Journal Club Eastern Virginia Medical School
Therapy Article

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CITATION: Gaffigan et al, **A Randomized Controlled Trial of Intravenous Haloperidol Vs. Intravenous Metoclopramide for Acute Migraine Therapy in the Emergency Department.** The Journal of Emergency Medicine, Vol. 49, No. 3, pp. 326-334, 2015

I. **WHAT IS BEING STUDIED?**	
1. Study Objective	This study compares the "efficacy of intravenous haloperidol with intravenous metoclopramide (both in combination with diphenhydramine for the treatment of acute migraine in the ED" .
2. Study Design	A prospective, double-blinded, randomized control trial on a convenience sample of 64 adults aged 18-50 years with migraine headache presenting from June 2013-February 2014 at a DOD teaching hospital with 75,000 annual ED visits.
3. Inclusion Criteria	Adult patients between 18 – 50 years presenting with their "typical migraine headache" and satisfying the Modified International Headache Society's criteria for migraine. (At least 2 of the following: Unilateral location, Throbbing character, worsening pain with routine activity, Moderate to Severe intensity, PLUS at least one of the following, nausea or vomiting, and photophobia or phonophobia.) Note: No mention of patients having a prior history or established diagnosis of migraine headaches or how they determined typicality of headache.
4. Exclusion Criteria	1) Known hypersensitivity to haloperidol, metoclopramide, of diphenhydramine, 2) history of heart disease, 3) Electrolyte abnormalities on I-stat testing, 4) Use of pro-dysrhythmic drugs, 5) Prolonged QT interval (>450ms), 6) Use of ergotamine derivative, triptan, or dopamine blocking agent in past 24h, 7) Hypothyroidism, 8) MAOI administration within 2 weeks, 9) Concurrent management for hemiplegic or basilar migraine or known neurologic disorder, 10) Severe hepatic impairment,

	11) Pregnant, 12) Breastfeeding, 13) History of cancer (except non-melanoma skin cancer), 14) Previous involvement in study, 15) Febrile to 38.06 or greater on presentation, 16) Any indication for further diagnostic testing (LP or CT scan), no mention as to whether this was determined before or after entry into study, 17) Presenting headache is different from patient's typical migraine headache Note: No mention was made as to how many people actually presented to the ED with headache during this time, just migraine headache. 138 people presented with "migraine headache," and 64 of these patients were enrolled.
5. Interventions Compared	Metoclopramide 10 mg IV versus haloperidol 5 mg IV. Both were paired with 25mg of IV diphenhydramine and a bolus infusion of 1000 ml of NaCl.
6. Outcomes Evaluated	1) Primary Outcome – Pain relief using a visual analog scale (VAS) within 80 minutes of treatment. A difference in 13mm between the 2 groups was thought to be significant. 2) Secondary Outcome Measures – time to maximal pain relief, use of rescue medication, VAS measurement of nausea, sedation, and anxiety/restlessness, QT intervals prior to and after treatment, response to follow-up questionnaire
II. **Are the results of the study valid**	
1. Was the assignment of patients randomized?	Yes. They used a random numbers generation maintained in their pharmacy.
2. Was randomization concealed (blinded)?	Yes.
3. Were patients analyzed in the groups to which they were randomized?	Yes.
4. Were patients in the treatment and control groups similar with respect to known prognostic factors?	The only information provided in this study was percentage of women and age. The groups were similar in age, with the mean age being 29. The haloperidol group had more women, with women making up 87%

	and the metoclopramide group being made up of 76% women.
III. **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
2. Were clinicians aware of group allocation?	No
3. Were outcome assessors aware of group allocation?	Uncertain. They do not describe who did the telephone follow-up or if they were blinded to intervention arm.
4. Was follow-up complete?	No. Of the 64 patients, 43 were reached for follow-up. 74% of the haloperidol group was reached and 61% of the metoclopramide group. Combined loss to f/u was 33%.
IV. What were the results? Answer the questions posed below	
1. How large was the treatment effect? (Difference between treatment and control group).	For the primary outcome, there was no statistically significant difference between the haloperidol and metoclopramide group. Both achieved statistically significant pain reduction (haloperidol by 57mm on VAS and Metoclopramide by 49mm) ($p<0.01$). Time to relief was not statistically significant 55 minutes for the metoclopramide group, and 56 minutes for the haloperidol group ($p>0.05$). No statistically sig. differences in rates of nausea, restlessness, and sedation, discharge time from the ED or patient satisfaction. ($p>0.05$). There was a significant difference in the use of rescue medications. In the haloperidol group, 1 of 31 (3%) required rescue medication (ketorolac and methylprednisolone) and 8 of 33 (24%) of the participants in the metoclopramide group received rescue medication (7 with IV ketorolac and 1 with IV morphine). In terms of side effects, baseline sleepiness was reported more commonly in the haloperidol group ($p<0.02$). This appeared to actually improve with treatment., No

	other statistically significant side effects where noted between the groups. In regards to QTc intervals, ONLY 45% of subjects got post-treatment ECG's. The mean QTc at baseline were equal and normal for both groups and were not statistically significant post-intervention in those that were performed. Table 5 suggests that metoclopramide arm has a trend towards longer QT prolongation,12 Ms. vs. 4 mos. In follow-up, restlessness was the only statistically significant reported measure with a higher percentage of the haloperidol group (43% vs. 10% p<.015) The authors do not report time associated with restlessness in f/u and this was not significant during the ED treatment period.
2. What was the estimated treatment effect at a 95% confidence interval? (Precision)	There were no CI's reported in this study.
V. **Will the results help me in caring for my patients? (Applicable?)**	
1. Were the study patients similar to my patient?	Probably not. Their military demographic was young (29 y/o) and mostly female 52/64 (81%) who have less co-morbidities than our patient population.
2. Were all clinically important outcomes considered?	I would also be interested in studying the time until next migraine headache in these groups. Additionally, I would be interested in measuring effect of these medications on other associated migraine factors such as photophobia, phonophobia, and visual changes. An economic analysis that included cost or time lost from work was not included.
3. Are the likely treatment benefits worth the potential harm and costs?	Possibly. In a very restricted patient population (young females with typical migraine and no comorbidities). This study was not powered to detect differences in QT prolongation. This is a rare but potentially harmful effect. Unlikely that sixty patients provide sufficient evidence to conclude no effect on QTc prolongation.

Study Limitations

1) **Small sample size. Underpowered to conclude no harms.**
2) **Convenience sample. They don't report on total number of headache patients seen in their ED over the study period, which would help to define their actual treatment group more clearly. They excluded all patients who stated that the presenting headache "differed" (how did it differ was it a bit worse, maybe a bit more nausea?) from their typical migraine. This predisposes to selection bias and probably those with lesser headaches.**
3) **They did not report on their indications for use and what percent of their patients got CT's or LP's (selection bias).**
4) **Single center study with very limited demographic**
5) **Poor follow-up (67%) and poor repeat ECG rate.**
6) **No reporting of confidence intervals was made. It would appear that the confidence intervals would have been too wide if they were included.**
7) **Study predominantly women**
8) **Medical history of subjects was not provided, particularly information on their migraine status (Were they diagnosed with migraine? Are they treated by a doctor for migraines? Do the patients just believe they have migraines?)**
9) **Patients that do not have a history of migraines may satisfy the Modified International Headache Society's criteria for migraine.**
10) **Their DoD database inly includes military hospitals and patients who presented to civilian hospitals would have been missed.**

Clinical Bottom Line:

I believe that this study does suggest that haloperidol may be another treatment option afforded us in the ED. Although the study was not adequately powered to detect QTc effects, it was not inferior to metoclopramide in symptom improvement in this patient population and may also reduce the need for rescue medication.