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Effect of Prophylactic Gabapentin on Postoperative Nausea and Vomiting After Laparoscopic Cholecystectomy: A Randomized Controlled Trial

Ahmadreza Soroush [1], Hosein Masoomi [1], Zhamak Khorgami [1*], Seyed Mojtaba Marashi [2], Roza Mofid [1]

[1] Department of Surgery, Shariati Hospital, Tehran University of Medical Sciences, Tehran, IR Iran
[2] Department of Anesthesiology, Shariati Hospital, Tehran University of Medical Sciences, Tehran, IR Iran

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ABSTRACT

Background: Postoperative nausea and vomiting (PONV) is a frequent and unpleasant adverse event associated with surgery. The reported incidence of PONV after laparoscopic cholecystectomy (LC) is quite high. Despite the use of different drugs to prevent or relieve PONV, it continues to be undermanaged. Recently, studies have been undertaken to determine if gabapentin can be useful for the prevention of PONV.
Objectives: We assessed the effect of perioperative gabapentin administration on PONV after LC.
Patients and Methods: We enrolled 92 patients scheduled to undergo LC for a randomized double-blind placebo-controlled study. Patients were divided into two groups of 46 patients. The intervention group received two doses of 600 mg gabapentin: one dose two hours before surgery and one dose six hours after surgery. Similarly Control group received capsules in the same size and shape as gabapentin capsules. All Patients were observed for PONV and adverse effects of the drug for 24 h. Metoclopramid (10 mg) was used as the antiemetic in patients with severe PONV in necessary circumstances. Total metoclopramid consumption were recorded.
Results: There were no demographic differences between the 2 study groups. Within 24 h of LC, 12 patients who received gabapentin (26.1%) and 30 patients who received a placebo (65.2%) experienced nausea ($P < 0.001$), while 10 patients in the intervention group (21.7%) and 24 patients in the control group (52.3%) vomited ($P = 0.002$). Metoclopramid was used to control PONV in 11 intervention patients (23.9%) and 29 control patients (63%; $P = 0.001$).
Conclusions: Perioperative administration of gabapentin significantly decreases the incidence of PONV and the requirement for postoperative antiemetic treatment following LC.

Implication for health policy/practice/research/medical education:
Findings are useful for all surgeons who perform laparoscopic surgeries in order to prevent postoperative nausea and vomiting.

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* *Corresponding author:* Zhamak Khorgami, Department of Surgery, Shariati Hospital, North Kargar Ave., Tehran, IR Iran. Tel: +98-2184902450, Fax: +98-2188633039, *E-mail:* khorgami@gmail.com

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1. Background

Postoperative nausea and vomiting (PONV) is among the common unpleasant complications that develop after general anesthesia, occurring in 25–30% of cases (1-3). Nausea and vomiting after laparoscopic cholecystectomy (LC) is common and has been reported in as many

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as 42–72% of patients (4). Despite use of different drugs to prevent and alleviate PONV, PONV continues to be undermanaged (5-7). Gabapentin, an analog of gamma aminobutyric acid, is generally used as an antiepileptic agent. Gabapentin is also used to treat neuropathic pain (8-10), postoperative pain (11, 12), and recently, studies have been undertaken to determine if gabapentin can be useful for prevention of nausea and vomiting. Such studies have demonstrated that gabapentin is effective for reducing the nausea and vomiting induced by chemotherapy (13) and surgeries like open cholecystectomy and LC (14, 15).

2. Objectives

We used a randomized controlled trial to study the antiemetic effect of perioperative gabapentin in patients who underwent LC.

3. Patients and Methods

This study was a randomized double-blind placebo-controlled trial and was performed at Shariati Hospital of Tehran University of Medical Sciences. The study conformed to the ethical guidelines of the 1989 declaration of Helsinki and the protocol was approved by an ethics committee at Tehran University of Medical Sciences. All patients provided informed written consent prior to participation in the study. Candidates scheduled to undergo elective or urgent LC between November 2008 and November 2009 were eligible for inclusion in this study. The exclusion criteria were as follows: patients with The American Society of Anesthesiologists (ASA) physical status > 1, body mass index (BMI) > 30, age < 17 or > 70 years, history of alcohol or opium use, renal or liver failure, concomitant diseases with nausea and vomiting, antacid use (because of interactions with gabapentin), use of antiemetics in the 24 h before surgery, pregnancy, breastfeeding, antidepressant use, use of calcium channel blockers, and conversion from LC to open surgery.

The primary outcome was the incidence of nausea and vomiting after LC. The secondary outcome was the effect of gabapentin on the duration of postsurgical hospital stays. The sample size needed to estimate the incidence of PONV after LC when the incidence is approximately 60% and to detect a 50% reduction in the rate of PONV with $\alpha = 0.05$ (one -tailed test) and power = 90% is 50%, was estimated to be 45 patients for each group. We assumed that there was a 5% chance that patients would drop out of the study after randomization; therefore, we increased the sample size to 48 patients in each group. On the basis of the prevalence of PONV and female-to-male ratio for LC, we determined that 40 female and 8 male patients would need to be assigned to each group. After enrollment, patients were randomly assigned to one of 2 groups (gabapentin or placebo) by using a stratified randomized block method. We used blocks of 8 computer- generated random number (2 blocks for male and 8 blocks for female patients) to assign patients to groups. After a patient was assigned to a treatment group, the assignment was recorded and placed in a sealed envelope by a person not otherwise involved in the study. A pharmacy assistant, who was also not otherwise involved in the study, removed the appropriate patient envelope and sent the designated trial medication to a nurse who was responsible for administering the drugs to patients. All patients, surgeons, nurses and physicians who participated in this study were blind to group assignments.

The patients in the intervention group received 600 mg of gabapentin two hours before surgery and again 6 h after surgery. Control group patients received a placebo that had the same size and shape as the gabapentin capsule. All patients were administered general anesthesia by using a similar anesthetic protocol. Premedication was 3 μg/kg fentanyl and 0.03 mg/kg midazolam. Anesthesia was induced using 5 mg/kg thiopental, and tracheal intubation was facilitated by injection of 0.5 mg/kg atracurium. Anesthesia was maintained with 0.6–1.5% isoflurane in 100% O_2 (without N_2O) and injection of 1 μg/kg fentanyl and 0.15 mg/kg atracurium every 30 min. At the end of the procedure, the neuromuscular block was reversed using 0.02 mg/kg atropine and 0.04 mg/kg neostigmine. After extubation, patients were moved to the post-anesthesia care unit. Patients were provided with fluid therapy. The volume of fluid and type of crystalloid injected was similar between the two groups. All patients received 5 cc/kg Ringer's solution before administration of anesthesia and 6 cc/kg serum-Ringer during surgery. Lost blood was replaced with serum-Ringer, at a volume equal to 3 times of that of the lost blood.

All patients were monitored for 24 h after surgery to determine PONV status. Patients were given 0.5 mg/kg pethidine to control pain and those patients with severe nausea or vomiting were given 10 mg metoclopramid intravenously. Drug adverse effects, and total pethidine and metoclopramid consumption were recorded. Statistical analyses were performed using SPSS version 18.0. We tested the normality of quantitative data distributions using Kolmogorov–Smirnov tests. Data were reported as means ± SD or medians and ranges. Data with a normal distribution was tested using independent *t* tests, and data that were not normally distributed was evaluated using Mann–Whitney *U* test. Qualitative data were analyzed using Chi-squared test. $P < 0.05$ was considered statistically significant.

4. Results

Of the 96 patients enrolled in the study, Four female patients were excluded (two female patients from each group) because their surgery was converted from LC to open surgery. A total of 92 patients remained, and each group included 46 patients. The mean patient age was 47.2 ± 15.2 years (range: 20–70 years). There were 38 (82.6%) female and 8 (17.4%) male patients in each group. The reasons for performing LC were as follows: biliary colic, 65 patients (70%); pancreatitis, 11 patients (13%); and

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cholecystitis, 16 patients (17%). The operative times for the invention and control groups were 63.1 ± 30.0 and 70.5 ± 29.8 min, respectively ($P = 0.238$) (*Table 1*). Twelve patients in the intervention group (26.1%) and 30 patients in the control group (65.2%) experienced postoperative nausea (OR = 5.3; 95% CI: 2.2–13.0, $P = 0.0009$). Ten patients in the intervention group (21.7%) and 24 (52.2%) patients in the control group had postoperative vomiting (OR = 3.9; 95% CI: 1.6–9.7, $P = 0.002$). In this study, 11 patients in the intervention group (23.9%) and 29 patients in the control group (63%) needed to use metoclopramid to control nausea and vomiting ($P = 0.001$) (*Table 2*).

The intervention group remained hospitalized for 1.4 ± 0.6 days (median: 1, range: 1–3) after surgery, while the control group remained hospitalized for 1.8 ± 0.6 days (median: 2, range: 1–3; $P = 0.003$). The mean dose pethidine was 18.3 ± 11.7 for the intervention group and 21.3 ± 11.8 for the control group ($P = 0.214$). No drug-related adverse effects were observed.

is unknown. Some factors that are associated with PONV include age, female gender, history of motion sickness, history of past PONV, not smoking, use of opioids as analgesics for postoperative pain, general anesthesia, and long duration of anesthesia. Surgical factors like intraperitoneal CO_2 with stretching and irritation of the peritoneum may also cause PONV (19-22).

Prescribing gabapentin to patients in the intervention group before and after LC resulted in significantly lower PONV, as compared to the control group. Gabapentin also reduced the need for administration of postoperative antiemetic treatment for the management of PONV. In a similar study, Pandey *et al.* showed that a single dose of 600 mg of gabapentin 2 h before LC significantly decreases the incidence of PONV (14). Khademi *et al.* also demonstrated positive effects of 600 mg gabapentin on PONV when administered before open cholecystectomy (23). Mohammadi *et al.* found that administration of 300 mg gabapentin before ambulatory laparoscopic surgery

Table 1. Demographic Clinical Characteristics of Patients Receiving Gabapentin or a Placebo Before and After Laparoscopic Cholecystectomy

	Gabapentin (n = 46)	Placebo (n = 46)	*P* value
Age, y, mean ± SD	46 ± 14.8	48.7 ± 15.5	0.38
Gender, No. (%)			0.61
Male	8 (17.4)	8 (17.4)	
Female	38 (82.6)	38 (82.6)	
Diagnosis, No. (%)			0.4
Cholecystitis	6 (13)	10 (21.7)	
Pancreatitis	7 (15.2)	4 (8.7)	
Biliary colic	33 (71.7)	32 (69.5)	
Operation duration, mean ± SD	63 ± 30	70 ± 30	0.238

Table 2. Adverse Effects and Results Following Laparoscopic Cholecystectomy in Patients Who Received Either Gabapentin or a Placebo Perioperatively

	Gabapentin (n = 46)	Placebo (n = 46)	*P* value
Incidence of nausea, No. (%)	12 (26.1)	30 (65.2)	0.0009
Incidence of vomiting, No. (%)	10 (21.7)	24 (52.2)	0.002
Antiemetic administration, No. (%)	11 (23.9)	29 (63)	0.001
Post-operative hospital admission, d, median (range)	1 (1-3)	2 (1-3)	0.003

5. Discussion

Although some of the ways that gabapentin influences the body are known, the mechanism of PONV prevention by gabapentin is not yet clear. Changes in tachykinin activity or reduction in opioid usage has been proposed as mechanisms of PONV reduction (16, 17). Gabapentin is effective for reducing the nausea and vomiting that is induced by chemotherapy (13). A possible mechanism for this effect is a change in tachykinin neurotransmitter activity in response to gabapentin (18). Therefore, tachykinin effects may be a mechanism common to nausea reduction after surgery and nausea reduction after chemotherapy. The etiology of PONV after surgeries such as LC decreased postoperative nausea, but did not change post-operative vomiting (15). These subtle differences may result from the different dosages used or the type of surgery patients underwent in these studies. Pethidine, used as a postoperative analgesic, can cause nausea and vomiting. Our analysis did not show a significant difference in the consumption of pethidine between the 2 groups. However, this study was focused on PONV, and we did not evaluate pain intensity by visual analogue scores or patient-controlled analgesia.

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Authors' Contribution

Ahmadreza Soroush: Developing idea and research protocol, and performing surgeries; Hosein Masoomi: Developing idea and research protocol, data collection and analysis; Zhamak Khorgami: Developing research protocol, performing surgeries, data Analysis, and scientific writing; Seyed Mojtaba Marashi: Developing research protocol and conducting anesthesia; Roza Mofid: Data analysis and scientific writing.

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