Original Research Paper

Volume - 7 | Issue - 6 | June - 2017 | ISSN - 2249-555X | IF : 4.894 | IC Value : 79.96

Anaesthesiology

# Combination of oral gabapentin and i.v. ondansetron for the prevention of postoperative nausea and vomiting in females after laparoscopic cholecystectomy surgery: a prospective and comparative study

| | |
|---|---|
| **Neeraj Kumar** | Senior Resident, Department of Anaesthesiology and critical care, AIIMS, Patna |
| **Shashi Kant** | Senior Resident, Department of Anaesthesiology and critical care, IGIMS, Patna |
| **Omprakash Sanjeev** | Senior Resident, Department of Anaesthesiology and critical care, RMLIMS, Lucknow |
| **Ajit Gupta** | Professor, Head, Department of Anaesthesiology and critical care, IGIMS, Patna |
| **Umesh Kumar Bhadani** | Professor, Head, Department of Anaesthesiology and critical care, AIIMS, Patna |
| **Manish Kumar** | Assistant Professor, Department of Pharmacology, IGIMS, Patna |

**ABSTRACT**

**Introduction :** As a gabapentin has been recently shown to be effective in the treatment of nausea and vomiting in various clinical settings. This study compared the antiemetic efficacy of oral gabapentin and gabapentin plus ondansetron in female patients undergoing laparoscopic cholecystectomy surgery.

**Material and Methods:** One hundred female patients undergoing laparoscopic cholecystectomy surgery under general anaesthesia were allocated randomly into two groups: group G received 300 mg oral gabapentin 1 h before anaesthesia as monotherapy and group GO received a combination of 300 mg oral gabapentin 1 h before anesthesia and 4 mg intravenous ondansetron at the end of surgery. Postoperative nausea, retching, vomiting, rescue antiemetic drug use, pain, rescue analgesic requirements and adverse effects were assessed at 0–2, 2–24 and 24–48 h after surgery. Postoperative nausea and vomiting (PONV) was defined as the presence of nausea, retching or vomiting.

**Results:** The incidence of complete response (no PONV and no rescue antiemetics up to 48 h postoperatively) was significantly higher in group G0 (26/40, 65%) than group G (16/40, 40%). There were no significant between-group differences in the incidence of emetic episodes, use of rescue antiemetics, severe emesis, use of rescue analgesics or any adverse effects. Postoperative pain scores were also similar among groups.

**Conclusions:** The combination with gabapentin and ondansetron is superior to either drug alone for prevention of PONV after laparoscopic cholecystectomy surgery.

**KEYWORDS :** Gabapentin, Ondansetron, Postoperative nausea and vomiting (PONV), Laparoscopic cholecystectomy surgery, Females

## Background

Postoperative nausea and vomiting (PONV) is a frequent complication after general anesthesia, with an overall incidence of 40–90% [1]. Although PONV is generally self-limited, it can cause rare but serious medical complications, such as aspiration of gastric contents, suture dehiscence, oesophageal rupture, subcutaneous emphysema or pneumothorax [2], all of which can significantly increase overall health care costs [3,4].

Laparoscopic cholecystectomy surgery has been reported to be associated with a high incidence of PONV: approximately 80% in the absence of prophylactic antiemetics. Thus, various pharmacologic agents, such as anticholinergic, antihistamines, promethazine, aprepitant, corticosteroids and 5-hydroxytryptamine (5-HT3) receptor antagonists, have been used to prevent and treat PONV in patients undergoing gynaecologic laparoscopy [5-7].

Ondansetron, is a 5 hydroxytryptamine type 3 receptor (5-HT3) that has anti vomiting effects on surgery patients [8,9].

Gabapentin developed for anticonvulsant effects and is effective in the treatment of neuropathic and chronic pain [10]. The administration of prophylactic gabapentin 600 mg orally reduced the incidence of PONV and antiemetic drug requirements after abdominal hysterectomy [11].

## Material and methods

A total number of 100 female patients were randomly selected and were classified as American Society of Anesthesiologists physical status I or II, aged 19–64 years and scheduled for therapeutic laparoscopic cholecystectomy surgery under general anesthesia at the Department of anaesthesia and critical care, Indira Gandhi Institute of Medical Sciences, Patna from June 2013 to December 2013 and the study was approved by the Institutional ethical committee. Written informed consent was obtained from each study patient before the administration of any study drugs.

### Exclusion criteria

1. Pregnancy or breastfeeding;
2. Psychological or psychiatric disease;
3. Administration of antiemetic medication or systemic corticosteroids within 24 h before surgery;
4. Vomiting within 24 h before surgery;
5. Alcohol or drug abuse; or
6. Known hypersensitivity or
7. Contra-indications to any of the drugs used in this study.

Out of 100 patients, 20 were excluded due to refusal to participate (15 patients), not meeting inclusion criteria (3 patients) and a cancellation of surgery (2 patient). So, the study included 80 patients, 40 each in group G and group GO. Patients in group G received oral gabapentin 300 mg with small sips of water 1 h before induction of anesthesia and patients in group GO received a combination of oral gabapentin 300 mg 1 h before induction of anesthesia and i.v. ondansetron at the end of surgery; 4 mg in a total volume of 2 ml at the end of surgery. The study drugs were administered by a physician who did not participate in data collection.

Risk factor for PONV consisting of female gender, non-smoking status, history of PONV and/or motion sickness, and postoperative opioid use, duration of anesthesia, and duration of surgery were recorded for each patient. All episodes of PONV (nausea, retching or vomiting) were recorded during the first 48 h after anesthesia for three time periods: 0–2, 2–24 and 24–48 h.

The primary outcome of this study was the incidence of a complete response within the first 48 h after anesthesia. Complete response was defined as the absence of PONV and lack of a need for rescue antiemetic therapy. Secondary outcomes were the incidence of severe nausea, emetic episodes and need for rescue antiemetics. Emetic episodes were defined as retching or vomiting. The severity of nausea was assessed according to an 11-point verbal numerical rating scale (VNRS, 0–10; 0 = no nausea, 10 = worst nausea imaginable) and

classified as mild (1–3), moderate (4–6) or severe (7–10). These assessments were performed at the same times as the episodes of PONV assessments.

The rescue antiemetic, i.v. metoclopramide 10 mg, was administered for severe nausea or two or more emetic episodes, or upon a request from the patient. If PONV persisted after metoclopramide administration, i.v. dexamethasone 4 mg was given. The number of administrations of rescue antiemetic drugs were recorded.

During the 48-h postoperative study period, patients were asked to rate their intensity of pain using an 11-point VNRS similar to that used for nausea. An i.v. bolus dose of 30 mg of ketorolac was administered upon request from the patient or when the VNRS pain score was ≥ 6. The number of rescue analgesic administrations was recorded. Data regarding adverse effects, such as dizziness, headache and drowsiness, was also collected. Postoperative sedation scores were evaluated using the following scale: 0 = awake, 1 = mild sedation, 2 = sleepy but arousable, and 3 = very sleepy All data were recorded by an independent anaesthesiologist who was blinded to the patient's group assignment.

**Statistical analyses**

The sample size calculation was based on the results of previously published studies in similar surgical populations [12]. The data were expressed as mean ± SD or number (%) of patients and analysis was done by one-way analysis of variance. Non-normally distributed data were expressed as median (interquartile range) and analysed using the Kruskal-Wallis test. Categorical variables were analyzed using the Chi-square test or Fisher's exact test, as appropriate. P-value < 0.05 was considered to indicate statistical significance.

**Results**

**Table 1- Patient characteristics and clinical data**

| Characteristics | Group G (n=40) | Group GO (n=40) | P value |
|---|---|---|---|
| Age (Years) | 42.2±13.4 | 41.3±8.5 | 0.720 |
| Height (cm) | 154.5± 4.4 | 155.8 ± 3.8 | 0.161 |
| Weight (Kg) | 54.5± 6.4 | 53.8± 7.2 | 0.647 |
| ASA Class (I/II) | 25/15 | 27/13 | |
| PONV | 3 (7.5) | 5 (12.5) | 0.500 |
| Motion sickness History | 2 (5) | 4 (10) | 0.430 |
| Duration of surgery (min) | 80.5± 23.4 | 81.3± 21.9 | 0.875 |
| Duration of anaesthesia | 100.7± 11.2 | 102.5± 10.5 | 0.460 |

PONV (postoperative nausea and vomiting); ASA (American Society of Anaesthesiologists physical status)

**Table 2- Incidence of PONV, emetic episodes, rescue antiemetics and complete response**

| Parameter | Group G (n =40) | Group GO (n=40) | P value |
|---|---|---|---|
| Post-operative 0-2 hour | | | |
| Nausea (0/1/2/3) | 20/5/10/5 | 30/2/2/6 | |
| Emetic episode | 5 (12.5) | 4 (10) | 0.752 |
| Rescue antiemetics | 5 (12.5) | 5 (12.5) | 1.000 |
| Post-operative 0-24 hour | | | |
| Nausea (0/1/2/3) | 18/6/8/8 | 32/3/4/1 | |
| Emetic episode | 8 (20) | 7(17.5) | 0.812 |
| Rescue antiemetics | 5 (12.5) | 4 (10) | 0.752 |
| Post-operative 24-48 hour | | | |
| Nausea (0/1/2/3) | 29/8/1/2 | 37/1/2/0 | |
| Emetic episode | 2 (5) | 1 (2.5) | 0.570 |
| Rescue antiemetics | 2 (5) | 1 (2.5) | 0.570 |
| Post-operative 0-48 hour | | | |
| Severe Nausea | 5 (12.5) | 3 (7.5) | 0.500 |
| Emetic episode | 11 (27.5) | 8 (20) | 0.535 |
| Rescue antiemetics | 9 (22.5) | 6 (15) | 0.477 |
| Complete response | 16 (40) | 26 (65) | 0.209 |

Data presented as n (%) of patients

Nausea: 0, none; 1, mild; 2, moderate; 3, severe; emetic episode: retching or vomiting; complete response: absence of postoperative nausea and vomiting and no need for rescue antiemetic therapy during the 48-h postoperative period

* P < 0.05 compared with group GO

**Table 3- Incidence of adverse effects, VNRS for pain and patients received rescue drug up to 48 h after anaesthesia**

| Parameters | Group G (n=40) | Group GO (n=40) | P value |
|---|---|---|---|
| Adverse events | | | |
| Dizziness | 5 (12.5) | 4 (10) | 0.752 |
| Headache | 3 (7.5) | 2(5) | 0.664 |
| Drowsiness | 1(2.5) | 1(2.5) | 1.000 |
| VNRS for postoperative pain | | | |
| Post-operative 0-2 hour | 5.3±2.0 | 5.9±2.3 | 0.216 |
| Post-operative 2-24 hour | 4.4±2.9 | 4.3±2.7 | 0.873 |
| Post-operative 24-48 hour | 1.5±1.3 | 1.3±1.1 | 0.459 |
| Rescue analgesic requirements | | | |
| Post-operative 0-2 hours | 6 (25) | 8 (20) | 0.621 |
| Post-operative 2-24 hour | 0 | 0 | |
| Post-operative 24-48 hour | 1(2.5) | 0 | |

**Discussion**

There is a high incidence of PONV in patients undergoing general anesthesia for laparoscopic cholecystectomy which is due to various reasons including prolonged $C0_2$ insufflations, residual pneumoperitoneum, gallbladder surgery, Isoflurane and Glycopyrrolate application, hypotension during the operation, history of movement disorders and PONV [4].

In this study, the incidence of PONV in patients undergoing laparoscopic cholecystectomy who received different antiemetic treatments was compared. Considering the fact that PONV is inevitable during the laparoscopic cholecystectomy, no placebo drug was applied due to the ethical reasons. The dosage applied in the research was based on the prescription used in other studies [8,11].

In Table 1, no statistically significant between-group differences were found in any demographic or clinical characteristic (P > 0.05).

The proportion of patients without nausea was significantly higher in group GO than in group G during the entire 48-h period after surgery (P < 0.05 for all comparisons). The number of complete responders (no PONV and no need for rescue antiemetics up to 48 h after surgery) was also higher in group G0 (65%) than in group G (40%; P = 0.027) whereas no significant difference was found. Group G0 had a lower incidence of severe nausea, emetic episodes and rescue antiemetic use compared with group G, but there were no statistically significant differences among the groups (P > 0.05 for all comparisons) (Table 2).

The rates of side effects, including dizziness, drowsiness and headache, were comparable among the three groups during the entire 48-h period. Additionally, there were no statistically significant differences among the three groups in VNRS pain scores or rescue analgesic requirements (Table 3). The sedation scores throughout the first 48 h after anaesthesia were also not significantly different among the three groups (P > 0.05).

In the present study, we found that the combination of oral gabapentin 300 mg and i.v. ondansetron 4 mg was more effective in preventing PONV than gabapentin monotherapy.

In general, 5-HT3 receptor antagonists plus various drugs from different classes, including i.v. dexamethasone 4–5 mg, i.v. droperidol 0.625–1.25 mg, and oral aprepitant 40 mg have been shown to reduce PONV to a greater extent than single therapy with any of the drugs [5,13-15]. These results are consistent with our study.

In this study, addition of gabapentin to ondansetron led to a further reduction in the incidence PONV (to 24%), without the appearance of substantial side effects. Furthermore, gabapentin is a relatively inexpensive and safe medication. Therefore, gabapentin may be a useful choice for combination therapy to prevent PONV, especially in high-risk patients.

In this study, it is interesting that the proportion of patients without nausea at 24–48 h after anesthesia was high in the group GO and duration (8–12 h) of action of gabapentin [16,17]. This is clinically

meaningful when considering the report that the PONV symptoms can appear up to at least 72 h after discharge from PACU [18]. This finding might be explained in part by the possibility of long-lasting (> possibly 24 h) antiemetic effect of gabapentin [2]. Further clinical trials are required to address this issue.

In the present study, the postoperative pain scores and use of rescue analgesic were not different among all groups whether they did or did not receive gabapentin. These findings were contrary to the results of several previous studies demonstrating that oral gabapentin 400 or 600 mg was effective in decreasing the postoperative pain and opioid consumption in patients undergoing surgery [11,19].

## Conclusions

In conclusion, the combination of gabapentin and ondensetron provided additional beneficial effects over gabapentin alone for high-risk patients requiring combination antiemetic prophylaxis. Based on the safety profile, known analgesic properties and cost, gabapentin might be usefully included in the list of pharmacotherapies for PONV prophylaxis in patients undergoing laparoscopic cholecystectomy surgery

**Source of Funding: None**
**Conflict of Interest: None**
**Ethical Clearance: Taken**

## References

1. Myles PS, Williams DL, Hendrata M, Anderson H, Weeks AM. Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10,811 patients. Br J Anaesth. 2000;84(1):6–10.
2. Achuthan S, Singh I, Varthya SB, Srinivasan A, Chakrabarti A, Hota D. Gabapentin prophylaxis for postoperative nausea and vomiting in abdominal surgeries: a quantitative analysis of evidence from randomized controlled clinical trials. Br J Anaesth. 2015; 114(4):588–97.
3. Hill RP, Lubarsky DA, Phillips-Bute B, Fortney JT, Creed MR, Glass PS, Gan TJ. Cost-effectiveness of prophylactic antiemetic therapy with ondansetron, droperidol, or placebo. Anesthesiology. 2000; 92(4):958–67.
4. Habib AS, Chen YT, Taguchi A, Hu XH, Gan TJ. Postoperative nausea and vomiting following inpatient surgeries in a teaching hospital: a retrospective database analysis. Curr Med Res Opin. 2006;22(6):1093–9.
5. Ham SY, Shim YH, Kim EH, Son MJ, Park WS, Lee JS. Aprepitant for antiemesis after laparoscopic gynaecological surgery: a randomised controlled trial. Eur J Anaesthesiol. 2016;33(2):90–5.
6. Joo J, Park YG, Baek J, Moon YE. Haloperidol dose combined with dexamethasone for PONV prophylaxis in high-risk patients undergoing gynecological laparoscopic surgery: a prospective, randomized, double-blind, dose–response and placebo-controlled study. BMC Anesthesiol. 2015;15:99.
7. Gan TJ, Candiotti KA, Klein SM, Rodriguez Y, Nielsen KC, White WD, Habib AS. Double-blind comparison of granisetron, promethazine, or a combination of both for the prevention of postoperative nausea and vomiting in females undergoing outpatient laparoscopies. Can J Anaesth. 2009;56(11):829–36.
8. Lee A, Done ML. The use of nonpharmacologic techniques to prevent postoperative nausea and vomiting: a meta-analysis. Anesth Analg. 1999;88(6):1362-9.
9. Tramer MR. A rational approach to the control of postoperative nausea and vomiting: evidence from systematic reviews. Part I. Efficacy and harm of antiemetic interventions, and methodological issues. Acta Anaesthesiol Scand. 2001;45(1):4-13
10. Moore RA, Wiffen PJ, Derry S, McQuary HJ. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database of Syst Rev. 2011;(3):CD007939.
11. Ajori L, Nazari L, Mazloomfard MM, Amiri Z. Effects of gabapentin on postoperative pain, nausea and vomiting after abdominal hysterectomy: a double blind randomized clinical trial. Arch Gynecol Obstet. 2012;285(3):677–82.
12. Fredman B, Jedeikin R, Olsfanger D, Flor P, Gruzman A. Residual pneumoperitoneum: a cause of postoperative pain after laparoscopic cholecystectomy. Anesth Analg. 1994; 79(1):152-4.
13. Eberhart LH, Morin AM, Bothner U, Georgieff M. Droperidol and 5-HT3-receptor antagonists, alone or in combination, for prophylaxis of postoperative nausea and vomiting. A meta-analysis of randomised controlled trials. Acta Anaesthesiol Scand. 2000;44(10):1252–7.
14. Ryu JH, Chang JE, Kim HR, Hwang JW, Oh AY, Do SH. Ramosetron vs. ramosetron plus dexamethasone for the prevention of postoperative nausea and vomiting (PONV) after laparoscopic cholecystectomy: prospective, randomized, and double-blind study. Int J Surg (London, England). 2013;11(2):183–7.
15. Bhattarai B, Shrestha S, Singh J. Comparison of efficacy of Ondansetron and Dexamethasone combination and Ondansetron alone in preventing postoperative nausea and vomiting after laparoscopic cholecystectomy. J Pak Med Assoc. 2014;64(3):242–6.
16. Naguib M, el Bakry AK, Khoshim MH, Channa AB, el Gammal M, el Gammal K, et al. Prophylactic antiemetic therapy with ondansetron, tropisetron, granisetron and metoclopramide in patients undergoing laparoscopic cholecystectomy: a randomized, double-blind comparison with placebo. Can J Anaesth. 1996;43(3):226-31. [PubMed]
17. Rose MA, Kam PCA. Gabapentin pharmacology and its use in pain management. Anesthesia. 2002; 57:451–62.
18. White PF, O'Hara JF, Roberson CR, Wender RH, Candiotti KA, Group P-OS. The impact of current antiemetic practices on patient outcomes: a prospective study on high-risk patients. Anesth Analg. 2008; 107(2):452-8.
19. Agrawal N, Chatterjee C, Khandelwal M, Chatterjee R, Gupta MM. Comparative study of preoperative use of oral gabapentin, intravenous dexamethasone and their combination in gynaecological procedure. Saudi J Anaesth. 2015;9(4):413–7.