

# Prophylactic gabapentin for prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: A randomized, double-blind, placebo-controlled study

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## ABSTRACT

**Background:** Gabapentin is an antiepileptic drug. Its antiemetic effect is demonstrated in chemotherapy-induced acute and delayed onset of nausea and vomiting in breast cancer patients.

**Aim:** To evaluate the antiemetic effect of gabapentin on incidence and severity of postoperative nausea and vomiting in laparoscopic cholecystectomy.

**Settings and Design:** Double-blind, randomized, placebo-controlled study.

**Materials and Methods:** Two hundred and fifty patients of ASA physical status I and II, scheduled for laparoscopic cholecystectomy were randomly assigned into two equal groups to receive 600 mg gabapentin or matching placebo two hours before surgery. Standard anaesthesia technique was used. Fentanyl was used as rescue postoperative analgesic. Ondansetron 4 mg was used intravenously as rescue medication for emesis. The total number of patients who had nausea or vomiting, and its severity and total fentanyl consumption in the first 24 hours were recorded.

**Statistical Analysis:** "Z test" was used to test the significance of severity of post-operative nausea and vomiting between groups. Fentanyl consumed in each group (Mean  $\pm$  SD) within 24 hrs was compared using student t test. *P* value < 0.05 was considered significant.

**Results:** There were no demographic difference between the two groups. Incidence of post-operative nausea and vomiting within 24 hrs after laparoscopic cholecystectomy was significantly lower in gabapentin group (46/125) than in the placebo group (75/125) (37.8% vs 60%; *P*=0.04). There was a significantly decreased fentanyl consumption in gabapentin group (221.2  $\pm$  92.4  $\mu$ g) as compared to placebo group (505.9  $\pm$  82.0  $\mu$ g; *P*=0.01).

**Conclusion:** Gabapentin effectively suppresses nausea and vomiting in laparoscopic cholecystectomy and post-operative rescue analgesic requirement.

**KEY WORDS:** Antiemetic, gabapentin, post-operative nausea, vomiting

Received : 01-12-05  
Review completed : 23-01-06  
Accepted : 23-02-06  
PubMed ID :  
J Postgrad Med 2006;52:97-101

Posto-perative nausea and vomiting (PONV) are among the most common complications following anaesthesia and surgery. The etiology of PONV is complex and is dependent on a variety of factors including the technique of anaesthesia patients' demographics and type and site of surgery. Laparoscopic cholecystectomy has emerged as a popular alternative to traditional cholecystectomy in the management of cholelithiasis.<sup>[1]</sup> It is reported that nearly 53-72% of patients require antiemetic therapy after laparoscopic cholecystectomy.<sup>[1,2]</sup>

Gabapentin, a structural analog of gamma amino butyric acid (GABA) is an antiepileptic drug.<sup>[3]</sup> It does not bind with plasma

proteins and is not metabolized in humans. After a single oral dose of 300 mg, mean maximum plasma concentrations are attained in 2-3 hr. Absorption kinetics of gabapentin are dose-dependent, possibly due to a saturable transport system.<sup>[3]</sup> The bio-availability of a single 300 mg oral dose of gabapentin is 60% and decreases with increasing dose. Elimination of gabapentin is by renal clearance and the elimination half life is about 5-7 hr after a single oral dose of 200 to 400 mg.<sup>[3]</sup>

Recently an open clinical study demonstrated the anti-emetic effect of gabapentin in chemotherapy-induced acute (within 24 hr) and delayed onset (days 2-5) of nausea and vomiting in breast cancer.<sup>[4]</sup> In the present clinical study, we have evaluated

the antiemetic effect of gabapentin on the incidence and severity of PONV in patients who underwent laparoscopic cholecystectomy.

### Materials and Methods

We recruited 250 patients of ASA physical status I and II, of both sexes scheduled for elective laparoscopic cholecystectomy for a double-blind, prospective, randomized and placebo-controlled study (sample size was determined on the assumption that the incidence of PONV is 70% following laparoscopic cholecystectomy and treatment with gabapentin would decrease it by 20%. For 90% of power of the test, 125 patients were required in each group). The exclusion criteria were: body weight more than 20% of the ideal body weight; those older than 60 years or younger than 18 years or smokers; history of drug or alcohol abuse; history of hypersensitivity to any drug, history of peptic ulcer disease or of bleeding diathesis or patients taking antacids; impaired kidney or liver functions; patients who had received antiemetics within 24 hr before scheduled surgery or received sedatives other than those determined by protocol, menstruating, pregnant or lactating females, patients who had history of motion sickness, patients on anti-depressants or calcium channels blockers or patients on whom laparoscopic cholecystectomy was converted into open cholecystectomy [Figure 1].

The day before surgery, all patients were visited for pre-anesthesia assessment and to explain the study protocol. All patients received oral lorazepam 2 mg the evening before surgery and the morning of surgery. Patients were randomly divided into two equal groups using a computer generated table of random numbers, to receive the medication orally two hours before surgery. Patients enrolled in the Gabapentin group

received 600 mg of gabapentin; while those in the placebo group received a placebo (capsule similar to gabapentin).

Anaesthesia was induced with propofol 2 mg/kg, fentanyl 3 µg/kg. Intubation of trachea was facilitated with vecuronium bromide 800 µg/kg. Anaesthesia was maintained with a propofol infusion 100-200 µg/kg/min and 70% nitrous oxide in oxygen and intermittent vecuronium bromide when indicated. After completion of the surgery, neuromuscular blockade was reversed with atropine 0.02 mg/kg and neostigmine 0.04 mg/kg and patients were extubated when adequate spontaneous ventilation was established and were transferred to post-anesthesia care unit (PACU). After approximately 6 hrs of stay in PACU, patients were transferred to their respective wards. A senior resident, who was not part of the anesthesia team and was blinded to the type of medication the patients had received, recorded PONV and the amount of rescue analgesic consumed by the patients. The PONV was defined as the subjective unpleasant sensation associated with awareness of urge to vomit (nausea, retching or vomiting had been grouped together). The severity of PONV was graded as follows.<sup>[5]</sup>

#### No PONV

Absence of any emetic episode or nausea

#### Mild PONV

The patient had only mild nausea or one emetic episode or short lasting nausea of any severity of less than 10 min which was triggered by exogenous stimulus and no antiemetic drug was required.

#### Moderate PONV

the patient had 1-2 emetic episodes or moderate or severe nausea without exogenous stimulus and patient required antiemetic therapy once.

#### Severe PONV

The patient had more than two emetic episodes or was nauseated more than twice and administration of at least one antiemetic was required.

Patients received patient-controlled analgesia for their pain management (PCA pump was set to fentanyl 1.0 mg/kg patient's activated dose with lockout interval of 10 minutes). The failure of treatment was defined when the patients had an episode of PONV within 24 hrs. The episodes of retching or vomiting were considered as vomiting events. Patients received ondansetron 4 mg intravenously when they demanded antiemetics.

The Institute's Ethics Committee approved the study protocol and written informed consent was obtained from each participant. The procedures followed in this were in accordance with ethical standards of the responsible committee on human experimentation as per Helsinki Declaration (1975, and as revised in 2000). Patients were recruited from the department of surgical gastroenterology from January 2003 to March 2004 till the required number of patients in each group had completed the study.

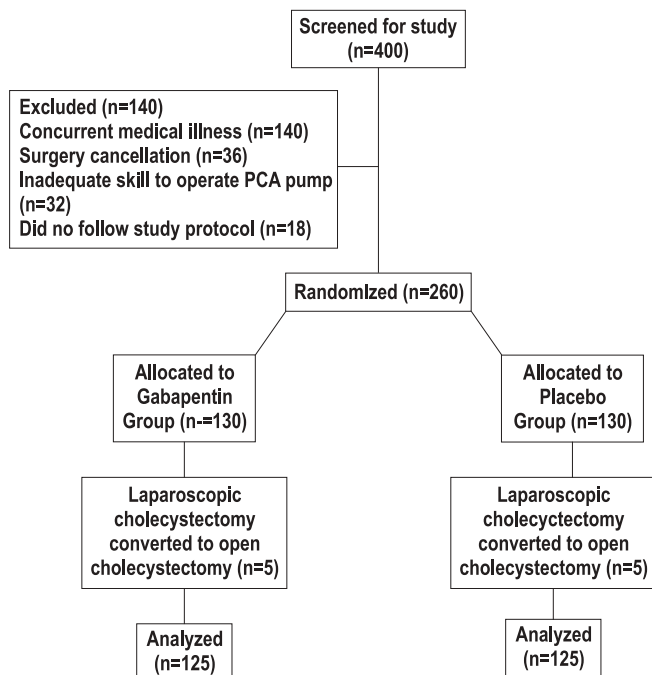


Figure 1: Flow diagram of patient distribution

**Statistical analysis**

After completion of the study, the data were entered into the statistical software package SPSS 9.0 (Chicago, USA). Data were presented as means and standard deviation for 95% confidence interval with 5% degree of freedom. Student ‘t’ test was used to compare the demographic data and for the incidence of PONV. The test of proportion “Z test” was used to test the significance of severity of PONV between the groups. Total fentanyl consumed in each group (Mean ± SD) within 24 hrs was compared using student t test. P value less than 0.05 was considered statistically significant.

**Results**

There were no demographic differences (age, weight, duration of surgery, and gender distribution) between the gabapentin and placebo groups [Table 1]. The incidence of PONV during the first 24 hr in patients after laparoscopic cholecystectomy was significantly lower in gabapentin group (46/125) 37.8% than 60% of the placebo group (75/125) (P=0.04) but there was no difference in the severity of PONV amongst the two groups [Table 2]. Gabapentin achieved complete control of established PONV (no emesis, no rescue treatment) in 79 patients whereas only 50 patients of placebo group had no PONV (P=0.04) with absolute risk reduction of 22.2% and relative risk reduction of 37%. The number of patients who would have to be treated to prevent one patient from experiencing PONV (number needed to treat, NNT) was 4.5. The incidence of side effects in both the groups was similar [Table 3]. However, the patients of placebo group consumed significantly higher amount of fentanyl compared to the patients of gabapentin group (505.9±82.0 µg vs 221.2±92.40 µg; P= 0.01) [Table 2] for their pain relief.

**Discussion**

Our study has demonstrated lower incidence of PONV during the first 24 hr after laparoscopic cholecystectomy in the group of patients who received prophylactic gabapentin 600 mg two

hr before surgery than those who received placebo. Gabapentin decreased the incidence of nausea and vomiting but it did not decrease the severity of PONV. Gabapentin also decreased the consumption of fentanyl in patients who received it prophylactically [Table 2].

The etiology of PONV following laparoscopic cholecystectomy remains unclear, but is probably associated with operative factors. These include the effect of intra-peritoneal CO<sub>2</sub> insufflation on residual stretching and irritation of the peritoneum.<sup>[5]</sup> Factors like age and gender of patient, obesity, technique of anesthesia employed, presence of post-operative pain, use of opioids for pain management and elective surgical procedures also influence the incidence of PONV. In a clinical study involving 17638 patients, the predictors for PONV were derived. This study demonstrated that an increase of 10 years in age decreased the likelihood of PONV by 13%; the risk for men was one-third that for women; a thirty minutes increase in the duration of anaesthesia increased the likelihood of PONV by 59%; and general anesthesia increased the likelihood of PONV by 11 times compared to other types of anesthesia.<sup>[6]</sup> A study conducted by Apfel *et al*. in Finland and Germany enrolling 2722 patients they identified four predictors for PONV based on logistic regression coefficients: female gender, history of motion sickness or PONV, non-smoking, and use of postoperative opioids. The incidence of PONV with each of the factors enumerated above was 10-21%, 39%, 61% and 79%, respectively.<sup>[7]</sup> In our study both the groups were comparable with regard to the risk of suffering PONV (gender distribution; exclusion of patients with the history of motion sickness or PONV or history of smoking; and use of postoperative opioids for pain management).

Gabapentin has been reported to be effective in the treatment of emesis in patients receiving cytotoxic drugs.<sup>[4]</sup> The precise mechanism of gabapentin in the prevention of nausea and vomiting induced by cytotoxic drugs is not known but mitigation of tachykinin neurotransmitter activity has been postulated to be useful.<sup>[8]</sup> There is evidence that tachykinins activity is part of

**Table 1: The demographic data of study groups**

	Gabapentin (n=125)	Placebo (n=125)
Age (in yrs Mean± SD)	42.8 ± 11.4	41.8 ± 11.1
Weight (Mean± SD)	58.3 ± 6.0	56.9 ± 7.2
Duration of surgery (in minutes Mean± SD)	57.7 ± 4.2	56.5 ± 5.0
Gender Male (n)	25	18
Female (n)	100	107

**Table 3: Incidence of side effects in the study groups**

Side effects	Gabapentin group (n=125)	Placebo group (n=125)
Drowsiness	4	2
Itching	1	3
Light headedness	2	0
Feeling on a ‘high’	1	0
Lack of concentration	2	1
Headache	2	0

**Table 2: Incidence of postoperative nausea and vomiting and its severity in study groups**

	Fentanyl consumption (in µg)	No PONV (n & %)	PONV & its grades (n)			
			Mild	Moderate	Severe	Total (n & %)
Gabapentin (n=125)	221.2 ± 92.4	79* (62.2)	9	31	6	46 (37.8)
Placebo (n=125)	505.9 ± 82.0	50 (40.0)	10	52	13	75 (60.0)
P value	0.01	0.04	0.8	0.06	0.06	0.04

Test of proportion to compare severity grades, Figures in parentheses indicate percentages, \* P value <0.05 (Gabapentin VS Placebo) and power of test 93%

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the pathogenesis of chemotherapy-induced emesis in ferrets, and a selective tachykinins-receptor antagonist improves both acute and delayed nausea and emesis induced by chemotherapy.<sup>[9]</sup> The etiology of PONV in patients undergoing laparoscopic cholecystectomy is not identical to that in patients receiving cytotoxic drugs but we assume that it may be one probable mechanism for prevention of PONV by gabapentin. Gabapentin has been demonstrated to decrease the opioids consumption in postoperative as well as neuropathic painful states.<sup>[10-14]</sup> This study also demonstrated a decrease in the amount of fentanyl consumption in gabapentin group. In our series the characteristics, characteristics technique of induction and maintenance of anaesthesia and use of postoperative analgesic were similar in both the groups. Therefore, the difference in the incidence of the PONV between the groups could only be attributed to gabapentin.

In conclusion, our results have demonstrated that prophylactic use of 600 mg of gabapentin two hour before laparoscopic cholecystectomy decreases the incidence of PONV but it does not affect the severity of PONV. It also decreases the amount of fentanyl required for postoperative pain management. Thus, along with antiemetic property, it possesses analgesic property. However, this antiemetic effect of gabapentin and its mechanism need to be further evaluated.

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