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Original Article

Olanzapine as an add-on, pre-operative anti-emetic drug for postoperative nausea or vomiting: a randomised controlled trial

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Summary

Postoperative nausea or vomiting occurs in up to 40% in patients with multiple risk factors, despite prophylaxis. Olanzapine is an antipsychotic drug that is used to prevent nausea and vomiting in palliative care and to treat chemotherapy-induced nausea and vomiting. This study aimed to examine whether pre-operative olanzapine, as a prophylactic anti-emetic added to intra-operative dexamethasone, ondansetron and total intravenous anaesthesia, reduced the incidence of postoperative nausea or vomiting. We performed a multiply-blinded randomised controlled trial in patients aged 18–60 years with cancer at high risk of postoperative nausea or vomiting (three or four risk factors according to the Apfel criteria) plus a previous history of chemotherapy-induced nausea and vomiting. Patients were allocated at random to receive 10 mg olanzapine or placebo orally 1 h before surgery in addition to a two-drug regimen (dexamethasone and ondansetron) and propofol anaesthesia to prevent postoperative nausea or vomiting. The primary outcome was the incidence of postoperative nausea or vomiting in the first 24 h after surgery. In total, 100 patients were enrolled; 47 in the olanzapine group and 49 in the control group completed the study. The baseline characteristics of the groups were similar. The incidence of postoperative nausea or vomiting in the first 24 h after surgery was lower in the olanzapine group (12/47, 26%) than in the control group (31/49, 63%) ($p = 0.008$, RR 0.40 (95%CI 0.21–0.79)). Adding pre-operative oral olanzapine to intra-operative dexamethasone and ondansetron was highly effective in reducing the risk of postoperative nausea or vomiting in the first 24 hours after surgery in patients with a previous history of chemotherapy-induced nausea and vomiting and at least three Apfel risk factors for postoperative nausea or vomiting.

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Introduction

Nausea and vomiting are common complications after surgery [1]. Known risk factors for postoperative nausea or vomiting (PONV) are female sex; non-smoking status; postoperative opioid use; previous history of PONV and/or motion sickness [1, 2]; and a history of chemotherapy-induced nausea and vomiting [3]. Several pharmacological classes are available for prophylaxis [4]. Prophylaxis requires a multimodal pharmacological approach. Even when prophylaxis is given based on published recommendations, the incidence of PONV has been shown to be as high as 40% [5].

Olanzapine is an antipsychotic drug that is used for the prevention of nausea and vomiting in palliative care and for the treatment of chemotherapy-induced nausea and vomiting [6]. An observational study reported that chronic use of atypical antipsychotics reduced the need for anti-emetics in the postoperative period [7]. A recently published randomised controlled trial [8] concluded that olanzapine in combination with ondansetron and dexamethasone decreases the risk of PONV by approximately 60% in the first 24 h after discharge from outpatient surgery compared with the group who received only ondansetron and dexamethasone [8].

The use of olanzapine as a prophylactic off-label anti-emetic drug specifically in patients at high risk for PONV has not been studied previously. We hypothesised that the addition of a third anti-emetic (olanzapine) to intra-operative dexamethasone and ondansetron, compared with the two anti-emetics (intra-operative dexamethasone and ondansetron) used for patients with cancer at high risk of PONV (three or four risk factors according to the Apfel criteria) plus a previous history of chemotherapy-induced nausea and vomiting, would result in a lower incidence of PONV within 24 h of surgery.

Methods

The institutional and national ethics authorities approved the protocol and we obtained written informed consent from the patients who participated in the study. No changes were made after trial commencement. This was a randomised, prospective, parallel-group, placebo-controlled trial. Patients, anaesthetists, investigators and statisticians were blinded to group assignment until the final analysis of the data.

We included patients from the Instituto do Câncer do Estado de São Paulo (ICESP), Brazil, which serves only patients with cancer. Eligible patients were adults aged 18–60 y who underwent medium or major surgery (defined as all types of oncologic surgery, except superficial procedures, ophthalmologic surgery and endoscopic procedures) related to the patient's oncological disease, and who reported a personal history of chemotherapy-induced nausea and vomiting, and who were at high risk of PONV (three or four Apfel risk factors). Exclusion criteria were an inability to swallow medications; current use of antipsychotic medications; history of allergy to olanzapine; pregnancy or lactation; history of a QT interval greater than 450 ms or history of torsades de pointes; serious cardiovascular disease; narrow-angle glaucoma; Parkinson's disease; dementia; hypotension on the day of surgery (systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg); refusal to participate in the study; contraindication to neuraxial block; and surgery performed laparoscopically.

Patients were assigned at random (1:1) via a computer-generated random number table to the olanzapine or placebo group by an off-site physician who was not involved in the study. Simple randomisation was done. The randomisation list was stored with the off-site physician and after a patient was enrolled in the study, investigators contacted this physician to ask the next sequence allocation. After enrolment in the study, patients were allocated to receive 10 mg olanzapine (olanzapine group) or placebo (control group) orally 1 h before surgery. Both groups received total intravenous anaesthesia, 4 mg dexamethasone intravenously after induction of anaesthesia and 4 mg ondansetron intravenously at the end of surgery.

The capsules (olanzapine and placebo) were completely identical in colour, weight and size. The medications were stored in bottles labelled A or B. The generated list indicated whether the patient received the medication labelled A or B. An investigator, not participating in the postoperative evaluation, administered the capsule (olanzapine 10 mg or placebo) orally to the patient approximately 1 h before the surgical procedure.

An anaesthetist performed epidural anaesthesia with local anaesthetics (dose at anaesthetist's discretion), 2 mg morphine and 100 mcg fentanyl and inserted a catheter. Total intravenous anaesthesia was performed using a target-controlled infusion of propofol, opioids (fentanyl or sufentanil) and neuromuscular blocking drugs (cisatracurium or rocuronium) in all patients. After induction of anaesthesia, dexamethasone 4 mg was administered intravenously to both groups. At the end of the surgical procedure, ondansetron 4 mg was administered intravenously to both groups. After surgery, neostigmine and atropine were administered at the anaesthetist's discretion.

Before discharge from the operating theatre, each patient received epidural patient-controlled analgesia

(PCA) with bupivacaine and fentanyl (1 $mg.ml^{-1}$ bupivacaine with $4mcg.ml^{-1}$ fentanyl, with a bolus of 3 ml, 15-min lock-out and 1-h limit of four doses). In patients in whom it was not possible to pass an epidural catheter, intravenous PCA was instituted with morphine (1 $mg.ml^{-1}$, with a bolus of 2 ml, 10-min lock-out and 1-h limit of six doses).

Anaesthetists and surgeons made the decision to refer a patient to the post-anaesthesia care unit (PACU) or to the ICU based on surgical and patient factors. No anti-emetics were given on a regularly scheduled basis postoperatively. Rescue anti-emetics (droperidol 0.625 mg intravenously every 6 h) were allowed at any time on patient request.

Postoperative nausea or vomiting was defined as nausea or vomiting (or retching) after surgery. Nausea was defined as an unpleasant sensation of having the urge to vomit. Vomiting was defined as a physical event of a forceful expulsion of gastric contents through the mouth. Retching was defined as when the content of the gastrointestinal tract was forced without expulsion of the vomitus. The primary outcome was the number of participants with PONV within 0–24 h postoperatively, where the time of leaving the operating theatre was considered time 0. According to Apfel et al., PONV within the first 24 h should be the primary endpoint [9]. Vomiting and retching data were collected separately. Because the pathophysiology is similar between the two symptoms, the results are shown as the number of participants with vomiting and/or retching [9].

Secondary outcomes were the number of participants who experienced nausea and vomiting/retching separately between 0 and 6 h, between 0 and 24 h and from 24 to 48 h after surgery; the number of participants with PONV at 6 h and 24–48 h after surgery; and the incidence of severe PONV (defined by the Clinically Important PONV Intensity Scale, online Supporting Information Table S1) [10]. We chose to include the incidence between 0 and 6 h to examine early PONV. Other secondary outcomes were patient's report of nausea severity if they experienced it (defined as mild, moderate or severe); side effects (dry mouth, itching, sleepiness, postoperative hypotension (defined as systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg)); headache; restlessness; anxiety; sleep disturbance; dizziness; urinary retention; akinesia (defined as inability to initiate movement); akathisia (defined as inability to remain still); dyskinesia (defined as irregular and involuntary muscle movements); dystonia (defined as muscle spasms in the neck, eyes, tongue or jaw); and drug-induced muscle rigidity (bradykinesia, rest tremor and postural instability). Data were collected postoperatively via direct participant interviews and were recorded in the REDCap (Research Electronic Data Capture) platform [11].

The investigators visited each participant at the end of 24 h and asked them about the presence of nausea, vomiting and retching that appeared in the last 24 h. They assessed the secondary outcomes at the end of each time interval, asked the participant about the outcomes that appeared during the period and checked the other data in the medical records.

The power calculation was based on the following parameters: type-1 error ($\alpha = 0.05$); type-2 error ($\beta = 0.2$); 95%CI; and a two-tailed significance test. We used STATA/IC 16.1 (StataCorp, College Station, TX, USA) to calculate the sample size. This indicated that 42 patients per group were needed to demonstrate a reduction in the incidence of PONV from 60% (mean of patients with four or five risk factors who received or did not receive prophylaxis) [3] to 30% (mean overall incidence of PONV) [12]. Anticipating a dropout rate of 20%, a total of 100 patients were enrolled.

Intention-to-treat analysis was performed primarily and included all patients who completed the initially allocated treatment. Per-protocol analysis was performed to evaluate the robustness of the primary analysis, without the influence of protocol deviations (see online Supporting Information Table S2 for a complete explanation). In the analysis, the comparison of the amount of opioids used postoperatively, except intra-operative intravenous and epidural opioids, was performed using equivalent doses of morphine [13, 14].

For the primary and secondary endpoints, we used the Pearson chi-squared or Fisher's exact test as appropriate. Normality of the distribution of continuous variables was assessed using the Shapiro–Wilk test. T-tests and Mann–Whitney U tests were used as appropriate. The relative risk (RR) and its respective 95% CI was calculated using the Poisson regression model. A statistically significant difference was defined as $p < 0.05$.

Results

From October 2018 to February 2021, 217 patients were considered eligible and 100 patients were allocated randomly into the study. After receiving the assigned drugs, two patients were excluded from the analysis due to cancellation of surgery and two were excluded due to the need for mechanical ventilation for > 48 h. No patients were lost to follow-up. Forty-seven patients in the olanzapine group and 49 patients in the control group completed the study and were evaluated. There was one patient with missing data (at 6 h due to mechanical ventilation) (Fig. 1).

Epidural anaesthesia was successful in 43/47 patients (92%) in the olanzapine group and 45/49 (92%) in the

control group. Placement of epidural catheters was attempted in all patients but was unsuccessful in 12 patients, equally divided over both groups, due to technical difficulties. Epidural PCA was established in all patients in whom epidural catheters were placed and intravenous PCA with morphine was established in those patients without epidural catheters. Twenty-two patients were admitted to the ICU postoperatively but did not receive mechanical

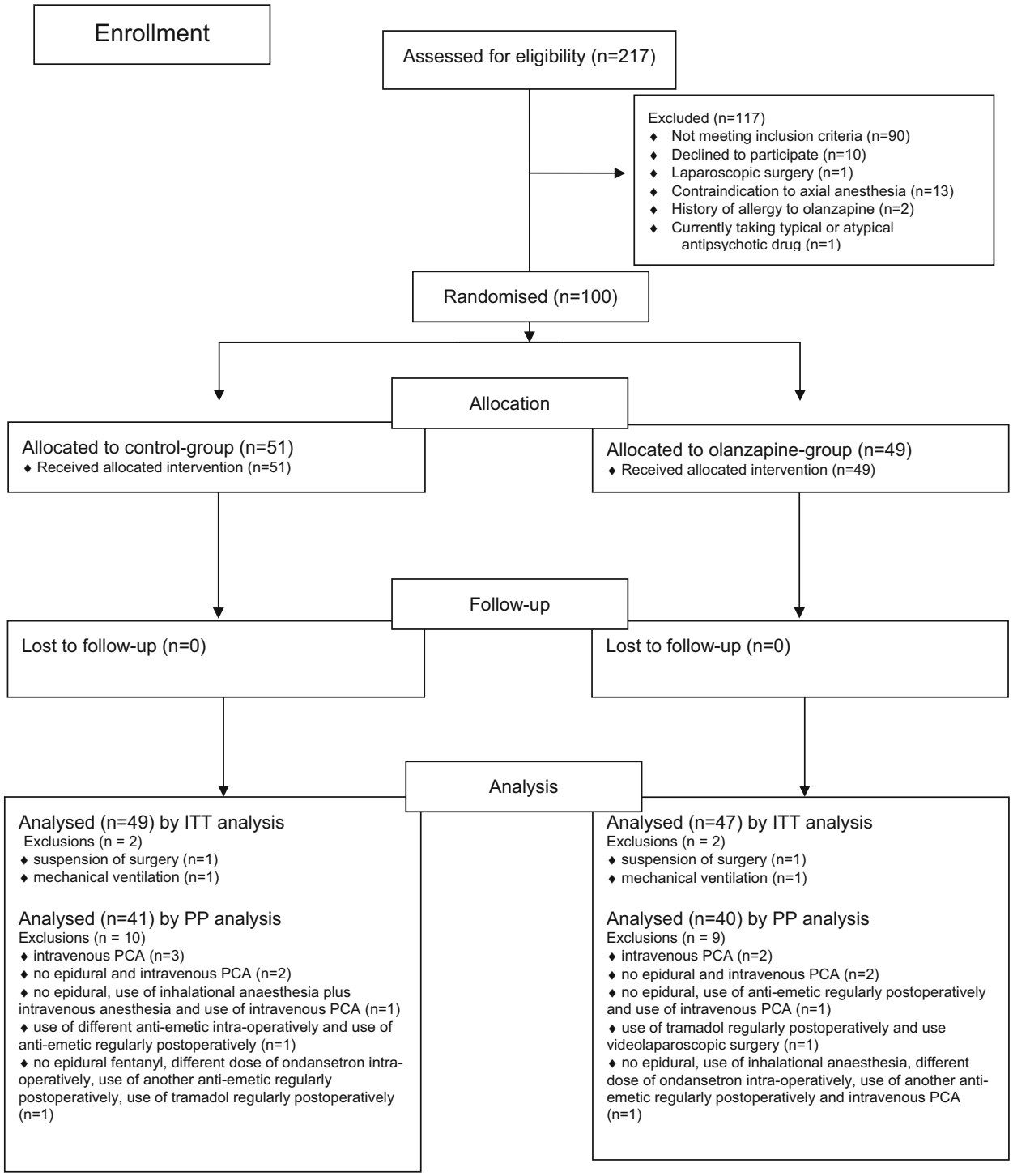

Figure 1 Study flow diagram. ITT, intention-to-treat analysis; PP, per-protocol analysis; PCA, patient-controlled analgesia.

ventilation or any additional treatment that could influence the incidence of PONV compared with ward patients. There were no statistically significant differences in ICU admission between the groups. The time between the pre-operative administration of the medication and the onset of anaesthesia varied according to the workflow from 1 to 2 h.

The olanzapine and control groups were well matched for baseline characteristics. There were no significant differences in surgical type or anaesthesia parameters (Tables 1 and 2). The surgical procedures performed were radical mastectomy with or without flap rotation; hysterectomy; gastroduodenopancreatectomy; gynaecological cytoreduction with or without cystectomy; abdominoperineal resection; hip arthroplasty; femur endoprosthesis surgery; pulmonary lobectomy; pulmonary metastasectomy; mediastinal tumour resection; hemipelvectomy; peritonectomy; expander exchanges; and myocutaneous flap.

The incidence of PONV in the first 24 h postoperatively was lower in the olanzapine group 12/47 (26%) than in the control group 31/49 (63%) p = 0.008. There was a 60% reduction in the incidence of PONV in the olanzapine group during the first 24 h (RR 0.40 (95% CI 0.21–0.79), p = 0.008). (Table 3). Patients allocated to the olanzapine group had a lower incidence of nausea between 0–6 h and 0–24 h (p = 0.045 and p = 0.008, respectively). A reduced incidence of vomiting at 6 h and 24 h was also observed in patients allocated to the olanzapine group. There were no statistically significant differences between groups within 24–48 h. No statistically significant differences were found in the amount of opioids used postoperatively between 0–24 h and 0–48 h (Table 2). The incidence of clinically important PONV in the first 24 h postoperatively was statistically significantly lower in the olanzapine group (2%) than in the control group (27%), p = 0.015 (Table 3). Patients in the olanzapine group requested fewer droperidol rescues (6.4%) than patients in the control group (36.7%) in the first 24 h after surgery (p < 0.001). The severity of nausea was lower in the olanzapine group during the first 24 h (Table 3). There were no statistically significant differences in the duration of PACU stay and ICU admission between groups. The most common side effects were dry mouth, itching and sleepiness but there were no statistically significant differences between groups (Table 4).

For the per-protocol analyses, 15 patients (seven from the olanzapine group, and eight from the control group) were excluded due to protocol deviations (Figure 1).

The incidence of nausea and vomiting/retching in the first 24 h after surgery was lower in the olanzapine group (10%) than in the control group (53.7%), p = 0.002. There was an 81% reduction in the incidence of PONV in the intervention group during the first 24 h. The complete per-protocol analysis can be found in the online Supporting Information Appendix S1.

Table 1 Characteristics and pre-operative data by group. Values are mean (SD) or number (proportion).

	Group	
	Olanzapine n = 47	**Control n = 49**
Age; y	44.6 (9.2)	43.8 (9.1)
Sex; female	45 (96%)	48 (98%)
Race*		
White	32 (68%)	26 (53%)
Brown	11 (23%)	12 (25%)
Black	4 (9%)	11 (22%)
BMI; $kg.m^{-2}$	26.2 (5.0)	26.7 (5.1)
Apfel score		
3	17 (36%)	21 (43%)
4	30 (64%)	28 (57%)
Previous PONV or motion sickness	33 (70%)	31 (63%)
Non-smoker	46 (98%)	47 (96%)
Chemotherapy-induced vomiting	32 (68%)	41 (84%)
Chemotherapy-induced nausea	47 (100%)	49 (100%)
Family history of PONV	23 (61%)	22 (47%)

PONV, postoperative nausea or vomiting.
*Official Brazilian Census categories.

Table 2 Characteristics of surgery, medication use and referral by group. Values are median (IQR [range]) or number (proportion).

	Group		
	Olanzapine n = 47	**Control n = 49**	**p value**
Duration of surgery; min	272 (153–470 [52–875])	240 (160–340 [64–659])	0.397
Duration of anaesthesia; min	383 (233–600 [97–934])	310 (227–438 [131–780])	0.156
Intravenous midazolam; mg	3 (2–5 [0–10])	3 (2–4 [0–10])	0.958
Intravenous fentanyl; mcg	250 (250–400 [20–750])	250 (200–500 [150–1250])	0.726
Intravenous neostigmine; mg	2 (2–2 [0–3])	2 (2–2 [0–3])	0.178
Crystalloids; ml	2000 (1500–3500 [600–4600])	2000 (1500–3000 [1000–5000])	0.266
Surgery speciality			
Breast	18 (38%)	24 (49%)	0.409
Plastic	12 (26%)	8 (16%)	
Gastrointestinal	8 (17%)	8 (16%)	
Gynaecology	4 (9%)	7 (15%)	
Orthopaedic	3 (6%)	0	
Thoracic	2 (4%)	2 (4%)	
Epidural anaesthesia (morphine plus fentanyl)	43 (92%)	45 (92%)	0.999
Epidural PCA	41 (87%)	43 (88%)	0.999
Intravenous PCA morphine	6 (13%)	6 (12%)	0.999
PACU; min	107 (75–157 [31–360])	90 (70–109 [40–291])	0.056
ICU	13 (28%)	7 (14%)	0.107

PCA, patient-controlled analgesia; PACU, post-anaesthesia care unit; ICU, intensive care unit.

Discussion

In patients at high risk of PONV and with a previous history of chemotherapy-induced nausea and vomiting who underwent surgery with total intravenous anaesthesia and epidural anaesthesia, olanzapine administration resulted in a clinically and statistically significant lower incidence of PONV in the first 24 h after surgery compared with a placebo control.

A recent consensus guideline [2] suggests that patients at high risk of PONV receive three or four multimodal prophylactic drugs, which include anti-emetic drugs and propofol anaesthesia. Despite giving the recommended prophylaxis with anti-emetics, the incidence of PONV was high in the control group at > 60% in the first 24 h. The 60% reduction in risk of PONV with olanzapine strongly suggests that adding olanzapine as a fourth drug in patients at high risk of PONV may be beneficial. Moreover, the olanzapine group had a significantly lower incidence of isolated nausea and vomiting up to 24 h after surgery, less clinically important PONV and requested fewer rescue anti-emetics.

Olanzapine may cause sedation [8, 15], but we found no evidence of a difference in sleepiness between the two groups. The side effects presented can also be due to the anaesthesia itself, since the clearance of the drugs used throughout the anaesthesia continues even after the end of the anaesthesia. Olanzapine is an atypical antipsychotic approved by the US Food and Drug Administration for the treatment of schizophrenia, mania and bipolar disorder [16]. It is not licensed for PONV but is already used for prophylaxis of chemotherapy-induced nausea and vomiting [17]. It acts by antagonising multiple receptors that play an important role in the pathophysiology of PONV, including dopaminergic (D1–D4), serotoninergic (5-HT2a, 5-HT2c, 5-HT3 and 5-HT6) and histaminergic receptors (H1). The bioavailability of oral olanzapine is 80–90%. It reaches a peak plasma concentration approximately 4–6 h after oral administration [18, 19].

According to Apfel et al. [20], each anti-emetic drug reduces the incidence of PONV by 26%. We found a larger point estimate of effect size in our olanzapine group though our confidence intervals include a similar effect size to Apfel et al. In the first 24 h after surgery, there was a 60% reduction in the incidence of PONV when we added olanzapine to standard treatment. We speculate that this greater effect of olanzapine may be due to its effects on multiple receptors.

Table 3 Primary and secondary endpoints by group. Values are number (proportion) or median (IQR [range]).

Outcome	Time	Olanzapine group n = 47	Control group n = 49	RR (95% CI)	p value
Primary outcome					
Postoperative nausea or vomiting/retching	0–24 h	12 (26%)	31 (63%)	0.40 (0.21–0.79)	0.008
Secondary outcome					
Nausea	0–6 h	8 (17%)	19 (40%)	0.43 (0.19–0.98)	0.045
	0–24 h	12 (26%)	31 (63%)	0.40 (0.21–0.79)	0.008
	24–48 h	12 (26%)	21 (43%)	0.60 (0.29–1.21)	0.152
Vomiting/retching	0–6 h	3 (6%)	14 (29%)	0.22 (0.06–0.76)	0.017
	0–24 h	4 (8.5%)	26 (53%)	0.16 (0.06–0.46)	0.001
	24–48 h	7 (15%)	13 (27%)	0.56 (0.22–1.41)	0.218
Nausea severity	0–6 h				
Mild		3 (38%)	4 (21%)		0.178
Moderate		4 (50%)	5 (26%)		
Severe		1 (13%)	10 (53%)		
Nausea severity	0–24 h				
Mild		7 (64%)	8 (26%)		0.035
Moderate		3 (27%)	8 (26%)		
Severe		1 (9%)	15 (48%)		
Nausea severity	24–48 h				
Mild		8 (67%)	9 (43%)		0.359
Moderate		1 (8%)	7 (33%)		
Severe		3 (25%)	5 (24%)		
Clinically important	0–6 h	0	4 (8%)	N/A	N/A
PONV	0–24 h	1 (2%)	13 (27%)	0.08 (0.01–0.61)	0.015
	24–48 h	1 (2%)	5 (10%)	0.21 (0.02–1.78)	0.152
Droperidol use as needed	0–24 h	3 (6%)	18 (37%)	0.17 (0.05–0.55)	<0.001
	24–48 h	4 (9%)	10 (20%)	0.41 (0.14–1.12)	0.099
Postoperative opioid use (MME)	0–24 h	36 (0–72 [0–576])	48 (36–144 [0–684])		0.094
	24–48 h	36 (0–216 [0–936])	60 (0–144 [0–1518])		0.861

PONV, postoperative nausea or vomiting; N/A, not applicable; MME, opioid oral morphine milligram equivalent.

Published research on the use of olanzapine for PONV prophylaxis is limited. The first randomised trial that used olanzapine pre-operatively was performed in 2013. The authors used only one anti-emetic for PONV prophylaxis (olanzapine 5 mg, olanzapine 10 mg or ondansetron 16 mg, orally) [21]. These authors concluded that these drugs and dosages all decreased the incidence of PONV compared with placebo ($p < 0.05$) in female patients who had breast surgery. However, there were no statistically significant differences between the olanzapine groups and ondansetron.

Published studies on the use of at least three and four anti-emetics are scarce. Our group published a trial [5] of the use of four prophylactic strategies (aprepitant, dexamethasone, ondansetron and propofol anaesthesia). The combination of these four drugs decreased the incidence of nausea and vomiting by 63% and 92%, respectively, in the first postoperative 24 h.

We found only one trial [8] that evaluated the combination of olanzapine, dexamethasone and ondansetron in ambulatory non-oncology gynaecological or plastic surgery, with similar results to our study. It found that the combination of the three anti-emetics decreased the incidence of PONV by 39% in the 24 h after surgery. The study included patients with all risks for PONV, from low- to high-risk patients, whereas we included only patients with a high risk of PONV and a previous history of chemotherapy-induced nausea and vomiting.

We deliberately designed the study to ensure best practice for PONV prophylaxis in the control group with dexamethasone, ondansetron and propofol anaesthesia for

Table 4 Side effects by group. Values are number (proportion).

	0–24 h			24–48 h		
	Olanzapine group	Control group	p value	Olanzapine group	Control group	p value
Side effects	21 (45%)	17 (35%)	0.317	15 (31%)	17 (36%)	0.564
Dry mouth	8 (17%)	10 (20%)	0.671	5 (10%)	7 (15%)	0.487
Itching	6 (13%)	8 (16%)	0.621	2 (4%)	3 (6%)	0.674
Sleepiness	6 (13%)	5 (10%)	0.694	3 (6%)	4 (9%)	0.712
Hypotension	5 (11%)	3 (6%)	0.482	2 (4%)	4 (9%)	0.431
Headache	2 (4%)	0	0.237	1 (2%)	2 (4%)	0.613
Restless	2 (4%)	0	0.237	1 (2%)	1 (2%)	1.000
Anxiety	0	1 (2%)	1.000	1 (2%)	0	1.000
Sleep disturbance	1 (2%)	0	0.490	1 (2%)	1 (2%)	1.000
Dizziness	5 (11%)	3 (6%)	0.482	2 (4%)	3 (6%)	0.674
Urinary retention	0	0		0	0	
Akinesia	0	0		0	0	
Akathisia	0	0		0	0	
Dyskinesia	0	0		0	0	
Dystonia	0	0		0	0	
Drug-induced muscle rigidity	0	0		0	0	

all participants to avoid a risk of exaggerated effects of the intervention.

Our study has limitations. Patients were not assessed for the presence of possible disorders that may reduce gastric motility or drug absorption. The time of olanzapine administration pre-operatively varied between patients from 1 to 2 h. Therefore, the peak serum concentration of olanzapine, which was approximately 4–6 h after administration [16], may have a variable relationship with the time of onset of PONV. However, this reflects real-world practice where drug timing will always be variable.

Our study is not generalisable to men, partly due to the Apfel criteria. We included only patients with three or four risk factors according to Apfel criteria, leading to a greater proportion of women being included. No objective scale was used to evaluate sleepiness and nausea severity. Patients might not have reported sleepiness and the intensity of nausea may have varied depending on the personal experiences of each patient.

In conclusion, oral pre-operative olanzapine (10 mg) plus propofol anaesthesia, intra-operative dexamethasone and ondansetron seem to be highly effective at reducing PONV risk in patients with oncological diseases with a high risk of PONV in the first 24 h after surgery.

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. Per-protocol analysis.
Table S1. Clinically important PONV intensity scale.
Table S2. Primary and secondary endpoints, by group.