

# Does the Addition of Dexamethasone to Standard Therapy for Acute Migraine Headache Decrease the Incidence of Recurrent Headache for Patients Treated in the Emergency Department? A Meta-analysis and Systematic Review of the Literature

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## Abstract

**Objectives:** Neurogenic inflammation is thought to play a role in the development and perpetuation of migraine headache. The emergency department (ED) administration of dexamethasone in addition to standard antimigraine therapy has been used to decrease the incidence of recurrent headaches at 24 to 72 hours following evaluation. This systematic review details the completed trials that have evaluated the use of dexamethasone in this role.

**Methods:** The authors searched MEDLINE, EMBASE, CINAHL, LILACS, recent emergency medicine scientific abstracts, and several prepublication trial registries for potential investigations related to the research question. The authors included studies that incorporated randomized, double-blind, placebo-controlled methodology and that were performed in the ED. A fixed-effects and random-effects model was used to obtain summary risk ratios (RRs) and 95% confidence intervals (CIs) for the self-reported outcome of moderate or severe headache on follow-up evaluation.

**Results:** A pooled analysis of seven trials involving 742 patients suggests a modest but significant benefit when dexamethasone is added to standard antimigraine therapy to reduce the rate of patients with moderate or severe headache on 24- to 72-hour follow-up evaluation (RR = 0.87, 95% CI = 0.80 to 0.95; absolute risk reduction = 9.7%). The treatment of 1,000 patients with acute migraine headache using dexamethasone in addition to standard antimigraine therapy would be expected to prevent 97 patients from experiencing the outcome of moderate or severe headache at 24 to 72 hours after ED evaluation. The sensitivity analysis yielded similar results with sequential trial elimination, indicating that no single trial was responsible for the overall result. Adverse effects related to the administration of a single dose of dexamethasone were infrequent, mild, and transient.

**Conclusions:** These results suggest that dexamethasone is efficacious in preventing headache recurrence and safe when added to standard treatment for the management of acute migraine headache in the ED.

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**Keywords:** dexamethasone, steroids, headache, migraine

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Migraine headache is a common health problem affecting up to 17% of women and 6% of men annually.<sup>1,2</sup> The medical literature supports the use of a variety of medications for acute abortive migraine therapy in the emergency department (ED), including 5-HT receptor agonists, dopamine antagonists, dihydroergotamine, nonsteroidal anti-inflammatories, and opioid analgesics. Despite initial success with these

therapies in the ED, up to two-thirds of patients will experience a recurrent headache within the first 48 hours.<sup>3-5</sup>

The pathogenesis of acute migraine and its recurrence is not clearly understood; however, there is growing evidence to support that neurogenic inflammation, stimulated by the release of vasoactive neuropeptides, plays a role in the development and perpetuation of migraine headache.<sup>6-8</sup> Consequently, it is thought that by suppressing this sterile inflammatory response, corticosteroids have a potential role in the acute treatment of migraines and reduction of migraine recurrence. The corticosteroid dexamethasone has been used as an anti-inflammatory agent in other central nervous system (CNS) inflammatory diseases, including acute bacterial meningitis, high-altitude cerebral edema, and vasogenic edema from CNS tumors. It has the advantages of superior potency, prolonged duration of action, and better CNS penetration compared to other corticosteroids.<sup>9,10</sup>

Uncontrolled clinical trials have shown that, in both the inpatient setting and the outpatient clinic setting, dexamethasone is highly effective in reducing the severity of migraine headache and the rate of headache recurrence.<sup>11-19</sup> Although initial controlled clinical trials demonstrated the same high-level of efficacy,<sup>20-26</sup> the results of several recent ED-based trials have questioned the utility of dexamethasone for this purpose.<sup>27-40</sup> The goals of this systematic review were to critically appraise the existing literature and to provide recommendations for patient care regarding the use of dexamethasone for the prevention of headache relapse in patients with acute migraine headache in the ED. Our primary outcome of interest was the proportion of migraine patients with self-reported symptoms of moderate or severe headache at 24- to 72-hour follow-up evaluation.

## METHODS

### Study Design

This is a meta-analysis of randomized controlled trials that was conducted according to the recommendations from the Quality of Reporting of Meta-Analysis (QUOROM) Statement.<sup>41</sup>

**Searching.** A comprehensive literature search of the MEDLINE database (1950–May 2008) was performed using the following using the terms (((((headache)) OR ((headache[MeSH])) OR ((migraine)) OR ((migraine disorders[MeSH])) AND ((((((steroids)) OR ((steroids [MeSH])) OR ((corticosteroids)) OR ((corticosteroids[MeSH])) OR ((dexamethasone)) OR ((dexamethasone[MeSH])))). Once a likely study was recognized, we used the MEDLINE tool “related articles” to seek additional articles. There were no language restrictions. We used a similar strategy within EMBASE, CINAHL, and LILACS. Within EMBASE, articles were limited to randomized or controlled clinical trials. We searched the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov to identify recently completed trials for inclusion. Furthermore, we scrutinized the

bibliography section of review articles to identify further studies that we may not have captured with our online search strategy. Finally, abstracts from major emergency medicine (EM) conferences (American Academy of Emergency Medicine, American College of Emergency Physicians, and Society for Academic Emergency Medicine) in the past 7 years were reviewed for supplementary data. Two of the authors (AS, BZ) performed an independent search using the above strategy to identify potentially relevant articles.

**Selection.** The following inclusion criteria were used to select articles for this review: 1) studies were randomized clinical trials, 2) study participants and treating physicians were blinded to treatment assignments, 3) patients were diagnosed with having an acute migraine headache, 4) therapy was initiated in the ED, 5) adjunctive therapy with dexamethasone was compared to a control group, 6) studies include the proportion of migraine patients with self-reported symptoms of moderate or severe headache at 24- to 72-hour follow-up evaluation. All three authors had to agree on selected articles for inclusion in this meta-analysis.

Scientific abstracts were included if they met the above criteria. Attempts were made to contact each primary author of a published abstract inquiring about trial methodology (specifically randomization and blinding techniques), side effects noted, and clarification of ambiguous data.

**Validity Assessment.** Trial quality was assessed using the Jadad scale for each reviewed study.<sup>42</sup> Using this scale, points are awarded depending on the quality of the description of the methods to generate the sequence of randomization and/or on the quality of the description of the method of double-blinding. If the trial had been described as randomized and/or double-blind, but there was no description of the methods used to generate the sequence of randomization or the double-blind conditions, one point was awarded in each case. If the method of generating the sequence of randomization and/or blinding had been described, one additional point was given to each item, if the method was appropriate. Appropriate randomization occurred if each study participant had equal chance of receiving intervention or placebo. Appropriate blinding occurred if the treating physician, study participant, or outcomes assessors could not identify the intervention being tested. A final point was awarded if the authors included a detailed description of withdrawals and dropouts. Two of the authors (AS, BZ) independently scored each of the included articles. Discrepancies were resolved by consensus opinion from all three authors.

**Data Abstraction.** Independently and in duplicate, two authors abstracted data from selected trials (AS, BZ). Individual trial characteristics, including study design, conduct, data analysis, and interpretation, were reviewed using recommendations from the revised CONSORT statement.<sup>43</sup> Information abstracted included the objective, study methodology, patient population,

enrollment location, additional interventions, study results, and noted adverse effects. The primary author of each trial was contacted electronically to clarify questions regarding reported trial methodology or outcomes analysis.

**Study Characteristics.** Criteria for migraine headache are based on definitions provided by the International Headache Society (IHS). Migraine without aura is diagnosed when the patient had experienced at least five prior migraines without aura, headache duration lasting 4 to 72 hours, the presence of either nausea/vomiting or photophobia/phonophobia, and at least two of the following: unilateral location, pulsating quality, moderate or severe intensity that inhibits daily activity, or aggravated by routine daily physical activity. Migraine with aura was diagnosed when the patient reported at least two prior migraines with aura and at least one of the following developing within 4 minutes of migraine and lasting no longer than 1 hour: unilateral visual symptoms, slowly expanding and moving geometric shapes, one-sided numbness and abnormal traveling sensation, one-sided weakness, or speech difficulty.

Two main headache relapse severity scales exist in the migraine literature. The first scale includes five different categories: no headache, mild headache without interference in daily activities, mild headache requiring home medication but without interference in daily activities, severe headache with interference in daily activities, and severe headache requiring physician visit. The second scale includes four categories: no headache, mild headache, moderate headache, and severe headache. We determined a priori that our primary outcome of moderate or severe headache includes the last two categories from first scale and the last two categories from second scale. For studies that report headache recurrence as a dichotomous variable (i.e., either present or absent), patients who reported the presence of headache on follow-up evaluation were included in the primary outcome. When the primary outcome data was not available in published form, the principal author of the study was contacted for additional information.

### Data Analysis

We calculated a pooled risk ratio (RR) and 95% confidence intervals (CIs) for the primary outcome using a fixed-effects model, followed by the random-effects model described by Der Simonian and Laird.<sup>44</sup> This random-effects model was selected because it provides a conservative estimate of treatment effect. Heterogeneity was explored through the use of Cochrane Q test for heterogeneity (which follows a chi-square distribution), an estimate of between-study variance known as tau-square, and an estimate of the amount of variance across studies due to heterogeneity rather than chance, known as  $I^2$  statistic.<sup>45</sup> On the basis of the pooled RR, we calculated the number needed to treat. The 95% CI for numbers needed to treat were calculated with the Newcombe-Wilson hybrid score method.<sup>46</sup> Publication bias was explored with the use of funnel plots,<sup>47</sup> the Egger regression asymmetry test,<sup>48</sup> and the Begg adjusted rank correlation test.<sup>49</sup> One author (AS) entered the abstracted data into an Excel (Microsoft

Corp., Redmond, WA) spreadsheet. We then used the "metan" and associated functions in Stata v. 10.1 (Stata-Corp, College Station, TX) to synthesize these data.

We determined a priori that our sensitivity analysis should focus on the impact of poor-quality studies (i.e., Jadad score < 3). To assess the effect of individual studies on the summary RR, we performed an influence analysis,<sup>50</sup> in which the pooled estimate was recalculated omitting one study at a time. Such a sensitivity analysis demonstrates robustness if all point estimates lie between the confidence limits of the overall summary estimate. There were no prespecified subgroup analyses.

## RESULTS

### Trial Flow

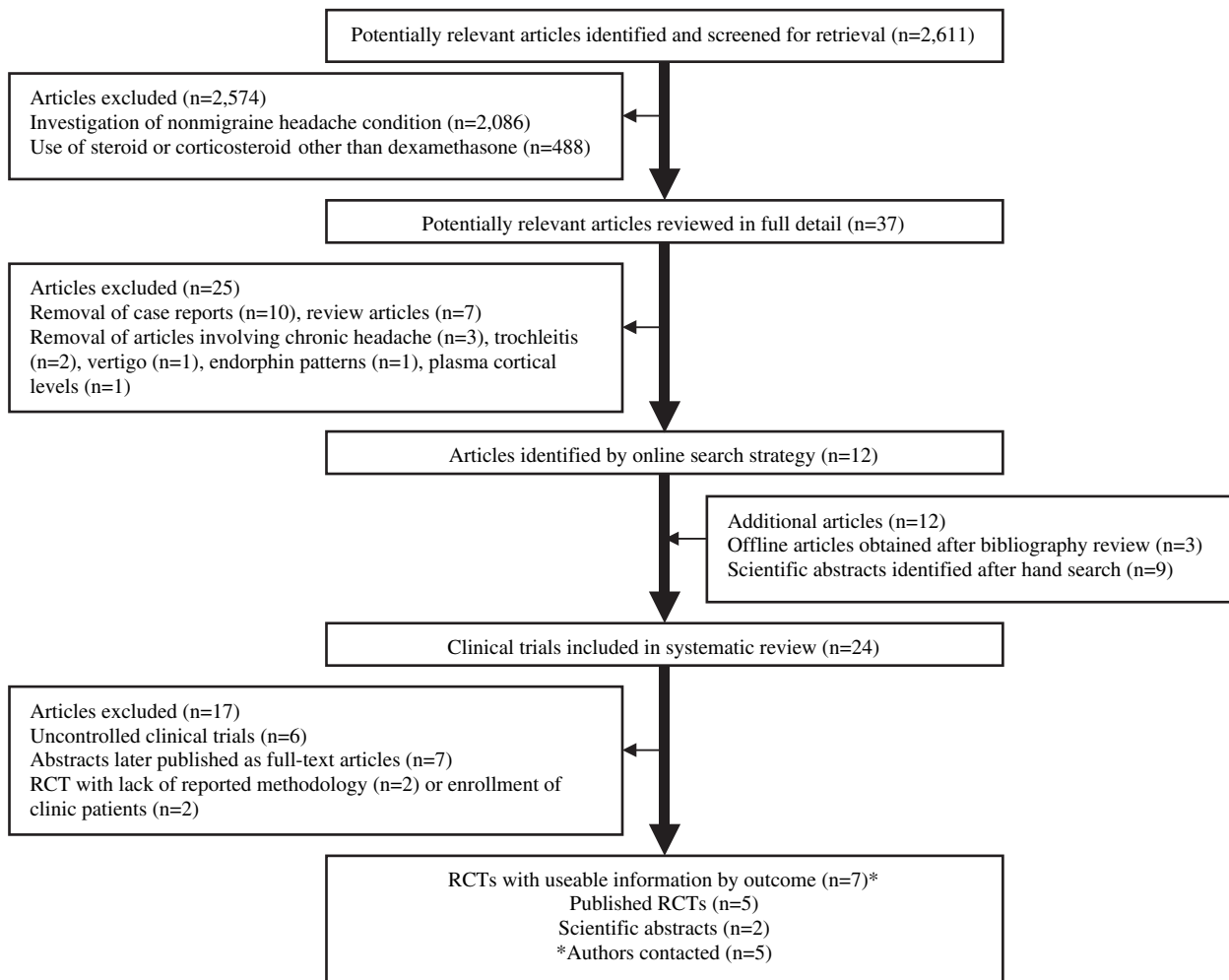
The MEDLINE search strategy identified 2,611 articles (Figure 1). Initial removal of investigations of nonmigraine headache conditions resulted in removal of 2,086 articles. Subsequent removal of 488 articles that used steroids or corticosteroids other than dexamethasone yielded 37 potentially appropriate articles to be included in the meta-analysis. A visual inspection of the titles of these 488 articles did not reveal any trials that evaluated a steroid other than dexamethasone for our primary outcome. The remaining 37 articles were reviewed in full detail. Twenty-five of these articles were excluded for various reasons (see Figure 1). Ultimately 12 articles were identified by the MEDLINE search strategy and included in our systematic review. Scrutinizing the bibliographies of the 37 potentially relevant articles yielded three additional articles that were obtained for full text review. Nine scientific abstracts were identified and appraised after review of scientific abstracts from major emergency medicine conferences. A search within EMBASE, LILACS, and CINAHL identified no additional articles. Finally, no additional trials were identified within the Cochrane Central Register of Controlled Trials or by searching ClinicalTrials.gov.

### Study Characteristics

Five articles followed the revised CONSORT statement guidelines for reporting of randomized controlled trials.<sup>34,37-40</sup> Two scientific abstracts were included in the final analysis.<sup>35,36</sup> Six primary authors, including both scientific abstract authors, were successfully contacted for additional trial information, including further details regarding adverse events, method of randomization and blinding, and verification of headache relapse rates.<sup>35-40</sup> All seven of the included trials had a final Jadad score of 5, indicating acceptable methodology with respect to randomization, blinding, and description of withdrawals and dropouts.

The characteristics and outcomes of six clinical trials that evaluated dexamethasone in the setting of acute migraine headache, but did not meet our prespecified inclusion criteria, are reported in Table 1. The characteristics and outcomes of the seven clinical trials included in our analysis are detailed in Tables 2 and 3.

There was clinical heterogeneity between trials with regards to use of concomitant antimigraine therapies,



**Figure 1.** Trial flow. RCT = randomized controlled trial.

the choice of severity scale used to describe the headache, dose of dexamethasone administered, and duration of follow-up for headache recurrence (Tables 2 and 3). With the exception of two trials, abortive migraine therapy was left to the discretion of the treating physician. Three studies used a five-category headache scale, and three studies used a four-category headache scale. One study reported headache recurrence as a dichotomous variable. The median dose of dexamethasone used was 15 mg (range, 8 to 24 mg). Dexamethasone was administered as a single intravenous injection in six of the trials and as oral tablets in the remaining trial. Duration of follow-up varied between 24 to 72 hours after evaluation in the ED.

### Quantitative Data Synthesis

**Primary Outcome.** Pooled data included the results from 742 patients encompassing seven high-quality clinical trials. The combined result of all trials, using either the fixed-effects or random-effects model, suggests a moderate benefit when dexamethasone is added to standard therapy for the acute migraine headache in the ED (RR = 0.87; 95% CI = 0.80 to 0.95; Figure 2). The pooled absolute risk reduction is 9.7%. The treatment of 1,000 patients with acute migraine headache using

dexamethasone in addition to standard antimigraine therapy would be expected to prevent 97 patients from experiencing the outcome of moderate or severe headache at 24 to 72 hours after ED evaluation.

There was no evidence of publication bias, nor was there evidence of significant statistical heterogeneity when evaluated by multiple standard tests. Absence of significant publication bias was identified by visual inspection of the funnel plot (Figure 3), Begg's test (z score 0.0, p = 1.0), and Egger regression asymmetry test (t for bias 0.19, p = 0.86). There was no significant heterogeneity when tested using the Cochrane Q statistic ( $\chi^2 = 4.11$ , p = 0.66) or tau-square test for heterogeneity ( $\tau^2 = 0.00$ ). The overall results of the  $I^2$  statistic did not show heterogeneity ( $I^2 = 0\%$ , 95% CI = 0% to 71%); however, the upper limit of the 95% CI of this test includes the possibility of moderate heterogeneity across studies.

**Side Effects and Adverse Events.** Side effects were incompletely recorded and, in some cases, difficult to differentiate from the underlying disease process. Overall, 26% of patients receiving dexamethasone and 23% of patients receiving placebo reported some adverse event (Table 4). The rates of restlessness, drowsiness,

Table 1  
Characteristics of Excluded Clinical Trials

Author, Year	Location	No. of Patients	Study Details	Intervention	Results	Reason for Exclusion
Gallagher, 1986 <sup>20</sup>	ED, NJ	130	Methods not described	Dexamethasone 8 mg IV vs. control group. All patients received meperidine 75–100 mg IV + promethazine 50 mg IV.	16/57 (28%) vs. 52/73 (71%) with moderate or severe headache at 24 hours; RR 0.39 favoring dexamethasone	Inadequate blinding and randomization
Klapper et al., 1991 <sup>21</sup>	Clinic, CO	30	PRCT, DB, PC	Dexamethasone 6 mg IV vs. placebo. All patients received metoclopramide 5–10 mg IV.	9/11 (82%) vs. 2/10 (20%) achieved 1 point of improvement on 4-point disability scale at 30 minutes	Clinic enrollment Primary outcome not reported
Monzillo et al., 2004 <sup>22</sup>	ED, Brazil	29	Methods not described	Dexamethasone 4 mg IV vs. haloperidol 5 mg IV. No additional therapy.	8/15 (53%) vs. 14/14 (100%) achieved 50% improvement in self-reported pain at 120 minutes	No control group Primary outcome not reported
Jivad et al., 2005 <sup>23</sup>	Clinic, Iran	72	PRCT, DB, PC	Dexamethasone 4 mg IV vs. DHE 1 mg IV. No additional therapy.	Self-reported pain level of 4 vs. 3 on 15-point pain scale at 30 minutes	Clinic enrollment No control group
Kaniecki, 2006 <sup>24</sup>	Clinic, PA	1,857 episodes	PRCT	Dexamethasone 24 mg PO vs. control group. All patients received etodolac 1200 mg PO.	90/941 (10%) vs. 220/916 (24%) with any headache at 72 hours; RR 0.40 favoring dexamethasone	Inadequate blinding and randomization Clinic enrollment
Baden et al., 2006 <sup>25</sup>	ED, TX	55	PRCT, DB, PC	Dexamethasone 10 mg IV vs. placebo. All patients were initially treated per physician preference.	4/31 (13%) vs. 8/24 (33%) with moderate or severe headache at 48–72 hours; RR 0.39 favoring dexamethasone	Potentially enrolled nonmigraine headache patients

DB = double-blind; DHE = dihydroergotamine; IV = intravenous; PC = placebo controlled; PO = by mouth; PRCT = prospective, randomized, controlled trial; RR = risk ratio.

nausea/vomiting, dizziness, moodiness, swelling, and cramps were similar between dexamethasone and placebo groups. The most commonly documented adverse effects attributable to dexamethasone were numbness/tingling ( $n = 4$  patients), flushing ( $n = 3$  patients), and irritation at the intravenous (IV) site ( $n = 2$  patients). One trial reported that 10 patients receiving dexamethasone reported an acute medication reaction; however, these reactions are not described.<sup>37</sup> Including these 10 reactions, dexamethasone-specific side effects were seen in 6% of the population. All of these reactions were considered transient and resolved without any additional therapy.

### Sensitivity and Subgroup Analysis

We performed an influence analysis of the data by sequential exclusion of each individual trial from the meta-analysis. The range of RR values obtained with this method was 0.86 to 0.90, well within the 95% CI of our summary outcome. Exclusion of the trial with the most influence on the results<sup>37</sup> resulted in modified summary RR of 0.87 (95% CI = 0.79 to 0.97). Exclusion

of the only trial that reached a statistically significant difference between the dexamethasone and placebo groups<sup>34</sup> resulted in a modified summary RR of 0.90 (95% CI = 0.82 to 0.99). Finally, exclusion of the only trial using oral dosing of dexamethasone,<sup>38</sup> resulted in a modified summary RR of 0.87 (95% CI = 0.79 to 0.95). It is likely that a significant number of the patients in one of the excluded studies suffered from migraine headache.<sup>25</sup> Including the results of this study with the seven others included in this analysis resulted in overall summary RR of 0.86 (95% CI = 0.79 to 0.94).

### DISCUSSION

The initial reports favoring the use of dexamethasone for acute migraine headache were limited to uncontrolled clinical trials. These studies indicate that approximately 90% of admitted hospital patients receiving dexamethasone in addition to standard antimigraine medications achieve headache resolution.<sup>13,19</sup> Comparable results were seen with the addition of dexamethasone to standard headache therapies

Table 2  
Characteristics of Included Clinical Trials

Author, Year	No. of Hospitals and Type	Location	No. of Patients	Definition of Migraine	Patient Demographics	Concomitant Migraine Therapy
Innes et al., 1999 <sup>34</sup>	Two centers: community and tertiary care hospital	British Columbia, Canada	98	IHS criteria	Average age 35 years % Female patients 80% Median pain score 8.4 Median HA duration 12 hours	Physician preference: 96% received antiemetic 29% received ketorolac 10% received opioid
Jones et al., 2003 <sup>35</sup>	One center: urban hospital	Michigan	70	IHS criteria	Not reported	Physician preference
Fiesseler et al., 2006 <sup>36</sup>	One center: suburban hospital	New Jersey	85	IHS criteria	Average age 38 years % Female patients (86%) Mean pain score 9.0	Physician preference
Friedman et al., 2007 <sup>37</sup>	Four centers: urban hospitals	New York	203	IHS criteria	Average age 37 years % Female patients 85% Median HA duration 48 hours	Metoclopramide 20–40 mg IV + Diphenhydramine 25 mg IV: 7% received NSAID, 2% received opioid
Kelly et al., 2008 <sup>38</sup>	Three centers: community hospitals	Melbourne, Australia	61	No specified criteria	Median age 40 years % Female patients 78% Median pain score 9.0 2/3 with HA duration <24 hours	Chlorpromazine 12.5–50 mg IV + 1–2 L of normal saline
Donaldson et al., 2008 <sup>39</sup>	Two centers: community and tertiary care hospital	Michigan	99	IHS criteria	Average age 36 years % Female patients 81% Mean pain score 8.8	Physician preference: 33% received antiemetic, 21% received ketorolac, 38% received opioid
Rowe et al., 2008 <sup>40</sup>	Four centers: urban hospitals	Alberta, Canada	126	IHS criteria	Average age 35 years % Female patients 81% Median pain score 8.0 1/2 with HA duration <24 hours	Physician preference: Metoclopramide recommended

Pain scores are based on a 10-point pain scale (1 = least, 10 = worst). All included studies were prospective randomized clinical trials that were double-blinded and placebo-controlled. All included studies had a final Jadad score of 5 (see text for details). HA = headache; IHS = International Headache Society; IV = intravenous; NSAID = nonsteroidal anti-inflammatory.

with patients treated primarily in specialty clinics and the ED.<sup>11,12,14–18</sup>

In 1986, Gallagher<sup>20</sup> published the first clinical trial with a control arm that supported the use of dexamethasone in the ED. In this trial of 130 patients, those receiving adjunctive dexamethasone therapy had a significantly lower rate of moderate or severe headache at 24 hours compared to the control group (28% vs. 71%,  $p < 0.05$ ). Although these results represent a dramatic

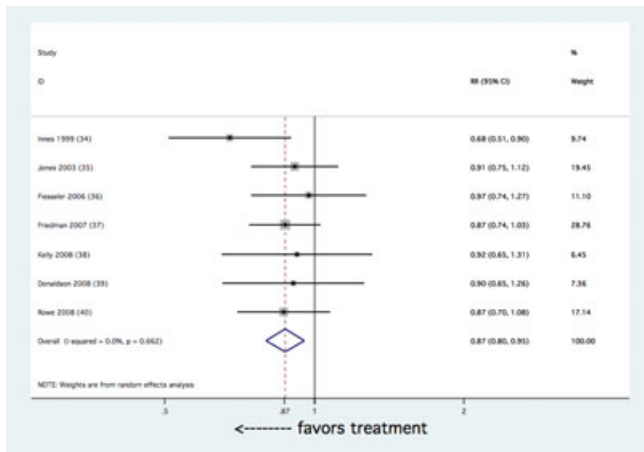
difference in headache resolution favoring dexamethasone, no details regarding randomization technique, blinding of patients or physicians, or description of withdrawals or dropouts were published.

Improvement in the rate of headache relapse was seen in a recently completed high-quality trial by Baden et al.<sup>25</sup> involving 57 ED patients with headaches of “benign etiology.” In this trial, patients randomized to adjunctive dexamethasone therapy had a favorable

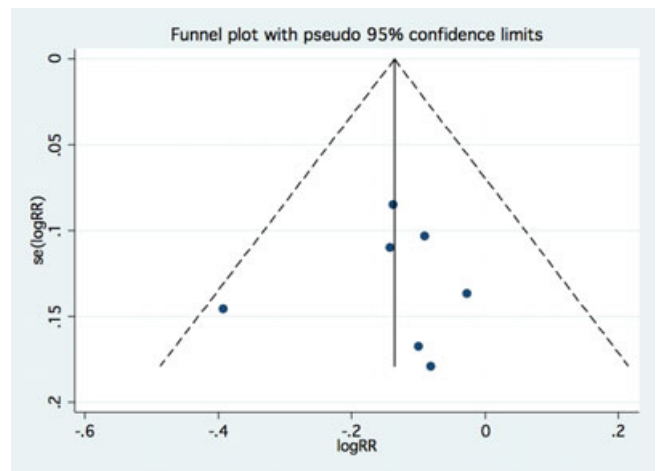
Table 3  
Primary Outcome

Author, Year	Headache Severity Scale*	Duration of Follow-up (hours)	Intervention	Moderate or Severe Headache on Follow-up (%)
Innes et al., 1999 <sup>34</sup>	5-point pain/disability scale	48–72	Dexamethasone 24 mg IV vs. placebo	9/49 (18) 22/49 (45)
Jones et al., 2003 <sup>35</sup>	5-point pain/disability scale	48	Dexamethasone 20 mg IV or IM vs. placebo	4/34 (12) 7/36 (19)
Fiesseler et al., 2006 <sup>36†</sup>	Modified 4-point pain scale	24–48	Dexamethasone 10 mg IV vs. placebo	12/44 (27) 12/41 (29)
Friedman et al., 2007 <sup>37†</sup>	Modified 4-point pain scale	24	Dexamethasone 10 mg IV vs. placebo	22/104 (21) 31/99 (31)
Kelly et al., 2008 <sup>38†</sup>	10-point VAS score modified into a 4-point pain scale	24	Dexamethasone 8 mg IV vs. placebo	9/30 (30) 11/31 (35)
Donaldson et al., 2008 <sup>39</sup>	Presence or absence of headache on reassessment	72	Dexamethasone 24 mg IV vs. placebo	21/57 (37) 18/42 (43)
Rowe et al., 2008 <sup>40</sup>	5-point pain/disability scale	48–72	Dexamethasone 8 mg PO vs. placebo	14/64 (22) 20/62 (32)

IV = intravenous; IM = intramuscular; PO = by mouth; VAS = visual analog scale.  
 \*See text for details.  
 †Authors contacted for clarification of published data to incorporate results into primary outcome.



**Figure 2.** Forest plot. The central square of each horizontal line represents the RR for each study. The lines demonstrate the range of the 95% CI. The vertical line at an RR of 1 is the line of no effect. % Weight indicated the influence exerted by each study on the pooled RR. The p-value for heterogeneity was 0.66 using the Cochran Q statistic. The I<sup>2</sup> statistic for heterogeneity was 0% (95% CI = 0% to 71%). CI = confidence interval; RR = risk ratio.



**Figure 3.** Funnel plot. Vertical solid line represents the logarithmic transformation of the overall estimated treatment effect (i.e., log [RR]), diagonal dotted lines represent pseudo-95% confidence limits for the estimated treatment effect, and the circles represent treatment effects of each of the seven studies. RR = risk ratio.

trend reducing the rate of moderate or severe headache at 48 to 72 hours compared to placebo (13% vs. 33%, p = 0.14). Although not specified in their trial, a significant number of these patients may have met the IHS definition of acute migraine headache. A recent study by Friedman et al.<sup>51</sup> noted that 60% of patients who

presented to an ED with primary headache met IHS criteria for migraine headache.

The results of our meta-analysis suggest a moderate benefit in preventing moderate or severe headache when dexamethasone is added to standard migraine therapies in the ED. These results remained consistent across our sensitivity analysis, including removal of the

Table 4  
Summary of Adverse Events

	Dexamethasone (No. of Patients)	Placebo (No. of Patients)
Rash	1	0
Blurred vision	1	0
Flushing	3	1
IV irritation	2	0
Numbness/tingling	4	0
Diarrhea	1	0
Acute medication reaction*	10	1
Moodiness	3	3
Swelling	2	3
Cramps	1	4
Restlessness	15	9
Drowsiness	31	32
Nausea/vomiting	20	26
Dizziness	5	3
Total	99/382 (26%)	82/360 (23%)

IV = intravenous. \* = adverse event not defined.<sup>37</sup>

trial with the largest impact on the results and removal of the single statistically positive trial favoring dexamethasone use.

Six of the seven included trials reported no statistical difference between the rates of recurrent headache between the treatment and placebo groups. In each of these trials a trend favoring dexamethasone was seen. The small number of patients in each of these trials may have limited the statistical power of each to detect a true difference between treatment and control groups (i.e., these trials may have been subject to a Type II error). One of the reasons for this type of error is when the difference in outcomes is smaller than expected; indeed in the trials that included this analysis, a 25% to 50% reduction in headache relapse was anticipated for power calculations. Our results are more consistent with a 10% reduction in headache relapse. Future trials should anticipate enrollment of 700 patients to show a 10% difference in event rate assuming a baseline event rate of 35% and an alpha error of 0.05 and beta error of 0.20.

Adverse effects such as nausea, vomiting, restlessness, and drowsiness were reported; however, these events may have been related to the underlying migraine headache or concomitantly administered abortive therapy. Furthermore, these complications were noted to be equivalent between the dexamethasone and placebo groups. The most commonly documented adverse effects attributable to dexamethasone were transient body tingling, flushing, and irritation at the IV site.

The results of our meta-analysis are similar to those published by Colman et al.<sup>52</sup> Compared to their analysis, our analysis included one added trial that evaluated oral dexamethasone and excluded one trial that may have included nonmigraine headache patients. Our analysis also provides supplementary information regarding other published trials that have evaluated dexamethasone as well as other corticosteroids in this role.

Overall, a single dose of dexamethasone, administered with standard antimigraine therapy, would be expected to reduce the rate of moderate or severe recurrent headache at 24 to 72 hours in approximately 1 out of 10 patients. Previous studies have found that both doctors and patients consider headache relapse to be an important aspect of treatment in patients with acute migraine headache.<sup>53-55</sup> Dexamethasone offers the promise of reducing the outcome of headache relapse at the expense of transient and well-tolerated side effects.

## LIMITATIONS

Publication bias is known to occur in meta-analyses, because studies with results that are significant and appealing, from well-funded sources, or of higher standard are more likely to be published than work without such features.<sup>56-58</sup> A contemporary move by major medical journals to require authors to preregister trials as a prerequisite for publication is anticipated to reduce the effect of publication bias on future systematic reviews. We attempted to limit our exposure to publication and selection bias by using multiple assessors, each using an extensive search strategy and a quality scale, to locate and grade potential trials. We assessed this bias through funnel plot testing and evaluation of Begg's and Eggers test for publication bias. Although the utility of these tests has been questioned when the number of studies included in the meta-analysis is small, none of our statistical tests evaluating for publication bias revealed evidence of significant bias.<sup>59</sup>

Studies addressing the same or similar questions that are included in a meta-analysis will be expected to vary in a number of ways. Differences in eligibility criteria, trial treatment regimens, concomitant treatments, definitions of outcome events, or length of follow-up can all contribute to the expected heterogeneity seen within meta-analyses. We assessed for these differences using several statistical tests for heterogeneity, including the Cochrane Q, tau-square test, and I<sup>2</sup> statistic. We were unable to identify significant differences with use of the Cochrane Q or tau-square statistic; however, the upper limit of the 95% CI for the I<sup>2</sup> statistic includes the possibility that a moderate amount of statistical heterogeneity was present in the included trials. This finding is not unexpected, given the small number of studies included in our analysis.<sup>60</sup>

The effects of confounding interventions and their impact on internal validity cannot be overlooked in this analysis. Only two trials specified a standard treatment regimen for all patients with acute migraine; the remainder allowed for an individual treatment approach. While this approach remains a threat on internal validity, it augments the external validity of the results by allowing physician preference in the treatment of migraine headache. Additionally, none of the trials limited or recorded the use of home medications in the 24 to 72 hours following ED evaluation. Although proper randomization within each trial, and combining the results into a meta-analysis, should limit the variability in physician treatment and home medication use

between groups, small, but significant, differences may have been present and may partially or fully explain the results presented here.

Ubiquitous application of our results to individual patients presenting to the ED with headache must be done with caution. In general, to be included in these studies, patients had to meet criteria outlined by the IHS for the diagnosis of migraine headache. Indiscriminate administration of dexamethasone to patients with nonmigraine headaches may not yield the results seen with our analysis. Notably, in all of the included trials, ED physicians made the diagnosis of acute migraine headache, increasing the applicability of our results.

## CONCLUSIONS

Although the results of our analysis suggest a modest but significant benefit when dexamethasone is added to standard headache therapies in the ED for the treatment of acute migraine headache, the limited number of trials reviewed and the small sample size within each trial limits the strength of our conclusion. However, the potential benefit in preventing a moderate or severe headache relapse in one of every nine patients treated is not offset by the mild and transient side effects attributable to a single dose of dexamethasone. Therefore, the addition of dexamethasone to standard antimigraine therapies is an acceptable management strategy to decrease the rate of headache relapse for patients presenting to the ED.

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