Original Article

Olanzapine versus standard antiemetic prophylaxis for the prevention of post-discharge nausea and vomiting after propofol-based general anaesthesia: A randomised controlled trial

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ABSTRACT

Background and Aims: Post-discharge nausea and vomiting (PDNV) is a pertinent problem in patients undergoing ambulatory surgery. The objective of this study was to assess the efficacy of the novel drug olanzapine, which has proved its efficiency in patients undergoing highly emetogenic chemotherapy for PDNV prevention. **Methods:** This randomised controlled trial recruited 106 adult patients (18–65 years) undergoing highly emetogenic daycare surgeries with propofol-based general anaesthesia (GA). Group O received preoperative oral olanzapine 10 mg, and Group C, acting as a control, received 8 mg of intravenous dexamethasone and 4 mg of ondansetron intraoperatively. The primary outcome was nausea (numeric rating scale >3) and/or vomiting 24 h after discharge. Secondary outcomes included nausea and vomiting in the post-anaesthesia care unit (PACU), severe nausea, vomiting and side effects. Normality was assessed using the Shapiro–Wilk test, and the independent samples *t*-test or the Mann–Whitney *U* test was used to compare continuous variables. Fisher's exact test was used to assess any non-random associations between the categorical variables. **Results:** The incidence and severity of postoperative nausea and vomiting were similar in both groups within PACU (four patients experienced nausea and vomiting, three had severe symptoms in Group O, $P = 0.057$) and in the post-discharge period (three patients in Group O had nausea and vomiting compared to five patients in Group C, of which four were severe, $P = 0.484$). The side effects (sedation, dizziness, and light-headedness) were comparable between the two groups. **Conclusion:** A single preoperative oral olanzapine can be an effective alternative to standard antiemetic prophylaxis involving dexamethasone and ondansetron for preventing PDNV in highly emetogenic daycare surgeries with propofol-based GA.

Keywords: Ambulatory surgery, dexamethasone, emetogenic, general anaesthesia, olanzapine, ondansetron, postoperative nausea and vomiting, propofol

INTRODUCTION

Post-discharge nausea and vomiting (PDNV) refers to nausea and vomiting experienced after discharge from a healthcare facility, extending up to 72 h post-discharge.[1] Ambulatory surgery gains traction as the world increasingly adopts enhanced recovery after surgery protocols to optimise patient outcomes. PDNV remains a significant concern as its aftermath endangers patient dissatisfaction, sleep disturbances and hindrance to the resumption of daily

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activities.[2,3] Severe retching from PDNV can result in wound dehiscence, oesophageal rupture, increased intracranial pressure and pneumothorax. Unplanned hospital readmissions due to PDNV escalate healthcare costs, which is a significant concern in resource-limited healthcare settings.

Current antiemetic prophylactic guidelines encompass using ondansetron, a serotoninergic (5-HT3) antagonist with a short half-life of approximately 3 h. While this is effective during the typical post-anaesthesia care unit (PACU) stay, it inadequately addresses PDNV.[4] Shifting from volatile anaesthetics to propofol-based anaesthesia offers similar advantages.[5] With its extended half-life, dexamethasone, however, does confer a benefit in reducing PDNV.[6]

Olanzapine, an atypical antipsychotic, antagonises multiple receptors involved in the pathophysiology of postoperative nausea and vomiting (PONV), including dopamine (D1–4), serotonin (5-HT 2a, 2c, 3 and 6), acetylcholine (muscarinic) and histamine (H1). Its peak action at 6 h and prolonged half-life of 30 h position it as an ideal candidate for managing PDNV.[7]

This study evaluated the benefits and side effect profile of a single preoperative oral olanzapine in preventing PDNV. The hypothesis rested on olanzapine's extended half-life and capacity to antagonise multiple receptors implicated in PONV. The study's primary objective was to determine the incidence of nausea [numerical rating scale (NRS) >3] and vomiting within 24 h post-discharge following daycare surgery. Secondary objectives included evaluating the incidence of severe post-discharge nausea (NRS >5) within 24 h post-discharge, nausea or vomiting immediately after surgery in PACU, the need for rescue antiemetics in PACU and side effects (sedation, dizziness, light-headedness) in the post-discharge setting.

METHODS

This single-centre, double-blinded, parallel-group, randomised controlled trial was conducted between December 2021 and December 2022, after obtaining approval from the Institutional Ethics Committee (INT/IEC/2021/CPL 1901, dated 28 September 2021) and trial registration done with the Clinical Trials Registry-India (CTRI/2021/12/038684, accessible at https://ctri.nic.in/). A pilot study was conducted in November 2021 to evaluate trial feasibility in our setting. Eligible patients were selected based on defined criteria and informed written consent was obtained from each participant during pre-anaesthesia check-ups for participation in the study and using the patient data for research and educational purposes. The study was carried out in accordance with the principles of the Declaration of Helsinki, 2013 and good clinical practice.

The study included male and female patients aged 18–65 years, with American Society of Anesthesiologists (ASA) physical status I and II, undergoing highly emetogenic daycare surgeries using propofol-based general anaesthesia.

In this study, highly emetogenic daycare surgery was determined using the Apfel score, with the threshold set at ≥4 risk factors- female gender, age <50 years, history of PONV or motion sickness, anticipated use of opioids in PACU and anticipated nausea in PACU.[8] The anticipation of nausea in PACU can be made if any of the following factors are present: the patient is a non-smoker, surgery lasting >1 h duration, fentanyl dose >125 μg given intraoperatively, the surgical approach involves arthroscopy, endoscopy, or laparoscopy, and type of surgery is cholecystectomy, otorhinolarmgology, hernia, prostrate, surgeries of the upper extremity or knee arthroscopy. Exclusion criteria encompassed surgeries lasting >2 h from the incision time, patients requiring hospitalisation, pregnant/lactating patients, patients having torsade de pointes arrhythmia or QTc >450 ms, myocardial infarction, unstable angina, arrhythmias, congestive heart failure, or contraindications to olanzapine use, such as Parkinson's disease, Lewy body dementia or other neurological disorders.

Random allocation into the study groups, Group O and Group C, was accomplished using computer-generated random number tables. Allocation concealment was achieved using sequentially numbered, opaque, sealed envelopes. In Group O, participants were administered a single per oral (PO) dose of 10 mg olanzapine 1 h before surgery with sips of water in the preoperative area. To maintain blinding, a placebo with the same morphology as olanzapine tablet (dummy) was provided to patients in Group C. During the intraoperative phase, Group C received standard antiemetic prophylaxis- intravenous (IV) dexamethasone 8 mg immediately after induction and IV ondansetron 4 mg approximately 30 min before emergence. Group O received saline injections as a placebo.

The study employed the innovative double dummy blinding technique to minimise potential biases. The study involved the administration of both placebo and active doses in alternating patterns. By doing so, any potential observer bias or placebo effects were mitigated. The dual administration of both types of doses accounted for variations in the route of drug delivery, bolstering the credibility of blinding throughout the study. Following the allocation of respective treatment groups through envelopes, the responsibility of drug administration was assigned to the anaesthesia provider. This provider recorded the study's endpoints, including completion of proforma, monitoring of patients in PACU and telephonic follow-up at 24 h following discharge. Data collection was managed by the principal investigator, who remained unaware of the specific treatment regimens under evaluation. Strict separation between the investigator and the knowledge of treatment allocation significantly reduced the potential for investigator bias.

Patients' demographic and clinical information, including age, gender, weight, ASA status, QTc interval, diagnosis, planned surgery, risk factor score for PDNV, time of incision, duration of surgery, total propofol use, opioid use and the presence of nausea, were recorded. General anaesthesia was induced using IV fentanyl 1–2 μg/kg and propofol 1.5–2.5 mg/kg; neuromuscular blockade was achieved with IV atracurium 0.5 mg/kg and maintenance with IV atracurium boluses at the discretion of the attending anaesthesiologist. IV propofol infusion was titrated to achieve a bispectral index/entropy value of 40–60. IV neostigmine and glycopyrrolate were administered for neuromuscular blockade reversal before tracheal extubation. PONV and side effects were evaluated using NRS. Nausea/vomiting with NRS >3 was considered significant, and the use of rescue antiemetics was noted. In PACU, IV ondansetron 4 mg was used as a rescue antiemetic. Patients were advised to take oral ondansetron as needed after discharge. Follow-up was conducted via telephone 24 h post-discharge; nausea/vomiting and severity of side effects were noted using NRS.

The primary outcome of this study was to assess the occurrence of nausea (NRS >3) and vomiting within 24 h following discharge from the hospital among patients undergoing daycare surgery. Secondary outcomes included the occurrence of nausea and vomiting in PACU, the necessity for rescue antiemetics in PACU, the incidence of severe PDNV within the initial 24-h period post-discharge, and the presence of side effects such as sedation, dizziness and light-headedness in the post-discharge setting.

The incidence of PDNV in patients with highly emetogenic daycare procedures had been fixed at 60% for the study, since patients with more than four risk factors were included.[8] We aimed to decrease the incidence by 30% in the treatment group, so that the study would be significant with a single PO dose of olanzapine before surgery. The sample size calculated was 49 per group with 80% power of the study to detect a difference at a two-sided alpha level at 0.05. After accounting for an attrition rate of 10%, the total sample size was 110.

Data were analysed using Statistical Package for the Social Sciences statistics software version 21.0 (IBM Corp, Armonk, NY, USA) statistical software. The primary objective, namely the occurrence of nausea (NRS > 3) and vomiting within 24 h post-discharge, was presented as mean [standard deviation (SD)]. Secondary outcomes, encompassing demographics, nausea and vomiting occurrences in PACU, severe nausea and side effects, were also reported as mean (SD). Normality was assessed using the Shapiro–Wilk test. Age comparison between groups was conducted using the *t*-test, while the Wilcoxon Mann–Whitney *U* test was employed for comparisons involving weight, duration of surgery, propofol dose, total intraoperative fentanyl dose and NRS scores for nausea and vomiting. In addition, Fisher's exact test was utilised to explore the association of PDNV risks between groups and the occurrence of nausea/vomiting in PACU between the groups. A two-tailed *P* value <0.05 was considered statistically significant with a 95% confidence interval.

RESULTS

One hundred twenty-five patients were initially assessed during the study period [Figure 1]. Following exclusions, 106 patients, 54 in Group O and 52 in Group C, were included in the final analysis.

Baseline characteristics were comparable; most patients in both groups were female [Table 1]. Table 2 gives a comparison of the duration of surgery, total propofol and fentanyl used intraoperatively between the two groups. Although not statistically significant, there was a slight increase in propofol use in Group C compared to Group O.

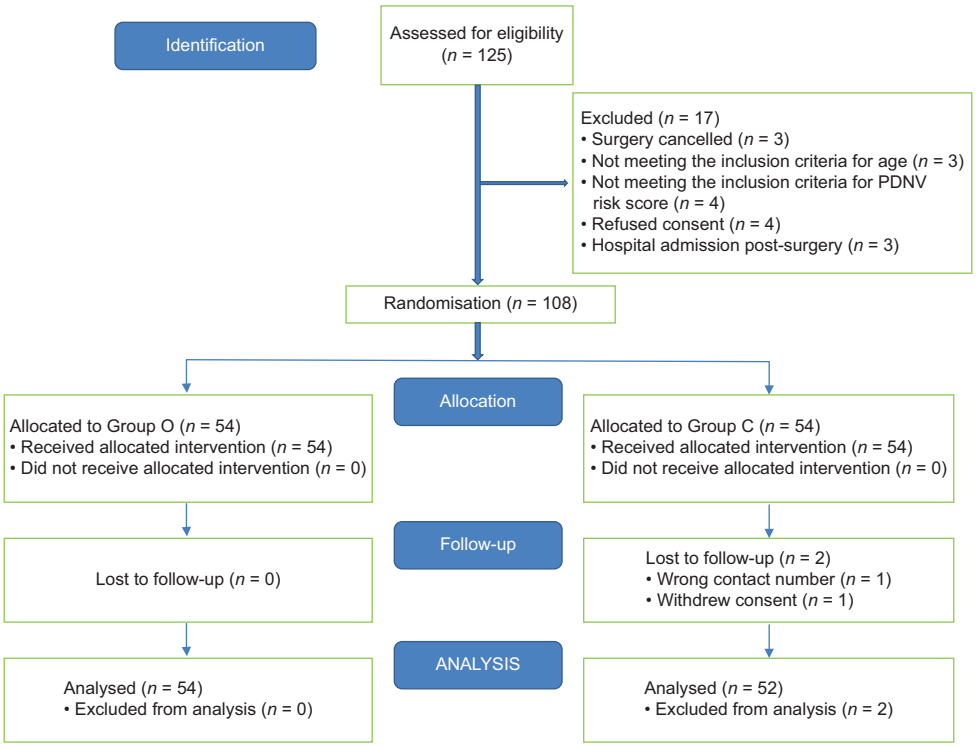

Figure 1: CONSORT diagram for visual representation. CONSORT = consolidated standards of reporting trials, PDNV = post-discharge nausea and vomiting

Table 1: Demographic variables and surgical details of the participants

Parameter	Group O (*n*=54)	Group C (*n*=52)
Age (years)	35.37 (9.00)	35.19 (9.76)
Gender (male/female), *n*	8/46	8/44
Weight (kg)	60.80 (14.55)	62.35 (13.22)
ASA, *n* (%)		
I	47 (87.00%)	42 (80.8%)
II	7 (13.0%)	10 (19.2%)
PDNV risk score	4.04 (0.19)	4.04 (0.28)
Surgical details *n* (%)		
Laparoscopic cholecystectomies	24 (44)	20 (38.5)
Mastectomy/lumpectomy	10 (18)	9 (17.3)
Hernioplasty	8 (14.8)	10 (19.2)
Hysteroscopic polypectomy, tubal ligation	5 (9.2)	7 (13.4)
Plastic surgery (contracture releases, isolated nerve repairs)	3 (5.5)	1 (1.9)
Orthopaedics (implant removal, core biopsy)	2 (3.7)	3 (5.7)
Ophthalmology (pars plana vitrectomy, orbital mass excisions)	2 (3.7)	2 (3.8)

Data represented as mean (standard deviation) or (percentage), *n*=number of patients. Group O=Olanzapine, Group C=Dexamethasone plus ondansetron (control), ASA=American Society of Anesthesiologists, PDNV=Post-discharge nausea and vomiting

There was no significant difference between the two groups in terms of the distribution of PDNV, which formed the study's primary outcome (χ^2 = 0.153, P = 1.000) [Table 2]. Strength of association between the two variables (Cramer›s V) =0.04 (little/no association). The relative risk of having PDNV with a 95% confidence interval in Group O was 0.85 (0.31, 1.57) compared to 1.15 (0.5, 1.84) in Group C. Similarly, the distribution of severe PDNV (NRS >5) was also similar with the relative risk of severe PDNV being 0.85 (0.31, 1.57) in Group O compared to 1.15 (0.5, 1.84) in Group C, with a 95% confidence interval. There were four cases of nausea and vomiting, with three being severe (NRS >5), all occurring in Group O and needing rescue antiemetics. There was no significant difference in the distribution of nausea and vomiting in PACU (χ^2 = 5.253, P = 0.057). Strength of association between the two variables (Cramer's V) = 0.22 (low association).

Table 2: Distribution of perioperative characteristics between the groups

Intraoperative characteristic	Group O (*n*=54)	Group C (*n*=52)	*P*
Duration of surgery (min)	66.57 (27.07) (59.35–73.79)	68.65 (27.53) (61.17–76.13)	0.685
Total propofol dose (mg)	468.89 (205.54) (414.01–523.77)	511.73 (188.43) (460.51–562.95)	0.215
Total intraoperative fentanyl dose (μg)	97.04 (24.92) (90.39–103.69)	98.85 (25.64) (84.55–113.15)	0.679
PACU characteristics			
Fentanyl use in PACU (yes)	11 (20.4%)	12 (23.1%)	0.735
Fentanyl dose in PACU (μg)	38.18 (18.88) (33.14–43.22)	35.83 (10.84) (32.89–38.77)	0.899
Nausea/vomiting in PACU (yes)	5 (9.3%)	0 (0.0%)	0.057
NRS for nausea/vomiting in PACU	4.60 (1.52) (4.20–5.00)	-	-
Severe nausea/vomiting in PACU (yes)	3 (5.6%)	0 (0.0%)	0.243
Rescue antiemetics (yes)	3 (5.6%)	0 (0.0%)	0.243
Post-discharge characteristics			
Nausea/vomiting post-discharge (yes)	3 (5.6%)	5 (9.6%)	0.484
NRS for nausea/vomiting post-discharge	6.00 (1.00) (5.74–6.26)	5.60 (1.14) (5.30–5.90)	0.733
Severe nausea/vomiting post-discharge (yes)	3 (5.6%)	4 (7.7%)	0.713
Side effects (yes)	9 (16.7%)	7 (13.5%)	0.645

Data represented as either mean (standard deviation) (95% confidence interval) or number (percentage), *n*=number of patients. Group O=Olanzapine, Group C=Dexamethasone plus ondansetron (control), NRS=Numerical rating scale, PACU=Post-anaesthesia care unit

There was no significant difference regarding side effects, with 16.7% of participants in Group O experiencing side effects compared to 13.5% in Group C. However, the median NRS for side effects was higher in Group O, indicating a greater perceived severity. NRS for side effects ranged between 3 and 7 in Group O compared to 3 and 4 in Group C.

DISCUSSION

In the present study, the incidence and severity of PDNV were comparable in both groups. Thus, the authors demonstrated that olanzapine is a promising intervention for PDNV prevention, positioning it as a viable alternative to the conventional dexamethasone plus ondansetron regimen, especially in situations where steroid administration can be counterproductive.

The occurrence of PDNV was lower than expected based on the study by Apfel *et al*.[8], which had predicted a PDNV risk of 60% in patients with four risk factors. The disparity in the outcome can be multifactorial- population/racial variation, method of anaesthesia delivery and a largely heterogeneous population recruited for the study, considering the kind of surgeries performed. The contribution of genetic susceptibility and ethnicity in PONV has been supported in studies pertaining to chemotherapy-[9] and pregnancy[10] -induced nausea and vomiting. These findings extend to the perioperative setup, with studies finding genetic polymorphisms of serotonin 5-Hydroxytryptamine 3 (5-HT3) receptors, mutations in type 2 dopamine receptors, neurokinin-1 receptor (TACR1), type 3 muscarinic acetylcholine receptor (CHRM3) and variations in the mu-type opioid receptor (OPRM1), all of which significantly affect an individual's susceptibility to nausea/vomiting.[11-16] Although studies have not been conducted, we can infer that inter-race genetic susceptibilities could be the reason for the lower incidence of primary outcomes in the Indian population.

Since the study was based on a propofol-based anaesthesia technique, it might explain the decreased incidence of early PONV; propofol having a short half-life does not explain decreased PDNV. It is already known that exposure to inhalational anaesthesia and opioids are among the strongest determinants of emesis perioperatively.[17] The absence of exposure to inhalational anaesthetics could partially explain the reduced primary outcome in our setting.

Grigio *et al*.,[18] in their latest study published in 2023, where olanzapine was used as an add-on to dexamethasone and propofol-based anaesthesia for preventing PONV in oncological surgeries, reiterate our findings.

While the study's strengths are evident, the authors acknowledge its limitations. The study was conducted at a single centre, potentially limiting the generalisability of our findings to broader patient populations. In addition, the heterogeneity of surgical procedures in the study might have influenced the overall PDNV incidence. Since only patients with ≥4 risk factors were considered according to the Apfel criteria, a more significant proportion of women were included in the study. The study was powered for a

significant difference, but no evidence for a difference was found due to time constraints. Future research involving multicentre trials and diverse patient groups could provide a more comprehensive understanding of olanzapine's effectiveness in preventing PDNV.

CONCLUSION

The oral drug olanzapine is a promising alternative to standard prophylaxis of PDNV in highly emetogenic daycare surgery with propofol-based anaesthesia as a single-dose preoperative intervention, providing an option in settings where immediate postoperative treatment is challenging.

Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval per the authors' institution policy.

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The study was done as a part of thesis work for the degree of MD anaesthesia and intensive care by the principal investigator Binayak Deb and received no extramural or intramural funding. All necessary drugs and equipment were arranged by the department store of the anaesthesia department, PGIMER Chandigarh, as a general protocol available to patients.

Conflicts of interest

There are no conflicts of interest.

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