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ORIGINAL RESEARCH

Droperidol *versus* ondansetron for nausea treatment within the emergency department

Lachlan PHILPOTT [1], Ellie CLEMENSEN [1] and Gabriel T LAU [1,2]

[1]Faculty of Medicine and Health, The University of New South Wales, Sydney, New South Wales, Australia, and [2]Emergency Department, Port Macquarie Base Hospital, Port Macquarie, New South Wales, Australia

Abstract

Objective: A randomised single-blind trial was undertaken in an adult ED population, comparing the effectiveness of droperidol 2.5 mg IV with ondansetron 8 mg IV for the treatment of nausea and vomiting.

Methods: Patients were randomly allocated to receive droperidol ($n = 60$) or ondansetron ($n = 60$). Patients rated their nausea severity on a Visual Analogue Scale (VAS) immediately before and 30 min after drug administration. The primary outcome was of symptom improvement, defined by a VAS change ≥−8 mm 30 min post-treatment. Mean VAS change and percentage experiencing desired effect were secondary outcomes compared.

Results: Of 120 study patients, 60 (50%) received droperidol or ondansetron. Symptom improvement occurred in 93% (56 of 60) and 87% (52 of 60), respectively ($P = 0.362$). Mean VAS change was −38 mm and −29 mm, respectively ($P = 0.031$). Percentage of patients indicating desired effect was 85% and 63%, respectively ($P = 0.006$). Additional antiemetics were required for 16% and 37% of subjects, respectively ($P = 0.006$).

Conclusion: There was no statistically significant difference in the primary outcome of symptom improvement between droperidol and ondansetron. Secondary outcomes which favour droperidol warrant further exploration.

Key words: *antiemetic, droperidol, emergency department, nausea, ondansetron.*

Key findings

- The present study did not demonstrate evidence of a difference in symptom improvement (VAS change ≥−8 mm) rates between droperidol and ondansetron.
- For the secondary outcome of between-group mean VAS change, a statistically significant difference was demonstrated, −38 mm reduction for droperidol 2.5 mg IV compared with −29 mm for ondansetron 8 mg IV.
- As droperidol had a higher proportion of patients experiencing the desired treatment effect, the difference in mean VAS change may indicate a clinical benefit.

Introduction

Successful treatment of nausea and vomiting within the ED is important for patient comfort and the prevention of complications. Most patients within the ED expect antiemetic treatment if symptoms are worse than mild, antiemetics to be effective by 30 min, and for treatment to make their symptoms a 'lot' less.[1] Ten randomised controlled trials on ED antiemetic use have been conducted since 2008, with no conclusive or clinically significant evidence showing superiority of one antiemetic over another or placebo.[2–10] The only study to find superior antiemetic efficacy of droperidol over placebo was an ED placebo-controlled trial from 2006.[11] Given the relative absence of a clearly superior antiemetic, pharmacological treatment of nausea in the ED appears to be governed by clinician preference, preferred route of administration and safety perceptions.

One issue with the reporting of past ED-based antiemetic trials is that the clinical interpretation of the primary outcome measures is not straightforward. The Visual Analogue Scale (VAS) has been used to measure antiemetic efficacy. Nausea severity is marked on a plain 100 mm horizontal line, with non-standardised labels at the left- (none, nil, minimal) and right-hand (severe) endpoints.[2,3,5,7–11] The VAS has been useful for measuring nausea as it reliably stratifies the population into severity subgroups, is sensitive in detecting change, and is easy to complete and understand.[12,13] The difference in mean VAS change between treatment groups has been the primary outcome measure of at least three ED-based placebo-control

Correspondence: Associate Professor Gabriel T Lau, Emergency Department, Port Macquarie Base Hospital, Wrights Road, Port Macquarie, NSW 2444, Australia. Email: gabriel.lau@health.nsw.gov.au

Lachlan Philpott, Medical Student; Ellie Clemensen, Medical Student; Gabriel T Lau, MD, FACEM, Emergency Physician.

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trials.[3,7,11] In contrast to more traditional between-group comparisons of mean change in VAS, it has recently been suggested that comparing rates of symptom improvement would be more meaningful, defined as a VAS change of ≥−8 mm.[14]

Ondansetron is a selective 5-HT_3 receptor antagonist with antiemetic properties. It is commonly given parenterally in the ED because of its safety profile and utility in other clinical settings (e.g. post-chemotherapy-related nausea).[15] Droperidol is a butyrophenone neuroleptic with effects caused by dopaminergic blockade of various brain receptors. It is an older medication with antiemetic properties making it useful in the treatment of nausea and vomiting.[16] Droperidol usage had fallen out of favour because of fears concerning QT interval prolongation and torsades de pointes.[17] However, its use has been revisited based on several studies demonstrating use without adverse events.[9,11,18] Although droperidol may be given in ED settings to treat nausea and vomiting, its efficacy compared to placebo is unclear, with mixed results being reported in studies, generally using a parenteral dose of 1.25 mg.[9,11] Use of a higher dose of droperidol (2.5 mg) has not been well studied.

The aim of the present study was to compare the effectiveness of ondansetron 8 mg IV with droperidol 2.5 mg IV for nausea and vomiting in ED patients. The primary outcome measure was symptom improvement, defined as VAS change ≥−8 mm, with between-group mean VAS change, patients experiencing a desired effect, and rates of additional antiemetic usage also being examined.

Identification of a superior medication could result in more rapid patient comfort, decreased length of stay in an ED, an earlier opportunity to transition patients onto oral hydration, and less likelihood of returning to the ED with recurrence of symptoms.

Methods

Study design

A multicentre single-blinded randomised trial involving a convenience sample of ED patients with nausea and/or vomiting was undertaken. The study was conducted across two primary ED sites, Port Macquarie Base Hospital (regional hospital, ED annual census 41 000 patients) and Kempsey District Hospital (rural district hospital, ED annual census 35 000 patients). Patients were recruited from 4 February 2020 to 18 August 2021. Participant flow is reported using the CONSORT methodology, refer to Figure 1. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12619001205123). The study was approved by the North Coast NSW Human Research Ethics Committee (2019/ETH12203). Patients provided written consent which was stored in a secure filling cabinet on site.

Population

Eligible participants were those reporting a nausea severity of 4+ on the 11-point (0–10) Numeric Rating Scale (NRS) and 18+ years of age. Exclusion criteria is outlined in Table 1.

Outcome measurement

The primary outcome was a between-group comparison of the percentage of patients reporting a VAS change of ≥−8 mm 30 min post-medication administration. As previously reported, this delivers a clinically interpretable representation of symptom improvement.[14] Symptoms were measured at the time of medication administration and after 30 min. The VAS was labelled as 'no nausea' on the far-left and 'worst nausea imaginable' on the far-right. Secondary outcomes included between-group comparisons of mean VAS change and the number of patients who received additional antiemetic medication, reported adverse effects, or experienced a desired effect. Post-medication sedation was recorded using the Richmond Agitation-Sedation Scale, a 10-point scale ranging from +4 (combative) to −5 (unarousable).[19]

Randomisation and blinding

A simple non-block, non-stratified, randomisation list was created using MS Excel random number function, with

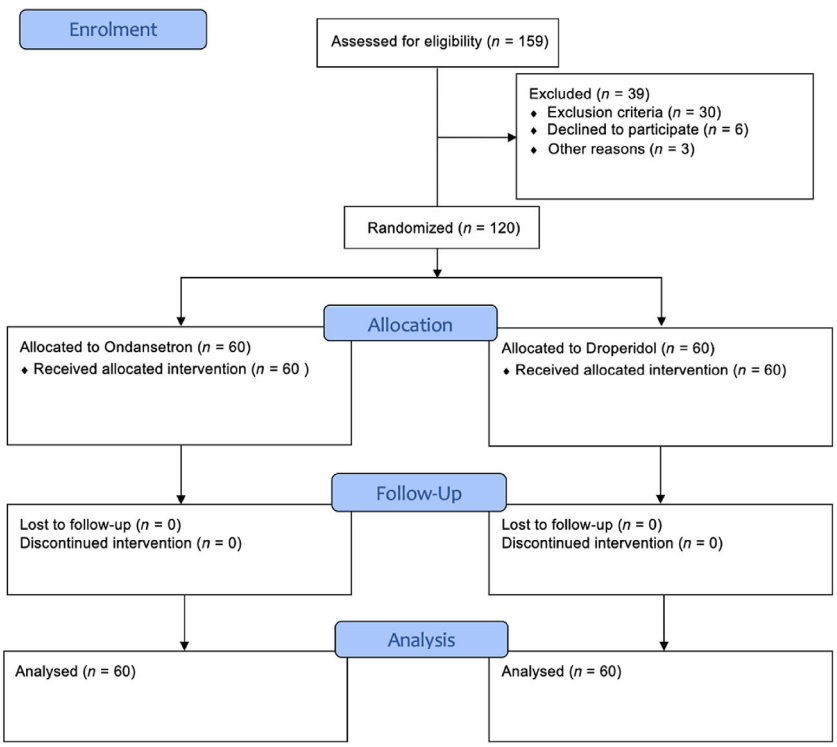

Figure 1. *Patient flow diagram.*

TABLE 1. *Exclusion criteria*

(1) Allergy to ondansetron or droperidol
(2) Clinical instability, subjectively determined by the treating clinician
(3) Contraindication to IV fluids
(4) Presence of Parkinson's disease or restless leg syndrome
(5) Presence of motion-related nausea or vertigo
(6) Pregnancy or breastfeeding
(7) Undergoing current chemotherapy or radiation
(8) Inability to not drive or operate machinery for 4 h
(9) Presence of cognitive impairment/language barrier preventing understanding of scales and outcome measures
(10) Received an antiemetic within the past 4 h
(11) Taking a regular dopamine antagonist

both intervention groups containing an equal number of participants. The data packets were numbered, which acted as the study identification. Data packet allocation to each site was non-block and non-stratified. Each data packet number was randomised to contain an intervention ticket instructing the practitioner to administer either ondansetron 8 mg IV or droperidol 2.5 mg IV.

Randomisation and preparation of data packets was completed by an investigator who was not involved in patient enrolment and assessment. Enrolled patients completing the case report form were not informed which drug would be administered. The investigator compiling the VAS measurements and other secondary outcomes was blinded to the study drug and was only unblinded during data entry.

Study drugs

Subjects were given either ondansetron 8 mg IV (Accord Healthcare Pty Ltd) or droperidol 2.5 mg IV (Droleptan, Phebra Pty Ltd). Two ampoules of ondansetron 4 mg were combined to make the 8 mg dose. Droperidol was provided in a 2.5 mg ampoule. The selected medication was drawn up into a syringe and administered undiluted.

Ondansetron was used because it is one of the most utilised antiemetics and has a known safety profile.[15] The dose of ondansetron was selected based on a recent ED antiemetic study.[9] Droperidol 2.5 mg IV was chosen because ED-based studies involving 1.25 mg IV have had mixed results,[9,11] whereas effectiveness of a 2.5 mg IV dose is supported in the postoperative setting.[20,21]

Recruitment and intervention

Emergency staff identified potential participants using an enrolment sheet listing an initial numerical nausea severity score along with inclusion/exclusion criteria. All recruited patients had an IV cannula inserted. After obtaining consent, the treating clinician removed a pre-allocated ticket from the next sequentially numbered study packet indicating to which treatment arm the patient would be assigned. The data packet number served as the study identification number and was entered onto the case report form.

Participants were blinded to which drug treatment they would be receiving and initially self-assessed their nausea severity on the initial VAS on the case report form. The treating clinician then provided the intervention medication of either ondansetron 8 mg or droperidol 2.5 mg as an IV bolus. This was followed by an IV infusion of 1 L of 0.9% sodium chloride over 4 h. After 30 min, participants again self-assessed their nausea severity on the second VAS on the case report form. Following the 30-min assessment, further antiemetic administration (drug and dosage) was at the discretion of the treating clinician.

Data collected included: age, sex, initial NRS, presumed reason for nausea, initial VAS, the time the antiemetic was given, VAS after 30 min, participant response regarding the intervention having a desired effect, any adverse events, and if further antiemetic medication was prescribed. The deidentified data was entered into a secure database (Microsoft Excel) by an investigator not involved with data collection.

Sample size

Sample size calculation was limited by the paucity of relevant previous literature. Based on an expected improvement rate of approximately 75% for ondansetron 8 mg IV and a desired improvement rate of 95% for droperidol 2.5 mg IV, 60 patients per group were required (alpha 0.05, power 80%).

Data analysis

Data analysis was performed using IBM SPSS Statistics 26. The analysis was intention to treat. Patient flow was reported using the CONSORT methodology. The primary outcome was reported as a proportion. Secondary outcomes examining desired effects and adverse effects were also reported as a proportion. The chi-squared test was used to compare treatment groups for these outcomes. As distribution approximates were normal, independent-samples *T*-test was employed to compare the mean VAS change difference between groups. Adverse events were recorded.

Results

Of the 159 patients initially recruited, 39 exclusions left 120 for analysis. Patient flow is detailed in Figure 1. The median age of the total participants was 50 years, 69% were female and the median baseline VAS rating was 68 mm. There were no significant differences in baseline characteristics between the study sites. Patient characteristics for the

whole sample and between-group comparisons are shown in Table 2. Of the total number of participants recruited in the present study, 60 received droperidol and 60 received ondansetron.

Symptom improvement (VAS change of ≥−8 mm) was reported by 93% (95% CI 87–98%) receiving droperidol and 87% (95% CI 77–95%) receiving ondansetron ($P = 0.362$, chi-squared test), detailed in Table 3. Regarding secondary VAS-related outcomes, the mean measured VAS change was −38 mm for the droperidol (95% CI −45 to −33) and −29 mm for the ondansetron treatment groups (95% CI −35 to −23) ($P = 0.031$, independent *T*-test). Between-group difference for VAS change is illustrated in Figure 2.

Participants indicating that treatment had the desired effect was reported by 85% (95% CI 75–93%) of the droperidol and 63% (95% CI 48–75%) of the ondansetron treatment groups ($P = 0.006$, chi-squared test). Additional antiemetics were received by 16% (95% CI 7–26%) of the droperidol and 37% (95% CI 23–48%) of the ondansetron treatment groups ($P = 0.016$, chi-squared test). Of the 28 who required further antiemetic medication, 22 had not experienced the desired treatment effect. These results are depicted in Table 3.

Drowsiness (−1), as measured by the Richmond Agitation Scale (Fig. 3), was experienced by 40% (95% CI 27–54%) of the droperidol group compared to the 11% (95% CI 2–21%) of the ondansetron group. Light sedation (−2) on the scale was

TABLE 2. *Baseline variables: total population and comparison between treatment groups*

Characteristic	Overall, $N = 120$	Droperidol, $N = 60$	Ondansetron, $N = 60$
Age (years), median (IQR)	50 (28–63)	49 (27–62)	51 (29–64)
Sex			
Female	83 (69%)	43 (72%)	40 (67%)
Baseline VAS (mm), median (IQR) $N = 120$	63 (48–79) $N = 120$	62 (48–78) $N = 60$	68 (47–79) $N = 60$
Major diagnostic group			
Gastroenteritis	28 (23%)	11 (18%) [8–28%]	17 (28%) [17–40%]
Other	21 (18%)	12 (20%) [10–30%]	9 (15%) [7–25%]
Abdominal pathology	19 (16%)	9 (15%) [7–25%]	10 (17%) [8–27%]
Generalised abdominal pain	12 (10%)	5 (8%) [2–17%]	7 (12%) [5–20%]
Infective	12 (10%)	8 (13%) [5–23%]	4 (7%) [2–13%]
Headache	11 (9%)	6 (10%) [3–18%]	5 (8%) [2–15%]
ETOH/Drugs	6 (5%)	3 (5%) [0–10%]	3 (5%) [0–12%]
Cannabis hyperemesis	6 (5%)	2 (3%) [0–8%]	4 (7%) [2–13%]
Bowel obstruction	5 (4%)	4 (7%) [2–13%]	1 (2%) [0–5%]

ETOH, ethanol; IQR, interquartile range; VAS, Visual Analogue Scale.

TABLE 3. *VAS changes and other secondary outcomes*

Outcome measure	Droperidol, $N = 60$	Ondansetron, $N = 60$	*P*-value	Between group differences
Measured VAS change ≥8 mm, *n* (%) [95% CI]	56 (93%) [87–98%]	52 (87%) [77–95%]	0.362	−6% [−28 to 7%] NNT = 16.7
Mean measured VAS change, mm [95% CI]	−38 [−45 to −33]	−29 [−35 to −23]	0.031	−9 [−18 to −1]
Experienced desired effect, *n* (%) [95% CI]	51 (85%) [75–93%]	35 (63%) [48–75%]	0.006	22% [9–44%] NNT = 4.5
Required further antiemetics, *n* = (%) [95% CI]	9 (16%) [7–26%]	19 (37%) [23–48%]	0.016	21% [5–40%] NNT = 4.8

NNT, number needed to treat; VAS, Visual Analogue Scale.

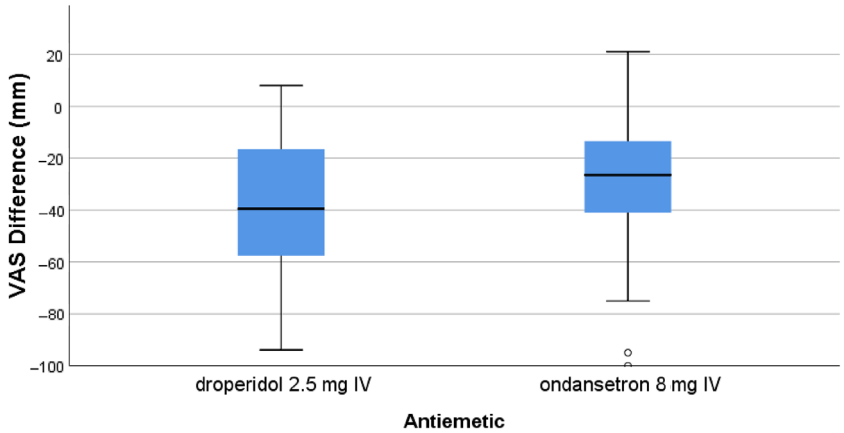

Figure 2. *Boxplot and whisker graph comparing Visual Analogue Scale difference by treatment group.*

experienced by 8% (95% CI 2–15%) of the droperidol group, compared to 4% (95% CI 0–11%) of the ondansetron group. The occurrence of headaches was 8% for droperidol and 5% for ondansetron. The occurrence of dizziness was 2% for droperidol and 5% for ondansetron. There were no reported episodes of akathisia or dystonic reactions during the time of assessment. No other adverse reactions were recorded among participants.

Discussion

The present study did not demonstrate evidence of a difference in symptom improvement (VAS change ≥−8 mm) rates. Although this similarity in primary outcome is generally consistent with the results of previous studies,[2–11] some differences should be noted. The only other study comparing these two medications reported similar symptom improvement rates of 80% and 75% for ondansetron 8 mg IV and droperidol 1.25 mg IV, respectively.[9] By contrast, in the present study symptom improvement rates were 87% and 93% for ondansetron 8 mg IV and droperidol 2.5 mg IV, the latter being a higher dose than previously used. The increased symptom improvement rate for droperidol in the present study met expectations, but the higher success rate for the previously used dose of ondansetron was unexpected. Such inter-study differences for the same drug regimens have previously been noted,[2–11] thus contributing to our inability to detect a statistically significant between-group difference.

For the secondary outcome of between-group mean VAS change, a statistically significant difference was demonstrated, which was not consistent with prior research.[2–10] The study comparing droperidol 1.25 mg IV with ondansetron 8 mg IV reported mean VAS changes of −29 and −34 mm, respectively.[9] In the present study, there was a relatively higher −38 mm reduction for droperidol 2.5 mg IV compared with −29 mm for the same ondansetron 8 mg IV regimen.

A clinical benefit from this greater reduction following the higher droperidol dose is supported by findings concerning the proportion of patients experiencing the desired treatment effect. For droperidol and ondansetron, respectively, these percentages were 85% and 63%. This suggests that although ondansetron was leading to symptom improvement at a similar rate to droperidol, it was not to the degree that the patient desired. This discrepancy between detectable improvement and patient expectations is known, with the present study adding weight to suggest that ED-based antiemetic study primary outcomes may require revisitation.[1,9] There was also a significantly lower rate of additional antiemetic drug use in the droperidol group (16% *vs* 37%) although determining reasons for further drug administration was beyond the scope of the present study.

There were no reports of akathisias, dystonic reactions, or extrapyramidal side effects for either medication. Additionally, there were no reports of over-sedation causing problems for assessment of symptoms at 30 min. The number of participants experiencing some level of sedation was considerably higher for the droperidol group, 48% compared to 15% for ondansetron. This difference is not surprising given that droperidol is used in higher doses for the management of psychosis-induced aggression and agitation.[22]

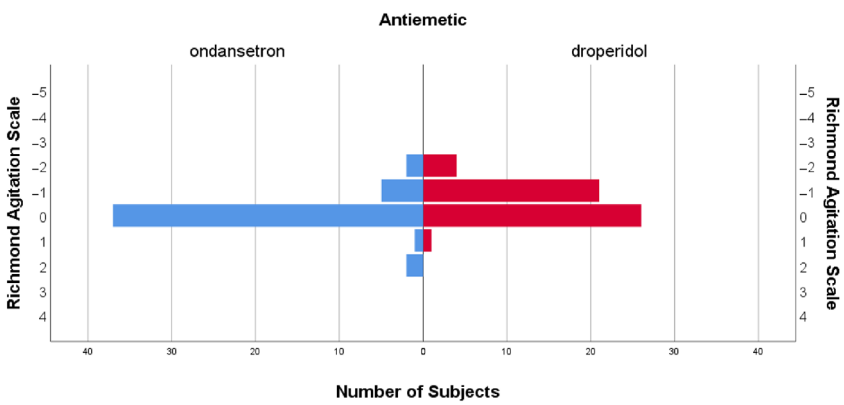

Figure 3. *Histogram Richmond Agitation Scale by treatment group. −5 = unrousable, −4 = deep sedation, −3 = moderate sedation, −2 = light sedation, −1 = drowsy, 0 = alert and calm, +1 = restless, +2 = agitated, +3 = very agitated, +4 = combative.*

The increased sedation may not have impacted on the perceived effects of droperidol. Given that more patients had a 'desired effect' with droperidol, it could be concluded that either the appropriate and timely alleviation of nausea symptoms is desirable even with a significant side effect profile, or that sedation and drowsiness may be considered by patients to be a desirable effect for an undesirable problem such as nausea.

Limitations

A limitation of the present study was that clinicians were not blinded to the intervention medication being administered to participants. Previous studies included a normal saline placebo arm in addition to the medications undergoing comparison.[3,7,9,11] A placebo group was not included in this analysis as this was simply a comparison between two recognised treatments. Although the study protocol suggested that all patients receive 1 L of saline over 4-h, the amount received was not recorded. Despite this, it is unlikely that there would have been a significant difference between groups. As a result of unexpectedly high symptom improvement rates for the ondansetron group, our sample was insufficient to detect a significant between-group difference for this outcome. The relationship between this and the clinical significance of the primary and other secondary outcomes has been discussed. Although the level of sedation from droperidol did not cause any patient-related adversity, we did not evaluate the potential impact from this on ED length of stay. The present study was undertaken in small regional EDs, with a case mix that may differ from metropolitan centres.

Conclusion

For adult ED patients with nausea, the present study did not reveal superior symptom improvement rates for droperidol 2.5 mg of IV compared to ondansetron 8 mg of IV. Superiority of droperidol for the amount of symptom reduction and in achieving the desired treatment effect warrant further exploration.

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Competing interests

None declared.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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