Critical Review Form
Therapy

Intravenous dexamethasone vs. placebo as adjunctive therapy to reduce the recurrence rate of acute migraine headaches: a multicenter, double-blinded, placebo-controlled randomized clinical trial, *Am J Emerg Med* 2008; 26: 124–130

Objective: **"To determine the efficacy of dexamethasone 24 mg IV in decreasing the recurrence rate of migraine headaches at 3 and 30 days post-treatment." (p. 125)**

Methods: **Two-hospital, ED-based double-blinded randomized, placebo controlled trial from November 2004 to November 2005. Eligible subjects had to meet International Headache Society criteria for migraine with and without aura. For migraine without aura this included at least five prior headaches without aura AND headache for 4 - 72 hours AND the presence of nausea/vomiting or photophobia/phonophobia AND at least two of the following: unilateral, pulsating, intensity that inhibits daily activity, or aggravated by daily physical activity. For migraine with aura the criteria were at least two prior migraines with aura AND at least one of the following within 4-minutes of migraine and lasting no longer than 1-hour: unilateral visual symptoms, one-sided numbness or abnormal traveling sensation, one-sided weakness, speech difficulty (Table 1, p. 125). Subjects were excluded if non-IV mediations were used or in the presence of pregnancy, fever, steroid allergy, GI bleeds in previous one-year, diabetic, hypertensive emergency, meningitis, stroke, narcotic-seeking behavior, or steroids within the preceding 30-days.**

After consent subjects would receive a study number and corresponding study packet containing the unlabeled study drug and case report forms. The primary outcome measure was headache recurrence at 3- and 30-days as ascertained by telephone follow-up by a blinded research assistant. Additionally, investigators asked about disability level secondary to the headache, presence of headache at ED discharge, ED medications received and overall ED visit satisfaction. The study drug was dexamethasone 24 mg IV.

Based upon an effect size of 22.5% (recurrence 45% in placebo vs. 22.5% in dexamethasone arm), 80% power and 2-sided $\alpha = .05$, investigators calculated a sample size of 108 and added in a 10% drop out rate.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. "After consent, patients would be assigned a study number and corresponding study packet". (p. 126)
2.	Was randomization concealed (blinded)?	Yes. "The patient, all individuals providing patient care, and associated research personnel were blinded to which study drug the patient received." (p. 126)
3.	Were patients analyzed in the groups to which they were randomized?	No clear intention-to-treat statement.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. No significant differences were noted between placebo and dexamethasone group. (Table 2, p. 126) "Both groups showed no differences in regard to age, sex, severity of headache on presentation, frequency of migraine attacks, and frequency of ED visits for those attacks. Initial functional disability was also similar between both groups. The data also identified no significant difference in the amount or type of medication received between the 2 groups." (p. 127)
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	No – see above.
2.	Were clinicians aware of group allocation?	No – see above.
3.	Were outcome assessors aware of group allocation?	No – see above.
4.	Was follow-up complete?	Among 115 enrolled patients, 16 were lost to follow-up at 3-days and another 3 were lost at 30-days leaving a total of 96 for analysis.

II.	What are the results (answer the questions posed below)?	
1.	How large was the treatment effect?	• Populations mean age 36 with ~ 80% female and 9/10 initial headache severity rating. • More steroid patients received narcotics (34% vs. 42%) • Dexamethasone showed non-significant improvement in headache resolution while in the ED (35.7% placebo vs. 47.3%, p= 0.305). • At 3-days dexamethasone showed *non-significant* decrease in post-ED discharge headache recurrence: 42.9% placebo (95% CI 29.1% - 57.8%) vs. 36.8% (95% CI 25.5% - 49.9%) p=0.6776. • No difference between groups regarding ED satisfaction or 3-day functional disability. • Dexamethasone patients reported significantly more dizziness at 3-days (16.1% vs. 2.5%, p=0.04) but not at 30-days. • A non-significantly increased proportion of dexamethasone subjects reported no disability at 3-days (55% placebo vs. 70% dexamethasone), a trend that did not persist to 30-days (70% placebo vs. 66% dexamethasone). • Similarly, headache recurrence rate differences became less marked at 30-days: 47% placebo, 43% dexamethasone. • When analyzing only those with headache resolution at ED discharge, no significant differences were noted 3-day headache recurrence: placebo 80% with no headache vs. 75% dexamethasone, p=0.7836.

2.	How precise was the estimate of the treatment effect?	95% CIs widely overlap.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Yes. ED patients with migraine headaches at two Detroit hospitals.
2.	Were all clinically important outcomes considered?	Yes, including potential adverse effects.
3.	Are the likely treatment benefits worth the potential harm and costs?	No, not based on this trial which demonstrated no benefit for IV dexamethasone to prevent migraine recurrence.

Limitations

1) **Significant lost to follow-up with twice as many lost to follow-up in the placebo group. Investigators could have conducted a sensitivity analysis to determine whether results would change if best-case and worst- case scenarios met by those lost. For example, if all 11 placebo subjects lost had headache recurrence at 3-days and all 5 dexamethasone had no headache recurrence the results would look like this:**

	Headache @ 3-days			
	Yes	**No**	**Total**	**ARR 0.23 (0.05-0.40)**
Dexamethasone	**21**	**42**	**63**	**NNT 4.3 (95% CI 2.5-20)**
Placebo	**31**	**24**	**55**	**p = 0.016**

2) **Small sample size with less than anticipated treatment effect so perhaps underpowered. Future larger trials or meta-analyses may help determine whether IV dexamethasone has lesser treatment effect for preventing migraine recurrence.**

3) **No clear statement of intention-to-treat analysis.**

4) **Routine headache care not standardized so may represent a confounding variable, although this design augments external validity and is a more pragmatic clinical trial design.**

Bottom Line

A single dose of dexamethasone (24 mg IV) in ED patients with International Headache Society defined migraine headache provides a non-significant trend towards headache resolution prior to discharge (ARR= 11.6%, p=0.305) and decreased 3-day headache recurrence (ARR = 6.1%, p=0.678). These trends in an underpowered sample size with smaller than expected treatment effect and no sensitivity analysis suggest that further research is required before steroids to prevent migraine recurrence can be advocated or discounted.