Impact of oral dexamethasone versus placebo after ED treatment of migraine with phenothiazines on the rate of recurrent headache: a randomised controlled trial

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Impact of oral dexamethasone versus placebo after ED treatment of migraine with phenothiazines on the rate of recurrent headache: a randomised controlled trial

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ABSTRACT

Objective: Evidence suggests that the rate of recurrent headache after treatment of migraine in the emergency department (ED) is high. The mechanisms for this are unclear, but neurogenic inflammation may play a role. There is conflicting evidence about whether adjuvant dexamethasone reduces the rate of recurrent headache. The aim of this study was to compare the rate of recurrent headache in patients with migraine randomised to receive a single dose of oral dexamethasone or placebo at discharge after treatment in the ED with intravenous phenothiazine.

Methods: A double-blind, randomised, placebo-controlled trial was conducted in the ED of three community teaching hospitals. Adult patients with physician-diagnosed migraine were treated with intravenous phenothiazine and at discharge were randomised to receive either 8 mg oral dexamethasone or placebo as a single dose. Follow-up was by telephone at 48–72 h and the proportion of patients with recurrent headache overall and in the subgroup with headache duration <24 h was recorded.

Results: 63 patients (76% women) of median age 39 years were enrolled, 61 of whom (97%) completed follow-up. The pooled rate of recurrent headache was 33%. 32 were randomised to placebo and 31 to dexamethasone. The rate of recurrent headache in the dexamethasone and control groups was 27% (8/30) vs 39% (12/31) (relative risk (RR) 0.69, 95% CI 0.33 to 1.45, $p = 0.47$). For 40 patients with headache lasting <24 h the rate of recurrent headache in the dexamethasone and control groups was 15% (3/20) vs 45% (9/20), a reduction in absolute risk of 30% (RR 0.33, 95% CI 0.11 to 1.05, $p = 0.08$).

Conclusion: A single oral dose of dexamethasone following phenothiazine treatment for migraine in the ED did not reduce the rate of recurrent headache. There is weak evidence for a possible benefit in the subgroup who present within <24 h of symptom onset. A multicentre trial to confirm this finding is warranted.

Available data suggest that the rate of recurrent headache after treatment of migraine in the emergency department (ED) is high (up to 87%).[1–5] Mechanisms for this are unclear, but one theory is that neurogenic inflammation plays a key role in this process.[6–9] Some small studies[10–13] have suggested that intravenous dexamethasone reduces the incidence of recurrent headache. This is supported by a small ED-based randomised controlled trial comparing intravenous adjuvant dexamethasone with placebo after treatment of migraine in the ED. A marked reduction in the rate of recurrent headache was observed with intravenous dexamethasone (10% vs 58%)[14] but subsequent reports, only available in abstract form, have failed to confirm this finding.[15–17] The main weakness of these studies is that, with one exception, they fail to control for initial ED treatment. As different treatments have been reported to have different rates of recurrent headache,[1–5] this is a significant factor requiring further study.

The aim of this study was to compare the rate of recurrent headache in patients with migraine in the ED randomised to receive either a single dose of oral dexamethasone or placebo at discharge after treatment with intravenous phenothiazines. Secondary aims were to compare the rate of recurrent headache in the subgroup with migraine duration of <24 h and the rate of adverse events between the groups.

METHODS

Study design and setting

A double-blind, randomised, placebo-controlled trial was conducted in the ED of three community teaching hospitals in Melbourne, Australia with an ED annual census of 75 000, 35 000 and 20 000, respectively. It was conducted between April 2005 and December 2006.

Selection of participants

Participants were a convenience sample of consenting adult patients (age >17 years) with physician-diagnosed migraine. Exclusion criteria were pregnancy, allergy to study medication, findings inconsistent with migraine, patients requiring hospital admission for further investigation and treatment, active peptic ulcer disease, type 1 diabetes mellitus, patients taking corticosteroids for another condition within the preceding 7 days, active systemic fungal infection and previous enrolment in the study.

Data collection and processing

Data collected prospectively included age, sex, migraine history, duration of the present attack, headache severity at presentation and discharge using a 10-point verbal rating scale (0–10), treatment in the ED and whether the patient had a lumbar puncture as part of the examination. Patients were contacted by telephone 48–72 h after discharge and questioned by a researcher

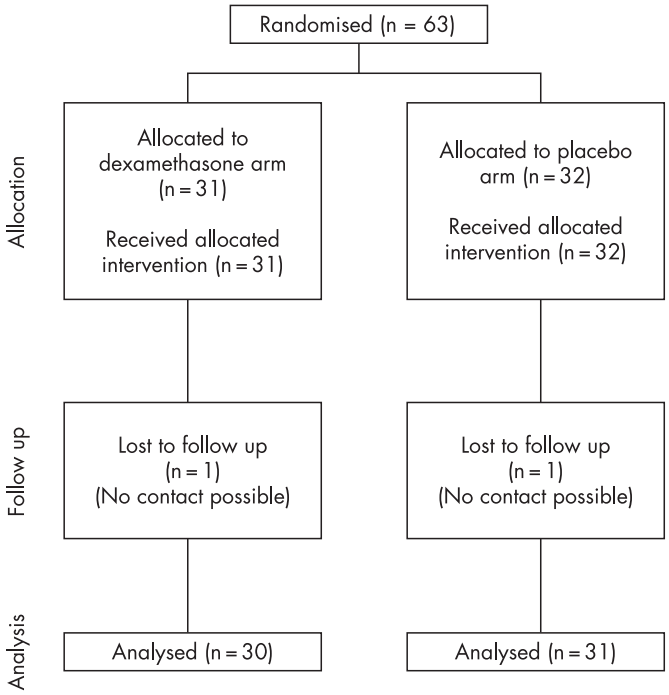

Figure 1 CONSORT diagram.

(blinded to the treatment given) using scripted questionnaires about recurrent headache, use of medications and contact with a healthcare provider.

Specific data on frequency of the headaches, medications taken before presentation at the ED or chronic medications were not collected.

Intervention

Patients received migraine abortive treatment with intravenous phenothiazines (chlorpromazine or prochlorperazine) according to established ED protocols (12.5–50 mg chlorpromazine administered intravenously together with 1–2 litres of normal saline solution or 12.5 mg intravenous prochlorperazine). Immediately before discharge the patients were randomised to receive either 8 mg oral dexamethasone or placebo as a single dose. Randomisation was performed independent of the investigators by a research pharmacist using random number allocation. The preparations were identical and numbered sequentially. The patient, clinician and research nurse undertaking follow-up were all blinded to the treatment given. The randomisation key was not available to researchers until the study and database had been closed.

Outcomes of interest

The primary outcomes of interest were the proportion of patients with recurrent headache at follow-up for the group overall and the subgroup with headache duration <24 h. The latter was a post hoc analysis. Recurrent headache was defined as a return of headache for those who were discharged from ED pain-free or a worsening of headache (≥2 points on a 10-point verbal rating scale) for those who were discharged with residual headache. Secondary outcomes were severity of any recurrent headache experienced, proportion of patients experiencing any adverse event and their type, analgesia use between discharge and follow-up and contact with a healthcare provider between discharge and follow-up.

Table 1 Characteristics of study sample

Characteristic	Dexamethasone group (N = 31)	Placebo group (N = 32)
Median age (years)	39	40.5
Female, n (%)	26 (84%)	23 (72%)
Migraine history, (%) (N = 30, missing data)	24 (80%)	26 (81%)
Aura, n (%) (N = 30, missing data)	14 (47%)	12 (38%)
Proportion presenting within 24 h of symptom onset, n (%)	20 (65%)	21 (66%)
Pain score at presentation (VRS 0–10, median)	9	9
Pain score at discharge (VRS 0–10, median)	2	1.5
Treated with IV chlorpromazine, n (%)	30 (97%)	31 (97%)
Lumbar puncture, n (%)	1 (3%)	0
Proportion pain-free at ED discharge, n (%)	7 (23%)	10 (31%)
Proportion with VRS ⩽2 at ED discharge, n (%)	23 (74%)	26 (81%)

VRS, verbal rating scale; ED, emergency room.

Data analysis

Intention to treat analysis was performed. Data were analysed by χ^2/Fisher test, relative risk ratio and non-parametric techniques using STATA and Analyse-It for Excel. We calculated that a sample size of 66 was needed to detect a 50% reduction in recurrent headache rate (from 60% to 30%) with 80% power and a p value of <0.05; 60% was chosen as it approximated the average of reported recurrent headache rates. The study was powered for the group overall and not the <24 h subgroup. The study was terminated just short of the desired sample size because of resource restraints and slow recruitment.

Ethical approval was obtained from the institutional ethics committee and individual informed written consent was obtained from all participants. The trial was registered with Clinical Trials.gov (ID number 00216736).

RESULTS

Characteristics of study subjects

Sixty-three patients (76% women) of median age 39 years (interquartile range 29–46) were enrolled, of whom 61 (97%) completed follow-up. Thirty-two patients were randomised to

Table 2 Characteristics of subgroup presenting within 24 h of symptom onset

Characteristic	Dexamethasone group (N = 20)	Placebo group (N = 21)
Median age (years)	38.5	42
Female, n (%)	17 (85%)	15 (71%)
Migraine history, (%)	19 (95%)	17 (81%)
Aura, N (%)	8 (40%)	10 (48%)
Pain score at presentation (VRS 0–10, median)	10	9
Pain score at discharge (VRS 0–10, median)	2.5	1
Treated with IV chlorpromazine, n (%)	20 (100%)	21 (100%)
Lumbar puncture, n (%)	1 (5%)	0
Proportion pain-free at ED discharge, n (%)	4 (20%)	9 (43%)
Proportion with VRS ⩽2 at ED discharge, n (%)	10 (50%)	18 (86%)

VRS, verbal rating scale; ED, emergency department.

Table 3 Outcomes for overall group

Characteristic	Dexamethasone group (N = 31)	Placebo group (N = 32)	Relative risk (95% CI)
Lost to follow-up	1	1	
Proportion pain-free at follow-up, n (%)	14 (47%)	13 (42%)	1.11 (0.64 to 1.96)
Proportion with recurrent headache, n (%)	8 (27%)	12 (39%)	0.69 (0.33 to 1.45)
Proportion seeking medical attention, n (%)	10 (33%)	8 (26%)	1.29 (0.59 to 2.82)
Proportion with analgesia use, n (%)	18 (60%)	19 (61%)	0.98 (0.65 to 1.47)

the placebo arm and 31 to the dexamethasone arm (fig 1). The characteristics of the overall group are shown in table 1 and the characteristics of the group presenting within 24 h of symptom onset are shown in table 2. For the 97% of the sample treated with chlorpromazine, the median dose was 25 mg which did not vary between groups.

Main results

The outcomes are summarised in table 3. Overall, the recurrent headache rate was 33% (95% confidence interval (CI) 22% to 46%). The recurrent headache rate in the control group was 39% (12/31, 95% CI 22% to 57%) compared with 27% (8/30, 95% CI 13% to 46%) in the dexamethasone group (relative risk (RR) 0.69, 95% CI 0.33 to 1.45; p = 0.47).

In the subgroup with headache duration <24 h (n = 40, table 4) the recurrent headache rate in the control group was 45% (9/20, 95% CI 24% to 68%) compared with 15% (3/20, 95% CI 4% to 39%) in the dexamethasone group, a 30% absolute risk reduction (RR 0.33, 95% CI 0.11 to 1.05; number needed to treat (NNT) 3.3, 95% CI 2 to 31; p = 0.08).

No adverse effects were reported in the placebo group. In the dexamethasone group there was one report of facial flushing, one of nausea, two of new-onset transient tingling in the hands or feet, one of blurred vision, one of a hot sensation in the legs and one of diarrhoea.

DISCUSSION

Migraine is a complex and potentially disabling condition. While many patients are successfully treated in the community, a proportion present to the ED with persistent severe symptoms. Even after successful treatment in the ED, it is quite common for the headache to recur with rates as high as 87% being reported.[1–5] Neurogenic inflammation has been hypothesised as playing a role in this process,[6–9] and small studies[10–14] have suggested that intravenous dexamethasone can reduce its occurrence. Subsequent ED studies (only available in abstract form) have failed to confirm this.[15–17] There are two main issues with these studies. All but one failed to control for initial ED treatment which is important as it is known that different treatments have differing recurrent headache rates.[1–5] Additionally, although both showed a lower rate of recurrence headache in the dexamethasone arm, they were underpowered to detect even a 50% reduction in recurrent headache rates based on the rates observed in their studies.

Our study failed to find a significant difference in recurrent headache rates between dexamethasone and placebo groups, although the point estimate of absolute risk reduction was 12%. This is not really surprising given what we now know from this study about the expected recurrent headache rate after ED treatment of migraine with phenothiazines. These data should inform the design of larger studies. For the subgroup with headache duration <24 h there was a reduction in the incidence of recurrent headache in the group who received dexamethasone (point estimate of absolute risk reduction 30%). This is a new finding and makes sense pathophysiologically as the mechanisms involved in generation of a recurrent headache have had less time to become established. If confirmed, this finding could change practice.

Our findings are similar to those of other studies with respect to overall results. The two other studies of intravenous dexamethasone after ED treatment reported a 10% absolute risk reduction of recurrent headache.[15 16] These data were not available when we were designing our study and would certainly have altered the sample size. The numbers have been too small in all the studies to determine whether the severity of recurrent headache is affected by the use of dexamethasone.

The relatively high rate of adverse events in the dexamethasone group was unexpected, but all were minor and transient. It is unclear whether this would be a barrier to future use of dexamethasone in routine clinical care.

An important finding was that more than one-third of patients experience significant recurrent headache and about 60% take additional analgesia in the 2–3 days after ED treatment. This suggests that all patients treated in the ED for migraine should receive a pain management plan in order to minimise residual disability and discomfort.

This study has some limitations that should be considered when interpreting the results. It is a small study so may not be generalisable. A convenience sample was used as resources were not available to fund dedicated researchers. We relied on staff to identify and enrol suitable patients. This may have introduced selection bias. Based on the recurrent headache rate found, which was lower than expected, the study was not adequately powered to detect a 50% reduction in recurrent headache for the group overall. To confirm an absolute risk reduction of 10% for

Table 4 Outcome for subgroup presenting within 24 h of symptom onset

Characteristic	Dexamethasone group (N = 20)	Placebo group (N = 21)	Relative risk (95% CI)
Lost to follow-up	1	0	
Proportion pain-free at follow-up, n (%)	11 (55%)	11 (55%)	1.00 (0.57 to 1.75)
Proportion with recurrent headache, n (%)	3 (15%)	9 (45%)	0.33 (0.11 to 1.05)
Proportion seeking medical attention, n (%)	5 (25%)	2 (10%)	2.50 (0.55 to 11.44)
Proportion with analgesia use, n (%)	12 (60%)	10 (50%)	1.20 (0.68 to 2.11)

the group overall, a sample of about 520 patients would be needed. To confirm the absolute risk reduction of 30% in the subgroup presenting <24 h after onset of symptoms, a sample of about 72 would be required. This study was not powered for analysis of the <24 h subgroup. Telephone follow-up was used which may introduce some recall bias.

CONCLUSION

A single oral dose of dexamethasone following phenothiazine treatment in the ED for migraine did not reduce the rate of recurrent headache. There is weak evidence for some benefit in the subgroup who present within <24 h of symptom onset. A multicentre trial to confirm this finding is warranted.

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Images in emergency medicine

"Reflections" on an interesting case: an oropharyngeal foreign body presenting as cleft palate

A 9-month-old girl was taken to Accident and Emergency by her worried parents when they noted an apparent hole on looking into her mouth. The child had stopped sucking her thumb 2 weeks previously but remained well otherwise. After examination she was suspected of having a palatal defect that had been missed on neonatal screening, and was referred to the local cleft palate team. On review at clinic 2 weeks later the palatal defect was, in fact, found to be a small mirror stuck between the hard and soft palate. This was removed under general anaesthetic later that day and the child was discharged home. Oral foreign bodies, although not common in children of this age, carry a risk of ingestion or aspiration if not detected, and the diagnosis must be considered in any previously well child noted to have an apparent change in the appearance of the oropharynx.

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Informed consent was obtained for publication.

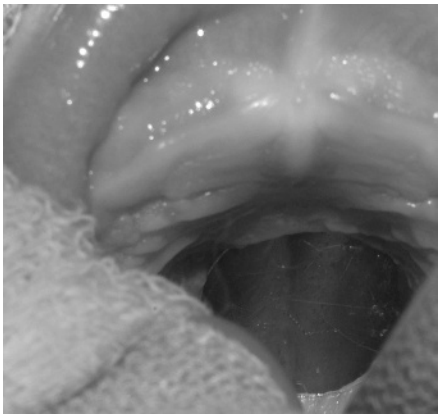

Figure 1 Photograph looking into the child's mouth (lower lip held open with swab). A small mirror is seen wedged firmly between the hard and soft palate.

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