

CLINICAL INVESTIGATION

Palonosetron as prophylaxis for post-discharge nausea and vomiting: a prospective, randomised, double-blind, placebo-controlled trial in ambulatory surgery

Antonio Moraitis^{1,*} , Tomi Myrberg² , Magnus Hultin³ , Helena Nyström³  and Jakob Walldén¹ 

¹Department of Surgical and Perioperative Sciences (Sundsvall), Faculty of Medicine, Umeå University, Umeå, Sweden, ²Department of Surgical and Perioperative Sciences (Sunderbyn), Faculty of Medicine, Umeå University, Umeå, Sweden and ³Department of Surgical and Perioperative Sciences (Umeå), Faculty of Medicine, Umeå University, Umeå, Sweden

*Corresponding author. E-mail: antonio.moraitis@umu.se

Abstract

Background: Approximately 25% of ambulatory surgery patients experience post-discharge nausea and vomiting (PDNV). We aimed to investigate whether palonosetron, a long-acting anti-emetic, decreases the incidence of PDNV in high-risk patients.

Methods: In this prospective, randomised, double-blind, placebo-controlled trial, 170 male and female patients undergoing ambulatory surgery under general anaesthesia, with a high predicted risk for PDNV, were randomised to receive either palonosetron 75 µg i.v. ($n=84$) or normal saline ($n=86$) before discharge. During the first 3 postoperative days (PODs), we measured outcomes using a patient questionnaire. The primary outcome was the incidence of a complete response (no nausea, vomiting, or use of rescue medication) until POD 2. Secondary outcomes included the incidence of PDNV each day until POD 3.

Results: The incidence of a complete response until POD 2 was 48% ($n=32$) in the palonosetron group and 36% ($n=25$) in the placebo group (odds ratio 1.69 [95% confidence interval: 0.85–3.37]; $P=0.131$). No significant difference in the incidence of PDNV was observed between the two groups on the day of surgery (47% vs 56%; $P=0.31$). Significant differences in the incidence of PDNV were found on POD 1 (18% vs 34%; $P=0.033$) and POD 2 (9% vs 27%; $P=0.007$). No differences were observed on POD 3 (15% vs 13%; $P=0.700$).

Conclusions: Compared with placebo, palonosetron did not reduce the overall incidence of PDNV up to POD 2. The lower incidence of PDNV on POD 1 and POD 2 in the palonosetron group requires further investigation.

Clinical trial registration: EudraCT 2015-003956-32.

Keywords: 5HT-3 antagonist; ambulatory surgery; day-care surgery; palonosetron; PDNV; PONV; post-discharge nausea and vomiting; prophylaxis

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Editor's key points

- Post-discharge nausea and vomiting (PDNV) in ambulatory surgery patients is common, distressing and potentially resource intensive. Long-acting agents are available but have not been studied in patients who are selected on the basis of postoperative nausea and vomiting while in hospital.
- In this randomised study, there was no significant difference in the incidence of the primary outcome (PDNV up to postoperative day two) in patients with high predicted risk for PDNV who received intravenous palonosetron or placebo at discharge. In day-by-day analyses, there were significant differences on postoperative days one and two, but not on the operative day or postoperative day three.
- This study identifies a useful strategy for targeting prevention to patients who are at high risk of PDNV, based on postoperative as well as pre- and intra-operative criteria. The secondary findings of differences on postoperative days one and two require further exploration.

After ambulatory surgery under general anaesthesia, the incidence of post-discharge nausea and vomiting (PDNV) is approximately 25% in all patients and up to 80% in patients with high predicted incidence.^{1–5} Besides patient morbidity and discomfort, PDNV may also lead to increased healthcare costs owing to potential re-admission, medical intervention, and increased workload for health professionals.^{3,6}

Surgical trauma, type of anaesthesia, and opioid administration all contribute to the risk of PDNV.⁷ The potential for PDNV can be predicted before discharge with a simplified risk score that includes five factors: age <50 yr, female sex, previous postoperative nausea and vomiting (PONV), postoperative nausea, or postoperative analgesia with opioids. If the patient meets three or more of these risk factors, the predicted incidence of PDNV is high.¹ PDNV has not been studied as extensively as PONV, which is usually limited to the first 24 h; consequently, clinical guidelines regarding PDNV prevention are not as readily available or established.^{1,3,8}

Anti-emetics with longer duration of action, such as long-acting 5-HT₃- and NK₁-receptor antagonists, have been studied for their potential use as PDNV prophylaxis.^{3,6,9–11} Palonosetron is a second-generation 5-HT₃ antagonist with a half-life of 40 h and an anti-emetic effect of up to 2 days.¹² Palonosetron has been investigated in patients undergoing chemotherapy or as PONV prophylaxis, with a reduction in incidence of approximately 25%, which is in line with other commonly used anti-emetics.^{11,13–16} Studies on the use of palonosetron as a PDNV prophylaxis are scarce; therefore, more studies are warranted.^{13,17,18} In addition, selectively administering long-acting anti-emetics to high-risk patients on the basis of a simplified PDNV risk score¹⁷ has not been studied before, to our knowledge.

Therefore, our aim was to determine whether i.v. palonosetron 75 µg (the recommended dose for use as PONV prophylaxis),^{3,11} administered before discharge, decreases the incidence of PDNV in patients with a high predicted risk for the

condition compared with placebo. Our primary objective was to record the incidence of a complete response (no nausea, vomiting, and use of rescue medication), and, based on the expected duration of palonosetron, we considered an observation period until the evening of postoperative day 2 (POD 2) as relevant. Secondary outcome objectives included the incidence of PDNV during each day until POD 3 and the potential side-effects of palonosetron.

Methods**Ethics approval**

This prospective, randomised, double-blind, placebo-controlled trial was conducted at two county hospitals in Sweden (Sundsvall and Sunderby Hospitals) between March 2017 and March 2020. The study protocol was approved by the Regional Ethics Committee in Umeå, Sweden, on March 15, 2016 (reference: 2016-15-31M) and the Swedish Medical Products Agency on March 8, 2016 (reference: 2015-003956-32). The trial was prospectively registered in the EU Clinical Trials Register as part of the approval process (publicly available through www.clinicaltrialsregister.eu reference: EudraCT 2015-003956-32). The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. All participants provided written informed consent.

Inclusion and exclusion criteria

The inclusion criteria were American Society of Anesthesiologists (ASA) physical status 1 or 2 in male and female adult patients aged ≥18 years who were planned to undergo ambulatory surgery under general anaesthesia and had the ability to understand and participate in the study. The exclusion criteria were allergy to the study drugs; collateral risks attributable to pregnancy or breastfeeding; intestinal obstruction that might become aggravated by palonosetron; psychiatric conditions that could affect follow-up compliance; and concomitant treatment with selective serotonin reuptake inhibitors or serotonin–norepinephrine reuptake inhibitors, which are risk factors for triggering a serotonin syndrome when treated with palonosetron.

Conduct of the study

Prospective patients were screened for eligibility and included in the study on the procedure day before anaesthesia and surgery. Anaesthesia management (including perioperative anti-emetic prophylaxis) and postoperative care were provided according to departmental routines and the judgement of the attending anaesthesiologist. Departmental routines for PONV prophylaxis were based on published guidelines.¹⁹ Before discharge from the ambulatory surgical department, the selected patients were evaluated using the simplified PDNV risk score.^{1,2} The score included five independent factors: female sex, age <50 yr, history of nausea or vomiting after previous anaesthesia, opioid administration in the post anaesthesia care unit (PACU), and nausea in the PACU. Patients with three or more risk factors (scores 3–5) were considered at high risk for PDNV and were included in the randomisation arm of the study. Patients with low risk of PDNV (scores 0–2) did not receive any intervention and were

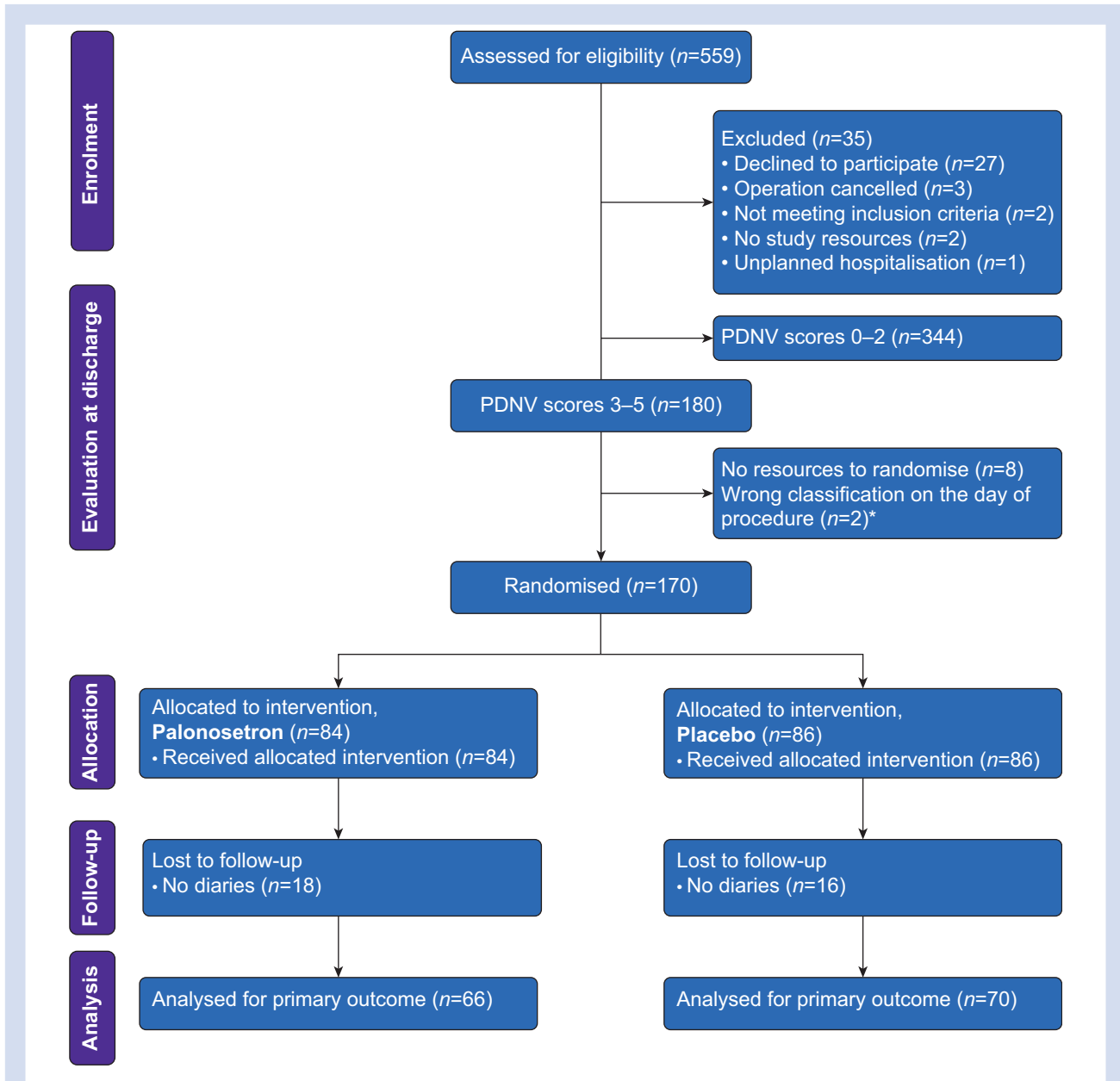


Fig 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. *Two patients with PDNV score of 3 wrongly classified with a score of 2 on the day of the procedure and were not randomised. PDNV, post-discharge nausea and vomiting.

not included for further analysis within the scope of this primary report (Fig. 1).

Randomisation and administration of the intervention drug

Before being discharged home, patients at high risk for PDNV were randomly assigned to either the intervention or placebo group, using a computer-generated block design, stratified for hospital use, in a 1:1 ratio. Allocations were concealed in sequentially numbered, opaque, sealed envelopes prepared by independent study monitors. A nurse,

who was not involved in the care of the patient, opened the numbered envelope and prepared a 3 ml syringe according to the allocation instructions, which either contained palonosetron 75 μg (1.5 ml; Aloxi® 50 $\mu\text{g ml}^{-1}$; Swedish Orphan Biovitrum, Solna, Sweden) or normal saline (1.5 ml). The syringe was labelled with the randomisation number and study identification. The documentation detailing the preparation of the syringe was placed in a separate envelope that was sealed and stored by the study monitor. All other individuals involved in the study (separate research nurse administering the drugs, patients, the research group, and healthcare staff) were

blind to the randomisation and the contents of the syringe. The study drug was administered intravenously, and the patients were observed for a minimum of 30 min before being discharged home.

Rescue anti-emetics

Because the randomised patients were identified as being at high risk for PDNV, we considered it unethical to not provide them with rescue anti-emetics. At discharge, all study participants were given a package of 10 ondansetron 4 mg tablets to be taken orally (one tablet one to three times per day) if they experienced nausea or vomiting. The use of rescue anti-emetics was considered a positive PDNV event included in the primary and secondary outcome measures.

Measurements and data handling

Baseline and perioperative data were collected from the patients and their medical records. After being discharged, the patients were followed up for 3 days with a paper-based questionnaire, which they were instructed to complete each evening (19.00–21.00) until POD 3. The questionnaire included questions regarding the presence, frequency, and intensity of nausea or vomiting. The presence of nausea and vomiting was answered with either yes or no and quantified by writing the number of events of either retching or vomiting that occurred for each time interval and whether the frequency was 'sometimes', 'often', 'most of the time', or 'all of the time'. The question, 'Has your nausea affected what you can do, like get out of bed, move around in bed, walk normally, or eat and drink?', was answered with either yes or no to determine whether patients were functionally affected by their eventual nausea. A numerical scale range of 0–10 was used to evaluate pain. The use of additional/rescue anti-emetics and symptoms classified as potential side-effects of palonosetron (headaches, vision disturbances, and sleeping difficulties) was also included in the questionnaire. The questionnaire is provided as Supplementary file 1.

Primary and secondary outcomes

The primary outcome was the incidence of a complete response (no nausea, vomiting, and use of rescue medication) until the evening of POD 2. The secondary outcomes were the incidence of PDNV (nausea and vomiting or use of rescue anti-emetics) during each day until POD 3 and the incidence of patients experiencing headaches, vision disturbances, and sleeping difficulties.

Safety

The patients were monitored for 30 min to assess immediate reactions to the study drug. The patients' medical records were screened for contacts with healthcare, re-admissions, or hospitalisations within 28 days postoperatively. According to GCP and the study protocol, the patients were assessed for adverse events (AE) and serious adverse events (SAE).

Sample-size calculation

The incidence of PDNV amongst high-risk patients (scores 3–5) was estimated to be 45% or more from discharge until the evening of POD 2.¹ If we considered a 50% reduction in the PDNV incidence as clinically relevant, with a power of 80% and significance of 5%, 138 participants would be required to detect

a 50% reduction in the incidence of patients with PDNV. To compensate for dropouts, we increased the sample size of randomised patients to 170. Furthermore, because only approximately 25% of the patients were expected to be at high risk for PDNV and be included in the randomisation arms, we estimated that approximately 650 patients would need to be included preoperatively.

Statistical analyses

Data were entered into a study database, and after the validation process and data cleaning, the database was locked. Thereafter, the randomisation of each subject was unblinded. The statistical analysis of the outcome measures was made as 'intention to treat'. SPSS (IBM SPSS Statistics for Windows, version 26.0; IBM Corp., Armonk, NY, USA) was used for the statistical analysis. Continuous variables were tested for normality both visually and with the Shapiro–Wilk test. Data are presented as numbers (*n*) with percentages (%), means with standard deviations, or medians with ranges (minimum–maximum), where applicable. We compared the two groups using χ^2 test. A two-tailed $P < 0.05$ was considered statistically significant. An odds ratio with 95% confidence interval (CI) was calculated for the variables.

Results

Of the 559 patients screened for participation, 524 were evaluated before discharge; 170 of the patients were at high risk for PDNV and were randomised. Owing to missing diaries, 34 of the randomised patients were lost during the follow-up period. The final cohort analysed for the primary outcome consisted of 136 randomised subjects (Fig. 1).

Subject characteristics

Most of the subjects were female ($n=123$; 90.4%) with a median age of 43 (18–82) years. All the patients, except for one, had an ASA physical status of 1–2. Anaesthesia was maintained with volatile ($n=83$; 61%) or i.v. agents ($n=52$; 38%) with missing data from one subject in the placebo group. One hundred and eighteen subjects (87%) received at least two anti-emetics perioperatively. No differences in baseline patient characteristics were observed between the study groups (Table 1).

Primary outcome

No difference was observed between the palonosetron and placebo groups in terms of the incidence of a complete response (i.e., no nausea, vomiting, or use of rescue anti-emetics until POD 2), with 32 (48%) subjects in the palonosetron group and 25 (36%) in the placebo group (odds ratio 1.69 [95% CI: 0.85–3.37]; $P=0.131$) (Table 2).

Secondary outcomes

No difference was observed between the two groups in the incidence of PDNV on the day of the surgery (palonosetron 47% vs. placebo 56%; $P=0.31$). Significant differences were observed in the incidence of PDNV on POD 1 (palonosetron 18% vs. placebo 34%; $P=0.033$) and POD 2 (palonosetron 9% vs. placebo 27%; $P=0.007$). No differences were observed on POD 3 (palonosetron 15% vs. placebo 13%; $P=0.700$) (Table 2). Amongst subjects experiencing nausea, no differences were observed

Table 1 Subjects baseline characteristics. Data are expressed as numbers (%) or medians (range). ASA, American Society of Anesthesiologists; ENT, ear, nose, and throat; PACU, postanesthesia care unit; PDNV, post-discharge nausea and vomiting; PONV, post-operative nausea and vomiting; PS, physical status classification. *One subject re-categorised to ASA PS 3 during data validation. The subject's medical history was deemed as not having any interference with the study and kept for analysis. †Missing values for one subject in the placebo group. ‡Missing values for one subject in the palonosetron group.

Variables	Palonosetron (n=66)	Placebo (n=70)
Sex, female, n (%)	59 (89.4)	64 (91.4)
Sex, male, n (%)	7 (10.6)	6 (8.6)
Age (yr)	42.1 (18.5–82.1)	45.3 (18.3–79.1)
Age <50 yr, n (%)	53 (80.3)	49 (70.0)
BMI, kg m ⁻²	25.6 (19.5–42.8)	26.5 (15.6–41.3)
Smoker, n (%)	7 (10.6)	5 (7.1)
ASA PS, n (%)		
1	39 (59.1)	35 (50.0)
2/3	27 (40.9)/0 (0)	34 (48.6)/1 (1.4)*
History of PONV, n (%)	35 (53.8)	38 (54.3)
History of motion sickness, n (%)	34 (51.5)	38 (54.2)
Procedure, n (%)		
General surgery	36 (54.5)	30 (42.9)
Orthopaedic	13 (19.7)	15 (21.4)
Urology	1 (1.5)	2 (2.9)
Gynaecology	11 (16.7)	15 (21.4)
ENT, oral, or maxillofacial	4 (6.1)	8 (11.4)
Ocular surgery	1 (1.5)	0 (0)
Operation time (min)	50 (7–161)	49 (4–201)
Anaesthesia time (min)	94 (30–211)	84.5 (15–250)
Maintenance of anaesthesia, n (%)		
Intravenous agents	26 (39.4)	26 (37.7)
Volatile agents	40 (60.6)	43 (62.3)
Tracheal intubation, n (%)	37 (56.1)	34 (49.3)†
Perioperative fluid administration (ml)	300 (50–1500)‡	275 (50–1300)
Intraoperative betamethasone, n (%)	64 (97.0)	67 (95.7)
Intraoperative ondansetron, n (%)	56 (84.8)	62 (88.6)
Intraoperative droperidol, n (%)	17 (25.8)	22 (31.5)
Number of prophylactic anti-emetics		
1	9 (13.6)	9 (12.9)
2	43 (65.2)	41 (58.6)
3	14 (21.2)	20 (28.6)
Nausea or vomiting in PACU, n (%)	24 (36.4)	29 (41.4)
Rescue opioids in PACU, n (%)	50 (75.8)	49 (70.0)
PDNV score before discharge, n (%)		
3	46 (69.7)	54 (77.1)
4	18 (27.3)	13 (18.6)
5	2 (3.0)	3 (4.3)
Trial site, n (%)		
Sundsvall Hospital	60	65
Sunderby Hospital	6	5

between the two groups in terms of the number of patients that were functionally affected (Supplementary file 2).

No differences were observed between the two groups in terms of the incidence of potential side-effects: headaches (38% vs. 34%; $P=0.66$), vision disturbance (21% vs. 11%; $P=0.12$), or sleeping difficulty (48% vs. 44%; $P=0.62$) until POD 3 (Table 3).

Adverse events

There were no SAEs in the study groups. Three AEs were reported in the palonosetron group, namely back pain on POD 5 ($n=1$), hiccups on POD 6 ($n=1$), and reoperation attributable to subcutaneous surgical bleeding (after laparoscopic cholecystectomy) on the day of the procedure combined with urinary retention after the reoperation ($n=1$). Three AEs were also reported in the placebo group, namely urinary retention on the day of the procedure ($n=1$), rapidly transient bradycardia (lowest heart rate 38 beats min^{-1})

immediately after administration of the study drug in a subject with a baseline heart rate of 50 beats min^{-1} ($n=1$), and an allergic reaction (in the placebo group) that required a visit to the emergency department on the first postoperative night ($n=1$).

Discussion

In this study, we used the simplified PDNV risk score to identify patients at high risk for PDNV and subsequently evaluated whether the long-acting anti-emetic palonosetron, administered before discharge, could reduce PDNV. Compared with placebo, palonosetron did not reduce the overall incidence of PDNV up to POD 2. Significant reductions in the incidence of nausea, vomiting, and use of rescue anti-emetics were observed on POD 1 and 2, which suggests that palonosetron might be beneficial for patients at high risk for PDNV, although further investigations are needed.

Table 2 Primary and secondary outcome variables. Data are expressed as numbers (%) or OR [95% CI]. *P<0.05 statistically significant (χ^2 test). Complete response: no nausea, no vomiting, and no use of rescue anti-emetics. CI, confidence interval; OR, odds ratio; POD, postoperative day.

	Palonosetron (n=66), n (%)	Placebo (n=70), n (%)	OR (95% CI)	P-value
Primary outcome				
Complete response; discharge to POD 2	32 (48)	25 (36)	1.69 [0.85–3.37]	0.131
Incidences of variables in primary outcome				
No nausea; discharge to POD 2	32 (48)	26 (37)	1.59 [0.80–3.16]	0.181
No vomiting; discharge to POD 2	53 (80)	47 (67)	2.00 [0.91–4.38]	0.082
No use of rescue anti-emetics; discharge to POD 2	43 (65)	39 (56)	1.49 [0.74–2.97]	0.261
Secondary outcomes				
PDNV incidence (nausea and vomiting)				
Day of surgery; after discharge	31 (47)	39 (56)	0.70 [0.36–1.38]	0.308
POD 1	12 (18)	24 (34)	0.43 [0.19–0.94]	0.033*
POD 2	6 (9)	19 (27)	0.27 [0.10–0.72]	0.007*
POD 3	10 (15)	9 (13)	1.21 [0.46–3.2]	0.700
Day of surgery; after discharge to POD 1	34 (52)	43 (61)	0.67 [0.34–1.32]	0.244
Day of surgery; after discharge to POD 2	34 (52)	44 (63)	0.63 [0.32–1.24]	0.181
Day of surgery; after discharge to POD 3	35 (53)	47 (67)	0.55 [0.28–1.11]	0.093
POD 1 to POD 2	12 (18)	47 (67)	0.35 [0.16–0.78]	0.009*
POD 1 to POD 3	16 (24)	30 (43)	0.43 [0.20–0.89]	0.022*
Use of anti-emetic rescue medications				
Day of surgery; after discharge	17 (26)	21 (30)	0.81 [0.38–1.72]	0.582
POD 1	7 (11)	15 (21)	0.44 [0.16–1.15]	0.087
POD 2	2 (3)	10 (14)	0.19 [0.04–0.89]	0.021*
POD 3	2 (3)	5 (7)	0.41 [0.08–2.17]	0.278
Day of surgery; after discharge to POD 1	20 (30)	29 (41)	0.61 [0.30–1.25]	0.177
Day of surgery; after discharge to POD 2	20 (30)	30 (43)	0.58 [0.29–1.18]	0.129
Day of surgery; after discharge to POD 3	21 (32)	31 (44)	0.59 [0.29–1.18]	0.135
POD 1 to POD 2	8 (12)	17 (24)	0.43 [0.17–1.08]	0.067
POD 1 to POD 3	10 (15)	18 (26)	0.52 [0.22–1.22]	0.128

The simplified PDNV risk score is applied *postoperatively* as opposed to the *preoperative* risk prediction of the Apfel score, which is often used to guide the perioperative PONV prophylaxis.²⁰ The PDNV score has been validated previously in a Swedish study, includes recovery measures, and considers the early outcome that is partly dependent on perioperative management and PONV prophylaxis.² We hypothesised that patients with high risk for PDNV would benefit from prophylaxis

before discharge and identified those patients with this prediction model.

The overall PDNV incidence of 67% found in our placebo group is in line with data from previous studies, with incidences of 40–80% reported in patients with high PDNV scores (≥ 3).¹² On the day of the procedure, the PDNV incidence was high in both the palonosetron and placebo groups (47% vs. 56%). We found no differences between the groups in terms of our primary outcome

Table 3 Headaches, vision disturbance, and sleeping difficulty. Data are expressed as numbers (%). CI, confidence interval; OR, odds ratio; POD, postoperative day.

	Palonosetron (n=66), n (%)	Placebo (n=70), n (%)	OR (95% CI)	P-value
Headache				
Day of surgery; after discharge	18 (27.3)	14 (20.0)	1.50 [0.68–3.33]	0.32
POD 1	12 (18.2)	16 (22.9)	0.75 [0.32–1.73]	0.50
POD 2	12 (18.2)	9 (12.9)	1.51 [0.59–3.85]	0.39
POD 3	10 (15.2)	11 (15.7)	0.96 [0.38–2.43]	0.93
Day of surgery; after discharge to POD 3	25 (37.9)	24 (34.3)	1.17 [0.58–2.36]	0.66
Vision disturbance				
Day of surgery; after discharge	12 (18.2)	6 (8.6)	2.37 [0.83–6.74]	0.10
POD 1	9 (13.6)	3 (4.3)	3.53 [0.91–13.65]	0.06
POD 2	5 (7.6)	1 (1.4)	5.66 [0.64–49.76]	0.08
POD 3	2 (3.0)	1 (1.4)	2.16 [0.19–24.36]	0.53
Day of surgery; after discharge to POD 3	14 (21.2)	8 (11.4)	2.09 [0.81–5.36]	0.12
Sleeping difficulty				
POD 1	28 (42.4)	25 (35.7)	1.33 [0.66–2.65]	0.42
POD 2	21 (31.8)	22 (31.4)	1.02 [0.49–2.10]	0.96
POD 3	2 (3.0)	5 (7.1)	0.41 [0.08–2.17]	0.28
Day of surgery; after discharge to POD 3	32 (48.5)	31 (44.3)	1.18 [0.60–2.33]	0.62

(complete response until POD 2). We observed differences between the groups on POD 1 and 2, which supports the rationale of the study that palonosetron decreases the incidence of PDNV.

Almost all patients with events of PDNV had their first event on the day of the procedure, and therefore, differences in POD 1 and POD 2 were not reflected in the primary outcome because they were classified as non-responders. Our study was conducted to detect major differences; hence, larger studies are warranted to detect smaller effect sizes of palonosetron. Although there may be possible differences on the day of the procedure, further studies should focus on reducing the overall high incidence of PDNV on the day of the procedure and not evaluating potential small differences. Williams and colleagues²¹ recently reported a retrospective review of quality improvement data, where an aggressive five-drug multimodal approach, including long-acting anti-emetics (palonosetron and aprepitant), had major effects on reducing PONV on the day of the procedure and POD 1, and they warrant studies of off-patent/multimodal anti-emesis.

Only few studies have used palonosetron as prophylaxis for PDNV. In a placebo-controlled trial, Hahm and colleagues²² included patients with established PONV and reported a higher complete response rate, up to the third day, when palonosetron was administered as the prophylaxis (65% vs. 38%). Kovac and colleagues¹⁸ administered palonosetron before the induction of anaesthesia in female patients undergoing elective gynaecological or breast surgery and found that the incidence of PONV was reduced for up to 72 h. Chun and colleagues¹⁶ reported a reduction in the incidence of PONV with palonosetron given during anaesthesia with a significant effect at 0–24 h (33% vs. 47%). However, patients in the study of Chun and colleagues¹⁶ had low risk for PDNV compared with our study. Our results are consistent with these reports, and we suggest that long-acting anti-emetics, such as palonosetron, could be incorporated in the guidelines, to a higher degree, for managing PONV and PDNV. Tailored prophylaxis of PDNV could be achieved using the postoperative simplified PDNV risk score and offering palonosetron to patients who have high predicted risks.^{3,10}

Palonosetron was generally well tolerated, and we found no major differences between the groups with respect to the potential side-effects (headache, visual disturbance, and sleeping difficulty). However, we did not detect differences in side-effects with low incidences; therefore, further investigations are warranted to detect possible differences. We observed a tendency of higher occurrences in the palonosetron group, with 21% of the patients reporting vision disturbance compared with 11% in the placebo group. Although the severity of these symptoms was mild, their potential risks must be further evaluated with sufficiently powered studies and considered when discussing a more liberal (or restrictive) approach to PONV and PDNV prophylaxis.

This study has some limitations. We used simple 'yes/no' questions, for nausea, vomiting, and rescue anti-emetics, as our outcome variables. However, there are no 'gold standard' for evaluating nausea and vomiting, and many studies have used a dichotomous outcome variable. Myles and Wengritzky²³ developed a validated tool to identify clinically important PONV, which includes the intensity of nausea and the number of vomits. Our questionnaire was partly based on the questions by Myles and Wengritzky,²³ and of patients experiencing nausea, no major differences were observed in the intensity of nausea between the groups. Furthermore, if

other domains of recovery are included in the evaluations, an important overall impact of nausea and vomiting can be described. We suggest that future PDNV studies use more extensive evaluation tools, such as the quality of recovery (QoR) scores (e.g., QoR-15 or QoR-40).^{24,25} In addition, some data were missing, mainly owing to a lack of compliance in answering and sending in the questionnaires. The number of missing diaries was similar in both groups (19% vs. 21%), and the baseline characteristics of the subjects were similar in the final two study groups analysed. The sample size was a significant limitation in this study, as the number of patients in the final study cohort did not reach the minimum number required for statistical power.

To the best of our knowledge, this is the first study to use the simplified PDNV risk score, in an ambulatory setting, to tailor additional long-acting anti-emetic prophylaxis before discharge. The PDNV score was first published in 2012 and has since been validated in at least three studies,^{2,26,27} but no study used the score as a tool to guide further management of PDNV.¹¹ Hahm and colleagues²² used a similar approach via the inclusion and randomisation of patients with PONV within the first 2 h who experienced reduced PDNV as a result of palonosetron administration (compared with the placebo). The benefit of using the PDNV score is that the need for opioids, a strong risk factor for nausea and vomiting, is included in the evaluation. Other clinical trials mainly administered palonosetron during anaesthesia for PONV/PDNV prophylaxis,^{8,14,15,22,28} and compared with our approach, more patients with lower risk for PDNV were given anti-emetics without clear benefits. However, there might be a rationale for a more liberal approach with regard to anti-emetic prophylaxis,^{3,8} even though more patients might experience mild side-effects.

Conclusions

Compared with the placebo, palonosetron did not reduce the overall incidence of post-discharge nausea and vomiting, and both groups had a high incidence on the day of the surgery. However, palonosetron did reduce the incidence of nausea and vomiting on postoperative days 1 and 2, which warrants further studies.

Authors' contributions

Study design: JW
Study planning: JW, TM, MH
Patient recruitment: JW, AM, TM
Data collection: JW, AM, TM
Data validation/analysis: AM, JW
Writing/revising of paper: all authors

Declaration of interest

JW has received lecture fees from AbbVie Sweden AB (Stockholm, Sweden).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bja.2023.04.034>.

References

1. Apfel CC, Philip BK, Cakmakaya OS, et al. Who is at risk for postdischarge nausea and vomiting after ambulatory surgery? *Anesthesiology* 2012; **117**: 475–86
2. Wallden J, Flodin J, Hultin M. Validation of a prediction model for post-discharge nausea and vomiting after general anaesthesia in a cohort of Swedish ambulatory surgery patients. *Eur J Anaesthesiol* 2016; **33**: 743–9
3. Gan TJ, Belani KG, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 2020; **131**: 411–48
4. Maras G, Bulut H. Prevalence of nausea-vomiting and coping strategies in patients undergoing outpatient surgery. *J Perianesth Nurs* 2021; **36**: 487–91
5. Stjernberg M, Schlichting E, Rustoen T, Valeberg BT, Smastuen MC, Raeder JC. Postdischarge pain, nausea and patient satisfaction after diagnostic and breast-conserving ambulatory surgery for breast cancer: a cross-sectional study. *Acta Anaesthesiol Scand* 2022; **66**: 317–25
6. Cao X, White PF, Ma H. An update on the management of postoperative nausea and vomiting. *J Anesth* 2017; **31**: 617–26
7. Horn CC, Wallisch WJ, Homanics GE, Williams JP. Pathophysiological and neurochemical mechanisms of postoperative nausea and vomiting. *Eur J Pharmacol* 2014; **722**: 55–66
8. Schlesinger T, Weibel S, Kranke P. Postoperative/post-discharge nausea and vomiting: evidence-based prevention and treatment. *Curr Opin Anaesthesiol* 2023; **36**: 109–16
9. Melton MS, Nielsen KC, Tucker M, Klein SM, Gan TJ. Long-acting serotonin antagonist (palonosetron) and the NK-1 receptor antagonists: does extended duration of action improve efficacy? *Anesthesiol Clin* 2014; **32**: 505–16
10. Elvir-Lazo OL, White PF, Yumul R, Cruz Eng H. Management strategies for the treatment and prevention of postoperative/postdischarge nausea and vomiting: an updated review. *F1000Res* 2020; **9**: F1000
11. Weibel S, Rucker G, Eberhart LH, et al. Drugs for preventing postoperative nausea and vomiting in adults after general anaesthesia: a network meta-analysis. *Cochrane Database Syst Rev* 2020; **10**: CD012859
12. Stoltz R, Parisi S, Shah A, Macciocchi A. Pharmacokinetics, metabolism and excretion of intravenous [14C]-palonosetron in healthy human volunteers. *Biopharm Drug Dispos* 2004; **25**: 329–37
13. Apfel CC, Jukar-Rao S. Is palonosetron also effective for opioid-induced and post-discharge nausea and vomiting? *Br J Anaesth* 2012; **108**: 371–3
14. Moon HY, Baek CW, Choi GJ, et al. Palonosetron and aprepitant for the prevention of postoperative nausea and vomiting in patients indicated for laparoscopic gynaecologic surgery: a double-blind randomised trial. *BMC Anesthesiol* 2014; **14**: 68
15. Moon YE, Joo J, Kim JE, Lee Y. Anti-emetic effect of ondansetron and palonosetron in thyroidectomy: a prospective, randomized, double-blind study. *Br J Anaesth* 2012; **108**: 417–22
16. Chun HR, Jeon IS, Park SY, Lee SJ, Kang SH, Kim SI. Efficacy of palonosetron for the prevention of postoperative nausea and vomiting: a randomized, double-blinded, placebo-controlled trial. *Br J Anaesth* 2014; **112**: 485–90
17. Dziadzko M, Aubrun F. Management of postdischarge nausea and vomiting. *Best Pract Res Clin Anaesthesiol* 2020; **34**: 771–8
18. Kovac AL, Eberhart L, Kotarski J, Clerici G, Apfel C, Palonosetron 04-07 Study Group. A randomized, double-blind study to evaluate the efficacy and safety of three different doses of palonosetron versus placebo in preventing postoperative nausea and vomiting over a 72-hour period. *Anesth Analg* 2008; **107**: 439–44
19. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 2014; **118**: 85–113
20. Apfel CC, Läärä E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. *Anesthesiology* 1999; **91**: 693–700
21. Williams BA, Holder-Murray JM, Nettrour JF, et al. Aim for zero: prevention of postoperative nausea and vomiting using an off-patent five-drug multimodal approach. *Br J Anaesth* 2023. in press
22. Hahm TS, Hwang JW, Kim WH, et al. A prospective, randomized, double-blind, multicenter trial to evaluate the therapeutic efficacy and safety of palonosetron in the treatment of postoperative nausea and vomiting over a 72-h period. *J Anesth* 2015; **29**: 21–8
23. Myles PS, Wengritzky R. Simplified postoperative nausea and vomiting impact scale for audit and post-discharge review. *Br J Anaesth* 2012; **108**: 423–9
24. Myles PS, Weitkamp B, Jones K, Melick J, Hensen S. Validity and reliability of a postoperative quality of recovery score: the QoR-40. *Br J Anaesth* 2000; **84**: 11–5
25. Myles PS, Shulman MA, Reilly J, Kasza J, Romero L. Measurement of quality of recovery after surgery using the 15-item quality of recovery scale: a systematic review and meta-analysis. *Br J Anaesth* 2022; **128**: 1029–39
26. Grass N, Bundy E. Postdischarge nausea and vomiting risk assessment in breast and gynecologic surgical patients. *J Perianesth Nurs* 2021; **36**: 339–44
27. Odom-Forren J, Jalota L, Moser DK, et al. Incidence and predictors of postdischarge nausea and vomiting in a 7-day population. *J Clin Anesth* 2013; **25**: 551–9
28. Lee WS, Lee KB, Lim S, Chang YG. Comparison of palonosetron, granisetron, and ramosetron for the prevention of postoperative nausea and vomiting after laparoscopic gynecologic surgery: a prospective randomized trial. *BMC Anesthesiol* 2015; **15**: 121