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Randomized Placebo-controlled Trial of Droperidol and Ondansetron for Adult Emergency Department Patients With Nausea

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ABSTRACT

Objective: The objective was to separately compare effectiveness of 1.25 mg of intravenous (IV) droperidol and 8 mg of IV ondansetron with 0.9% saline placebo for adult emergency department (ED) patients with nausea. A novel primary outcome measure, expected to aid clinical interpretation of reported results, was employed.

Methods: A randomized controlled trial was conducted at the three EDs of Monash Health, Melbourne, Australia. The design was to demonstrate superiority of the active drugs over placebo. The primary outcome measure of symptom improvement was defined as a visual analog scale (VAS) rating change of –8 mm or more from baseline at 30 minutes posttreatment. Mean VAS changes per group and percentages experiencing the desired treatment effect were also compared. The study was concluded after recruitment of 215 of the planned 378 patients, as interim analysis confirmed that continuation could not result in a finding of superiority.

Results: Of 215 patients, 73 (34%), 71 (33%), and 71 (33%) received droperidol, ondansetron, and placebo. Symptom improvement occurred in 75% (95% confidence interval [CI] = 64% to 85%), 80% (95% CI = 69% to 89%), and 76% (95% CI = 64% to 85%), respectively. Mean VAS changes were –29 mm (95% CI = –36 to –23 mm), –34 mm (95% CI = –41 to –28 mm), and –24 mm (95% CI = –29 to –19 mm), respectively. Desired treatment effects were experienced by 77% (95% CI = 65% to 86%), 73% (95% CI = 61% to 83%), and 59% (95% CI = 47% to 71%), respectively.

Conclusion: For adult ED patients with nausea, superiority was not demonstrated for droperidol or ondansetron over placebo.

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Emergency department (ED) patients commonly suffer nausea and vomiting as part of their presenting symptom complex.[1] Effective treatment is desirable to alleviate patient distress and to reduce the potential for complications. Surveys report that ED patients with nausea expect to receive antiemetic drugs, and that ED doctors are willing to prescribe them.[2,3] ED-based trials, however, have failed to demonstrate superiority for commonly used antiemetic drugs over placebo.[4–7] Doubts have been expressed about these seemingly counterintuitive findings.[8,9] Possible limitations of the currently used outcome measures for the detection of real differences and the difficulty of interpreting the main study results have been highlighted.[10,11]

From 2000 to the present time, ED-based antiemetic trials have all used the standard 100-mm visual analog scale (VAS).[4–6,12–15] Patients rate severity at baseline and after a defined posttreatment period; the change is measured in millimeters. Use of the VAS to monitor nausea severity has a number of advantages. It reliably discriminates between severity subgroups,[16,17] is sensitive for the detection of change, and is easy for patients to use and understand.[18] Difference in mean VAS change between treatment groups has been the primary outcome measure for all three ED-based placebo-controlled trials conducted to date.[4–6] Findings of superiority or equivalence have been based on the statistical significance of the between-group differences, but the clinical interpretation of these results is not straightforward.[10] The "minimum clinically significant difference" (MCSD) for nausea on the VAS, defined as the mean VAS change reported by people who describe their symptoms as being "a little less," was intended to address this difficulty.[16,17] While the MCSD varies a little with baseline severity, it is generally accepted as being between –15 and –20 mm.[16,17] Its usefulness as an aid in antiemetic research, however, has proved to be limited. The seven ED-based antiemetic studies published from 2000 to 2014 reported mean VAS changes of between –22 and –41 mm for 16 of the 19 different treatment groups.[4–6,12–15] As these changes are greater than the MCSD, it can only be inferred that most patients in all groups were improved to some degree. Even if a between-group difference is statistically significant, the clinical significance is difficult to determine when the mean VAS change for both groups is in excess of the MCSD.[10]

To reconsider the prerequisite for a primary outcome measure, it should provide the best evidence with regard to the primary objective. The primary objective of antiemetic treatment for ED patients with nausea is clinically significant symptom improvement. Mean group VAS change does not provide direct evidence for this objective.[10,11] Recent research has demonstrated that ED patients with symptom improvement ("a little less" or "a lot less") reliably report VAS reductions in excess of –5 mm.[11] This is not surprising, since when symptoms remain "the same," multiple studies have reported the upper 95% confidence limits of the reported VAS change for this group to be between –5 and –9 mm.[11,16,17] It follows logically that if symptoms are no longer "the same," they are almost certain to be improved. One study has also found that percentage VAS change from baseline also accurately predicts symptom improvement, reported best cut-off levels for percentage change of –20% and for measured change of –8 mm (R. Meek and A. Graudins, manuscript submitted for publication). From an analysis point of view, compared with treating VAS change as a continuous variable, its reduction to a binary outcome must lessen its sensitivity for detection of between-group differences.[19] This may seem undesirable, but the advantage in this setting is that it will allow the primary objective of symptom improvement to be directly compared between groups.[10,11] In conjunction with more standardly used outcome measures, this should aid the clinical interpretability of results. In turn, this may help clarify the issue of antiemetic drug effectiveness for ED patients,[10] but the usefulness of VAS change cutoff levels is yet to be demonstrated in a prospective antiemetic trial.

The aim of this study was to separately compare droperidol and ondansetron to placebo for the treatment of adult ED patients with nausea. The primary outcome was symptom improvement, which was defined using a measured VAS change cutoff level of –8 mm. Mean measured VAS change, mean percentage VAS change, a percentage VAS change cutoff level of –20%, and patients' experiencing of the desired treatment effect were included as secondary outcomes.

METHODS

Study Design, Setting, and Period

A triple-blind, randomized, controlled trial was designed to demonstrate the superiority of two antiemetic drugs, droperidol and ondansetron, over placebo. The study was conducted at the three EDs of Monash Health, Melbourne, Victoria, Australia. These are Monash Medical Centre (tertiary referral hospital,

ED annual census 79,000 patients), Dandenong Hospital (urban district hospital, ED annual census 72,000 patients), Casey Hospital (urban district hospital, ED annual census 67,000 patients). A convenience sample of eligible patients was recruited from April 1, 2017, to November 10, 2017. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617000224325). Study conduct was approved by the Monash Health Human Research Ethics Committee (HREC).

Eligibility Criteria

Inclusion. Patients aged 18 years or more, with nausea severity at recruitment of 4 or more from any underlying cause. The severity screening used an 11-point verbal rating scale, with 0 being described as no nausea and 10 as the worst nausea imaginable.

Exclusion. Exclusion criteria included the following: 1) allergy to ondansetron or droperidol; 2) prior use (previous 4 hours) of an antiemetic drug (including ondansetron, droperidol, metoclopramide, promethazine, chlorpromazine, prochlorperazine, and any steroid medication [this was done to prevent potential confounding from any of residual ongoing effects of the previously administered drug, possible receipt of varying doses of a study drug, or uncertain effect on outcome of receipt of multiple antiemetics from different drug groups]); 3) too unwell to participate for any reason (e.g., cardiovascular instability or altered mental state [this was subjectively at the discretion of the attending physician and was not further defined]); 4) contraindication to a normal saline infusion (e.g., fluid-restricted patients); 5) Parkinson's disease or restless leg syndrome; 6) current use of a dopamine antagonist medication (including amisulpride, chlorpromazine, clopenthixol or flupenthixol, domperidone, haloperidol, paliperidone, quetiapine, risperidone, thioridazine); 7) cognitive impairment or language barrier compromising study understanding; 8) pregnant or breastfeeding women; or 9) chemotherapy- or radiotherapy-induced nausea.

Objectives and Measures

Primary Objective. The primary objective was the between-group comparisons of the number (percentage) of patients with a measured VAS change of –8 mm or more.

VAS-related Secondary Objectives. The VAS-related secondary objectives were the between-group comparisons of mean measured VAS change, the between-group comparisons of mean percentage VAS change, and the between-group comparisons of the number (percentage) of patients with a percentage VAS change of –20% or more.

VAS-related Outcome Measures. Nausea severity was rated at baseline (t0) and 30 minutes (t30) posttreatment on a VAS. The VAS was labeled as "no nausea" at the left and "worst nausea imaginable" at the right. Measures in millimeters were taken from the left end. Measured change was calculated as t30–t0, as per previous literature. Percentage change was calculated as (t30–t0)/t0. Measured and percentage VAS change cutoff levels of –8 mm and –20% were used to categorize patients as "improved" or "nonimproved." At the time of trial registration, use of only a measured VAS change cutoff of –5 mm was planned. This was based on the one relevant report available at the time.[11] The measured cutoff was altered to –8 mm and the –20% cutoff included due to the findings of a currently unpublished study. This analysis pooled data from three nausea measurement studies that linked VAS and described change in a similar way.[3,11,17] Receiver operating characteristic curve analyses found that both measured and percentage VAS change had equally high accuracy for detection of symptom improvement, with best cut points of –8 mm and –20%.

Other Secondary Objectives and Measures. Other secondary objectives and measures included 1) between-group comparisons of number (percentage) of patients experiencing the desired treatment effect (this was elicited from direct questioning —"The drug I received had the desired effect for me: Yes or No"); 2) number (percentage) of patients requesting additional antiemetic drugs; and 3) adverse events are reported for each group. The most frequently expected events of agitation/sedation (droperidol), dizziness (droperidol), and headache (ondansetron) were specifically assessed. The presence and degree of agitation or sedation was rated on the Richmond Agitation-Sedation Scale (RASS) at the time of the 30-minute nausea severity rating by the attending physician (+4 = combative, +3 = very agitated, +2 = agitated, +1 = restless, 0 = alert and calm, –1 = drowsy, –2 = light sedation, –3 = moderate sedation, –4 = deep sedation, –5 = unrousable). Presence/severity of headache and dizziness were rated on

an adjectival scale as none, mild, moderate, or severe. Any other adverse events of any type were to be noted as free text.

Randomization, Blinding, and Study Drug Preparation

A simple (nonblock, nonstratified) randomization list was generated in the Monash Clinical Trials Pharmacy, where the study drugs were then prepared. Study drugs appeared identical as 4 mL of clear fluid in a 5-mL syringe. Each syringe was labeled with a unique study identification number, the HREC study reference number, and an expiry date. These were kept refrigerated and had a shelf life of 7 days. Prepared study drugs were delivered to each ED as required. While randomization was nonblock, initial deliveries to the Dandenong Hospital, Monash Medical Centre, and Casey Hospital sites commenced, respectively, at number one, number 200, and number 300 on the randomization list. Subsequent deliveries to each site followed in numerical order from those starting numbers.

Study Drugs

Droperidol (Droleptan, Phebra Pty Ltd): 0.5 mL from the 2.5 mg/mL ampoule was diluted with 3.5 mL of 0.9% saline to make a total of 1.25 mg in 4 mL.

Ondansetron (Ondansetron MYX, Mayne Pharma International Pty Ltd): Two of the 4 mg/mL two mL ampoules remained undiluted to make a total of 8 mg in 4 mL.

Placebo: The syringe contained 4 mL of 0.9% sodium chloride.

Study Drug Choice. Droperidol 1.25 mg intravenous (IV) is the only antiemetic drug to have shown a statistically significant greater reduction in mean VAS rating in comparison with placebo.[4] Ondansetron is the most commonly used antiemetic in the ED setting;[2] the 8 mg IV dose was chosen as studies have reported 4 mg IV ondansetron to be equivalent with placebo.[5,6]

Recruitment and Study Procedure

Study education took place prior to and throughout the study period. Sixteen final-year medical students volunteered to assist with recruitment and underwent training with regard to conduct of the study. They were present at a range of times between 08:00 and 24:00, on a variety of days at any of the three study sites. When present, the student assistants monitored the electronic ED tracking system to identify patients with nausea. On these occasions the student would check eligibility by completing an enrollment form which detailed the inclusion and exclusion criteria. If eligible, the student obtained consent and engaged with the clinical staff for the required study drug and IV fluid prescriptions. Attending emergency physicians were also asked to consider recruitment of any patient for whom they intended prescribing an IV antiemetic drug for nausea from any underlying cause. If a student assistant was present, he or she was notified and assisted with the study requirements. If no student was present, the attending physician was asked to complete the enrollment form and obtain informed consent. This enabled patients to be recruited at any time of any day, regardless of whether a student assistant was present or not. It was not feasible to have student assistants present at all sites on every shift of every day. Following enrollment, an IV infusion of 0.9% saline at a rate of 1,000 mL over 4 hours was commenced and the study drug was obtained from the ED medication room refrigerator. After the baseline VAS rating was recorded, the study drug was administered as a hand-delivered, 2-minute IV infusion. At 30 minutes post-treatment, the second VAS rating was taken. At this time, the baseline rating was overleaf and not readily visible, although the patient was not prevented from viewing it if he or she wished. At this time, the patient-centered efficacy question was asked by either the student assistant or the attending clinician (nurse or physician), and information on the specified adverse events was completed. Student assistants confirmed the RASS rating with the attending physician. Other undefined adverse events of any type could be added by either the student or an attending clinician at any time during the ED episode of care. Regardless of other recorded responses, the patient was offered further antiemetic medication. Ondansetron 8 mg IV was recommended, but final choice was at physician discretion. When the inclusion criterion was met but the patient was not recruited, student assistants and recruiting ED clinicians were asked to record reasons for this (e.g., exclusion criteria, patient declined) on an enrollment form.

Data Analysis

Participant flow is reported using the Consort methodology; the analysis is intention to treat. Baseline information of age, sex, initial severity, and underlying condition are reported for each study site. Patients

who were improved and those experiencing the desired effect are reported as number (%) and compared using the chi-square test. As distribution approximates normal, VAS rating change is reported as mean millimeters with 95% confidence intervals (CI)s; mean VAS change was compared using an independent-samples t-test. Use of additional medication and occurrence of adverse events are described.

Data were entered by one investigator (RM) into a secure database (Microsoft Excel 2007) at which time it was deidentified. A random sample of 10% was checked for accuracy by another investigator (SC). Data were analyzed using Stata Version 12.0 statistical software.

Sample Size

This was informed by reanalysis of the raw data from one previous ED-based study, which compared ondansetron (4 mg IV) with placebo.[6] VAS reduction of −8 mm or more was reported by 79 and 57% of patients, respectively.[10] Replication of this result required a sample of 111 per group to demonstrate superiority for ondansetron over placebo ($\alpha = 0.05$, $\beta = 0.90$). This would give a potential between-group difference of 22% (95% CI = 10%–34%) and number needed to treat (NNT) of 5 (95% CI = 3–10). While dependent on the clinical circumstances, a single-digit NNT with an upper 95% confidence limit of 10 or less would generally be considered clinically worthwhile.[20] For this reason, this level of difference was accepted as being clinically significant for this study. No corresponding information was available for droperidol. To allow for a dropout rate of up to 10%, the aim was to recruit 126 patients per group, for a total of 378. The secondary outcomes were not considered relevant for sample size calculation.

Table 1
Baseline Variables: Total Population and Comparison Between Treatment Groups

Variable	Total (*n* = 215)	Droperidol (*n* = 73)	Ondansetron (*n* = 71)	Placebo (*n* = 71)
Study site				
DH	145 (68%)	49 (67%) [55–78]	49 (69%) [57–79]	47 (66%) [54–77]
MMC	50 (23%)	18 (25%) [15–36]	15 (25%) [12–32]	17 (24%) [15–36]
CH	20 (9%)	6 (8%) [3–17]	7 (10%) [4–19]	7 (10%) [4–19]
Age (years), median (IQR)	44 (32–60)	42 (31–61)	47 (36–63)	44 (26–58)
Male sex, *n* (%) [95% CI]	87 (40%) [34–47]	30 (41%) [30–53]	26 (37%) [25–49]	31 (44%) [32–56]
Baseline VAS (mm), median (IQR)	60 (47–75)	60 (47–80)	59 (47–75)	62 (46–75)
Major diagnostic groups (*n* > 10)				
Gastroenteritis	42 (20%)	11 (15%) [8 - 25]	12 (17%) [9 - 28]	19 (27%) [17 - 39]
Infective illness	40 (19%)	17 (23%) [14–35]	9 (13%) [6–23]	14 (20%) [11–31]
AP–U	29 (13%)	7 (10%) [4–19]	12 (17%) [9–28]	10 (14%) [7–24]
AP–S	28 (13%)	10 (14%) [7–24]	10 (14%) [7–24]	8 (11%) [5–21]
Opioid-related	17 (8%)	3 (4%) [1–12]	11 (15%) [8–26]	3 (4%) [1–12]
Gastritis (type unspecified)	13 (6%)	9 (12%) [6–22]	0 (0%) [0–5]	4 (6%) [2–14]
Drug/alcohol (excluding opioids)	12 (6%)	4 (5%) [2–13]	4 (6%) [2–14]	4 (6%) [2–14]
Other	34 (16%)	12 (16%) [9–27]	13 (18%) [10–29]	9 (13%) [6–23]

AP–S = abdominal pain, associated with specified condition (e.g., appendicitis, pancreatitis); AP–U = abdominal pain, underlying condition unspecified/unknown; CH = Casey Hospital; DH = Dandenong Hospital; IQR = interquartile range; MMC = Monash Medical Centre.

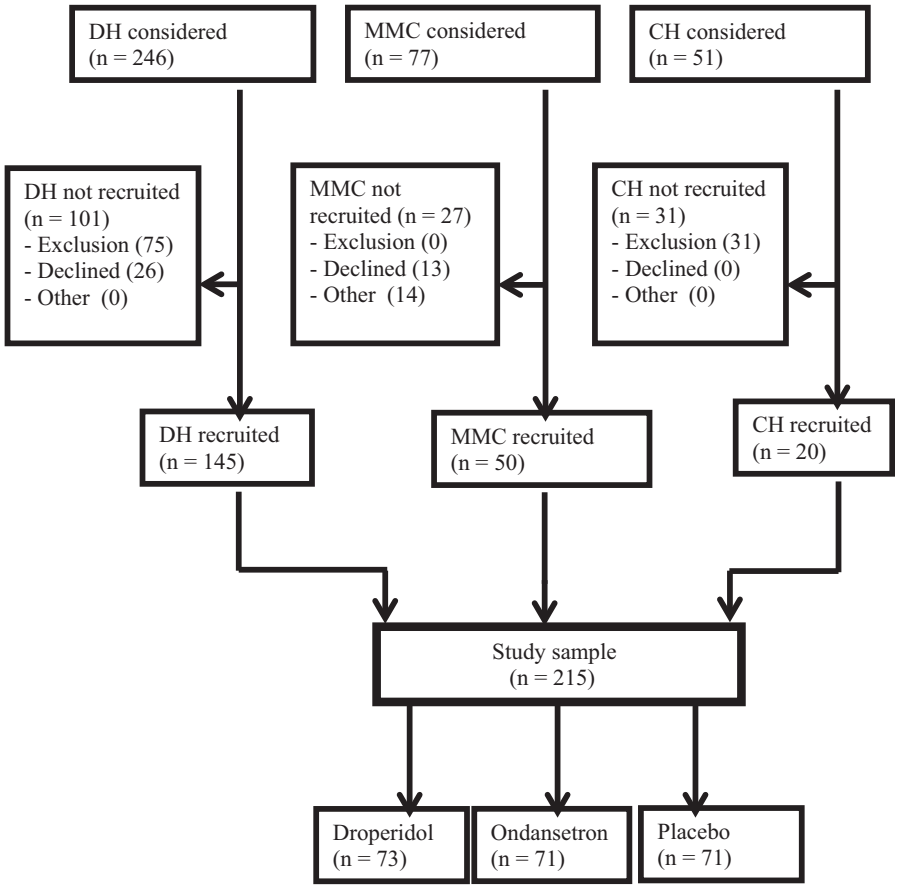

Figure 1. Patient flow diagram. CH = Casey Hospital; DH = Dandenong Hospital; MMC = Monash Medical Centre.

Table 2
VAS Changes and Experiencing of the Desired Effect: Individual Treatment Groups and Between-group Differences

	Individual Treatment Groups			Between-group Differences		
Outcome Measure	Droperidol (*n* = 73)	Ondansetron (*n* = 71)	Placebo (*n* = 71)	Droperidol–Placebo	Ondansetron–Placebo	Ondansetron–Droperidol
Measured VAS change ≥ –8 mm, *n* (%) [95% CI]	55 (75%) [64 to 85]	57 (80%) [69 to 89]	54 (76%) [64 to 85]	–1% [–15 to 13] NNT = 99*	4% [–10 to 18] NNT = 25	5% [–9 to 19] NNT = 20
Mean measured VAS change, mm [95% CI]	–29 [–36 to –23]	–34 [–41 to –28]	–24 [–29 to –19]	5 [–3 to 13]	10 [2 to 18]	5 [–4 to 14]
Percentage VAS change ≥ 20%, *n* (%) [95% CI]	54 (74%) [62 to 84]	53 (75%) [63 to 84]	52 (73%) [61 to 83]	1% [–13 to 15] NNT = 99	2% [–12 to 16] NNT = 50	–1% [–15 to 13] NNT = 99†
Mean percentage VAS change, % [95% CI]	–50% [–59 to –40]	–55% [–64 to –46]	–41% [–49 to –33]	9% [–3 to 21]	14% [–2 to 26]	5% [–8 to 18]
Experienced desired effect, *n* (%) [95% CI]	56 (77%) [65 to 86]	52 (73%) [61 to 83]	42 (59%) [47 to 71]	18% [3 to 33] NNT = 5	14% [–1 to 29] NNT = 7	–4% [–18 to 10] NNT = 5†

NNT = number needed to treat; VAS = visual analog scale.
*Favoring placebo.
†Favoring droperidol; others favor first named treatment.

Interim Analysis and Sensitivity Analysis

Due to ongoing concerns about the limited support for the calculated sample size, an interim analysis was performed after recruitment of 215 patients. Specialist statistical advice confirmed that there was no realistic prospect of demonstrating superiority for the active drugs over placebo by continuing recruitment to the planned sample size. A sensitivity analysis was

conducted: additional potential treatment successes ("best imaginable" for the active drugs and "lowest imaginable" for placebo) were calculated as follows: (remaining number per group to reach $n = 111$) × (upper 95% confidence limit for active drugs or lower 95% confidence limit for placebo). This number was added to the actual number of improved patients in each group at the time of the analysis. "Best imaginable" between-group differences were calculated from these theoretical treatment success rates.

RESULTS

Characteristics of the Study Subjects

A total of 215 patients were recruited, 145 (68%) at Dandenong Hospital, 50 (23%) at Monash Medical Centre, and 20 (9%) at Casey Hospital. The median age of all participants was 44 years (range = 18–91 years), 40% were male, and the mean baseline VAS rating was 61 mm (95% CI = 58–65 mm). There were no significant differences in baseline characteristics between sites (Table 1). Patient flow is detailed in Figure 1.

Of the 215 patients, 73 (34%), 71 (33%), and 71 (33%) received droperidol, ondansetron, and placebo, respectively. Similar proportions were recruited to each group at each study site; between-group differences for age, sex, baseline severity and diagnostic groupings were not significant (Table 1). The median time between study drug administration and the second VAS rating was 30 minutes (interquartile range [IQR] = 30–35 minutes).

Main Results

Primary Outcome. Numbers with VAS change of –8 mm or more for droperidol, ondansetron, and placebo were similar, being 55 of 73 (75%, 95% CI = 64%–85%), 57 of 71 (80%, 95% CI = 69%–89%), and 54 of 71 (76%, 95% CI = 64%–85%), respectively ($p = 0.75$, Pearson chi-square). The between-group differences and NNT are shown in Table 2.

Secondary VAS-related Outcomes. The mean measured VAS changes for the droperidol, ondansetron, and placebo groups were –29 mm (95% CI = –36 to –23 mm), –34 mm (95% CI = –41 to –28 mm), and –24 mm (95% CI = –29 to –19 mm); the mean percentage VAS changes were –50% (95% CI = –59% to –40%), –55% (95% CI = –64% to –46%), and –41% (95% CI = –49% to –33%), respectively. Percentage VAS change of –20% or more was reported by 74% (95% CI = 62% to 84%), 75% (95% CI = 63% to 84%), and 73% (95% CI = 61% to 83%), respectively. Treatment having the desired effect was reported for droperidol, ondansetron, and placebo by 77% (95% CI = 65%–86%), 73% (95%

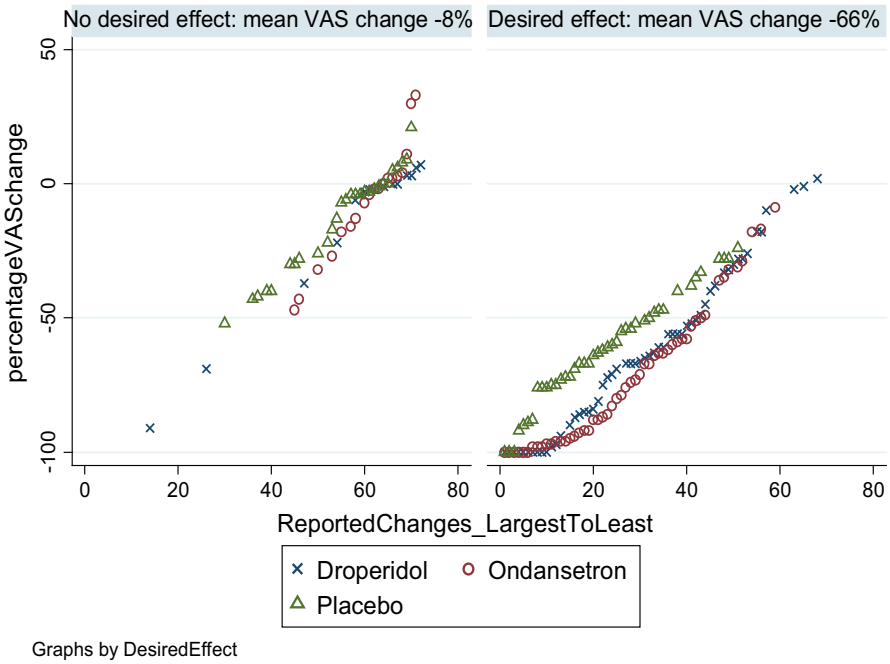

Figure 2. Individual percentage VAS changes: desired treatment effect or not for each treatment group. Percentage VAS change is shown for each patient in sequence from the largest to the least amounts of reported change. VAS = visual analog scale.

CI = 61%–83%), and 59% (95% CI = 47%–71%), respectively. Full values, between-group differences and NNT (where applicable) are shown in Table 2. Measured and percentage VAS reductions were significantly greater when the desired effect was experienced versus not (both $p < 0.001$, independent-samples t-test). For measured VAS change this was –39 mm (95% CI = –43 to –36 mm) versus –7 mm (95% CI = –11 to –2 mm); for percentage VAS change this was –66% (95% CI = –70% to –62%) versus –8% (95% CI = –15% to –1%). Individual patient percentage VAS changes for those experiencing the desired treatment effect versus not are illustrated for each treatment group in Figure 2.

Other Secondary Outcomes. Additional antiemetic medication was requested by 11 of 73 (15%, 95% CI = 8%–25%), 16 of 71 (23%, 95% CI = 13%–34%), and 21 of 71 (30%, 95% CI = 19%–42%), respectively. Of the 48 who requested extra medication, 43 (90%) had not experienced the desired treatment effect.

A reduced level of alertness (moderate sedation, light sedation or drowsiness) was noted significantly more often in the droperidol group, compared with the ondansetron and placebo groups (27/73 [37%, 95% CI = 26%–49%] vs. 9/71 [13%, 95% CI = 6%–23%] and 12/71 [17%, 95% CI = 9%–28%], respectively, $p = 0.001$ [Pearson chi-square]). Restlessness or agitation was noted for four of 73 (5%, 95% CI = 2%–13%), two of 71 (3%, 95% CI = 0%–10%), and two of 71 (3%, 95% CI = 0%–10%), respectively. Headache was reported by 12 of 73 (16%), 13 of 71 (18%), and 20 of 71 (28%), respectively. Dizziness was reported by 11 of 73 (15%), five of 71 (7%), and 11 of 71 (15%), respectively.

Sensitivity Analysis and Quality Control

Calculations for the sensitivity analysis, as defined, found that the greatest imaginable treatment success rates for droperidol and ondansetron, and lowest imaginable for placebo, were 87 of 111 (79%, 95% CI = 71%–87%) and 93 of 111 (84%, 95% CI = 77%–91%) versus 80/111 (72%, 95% CI = 64–80), respectively. The differences between the three groups was not statistically significant ($p = 0.12$, Pearson chi-square). VAS change was remeasured from 22 randomly selected case report forms. Of these, the measured VAS change differed by 0 to 1 mm for 19 (87%) and by 2 to 3 mm for three (13%).

Nonenrolled Patients

Data were collected on 159 nonenrolled patients who met inclusion criteria. Median age was 49 years (IQR = 32–67 years) and 124 (78%) were female. Of the 159, a total of 106 (67%) had exclusion criteria. The most frequent were as follows : 43 (41%) received an antiemetic drug prior to ED arrival, 21 (20%) had cognitive impairment, and 16 (15%) were pregnant. Of the 53 without exclusion criteria, 39 (74%) declined participation; the remaining 14 were not recruited for a variety of reasons including ED activity at the time and lack of an available study drug syringe.

DISCUSSION

For a population of adult ED patients with nausea from any underlying cause, this study did not demonstrate superiority for either droperidol or ondansetron in comparison with placebo. VAS reductions of –8 mm or more were reported by 75, 80, and 76%, respectively. While the between-group comparison favored ondansetron over placebo, the 4% difference was not statistically significant; the NNT of 25 is not clinically worthwhile. This is not to say that all treatments are equally effective. This was not designed as an equivalence trial, which would be unusual for a placebo-controlled study. It should also be noted that in this setting, placebo does not equate with "no treatment." Patients are still being actively managed for the primary condition to which their nausea relates. As expected, the symptom improvement rates predicted by the percentage VAS change cutoff level of –20% were almost identical to those detected by the measured VAS change cutoff.

Although the primary outcome measure of symptom improvement differs from that used in the previous research on the topic, the finding remains generally consistent.[4–7] Ever since the first ED-based, placebo-controlled antiemetic trial was published in 2006,[4] there has been a consistent lack of support for the effectiveness of antiemetic drugs in the ED setting.[4–7] In the past, a number of reasons have been proposed in the literature as to why the multiple study findings might be erroneous.[8,9] The difficulty in accepting that antiemetic drugs may offer little for ED patients might stem from the decades of apparent support for their effectiveness in the postoperative and oncology settings. In those fields, studies have consistently demonstrated that the prophylactic administration of antiemetic drugs reduces the incidence of poststimulus

(anesthetic or chemotherapy) nausea and vomiting.[21–25] Interestingly, however, when nausea does develop after delivery of chemotherapy or in postoperative patients, difference in its severity has not been demonstrated between treatment groups.[24,26] Perhaps antiemetic drugs are more effective for prevention than they are for cure.

A number of the secondary outcomes were of interest. While the percentages reporting symptom improvement were similar between all groups, experiencing of the desired treatment effect was not. This was reported by 77 and 73% for droperidol and ondansetron, but only by 59% of the placebo group. This may seem inconsistent with the symptom improvement results, but these outcomes reflect different amounts of symptom change. The VAS change cutoff levels identify patients whose symptoms are either "a little less" or "a lot less," while experiencing the desired effect requires symptoms to be "a lot less."[3] Given this, the difference in the desired effect findings is most likely explained by the relative difference in the mean VAS changes between groups. For measured change, these were −29, −34, and −24 mm for the droperidol, ondansetron, and placebo groups. It is conceivable that the somewhat lesser mean VAS change for the placebo group resulted from fewer patients having the greater VAS reductions, which are reported when symptoms become "a lot less." This inference is supported by relatively more in the placebo group requesting additional medication (30%) in comparison with the droperidol and ondansetron groups (15 and 23%). It has previously been reported that most patients wanting additional antiemetic medication are those who have improved but not by the desired amount.[3] The NNT for experiencing the desired effect of 5 and 7 for droperidol and ondansetron, in comparison with placebo, may be clinically worthwhile but these point estimates are fairly imprecise. Despite this, it may still be useful to balance this information against other factors such as drug costs and side effects when making individual treatment recommendations. For the drugs used in this study, the costs are low and the reasonably minor adverse effects did not require any treatment.

The purpose of primarily comparing symptom improvement rates between groups was to enable findings that directly related to the primary treatment objective to be presented in a format that is easy to clinically interpret.[10] It was hoped that this would aid understanding of relative treatment effectiveness in a way which might be beneficial for both treating doctors and patients. It is not useful, for example, to inform a patient that without antiemetic drug treatment their nausea severity is likely to improve by about −24 mm on the VAS, but that on average, ondansetron might reduce it by −34 mm. The following seems far more helpful: "Whether or not you have an antinausea drug, there is a 75 to 80% chance that your nausea will ease as your underlying condition is treated. Ondansetron might give a little extra benefit to about one-in-seven of those who do improve. There are some people, however, whose nausea will not quickly settle no matter what we do. Ondansetron may have some side-effects, but these are usually fairly mild."

With regard to future ED-based antiemetic research, it should be remembered that the studies to date have only examined the response to a single administration of one drug at 30 or 60 minutes posttreatment. The response to higher drug doses, repeated dosages over a longer time period, or the concurrent delivery of antiemetic drugs from different groups may be quite different. Characterizing treatment responders versus non-responders could also be of value and the need for condition-specific research has never been entirely discounted.[27]

LIMITATIONS

Consideration of the outcome measures used in ED-based antiemetic studies remains important. Between-group comparisons of mean VAS change have previously failed to demonstrate superiority for antiemetic drugs over placebo. The VAS change cutoff level included as an outcome measure in this study may have aided clinical interpretation of the results, but it also failed to demonstrate superiority for the active drugs. For ED patients, antiemetic drugs may truly provide little additional benefit to that derived from treatment of their underlying condition. It may also be that outcome measures and methods of analysis capable of detecting a real difference are yet to be determined and successfully trialed.

The original sample size calculation for the study was based on "anticipated" symptom improvement rates for ondansetron and placebo of 79 and 57%. As this was drawn from a post hoc analysis of only one study,[6,10] doubts about the accuracy of the estimate persisted. For this reason, conduct of an interim analysis was deemed prudent, and in retrospect, not

preplanning this was an error. At that time, it was found that the "actual" and "anticipated" symptom improvement rates for the placebo group were markedly different (76% vs. 57%). Also, the mean VAS change of –29 mm for droperidol was much lower than the –55 mm previously reported.[4] The degree of these differences is probably not surprising given the known variation in mean VAS changes for the same treatment regimens in different ED-based studies. For example, two different studies reported posttreatment mean VAS changes for ondansetron (4 mg IV) of –34 and –22 mm;[5,13] two other studies reported mean VAS changes for placebo of –39 and –16 mm.[4,5] This is despite patient populations appearing otherwise similar.

Other potential limitations include that the convenience sample may not be representative of all ED patients with nausea. Recruitment was probably more frequent when student research assistants were present, but the number of patients enrolled by students versus duty clinical staff was not recorded. Although incomplete, monitoring of reasons for nonrecruitment was attempted. Prehospital antiemetic administration was the most frequent reason for exclusion. This may have led to recruitment of fewer patients with severe nausea; the potential impact of this on results is unknown. Although the study instructions dictated that all patients have 1000 mL of IV 0.9% saline running at a 4-hourly rate, exact amounts of fluid received during the 30-minute study period may have varied.

CONCLUSIONS

For adult ED patients with nausea, this study did not demonstrate superior symptom improvement rates for 1.25 mg of intravenous droperidol or 8 mg of intravenous ondansetron in comparison with placebo. The marginally greater mean visual analog scale reductions and rates of experiencing the desired treatment effect in the active drug groups may aid treatment decision making in individual cases.

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