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Randomized Controlled Double-Blind Trial Comparing Haloperidol Combined with Conventional Therapy to Conventional Therapy Alone in Patients with Symptomatic Gastroparesis

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ABSTRACT

Objective: Gastroparesis is a debilitating condition that causes nausea, vomiting, and abdominal pain. Management includes analgesics and antiemetics, but symptoms are often refractory. Haloperidol has been utilized in the palliative care setting for similar symptoms. The study objective was to determine whether haloperidol as an adjunct to conventional therapy would improve symptoms in gastroparesis patients presenting to the emergency department.

Methods and trial design: This was a randomized, double-blind, placebo-controlled trial of adult emergency department patients with acute exacerbation of previously diagnosed gastroparesis. The treatment group received 5 mg haloperidol plus conventional therapy (determined by the treating physician). The control group received a placebo plus conventional therapy. The severity of each subject's abdominal pain and nausea were assessed before intervention and every 15 minutes thereafter for 1 hour using a 10-point scale for pain and a 5-point scale for nausea. Primary outcomes were decreased pain and nausea 1 hour after treatment.

Results and Adverse Effects: Of the 33 study patients, 15 were randomized to receive haloperidol. Before treatment, the mean intensity of pain was 8.5 in the haloperidol group and 8.28 in the placebo group; mean pretreatment nausea scores were 4.53 and 4.11, respectively. One hour after therapy, the mean pain and nausea scores in the haloperidol group were 3.13 and 1.83 compared to 7.17 and 3.39 in the placebo group. The reduction in mean pain intensity therapy was 5.37 in the haloperidol group ($p \leq 0.001$) compared to 1.11 in the placebo group ($p = 0.11$). The reduction in mean nausea score was 2.70 in the haloperidol group ($p \leq 0.001$) and 0.72 in the placebo group ($p = 0.05$). Therefore, the reductions in symptom scores were statistically significant in the haloperidol group but not in the placebo group. No adverse events were reported.

Conclusions: Haloperidol as an adjunctive therapy is superior to placebo for acute gastroparesis symptoms.

INTRODUCTION

Background

Gastroparesis, defined as delayed gastric emptying in the absence of mechanical obstruction, is characterized by nausea, vomiting, postprandial fullness, early satiety, and abdominal pain or discomfort.[1,2] The most common etiologies of gastroparesis are diabetes mellitus (approximately 30% of patients) and surgery (19%); gastroparesis is idiopathic in 36% of patients.[1]

The only drug approved by the U.S. Food and Drug Administration for gastroparesis is metoclopramide, a dopaminergic receptor antagonist with prokinetic and antiemetic properties.[3] Unfortunately, in many cases this drug does not adequately address patients' symptoms. When symptoms become intractable, patients often present to the emergency department (ED).

Nausea is the most prevalent symptom among gastroparesis patients,[4] with more than 40% of them reporting it to be the most debilitating symptom.[5] When gastroparesis patients present to the ED for nausea and vomiting, various drugs are commonly used in addition to metoclopramide. These include histamine antagonists (e.g., promethazine, meclizine) and the serotonin 5-HT_3 antagonist ondansetron. Prokinetic agents such as the motilin receptor agonist erythromycin[6] and the serotonin 5-HT_4 receptor agonist cisapride have also been used[7] but are less popular because of their cardiotoxicity. In addition to antiemetics, analgesic drugs such as opiates are often utilized to treat the abdominal pain present in up to 72% of patients,[8] but these drugs can be counterproductive to overall therapy goals because they can exacerbate nausea and vomiting and delay gastric emptying.[9]

Haloperidol is a potent dopamine receptor antagonist that blocks receptors in the chemoreceptor trigger zone of the brain. The drug has been used to treat nausea and vomiting in the palliative care and postoperative settings for decades.[10-13] Despite haloperidol's widespread use as an antiemetic, however, no randomized controlled trial has been done to evaluate its effectiveness for the treatment of nausea and vomiting in any setting.[10] Furthermore, an analgesic effect of haloperidol has been linked to its isomeric similarity to meperidine as it relates to the opiate receptor.[14] Severe neuropathic pain unrelieved by intravenous injection of morphine and diazepam but completely relieved by intravenous haloperidol has been documented.[15]

Importance

Gastroparesis affects roughly 5 million people in the United States, with a greater proportion of women affected than men.[16] It is estimated that 20-40% of patients with long-term diabetes have the disorder. A study of gastroparesis patients found that within a 2-week study period, 90% had nausea and 60% had multiple vomiting episodes in a day; the disease was also associated with reduced quality of life.[3] Other studies have found that gastroparesis results in frequent ED visits for intractable symptoms and hospitalizations that last for several days.[1,17]

Objectives of this Investigation

This study's aim was to determine whether haloperidol in addition to conventional therapy was superior to conventional therapy alone for the treatment of nausea and abdominal pain in gastroparesis patients who presented to the ED.

METHODS

Study Design and Setting

This randomized, double-blind, placebo-controlled trial was performed at two urban hospitals: an academic private tertiary care hospital with 55,000 annual ED visits and an academic county hospital with 62,000 annual ED visits. The study was approved by the institutional review board. Once patients were identified as having a gastroparesis exacerbation, they were invited to participate in the study. We obtained written informed consent from all participants. Patients were enrolled between January 2013 and January 2015. Trial registration number: NCT02057549 ClinicalTrials.gov. Unique Protocol ID: 13040380.

Selection of Participants (Eligibility Criteria)

All adult patients with a previous diagnosis of gastroparesis who presented to the ED with nausea, vomiting, and abdominal pain attributable to their gastroparesis were invited to participate. Exclusion criteria included age less than 18 years, past history or current evidence of QT prolongation, hypotension (systolic blood pressure < 90 mm Hg), presence of other acute abdominal pathologic conditions, allergy to haloperidol, pregnancy, incarcerated status, or an inability to give informed consent.

Interventions, Randomization and Blinding

Patients who presented with an acute exacerbation of gastroparesis were assessed for eligibility. An electrocardiogram was obtained on all patients to evaluate the QT interval. Female patients of childbearing age had a pregnancy test performed.

Enrolled patients were randomized to the experimental or control group and were administered 5 mg haloperidol intravenously or an equivalent volume of placebo, both of which were prepackaged and coded with a study ID number provided by the investigational pharmacy. Randomization sequence was created using Stata 9.0 (StataCorp, College Station, TX, USA) statistical software and was stratified by center with a 1:1 allocation using random block sizes of 2 and 4. The haloperidol and placebo were identical in appearance. They were pre-packed in syringes and consecutively numbered for each patient according to the randomization schedule. Each patient received the intravenous medication provided by an ED nurse not participating in the study. Participants, investigators, and treating physicians were blinded to the study group assignment. In addition to study medication, patients received conventional therapy, which was chosen by the treating physician.

Cardiac activity, pulse oximetry and blood pressure were monitored until patient disposition was made. Symptoms were reassessed, and patients were observed for adverse events every 15 minutes for 1 hour after the haloperidol or placebo was given. At that time, patients were given additional therapy for symptoms if needed**.**

Methods and Measurements

The intensity of the patient's abdominal pain was measured upon randomization and at 15-minute intervals for 1 hour after the intervention using a validated 10-point visual analog scale (VAS). Nausea intensity was scored using a 5-point VAS at the same time points. The higher numbers on each scale reflected worse symptom intensity.

Outcomes

The primary outcomes of interest were changes in the intensity of abdominal pain and nausea one hour after administration of the study medication. Secondary outcomes were disposition status (hospital admission or discharge), ED length of stay, and nausea resolution at 1 hour. Nausea resolution was defined as the patient not requesting additional antiemetic medication.

Sample Size

The effect size was calculated for significant differences at 60 minutes (main outcome). For the primary outcome, we expected 50% of the patients in the treatment group to experience nausea and pain symptom relief, with a SD of 30%. We predicted that 25% of patients in the placebo group, with a SD of 20%, would experience symptom relief. For an alpha and beta level of 5 and 20% respectively, a sample size of 18 subjects in each group were required for the expected effect size.

Analysis

We calculated descriptive statistics for demographic characteristics of the haloperidol and placebo groups. Continuous variables are presented as medians with interquartile ranges, and categorical or ordinal variables are presented as frequencies with percentages. To assess demographic and conventional therapy use differences between the two groups the Mann-Whitney U test or t test was used for continuous variables and the Fisher's exact test or chi-square test for categorical and ordinal variables. Changes in patients' pain and nausea intensity between the initial assessment and follow-up times were also analyzed utilizing a paired T test. Additionally we evaluated the size of the effect of the intervention by calculating the Cohen's d for paired T tests. A p value < 0.05 (two-tailed) was considered

statistically significant for all tests. All analyses were conducted using IBM SPSS Statistics software (version 23.0 Armonk, NY: IBM Corp.).

RESULTS

Characteristics of Study Subjects

Forty one patients met inclusion criteria. Eight patients were excluded (Figure 1). As a result, 33 participants were included in the analysis. Twelve patients (36 %) were enrolled at the private hospital, and 21 patients (64 %) were enrolled at the county hospital. There were 18 (55 %) patients in the placebo and 15 (45 %) in the haloperidol group. Demographic and baseline pain and nausea characteristics of the two groups are summarized in Table 1.

Main Results

The two groups were similar in terms of the conventional therapy received (Table 2). Patients in the haloperidol group had significant improvement of pain and nausea scores at one hour in comparison to those in the placebo group. In the haloperidol group, disposition was made sooner and more patients were discharged home. The most frequently used antiemetic agents were metoclopramide and ondansetron. The most common analgesics used were morphine and hydromorphone (Table 2). In addition, some patients received additional medications like famotidine and diphenhydramine among others listed in the same table. One patient in the haloperidol group received no other medication prior to receiving the study drug. The majority of patients were treated with crystalloid intravenous fluids. The initial differences of mean pain and nausea intensity scores at arrival were higher in the haloperidol group than in the placebo group, but the differences were not significant (Tables 1).

For both pain and nausea, the mean scores were lower in the haloperidol group than in the placebo group at every time point after the intervention.

The reduction in mean pain intensity from before therapy to one hour after therapy was 5.37 points in the haloperidol group ($p \leq 0.001$) compared to 1.11 in the placebo group ($p = 0.11$; Table 3, and Figures 2A&2B. The reduction in mean nausea score from before intervention to 1 hour after therapy was 2.70 in the haloperidol group ($p \leq 0.001$) and 0.72 in the placebo group ($p = 0.05$; Table 4 and figures 3A&3B). Thus, pain and nausea were statistically significantly reduced in the haloperidol group but not in the placebo group. The effect sizes observed for pain and nausea in the group receiving haloperidol were 1.51 and 1.22.

Given that some patients received opioids before the intervention, we analyzed the differences in pain and nausea at one hour after the intervention in the subgroup of 21 patients who did not receive these medications. The reduction in the mean pain intensity was 5 points in the nine patients who received haloperidol ($p \leq 0.001$) compared to 1.31 in the 13 patients who received placebo ($p = .14$). A similar effect was observed for nausea, the reduction in the mean nausea score was 2.61 points in patients receiving haloperidol ($p \leq 0.01$) compared to .77 in the group receiving placebo ($p = .13$).

A smaller percentage of patients in the haloperidol group were admitted to the hospital (4 patients, 26.7%) compared to the placebo group (13, 72.2%; $p =0.009$). The median lengths of stay in the ED were 4.8 hours and 9 hours for the haloperidol and placebo groups, respectively ($p =0.77$). Overall, patients in the haloperidol group experienced no adverse events and required hospital admission less often than placebo group patients.

LIMITATIONS

This study had a small sample size that might introduce a type I error which may be unmasked in a larger study. In addition, the lack of adverse events, including QT prolongation and dystonic reactions, found in our study may be secondary to the study's

small size. A larger study is needed to validate haloperidol's safety in gastroparesis, particularly when used in combination with other agents.

Finally, while the conventional therapy agents used in the two groups were similar in terms of drug category, conventional therapy was heterogeneous among patients (Table 2). This makes it difficult to attribute the reduction of symptom intensity to haloperidol alone. However, due to the wide practice variation and large number of agents available, we did not believe it was appropriate to mandate a single treatment regimen.

DISCUSSION

Haloperidol is a typical butyrophenone-type antipsychotic developed in Belgium in 1958. It was approved by the U.S. Food and Drug Administration (FDA) in1967. Its main use became the treatment of schizophrenia, tics in Tourette syndrome, mania in bipolar disorder, delirium, agitation, acute psychosis, and hallucinations in alcohol withdrawal.[18] Adverse effects associated to the use of intravenous haloperidol have been extensively described. These include hypotension, extrapyramidal movements, akathisia, neuroleptic malignant syndrome, and QT interval prolongation among others.[19] The introduction of newer pharmacological products with safer side-effects profiles might explain a decline in its use as a first choice psychiatric agent. However, haloperidol has maintained an established role in the treatment of nausea and vomiting, and other gastrointestinal diseases.[20] Interestingly, despite the widespread use of this agent for its antiemetic properties in palliative and postoperative care, to our knowledge there has never been a randomized trial comparing haloperidol to placebo for nausea and vomiting in any other clinical setting.[10-13] Furthermore, a few trials comparing haloperidol to other drugs for the treatment of nausea and vomiting have been done in the palliative care setting, but they were not randomized controlled trials.[10]

There have been ED-based randomized placebo-controlled trials of more common antiemetics such as promethazine and metoclopramide.[21] However, a recent Cochrane review of eight trials that included a total of 952 patients treated for nausea and vomiting in the ED setting showed no definitive evidence to support the superiority of one drug over another including metoclopramide, ondansetron, prochlorperazine and promethazine over placebo.[22]

Our study showed for the first time that haloperidol in addition to conventional therapy was superior to placebo plus conventional therapy in decreasing nausea and abdominal pain in ED gastroparesis patients. After administration of the study medication, haloperidol outperformed placebo at reducing symptoms at 15, 30, 45, and 60 minutes. Patients in the haloperidol group experienced no adverse events and required hospital admission less often than placebo group patients.

Although haloperidol has not demonstrated direct effect on pain receptors, its isomeric similarity to meperidine may make it active at opiate receptors.[14] In addition, studies in animals have shown its effect in the NDMA pain modulation pathway, which might also explain its effectiveness for pain control.[23-25] The analgesic mechanisms attributed to haloperidol might not be clearly elucidated, but randomized clinical trials of intravenous haloperidol have shown safety and effectiveness in treating patients with migraine headache and acute pain in palliative care.[26, 27] In the patient with acute gastroparesis, the combination of an effective antiemetic with good analgesic qualities seems to provide a better therapeutic option for symptoms control.

In conclusion, this is the first randomized, double-blind, placebo-controlled trial to assess the efficacy of haloperidol as an adjunctive therapy for gastroparesis symptoms in the ED. Haloperidol was superior to placebo in reducing nausea and pain, and our findings suggest that the addition of haloperidol to conventional therapy was better than conventional therapy

alone. And therefore our study suggests that haloperidol is an effective first line agent in combination with standard analgesic and antiemetic agents for the treatment of gastroparesis in the ED. Further studies with larger sample sizes and better control over concomitant therapy are needed to confirm the effectiveness and safety of haloperidol for the treatment of intractable nausea and abdominal pain. Larger trials would also evaluate the external validity of our findings.

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Table 1. Univariate analysis of demographic and clinical factors associated with differences in the groups of study.

Characteristic	Total N (%)	Haloperidol N (%)	Placebo N (%)	p-value
Age, median (IQR)	46 (36.5 - 49)	47 (31 - 48)	45 (34.5 – 49.2)	.87*
Sex				.70**
Men	9 (27.3)	5 (33.3)	4 (22.2)	
Women	24 (72.9)	10 (66.7)	14 (77.8)	
Race				.80
White	19 (57.6)	9 (60)	10 (55.6)	
Black	14 (42.4)	6 (40)	8 (44.4)	
Ethnicity				.82
Hispanic	13 (40.6)	6 (42.9)	7 (38.9)	
Non- Hispanic	19 (59.4)	8 (57.1)	11 (61.1)	
Admitted				.009
Yes	17 (51.5)	4 (26.7)	13 (72.2)	
No	16 (48.5)	11 (73.3)	5 (27.8)	
Median length of stay, hrs (IQR)	9 (4.9 - 10)	4.8 (4 - 10)	9 (6.3 – 10.9)	.77*
Pain at arrival, median (IQR)	10 (10 - 10)	10 (10 - 10)	10 (8.7 - 10)	UC
Nausea at arrival, median (IQR)	5 (5 - 5)	5 (5 - 5)	5 (4.5 - 5)	UC
Satisfaction , median (IQR)	4 ()	4.5 (3.7 - 5)	3 (2 – 4.2)	.20*

*Mann-Whitney U test; **Fisher's exact test; IQR, interquartile range; UC, Unable to compute values are the same across categories

Satisfaction; Scale 1-5 (1=Dissatisfied, 2=Somewhat Dissatisfied, 3=Neutral, 4=Somewhat Satisfied, 5=Very satisfied)

Table 2. Differences in medications given before and after administration of haloperidol or placebo.

	Total N (%)	Haloperidol N (%)	Placebo N (%)	p-value	Total N (%)	Haloperidol N (%)	Placebo N (%)	p-value
Time of administration	**Before trial**				**After Trial**			
Hydromorphone				**.99***				**.41***
Yes	**4 (12.1)**	**2 (13.3)**	**2 (11.1)**		**7 (21.2)**	**2 (13.3)**	**5 (27.8)**	
No	**29 (87.9)**	**13 (86.7)**	**16 (88.9)**		**26 (78.8)**	**13 (86.7)**	**13 (72.2)**	
Morphine				**.49***				**.05***
Yes	**11 (33.3)**	**6 (40)**	**5 (27.8)**		**8 (24.2)**	**1 (6.7)**	**7 (38.9)**	
No	**22 (66.7)**	**9 (60)**	**13 (72.2)**		**25 (75.8)**	**14 (93.3)**	**11 (61.1)**	
Metoclopramide				**.72***				**.05***
Yes	**13 (39.4**	**5 (33.3)**	**8 (44.4)**		**8 (24.2)**	**1 (6.7)**	**7 (38.9)**	
No	**20 (60.6)**	**10 (66.7)**	**10 (55.6)**		**25 (75.8)**	**14 (93.3)**	**11 (61.1)**	
Ondansetron				**.17***				**.41***
Yes	**13 (39.4)**	**8 (53.3)**	**5 (27.8)**		**7 (21.2)**	**2 (13.3)**	**5 (27.8)**	
No	**20 (60.6)**	**7 (46.7)**	**13 (72.2)**		**26 (78.8)**	**13 (86.7)**	**13 (72.2)**	
Promethazine				**.67***				**.99***
Yes	**7 (21.2)**	**4 (26.7)**	**3 (16.7)**		**1 (3)**	**0**	**1 (5.6)**	
No	**26 (78.8)**	**11(73.3)**	**15 (83.3)**		**32 (97)**	**15 (100)**	**17 (94.4)**	
Pantoprazole				**.72***				
Yes	**20(60.6)**	**10 (66.7)**	**10 (55.6)**					
No	**13(39.4)**	**5 (33.3)**	**8 (44.4)**					
Famotidine				**.99***				
Yes	**3 (9.1)**	**1 (6.7)**	**2 (11.1)**					
No	**30 (90.9)**	**14 (93.3)**	**16 (88.9)**					
Erythromycin				**.45***				
Yes	**1 (3)**	**1 (6.7)**	**0**					
No	**32 (97)**	**14 (93.3)**	**18 (100)**					
Diphenhydramine				**.45***				**.99***
Yes	**1 (3)**	**1 (6.7)**	**0**		**1(3)**	**0**	**1 (5.6)**	
No	**32 (97)**	**14 (93.3)**	**18 (100)**		**32(97)**	**15(100)**	**17 (94.4)**	
Magnesium hydroxide				**.58***				
Yes	**3 (9.1)**	**2 (13.3)**	**1 (5.6)**					
No	**30 (90.9)**	**13 (86.7)**	**17 (94.4)**					
Haloperidol								**.99***
Yes					**1 (3)**	**0**	**1(5.6)**	
No					**0**	**15(100)**	**17(94.4)**	
Lorazepam								
Yes					**1(3)**	**0**	**1(5.6)**	
No					**32(3)**	**15(100)**	**17(94.4)**	

***Fisher's exact test**

OUTCOME PAIN

Table 3. The pain levels measured before the intervention and the differences observed in pain levels reported by patients at several points in time after receiving haloperidol or placebo

Pain	**Haloperidol Group**					**Placebo Group**				
Time points measured	Pairs	Mean pain (sd)	Mean diff	Paired T test (df)	p-value	Pairs	Mean pain (sd)	Mean diff	Paired T test (df)	p-value
Before treatment (reference)	NA	8.50 (1.82)	NA	NA		NA	8.28 (1.77)	NA	NA	
At 15 minutes - reference	15	6.13 (2.85)	-2.37*	T(14)=3.02		18	8.22 (1.66)	-.05	T(17)=19.50	
At 30 minutes - reference	15	4.67 (3.59)	-3.83**	T(14)=4.16		18	8.06 (1.86)	-.21	T(17)=.53	
At 45 minutes - reference	15	3.20 (3.56)	-5.30**	T(14)=5.77		17	7.82 (1.91)	-.59[&]	T(16)=1.15	
At 60 minutes - reference	15	3.13 (3.60)	-5.37**	T(14)=5.87	≤0.001	18	7.17 (2.81)	-1.11	T(17)=1.70	0 .11

sd, Standard deviation; diff, Difference; df, Degrees of freedom; NA, Not available
&Due to a pair lost, the mean reference level for pain is 8.41
*p ≤ .01 **p ≤ .001
Note: Pain was measured using a visual analog scale from 0 to 10

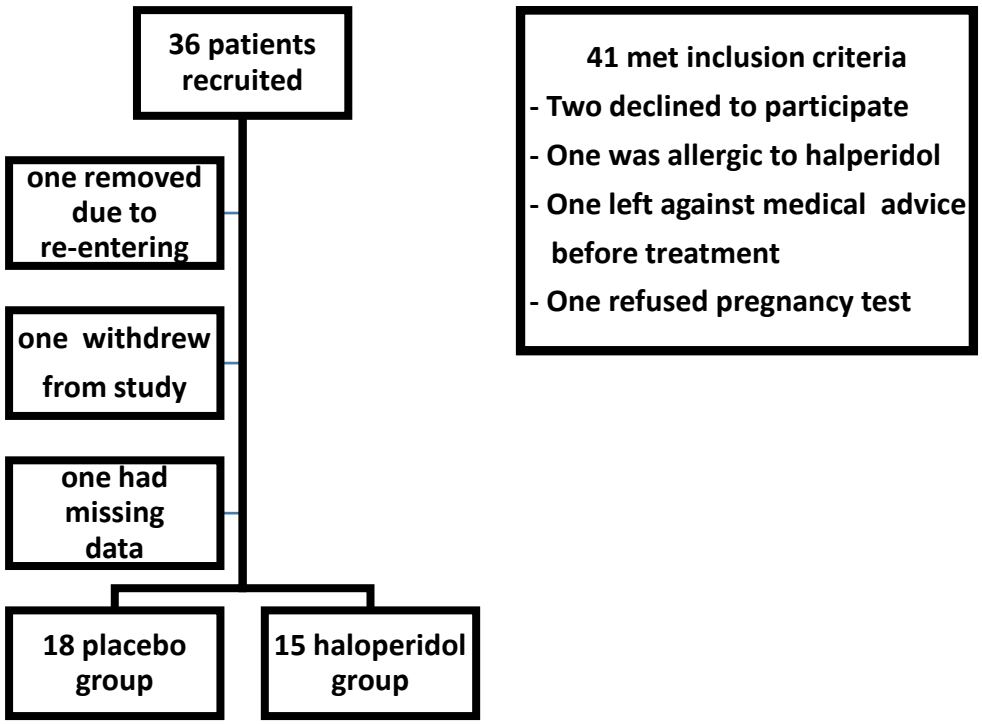
OUTCOME NAUSEA

Table 4. The nausea levels measured before the intervention and the differences observed in nausea levels reported by patients at several points in time after receiving haloperidol or placebo

Nausea	Haloperidol Group					Placebo Group				
Time points measured	Pairs	Mean nausea (sd)	Mean diff	Paired T test (df)	P value	Pairs	Mean nausea (sd)	Mean diff	Paired T test (df)	P value
Before treatment (reference)	NA	4.53 (.83)	NA	NA		NA	4.11 (.96)	NA	NA	
At 15 minutes - reference	15	3.27 (1.74)	-1.26	T(14)=2.85**		18	3.67 (1.24)	-.44	T(17)=2.41*	
At 30 minutes - reference	15	2.20 (1.96)	-2.33	T14)=4.37***		18	3.67 (1.37)	-.44	T(17)=1.81	
At 45 minutes - reference	14	1.86 (1.91)	-2.64[&]	T(13)=4.89***		17	3.88 (1.45)	-.30^	T(16)=1.16	
At 60 minutes - reference	15	1.83 (1.92)	-2.70	T(15)=4.75***	≤ 0.001)	18	3.39 (1.68)	-.72	T17)=2.06	0.05

sd, Standard deviation; diff, Difference; df, Degrees of freedom; NA, Not available
&Due to a pair lost, the mean reference level for nausea is 4.50
^Due to a pair lost, the mean reference level for nausea is 4.18
*p < .05 **p ≤ .01 ***p ≤ .001
Nausea measured in scale from 0-5 (0=I could eat, 1=almost gone, 2=mild nausea, 3=moderate nausea, 4=severe nausea, 5=still vomiting)

Figure 1. **Flow chart.**



FIGURES OUTCOME PAIN

Figure 2 A) Patients who received haloperidol

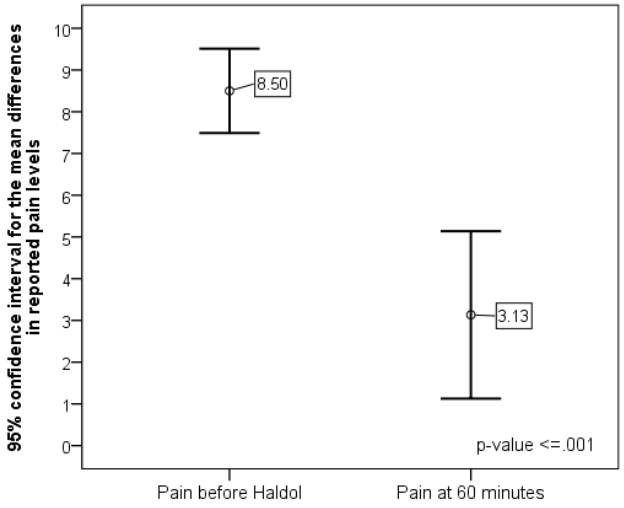


Figure 2 B) Patients who received placebo

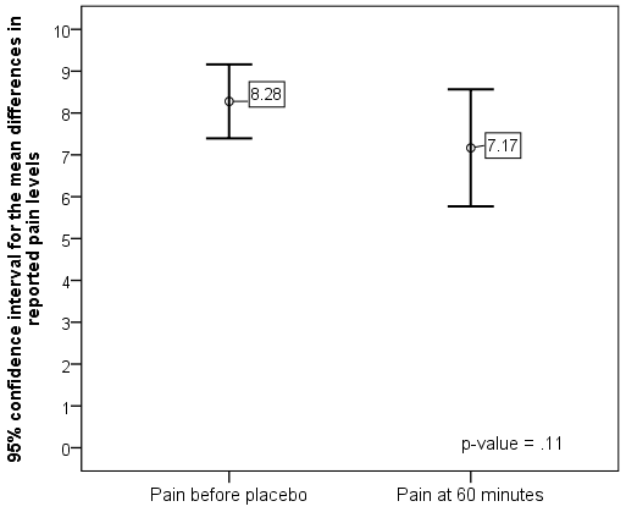


Figure. 2A. Pain intensity in a 10-point VAS at 60 minutes after haloperidol administration. **Figure. 2B**. Displays same information for patients receiving Placebo. Diagram shows 95% confidence intervals for the mean differences of pain levels. The tests show a statistical difference between the groups favoring the Haloperidol group (P < .001).

FIGURES OUTCOME NAUSEA

Figure 3 A) Patients who received haloperidol

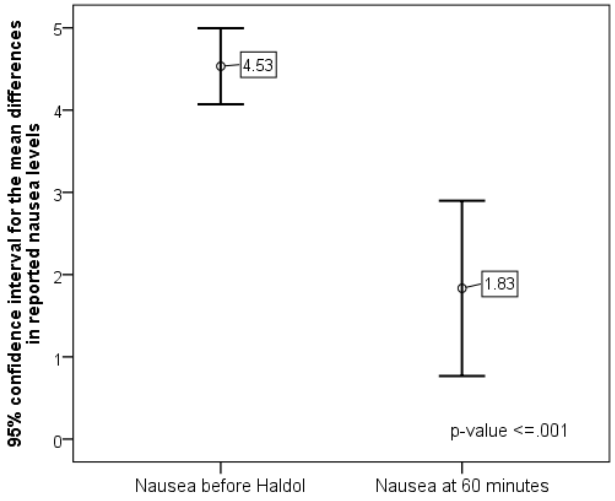


Figure 3 B) Patients who received placebo

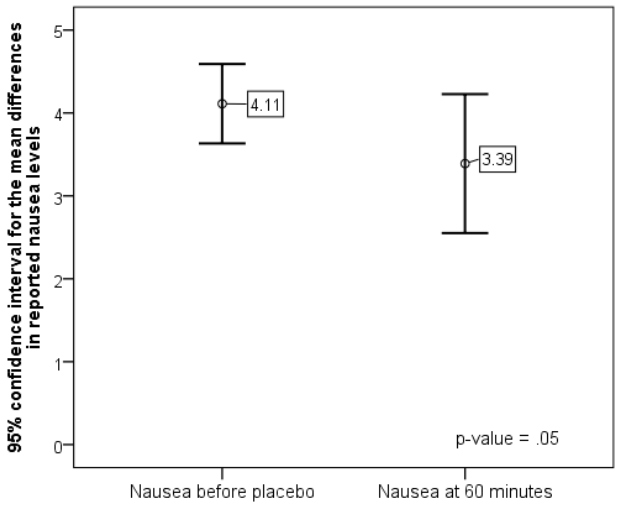


Figure. 3A. Nausea intensity in a 5-point scale at 60 minutes after haloperidol administration. **Figure**. **3B.** Displays same information for patients receiving Placebo. Diagram shows 95% confidence intervals for the mean differences of nausea levels. The tests show a statistical difference between the groups favoring the Haloperidol group (P < .001).