 24 hours after ED discharge to ascertain headache status, satisfaction with treatment, and occurrence of adverse events.

Outcome Measures
As a primary endpoint, we used an 11-point numeric rating scale11 that asked patients to assign their pain a number between zero and 10, with zero representing no pain and 10 representing the worst pain imaginable. The primary outcome was the between-group difference in the 1-hour change in this scale. Secondary outcome measures included (1) response to the question, Do you want to receive the same medication the next time you come to the ED with a headache?; (2) headache freedom achieved in the ED without the use of rescue medication; (3) receipt of rescue medication at any time during the ED visit, defined as any medication administered specifically to alleviate headache; (4) sustained headache freedom, defined as achieving headache freedom in the ED and maintaining it for 24 hours without rescue medication; (5) use of rescue medication during the 24 hours after initial medication administration; and (6) percentage improvement in pain score between baseline and 1 hour, defined as (baseline pain score–1-hour pain score)/baseline pain score.

One hour after medication administration, we asked patients whether they felt drowsy and had them choose one of the following 3 options: no drowsiness, a little bit drowsy but able to function, or too drowsy to function. At the follow-up telephone call, we asked patients whether they felt restless at any time after receiving the intravenous medication in the ED and had them choose one of the following 3 options: no restlessness, a little bit restless, or very restless. We also asked them at 1 and 2 hours and at the 24-hour follow-up interview whether they

Table 1. Baseline characteristics of the entire study population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ketorolac (n=60)</th>
<th>Metoclopramide+ Diphenhydramine (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR), y</td>
<td>38 (26, 46)</td>
<td>38 (29, 48)</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>48 (80)</td>
<td>42 (70)</td>
</tr>
<tr>
<td>Race/ethnicity, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Black</td>
<td>11 (18)</td>
<td>17 (28)</td>
</tr>
<tr>
<td>Latino</td>
<td>40 (67)</td>
<td>34 (57)</td>
</tr>
<tr>
<td>White</td>
<td>1 (2)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Mixed</td>
<td>3 (5)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (8)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Refused</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Median duration of headache (IQR), h</td>
<td>72 (48, 168)</td>
<td>72 (24, 144)</td>
</tr>
<tr>
<td>Median number of days with headache during the previous 3 mo (IQR)</td>
<td>5 (2, 10)</td>
<td>5 (2, 10)</td>
</tr>
<tr>
<td>Medical history of migraine headaches, No. (%)</td>
<td>16 (27)</td>
<td>11 (18)</td>
</tr>
<tr>
<td>Median baseline NRS pain score, on a scale from 0–10 with 0=no pain and 10=worst imaginable (IQR)</td>
<td>8 (7, 10)</td>
<td>8 (7, 9)</td>
</tr>
</tbody>
</table>

IQR, interquartile range; NRS, numerical rating scale; h, hours; mo, months; n, number.
experienced any other symptoms. If they answered in the
affirmative, their symptoms were elicited with an open-ended
question.

Research associates collected data with paper data collection
forms. The principal investigator, who remained blinded to
allocation assignment during this process, then transcribed the
data into SPSS (version 19; SPSS, Inc., Chicago, IL).

**Primary Data Analysis**

According to previous work, our sample size calculation
assumed normal distribution and a conservative $\alpha$ and was
driven by the need to identify statistically significant between-
group differences in the subgroup of patients with tension-type
headache. We estimated that a sample size of 44 patients in each
arm would give us a power of 0.8 to detect a between-group
difference in improvement in pain score of 2.0 units, a
difference considered clinically robust. We estimated that
enrolling 88 patients with tension-type headache would require
enrolling 50% more patients, ie, about 130 patients with bland
headache, but planned to stop as soon as we had obtained
complete data on the subset of 88 patients with tension-type
headache.

When analyzed, the continuous outcome data did not
distribute normally, so we presented these data as medians with
interquartile range and used the Hodges-Lehman estimate to
construct 95% confidence interval (CI) for difference between
medians. We expressed between-group differences in
dichotomous outcomes as proportions bounded by 95% CIs
and report for these the number needed to treat, that is, the
number of patients who would need to be treated with the more
efficacious medication rather than the less efficacious one for a
single patient to achieve the target outcome of interest.

We analyzed data with a per-protocol analysis. This seemed
to us more clinically sensible than an intention-to-treat strategy
because, on review of the data set before unblinding, 3
randomized patients clearly were enrolled in error according to
their ultimate diagnoses: subarachnoid hemorrhage, brain
abscess, and malaria. Thus, as shown in the Consolidated
Standards of Reporting Trials (CONSORT) diagram (Figure
1), we excluded these patients from further analysis.

**RESULTS**

Enrollment for this study began in November 2009 and
continued for 35 months. During this time, we approached 783
patients for participation and included 120 in the analysis
(Figure 2). Of the 120 patients enrolled with bland headache, 89
of these met criteria for tension-type headache.

Baseline characteristics were comparable between the 2
groups (Table 1).

Patients with nonmigraine, noncluster recurrent headache
who received the metoclopramide combination had greater pain
relief than those randomized to ketorolac, as measured by
change in pain scores (Table 2, Figure 3, Appendix E2 available
online at http://www.annemergmed.com). The patients who
received the metoclopramide combination were also more likely
to achieve headache freedom in the ED, experience sustained
headache freedom throughout the 24 hours after medication
administration, and reported wanting the same medication if
treated again in the ED for similar headache (Table 3). These

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**Table 2. Change in numeric rating scale between baseline and 1 hour postbaseline.**

<table>
<thead>
<tr>
<th>Population</th>
<th>Ketorolac Median Improvement (IQR), N</th>
<th>Metoclopramide+Diphenhydramine Median Improvement (IQR), N</th>
<th>95% CI for Difference Between Medians*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonmigraine, noncluster recurrent headache</td>
<td>3 (2, 6), 60</td>
<td>5 (3, 7), 60</td>
<td>0, 3</td>
</tr>
<tr>
<td>Tension-type headache</td>
<td>3 (2, 6), 46</td>
<td>5 (3, 7), 43</td>
<td>0, 3</td>
</tr>
</tbody>
</table>

*Independent-samples Hodges-Lehman estimate.
patients were less likely to require rescue medications (Table 3). At 1 hour, patients who received the metoclopramide combination improved by a median of 71% (IQR 35%, 100%), whereas those who received ketorolac improved by a median of 44% (IQR 23%, 83%) (Figure 4). These findings were nearly identical to the outcome data for the subset of patients with tension-type headache (Tables 2 and 4).

There were no serious or unexpected adverse events. The development of new symptoms after investigational medication administration was reported by 14 of 60 (23%) patients in the ketorolac arm and 12 of 60 (20%) patients in the metoclopramide arm (95% CI for difference of 3% to 11% to 18%). These mostly consisted of evolving headache descriptions such as pulsating pain, severe headache, and facial pressure. Drowsiness at 1 hour was more common among patients who received the metoclopramide combination, although drowsiness sufficient to impair function was uncommon in both groups (Table 5). Restlessness after receiving the investigational medications was evenly distributed between the 2 groups (Table 5). In general, the medications were very well tolerated. Of the 16 patients who reported they would not want to receive the same medication at the next visit, all cited lack of efficacy rather than adverse effects as their rationale. Other infrequent adverse events are listed in Table 5.

LIMITATIONS

We sought to exclude patients with migraine from this study according to strict application of International Headache Society criteria to the patient’s self-described headache characteristics at enrollment. However, during their time in the ED, some patients developed nausea or had their headache evolve into a typical migraine headache. This is a relatively common phenomenon that has been reported previously. The effect of this may have been to dilute our “homogenous” population of tension-type headache, potentially causing misclassification bias, which tends to drive outcomes toward the null.

A second limitation, which is common to most single-site studies, is that, despite the internal validity of our findings, we conducted this research in 1 urban ED in the Bronx, NY, caring for a largely nonwhite underserved population. This necessarily limits any claims of external validity or generalizability.

Finally, it took us nearly 3 years to enroll enough patients to meet our sample size requirements. We believe this reflects the clinical reality that the majority of recurrent headache disorders treated in emergency practice are migraine or probable migraine. Despite the prevalence of tension-type headache in the population, acute episodes of severe or functionally disabling tension-type headache are relatively uncommon in the ED.15

DISCUSSION

The preponderance of data from this study suggests that the intravenous combination of metoclopramide 20 mg and diphenhydramine 25 mg is more efficacious than 30 mg of intravenous ketorolac for treatment of acute nonmigraine, noncluster recurrent headaches and for tension-type headache.

Table 3. Categorical outcomes among all patients with nonmigraine, noncluster recurrent headache.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ketorolac (%)</th>
<th>Metoclopramide + Diphenhydramine (%)</th>
<th>Difference (95% CI), %</th>
<th>Number Needed to Treat (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Would want to receive the same medication during the next ED visit for headache</td>
<td>45/57 (79)</td>
<td>53/57 (93)</td>
<td>14 (2 to 27)</td>
<td>7 (4 to 65)</td>
</tr>
<tr>
<td>Achieved headache freedom in the ED without requiring rescue medication</td>
<td>16/60 (27)</td>
<td>27/60 (45)</td>
<td>18 (1 to 35)</td>
<td>6 (3 to 67)</td>
</tr>
<tr>
<td>Required rescue medication in the ED</td>
<td>27/60 (45)</td>
<td>8/60 (13)</td>
<td>32 (16 to 47)</td>
<td>3 (2 to 6)</td>
</tr>
<tr>
<td>Achieved headache freedom in the ED without requiring rescue medication and maintained headache freedom for 24 h</td>
<td>5/60 (8)</td>
<td>16/60 (27)</td>
<td>19 (5 to 32)</td>
<td>6 (3 to 20)</td>
</tr>
<tr>
<td>Required analgesic medication within 24 h of ED discharge</td>
<td>27/57 (47)</td>
<td>20/57 (35)</td>
<td>12 (–6 to 30)</td>
<td>Insufficient difference between groups—unable to calculate NNT</td>
</tr>
</tbody>
</table>

NNT, number needed to treat.
Patients who received metoclopramide were significantly more likely than patients who received ketorolac to achieve headache relief in the ED, experience sustained headache freedom during the 24 hours after medication administration, and report wanting the same medication if treated again in the ED for similar headache. They were also 3 times less likely to require rescue medication than patients who received ketorolac.

Both treatments used in this study were well tolerated. Restlessness, a common akathetic adverse effect of metoclopramide, seems to have been prevented successfully by the coadministration of diphenhydramine. The metoclopramide combination caused mild drowsiness in two thirds of the patients who received it compared with about one third of patients who received ketorolac. However, of the patients who reported some level of drowsiness, very few reported being “too drowsy to function.” A lower dose of metoclopramide may lessen the rate of drowsiness, although this may also lessen the efficacy. The choice of any treatment reflects a tradeoff between efficacy and adverse effects. In this case, the consistency and the magnitude of the findings supporting the metoclopramide combination over ketorolac coupled with the patients’ frequently stated desire to receive this medication again, suggest that the benefits of the metoclopramide+diphenhydramine outweigh the harm.

Others have demonstrated that intravenous chlorpromazine, another dopamine antagonist, and intravenous metoclopramide are more effective than placebo for tension-type headache. Bigal et al² tested chlorpromazine, dosed at 0.1 mg/kg, versus placebo in a randomized double-blind study conducted in public health clinics in Brazil. These authors reported a number needed to treat of 2 versus placebo for achieving a pain-free state by 60 minutes. Cicek et al³ randomized 140 patients with acute tension-type headache to receive metoclopramide 10 mg intravenous alone, metoclopramide 10 mg intravenous+pethidine (meperidine) 50 mg intramuscularly, pethidine 50 mg intramuscularly alone, or placebo. With regard

Table 4. Categorical outcomes among all patients with tension-type headache.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ketorolac (n=60) (%)</th>
<th>Metoclopramide+Diphenhydramine (n=60) (%)</th>
<th>Difference (95% CI), (%)</th>
<th>Number Needed to Treat (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Would want to receive the same medication during the next ED visit for headache</td>
<td>34/43 (79)</td>
<td>37/40 (93)</td>
<td>14 (–1 to 28)</td>
<td>Insufficient difference between groups—unable to calculate NNT</td>
</tr>
<tr>
<td>Achieved headache freedom in the ED without requiring rescue medication</td>
<td>10/46 (22)</td>
<td>20/43 (47)</td>
<td>25 (6 to 44)</td>
<td>5 (2 to 18)</td>
</tr>
<tr>
<td>Required rescue medication in the ED</td>
<td>20/46 (44)</td>
<td>6/43 (14)</td>
<td>30 (12 to 47)</td>
<td>4 (2 to 8)</td>
</tr>
<tr>
<td>Achieved headache freedom in the ED without requiring rescue medication and maintained headache freedom for 24 h</td>
<td>4/46 (9)</td>
<td>11/43 (26)</td>
<td>17 (2 to 32)</td>
<td>6 (3 to 66)</td>
</tr>
<tr>
<td>Required analgesic medication within 24 h of ED discharge</td>
<td>21/43 (49)</td>
<td>16/40 (40)</td>
<td>9 (–12 to 30)</td>
<td>Insufficient difference between groups—unable to calculate NNT</td>
</tr>
</tbody>
</table>

Table 5. Adverse events among entire study population.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Ketorolac (n=60) (%)</th>
<th>Metoclopramide+Diphenhydramine (n=60) (%)</th>
<th>Difference (95% CI), (%)</th>
<th>For no drowsiness: 29 (12 to 47)</th>
<th>For no restlessness: 1 (–13 to 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsy at 1 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>38 (64)</td>
<td>21 (35)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A little bit drowsy but able to function</td>
<td>18 (31)</td>
<td>38 (63)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Too drowsy to function</td>
<td>3 (5)</td>
<td>1 (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not sure/did not answer</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restless after receiving intravenous medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>47 (85)</td>
<td>48 (86)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A little bit restless</td>
<td>7 (13)</td>
<td>6 (11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very restless</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not sure/did not answer</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>2</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck/back pain</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations*</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal olfaction*</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*One patient who received ketorolac reported a rapid heartbeat after ED discharge, for which the patient did not seek medical attention. One patient who received metoclopramide reported a self-limited change in sense of smell.
to need for rescue medication, the authors reported a number needed to treat of 2 for metoclopramide versus placebo and a number needed to treat of 3.5 for metoclopramide versus pethidine.

The fact that both migraine and tension-type headaches appear to respond well to metoclopramide, a medication without inherent analgesic properties, raises intriguing questions about headache nosology.\(^6\) It may be that tension-type headache and migraine are unique disease processes with a common final nociceptive pathway where metoclopramide may act. Alternatively, it may be that these 2 headache types share a similar pathophysiology, which presents with multiple phenotypes. To the best of our knowledge, there are no pharmacodynamic or mechanistic data that explain metoclopramide’s efficacy in acute headache.

During this study, once migraine and cluster headache had been excluded, we did not seek to classify any additional headache disorders other than tension-type headache. We assumed homogeneity of response among the various uncommon headaches that do not meet migraine, cluster, or tension-type criteria, such as nummular headache,\(^17\) noninfectious rhinosinusitis-like headache,\(^18\) and hemicrania continua,\(^15\) an assumption that may not be strictly correct. Hemicrania continua, for example, is defined by its response to indomethacin\(^15\) and thus may be more likely to respond to ketorolac. However, the subset of patients with tension-type headache responded identically to each medication compared with the study population as a whole. This leads us to conclude that these less common headache types either were underrepresented in our study population or responded to the investigational medications in a manner comparable to tension-type headache.

In conclusion, for adults presenting to an ED with tension-type headache or with nonmigraine, noncluster recurrent headache, intravenous metoclopramide + diphenhydramine provided more headache relief than intravenous ketorolac.

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Author contributions: BWF, CS, DE, PEB, and EJG conceived and designed the study. BWF, VA, and CC reviewed data for integrity and to confirm diagnosis. BWF and DE supervised the conduct of the trial and data collection. BWF analyzed the data and drafted the article, and all authors contributed substantially to its revision. BWF takes responsibility for the paper as a whole.

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7. Baden EY, Hunter CJ. Intravenous dexamethasone to prevent the recurrence of benign headache after discharge from the emergency department: a randomized, double-blind, placebo-controlled clinical trial. CJEM. 2006;8:393-400.
13. Corbo J, et al. Randomized clinical trial of intravenous magnesium sulfate as an adjunctive medication for emergency
APPENDIX E1. Data collection form.

<table>
<thead>
<tr>
<th>Baseline Pain Assessment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 On a scale from 0 to 10, with 0 being no pain and 10 being the worst pain imaginable, how bad is your headache right now</td>
</tr>
<tr>
<td>2 How would you describe the intensity of your headache right now:</td>
</tr>
<tr>
<td>3 During this headache, have you been able to do your usual daily activities?</td>
</tr>
</tbody>
</table>

Return in 30 minutes and ask:

| 1 How would you describe the intensity of your headache: | none⁰  mild¹  moderate²  severe³  sleeping⁴ |

<table>
<thead>
<tr>
<th>1 hr Pain Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 On a scale from 0 to 10, with 0 being no pain and 10 being the worst pain imaginable, how bad is your headache right now</td>
</tr>
<tr>
<td>2 How would you describe the intensity of your headache right now:</td>
</tr>
<tr>
<td>3 Right now, do you think you could do your usual daily activities?</td>
</tr>
<tr>
<td>4 Since you received the study medications,</td>
</tr>
</tbody>
</table>
### Follow-up Pain Assessment

1. On a scale from 0 to 10, with 0 being no pain and 10 being the worst pain imaginable, how bad was your worst headache since you were discharged from the emergency room?

2. How would you describe the intensity of your worst headache since you were discharged from the emergency room?

3. Since you were discharged from the emergency room, have you been able to do your usual daily activities?

4. The next time you come to the emergency room with a headache, do you want to be given the same medication?

5. If “No” Why not?

6. After you received the intravenous medication in the emergency room, did you feel restless?

7. Did you take any medication after you left the emergency room?

8. If “Yes” Which one?

9. If “Yes” Other medication
10 Since you were discharged from the ER, have you had any other symptoms: 

No  Yes

11 If patient has had other symptoms write here:

12 If patient has had other symptoms write here:

**APPENDIX E2.** Histograms of pain scores at baseline, one hour, and baseline–one hour for each medication arm.

---

**Primary outcome: Baseline – 1 hour pain score**

* study med: Ketorolac

- **Baseline pain score**
  - Mean = 7.98
  - Std. Dev. = 1.80
  - N = 60

- **1hr pain score**
  - Mean = 4.22
  - Std. Dev. = 3.29
  - N = 60

---

*Mean = 3.77
Std. Dev. = 2.58
N = 60*

*Mean = 8.17
Std. Dev. = 1.49
N = 60*
Treatment for Recurrent Headaches

Friedman et al

1hr pain score
study med: Metoclopramide + diphenhydramine

Mean = 2.95
Std. Dev. = 2.943
N = 60

Primary outcome: Baseline – 1 hour pain score
study med: Metoclopramide + diphenhydramine

Mean = 5.32
Std. Dev. = 2.781
N = 60

Primary outcome: NRS baseline – NRS 1 hour