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https://doi.org/10.1016/j.jemermed.2020.04.018

Original Contributions

TREATMENT OF HEADACHE IN THE EMERGENCY DEPARTMENT: HALOPERIDOL IN THE ACUTE SETTING (THE-HA STUDY): A RANDOMIZED CLINICAL TRIAL

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□ Abstract—Background: Headache is a common complaint of emergency department (ED) patients and current treatment varies with significant limitations. Objective: Our aim was to evaluate the efficacy and safety of 2.5 mg i.v. haloperidol in the treatment of severe benign headache in the ED. Methods: A randomized, double-blind, placebo-controlled trial was performed in the ED of a single high-volume teaching hospital. Convenience sampling identified 287 eligible patients 13 to 55 years old with benign headache. One hundred and eighteen patients were enrolled to receive either 2.5 mg of haloperidol i.v. or placebo. The primary outcome measure was pain reduction at 60 min. Patients were evaluated for adverse events and follow-up was conducted after discharge. QT measurement was performed at baseline and discharge. Results: Fifty-eight patients received haloperidol and 60 patients received placebo. Patients in the haloperidol group reported an average 4.77-unit reduction in visual analogue scale score at 60 min compared to a 1.87-unit reduction in the control group. Thirty-four patients (58.6%) in the haloperidol group had complete resolution of their headache. Treatment with rescue ketorolac was required in 78.3% of the control group and 31% of the haloperidol group. Adverse events were uncommon, benign, and easily treated. No patients in the haloperidol group were found to have QT lengthening. Conclusions: This study suggests that 2.5 mg i.v. haloperidol is a rapid and effective treatment for acute, severe, benign headache in ED patients aged 18 to 55 years. Further study is warranted to confirm these results in adolescents. Trial Registration: ClinicalTrials.gov Identifier NCT02747511. © 2020 Elsevier Inc. All rights reserved.

□ Keywords—headache; migraine; haloperidol; treatment; management; emergency department; QT; pain; haldol; placebo; ketorolac; pediatric

INTRODUCTION

Headache is the fifth leading cause of patients presenting to the emergency department (ED) in the United States. More than 3.8 million patients over age 15 years and 246,000 children required treatment for headache in an ED in the Unites States in 2013 [1]. Refractory headache and migraines pose a difficult problem for the patient and clinician in the ED. Wide variation exists in the agents used to treat acute headache. Current treatment varies based on location and clinician, but typically involves a combination of i.v. antiemetic, diphenhydramine, and nonsteroidal anti-inflammatory drug. In some cases, i.v. corticosteroids and ergotamines are also utilized for refractory headache [2]. Allergy to these medications, treatment failure, cost, limited manufacturer availability of certain drugs, and unwanted adverse effects have led to a search for better treatment options in the ED. In addition, recent initiatives to limit opioid use in the ED have resulted in the need for alternative options to manage patients with refractory headache [2,3].

Butyrophenones, such as haloperidol, have been reported to be an effective treatment for acute headache in the ED (4–12). Butyrophenones act on the dopamine receptors that are abundant in various areas of the brain, including the brainstem nuclei and the sympathetic basal ganglia. They are thought to alter and regulate autonomic nerves throughout the neurologic, visceral, gastrointestinal, and cardiovascular systems, among others. Stimulation of these nerves is thought to cause the pain, nausea, anxiety, and hemodynamic response seen in acute headache. Dopamine receptors are located in the cerebral vasculature, which is the rationale for using a dopaminergic agent in the treatment of migraine.

Haloperidol is pharmacologically similar to the phenothiazines. Haloperidol is an antipsychotic agent that has strong affinity for the dopamine 2 receptors, which accounts for its neuroleptic abilities. It also has some affinity for dopamine 1 receptors, 5-HT2 serotonin receptors, and α1 adrenergic receptors (6). For many years, phenothiazines, such as prochlorperazine (Compazine), have been used in the treatment of pain, nausea, and vomiting associated with migraine (13). Some data have suggested they may be beneficial as cessation agents in the treatment of migraine (14).

Droperidol has been studied extensively in randomized controlled trials for the treatment of migraine (8–12). The few studies published on haloperidol for acute headache have had small sample size, inferior methods, and use varying doses, all > 5 mg (4–7). Only one publication to date has compared haloperidol to placebo in the treatment of headache (6). Among these limited studies, haloperidol has a marked improvement in patient-reported visual analogue scale (VAS) scores with no adverse cardiovascular events (4–7). Proposed side effects of haloperidol include anxiety, akathisia, and somnolence.

While research shows promising efficacy of haloperidol for migraine treatment in the ED, the cardiovascular effects and reported QTc prolongation limit its use. QT prolongation leading to fatal cardiac dysrhythmias had been postulated. The U.S. Food and Drug Administration (FDA) has implemented a warning about the risk of torsades de pointes with i.v. administration. This risk increases with a baseline QTc > 450 ms or existing conditions, including electrolyte imbalance, heart disease, or prodysrhythmic drugs. Although the FDA has advised continuous cardiac monitoring in patients receiving haloperidol, a retrospective review has demonstrated that 6 mg of haloperidol is the lowest reported dose to cause cardiac arrest, and no reports of QT prolongation or torsades have been described with < 2 mg of i.v. haloperidol (15).

Our primary objective was to determine the effectiveness of 2.5 mg i.v. haloperidol in the treatment of acute headache in patients aged 13 to 55 years in the ED. Secondary outcomes included evaluation of the effectiveness in patients aged 13 to 17 years, time of VAS change, side effect profile, and safety of i.v. haloperidol at a lower dosing regimen. We hypothesize that low-dose i.v. haloperidol is a fast and effective treatment approach to managing benign headache in the ED.

MATERIALS AND METHODS

Study Setting

This was a single-center, prospective, randomized, placebo-controlled, double-blinded trial. It was conducted in a community-based teaching hospital and level I trauma center that receives approximately 100,000 visits per year. Data collection took place from October 2015 to June 2016 for 20 h per day. Patients were not recruited from 4 AM to 8 AM due to lack of ED pharmacist during these hours. The Institutional Review Board (IRB) at the participating site approved the study protocol.

Sample Size Calculation

We used data from a small randomized controlled trial to determine the sample size required to detect a moderate improvement in VAS by haloperidol (Haldol). Based on those data, a conservative effect (i.e., assuming independence between pairs of data within subject) of the standard deviation of the paired difference in VAS from baseline to endpoint is 4.2 VAS units. Using SAS software's (version 9; SAS Institute, Cary, NC) power procedure, we determined that a sample size of 71 per group will provide 80% power to detect a moderate treatment effect size, defined as a reduction in mean VAS of 2 units by treatment relative to that observed in placebo subjects. We performed an unplanned interim analysis in July 2016 based on a large proportion of observed headache resolution. This revealed excellent power and significant results with 118 patients enrolled. Study enrollment was concluded early and closed with the IRB.

Participants

Convenience sampling was performed on patients aged 13 to 55 years presenting to the ED with a chief complaint of headache or migraine. Patients were identified by triage nursing staff, who notified an on-call investigator responsible for directly evaluating and enrolling patients in the study. Patients were excluded if any of the

following were present: abnormal blood pressure (> 200/100 mm Hg), sudden or rapid onset (normal to worst pain in minutes), fever, acute trauma, history of brain mass, history of stroke, history of abnormal intracranial anatomy, QT > 450 ms on the cardiac monitor strip, altered mental status (Glasgow Coma Scale score < 15), allergy to haloperidol, any abnormalities on neurologic examination, any clinician concern that would require computed tomography scan of brain, pregnancy, or any prisoner or ward of the state. All patients and guardians, when applicable, provided informed consent. We obtained assent from minors when applicable.

Study Procedures

We randomized patients to a treatment group based on a standard sequential envelope randomization performed by the Division of Biostatistics at Western Michigan University, Homer Stryker M.D. School of Medicine. Pharmacy personnel were unblinded at the time of enrollment. All physicians, nurses, patients, and providers were blinded to the treatment group. Patients received haloperidol 2.5 mg diluted to a final concentration of 5 mL with 0.9% sodium chloride or 5 mL of 0.9% sodium chloride. Nurses were instructed to push the medication slowly over 1 to 2 min. After drug administration, vital signs, pain score, and side effects were documented at 0, 30, 60, and 90 min, and at discharge. Patients were placed on the cardiac monitor throughout their stay in the ED. Each patient's QT was measured on the cardiac monitor prior to medication administration and at discharge. VAS was taken at each time point of reassessment. If the patient did not have at least a 50% reduction in VAS at the 60-min assessment, ketorolac i.v. was offered for rescue medication, with 30 mg i.v. in adults and 15 mg i.v. in patients aged 13 to 17 years or weighing < 50 kg. In patients with an allergy to ketorolac, metoclopramide 10 mg i.v. was offered as rescue medication. Patients who required rescue medication were observed an additional 60 min prior to discharge, and repeat VAS and vital signs were recorded at 120 min. Headache resolution was defined as a VAS pain score of 0 or 1 at 30, 60, or 90 min, or at discharge.

We used diphenhydramine 25 mg or 50 mg i.v. to treat akathisia if the patient reported this side effect when asked at 30, 60, or 90 min. Akathisia was defined as a reported feeling of restlessness or anxiety. If they had an allergy to diphenhydramine, lorazepam 0.5 to 1 mg i.v. was used. If both the study medication and rescue medication failed to improve the patient's symptoms at 120 min, further treatment was determined by the primary emergency physician. We made phone calls to patients after 24 h post discharge to collect final follow-up data.

Data Collection and Outcome Measures

Demographic and study data were collected by the investigator and entered into Research Electronic Data Capture (REDCap). The primary outcome measure evaluated was the change in baseline VAS at 30, 60, 90 min, and at discharge after study drug was administered. Secondary outcome measures included time interval to pain relief, degree of pain relief (measured in percent reduction of VAS at each time point), side effects observed, and change in QT interval. Follow-up data were collected via phone interview at > 24 h, and included repeat VAS, occurrence of any side effects from medications, any reported return of symptoms by 24 h, any subsequent medical visits due to headache (primary care or ED visit), and patient preference for requesting study drug for treatment of future headache.

Statistical Analysis

Frequencies and proportions were obtained for categorical items. Means, ranges, and standard deviations (SD) were calculated. We assessed treatment groups for homogeneity using chi-square test of independence and two-sample *t*-test. Changes in VAS from 0 to 30 min and 0 to 60 min were compared individually for haloperidol and control cohorts using means and SD. Changes in VAS for 90 and 120 min compared to VAS prior to treatment and at 60 min were performed for haloperidol and control groups, with and without rescue treatment, using means and SD.

The proportion of patients that received ketorolac was compared for haloperidol and control groups using Fisher exact test. Proportion of patients that received diphenhydramine in haloperidol and control groups were compared using the chi-square test of independence. The average QT interval at admission, at discharge, and average change in QT from admission to discharge were compared for haloperidol and control groups using means and SD. Statistical analysis was conducted using SAS software, version 9.4 (SAS Institute).

RESULTS

Over a 9-month period, we randomized a total of 118 patients to treatment groups, resulting in 58 patients in the haloperidol group and 60 patients in the placebo group. Study enrollment details are displayed in Figure 1.

Demographics and Baseline Characteristics

Demographic and baseline characteristics are presented in Table 1. A total of 70 patients (59.3%) had a history of migraine, with no significant difference between
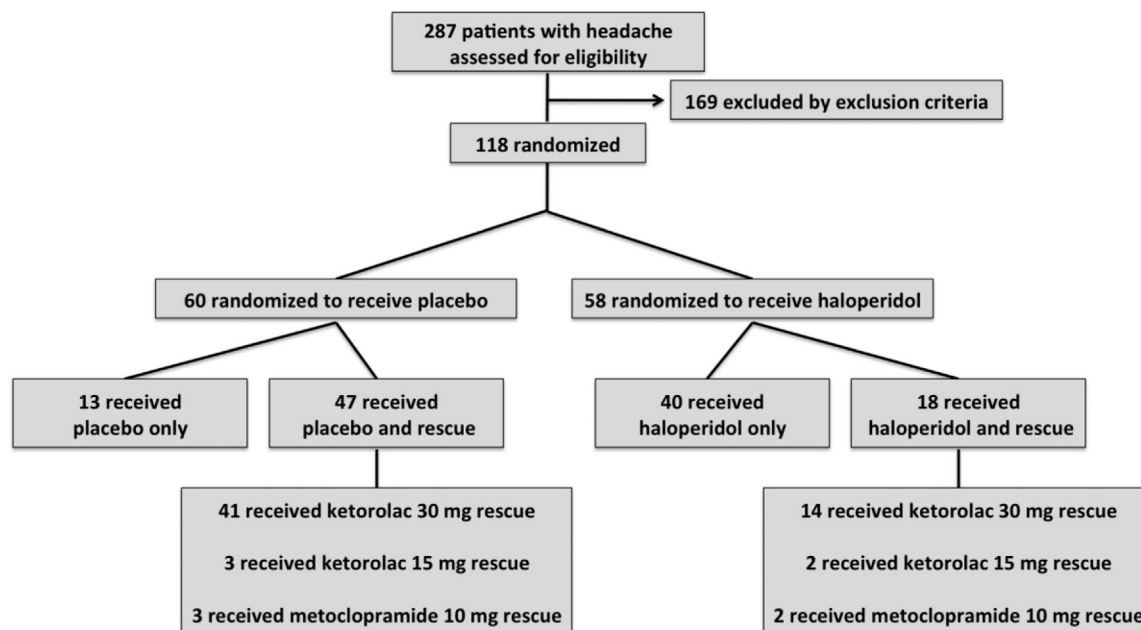
Figure 1. Study enrollment details.

treatment groups. At baseline, 107 patients (90.7%) had a headache defined as severe (VAS pain score > 7). Ten patients (8.5%) had a moderate headache (VAS pain score 4–6) and only 1 patient with a mild headache (VAS score < 4). Characteristics of the two treatment groups were equally matched in non-gender demographics, weight, age, and pain severity. Nine pediatric patients were enrolled.

Efficacy

There was a statistically significant greater reduction in pain in the haloperidol group. Mean (SD) baseline VAS was 8.40 (1.50) and 8.35 (1.54) in the haloperidol and control groups, respectively. The haloperidol group reported a mean 4.77-unit reduction in VAS at 60 min compared to a 1.87-unit reduction in the control group. As seen in Figure 2A, the patients receiving haloperidol

had a greater pain reduction from baseline at 30 and 60 min. Both of these time points for the haloperidol group were statistically significant ($p = 0.003$ and $p < 0.0001$).

The majority of patients in the haloperidol group (37 patients [64.9%]) experienced at least 50% pain relief at 60 min compared to 13 patients (21.7%) in the control group. Twenty patients (34.5%) in the treatment group reported 50% pain relief at 30 min compared to 7 patients (11.7%) in the control group (Table 2). In the haloperidol group, only 18 patients (31%) reported inadequate pain relief requiring rescue medication. In contrast, in the placebo group, most of the patients (47 patients [78.3%]) reported inadequate pain relief, with all of those patients choosing to receive rescue medication. Of patients in the haloperidol group, 34 (58.6%) had complete resolution of their headache prior to discharge, defined as a headache of 0 to 1 on VAS.

Table 1. Demographics and Baseline Characteristics

Variable	Overall (n = 118)	Haloperidol (n = 58)	Control (n = 60)	*p* Value
Age, y, median	31.5	32.5	29.5	0.53
Child (13–17 y), n (%)	—	5 (8.6)	4 (6.7)	0.73
Sex, female, n (%)	86 (72.9)	37 (63.8)	49 (81.7)	—
Race, n (%)				0.44
Caucasian	81 (68.6)	43 (74.1)	38 (63.3)	
African American	34 (28.81)	14 (24.14)	20 (33.3)	
Other	3 (2.5)	1 (1.7)	2 (3.3)	
Weight, kg, mean (SD)	83.71 (23.8)	83.55 (23.8)	83.87 (24.0)	0.89
History of migraines, n (%)	70 (59.3)	38 (65.5)	32 (53.3)	0.82

SD = standard deviation.
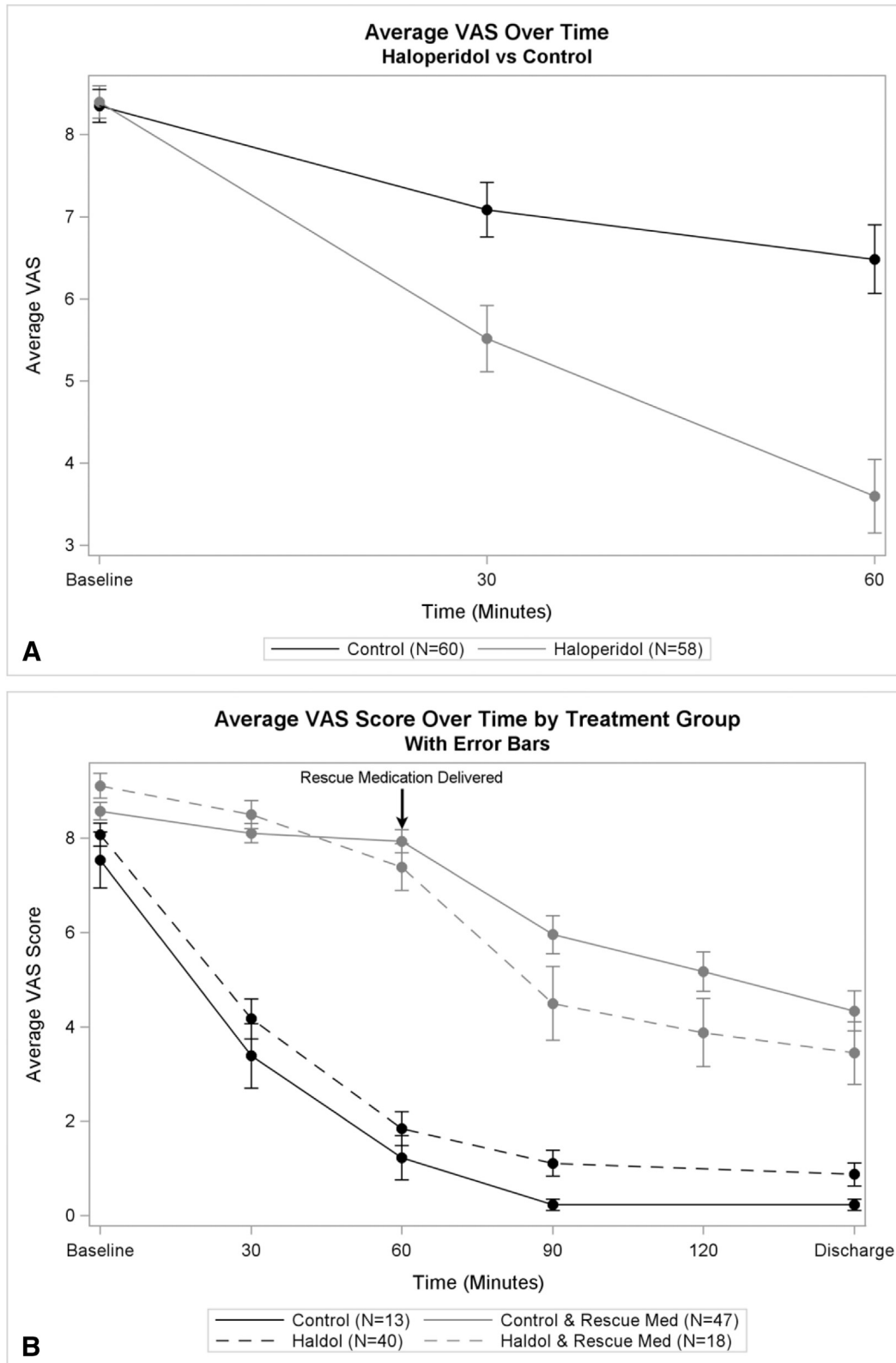
Figure 2. (A) Comparison of the mean change in pain scores at 30 and 60 min for haloperidol and control groups. (B) Mean pain scores comparing haloperidol and control groups with rescue medication from time 0 to discharge. VAS = visual analogue scale.

Table 2. Pain Relief > 50%

Time Point	Haloperidol, n (%)	Control, n (%)	p Value
At 30 min	20 (34.5)	7 (11.7)	0.003
At 60 min	37 (63.8)	13 (21.7)	< 0.0001

Data are reported as those who received > 50% pain relief compared to baseline.

Rescue Medication Use

At the 60-min time point, the proportion of patients in the haloperidol group that received rescue medication (ketorolac 30 mg or 15 mg, or metoclopramide 10 mg) was 18 (31%). Of those treated with placebo, 47 (78.3%) required rescue medication. Figure 1 demonstrates the rescue medication and dosage used by each patient in the control and haloperidol groups.

As seen in Figure 2B, the patients receiving haloperidol only had a greater pain reduction from baseline compared to those that received haloperidol in addition to any of the rescue medications. Additional comparisons of VAS reduction for each subgroup that received rescue can be seen in Figure 2B. The small group of patients receiving placebo only (14 patients) had lower reported pain at baseline, with a mean pain score of 7.54, and had a mean (SD) cumulative reduction in pain of 7.31 (2.06) compared to initial VAS. Patients that received placebo and then subsequently received rescue medication with ketorolac 30 mg had a mean (SD) cumulative pain reduction of 2.22 (2.25) at 30 min and 3.07 (2.72) at 60 min.

Safety

Side effects at 30- and 60-min time points for each treatment group were minimal and are listed in Table 3. Patients with anxiety or restlessness were treated with diphenhydramine in 7 patients and lorazepam in 2 patients at 30 min, with complete resolution of side effects in 8 of 9 patients (89%). Overall, the most common adverse event was "nausea/vomiting."

Mean (SD) QT in the haloperidol group (366.16 [30.91] ms) was not statistically different than in the control group (357.17 [37.83] ms). The mean change in QT at discharge (8.74 vs. 6.5) was also not statistically different or clinically significant. There were no observable dysrhythmias in either group. No patient complained of chest pain or palpitations, and no clinically significant increase in heart rate was observed.

Follow-Up at 24 h

At the 24-h follow-up, 8 haloperidol patients (14.6%) and 4 placebo-treated patients (7%) reported side effects. Two patients who were treated with haloperidol reported restlessness or anxiety at follow-up. Forty-four treatment group patients (75.9%) requested haloperidol in the future compared to 21 (35%) in the control group. The haloperidol group experienced less return of symptoms after 24 h than did the control group, 18 patients (32.7%) compared to 29 patients (50.9%), respectively. The haloperidol group also had fewer patients return for additional care after 24 h, 4 patients (7.3%) vs. 10 (17.5%) in the control group. Three patients from each study group were lost to follow-up.

DISCUSSION

The current study demonstrated haloperidol to be successful in reducing pain for acute benign headache in the ED. This study is the largest prospective cohort and randomized controlled trial on this subject to date (4–7). Our study represents the first randomized controlled trial utilizing a low-dose haloperidol of 2.5 mg for the treatment of acute headache.

Haloperidol was associated with few side effects that were easily treated. Akathisia was experienced by 13.8% of haloperidol-treated patients, significantly lower

Table 3. Side Effects at 30 and 60 Min After Treatment

Time Point	Side Effect	Haloperidol, n (%)	Control, n (%)	p Value
30 min	Overall patients reporting	14 (24.1)	5 (8.3)	0.024
	Anxiety	4 (6.9)	0 (0.0)	0.055
	Restlessness	6 (10.3)	0 (0.0)	0.012
	Dizziness	0 (0.0)	0 (0.0)	—
	Nausea/vomiting	2 (3.4)	4 (6.7)	0.680
	Other	4 (6.9)	1 (1.7)	0.203
60 min	Overall patients reporting	3 (5.2)	5 (8.3)	0.718
	Anxiety	1 (1.7)	1 (1.7)	1.000
	Restlessness	0 (0.0)	2 (3.3)	0.496
	Dizziness	0 (0.0)	0 (0.0)	—
	Nausea/vomiting	0 (0.0)	4 (6.7)	0.119
	Other	2 (3.4)	0 (0.0)	0.239

than the reported incidence in previous studies (6,7). This is likely due to the lower dose of haloperidol used, 2.5 mg compared to 5 mg. Despite nausea and vomiting being the most common reported adverse event, this is a known symptom of migraine and was likely associated with the presenting headache instead. Other side effects were infrequent and benign. Somnolence was not observed. Patients in this study had significantly less akathisia and sedation than previous studies using higher-dose haloperidol and routine diphenhydramine pretreatment (7). We believe this suggests that standard pretreatment with diphenhydramine is unnecessary when utilizing haloperidol at lower doses.

Interestingly, a small cohort of 14 patients in the control arm had > 50% reduction of pain at 60 min with administration of 5 mL 0.9% sodium chloride alone. Patients in this cohort did start with a lower mean VAS of 7.54 compared to 8.5 to 9 in other groups. This suggests that their headache was not as severe initially. Placebo effect, being placed in a dark quiet room, and rest are possible hypotheses to explain this improvement.

Like droperidol, haloperidol has the potential to cause QT prolongation. Prior studies have observed ventricular dysrhythmias, but with antipsychotics used in much higher doses for delirium and the critically ill (16,17). A meta-analysis of similar studies calculated the risk of dysrhythmia at lower doses of haloperidol, between 0.25 and 5 mg i.v., to be 0.21% (18). Notably, in our study, QT prolongation did not occur in any of the patients receiving haloperidol. This suggests an electrocardiogram prior to low-dose haloperidol administration intravenously, which is required at some institutions, may not be indicated. Our findings are similar to other studies published on i.v. haloperidol given for headache (7). However, the small sample size may not have identified a clinically significant incidence of this occurrence.

Of the 118 patients enrolled, approximately 95% were reached for follow-up. This large number may be due to the smaller community in which this study was conducted. Patient satisfaction in those receiving haloperidol was favorable. More than twice as many patients receiving haloperidol (77.4%) reported that they would request this medication again, compared to control. Almost all of those patients also reported that they would request it again when we contacted them for follow-up. Patient preference for medications often influences the treatment selected by a provider and patient buy-in is important in successful treatment of acute pain.

Limitations

The authors do recognize several limitations to this study. Females represented the majority within each group; however, their distribution was slightly greater in the control group than the haloperidol group. Our study demographics were the function of a randomized double-blinded protocol, thus the male to female distribution in the haloperidol group was due to chance alone. Had our pool of subjects been larger, the difference between groups would have likely equilibrated.

In the haloperidol group, 5 patients left the study prior to completion of the study requirements. All patients had improvement of headache and did not want to wait for further data collection at 60 or 90 min. Follow-up data were still collected for these individuals. All patients denied restlessness or akathisia as a cause for leaving.

Nine pediatric patients were enrolled during the study period, with 5 receiving haloperidol. The results in this cohort were similar to those of their adult counterparts. The small sample size in this cohort limits the conclusions that can be drawn regarding the pediatric population. Limited enrollment can be attributed to decreased incidence of severe benign headache in this age group, difficulty getting consent from parents, and possibly increased diagnostic evaluation of severe headache in the pediatric population. Nonetheless, larger studies are needed to determine both the safety and efficacy of haloperidol in this age group.

The use of convenience sampling has inherent flaws. Using multiple physicians as trained investigators to enroll patients 20 h per day and the screening and logging of all patients with excluded headaches helped minimize these limitations.

The exclusion criteria were intended to select benign headache patients presenting to the ED. We did not differentiate type of benign headache intentionally to better match practice patterns of working emergency physicians. Current data support that differentiating the type of primary headache did not result in change in medications used and was not relevant to their treatment in the ED (19). Efficacy was unchanged in the patients previously diagnosed with migraine compared to those that were not in our study. This is similar to previous studies on treatment of primary headache in the ED (19). A larger sample size is needed to determine the frequency of misclassifications of serious headache as "benign" based on these criteria.

CONCLUSIONS

In the ED, 2.5 mg of i.v. haloperidol is a rapid and effective treatment for acute, severe, benign headache in patients aged between 18 and 55 years. Further clinical study is warranted to confirm these results in adolescents.

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ARTICLE SUMMARY

1. Why is the topic important?

Headache is the fifth leading cause of patients presenting to the emergency department (ED) in the United States. More than 3.8 million patients over age 15 years and 246,000 children required treatment for headache in an ED in the United States in 2013. Refractory headache and migraines pose a difficult problem for the patient and clinician in the ED. Wide variation exists in the agents used to treat acute headache. In addition, current treatment options often have unpleasant side effects, such as anxiety and akathisia or requiring multiple doses of multiple medications to achieve headache relief.

2. What does this study attempt to show?

This study hopes to demonstrate that haloperidol is a fast and effective agent in treating severe benign headache in the ED. It also hopes to demonstrate that it does not effect QT measurements given intravenously at this dosage. Haloperidol at lower doses than previously used are likely to be equally efficacious and cause fewer side effects than other standard agents or higher doses of haloperidol. The study attempts to demonstrate that the treatment option is equally safe and effective in adolescents 13 to 17 years old.

3. What are the key findings?

Haloperidol successfully reduced pain in headache patients greater than placebo or rescue medication of haloperidol. A majority (65%) of haloperidol patients had > 50% reduction of headache compared to 21.7% of placebo patients. Mean reduction in headache in the treatment group was 4.77 units on the VAS. Almost 60% of patients in the treatment group had complete resolution of their headache. There was no prolongation of QT interval and patients had significantly less akathisia than previous reports. Adolescent findings were similar to their adult counterparts, however, the small sample size is a limitation.

4. How is patient care impacted?

Haloperidol at 2.5 mg i.v. is an effective agent to be used for severe headache or migraine in the ED. Fewer side effects occur at lower dosing, which will improve patient satisfaction. This will give emergency physicians another option for treating headache effectively with less polypharmacy. No change in QT was noted at this dose of haloperidol intravenously. Preliminary study results in adolescents are promising and more research should be conducted in this area.