

Parenteral dexamethasone for acute severe migraine headache: meta-analysis of randomised controlled trials for preventing recurrence

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BMJ 2008;336:1359-61
doi:10.1136/bmj.39566.806725.BE

ABSTRACT

Objective To examine the effectiveness of parenteral corticosteroids for the relief of acute severe migraine headache and prevention of recurrent headaches.

Design Meta-analysis.

Data sources Electronic databases (Cochrane Central Register of Controlled Trials, Medline, Embase, LILACS, and CINAHL), conference proceedings, clinical practice guidelines, contacts with industry, and correspondence with authors.

Selection criteria Randomised controlled trials in which corticosteroids (alone or combined with standard abortive therapy) were compared with placebo or any other standard treatment for acute migraine in adults.

Review methods Two reviewers independently assessed relevance, inclusion, and study quality. Weighted mean differences and relative risks were calculated and are reported with 95% confidence intervals.

Results From 666 potentially relevant abstracts, seven studies met the inclusion criteria. All included trials used standard abortive therapy and subsequently compared single dose parenteral dexamethasone with placebo, examining pain relief and recurrence of headache within 72 hours. Dexamethasone and placebo provided similar pain reduction (weighted mean difference 0.37, 95% confidence interval -0.20 to 0.94). Dexamethasone was, however, more effective than placebo in reducing recurrence rates (relative risk 0.74, 95% confidence interval 0.60 to 0.90). Side effect profiles between dexamethasone and placebo groups were similar.

Conclusion When added to standard abortive therapy for migraine headache, single dose parenteral dexamethasone is associated with a 26% relative reduction in headache recurrence (number needed to treat=9) within 72 hours.

INTRODUCTION

An inflammatory process may be one of several factors underlying migraine pathophysiology. Moderating the inflammatory cascade may therefore help to relieve migraine headache and prevent its recurrence. Despite the appeal of using corticosteroids and non-steroidal anti-inflammatory drugs to treat migraine, published reports suggest that corticosteroids are infrequently used for acute severe migraine in the emergency setting.¹

We assessed the evidence from controlled trials on the effectiveness and tolerability of parenteral corticosteroids for the relief of acute migraine headache in adults and the prevention of recurrences.

METHODS

We searched several databases (see bmj.com); hand searched conference proceedings; reviewed clinical practice guidelines for acute migraine; searched websites housing clinical trial details, theses, or dissertations; and contacted pharmaceutical companies, authors of identified studies, and experts in headache.

Eligible studies for review were randomised controlled trials of parenteral corticosteroids given for acute severe migraine in adults along with reasonable criteria to distinguish migraine from other headache types. We only included trials done in emergency departments or headache clinics, indicating that the migraine was an acute and severe event. Parenteral delivery was chosen to reflect that of the emergency setting, where steroids are delivered intravenously or intramuscularly to avoid the nausea and vomiting associated with migraine.¹

The primary outcome was recurrence of migraine headache 24 to 72 hours after treatment. The original migraine must have largely resolved to meet the definition of recurrent migraine. Not all trials tackled this, but because the trials were in emergency departments or headache clinics we assumed that patients would not have been discharged without substantial pain relief. Secondary outcomes were reduction in headache pain after treatment on a 10 cm visual analogue scale, and adverse events associated with treatment. We assessed the internal validity of trials using Jadad's scale (score 0-5),² with higher scores indicating higher quality.

We pooled the results of studies using fixed effects models, if appropriate, after consideration of heterogeneity among trials. For dichotomous variables we calculated individual and pooled statistics as relative risks (95% confidence intervals). For continuous outcomes we calculated the mean differences reported from individual trials, and we pooled statistics as weighted mean differences (95% confidence intervals). We used χ^2 and I^2 statistics to test for heterogeneity.³

This article is an abridged version of a paper published on bmj.com. Cite this article as: *BMJ* 2008, doi: 10.1136/bmj.39566.806725.BE

We completed a priori subgroup analyses comparing intramuscular administration with intravenous administration. In addition, we carried out retrospective subgroup analyses of dosage and duration of follow-up.

RESULTS

Seven of 18 manuscripts assessed were eligible for inclusion in this review.^{w1-w7} Five were published primary papers and two were in abstract form. The included trials all used dexamethasone and had similar study methods (see bmj.com). The quality of the studies was high as most concealed allocation from the patients and treating clinicians, were double blinded, and reported losses to follow-up.

All seven studies (n=738) reported a lower recurrence of migraine within 24-72 hours of treatment among the dexamethasone groups than placebo groups (figure). Effect sizes varied slightly among trials; however, heterogeneity was non-significant (I²=3.4%). The pooled results indicated a significant reduction in recurrence among those treated with dexamethasone plus standard abortive care (relative risk 0.74, 95% confidence interval 0.60 to 0.90). The estimated number needed to treat to prevent one recurrent headache was 9 (95% confidence interval 6 to 25).

Four studies (n=455) reported mean differences in headache pain from baseline to discharge.^{w2 w3 w5 w7} The results suggest no benefit in initial pain reduction for treatments including dexamethasone compared with placebo (weighted mean difference 0.37, 95% confidence interval -0.20 to 0.94); however, this study pooling demonstrated moderate heterogeneity (I²=46.2%).

Six of the studies (n=626) reported on specific adverse events.^{w1-w3 w5-w7} No significant differences were found between dexamethasone and placebo

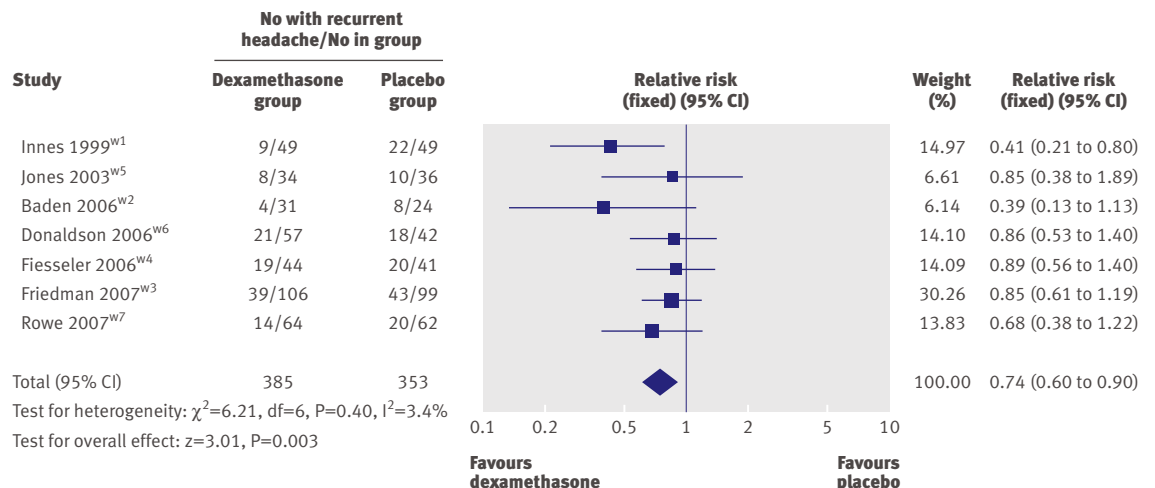
groups for restlessness, drowsiness, tingling, numbness, or swelling (see bmj.com). Patients treated with dexamethasone were more likely to have dizziness (relative risk 2.15, 0.98 to 4.74) but less likely to have nausea (0.70, 0.48 to 1.02) or “other” adverse events (0.50, 0.30 to 0.82).

In one study^{w5} 47 patients received intramuscular treatment, allowing for an a priori subgroup comparison with those receiving intravenous treatment in the same and other studies (n=592). No significant differences were found between the intramuscular (relative risk 0.59, 0.19 to 1.81) and intravenous routes (0.75, 0.61 to 0.91) for recurrent migraine.

Studies using less than 15 mg (n=3) of dexamethasone reported a weaker treatment effect (relative risk 0.80, 0.62 to 1.04) than those using 15 mg or more (0.67, 0.50 to 0.91); the difference was not significant (χ²=0.74; df=1; P=0.39). Stronger evidence suggested that studies with longer follow-up showed a stronger treatment effect with dexamethasone. Studies with a follow-up period of 48 hours or less showed a weaker treatment effect (relative risk 0.86, 0.66 to 1.11) than those with longer follow-up periods (0.61, 0.45 to 0.84); the difference was significant (χ²=4.33; df=1; P=0.037).

DISCUSSION

This systematic review summarises available evidence for the use of parenteral corticosteroids in treating acute severe migraine headaches. We identified seven high quality randomised controlled trials evaluating dexamethasone in acute migraine. Our results suggest that, when added to standard abortive therapy, dexamethasone reduces the recurrence of headache within 72 hours. Only nine patients would need to be treated to prevent one recurrent headache. Dexamethasone is readily available and familiar to most doctors,⁴ and when used as a single parenteral dose—as in all of the



Effectiveness of dexamethasone plus standard abortive therapy for recurrent migraine headache compared with placebo plus standard abortive therapy

WHAT IS ALREADY KNOWN ON THIS TOPIC

Recurrent headache is common within 24-72 hours after treatment for acute severe migraine headache

Inflammation may play a part in migraine, and corticosteroids might reduce the rate of recurrent headache

WHAT THIS STUDY ADDS

Dexamethasone reduces rates of recurrent headache after treatment for acute severe migraine headache

Evidence is lacking that dexamethasone provides immediate pain relief from migraine

included trials—is well tolerated, causing only minor side effects. This review does not support the use of corticosteroids for immediate relief of acute migraine. Evidence from four included studies suggests that dexamethasone does not significantly reduce pain scores before discharge from an emergency department, but that its potential benefits are more related to a reduction in recurrence of headaches.

The trials show apparent benefit of steroid treatment for acute severe migraine headache, but several problems remain unresolved. We could not identify the characteristics of patients most likely to benefit from this treatment because of the relatively small number of patients available for subgroup analysis, although two studies suggested that treatment effect is related to duration of headache and that dexamethasone may be more useful for prolonged severe headaches.^{w3 w7} Also, we could not clarify the relation between different abortive agents provided in the emergency department and headache recurrence rates, nor the potential interaction between these agents and dexamethasone. Consequently, the differing use of primary abortive agents across studies may be an important confounder. One trial suggested that more severe residual pain was associated with greater risk of headache relapse.^{w7}

Finally, although we did not evaluate the effectiveness of oral corticosteroids, it is possible that they have beneficial effects similar to those delivered parenterally. Two recent randomised placebo controlled trials using oral dexamethasone⁵ and prednisone,⁶ however, failed to show a benefit of oral corticosteroids when added to abortive therapy for the prevention of recurrent migraine headache. Recent evidence suggests that oral non-steroidal anti-inflammatory drugs may also be effective in the prevention of recurrent migraine headache in a primary care population.⁷

Limitations

This review has some limitations. Firstly, despite the use of appropriate and similar criteria to assess

patient eligibility across included studies, it is likely that people with non-migraine headache were enrolled. Importantly, the studies reviewed were carried out in emergency departments and headache clinics; the results are likely to be generalisable to similar settings but may not be generalisable to primary care or other outpatient settings. Secondly, although it is likely that single dose dexamethasone is relatively safe, the studies did not follow patients beyond 72 hours and may have missed uncommon or delayed adverse events.

Finally, recent evidence suggests that publication bias is less pervasive in the emergency department literature⁸; however, trials reporting negative findings are less likely to be published and more likely to be excluded from systematic review, potentially biasing the study conclusions. We believe that our comprehensive search strategy minimised any such bias. In fact, we included two unpublished trials^{w4 w5} and all but one trial^{w1} with “negative” findings.

In conclusion, when added to standard abortive migraine therapy, single dose parenteral dexamethasone is associated with a 26% relative reduction in recurrent headache occurring within 72 hours.

We thank the department of emergency medicine at the University of Alberta; ICN Pharmaceuticals and Faulding Pharmaceutical for responding to our requests for unpublished data; and A Bastani, a corresponding study author. Data from this study were reported at the Canadian Association of Emergency Physicians annual scientific meeting, Winnipeg, MB, Canada, 14-17 June, 2003.

Contributors: See bmj.com.

Funding: BHR is supported by the 21st century Canada research chairs programme through the government of Canada. The Canadian Association of Emergency Physicians Research Consortium provided partial support for this study.

Competing interests: GDI, BWF, and BHR are primary authors of included trials. MDB and IC are coauthors of included trials.

Ethical approval: Not required.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Accepted: 11 April 2008