www.jmscr.igmpublication.org
Impact Factor (SJIF): 6.379
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v6i4.02

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Comparison of intravenous ondansetron and palonosetron in prevention of postoperative nausea and vomiting in patients posted for elective laproscopic cholecystectomy

Authors
Dr Manoj Singhal[1], Dr Chiranji Lal Khedia[2], Dr Hansraj Charan[3]
Department of Anesthesiology and Pain Medicine, Govt. Medical College Kota
Corresponding Author
Dr Chiranji Lal Khedia
Email: *khedia7685@gmail.com*

Abstract
Introduction: *PONV is a major complication after anaesthesia, present in 20-30% range[1]. We compared efficacy and tolerance of ondansetron and palonosetron for PONV prohylaxis in patients posted for elective laproscopic cholecystectomy.*
Method: *60 patients of age 20-60 years ,ASA I and II, scheduled for elective laproscopic cholecystectomy were randomized double blindly to receive either 8 mgbolus IV ondansetron and 16 mg was added to the PCA mixture (O group),or 0.075mg palonosetron only bolus dose (P group). Pregnancy, known hypersensitivity to both drugs, migraine, motion sickness were excluded. Chi squre test and Fisher exact test were used for statistic evaluation. Microsoft excel and epi info version 3.4.3 were used. P value <.05 considered significant. PONV (0 no nausea, 1 nausea,2 retching,3 vomiting), rescue antiemetics and side effects were assessed in 24 hr postoperative period.*
Result: *Both groups were comparable in demographic parameters (age, sex, weight). Overall incidence of PONV did not differ significantly (p=.57) but patients, who needed rescue antiemetics were significantly less in group P than group O (P=<.05). Additionally side effects were also less in group P.*
Conclusion: *In patients undergoing elective laproscopic chlecystectomy, use of palonosetron significantly reduced need of rescue antiemetics. Incidence of PONV and side effects were also less with P group.*
Keywords: *PONV, palonosetron, ondansetron.*

Introduction

Postoperative nausea and vomiting, remains a significant problem in modern anaesthetic practice, occurs after both general and regional anaesthesia. The incidence of postoperative emesis in large studies has been reported to be in the 20-30% range.[1] These factors prevent patients to return home at the end of the day, after surgery. Sometimes these factors necessitate readmission to the hospital.

The use of opioid-based intravenous-patient controlled analgesia (IV-PCA) for controlling postoperative pain has become widespread. Yet while IV-PCA is effective in controlling postoperative pain, continuous administration of opioid can cause or aggravate postoperative nausea and vomiting (PONV). PONV is the most common reason why patients choose to stop IV-PCA.

Thus there have been many studies on methods and drugs to prevent PONV. The 5-Hydroxytryptamine (5-HT_3) receptor antagonist is being commonly used because it is more effective in PONV prevention and treatment than other antiemetics and has few side effects[2]. Among 5-HT_3 receptor antagonists, ondansetron is the most widely used drug, granisetron and ramosetron are also used. Recently, palonosetron has been reported to be effective against chemotherapy-induced nausea and vomiting[3,4] and effective in the prevention of PONV[5,6].

Palonosetron is a newly developed 5-HT_3 receptor antagonist. Its receptor-affinity is more potent than other antagonists. Its plasma half-life is very long[7,8], Also it is known to be more effective than ondansetron against nausea and vomiting in patients using anticancer drugs[4]. However, studies comparing the effects of preventing PONV between palonosetron and other 5-HT_3 receptor antagonists are sparse.

Thus we compared the effects of palonosetron and ondansetron in PONV prevention in patients who underwent laparoscopic cholecystectomy surgery and used IV-PCA after surgery.

Methodology

Data was randomly collected from 60 ASA I and II patients scheduled for *laproscopic chlecystectomy*, aged between 20-60 years at GMC Kota, Rajasthan. These patients were randomly devided in Group P and Group O. The study was conducted over a period of two years.

Inclusion criteria

- ASA 1and ASA 2 patients.
- 20-60 age group.

Exclusion criteria

- Documented hypersensitivity to any of the study drugs.
- Patients with history of migraine, motion sickness or previous PONV.
- Patients who are pregnant or menstruating.
- Patients who have taken antiemetic drugs within 24 hours before surgery.
- Patients with history of neurological or renal diseases.

Technique

The study was a prospective, randomized, double blinded one. Written informed consent was taken from all patients. Pre-anaesthetic medication was given with ranitidine 150 mg and tab alprazolam 0.5 mg, the night before and morning of surgery. SpO_2, NIBP, ECG monitors were attached. The baseline values were recorded. IV access was established. Patients were randomly allocated into two groups.

1) Those who receive ondansetron (8 mg) IV bolus before induction of anesthesia anesthesia and 16 mg was added in IV PCA mixture and .(Group O)
2) Those who receive only bolus dose of IV Palonosetron (0.075 mg) before induction of anesthesia (Group-P)

All patients were kept in the NPO state for 8 h or longer. The patients did not receive premedication. General anesthesia was induced with propofol 1.5-2 mg/kg and fentanyl 1 µg/kg. Tracheal intubation was facilitated with rocuronium 0.8-1 mg/kg. Anesthesia was maintained with sevoflurane 1.5-3 vol% and O_2-N_2O 3 L/min (FiO_2 0.5), and fentanyl 1-2 µg/kg/hr . Heart rate and blood pressure were kept in the 20% range of base-line before anesthesia. Mechanical ventilation was performed so that $P_{ET}CO_2$ was 30-35 mmHg. When the surgery was over, pyridostigmine and glycopyrrolate were used for reversing muscle relaxation. The patient was extubated with the return of consciousness and the stabilization of spontaneous breathing.

The patients were randomly assigned to the ondansetron group (n = 50) and the palonosetron group (n = 50). In the ondansetron group, ondansetron 8 mg (4 ml) was i.v. administered as a bolus injection immediately before anesthesia induction. Ondansetron 16 mg (8 ml) was added in IV-PCA and was continuously infused. In the palonosetron group, palonosetron 0.075 mg (4 ml) was i.v. administered immediately before anesthesia induction and normal saline 8 ml was

added to the IV-PCA. In both groups, fentanyl 600 µg and ketorolac 240 mg were diluted with normal saline 100 ml. The basal rate for IV-PCA was 2 ml/h, bolus injection was 2 ml, and the lockout time was set at 15 min. Both groups used identical syringes for bolus intravenous injection and the same type of IV-PCA machine. Fifteen min before the end of the surgery, continuous intravenous administration of fentanyl was discontinued and IV-PCA was infused. After the surgery, if the patient wanted additional analgesics, ketorolac 30 mg was given.

Postoperatively all episodes of PONV experienced by the patient during the first 24 hours after anaesthesia, was recorded by direct questioning. These were assessed by a nausea and vomiting score. Rescue anti-emetic i.e. inj.metoclopramide was used if patient had nausea or vomiting.

Statistical analysis

At the end of the study, the data was compiled systematically and was subjected to statistical analysis using 'Chi-square' test and Microsoft excel and Epi info version 3.4.3.

Results

Demographic data & Type of surgery

The age, sex, weight of patients & type of surgery in the two groups (O and P) were comparable and there was no significant difference. (p value >0.05).

Hemodynamic parameters

Study period was from baseline to 24 hrs. (5 min., 15min., 30min., 1hr, 2hr, 12 hr,24 hr) in both groups O and P groups. Patients were hemodynamically stable in both groups.

There was no statistically significant difference in mean pulse rate, Systolic BP & SPO_2 throughout the study period (baseline to 24 hr) in both group.

PONV and Adverse effects

In Early (<1 hr) Period .In group O 19 out of 30 did not have any nausea. While in P 23 out of 30 did not have any nausea. P value (>.05).In Late (1-24 hr) period, In group O 20 out of 30 did not have any nausea, while in P 27 out of 30 did not have any nausea. p value(>.05) .In early study period (0-1 hr) 5 patients out of 30 showed adverse effects like headache and dizziness in group O. 1 patients out of 30 showed adverse effects like headache and dizziness in group P. In late study period (1-24 hr) 1 patients out of 30 showed adverse effects in group O. 0 patients out of 30 showed adverse effects like headache and dizziness in group P. There was no statistically significant difference in both group (p value>.05).

Need of Rescue Antiemetic

In group O;9 out of 30 patient needed rescue antiemetic and in group P, 2 out of 30 needed it in early study period (<1 hr). In group O,8 out of 30 patient needed rescue antiemetic and in group P 1 out of 30 needed it in late study period(1-24 hr). This result showed ststistically significance. p value in early period was .04.in late period p value was .015. both these values were statistically significant.

Table 1: Incidence of PONV <1 HR

	Group O	Group P	P Value
< 1 hr			
No Nausea=0	19	23	>.05
Nausea=1	10	7	.57
Retching=2	1	0	>.99
Vomiting=3	0	0	0

Figure 1: Incidence of PONV in <1 hour

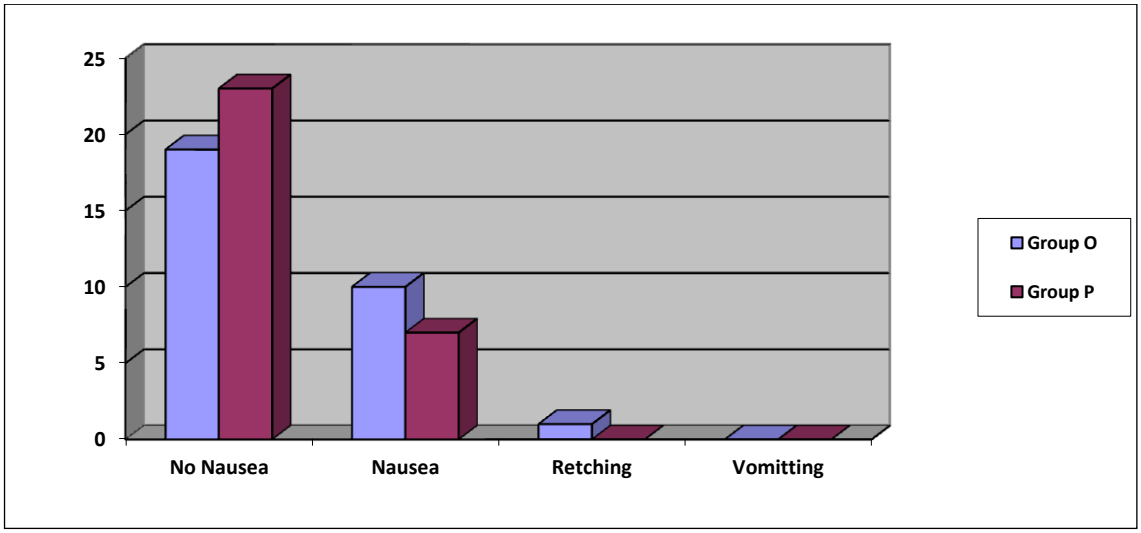


Table 2: PONV Score in 1-24 Hour

	Group O	Group P	P Value
1-24 hr			
No Nausea=0	20	27	>.05
Nausea=1	8	3	.18
Retching=2	1	0	>.99
Vomiting=3	1	0	>.99

Figure 2: Incidence of PONV in 1-24 Hour

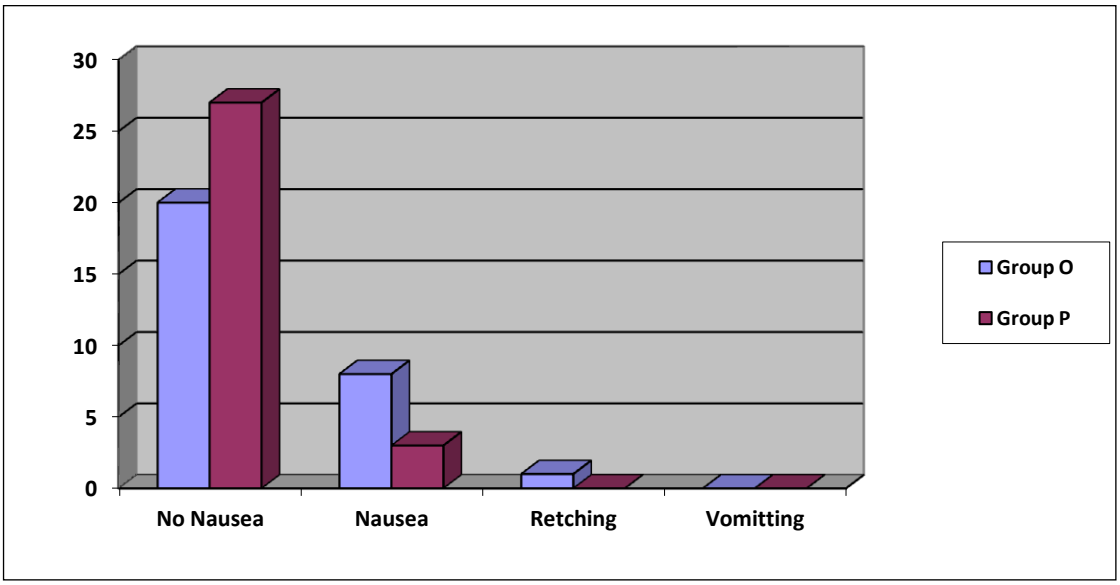


Table 3: Incidence of Adverse Effects In Both Groups

Side effect	Group O	Group P	P value
<1 hr	5	1	.19
1-24 hr	1	0	>.99

Figure 3: Incidence of adverse effects in 24 Hours

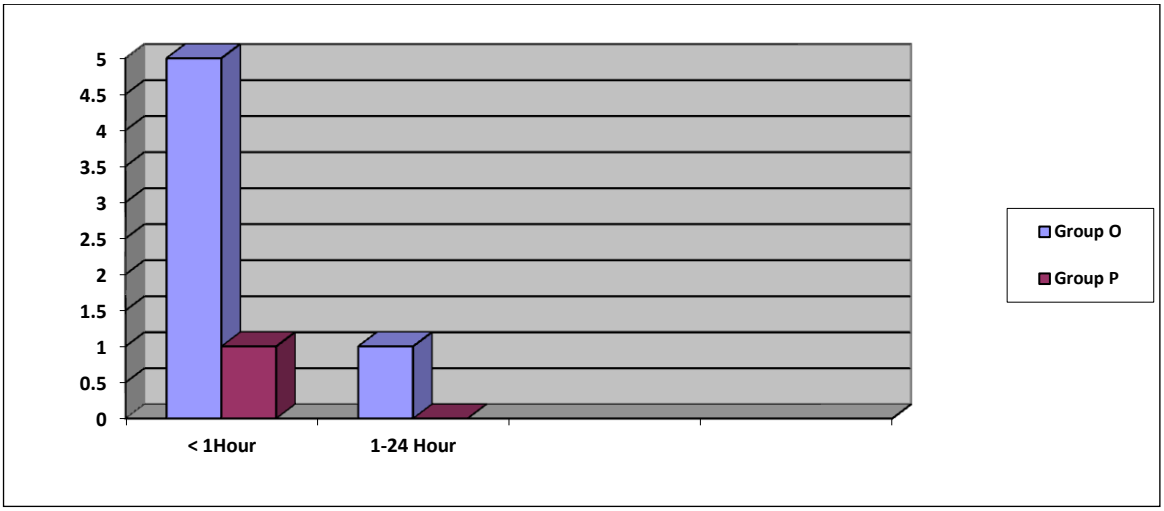
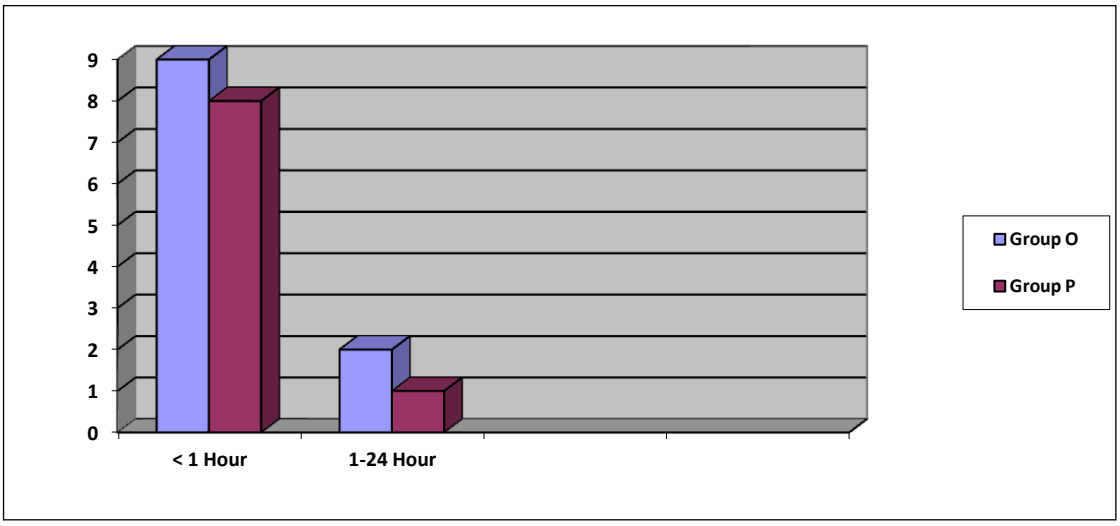


Table 4: Need of Rescue Antiemetc I.V. Metoclopramide

Rescue antiemetics	Group O	Group P	P value
<1 hr	9	2	.04
1-24 hr	8	1	.015

.

Figure 4: Need of rescue antiemetic I.V. Metoclopramide



Discussion

Post operative nausea and vomiting (PONV) is a common problem and distressing symptom in surgical patient population. Pathophysiology, of PONV in middle ear surgeries being vestibular stimulation, increase in middle ear pressure, and presence of swallowed blood in adenotonsil-lectomy procedures.[1] General anaesthesia with inhalational agents is associated with an average PONV incidence of 20-30 % in surgical patients.[2]

Apfel et al.[10] stated that among patients receiving inhaled anesthesia, female, a history of PONV or motion sickness, non-smoker, and postoperatively using opioid were the more important risk factors of PONV, and each additional risk factor increased the PONV incidence rate to 21, 39, 61, and 79%.

The boundary of the present study was restricted to female non-smoker who used opioids for IV-PCA. These patients belonged to the high risk group since they had three of the risk factors listed by Apfel et al.[10] and had laparoscopic surgery,

which is known for a high incidence of PONV. So they were expected to have a high PONV incidence rate[11,12]. Thus on an ethical reasons, the study did not include a control group.

Opioid-based IV-PCA is a safe method for managing postoperative pain with a high rate of satisfaction because the patient self-infuses additional doses when necessary and keeps the drug's plasma concentration stable[13]. However, postoperative opioid use had caused PONV in many studies[10]. When PONV occurs while using IV-PCA, patients do not infuse adequate doses for pain control[14]. Sometimes patients voluntarily stop PCA, so antiemetics are used for PONV prevention.

Many types of 5-HT_3 receptor antagonists are being currently used to prevent PONV. It affects the receptors of 5-HT_3 in the mucous membrane of the stomach and the central chemoreceptor trigger zone and suppresses nausea and vomiting. Among them, ondansetron is the most widely used type [15].

Palonosetron is a second generation serotonin 5-HT_3 receptor antagonist. Unlike other antagonists, it has unique structural, pharmacological, clinical characteristics. Other antagonists directly compete with serotonin, but palonosetron has an indirect effect by its allosteric binding with 5-HT_3 receptors[16]. Also it suppresses the response induced by substance P, has negative cooperativity with neurokinin-1 receptors by cross-talk, and creates an antiemetic effect[17]. These explain strong receptor-affinity of palonosetron and its long plasma half-life.

In high-risk groups for PONV such as in the present study, combination treatments such as TIVA with propofol and other drugs are recommended[18]. However, the present study aimed at comparing the effects of two drugs, so combination preventive methods could not be used. Instead, extensive literature was reviewed to find and use the method that best prevents PONV [5,6,9,19-21]. There have been many studies on optimal dose and usage of ondansetron. Generally an iv. injection of 8 mg is suggested as appropriate[19]. There are reports that when using opioid-based IV-PCA, adding ondansetron decreases PONV[20,21]. Palonosetron 0.075 mg is reported to be more effective in PONV prevention than 0.025 mg and 0.050 mg [5,6]. The findings of the studies above were collated so that in the present study, ondansetron 8 mg was infused as a bolus and 16 mg was added to IV-PCA and continuously infused. Palonosetron 0.075 mg was infused as a bolus.

Recently there have been studies comparing the effects of palonosetron and other 5-HT_3 receptor antagonists on PONV prevention [22-24]. Park and Cho [22] studied the use of ondansetron 8 mg and palonosetron 0.075 mg before anesthesia induction on patients with two or more risk factors. Palonosetron (42.2%) was far better than ondansetron (66.7%) in PONV prevention up to 24 h. Moon et al.[23] compared the effects of ondansetron and palonosetron in PONV prevention in high-risk patients with three or more risk factors. Similar to the present study, ondansetron was added to IV-PCA. As a result, palonosetron was far more effective than ondansetron in PONV prevention for 2-24 h (42% vs. 62%). However, in the present study the PONV incidence rates were similar in the palonosetron group and the ondansetron group(P value 0.31). But fewer patients needed rescue antiemetics in group P than in groups O (3 vs. 13 patients, respectively; ($p < 0.01$) during 0-48 h postoperatively.

In the present study, the method used in the ondansetron group (which used 8 mg as i.v. bolus and continuous iv. infusion of 16 mg addition in IV-PCA) was noteworthy in its remarkable effect in PONV prevention.

Palonosetron, as a 5-HT_3 receptor antagonist, also has side-effects such as headache, dizziness, and drowsiness. In the present study the two groups showed no difference in the incidence of side-effects. Recently the US FDA has warned against the use of ondansetron, which like droperidol, can cause severe heart complications such as QTc

interval prolongation. But palonosetron is not known to have such severe side effects[7].

For ethical reasons, this study did not include a control group using placebos for high-risk patients for PONV. Thus the present study is limited in the sense that it could not defind the base incidence rate for PONV in this particular procedure. Another limitations of the present study is that equipotent doses of the two drugs were not used; instead optimal doses were used for comparisons. For further study, these limitations need to be addressed and many other methods should be used with a large patient size.

Conclusion

PONV is multifactorial and combination of drugs with different mechanisms of action is more effective. Patients at moderate risk for PONV should receive combination therapy with one or more prophylactic drugs from different classes. It is also found that combinations act synergistically Overall incidence of PONV and adverse effects were less with combination of drugs. Need of antiemetic was significantly less with Palonosetron (p value<.05) in elective laproscopic cholecystectomy.

References

1. Apfel CC, post operative nausea and vomiting, 7th edition, *Churchill-livingstone elesvier publications. Miller's anaesthesia,* pp 2729-51.
2. Gan TJ, Meyer T, Apfel CC, Chung F, Davis PJ, Eubanks S, et al. Consensus guidelines for managing postoperative nausea and vomiting. Anesth Analg. 2003; 97:62–71. [PubMed]
3. Eisenberg P, MacKintosh FR, Ritch P, Cornett PA, Macciocchi A. Efficacy, safety and pharmacokinetics of palonosetron in patients receiving highly emetogenic cisplatin-based chemotherapy: a dose-ranging clinical study. Ann Oncol. 2004;15:330–337. [PubMed]
4. Aapro MS, Grunberg SM, Manikhas GM, Olivares G, Suarez T, Tjulandin SA, et al. A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Ann Oncol. 2006;17:1441–1449.[PubMed]
5. Kovac AL, Eberhart L, Kotarski J, Clerici G, Apfel C. 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;107:439–444. [PubMed]
6. Candiotti KA, Kovac AL, Melson TI, Clerici G, Joo Gan T. A randomized, double-blind study to evaluate the efficacy and safety of three different doses of palonosetron versus placebo for preventing postoperative nausea and vomiting. Anesth Analg. 2008;107:445–451. [PubMed]
7. 7. Yang LP, Scott LJ. Palonosetron: in the prevention of nausea and vomiting. Drugs. 2009;69:2257–2278.[PubMed]
8. Stoltz R, Cyong JC, Shah A, Parisi S. Pharmacokinetic and safety evaluation of palonosetron, a 5-hydroxytryptamine-3 receptor antagonist, in U.S. and Japanese healthy subjects. J Clin Pharmacol. 2004;44:520–531. [PubMed]
9. White LA, Vanarase M, Brockbank K, Barrett RF. Patient-controlled analgesia and postoperative nausea and vomiting: efficacy of a continuous infusion of ondansetron. Anaesthesia. 2001;56:365–369. [PubMed]
10. Apfel CC, Laara 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. [PubMed]

11. Kovac AL. Prevention and treatment of postoperative nausea and vomiting. Drugs. 2000;59:213–243.[PubMed]
12. Lerman J. Surgical and patient factors involved in postoperative nausea and vomiting. Br J Anaesth. 1992;69(7 Suppl 1):24S–32S. [PubMed]
13. Walder B, Schafer M, Henzi I, Tramer MR. Efficacy and safety of patient-controlled opioid analgesia for acute postoperative pain. A quantitative systematic review. Acta Anaesthesiol Scand. 2001;45:795–804.[PubMed]
14. Tramer MR, Walder B. Efficacy and adverse effects of prophylactic antiemetics during patient-controlled analgesia therapy a quantitative systematic review. Anesth Analg. 1999;88:1354–1361.[PubMed]
15. Bunce KT, Tyers MB. The role of 5-HT in postoperative nausea and vomiting. Br J Anaesth. 1992;69(7 Suppl 1):60S–62S. [PubMed]
16. Rojas C, Stathis M, Thomas AG, Massuda EB, Alt J, Zhang J, et al. Palonosetron exhibits unique molecular interactions with the 5-HT_3 receptor. Anesth Analg. 2008;107:469–478. [PubMed]
17. Rojas C, Li Y, Zhang J, Stathis M, Alt J, Thomas AG, et al. The antiemetic 5-HT_3 receptor antagonist palonosetron inhibits substance P-mediated responses in vitro and in vivo. J Pharmacol Exp Ther. 2010;335:362–368. [PMC free article] [PubMed]
18. Habib AS, Gan TJ. Evidence-based management of postoperative nausea and vomiting: a review. Can J Anaesth. 2004;51:326–341. [PubMed]
19. Tramer MR, Reynolds DJ, Moore RA, McQuay HJ. Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized placebo-controlled trials. Anesthesiology. 1997;87:1277–1289. [PubMed]
20. Choi DK, Chin JH, Lee EH, Lim OB, Chung CH, Ro YJ, et al. Prophylactic control of post-operative nausea and vomiting using ondansetron and ramosetron after cardiac surgery. Acta Anaesthesiol Scand. 2010;54:962–969. [PubMed]
21. Lim SM, Kim JY, Kang H, Baek CW, Park JW, Jung YH, et al. The effects of continuous infusion of ondansetron on postoperative nausea and vomiting in patients receiving IV-patient controlled analgesia following gynecological surgery Korean J Anesthesiol. 2008;55:176–181.
22. Park SK, Cho EJ. A randomized, double-blind trial of palonosetron compared with ondansetron in preventing postoperative nausea and vomiting after gynaecological laparoscopic surgery. J Int Med Res. 2011;39:399–407. [PubMed]
23. 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;108:417–422. [PubMed]
24. Bhattacharjee DP, Dawn S, Nayak S, Roy PR, Acharya A, Dey R. A comparative study between palonosetron and granisetron to prevent postoperative nausea and vomiting after laparoscopic cholecystectomy. J Anaesthesiol Clin Pharmacol. 2010;26:480–483. [PMC free article] [PubMed]