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A prospective, randomized, double-blind trial of intravenous chlorpromazine versus intravenous prochlorperazine for the treatment of acute migraine in adults presenting to the emergency department

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Conflict of interest statement

The authors whose names are listed above certify that they have no affiliations or involvement in any organisation or entity with any financial interest (such as honoraria, educational grants, memberships, employments, consultancies, stock ownership, or other equity interest) or non-financial interest such as personal or professional relationships, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Abbreviations: Emergency Department - ED, intravenous - IV, intramuscular – IM, coronavirus disease 2019 - COVID-19, identification - ID, numeric rating scale – NRS, standard deviation – SD, interquartile range – IQR, bootstrapped quantile regression - BSqreg, systolic blood pressure – SBP, confidence interval – CI, corrected QT interval – QTc.

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Abstract

Objective: To compare the efficacy of intravenous chlorpromazine versus intravenous prochlorperazine for the treatment of acute migraine in adults presenting to the Emergency Department.

Background: Migraine is a common, incapacitating neurological condition. Although chlorpromazine and prochlorperazine are known to be safe, efficacious treatments for migraine, they have never been directly compared.

Design: We performed a prospective, randomized, double-blind clinical trial at a tertiary hospital in Melbourne, Australia. Adults aged 18-65 years, who presented with migraine, were eligible for recruitment. Sixty-six were randomized to either chlorpromazine 12.5mg or prochlorperazine 12.5mg, both infused in 500mL of sodium chloride 0.9% over 30 minutes. Headache severity score, nausea severity score and the presence of photophobia and phonophobia were assessed at 0, 30, 60 and 120 minutes. Adverse effects and the need for rescue therapy were recorded. The primary outcome was a reduction in headache severity score from baseline at 60 minutes post commencement of the study medicine infusion.

Results: Sixty-five patients were included in the analysis. There was a median reduction in headache severity score at 60 minutes of 3.0 (IQR 1.0 – 4.0) in the chlorpromazine arm versus 2.0 (1.0 – 4.0) in the prochlorperazine arm (median difference -0.5 (95% confidence interval, -1.9 to 0.9)). We saw no evidence of a difference in secondary outcomes at 30, 60, or 120 minutes. Side effects were reported in 16/32 (50%) patients in the chlorpromazine group versus 7/33 (21%) in the prochlorperazine group (P=0.020). Rescue therapy was required in 12/33 (36%) patients in the chlorpromazine group versus 7/32 (22%) in the prochlorperazine group (P =0.277).

Conclusions: Both chlorpromazine and prochlorperazine are efficacious treatments for acute migraine in adult patients presenting to the Emergency Department. This trial found no evidence of superiority of either agent over the other. Caution should be used when prescribing these medicines in the borderline hypotensive patient; in that circumstance prochlorperazine should be preferentially used.

Introduction

Migraine is a common and incapacitating neurological condition. In the Global Burden of Disease survey (2016), migraine was ranked as the sixth most prevalent chronic disorder in the world and the second commonest cause of years of life lived with disability[1]. An estimated 1.04 billion individuals suffered from migraine in 2016; and 18% of women and 6% of men will suffer migraines each year[1,2].

Patients presenting to the Emergency Department (ED) with migraine have often failed outpatient therapy and may exhibit severe and persistent symptoms[3]. Oral therapy is frequently ineffective for these patients due to associated vomiting, typically requiring parenteral therapy in the ED[4]. Optimal treatment should work quickly and have no significant or long-lasting side effects. This allows patients to obtain relief from their symptoms and to be discharged from the ED in a timely fashion.

Since the 1980s, the anti-migraine effects of the phenothiazine medicines, prochlorperazine and chlorpromazine have been recognised[5,6,7]. Both medicines are relatively cheap compared to newer anti-migraine medicines, are readily available in Australasian EDs and have been subject to multiple studies[3-13]. These agents have been shown to be safe and effective in migraine treatment, when compared to placebo[7,8] and other pharmaceutical interventions[3,4,9-13]. However, the direct efficacy of prochlorperazine versus chlorpromazine as treatment for acute migraine has never been studied in adults.

The lack of direct comparative data in adults makes formulation of treatment guidelines difficult. No consensus on the optimal choice between prochlorperazine and chlorpromazine exists. Direct comparison is difficult as previous studies have utilised different scoring techniques, doses, outcomes and end points. In addition, migraineurs presenting to the ED often do not expect to be completely pain free but wish for partial symptom relief, making studying outcomes difficult[14].

Pooled effectiveness data from ED studies have shown chlorpromazine to be clinically successful in 85% of patients and IV (intravenous) or IM (intramuscular) prochlorperazine to be successful in 71%[15]. However, two recent review articles[16,17] published on the management of migraine showed different results. Orr *et al*[16] reviewed the evidence surrounding parenteral therapies for acute migraine. They sought to address which injectable medications should be considered first line for adults who present to ED with acute migraine.

They recommended the use of IV metoclopramide, IV prochlorperazine or subcutaneous sumatriptan. They commented that IV chlorpromazine may be offered. The second review article, by Marmura *et al*[17], gave both chlorpromazine and prochlorperazine level B status; medicines which are probably effective, based on available evidence.

Thus, there is no clear consensus on what is the most efficacious treatment for acute migraine from the existing literature for patients presenting to the ED. Given its superior success rate from pooled effectiveness data[15] we hypothesised that IV chlorpromazine with IV fluid would be more efficacious than IV prochlorperazine with IV fluid, for the treatment of acute migraine in adult ED patients.

In this prospective, randomized, double-blind clinical trial we aimed to compare the efficacy of intravenous chlorpromazine versus intravenous prochlorperazine, both with IV fluid, for the treatment of acute migraine in adults presenting to the Emergency Department.

Methods

Study design

This was a prospective, randomized, double-blind clinical trial comparing the efficacy of chlorpromazine with IV fluid versus prochlorperazine with IV fluid for the management of acute migraine in adults aged 18-65 years. This single centre study was performed in the Emergency Department at Austin Health in Melbourne, Victoria, Australia. Austin Health is a large tertiary facility, offering a wide range of clinical services. The ED receives over 90,000 presentations per annum. The project received ethical approval from the Austin Health Human Research Ethics Committee and was registered with the Australian New Zealand Clinical Trials Registry (ID No. ACTRN12618000138280). The trial was conducted according to the original protocol and no changes were made after initiation of the trial.

Participants

Eligible participants needed to meet a modified version of the International Classification of Headache Disorders diagnostic criteria for migraine with or without aura[18]. Participants also needed to meet Austin Health's ED migraine management guideline to be eligible for

inclusion. This guideline incorporates both the International Classification of Headache Disorders diagnostic criteria, as well as the exclusion criteria listed in below. We used a modified version of the diagnostic criteria for migraine without aura, since we hypothesised that few patients would be able to recall the exact number of migraines they had previously suffered, and therefore enrolled patients in whom this was not the first episode of migraine. This modification has been employed in previous studies[11].

Excluded were patients with first headache of this nature; worst headache they had suffered; new onset headache after age 50 (if not previously investigated); headache with an unusual or atypical character that did not fulfil the criteria for migraine; migraine with associated confusion or loss of consciousness; seizure; fever, myalgia or suspicion of meningism on exam; abnormal neurological exam; temporal artery tenderness; an allergy or contra-indication to either study medicine; pregnancy or breastfeeding; or Parkinson's disease.

Participants were enrolled over a 23-month period from April 2018 until the outbreak of the coronavirus disease 2019 (COVID-19) pandemic in March 2020. Patients were recruited 24 hours per day via direct referral from the treating physician and the triage nursing staff, and through monitoring the triage screen list during business hours.

Consent

Since ED patients with migraine are often considerably compromised by their symptoms (severe headache, photophobia, nausea and vomiting), a modified informed consent process was approved by the ethics committee. Eligible participants had the study explained to them by a study investigator or senior ED doctor (according to a verbal consent script). Informed verbal consent to participate was sought and documented. Patients were given a written patient information and consent form at the time of verbal consent, and were asked to read and sign this at any time prior to discharge from the ED. We hoped that this would reduce selection bias as we expected that a substantial proportion of patients would decline to participate if the standard informed, signed consent process was required prior to their migraine symptoms being treated.

Randomization and allocation concealment

Study packs were assembled by the ED pharmacy department. Packs came in opaque envelopes with concealed contents. Each pack contained 2 data collection sheets labelled with the study identification (ID) number, and another opaque envelope which was labelled "To be opened by the nurse in charge/a nurse not involved with the patient care". This contained a vial of study medicine and instructions on how to make up the infusion, as well as a label for the infusion bag of 500mL sodium chloride 0.9% stating "patient is enrolled in a clinical trial, this pack contains sodium chloride 0.9% with either 12.5mg chlorpromazine or 12.5mg prochlorperazine". To maintain blinding of the treating staff, this nurse was not permitted to divulge the identification of the medication.

Study packs were randomized by the pharmacy department using a random number generator in a 1:1 ratio in blocks of 12. They were labelled sequentially and the treating doctor was advised to take the lowest numbered pack available. It was not possible to determine the allocation or contents of the pack from the exterior.

The pharmacy department kept a list of the study ID numbers with the allocated study drug. The trial investigators, recruiting physician, treating physician, treating nurse and patient were all blinded to the contents of the study pack, the treatment arm, and the study drug allocation list.

Interventions

Patients received either prochlorperazine 12.5mg in 500mL sodium chloride 0.9% or chlorpromazine 12.5mg in 500mL sodium chloride 0.9%, with each infused over 30 minutes.

Assessment of Outcomes

At time 0, 30, 60 and 120 minutes after commencement of the study infusion the following were recorded: headache severity score; nausea severity score; presence of photophobia and phonophobia; bedside observations including heart rate, blood pressure, respiratory rate,

oxygen saturations and temperature. At 120 minutes, a postural blood pressure recording was performed. Side effects, and the need for rescue therapy at 60 and 120 minutes were recorded. At 120 minutes medical staff were asked to complete a modified Prince Henry Hospital akathisia rating scale.

The headache severity score was recorded using a numeric rating scale (NRS) for pain. This is an 11-point scale (range 0-10) for participant self-reporting of pain. It has been used in previous migraine studies[9], has been validated[19] and has been subject to evaluation through systematic literature review[20].

The NRS for nausea is an 11-point scale (range 0-10) for patient self-reporting of nausea and vomiting. This has been previously validated as a tool for nausea and vomiting assessment in the ED[21].

A modified Prince Henry Hospital akathisia rating scale was chosen to assess for the presence of akathisia. This rating scale was originally developed by Sachdev in 1994[22], and has since been modified and made more user friendly. It has been used in previous ED studies of akathisia[23,24].

Primary and secondary outcomes

The primary outcome measure was change in headache severity score 60 minutes post commencement of the study medicine infusion. Secondary outcomes included change in headache severity score at 30 and 120 minutes, the change in nausea severity score at 30, 60 and 120 minutes, the reduction in presence of photophobia, and phonophobia at 30, 60 and 120 minutes post study medicine infusion, the presence of side effects including hypotension, postural hypotension, dystonic reactions and akathisia, and the number of patients from each group requiring rescue therapy.

Rescue therapy

After assessment of primary and secondary outcomes at 60 minutes participants still suffering from severe migraine symptoms despite treatment could be given rescue therapy initiated by

their treating doctor. This could be any medication, except either study drug. This was recorded on the data collection sheet. At 120 minutes after cessation of the trial, if the participants symptoms were not sufficiently relieved by the study medication, the treating doctor was allowed to break the blinding to determine which arm of the trial the patient was allocated to, and administer rescue therapy at their discretion. Again, this was recorded on the data collection sheet.

Sample size, justification and power calculation

The sample size was based upon the primary endpoint of NRS pain score at 60 minutes post-administration of the study medicine. A minimum sample size of 33 participants in each group was required to demonstrate a clinically significant difference in the mean pain scores of 2 at 60 minutes (expected standard deviation (SD) 2.5, based on previous studies[3,4,25]) with a two-sided alpha value of 0.05 and power of 90%. This number was rounded up to 35 participants in each group (total 70) to account for the estimation of the SD and to afford additional power to the study.

Statistical methods of data analysis

Descriptive statistics (mean, median, interquartile range (IQR), SD, and percentages) were calculated using IBM SPSS Statistics Version 25 (SPSS Inc., Chicago, Il) and Microsoft Excel (Microsoft Office Home and Student 2019, Microsoft, Redmond, WA,).

The interval variable of NRS for the primary and secondary outcome of reduction in headache severity score and reduction in nausea severity score at 30, 60 and 120 minutes did not have a normal distribution therefore median regression adjusted for baseline headache score and baseline nausea score, using bootstrapped quantile regression was used. Additional post-hoc sensitivity analyses on the primary outcome of reduction in headache severity score at 60 minutes adjusted for the baseline variables of age and length of headache were conducted using bootstrapped quantile regression, due to the observed imbalance in these baseline characteristics between the two groups . Both were performed using Stata IC 15 (StataCorp, Stata Statistical Software, College Station, TX).

The secondary outcomes of the reduction in the presence of photophobia and phonophobia at 30, 60 and 120 minutes were nominal variables and were analysed using Pearson's Chi-squared test (two-tailed test).

The secondary outcomes of the presence of side effects including hypotension, postural hypotension, dystonic reactions and akathisia, and the number of patients from each group requiring rescue therapy were nominal variables and were analysed using Fisher's Exact test.

The secondary outcome of objective and subjective akathisia score and the secondary outcome of mean length of stay were continuous variables and were both evaluated using the Student's Independent t-test (two-tailed).

All analyses were performed in IBM SPSS Statistics Version 25, unless otherwise stated, and a *P*-value of < 0.05 was defined to be statistically significant.

Results

Due to the outbreak of the COVID-19 global pandemic, recruitment was halted in March 2020. Sixty-six patients were recruited in total, 33 were randomized to receive prochlorperazine and 33 to receive chlorpromazine. One patient withdrew from the chlorpromazine group after initiation of treatment. A flow chart of patients flow through the trial is shown in Figure 1. Baseline characteristics between the two groups are shown in Table 1.

Primary outcome data is shown in Table 2. There was a median reduction (IQR) in headache severity score at 60 minutes, adjusted for baseline headache score, of 3.0 (1.0 – 4.0) in the chlorpromazine group vs. 2.0 (1.0 – 4.0) in the prochlorperazine group (median difference -0.5, 95% CI -1.9 to 0.9, *P*=0.468). No statistically significant effect between the groups was identified.

Post hoc additional sensitivity analyses adjusted for age and headache length were performed. There was no significant difference in the primary outcome of reduction in headache severity score at 60 minutes after adjusting for age, median difference -1.0 (95% CI -2.8 to 0.8,

P=0.271); or for headache length, median difference -1.0 (95% CI -2.7 to 0.7, *P* =0.232) for chlorpromazine vs. prochlorperazine.

No significant differences in the secondary outcomes of reduction in headache severity score at other time points; or reduction in nausea severity score (Table 2.) or reduction in photophobia and phonophobia at any time point between the two medicines (Table 3.) were identified.

Significantly more patients in total experienced side effects (Table 4.) in the chlorpromazine group (16/32 (50%)) versus the prochlorperazine group (7/33 (21%), p=0.020), with significantly more patients in the chlorpromazine group experiencing a drop in systolic blood pressure of greater than 20mmHg, 8 (25%) vs 2 (6%) (p = 0.044). Four (13%) patients developed postural hypotension (defined as a drop in systolic blood pressure of more than 20mmHg on standing), and 2 patients had syncopal events in the chlorpromazine group (versus 0 in the prochlorperazine group), although neither result reached significance. 12/33 (36%) patients in the prochlorperazine arm versus 7/32 (22%) patients in the chlorpromazine arm required rescue therapy (*P* =0.277). One patient in each arm required benztropine for akathisia. No difference in akathisia scores between the groups (Table 5) was observed. Only 25 patients were assessed for akathisia, as patients were often discharged either overnight before an akathisia assessment was performed, or by junior staff who were not aware of the requirement for akathisia assessment prior to discharge.

No difference in length of stay between the two arms was observed; patients in the chlorpromazine arm spent a mean duration of 472 minutes in hospital vs. 427 minutes in the prochlorperazine arm (mean difference 45.2 minutes, 95% CI -75 to 165 minutes).

Discussion

This randomised double-blind trial found no evidence for a difference in efficacy between intravenous chlorpromazine and intravenous prochlorperazine, with IV fluid, in the reduction in headache severity score in adult patients presenting to the ED with acute migraine. Neither medicine showed a significant greater reduction in nausea severity score at any time point, nor a significant reduction in photophobia or phonophobia when compared against the other.

Treatment with chlorpromazine was associated with significantly more side effects including hypotension and syncope, which may explain why patients in the chlorpromazine arm had a slightly longer mean length of stay in hospital. We would advise treating physicians to use caution if prescribing chlorpromazine to borderline hypotensive patients, and suggest prochlorperazine be used instead.

As prochlorperazine was similar to chlorpromazine in reduction in headache severity score, we believe that further investigation into migraine treatment with phenothiazines is warranted. It is recommended that chlorpromazine be administered concomitantly with IV fluids, due to its hypotensive effects[6,8], however prochlorperazine can be given IM. Intramuscular treatment would not require IV access, or admission for administration of an IV infusion. We hypothesize this may be cost-saving, allow earlier discharge from the ED, as well as negating the need for intravenous access, with all of its associated complications. Since patients with migraine have often had reduced oral intake some of their symptoms could be attributed to dehydration; therefore, IV fluid administration may augment the anti-migraine effects of medications given to treat migraine. Further investigation is recommended.

Limitations

Selection bias may have been introduced during the recruitment of patients. During business hours (Monday to Friday, 0800 until 1600), we actively recruited patients by monitoring the triage screen for potential candidates, however out of hours we relied on the triage nurse or treating doctor to refer patients. There were regular updates, emails and teaching sessions on the study protocol to encourage referrals out of hours, however given the high turnover of junior doctors we may have missed recruiting a proportion of patients on weekends and overnight, and this was potentially reflected in our long period of recruitment. Patients with more severe symptoms, may have been less likely to be referred, given the perceived potential delay to treatment and the wish of treating physicians to relieve patients' symptoms rapidly. We tried to reduce this bias by using a modified consent process of verbal consent initially. In addition, during the study period the Victorian Ambulance Paramedics began to treat patients with headache with prochlorperazine. This meant that at least 5 patients were not eligible for participation in this study as they received IM prochlorperazine as part of

their pre-hospital management. Since these patients arrived by ambulance, we can hypothesize they had significant symptoms.

We did not meet our minimum sample size of 33 participants in each arm as the trial was stopped early due to the COVID-19 pandemic. However, the difference between the groups in the primary study outcome was less than what was deemed, *a priori*, to be a clinically significant difference.

The investigators chose not to include a placebo arm. Patients with migraine who present to the ED often experience severe symptoms. Contrary to the popular belief that IV fluid is an effective treatment for the nausea and vomiting related dehydration and headache in migraine, 2 studies have shown that IV fluid alone is not effective as a treatment for migraine[26,27]. Therefore we felt that recruitment would be significantly limited if we chose to include a placebo arm with patients only receiving IV fluid.

In this trial we only included patients aged 18-65. The side effects of hypotension, postural hypotension, and syncope may be more common in ages outside the range included in the study population, due to their susceptibility, co-morbidities and medication history. Caution should be used when prescribing the study medicines to patients outside the study population age range.

In our institution we do not routinely monitor or check a patient's corrected QT interval (QTc) prior to, during, or after administration of either study drug. Although chlorpromazine is known to prolong the QTc, cases of Torsades de Pointes and ventricular arrhythmias are usually in the setting of much higher daily doses, or in the presence of other QTc prolonging medications[28]. Caution should be used when prescribing chlorpromazine to patients with a known history of prolonged QTc, or if they are taking other QTc prolonging medications.

Although the phenothiazines have been shown to be efficacious treatments for migraine, their use is limited by the need for observation for side effects, and the need for appropriate supervised transport home. This may limit their use in a busy ED setting.

Chlorpromazine is used 'off-label' for the treatment of migraine in Australia and therefore there is no agreed standard dose. Previous trials have used weight-based dosing regimens of

0.1 mg/kg[4,8] as well as fixed doses of 12.5 mg, repeated as needed[10], or 25 mg[12]. As we were unable to perform weight-based dosing and keep this trial double-blinded, we opted for a chlorpromazine dose of 12.5 mg. This may have meant that patients with a larger body habitus were under-dosed, and therefore did not obtain the expected treatment effect. However, it is likely patients would have experienced more side effects at larger doses. Prochlorperazine is approved for use in nausea and vomiting at a dose of 12.5mg IM in Australia. It is not approved for use as an IV medication, however previous trials have used 10mg IV for the treatment of migraine[3,9,11,13]. Prochlorperazine is presented as 12.5mg/mL in Australia, this is the dose routinely used in Australia EDs, and thus the dose we chose for this trial. This may have meant that patients were over-dosed compared to previous trials and therefore achieved greater symptomatic relief.

Previous evidence also highlights the issue of prochlorperazine's stability in sodium chloride 0.9%. In 1994 El-Yazigi et al[29] found that prochlorperazine lost approximately 21% of its original amount in sodium chloride 0.9% within 1.75 hours. In our study, while the infusions were made immediately prior to use, they were infused over a 30-minute period. Therefore, some prochlorperazine may have been lost during this period.

Conclusion

Both chlorpromazine and prochlorperazine are efficacious medicines for the treatment of acute migraine in adult patients presenting to the ED. Neither showed a greater clinical improvement in reduction in headache severity score over the other. Chlorpromazine was associated with more side effects, and patients treated with prochlorperazine required more rescue therapy.

Either medicine may be used to treat adult patients with migraine although chlorpromazine may be best avoided if the patient has low blood pressure. Further investigation into the use of IM prochlorperazine for the treatment of migraine is recommended.

References:

1. GBD 2016 Headache Collaborators. Global, regional and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*. 2018; 17:954-976.

2. Lipton RB, Stewart, WF, Diamond D, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache*. 2001; 41: 646-57

3. Miller MA, Levsky ME, Enslow W, Rosin A. Randomised evaluation of octreotide vs prochlorperazine for ED treatment of migraine headache. *The American Journal of Emergency Medicine.* 2009; 27;160-164.

4. Cameron JD, Lane PL, Speechley M. Intravenous chlorpromazine versus intravenous metoclopramide in acute migraine headache. *Academic Emergency Medicine.* 1995; 2:597-602.

5. Kain BF. Non-narcotic relief of acute migraine. *Canadian Family Physician*. 1982: 28: 2037-2038.

6. Lane RL, Ross MD. Intravenous chlorpromazine - preliminary results in acute migraine. *Headache.* 1985; 25: 302-304.

7. Jones J, Sklar D, Dougherty J, White W. Randomised double blind trial of intravenous prochlorperazine for the treatment of acute headache. *JAMA.* 1989; 261:1174-1176.

8. Bigal ME, Bordini CA, Speciali JG. Intravenous chlorpromazine in the emergency department treatment of migraines: a randomised controlled trial. *The Journal of Emergency Medicine.* 2002; 23:141-148.

9. Friedman BW, Esses D et al. A randomised controlled trial of prochlorperazine versus metoclopramide for treatment of acute migraine. *Annals of Emergency Medicine*. 2008; 52:399-406.

10. Kelly AM, Ardagh M, Curry C, D'Antonio J, and Zebic S. Intravenous chlorpromazine versus intramuscular sumatriptan for acute migraine. J*ournal of Accident and Emergency Medicine*. 1997; 14:209-211.

11. Kostic MA, Gutierrez FJ, Rieg TS, Moore TS, Gendron RT. A prospective, randomised trial of intravenous prochlorperazine versus subcutaneous sumatriptan in acute migraine therapy in the Emergency Department. *Annals of Emergency Medicine.* 2010; 56:1-6.

12. Shrestha M, Singh R, Moredon J, Hayes JE. Ketoralac versus chlorpromazine in the treatment of acute migraine without aura. *Archives of Internal Medicine.* 1996; 156:1725-1728.

13. Coppola M, Yealy DM, Leibold RA. Randomised, placebo-controlled evaluation of prochlorperazine versus metoclopramide for emergency department treatment of migraine headache. *Annals of Emergency Medicine.* 1995; 26:541-546.

14. Friedman BW, Bijur PE, Lipton RB. Standardising emergency department based migraine research: an analysis of commonly used clinical trial outcome measures. *Acad Emerg Med.* 2010; 12:72-92.

15. Cameron P, Jelink G, Kelly AM, Brown C and Little M. Editors: Cameron, P and Little M. *Textbook of Adult Emergency Medicine.* Churchill Livingston, London, 2014.

16. Orr SL, Friedman, BW, Christie S et al. Management of adults with acute migraine in the emergency department: The American Headache Society evidence assessment of parenteral pharmacotherapies. *Headache*. 2016;56:911-940.

17. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: The American Headache Society evidence assessment of migraine pharmacotherapies. *Headache*. 2015; 55:3-20.

18. International Headache Society (2016). *The International Classification of Headache Disorders. 3rd Edition*. Accessed at https://www.ichd-3.org/ on 25/2/17.

19. Bijur PE, Latimer CT, Gallagher J. Validation of a verbally administered numerical rating scale of acute pain for use in the Emergency Department. *Academic Emergency Medicine*. 2003; 10(4):390-392.

20. Hjermstad MJ, Fayers PM, Haugen DF et al. Studies comparing numerical rating scales, verbal rating scales and visual analogue scales for assessment of pain intensity in adults: a systemic literature review. *Journal of Pain and Symptoms Management*. 2011;41:6: 1-73-1093.

21. Meek R, Egerton-Warburton D, Mee MJ, Braitberg G. Measurement and monitoring of nausea severity in emergency department patients: A comparison of scales and exploration of treatment efficacy outcome measures. *Academic Emergency Medicine* 2015;22: 685-693.

22. Sachdev P. A rating scale for acute drug-induced akathisia: development, reliability, and validity. *Biological Psychiatry.* 1994;15,35(4): 263-271.

23. Leow FHP, Knott JC, Abu Hassan F et al. Risk and severity of akathisia following administration of metoclopramide in the emergency department. *Journal of Pharmacy Practice and Research.* 2006;36(3): 194-198.

24. Vinson DR. Diphenhydramine in the treatment of akathisia induced by prochlorperazine. *The Journal of Emergency Medicine.* 2004;26(3): 265-270.

25. Lane PL, McLellan BA, Baggoley CJ. Comparative efficacy of chlorpromazine and meperidine with dimenhydrinate in migraine headache. *Annals of Emergency Medicine.* 1989; 18:360-365.

26. Edward J, Balbin B, Nerenberg R et al. Intravenous fluids for migraine: a post hoc analysis of clinical trial data. *The American Journal of Emergency Medicine.* 2016; 34(4):713-716.

27. Richer L, Craig W, Rowe B. Randomized controlled trial of treatment expectation and intravenous fluid in pediatric migraine. *Headache*. 2014; 54(9):1496-1505.

28. Hoehns JD, Stanford RH, Geraets DR et al. Torsades de Pointes associated with chlorpromazine: Case report and review of associated ventricular arrhythmias. *Pharmacotherapy*. 2001; 21(7):871-883.

29. El-Yazigi A, Wahab FA, Afrane B. Stability study and content uniformity of prochlorperazine in pharmaceutical preparations by liquid chromatography. *Journal of Chromatography A*. 1995; 690:71-76.

Tables and Figures:

Table 1. Baseline characteristics on arrival to ED.

	Chlorpromazine (n=32)	Prochlorperazine (n=33)
Age, years, mean ± SD	36.7 ± 10.7	42.5 ± 11.8
Female, n (%)	24 (75)	29 (88)

No past medical history (except migraine), n (%)	17 (53)	17† (55)
No regular medications, n (%)	18 (56)	13† (42)
No medication taken before trial, n (%)	5 (16)	3† (10)
Pain score on arrival, mean ± SD	7.2 ± 1.7	7.3 ± 1.8
Nausea and vomiting present, n (%)	23 (72)	18† (58)
Presence of photophobia, n (%)	24 (75)	26 (79)
Presence of phonophobia, n (%)	14 (44)	15 (45)
Aura present, n (%)	16 (50)	14† (45)
Duration of headache, minutes, median (IQR)	807 (433 – 6840)	2880 (883 - 4680)‡

† Not documented for 2 patients

‡ Not documented for 3 patients

Table 2. Primary and secondary outcome results for reduction in headache and nausea severity scores adjusted for baseline score

	Chlorpromazine (n = 32)	Prochlorperazine (n = 33)	Baseline-adjusted median difference between groups (95% CI)	*P-value*
Median (IQR) reduction in headache severity score at:				
30 minutes †	1.0 (0.0 – 2.0)	2.0 (0.8 – 2.5)	0.5 (-0.3 – 1.3)	0.213
60 minutes	3.0 (1.0 – 4.0)	2.0 (1.0 – 4.0)	-0.5 (-1.9 – 0.9)	0.468
120 minutes ‡	4.0 (3.0 – 6.5)	3.0 (1.9– 6.0)	-1.1 (-3.2 – 0.9)	0.264

Median reduction (IQR) in nausea severity score at:				
30 minutes [§]	0.0 (0.0 – 2.0)	0.0 (0.0 – 1.9)	0 (-0.03 – 0.03)	> 0.999
60 minutes [¶]	0.5 (0.0 – 3.0)	0.0 (0.0 – 4.0)	0 (-0.1 – 0.1)	> 0.999
120 minutes [|]	0.5 (0.0 – 4.0)	1.0 (0.0 – 5.0)	*	

Data analysed using median regression adjusted for baseline headache and nausea severity scores using bootstrapped quantile regression (BSqreg) based on 500 bootstrap samples

[†] 1 missing from chlorpromazine group

[‡] 3 missing from chlorpromazine group and 3 missing from prochlorperazine group

[§] 2 missing from chlorpromazine group and 1 missing from prochlorperazine group

[¶] 2 missing from each group

[|] 4 missing from chlorpromazine group and 4 missing from both groups

* At time 120 minutes the statistical model did not achieve convergence

Table 3. Secondary outcome results for reduction in photophobia and phonophobia

Outcome	Chlorpromazine (n=32)	Prochlorperazine (n=33)	*P-value*
Number of patients with photophobia at:			
0 minutes, n (%)	24 (75)	26 (79)	0.717
30 minutes, n (%)[†]	17 (57)	21 (64)	0.572
60 minutes, n (%)[‡]	13 (43)	15 (50)	0.527
120 minutes, n (%)[§]	9 (31)	10 (34)	0.780
Number of patients with phonophobia at:			
0 minutes, n (%)	14 (44)	15 (45)	0.890
30 minutes, n (%)[†]	8 (27)	12 (36)	0.409
60 minutes, n (%)[‡]	9 (30)	11 (37)	0.587

120 minutes, n (%)§	5 (17)	7 (23)	0.517

Data analysed using Pearson's Chi-squared test

† Not documented for two patients in chlorpromazine arm

‡ Not documented for two patients in chlorpromazine arm, and three patients in prochlorperazine arm

§ Not documented for three patients in chlorpromazine arm and three patients in prochlorperazine arm

Table 4. Side effects and need for rescue medication

Side effect	Chlorpromazine (n=32)	Prochlorperazine (n=33)	*P-value*
Hypotension, SBP† < 90 mmHg, n (%)	2 (6)	1 (3)	0.613
Drop in SBP† > 20 mmHg, n (%)	8 (25)	2 (6)	0.044*
Postural hypotension (drop in standing SBP >20 mmHg), n (%)	4 (13)	0 (0)	0.053
Syncope, n (%)	2 (6)	0 (0)	0.238
Restlessness, n (%)	2 (6)	2 (6)	0.999
Drowsiness/lethargy, n (%)	4 (13)	3 (9)	0.708
Required benztropine for akathisia, n (%)	1 (3)	1 (3)	0.999
Number of patients requiring rescue therapy, n (%)	7 (22)	12 (36)	0.277

Data analysed using Fisher's Exact test

* Significant at $P < 0.05$

† Systolic Blood Pressure (SBP)

Table 5. Objective and subjective akathisia score			
	Chlorpromazine (n=25)	Prochlorperazine (n=25)	Mean difference (CI)
Mean objective akathisia score†	0.68	0.36	0.32 (-0.59 – 1.23)
Mean subjective akathisia score†	0.64	0.60	0.04 (-1.14 – 1.22)

Data analysed using The Student's Independent t-test

† Documented for 25 patients in each arm

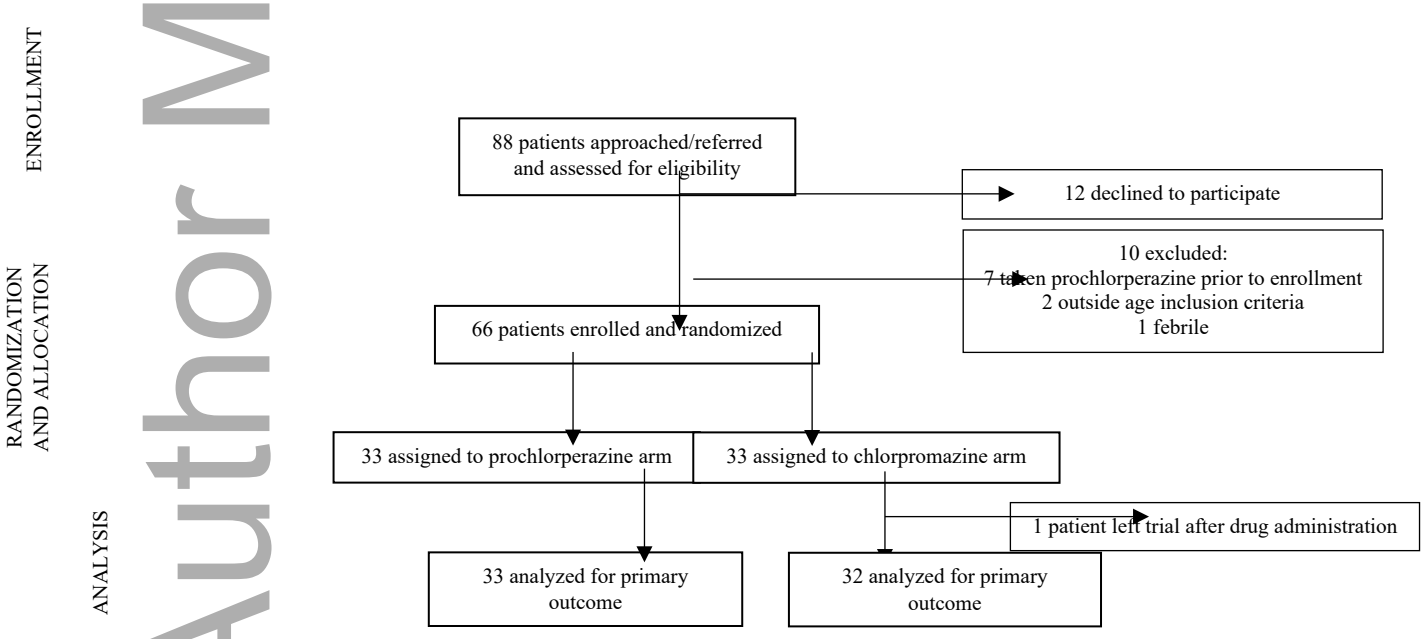

Figure 1. Flowchart of progress through trial