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The relative efficacy of meperidine for the treatment of acute migraine: A meta-analysis of randomized controlled trials

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Abstract

Background—Despite guidelines recommending against opioids as first line treatment for acute migraine, meperidine is the agent used most commonly in North American emergency departments (ED). Clinical trials performed to date have been small and have not arrived at consistent conclusions about the efficacy of meperidine. We performed a systematic review and meta-analysis to determine the relative efficacy and side effect profile of opioids compared to non-opioid active comparators for the treatment of acute migraine.

Methods—We searched multiple sources (Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, and LILACS, emergency and headache medicine conference proceedings) for randomized controlled trials comparing parenteral opioid and non-opioid active comparators for the treatment of acute migraine headache. Our primary outcome was relief of headache. If this was unavailable, we accepted rescue medication use or we transformed Visual Analog Scale (VAS) change scores using an established procedure. We grouped studies by comparator: a regimen containing dihydroergotamine (DHE), anti-emetic alone, or ketorolac. For each study, we calculated an odds ratio (OR) of headache relief and then assessed clinical and statistical heterogeneity for the group of studies. We then pooled the ORs of headache relief using a random effects model.

Results—From 899 citations, 19 clinical trials were identified, of which 11 were appropriate and had available data. Four trials compared meperidine to DHE, four compared meperidine to an anti-emetic, and three compared meperidine to ketorolac. Meperidine was less effective than DHE at providing headache relief (OR = 0.30; 95% CI: 0.09, 0.97) and trended towards less efficacy than the antiemetics (OR = 0.46; 95% CI: 0.19, 1.11); however, the efficacy of meperidine was similar to ketorolac (OR = 1.75; 95% CI: 0.84, 3.61). Compared to DHE, meperidine caused more sedation (OR = 3.52; 95% CI: 0.87, 14.19) and dizziness (OR = 8.67; 95% CI: 2.66, 28.23). Compared to the anti-emetics, meperidine caused less akathisia (OR = 0.10; 95% CI: 0.02, 0.57). Meperidine and ketorolac use resulted in similar rates of gastro-intestinal side effects (OR = 1.27; 95% CI: 0.31, 5.15) and sedation (OR = 1.70; 95% CI: 0.23, 12.72).

Conclusion—Meperidine is less efficacious and associated with more side effects than DHE regimens in acute migraine headache. There was also a trend towards decreased efficacy of meperidine compared to anti-emetics. There were no statistically significant differences in efficacy

between meperidine and ketorolac. Clinicians should consider alternatives to meperidine when treating acute migraine with injectable agents.

Introduction

Migraine headache is a disorder that afflicts millions of North American patients¹, resulting in nearly one million presentations to emergency departments (EDs) annually². Parenteral opioids are used in 51% of all migraine visits to US EDs and are the therapeutic agent used most commonly in Canadian EDs^{2,3}. Meperidine, the individual opioid agent used most frequently, is administered in 36% of all US migraine visits².

Several consensus guideline statements caution against the use of opioids as first-line treatment for migraine, citing lack of efficacy, adverse medication effects, the potential for addiction or ED recidivism, and development of medication-overuse headache^{3–5}. Supporting these consensus statements are multiple small studies that often fail to demonstrate a clinically important difference between the opioid and the active comparator. Two previous systematic reviews of parenteral treatment for acute migraine combined opioids with other comparators, thus not addressing the independent efficacy of opioids^{6,7}. Because opioids are frequently employed for patients with acute migraine in the context of emergency care, we conducted a systematic review and meta-analysis to identify and compare the efficacy of opioids with non-opioid active comparators for the management of acute migraine headaches.

Methods

Design

This was a systematic review and meta-analysis to determine the efficacy, adverse event profile, and frequency of recurrent headache after treatment with injectable opioids compared with other active agents for the treatment of acute migraine.

Searching

Our search strategy is summarized in Table 1. Using this strategy, we searched the Cochrane Registry of Controlled Trials, MEDLINE, EMBASE, LILACS, and CINAHL, from earliest indexing until April, 2007. We identified unpublished research by searching through electronically published abstracts from national meetings of emergency medicine, neurology, and headache medicine societies from 1985 to 2007. We reviewed all references from identified trials, guideline statements, and on-topic reviews and consulted with experts in the fields of emergency and headache medicine. In addition, we searched for similar systematic reviews and meta-analyses and used the PubMed related articles feature for all identified trials. The MEDLINE search was updated in April 2008 and no additional studies meeting the inclusion criteria were identified.

Inclusion/Exclusion Criteria

Studies were selected for inclusion if they were randomized controlled trials (RCTs) of an injectable opioid versus an active comparator for the treatment of acute migraine regardless of language of publication. Injectable was defined as administration through intravenous, intramuscular, or subcutaneous routes. Acute migraine was defined using criteria established by the International Classification of Headache Disorders (ICHD)⁸. If ICHD criteria were not applied or if the study pre-dated these criteria, the study was included if a reasonable attempt had been made to include migraine headaches rather than all benign headaches. Studies were only included if they presented data on headache intensity within two hours of treatment.

Study Selection

One author (BWF) screened all abstracts identified by the search for potential eligibility. If eligibility was possible, the article was requested and submitted to two other authors for review (MSF, MLH).

Data abstraction

Primary data abstraction was performed by two authors (MSF, MLH). Disagreements were resolved by consensus when possible or by review of a third author (BWF).

Outcomes

The primary outcome for this analysis was relief of headache within one hour of medication administration. The original authors' definition of relief was used. If the rate of relief was not reported, we included use of rescue medication instead. If neither outcome was available, we transformed change in Visual Analog Score (VAS) into a dichotomous outcome as discussed below. As secondary outcomes, we also report relative risk (RR) for each of the primary efficacy analyses, functional disability after medication administration, recurrence of the headache after initial treatment and adverse effects associated with the study medication.

Quality Assessment

A Jadad score was calculated for each study using standard methodology⁹. Two reviewers independently recorded the Jadad score. Disagreements were resolved by consensus.

Analysis

In the primary analysis, we calculated the odds ratio (OR) and 95% confidence intervals (CI) for headache relief in the opioid group versus the comparator for each included study. For studies only reporting mean change in VAS and standard deviation (SD), we computed the mean difference (MD) per trial and pooled these using standardized mean difference (SMD). The standard error of the SMD was calculated and then converted to an OR with 95% CI using an established methodology¹⁰. If SD was not documented, we requested this information from study authors. If the corresponding author did not have this information, we imputed the value and tested the assumption in sensitivity analysis consistent with recommendations from the Cochrane Handbook¹⁰. We also calculated relative risk (RR) for each study and calculated a pooled RR for each comparison type. Because there is no procedure available to convert continuous outcomes to the RR directly, in certain cases, we approximated the RR from the OR using a described method¹¹. We emphasize that this is an approximation as the method relies on knowing the rate of headache relief in the comparator population, which we imputed from the remaining studies of that comparator type.

We grouped studies into the following categories for analysis, according to the class of the comparator drug: dihydroergotamine (DHE), alone or as part of a two-drug regimen; anti-emetic alone; or ketorolac. Within the groups, we determined the clinical and statistical heterogeneity of effect estimates. We made a conservative choice to pool studies with a random effects analysis although we also looked at the fixed effects analysis as a sensitivity analysis. We performed all analyses using RevMan version 4.3 (The Cochrane Collaboration, Copenhagen).

Results

Search Results and Study Selection

Our search identified 899 abstracts. We requested 23 articles for full text review and ultimately identified 11 studies involving 12 comparisons that met our entry criteria^{12–22}. One study

included an arm with meperidine and another with butorphanol[11]. Because all the other trials included meperidine or its analog, pethidine, we did not aggregate the butorphanol data with the other studies. A flow diagram of the process of study selection is presented in Figure 1.

Description of Included Studies

Table 2 characterizes the included studies. Meperidine was used in doses ranging from 50mg to 100mg, though most commonly administered as 75mg. In two studies, a weight-based dosing regimen was used. In four trials, meperidine was compared to a medication regimen containing DHE, in four trials it was compared to an anti-emetic alone, and in three trials it was compared to ketorolac. In eight of the studies, meperidine was co-administered with an antihistamine per common clinical practice.

DHE vs Meperidine

In comparisons with DHE regimens, two studies reported our primary outcome, proportion with headache relief^{13,17}. One study reported mean difference in VAS¹² and the final study reported only the mean percent improvement on a 5 point headache relief Likert scale²¹. The OR in each of these studies favored the DHE regimen over meperidine, although this result was statistically significant in only two of the four studies. One study reported a very sizable benefit of the DHE regimen for headache relief (OR = 0.02; 95% CI: 0.0, 0.23)[16]. We could not find any distinguishing characteristic of that trial to explain the finding. One study used a higher dose of meperidine (1.5mg/kg) and a DHE regimen that did not contain metoclopramide¹³; these differences in study design likely explain why a larger benefit to DHE was not found in that trial. The random effects pooled estimate favored DHE for headache relief (OR = 0.30; 95% CI: 0.09, 0.97); however, the statistical heterogeneity was high (I² = 73%). The random effects pooled RR was 0.53 (95% CI 0.24–1.17), meaning that meperidine provided headache relief about half as often as the DHE regimens.

Anti-emetics vs Meperidine

Four different anti-emetics were compared with four different doses of meperidine. One study reported the proportion with headache relief¹⁸ and three studies reported use of rescue medication^{14,20,22}. In three of the studies, the OR favored the anti-emetic, though these ORs were not statistically significant. The remaining study used methotrimeprazine as its active comparator²², an anti-emetic that is not commonly used for the treatment of migraine². The random effects pooled estimate favored the anti-emetics for headache relief (OR = 0.46; 95% CI: 0.19, 1.11); statistical heterogeneity was moderate (I² = 51%). The random effects pooled RR was 0.81 (95% CI 0.66–1.00), meaning that meperidine provided headache relief 81% as often as the anti-emetics, though this interpretation is limited by the lack of statistical significance of the primary analysis.

Ketorolac vs Meperidine

The OR favored meperidine in all studies comparing meperidine and ketorolac, though never statistically significantly. The odds ratio of headache relief from both a random effects and fixed effects analysis was 1.75 (95% CI: 0.84, 3.61); there was no significant statistical heterogeneity (I² = 0). The random effects pooled RR was 1.23 (95% CI 0.90–1.68).

Secondary Outcomes

Functional disability was reported by two trials. Carelton et.al. reported 14% of 75 patients randomized to meperidine and 32% of 74 randomized to DHE were initially functionally impaired but then able to perform their usual activities 60 minutes after treatment (difference = 18%, 95% CI: 5, 31%)¹³. Larkin et.al. reported that 25% of 16 patients randomized to

meperidine and 0 of 15 randomized to ketorolac could return to work unimpaired 60 minutes after treatment (difference = 25%, 95% CI: 3,47%)¹⁹.

Recurrence of headache after treatment outcomes were reported by three studies. Carleton et.al. reported 71% of 65 patients randomized to meperidine and 64% of 72 randomized to DHE experienced headache over the 24 hours after ED discharge (difference = 7%; 95% CI: -9, 23%)¹³. Scherl et.al. reported 33% of 12 patients randomized to meperidine and 54% of 13 randomized to DHE used additional pain medication within 24 hours (difference 21%; 95% CI -17, 59%)²¹. Stiell et.al. reported that 30% of 30 patients randomized to meperidine and 10% of 29 patients randomized to the anti-emetic returned to the hospital for further treatment of headache (difference =20%; 95%CI 0, 40%)²².

Side effects

A variety of side effects were reported for each comparison and are listed in Table 3. Compared to DHE, meperidine caused more sedation (OR = 3.52; 95% CI: 0.87, 14.19) and dizziness (OR = 8.67; 95% CI: 2.66, 28.23). Compared to an anti-emetic, meperidine caused less akathisia (OR = 0.10; 95% CI: 0.02, 0.57).

No study reported long-term follow-up of their patients.

Parenteral butorphanol was compared to DHE + metoclopramide in one trial¹². There were no statistically significant or clinically relevant differences in efficacy or adverse effects between these two comparators.

Limitations

Some limitations of this review should be acknowledged. First, despite appropriate and similar patient eligibility criteria across included studies, it is likely that individuals with non-migraine headache were enrolled in the trials. We attempted to restrict the included studies using ICHD criteria; however, this was not always possible. We consider this a conservative bias that may have underestimated the treatment effect given the general efficacy of meperidine as an analgesic and the uncertain efficacy of DHE and some anti-emetics in non-migraine headache syndromes.

Second, we retrieved few studies for each of the three comparisons. Small numbers prohibit robust conclusions. We could not therefore explore the effect of study level predictors such as dose of meperidine or co-administered anti-histamines on pooled results. There was a fair amount of diversity with regard to these two study characteristics reflecting the range of clinical practice. Also, there is a possibility that our results are confounded by other external variables such as inclusion criteria, year of publication, methodologic quality or outcome reported. We did notice a tendency towards more extreme ORs in less methodologically rigorous studies. Similarly, small numbers prohibit exploring the role of publication bias. Recent evidence suggests that publication bias is less pervasive in the ED literature²³; however, negative trials are less likely to be published and more likely to be excluded from a review of this nature, potentially biasing the study conclusions. We believe that our comprehensive search strategy, which included a hand-search of recent conference proceedings to identify unpublished trials, minimized any such bias.

Third, selection and retrieval bias are always a concern in systematic reviews. However, all potentially relevant manuscripts were screened by two independent reviewers using standardized eligibility criteria, decreasing the likelihood of this bias.

Finally, there was a substantial amount of clinical diversity in all three of our analyses and statistical heterogeneity in two of these analyses. Other authors who have performed similar

analyses chose not to calculate the summary effect estimate because of disparate outcomes reported and statistical heterogeneity⁶⁷. We were reassured by the fact that all but one of the ORs lay on the same side of the Forest plots as the summary odds ratios. Unlike the previous work, we analyzed proportion requiring rescue medication when headache relief was not available. In the four trials that reported this outcome, we believe this to be an adequate surrogate for headache relief. Also, in the DHE analysis, we transformed change in VAS to an odds ratio using a standard procedure to enable meta-analysis with the other trials. As the transformed values fell closer to the null when compared with studies in which the primary outcome was available, we felt that inclusion of these estimates was a conservative choice.

Discussion

This systematic review and meta-analysis found that meperidine was significantly less efficacious than DHE regimens for the treatment of acute migraine, caused more dizziness and sedation, and was less likely to result in return to normal functioning. There was a trend towards decreased efficacy of meperidine versus the anti-emetics and a higher rate of return to the hospital in those who received meperidine, though the anti-emetics caused a higher rate of akathisia. There were no substantial differences in efficacy or adverse event profile between meperidine and ketorolac.

Our conclusions are in keeping with guidelines published by the Canadian Association of Emergency Physicians and by the US Headache Consortium⁴⁵, both of which present data from individual trials to argue that opioids should not be used as primary treatment for acute migraine. One systemic review, using many of the same clinical trials, concluded that DHE administered with an anti-emetic was as effective, if not more so, than multiple other treatments for acute migraine including meperidine⁷. A systematic review of metoclopramide, an anti-emetic, versus a host of comparators including meperidine, concluded that patients who received metoclopramide were equally or more likely to report headache improvement⁶. Overall, the evidence here and elsewhere suggests that other agents are more effective than meperidine and produce fewer side effects.

Emergency medicine proponents of opioid use argue that these medications are highly effective, well-tolerated, and safe, and are important analgesics in a practitioner's armamentarium^{24–26}. However, the data supporting these arguments primarily included patients with abdominal or flank pain and not headache patients. The wide variety of effective migraine-specific agents, such as the triptans, DHE, the anti-emetics and other agents should relegate opioids to secondary status for the treatment of acute migraine. In contrast to the opioids, the migraine-specific agents seem to abort the pathological process of the acute migraine, rather than just relieving the pain²⁷.

Meperidine is commonly administered for the treatment of acute migraine in North American EDs. We have demonstrated that this practice is suboptimal. It remains unclear why emergency physicians use meperidine despite guideline statements to the contrary². This may be related to patient-centered reasons such as familiarity with meperidine, a history of successful treatment of previous headaches with meperidine, or desire for an opioid induced euphoria. Physicians may have concerns about adverse medication effects with alternate therapies, may be comfortable with dosing and administration of meperidine, or may not have been persuaded by a complicated evidence base. Clinicians should consider our results when choosing a therapy for an acute migraine, though they may also be guided by other factors such as contraindications and a patient's previous response to treatment. Some EDs have begun to eliminate meperidine from their formulary due to concerns regarding toxic metabolite accumulation and associated adverse events such as seizures. The effects of this action on treatment patterns in

North American EDs have yet to be reported. Future research should measure provider choices and reasoning in different clinical scenarios and assess the impact of patient preferences.

Some issues remain unanswered. We did not find sufficient data to support or refute the contention that treatment of migraine with opioids was associated with medication-overuse headache or addiction. Also, we did not identify any clinical trials using parenteral morphine or hydromorphone for the treatment of migraine or that compared sumatriptan to an opioid. Thus the relative efficacy and side effect profile of these medications remains unknown. In the studies we identified, DHE was often co-administered with metoclopramide, an agent with known efficacy in migraine⁶²⁸. It is unclear which agent was driving the efficacy and whether the two combined provided more headache relief than either alone. Similarly, it is unknown whether anti-histamines co-administered with meperidine enhance efficacy. We did not have enough power to address this issue in our analysis—it is a hypothesis that will need to be answered in a clinical trial.

In conclusion, meperidine is less likely to relieve migraine than DHE regimens and is associated with more adverse effects. There was also a trend towards decreased efficacy of meperidine compared to anti-emetics. Insufficient evidence exists when comparing meperidine and ketorolac, though differences in efficacy between the two are minimal. Clinicians should consider alternatives to meperidine when treating acute migraine with injectable agents.

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Figure 1.
QUORUM flow diagram for selection of trials²⁹

2a: A comparison of meperidine versus dihydroergotamine regimens (DHE)

2b: A comparison of meperidine versus anti-emetics

Figure 2.

Forest plots of meperidine versus active comparators. These plots demonstrate odds of not obtaining headache relief.

Table 1
 OVID Medline Search strategy used to identify citations for this review of opioids
 in acute migraine *

1	migraine.mp. [†]
2	exp migraine/
3	headache\$.mp.
4	1 or 2 or 3
5	exp opioid analgesics/
6	meperidine/or pethidine/or (meperidine or pethidine).mp.
7	hydromorphone/or hydromorphone.mp.
8	fentanyl/or fentanyl.mp.
9	butorphanol/or butorphanol.mp.
10	5 or 6 or 7 or 8 or 9
11	4 and 10
12	limit 11 to "therapeutics (sensitivity 2 or more terms)"

* OVID Medline searches the same MEDLINE database as PubMed. Variations in suffixes used to access individual field such as subject headings and textwords are mentioned below. Strategies may be combined by connecting the line number with "and" or "or" to generate the intersection or union of the retrieved citations. We followed a similar approach when we searched the Embase (not shown).

[†] Forward slash marks indicate subject heading (MeSH headings). Dollar sign implies any words or phrases containing characters to the left of it will be included. ".mp." refers to the field keyword which recruits articles that contain the text to the left of it in the title, subject heading, or abstract. "exp" explodes terms to include records linked to this term within a medical subject heading.

Table 2

Characteristics of included studies.

Author, year	Headache type, setting	N	Opioid Dose	Administered with opioid	Comparator	Administered with comparator	Time to primary outcome	Jadad score	Primary Outcome used
Cicek, 2004	Vascular headache, ED	99	Pethidine 50mg IM	None	Metoclopramide 10mg IV	None	60 min.	4	Rescue med
Richman, 2002	IHS migraine, ED	29	Meperidine 1.5mg/kg IM	None	Droperidol 2.5mg IM	None	30 min.	2	Rescue med
Carleton, 1998	Vascular headache, ED	156	Meperidine 1.5mg/kg IM	Hydroxyzine 0.7mg/kg IM	DHE 1mg IM	Hydroxyzine 0.7mg/kg IM	60 min.	5	Headache relief
Davis, 1995	EP diagnosed migraine, ED	42	Meperidine 75mg IM	Promethazine 25mg IM	Ketorolac 60mg IM	None	60 min.	5	Headache relief
Scherl, 1995	Migraine criteria, clinic	27	Meperidine 75mg IM	Promethazine IM	DHE 0.5mg IV	Metoclopramide	60 min	3	SMD change pain score
Klapper, 1993	Physician diagnosed migraine, clinic	28	Meperidine 75mg IM	Hydroxyzine 75mg IM	DHE 1mg IV	Metoclopramide 10mg IV	60 min.	2	Headache relief
Larkin, 1992	EP diagnosed migraine, ED	31	Meperidine 75mg IM	None	Ketorolac 30mg IM	None	60 min.	5	Headache relief
Duarte, 1992	IHS migraine, ED	50	Meperidine 100mg IM	Hydroxyzine 50mg IM	Ketorolac 60mg IM	None	60 min.	4	Headache relief
Stiell, 1991	Migraine score, ED	74	Meperidine 75mg IM	Dimenhydrinate 50mg IM	Methotrimeprazine 37.5mg IM	None	60 min.	5	Rescue med
Belgrade, 1989	Migraine score, ED	43 [*]	1)Meperidine 75mg IM 2) Butorphanol 2mg IM	1)Hydroxyzine 50mg IM 2)None	DHE 1mg IV	Metoclopramide 1mg IV	30 min.	2	SMD VAS change
Lane, 1989	EP diagnosed migraine, ED	46	Meperidine 0.4 mg/kg x 3 doses	Dimenhydrinate 25mg	Chlorpromazine 0.1 mg/kg	None	60 min.	3	Headache relief

Notes: N=total number of patients included in the primary efficacy analysis; EP= emergency physician; ED = emergency department; Rescue med = Requirement of rescue medication for persistent headache; IHS= International Headache Society's International Classification of Headache Disorders; DHE= dihydroergotamine; SMD = standardized mean difference. Jadad score is a five point scale that measures methodological quality by assessing features such as method of randomization and allocation concealment. Scores above two are generally considered to represent higher quality studies.

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In the Belgrade study, 22 patients received meperidine, 21 received DHE, and 19 received butorphanol

Table 3
Summary effect measures of side effects of meperidine versus comparator in the treatment of acute migraine headache

	Number of studies	n/N Meperidine	n/N Comparator	I squared	Pooled OR(95%CI)
Meperidine versus DHE					
Any side effect	2	40/100	47/99	82%	0.49 (0.09, 2.64)
Gastro-intestinal	3	10/120	20/120	64%	0.47 (0.10, 2.34)
Sedation	3	37/113	21/113	55%	3.52 (0.87, 14.19)
Dizziness	3	22/113	3/113	0	8.74 (2.67, 28.64)
Meperidine versus anti-emetic					
Any side effect	2	34/71	30/74	78%	1.06 (0.22, 4.99)
Sedation	4	52/157	54/161	36%	0.90 (0.42, 1.94)
Dizziness	3	37/143	28/146	91%	1.23 (0.08, 17.91)
Akathisia, restlessness, or anxiety	3	0/135	12/137	0	0.11 (0.02, 0.63)
Meperidine versus Ketorolac					
Any side effect	1	12/25	7/25	NA	2.37 (0.73, 7.68)
Gastro-intestinal side	2	5/41	4/40	0	1.27 (0.31, 5.17)
Sedation	2	9/41	5/40	59%	1.84 (0.88, 3.84)

Notes: n= number of patients reporting side effects summed across studies, N=at risk population summed across studies.