ADVANCES

Intravenous dexamethasone to prevent the recurrence of benign headache after discharge from the emergency department: a randomized, double-blind, placebo-controlled clinical trial

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ABSTRACT

Objective: To evaluate whether the addition of intravenous (IV) dexamethasone to standard emergency department (ED) benign headache therapy would reduce the incidence of headache recurrence at 48–72 hours.

Methods: This randomized, double-blind, placebo-controlled clinical trial of adult patients presenting with the chief complaint of headache was conducted in the ED of 2 academic, urban Level 1 hospitals. Headache evaluation and therapy were determined by the treating physician, and, before discharge, patients were administered either 10 mg of IV dexamethasone or placebo. The treatment groups had similar baseline characteristics, abortive therapy, IV fluids and degree of pain relief achieved before discharge. Patients were contacted 48–72 hours following discharge and asked whether their headache was "better," "worse" or "remained unchanged" when compared with their symptoms at discharge. Those whose headaches were "worse" or "unchanged," and those who reported a return of headache after being pain free at discharge were considered to be treatment failures and classified as having had a recurrence. The patient's headache at follow-up was further categorized as severe (i.e., provoking another physician visit or interfering with daily activity) or mild (i.e., requiring self-medication or no treatment).

Results: Fifty-seven patients met the inclusion criteria and 2 were lost to follow-up, leaving 55 for analysis. At follow-up, 9.7% (3/31) of those receiving dexamethasone had headache recurrence, versus 58.3% (14/24) of those receiving placebo ($p < 0.001$). Four dexamethasone recipients (12.9%) had severe headaches at follow-up compared with 8 (33.3%) in the placebo group ($p = 0.14$).

Conclusions: In this study, IV dexamethasone reduced headache recurrence at 48–72-hour follow-up. Given its excellent safety profile and likely benefit, IV dexamethasone should be considered for ED headache patients after standard evaluation and therapy.

Key words: benign headache; migraine; cephalgia; dexamethasone

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RÉSUMÉ

Objectif : Déterminer si l'ajout de dexaméthasone intraveineuse (IV) au traitement standard contre le mal de tête bénin à l'urgence réduirait l'incidence de rechute à 48–72 heures.

Méthodes : Cet essai clinique randomizé à double insu contrôlé par placebo portant sur des patients adultes qui se sont présentés en se plaignant principalement d'un mal de tête a été réalisé à l'urgence de deux hôpitaux universitaires urbains de niveau 1. L'évaluation et le traitement du mal de tête ont été déterminés par le médecin traitant et, avant leur départ, les patients ont reçu soit 10 mg de dexaméthasone IV, soit un placebo. Les sujets traités présentaient des caractéristiques de base semblables, une thérapie infructueuse, des liquides IV et une douleur soulagée jusqu'à un certain point avant leur départ. On a communiqué avec les patients de 48 à 72 heures après leur départ pour leur demander si leur mal de tête était «mieux», «pire» ou «inchangé» comparativement aux symptômes qu'ils avaient à leur départ de l'urgence. On a considéré que ceux dont le mal de tête était «pire» ou «inchangé» et ceux qui ont déclaré que leur mal de tête était revenu après ne plus avoir eu de douleur au moment de quitter l'urgence constituaient des échecs du traitement et on les a classés comme victimes d'une rechute. On a classé en outre le mal de tête du patient au moment du suivi comme grave (c.-à-d. qui a provoqué une autre consultation de médecin ou a nui aux activités de la vie quotidienne) ou léger (c.-à-d. qui a nécessité une automédication ou n'a nécessité aucun traitement).

Résultats : Cinquante-sept patients ont satisfait aux critères d'inclusion et on en a perdu deux au suivi, ce qui en a laissé 55 pour l'analyze. Au moment du suivi, 9,7 % (3/31) de ceux qui recevaient de la dexaméthasone ont vu leur mal de tête réapparaître comparativement à 58,3 % (14/24) de ceux qui ont reçu un placebo ($p < 0{,}001$). Quatre sujets qui ont reçu de la dexaméthasone (12,9 %) avaient un mal de tête sérieux au suivi comparativement à 8 (33,3 %) du groupe de ceux qui ont reçu un placebo ($p = 0{,}14$).

Conclusions : Dans le cadre de cette étude, la dexaméthasone IV a réduit la récidive du mal de tête au suivi à 48–72 heures. Compte tenu de son excellent profil d'innocuité et de son avantage probable, il faudrait envisager d'administrer de la dexaméthasone IV aux patients se présentent à l'urgence avec un mal de tête, après une évaluation et un traitement standard.

Introduction

Headaches are a common cause of emergency department (ED) visits. Up to 85% of the US adult population complains of headaches occasionally, and it is the chief complaint in 2%–5% of all ED visits.[1,2] The vast majority of headaches in patients presenting to the ED are benign, with tension headaches representing 50%, migraine headaches 10% and mixed-type 30%.[1]

In clinical practice, the distinction between migraine and tension-type headaches is often blurred. The International Headache Society classification for benign idiopathic headache acknowledges that some patients may simultaneously satisfy diagnostic criteria for migraine and tension-type headaches.[3] Both are characterized by similar abnormal vascular flow and inflammatory responses, suggesting that they may represent variations of the same disease process.[4–6] For purposes of ED headache treatment, there is usually little need to differentiate between these benign headache etiologies.[7,8]

Although the acute symptoms can generally be relieved, 8%–66% of patients will suffer a recurrence within 48 hours,[9–16] and inflammation appears to play a critical role in these recurrences.[17–20] Therefore, prolonged suppression of this inflammatory process may be an important component of acute headache management. Dexamethasone, a corticosteroid with 25 times the anti-inflammatory potency of hydrocortisone,[21] has been tested as a treatment for migraines, with generally positive results.[22–24] By suppressing the sterile inflammatory response, dexamethasone may also prevent the recurrence of benign headaches after successful ED treatment.

The purpose of this study was to determine whether patients discharged from the ED after treatment for a benign headache have a lower incidence of recurrence when treated with intravenous (IV) dexamethasone before discharge. Our secondary aim was to determine whether such administration of dexamethasone could improve patients' quality of life by reducing the number of return ED or primary care clinic visits for "rescue" therapy, thus allowing them to return to normal daily activities.

Methods

Study design

We performed a randomized, double-blind, placebo-con-

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trolled clinical trial with allocation concealment. The Institutional Review Board that serves both hospitals approved the study, and all subjects provided written informed consent. Additionally, subjects signed a release of medical information form.

Setting and patients

The study was conducted in the ED of 2 military, academic, urban Level-1 Trauma Centers with a combined annual census of approximately 130 000 patients. Both are staffed full time by board-certified emergency medicine (EM) physicians and both train EM residents. Enrolment began Mar. 1, 2003, and ended Dec. 31, 2003, when the study was terminated. We approached a convenience sample of ED patients for enrolment. Patients were eligible if they were at least 18 years of age, were considered by the treating physician to have a headache of a benign etiology, and were safe for discharge home. Patients were excluded if they were pregnant; had findings inconsistent with a benign headache (e.g., fever, meningismus, focal neurologic findings, or anything else that concerned the treating physician); had an allergy to the study drug; had active peptic ulcer disease; had diabetes mellitus type 1; had an active systemic fungal infection; had used steroids in the previous 7 days, or had been previously enrolled in this study.

Study protocol

Each potential subject received a headache evaluation, including a history, physical and neurologic exam, appropriate diagnostic studies, and headache therapy. Eligible patients included those who required an IV and were felt to be safe for discharge from the ED. The hospital pharmacist created the randomization table and coded the study medications in advance. Either 1.0 mL of dexamethasone (10 mg/mL) or 1.0 mL of normal saline (placebo) was placed into each respective syringe and labelled with a code number. Once consent for study enrolment was obtained, the next consecutive study packet was used. Each subject had an individual data sheet prepared by their emergency physician that included baseline demographic information, vital signs, medication(s) and IV fluids used. The type and dose of headache therapy was left to the discretion of the emergency physician. After ED treatment was considered to be satisfactory, patients received dexamethasone 10 mg IV or placebo, administered over 5–10 minutes by a blinded ED nurse. The dexamethasone and normal saline used were part of the usual inpatient pharmacy stock, and no additional resources were required. Patients rated the pain level of their headache using a 10-cm Visual Analog Scale (VAS) (0 = pain free; 10 = worst pain ever) before ED intervention and before ED discharge.

Measurements and outcomes

Blinded investigators contacted patients by telephone 48–72 hours after discharge and completed a standardized questionnaire. Patients who were pain free at ED discharge were asked whether their headache had returned. Those who were not pain free at discharge were asked whether their headache was "better," "worse" or "remained unchanged" compared with their residual headache at discharge. Patients whose headaches were "worse" or "unchanged," and those who reported headache return (after being pain free at discharge) were considered to be treatment failures and classified as having a recurrence. Recurrent headaches were also classified as class A (provoking another physician visit), class B (interfering with normal daily activity but not provoking another physician visit), class C (required self-dispensing of prescribed medications but not limiting activity) or class D (requiring no treatment). Class A and B were rated as "severe," and class C and D were classified as "mild" to allow for direct comparison to previous studies.[15,16,25] Finally, patients were asked to describe any unusual side effects. Our primary outcome was the percentage of patients that experienced headache recurrence at 48–72 hours. Our secondary outcome was the percentage of patients who had a severe headache at 48–72 hours.

Data analysis

To determine the difference between treatment groups at follow-up, headache recurrence and headache severity were compared using a Pearson's χ^2 2×2 contingency test with continuity correction. Logistical regression analysis was used to evaluate the effect of treatment in conjunction with other ED interventions. Independent sample *t* tests were used to determine if treatment groups were similar at baseline before ED intervention. Analysis of variance (ANOVA) was used to determine the impact of pain relief achieved in the ED on the rate of recurrence at follow-up.

In estimating the necessary sample size, we assumed that recurrence rate with placebo treatment would be 40% and that a 20% decrease would be clinically significant. Ninety-four subjects per group were needed to detect the expected difference in outcome with a level of confidence of 95% and a power of 80%. A single interim analysis was planned after 10 months of patient enrolment and was to be stopped if our primary outcome reached statistical significance ($p < 0.05$) and the 2 groups were otherwise similar.

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Results

At the scheduled 10-month interim analysis, 57 patients had been enrolled and 2 were lost to follow-up, leaving 55 patients eligible for analysis: 31 in the dexamethasone treatment group and 24 in the placebo treatment group. Because the interim analysis showed a highly statistically significant difference between groups for the primary outcome, the study was terminated early.

Table 1 summarizes demographic information as well as ED interventions provided. At baseline there were no statistically significant demographic differences between the 2 treatment groups. Additionally, patients were similar with respect to initial headache severity, as measured by the VAS, and with respect to pain relief achieved before ED discharge. Time to patient follow-up was similar between the 2 groups. Both the dexamethasone and placebo treatment groups achieved statistically significant pain reduction during their ED stays ($p < 0.001$ for both groups). Finally, patients were not statistically different in regard to

Table 1. Demographic information and emergency department (ED) intervention for the 55 patients with headache who participated in the study

Variable	Dexamethasone (n = 31)	Placebo (n = 24)	p
Characteristic			
Mean age, yr (and SD)	34.5 (12.6)	32.6 (13.0)	0.58
Females, no. (and %)	18 (58.1)	17 (70.8)	0.49
History of migraine, no. (and %)	14 (45.2)	10 (41.7)	1.0
VAS pain score, mm (and SD)			
Initial	75.0 (17.5)	77.3 (19.5)	0.64
At discharge	20.4 (19.5)	25.8 (20.7)	0.33
Pain relief achieved in ED	53.3 (20.0)*	50.6 (23.3)*	0.71
ED evaluation			
Lumbar puncture, no. (and %)	4 (12.9)	3 (12.5)	1.0
ED treatment			
IV fluid in liters (and SD)	1.4 (0.6)	1.3 (0.6)	0.33
Antiemetic,† no. (and %)	29 (93.5)	19 (79.1)	0.22
Metoclopramide	22	14	
Prochlorperazine® (phenothiazine)	1	0	
Promethazine	8	6	
NSAID, no. (and %)	23 (74.2)	17 (70.8)	1.0
Ibuprofen	22	16	
Ketorolac	1	1	
Opioid,† no. and %)	15 (48.4)	9 (37.5)	0.58
Fentanyl	2	0	
Hydromorphone	1	0	
Meperidine	3	3	
Morphine sulfate	7	6	
Percocet®‡	3	0	
Vicodin®‡	1	0	
Other agent, no. (and %)	13 (41.9)	5 (20.8)	0.15
Acetaminophen	2	0	
Caffeine	3	0	
DHE 45® (dihydroergotamine)	1	1	
Diphenhydramine	2	2	
Lorazepam® (benzodiazepine)	2	1	
Sumatriptan	3	1	

*$p < 0.001$ for the pain reduction achieved within both the dexamethasone and placebo groups
†Some patients received more than one agent within the identified category
‡Narcotic analgesic + acetaminophen
SD = standard deviation; VAS = Visual Analog Scale; IV = intravenous; NSAID = non-steroidal anti-inflammatory drug

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the amount of IV fluids received and the category of medications used for symptom relief.

Table 2 shows that, at 48–72-hour follow-up, 3/31 dexamethasone patients (9.7%; 95% confidence interval [CI] 0.0%–20.1%) had headache recurrence, versus 14/24 (58.3%; 95% CI 38.6%–78%) in the placebo group ($p < 0.001$). Table 3 shows the secondary outcome of headache severity at 48–72 hours. Four patients (12.9%; 95% CI 4.7%–29.6%) in the dexamethasone group had a severe headache (class A or B) at follow-up compared with 8 (33.3%; 95% CI 14.5%–52.2%) in the placebo group ($p = 0.14$). Likewise there was not a statistically significant difference in mild headaches (class C or D) at follow-up ($p = 0.15$).

Table 4 summarizes adverse effects at 48–72 hours. Six patients reported adverse reactions in the dexamethasone group, compared with 5 in the placebo group (19.4% v. 20.8%; $p = 1.0$). None of these effects were consistent with anaphylaxis or an anaphylactoid reaction; nor did they necessitate a physician evaluation or negatively impair patient-perceived quality of life.

Discussion

Evaluation of headache treatment is complex, and there are many different ways to define success. Traditionally, acute symptomatic relief in the ED was believed to be the final end point; however, medications currently used for ED headache management may not provide sustained relief after patient discharge. Reported rates of post-treatment relapse include 34%–53% for sumatriptan,[10–12] 11%–66% for chlorpromazine,[13,26] 24%–56% for meperidine[27,28] and 87% for intramuscular (IM) ketorolac.[28] The pathogenesis of acute benign headache (and headache recurrence) remains controversial, but previous studies support the hypothesis that neurogenic inflammation plays a central role.[17–20,29,30]

Dexamethasone is a potent anti-inflammatory corticosteroid with almost no mineralocorticoid effect. With a half-life of 36–72 hours it should effectively suppress inflammation during the period when patients are most likely to experience a headache recurrence, potentially making it an ideal agent for a one-time administration before ED discharge. Our objective was to determine whether IV dexamethasone prevents recurrence of benign headaches after successful ED treatment. We included patients with all types of benign headaches and did not limit the study only to patients meeting International Headache Society criteria for migraine. We felt this to be more representative of the everyday practice of EM. Furthermore, if migraine, tension and mixed-type headaches are variations of the same disease process, similar treatment is appropriate.

We considered any patient with "no change" or a "worse" headache or a return of their headache at 48–72 hours follow-up to represent recurrences. We anticipated that some patients may not get complete pain relief in the ED and thus designed our study to capture both the patients with complete pain relief whose headache recurred, and those patients whose headache improved but did not completely resolve. To our surprise, only 4 patients were completely pain-free at discharge. We also addressed headache severity at follow-up. By using the end points of "repeat physician visit" and "interfering with normal daily activities" we were able to compare our results with other ED studies[15,16,25] that used similar end points.

The 58.3% headache recurrence rate at 48–72 hours follow-up for the placebo group is compatible with previous

Table 2. Patient group information at 48–72-hour follow-up

Variable	Dexamethasone ($n = 31$)	Placebo ($n = 24$)	p
Time to follow-up, h (and SD)	69.4 (14.3)	67.4 (12.6)	0.59
Headache recurrence, no. (and %)	3 (9.7)	14 (58.3)	<0.001

SD = standard deviation

Table 3. Headache severity at 48–72-hour follow-up

Severity class	Dexamethasone ($n = 31$)	Placebo ($n = 24$)	p
A (provoked repeat physician visit)	3	7	
B (precluded return to normal activity)	1	1	
A+B = severe headache, no. (and %)	4 (12.9)	8 (33.3)	0.14
C (self-dispensed prescriptions only)	14	11	
D (no further treatment necessary)	13	5	
C+D = mild headache, no. (and %)	27 (87.1)	16 (66.7)	0.15

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reported treatment failure rates of 6%–66%. The addition of 10 mg of IV dexamethasone before discharge decreased the rate to 12.6% ($p < 0.001$) and, in this study, no other factors, including gender, migraine history, headache severity at presentation or discharge, type of medications dispensed, or having a lumbar puncture performed were independent predictors of headache recurrence. Additionally, dexamethasone reduced the rate of our secondary outcome (i.e., severe headaches at 48–72 hours) from 33.3% to 12.9%; however, this did not reach statistical significance ($p = 0.14$). Early termination of the study precludes definitive conclusions to be made regarding the secondary end point.

Previous evidence for the use of steroids for acute headache treatment in the ED is limited and focuses primarily on its use in the treatment of migraine headaches. Several prior prospective studies are worth noting.[22–24]

Gallagher studied migraine sufferers presenting to the ED and found that the addition of 8 mg of IM dexamethasone to meperidine and prochlorperazine reduced the incidence of recurrent headache from 71% to 28% at 24 hours follow-up.[22] Klapper and colleagues reported that migraine sufferers in an outpatient headache clinic more often returned to a functional level when dexamethasone 6 mg IV was added to metoclopramide treatment.[23] Finally, Saadah studied migraine sufferers presenting to an outpatient office,[24] reported an 80%–90% response rate to 10 or 20 mg of IV dexamethasone. Increasing the dose from 10 to 20 mg did not improve the response and relapse rates. Although none of these studies were randomized and placebo-controlled or blinded, they do support the use of dexamethasone for the treatment of migraine headaches.

Table 4. Adverse events in the 55 patients who participated in the study

Event	Dexamethasone ($n = 31$)	Placebo ($n = 24$)	p
Tingling	3	0	
Numbness	1	0	
Hiccups	1	0	
Insomnia	1	0	
Cramps	0	1	
Nausea	0	1	
Diarrhea	0	1	
Auditory hallucinations	0	1	
Dizziness	0	1	
Severe adverse reaction*	0	0	
Total no. of patients in each group who had an adverse event (and %)	6 (19.4)	5 (20.8)	1.0

*Any reaction consistent with anaphylaxis or anaphylactoid reaction, or requiring physician evaluation or impairing quality of life.

Our secondary outcome is similar to those reported by previous studies.[15,16,25] Innes and colleagues compared 24 mg of IV dexamethasone versus placebo following successful ED treatment of migraine headaches. They report a decrease in severe headache recurrence from 45% (22/49) in the placebo group to 18% (9/49) in the dexamethasone group at 48–72-hour follow-up.[15] Their results reached statistical significance, but ours did not. Since we had different interim analysis criteria (theirs was the enrolment of 100 patients, ours was 10 months) they were able to enroll more patients. Additionally, they used a higher dexamethasone dose.

Recently, Jones and colleagues reported, in an abstract, the use of 20 mg of IV dexamethasone to prevent the recurrence of migraine headache in 70 patients treated in the ED.[16] Dexamethasone reduced the rate of severe recurrence from 19% (7/36) to 12% (4/34) but it did not reach statistical significance. Currently, Friedman is the principal investigator of a Phase III, multicentre efficacy study of 10 mg of IV dexamethasone versus placebo as adjuvant therapy for acute migraine therapy in the ED setting. The outcomes being analyzed are persistence of no headache at 24 hours and disability scores at 2 and 24 hours. At the time of submission for publication, no interim results are available.[25]

Although long-term corticosteroid therapy is associated with multiple adverse effects, single-dose therapy is not. At equipotent anti-inflammatory doses, dexamethasone almost completely lacks the sodium-retaining property of hydrocortisone, minimizing unwanted side effects.[31] In our study the incidence of minor effects was rare (19.4%) and was similar to placebo (20.8%), with no reported severe adverse reactions. Additionally, a MEDLINE search uncovered only 1 case report of a death from disseminated strongyloidiasis following a one-time dose of dexamethasone.[32]

Limitations and future research

We enrolled a convenience sample; ideally we would have enrolled consecutive eligible and consenting patients, but in our EDs we were not able to approach all eligible patients. Thus, we may have an unrecognized selection bias. In addition, headache management and treatment were not standardized. We chose not to standardize ED treatment because this may have precluded physician and patient participation, and it is not reflective of the everyday approach to headache management. Table 1 suggests that randomization and blinding were successful in ensuring

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similar patient populations at baseline, although we may not have enrolled enough patients to uncover true differences in the 2 groups.

Our dexamethasone dose was not weight based. This would have made the study logistically difficult since the blinded drug had to be pre-packaged. Also, there was no precedent to do so. Prior studies using dexamethasone for headaches in adults used 1 predetermined dose ranging from 6–24 mg IV/IM. We chose 10 mg for ease of packaging since our institution's dexamethasone strength was 10 mg/1 mL and the only study directly comparing different strengths did not show any benefit of 20 mg over 10 mg.[24]

Our study did not have large enough numbers for subgroup analysis, and it is possible that different patient groups (e.g., those with migraine or those having lumbar puncture) or treatment groups (e.g., those receiving opioids) might have had more, or less, benefit from dexamethasone. There are potential issues with terminating the study early after interim analysis; however, this decision is supported even when scrutinized retrospectively by the most conservative theoretical statistical models. Both Peto's rule of a fixed minimized α' and 0.001 for efficacy for interim analysis,[33,34] and an O'Brien and Fleming p value of 0.05 for first interim analysis between 2 treatment groups[34] support the early termination since the p value for our primary outcome was so overwhelmingly statistically significant ($p < 0.001$).

Innes and colleagues found that higher doses (24 mg) of dexamethasone were beneficial,[15] and future research might address the optimal dose of dexamethasone. Additionally, in that oral dexamethasone is as effective as IM for the treatment of pediatric croup,[35] future studies could evaluate the role of oral dexamethasone for headache management, which would reduce the pain, expense, nursing intervention and patient time associated with IV or IM administration. Finally, although our data suggest a beneficial effect at 72 hours, it would be interesting to determine whether this benefit is maintained with longer (e.g., 10–14-day) follow-up periods.

Conclusion

In this study, IV dexamethasone reduced headache recurrence at 48–72 hour follow-up. Given its excellent safety profile and likely benefit, IV dexamethasone should be considered for ED headache patients after standard evaluation and therapy.

Competing interests: None declared.

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