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Prevention of postoperative nausea and vomiting with metoclopramide, droperidol and ondansetron: a randomized, double-blind comparison with placebo in ambulatory surgery[1]

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Abstract

In order to compare the efficacy of metoclopramide, droperidol and two different doses of ondansetron in the prevention of postoperative nausea and vomiting (PONV) after ambulatory surgery, a prospective, randomized, double-blind, placebo-controlled study was performed in 264 patients. The incidence of PONV was 6% and no antiemetic was more effective than placebo in preventing this complication during the 24 h after surgery. © 1997 Elsevier Science B.V.

Keywords: Anaesthesia; Outpatient; Ambulatory; Nausea; Vomiting; Postoperative complications; Antiemetic; Metoclopramide; Droperidol; Ondansetron

1. Introduction

The number of surgical procedures performed on an outpatient basis has increased in the last years, accounting for ≈15 to 30% surgical procedures performed in Europe and up to 50–60% in the USA [1]. Hospital admissions following ambulatory surgery are an important index of outcome and in economic terms a major contributor to direct and indirect costs for both the hospital and patients [2]. Reports of admissions range from 0.09% to 16% [3]. By categorizing them as either avoidable or unavoidable, corrective measures can be taken to reduce the avoidable category. In this regard, the most frequent avoidable anaesthetic reason of unexpected hospital admission is intractable postoperative nausea and vomiting (PONV) [7% of total causes] [3].

Reported incidences of PONV in the ambulatory setting range from 20% to 40% in adult patients [4] and up to 73% in paediatric patients [5], depending on several factors such as the patient's age and sex [6], type and length of surgery [4], anaesthetic technique [7], the patient's ambulatory status, previous history, anxiety, pain [8], and time of the menstrual cycle [9]. Different agents such as antihistamines (e.g., hydroxyzine, promethazine), anticholinergics (e.g., scopolamine, hyoscine), dopamine-receptor antagonists (e.g., metoclopramide), butyrophenones (e.g., droperidol), seretonin-receptor antagonists (e.g., ondansetron, granisetron, tropisetron), and more recently sympathomimetics (e.g., ephedrine) are currently being used to prevent PONV. Many studies demonstrate the prophylactic antiemetic efficacy and safety of these drugs in placebo-controlled studies [10–16]. However, the optimal regimen in the prevention of PONV is still not known, due to the lack of comparative trials between drugs currently being used [17].

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Table 1
Demographic data, ASA physical status of the patients, type of anaesthesia, and type of surgery in each treatment group

Characteristics	Metoclopramide (%)	Droperidol (%)	Ondansetron (%)		Placebo (%)	*P*
			2 mg	4 mg		
Patients	20.2	19.3	21	21	18.5	
Sex						
Male	48.1	45.3	47.7	43.1	42.9	
Female	51.9	54.7	52.3	56.9	57.1	0.606
ASA						
I	86.7	88.6	85.1	85.2	86	
II	13.3	11.4	14.9	14.8	14	0.928
Type of anesthesia						
General	68.1	73.3	79.6	73.5	75.3	
Spinal	31.9	26.7	20.4	26.5	24.7	0.179
Type of surgery						
ENT	42.5	46.7	49	42.8	62.8	
General surgery	42.5	35.5	31	38.8	25.6	
Gynaecology	12.8	15.6	20	16.3	11.6	
Orthopaedics	2.2	2.2	0	2.1	0	0.775
Mean ± SD						
Age (years)	29.1 ± 20.6	27.2 ± 22.9	28.6 ± 22.21	34.1 ± 22.2	28.4 ± 18.3	0.608
Age (<14 years)	6.4 ± 2.2	5.1 ± 1.3	6.3 ± 2.7	6.6 ± 7.8	6.6 ± 2.4	0.216
Weight (kg)	56.1 ± 24.1	52.5 ± 24.9	51.7 ± 21.4	60.4 ± 22.3	59.7 ± 24.9	0.282
Height (cm)	151.7 ± 22.7	149.3 ± 24.9	149.2 ± 22.4	155.4 ± 21.2	155.9 ± 23.1	0.506
Body mass index	22.7 ± 5.5	21.8 ± 5.1	21.8 ± 5.7	23.9 ± 4.9	23.1 ± 5.5	0.281

The purpose of this study was to compare the efficacy of metoclopramide, droperidol and two different doses of ondansetron in the prevention of postoperative nausea and vomiting after ambulatory surgery.

2. Patients and methods

This study was prospective, randomized, double-blind, and placebo-controlled. Approval of the hospital's Investigational Review Board and written informed consent from all patients were obtained.

2.1. Selection criteria

Patients scheduled to undergo elective, outpatient surgery were included. Patients considered to be appropriate candidates were those of physical status 1 (healthy patient), 2 (patient with mild systemic disease), and 3 (stable patients with severe systemic disease that is not incapacitating) of the American Society of Anesthesiologists (ASA) classification. Patients were excluded from the study if they were pregnant, had nausea or vomiting 24 h before surgery, had received any prophylactic antiemetic preceding surgery, had gastric suction during or after the operation, were more than 75% over their ideal body weight, had abnormalities in clinical laboratory tests of liver function, were under therapy with digoxin, levodopa or xanthines, or needed aggressive ventilation via face mask during anaesthesia. Age itself was not part of the selection criteria, except that the lower limit was 3 years.

2.2. Antiemetic protocol

Patients were randomly allocated into five groups: 0,9% saline (as control), metoclopramide 10 mg (0,1 mg/kg in paediatric patients), droperidol 1.25 mg (0.025 mg/kg in paediatric patients), ondansetron 4 mg (2 mg in paediatric patients), and ondansetron 2 mg (1 mg in paediatric patients). The appropriate volume of antiemetic was admixed with 0.9% sodium chloride solution to a final volume of 100 ml (50 ml in paediatric patients), and administered intravenously in a double-blind fashion over 15 min immediately before the induction of anaesthesia.

2.3. Anaesthetic technique

Premedication was not used. A standard anaesthetic technique was used for all patients.

In the case of general anaesthesia atropine 0.01 mg/kg was administered prior to induction. Anaesthesia was induced with propofol 2 mg/kg and the trachea was intubated with a tube with cuff after intravenous administration of vecuronium 0.1 mg Kg^{-1}. Anaesthesia was maintained with a propofol infusion at 10 mg Kg^{-1} h^{-1} and air in 40% oxygen. End-tidal carbon dioxide was maintained at 35–45 mmHg. Alfentanil was used for analgesia at a dose of 10–15 μg Kg^{-1}.

Table 2
Surgical procedures performed in each group

	Metoclopramide	Droperidol	Ondansetron		Placebo
	n (%)	*n* (%)	2 mg *n* (%)	4 mg *n* (%)	*n* (%)
Otorhinolaryngology					
Tonsillectomy	16 (21)	18 (23.7)	13 (17.1)	12 (15.8)	17 (22.4)
Septal surgery	1 (9.1)	0 (0)	6 (54.5)	1 (9.1)	3 (27.3)
Myringotomy	1 (9.1)	1 (9.1)	4 (36.3)	2 (18.2)	3 (27.3)
Microlaryngeal surgery	2 (13.3)	2 (13.3)	1 (6.7)	6 (40)	4 (26.7)
General surgery					
Varicose vein surgery	3 (27.3)	2 (18.2)	1 (9.1)	4 (36.3)	1 (9. 1)
Cystis pilonidalis resection	5 (29.4)	3 (17.6)	2 (11.8)	4 (23.5)	3 (17.7)
Cervical adenopathy biopsy	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)
Esophagus endoscopy	3 (27.3)	2 (18.2)	1 (9.1)	4 (36.3)	1 (9.1)
Anal fistula excision	1 (33.3)	0 (0)	1 (33.3)	1 (33.3)	0 (0)
Herniorrhaphy	8 (22.2)	8 (22.2)	8 (22.2)	6 (16.7)	6 (16.7)
Abscess incision and drainage	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
Orthopaedics					
Arthroscopy	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
Muscular biopsy	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Bone biopsy	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
Gynaecology					
Dilatation and curettage	5 (15.6)	6 (18.8)	8 (25)	8 (25)	5 (15.6)
Conization	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Polypectomy	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)
Breast biopsy	0 (0)	1 (50)	1 (50)	0 (0)	0 (0)

Arterial pressure and heart rate were kept within 20% of preanaesthetic values. Before extubation of the trachea neuromuscular blockade was antagonized with neostigmine 0.05 mg Kg^{-1} and atropine 0.01 mg Kg^{-1}. Postoperative pain was treated with metamizol 2 g iv. Tramadol 1 mg Kg^{-1} iv was used in patients who could not tolerate metamizol, or where analgesia was insufficient.

Spinal anaesthesia was performed with the patient in the lateral decubitus position. A 25-gauge Whitacre spinal needle was inserted via the introducer at the L3-4 interspace using the midline approach. Hyperbaric 5% lignocaine (1 mg/kg) was administered in all cases.

2.4. Data collection

All patients were transferred postoperatively to the recovery room, and afterwards to the day hospital before discharge home. The same trained nurses monitored all patients and also registered the vital signs, and any adverse events.

For the purpose of data collection, no distinction was made between vomiting and retching. The occurrence of emetic episodes (defined as a vomiting or retching event, or any combination of them that occurred within a minute) and the presence of nausea were recorded prior to the study drug infusion, and during the following time intervals: 0–0.5, 0.5–1, 1–1.5, 1.5–2 h after the end of anaesthesia, between discharge home and the first 12 h after the operation, and between 12 and 24 h after the operation (by a telephone interview).

Rescue therapy (ondansetron 4 mg, 2 mg in paediatric patients) was given at any time upon patient request, after more than 3 emetic episodes, or after nausea lasting more than 15 min. The administration of postoperative rescue therapy was considered as treatment failure.

2.5. Statistical analysis

Patients were randomized using a computer-generated randomization. Analysis was made by intention to treat using the BMDP statistical package® (Dynamic version) [18]. Chi square test was used to compare qualitative variables between the five groups (sex, ASA, type of anaesthesia and type of surgery). For continuous variables analysis of the variance test and the Kruskal-Wallis test (for non-parametric variables) were used. Relative risk (RR) and its 95% confidence intervals (95% CI) were calculated using the StatCalc option of the Epi Info® 6.0 version [19]. A P-value of 0.05 was considered significant. Data are reported as mean $\pm$ standard deviation (SD). All statistical comparisons were placebo versus each group, and between groups, with regard to the proportion of patients free of emetic episodes over the 24 h study (principal variable), the proportion of patients reporting no nausea over the 24 h study, and time of onset of nausea and/or emetic episodes (secondary variables).

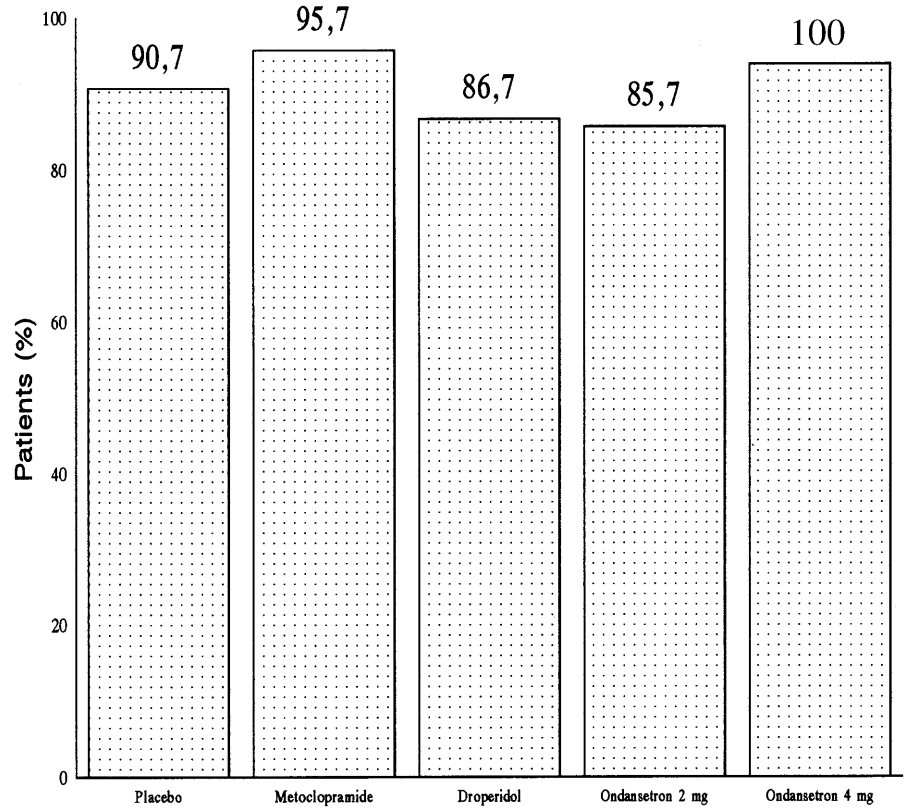

Fig. 1. Percentage of patients free of emetic episodes in each group ($P > 0.05$).

3. Results

3.1. Patient characteristics

Following the previous criteria 264 caucasian patients were included in the study. Thirty one of them were excluded because the procedure was finally scheduled for local anaesthesia ($n = 6$) or because lack of information during data collection ($n = 25$). No patient had a nasogastric tube inserted during the study period. Rescue therapy was administered in two patients. Detailed demographic data, ASA physical status of the patients, type of anaesthesia, and type of surgery in each treatment group are shown in Table 1. There were no significant epidemiologic differences between the groups ($P > 0.05$). The groups were well matched for types of operation and anaesthesia performed. All the surgical procedures performed are shown in Table 2.

3.2. Efficacy

The combined overall incidence of emetic epidodes and/or nausea during the first 24 h after anaesthesia was 6%. Symptomatic patients consistently were male (71.4%) with a mean age of 9 ± 11 years (range: 6–48 years), undergoing ENT surgery (9.6% of emetic episodes and 4.3% of nausea). The incidence of PONV was 7% after general anaesthesia and 2.1% after spinal anaesthesia ($P = 0.223$).

No antiemetic was more effective than placebo in preventing emetic episodes during the 24 h after surgery. The percentage of patients with no emetic episodes was above 80% in all groups (Fig. 1). One hundred percent of the patients in the ondansetron 4 mg group were free of emetic episodes. The same results were found when calculated for the type of anaesthesia (Fig. 2) and the type of surgery (Fig. 3).

Nausea scores were also not significantly different between the five groups. The number of patients free of nausea ranged from 100% for metoclopramide, to 93.9% for ondansetron 4 mg ($P > 0.05$).

The incidence of nausea or emetic episodes versus time was maximum at the first hour (1.7%) and between 12 and 24 h (2.1%).

When the relative risks of experiencing nausea and vomiting were calculated (Table 3), patients receiving ondansetron 4 mg were found to be more likely to experience these symptoms when compared to placebo (risk ratio = 1.8 and 95% confidence interval = 0.5–6.6), although there were no significant differences.

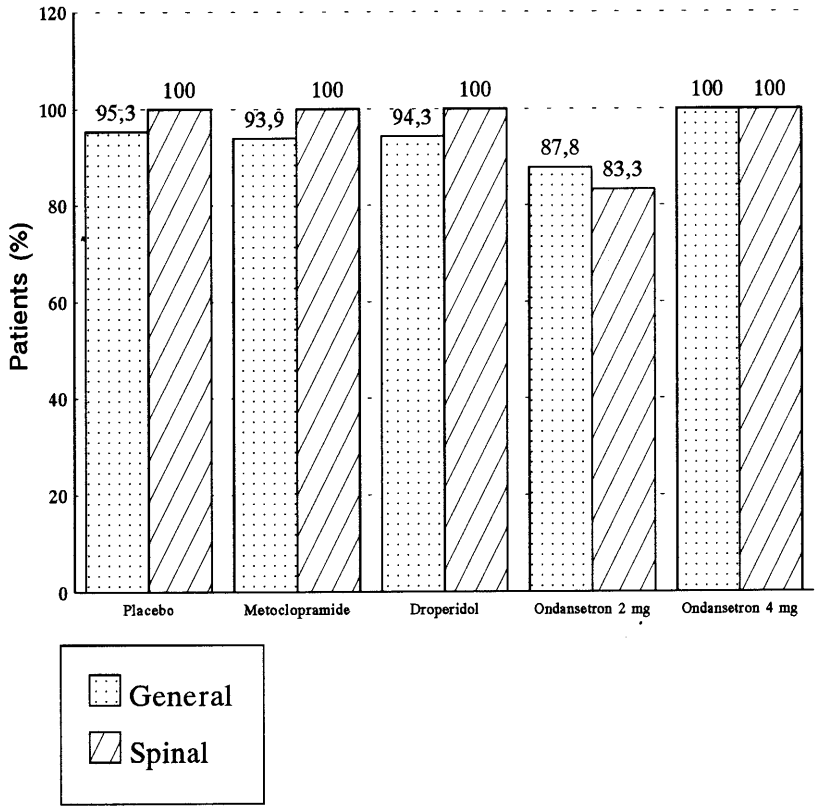

Fig. 2. Percentage of patients free of emetic episodes depending on the type of anaesthesia ($P > 0.05$).

4. Discussion

Postoperative nausea and vomiting are common and unpleasant sequelae of anaesthesia and surgery, they are often painful, may contribute to patient and parental anxiety, require extra nursing time, and influence postanaesthesia care unit stay [20]. They are considered to be the most frequent cause of anaesthesia-related hospital admissions following ambulatory surgery [3,21]. Commonly used antiemetics are generally effective in preventing PONV [10–16], although they have variable degrees of success and sometimes are associated with unacceptable side effects, such as sedation and extrapiramidal movements [22,23]. Moreover, patients have a variable risk for PONV depending on influencing factors: age, sex, weight, anxiety, preoperative medications, type of anaesthesia, type and duration of surgery, previous history of nausea and vomiting, etc [4]. Based on this evidence, should routine preoperative antiemetic prophylaxis be used? The existing comparative trials make it is possible to assess the relative merits of any agent with regard to anything but drug cost [17].

In this study, no significative differences were found in the frequency of PONV during the first 24 h after anaesthesia in patients receiving prophylactic antiemetic treatment with metoclopramide, droperidol and two different doses of ondansetron when compared to placebo ($P > 0.05$). The treatment groups were similar for patient characteristics, surgical procedures, type of anaesthesia administered and analgesics used postoperatively. Therefore, the differences in the frequency of PONV among the groups can be attributed to the differences in the drugs tested. There were no laparoscopic procedures performed in the study and the percentage of paediatric procedures was not high in any group. This may support the low nausea and vomiting scores reported. As propofol has a lower incidence of PONV associated with its use (0–23%), it is possible that this may have influenced the overall incidence observed [24–27]. Nevertheless, our results show a global rate of PONV comparable to previous reports [28]. The results of this study do not support the routine preoperative administration of a prophylactic antiemetic, at least in the type of ambulatory procedures tested when propofol is used as the induction and maintenance agent. In our study all antiemetics were administered immediately before surgery, but some authors suggest that efficacy of droperidol could be improved if it is administered towards the end of surgery [29].

Our hospital pharmacy pays 2014 pesetas for ondansetron 4 mg, 1007 pesetas for ondansetron 2 mg, 36 pesetas for metoclopramide 10 mg (one ampoule) and

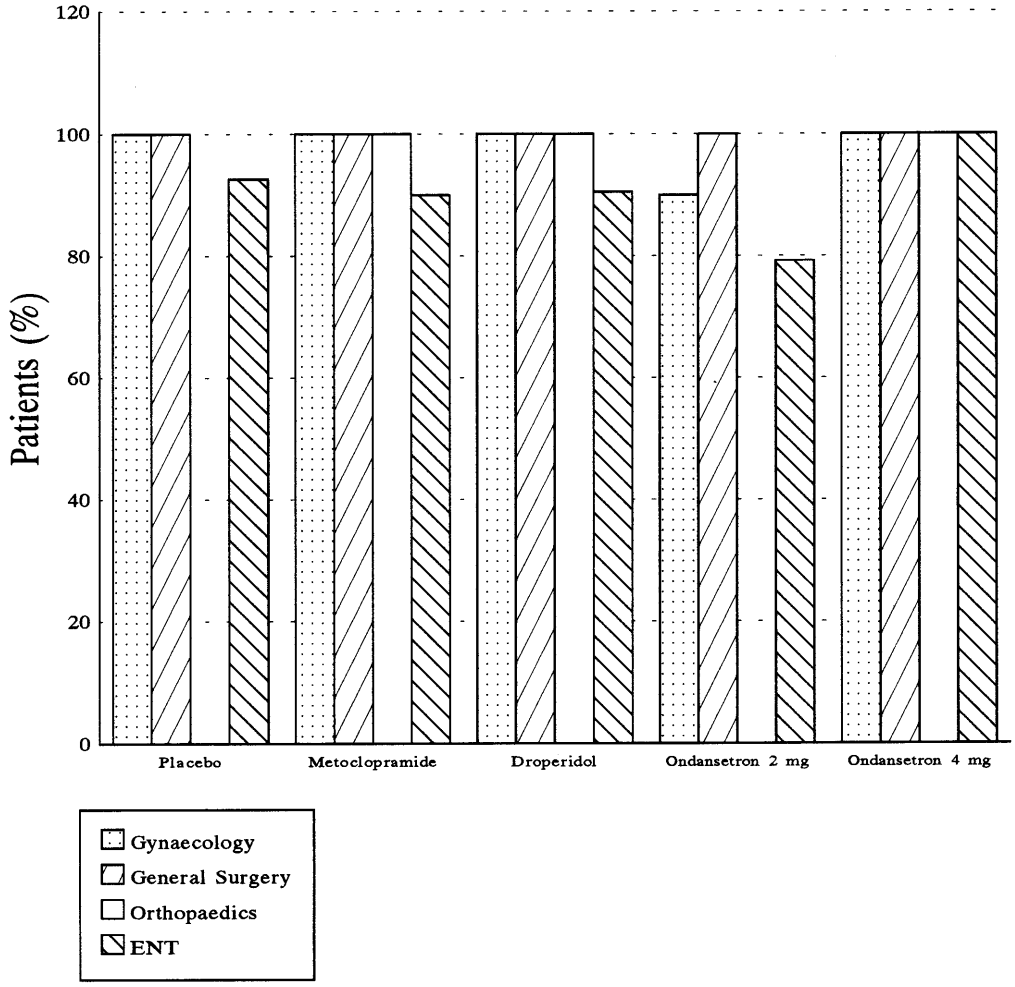

Fig. 3. Percentage of patients free of emetic episodes in each group by type of surgery ($P > 0.05$).

52 pesetas for droperidol 7.5 mg (one ampoule). A rational therapeutic selection must ensure clinical efficacy, low complications, shorter length of time in the recovery room or in the hospital, less readmissions in outpatient surgery, and minimal cost. It is time to perform clinical trials comparing the antiemetics currently being used for this indication. The combination of two antiemetic medications with different site of action could be more effective than one drug alone [30], and should be included for study in the high risk population. Cost-effective rational selection should drive the decision when clinical efficacies are equal [31]. On the basis of our results, we abandoned the routine use of drugs for the prophylaxis of PONV in the type of surgery studied when propofol was used, except in high risk patients.

In conclusion, this study suggest that preoperative administration of metoclopramide, droperidol and two different doses of ondansetron are not superior to placebo for preventing PONV. Until more information becomes available, the key to judicious use of a prophy

Table 3
Incidence and relative risk of postoperative nausea, emetic episode or both for each group

	Total	Cases	RR	95% CI
Nausea				
Placebo	43	1	1[a]	
Metoclopramide	47	0	–	
Droperidol	45	1	1.0	0.1–14.8
Ondansetron 2 mg	49	3	2.6	0.3–24.4
Ondansetron 4 mg	49	1	0.9	0.1–13.6
Emetic episodes				
Placebo	43	2	1[a]	
Metoclopramide	47	2	0.9	0.1–6.2
Droperidol	45	2	1.0	0.1–6.5
Ondansetron 2 mg	49	6	2.6	0.6–12.4
Ondansetron 4 mg	49	0	–	
Nausea or emetic episodes				
Placebo	43	3	1[a]	
Metoclopramide	47	2	0.6	0.1–3.5
Droperidol	45	2	0.6	0.1–3.6
Ondansetron 2 mg	49	6	1.8	0.5–6.6
Ondansetron 4 mg	49	1	0.3	0.0–2.7

[a]Reference group; RR: risk ratio; 95% CI: 95% confidence interval.

lactic antiemetic should be the preoperative identification of patients who are at high risk of PONV.

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