Effects of Preoperative Gabapentin on Postoperative Nausea and Vomiting after Open Cholecystectomy: A Prospective Randomized Double-Blind Placebo-Controlled Study

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Key Words

Gabapentin · Postoperative nausea and vomiting · Open cholecystectomy

Abstract

Objective: To evaluate the effect of gabapentin on the incidence and severity of postoperative nausea and vomiting (PONV) after open cholecystectomy. **Subjects and Methods:** A total of 90 patients scheduled for elective open cholecystectomy were randomly assigned to either a gabapentin group (600 mg, 2 h before surgery) or a placebo group. For the analysis, 1 patient was excluded from the gabapentin group and 2 patients from the placebo group. A standard technique was used for anesthesia. Pethidine and metoclopramide were used for postoperative management of pain and nausea/vomiting, respectively. The prevalence of PONV, its severity (measured on visual analogue scale, VAS), and total pethidine and metoclopramide use in the first 24 h after the operation were recorded. **Results:** There were no demographic differences between the two groups. Of the 44 patients given gabapentin, 16 (36.6%) and 28 of 43 (65.2%) placebo patients developed PONV; the difference was statistically significant ($p = 0.02$). However, there was no difference in the severity of PONV between the gabapentin and placebo groups ($p = 0.12$). Gabapentin patients used less pethidine (28.33 ± 129 mg) and metoclopramide ($6.0 \pm$

6.3 mg) than the placebo group (35.1 ± 15.1 and 9.33 ± 7.1 mg, respectively). The differences were statistically significant (pethidine: $p = 0.002$, metoclopramide: $p = 0.033$). However, gabapentin did not reduce postoperative pain significantly ($p = 0.096$). **Conclusion:** Our data show that gabapentin not only reduced PONV after open cholecystectomy, but also reduced the need for additional postoperative analgesics.

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Introduction

Postoperative nausea and vomiting (PONV) are common complications following anesthesia and surgery. The etiology of PONV is complex and dependent on a variety of factors, including the technique of anesthesia, patient demographics, and type and site of surgery [1].

Gabapentin (brand name Neurontin) is a γ -aminobutyric acid (GABA) analogue. Gabapentin was originally approved in the USA by the Food and Drug Administration in 1994 for use as an adjunctive medication to control partial seizures (effective when added to other anti-seizure drugs). In 2002, an indication was added for treating post-herpetic neuralgia (neuropathic pain following shingles), other painful neuropathies, and nerve-related pain [2]. Its exact mechanism of action is unknown, but

its therapeutic action on neuropathic pain is thought to involve voltage-gated N-type calcium ion channels. It is thought to bind to the $\alpha 2\delta$ subunit (1 and 2) [3] of the voltage-dependent calcium channel in the central nervous system [4].

Guttuso et al. [5] demonstrated in an open clinical study the antiemetic effect of gabapentin in chemotherapy-induced acute (within 24 h) and delayed onset (days 2–5) nausea and vomiting in breast cancer. Pandey et al. [1] showed that gabapentin successfully reduced PONV after laparoscopic cholecystectomy. In the present clinical study, we evaluated the antiemetic effect of gabapentin on the incidence and severity of PONV in patients who underwent open cholecystectomy.

Subjects and Methods

Patients

This study was a double-blind placebo-controlled prospective clinical trial. We enrolled 90 American Society of Anesthesiologists physical status I and II patients of both sexes who were scheduled for elective open cholecystectomy. This study was approved by the Institutional Review Board of the Fasa University of Medical Sciences. All the patients filled in the informed consent form. Based on 0.9 power to detect a significant difference ($p = 0.05$, two-sided), 40 patients were required for each study group. To compensate for non-evaluable patients, we planned to enroll 45 patients per group. Patients with a BMI >30 ; a history of previous severe PONV; a history of motion sickness; significant gastrointestinal problems; recent antiemetic drug use; who were older than 60 years or younger than 18 years; who had impaired kidney or liver functions; who were menstruating, pregnant or lactating females; or who were smokers were excluded from the study. Overall, 158 patients were screened for the study, of whom 90 patients finished.

Study Protocol

At the first visit, each patient was given a sealed envelope containing their admission number in the order of referral. This was performed by a nurse who was blinded to the study. Using medical chart numbers, the patients were divided into two groups: the gabapentin group ($n = 45$; odd numbers) and the placebo group ($n = 45$; even numbers). One patient from the gabapentin group and two from the placebo group did not follow through with the study, and hence were not included in the analysis.

All patients were visited for preanesthetic assessment and to explain the study protocol the day before the surgery. Patients enrolled in the gabapentin group received 600 mg (two 300 mg tablets), while those in the placebo group received two placebo (capsules similar in appearance to gabapentin). All the patients received 1 g ceftriaxone 30 min before surgery as antibiotic prophylaxis. All the patients underwent the same anesthetic protocol. The patients received midazolam (0.01 mg/kg) and morphine (0.1 mg/kg) as premedication. Anesthesia was induced in the patients with thiopental sodium (3–5 mg/kg) and atracurium (0.4

Table 1. Demographic characteristics of the patients

	Gabapentin (n = 44)	Placebo (n = 43)	p value
Females	41 (93.2)	39 (90.7)	0.091
Males	3 (6.8)	4 (9.3)	0.076
Age, years	51.3 $\pm$ 16.7	52.1 $\pm$ 13.6	0.868
BMI	23.4 $\pm$ 3.04	23.5 $\pm$ 2.85	0.902
MAP, mm Hg	95.8 $\pm$ 7.93	93.2 $\pm$ 6.28	0.995
IV fluid intake, ml	1,066.6 $\pm$ 28.7	1,146.6 $\pm$ 43.4	0.136
Duration of surgery, min	39.6 $\pm$ 5.1	38.8 $\pm$ 4.9	0.601

Figures in parentheses are percentages. MAP = Mean arterial pressure.

mg/kg). After 2–3 min of mask ventilation and reassurance of muscle relaxation, endotracheal intubation was carried out. During the maintenance of anesthesia, patients received a 50:50 combination of oxygen and nitrous oxide, and also isoflurane 1.5–2.5%. After completion of surgery, neuromuscular blockade was reversed with neostigmine (2.5 mg) and atropine (1.25 mg/kg). Subcostal open cholecystectomy was performed in all the patients by the same surgeon (M.H.H.), who was blinded to the study. Patients were extubated when adequate spontaneous ventilation was established, and were transferred to recovery unit. After approximately 1 h in the recovery unit, patients were transferred to their respective wards.

The presence of PONV, the number of episodes and its severity were recorded by a physician who was blinded to the study. Severity of patients' pain and nausea were measured quantitatively using a 10-cm linear visual analogue scale (VAS) at 1, 4, 6, 12, 18 and 24 h after the surgery. Pethidine (0.5 mg/kg) was given intravenously to patients who had a pain score more than 4. Patients who had a VAS score more than 4 in nausea also received metoclopramide (10 mg) intravenously.

Statistical Analysis

The Statistical Package for Social Science, SPSS for Windows, version 15.0 (SPSS, Chicago, Ill., USA) was used for data analysis. Paired t tests were used to compare results within groups; independent t tests were used to compare results between the groups; χ^2 tests were used to compare proportions. Data are reported as means $\pm$ SD for 95% CI with 5% degree of freedom. A 2-sided p value <0.05 was considered statistically significant.

Results

There were no demographic differences (gender distribution, age, BMI, duration of surgery, mean arterial pressure and IV fluid intake during the surgery) between the 2 study groups (table 1). In the first 24 h after open cholecystectomy, 16 (36.6%) patients in the gabapentin

Table 2. Incidence of PONV and its severity

	Gabapentin (n = 44)	Placebo (n = 43)	p value
PONV incidence	16 (36.6%)	28 (65.2%)	0.021
Severity of PONV	4.4 ± 2.13	5.6 ± 1.95	0.119
Postoperative pain	4.46 ± 0.83	5.13 ± 1.24	0.096
Metoclopramide use, mg	6.0 ± 6.3	9.33 ± 7.1	0.033
Pethidine use, mg	28.33 ± 12.9	35.1 ± 15.1	0.002

group and 28 (65.2%) in the placebo group developed PONV ($p = 0.021$). There was no significant difference in the severity of PONV between the two groups (table 2). However, the metoclopramide use for control of PONV was significantly lower ($p = 0.033$) in the gabapentin group (6.0 ± 6.3 mg) compared to the control group (9.33 ± 7.1 mg). The mean VAS scores for postoperative pain in the gabapentin and placebo groups were 4.46 ± 0.83 and 5.13 ± 1.24 , respectively, and the difference was not statistically significant ($p = 0.096$). However, patients in the placebo group used significantly more pethidine compared to the patients in the gabapentin group (35.1 ± 15.1 vs. 28.33 ± 12.9 mg; $p = 0.002$) for pain relief (table 2).

Discussion

Our study showed that gabapentin significantly reduced the incidence of PONV after open cholecystectomy surgery, but it did not decrease the severity of PONV. It also reduced the need for postoperative pethidine and metoclopramide administration for the management of pain and PONV, thus indicating that gabapentin possess antiemetic and analgesic properties. However, it did not reduce postoperative pain, as measured by the VAS.

It has been reported that one third of patients undergoing general anesthesia suffer from PONV [6]. Although more than 1,000 investigations on the prevention or treatment of PONV have been published, the incidence of PONV has not changed over the past two decades [7]. The etiology of PONV following open cholecystectomy remains unclear, but it is probably associated with operative factors. Previous studies [8, 9] have shown that female gender, longer anesthesia time, general anesthesia, not smoking, use of postoperative opioids and previous PONV and/or motion sickness were associated with in-

creased incidence and severity of PONV. Although less important, PONV may also be influenced by the type of surgery as well: strabismus correction and laparoscopic surgery especially have been described as risk factors for PONV [10, 11]. Most of the previous studies that addressed the effect of gabapentin on reducing PONV incidence and severity have been performed on laparoscopic surgery procedures [1, 12].

Our study confirmed previous studies [1, 13] involving the use of gabapentin in patients undergoing laparoscopic cholecystectomy. Pandey et al. [1] in a randomized double-blind placebo-controlled study showed that preoperative administration of 600 mg gabapentin significantly reduced the incidence of PONV in patients undergoing laparoscopic cholecystectomy (46/125 vs. 75/125; $p = 0.04$). It also reduced postoperative fentanyl use for pain control. However, it did not have any significant effect on the severity of PONV. In another study, performed by Mohammadi and Seyedi [13], it was shown that 300 mg gabapentin given preoperatively significantly reduced the severity of PONV and the need for additional analgesic after laparoscopic surgery for assisted reproductive technologies, but it did not reduce the incidence of PONV.

Apparently, gabapentin has also been shown to reduce the incidence of nausea and vomiting after chemotherapy by a postulated mechanism of mitigation of tachykinin neurotransmitter activity [14]. The etiology of PONV in patients undergoing open cholecystectomy is not identical to that in patients receiving cytotoxic drugs, but we assume that it may be one probable mechanism in the prevention of PONV by gabapentin. As all the variables were similar between study groups, the difference in the incidence of PONV could only be attributed to gabapentin.

Conclusion

Our data show that gabapentin not only reduced PONV after open cholecystectomy, but also reduced the need for additional postoperative analgesics.

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