

Gabapentin for post-operative nausea and vomiting: a pilot study

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ABSTRACT

Background: Gabapentin has been used in perioperative setting for the management of post-operative pain for surgery performed under general anaesthesia. Post-operative nausea and vomiting (PONV) even with the use of newer agents remains a major problem. The primary aim of this study was to see if gabapentin use decreased PONV.

Methods: A total of 40 patients undergoing elective laparoscopic cholecystectomy under general anesthesia with standardized premedication and anesthetics were randomized to receive gabapentin or a matching placebo. The patients in Group I received gabapentin 600 mg orally 2 hrs before surgery and 12 hrs after the first dose. The patients in Group II received a matching placebo orally 2 hrs before surgery and 12hrs after the first dose. Patients in both groups received diclofenac sodium 75 mg i.m b.i.d for pain and ondansetron 4 mg i.v for PONV. Additional doses were given on demand and recorded. The treatment was double blinded.

Results: The present study did not find significant reduction in PONV score and antiemetic consumption in gabapentin group when compared to a placebo for a period of 24 hrs.

Conclusions: Gabapentin in the doses used was found to ineffective in post-operative nausea and vomiting in patients undergoing planned laparoscopic cholecystectomy with standardized pre-anaesthetic and anaesthetic medication.

Keywords: Gabapentin, Post-operative nausea and vomiting, Cholecystectomy

INTRODUCTION

Surgery right from its inception has always provided better and long lasting cure for the disease for which it was performed, but at the same time has been associated with pain and post-operative suffering.¹ Operative injury is likely to be followed by: pain, nausea and vomiting, infections, ileus and Constipation, impaired lung function, urinary retention, pruritus, risk of thromboembolism etc.² PONV is one of the most common complications of surgery under general anesthesia. In spite of advances in anesthesia, the incidence of PONV has been reported to be in the range of 20-30 %.³ It has been described as “the big little problem” following ambulatory surgery.⁴

Pathophysiology of PONV

There are three major components of vomit reflex, the emetic detectors, integrative mechanism, and motor output. The main sensors of somatic stimuli are located in the gut and chemo-receptor trigger zone (CTZ). The emetic stimuli in gut are detected by two types of vagal afferent fibers.

Mechanoreceptors

They are located in the muscular wall of the gut and are activated by contraction and distension of the gut, on physical damage and manipulation during surgery.

Chemoreceptors

They are located in the mucosa of the upper gut and sensitive to noxious chemical stimuli. Emetic center is diffusely located in lateral reticular formation of medulla and mediates vomiting response through efferent responses through vagus, phrenic and spinal nerves of abdominal muscles. The emetic center receives inputs from higher cortical centers and somatic structures (git, pharynx heart, testes etc.) and from optic, olfactory, vagus, glossopharyngeal and trigeminal nerves. An important input is from the CTZ located in the area postrema, which is highly vascular, and no blood brain barrier exists here.⁵ Hence that chemicals in blood and cerebrospinal fluid can stimulate it. Central structures involved in vomiting response are rich in dopaminergic, muscarinic, serotonergic, histaminic, neurokinin-1 and opioid - receptors. Various antiemetics exert their effect by acting on one or more of these receptors. None of them can eliminate nausea and vomiting associated with all emetogenic stimuli.³

Prevention is the best management, but it is not always possible to completely eliminate PONV. Anti-emetics are the main stay of therapy for PONV. The main pharmacological classes of drugs used in the treatment are anti-cholinergics, anti-dopaminergic, anti-histaminic, anti-seratonegic (5HT₃ antagonists) and glucocorticoids. Despite being better than placebo, the efficacy of currently available anti-emetics is often poor. Combination of anti-emetics as a multi modal therapy may sometimes be needed to control PONV successfully. Newer agents such as synthetic cannabinoids (nabilone, dronabinol) have shown to be of use in controlling nausea and vomiting, but cause hallucinations and decrease gut motility, therefore the search for safer and better tolerated entiemetics is still on.^{6,7} Clinical trials with a new class of drugs “neurokinin receptor antagonist” (NK-1 antagonists) have shown promise in treatment of nausea and vomiting. Aprepitant and vofipritant are the two drugs in this class, which have shown promise.⁸ One more drug that has shown some efficacy in controlling chemotherapy induced and post-operative nausea and vomiting (PONV) is gabapentin. NK-1 antagonism has been hypothesized as one of the probable mechanisms of its efficacy as an antiemetic; the other being a decrease in opioids consumption.^{9,10}

Various strategies have been devised to relieve PONV. The pharmacological agents that have been tried until date have their limitations and influence the overall recovery of the patient. The search for an effective antiemetic, which has no effect on other recovery parameters and is free from drug interactions that might occur due to numerous drugs used in the peri-operative setting led to the discovery of multimodal effects of gabapentin.

Gabapentin, which was introduced for treatment of partial seizures later shown to alleviate nausea vomiting associated with chemotherapy and a clinical trial to see its role in PONV has also shown positive results.^{11,12} In an anecdotal report, it was noted that complete resolution of chemotherapy induced

nausea and vomiting occurred in a patient who was put on gabapentin. An open-label study with gabapentin 300 mg thrice a day, orally for chemotherapy induced nausea and vomiting was conducted and found gabapentin to be highly effective.¹¹ The authors of the above study have reported NK-1 antagonism as the possible mechanism of gabapentin in PONV.¹¹

Further, gabapentin was found to decrease post-operative opioid consumption and at the same time reduce incidence of PONV when 600 mg per oral was administered 2 hrs prior to laparoscopic cholecystectomy.¹² Gabapentin was found to secondarily decrease PONV in patients undergoing vaginal hysterectomy.¹³

Simultaneously, there are contradictory studies also. A study done in thyroid surgery did not find any difference in frequency of nausea or vomiting between the two groups.¹⁴ Another study done in patients undergoing rhinoplasty or endoscopic sinus surgery also did not show any difference in PONV between the groups.¹⁵ Thus, the role of gabapentin in reducing PONV is controversial and needs further studies to establish its status in PONV.

METHODS

This study was carried out in the Departments of pharmacology, surgery and anesthesiology, Himalayan Institute of Medical Sciences, Dehradun. Approval from institutional ethics committee was obtained to conduct the study. Prior to initiation of study, written informed consent from the patient/legal guardian of the patient was obtained after full explanation of elements contained in the research protocol. A total number of 40 patients were included in the study.

Study design

This was a “randomized double-blind placebo-controlled parallel group study” done in patients undergoing elective laparoscopic cholecystectomy under general anesthesia with standardized premedication and anesthetics.

Patients between 18 and 60 years of age and having American Society of Anesthesiologist (ASA) physical Status I and II,¹⁶ who were diagnosed on ultrasound of having uncomplicated gall stones were included in the study.

Patients with a history of smoking, alcohol or drug abuse, bleeding diathesis analgesic or antacid use in recent past, impaired renal or hepatic function, motion sickness or taking anti-depressants or calcium channel blockers were excluded from the study. Pregnant and lactating females were also excluded.

Patients of both sexes, fulfilling the criteria given above, having normal investigations and scheduled for surgery were randomized into two groups: group I (The gabapentin group) and Group II (The placebo group).

Randomization was done using table of random numbers with odd numbers assigned to gabapentin group and even numbers assigned to placebo group. The randomization schedule was maintained by a person not directly involved in observation of patients. The treatment was blinded by the use of placebo capsules, which were identical to the capsules of gabapentin in color, shape, size and weight. Neither the patient nor the prescriber knew about the treatment given.

The patients of group I received gabapentin 600 mg orally 2 hrs before surgery and 12 hrs after the first dose i.e. a total dose of 1200 mg on the day of surgery. The patients in group II received a matching placebo orally 2 hrs before surgery and 12 hrs after the first dose. Patients in both the groups were given diclofenac sodium 75 mg i.m, b.i.d for pain relief and 4 mg ondansetron i.v for PONV. The treatment was double-blinded.

Anesthesia was induced by propofol 2 mg/kg and fentanyl 3 µg/kg. Intubation was facilitated with vecuronium bromide 800 µg/kg. Anesthesia was maintained with isoflurane (1%) and 70% nitrous oxide with oxygen and intermittent vecuronium when indicated. After the completion of surgery neuro-muscular block was reversed with atropine 0.02 mg/kg and neostigmine 0.04 mg/kg. Additional ondansetron 4 mg, i.v was given when the patient complained of nausea and vomiting. After about 6 hrs stay in post-anesthesia care unit (PACU), patients were shifted to the ward. Severity of PONV was graded on a four point (0 to 3) PONV scale.¹⁷ Rescue antiemetic (4 mg ondansetron i.v) consumed by the patient was noted in both groups for first 24 hrs post-operatively. PONV scores were taken at 1, 4, 8, 12 and 24 hrs.

PONV was scored as: 0=No nausea and vomiting; 1=Mild nausea not requiring treatment; 2=Moderate nausea, mild vomiting and requiring treatment; 3=severe vomiting.¹⁷ Additional antiemetic requirement in 24 hrs post-operative period were recorded.

Statistical analysis

PONV scores were compared between the groups using Mann–Whitney test (non-parametric test). $p < 0.05$ was taken as significant. All results were expressed as mean±standard error. Additional antiemetic consumption in 24 hrs was compared using un-paired t-test.

RESULTS

Both the groups were comparable in demographic profile i.e., age, sex, weight, height, and physical status (Table 1). The PONV scores at 1, 4, 8, 12 hrs post-operatively in the gabapentin group were 0.85 ± 0.19 , 0.8 ± 0.19 , 0.15 ± 0.08 and 0.05 ± 0.05 and in the placebo group were 0.95 ± 0.17 , 0.95 ± 0.18 , 0.15 ± 0.08 and 0.1 ± 0.06 , $p = 0.70$, 0.57 , 1.0 and 0.56 for intergroup comparison respectively, which were

Table 1: Demographic profile of patients in gabapentin and placebo groups.

| Parameter | Gabapentin | Placebo |
|--------------------|------------|-----------|
| Age (years) | 44.8±2.7 | 41±2.4 |
| Male: Female ratio | 7:13 | 1:2 |
| Height (cm) | 158.1±1.8 | 159.7±2.2 |
| Weight (kg) | 65.4±2.2 | 66.4±2.04 |
| ASA grade (%) | | |
| I | 18 (90) | 17 (85) |
| II | 2 (10) | 3 (15) |

ASA: American Society of Anesthesiologist

not significant. None of the patients experienced PONV at 24 hrs (Table 2 and Figure 1).

Additional antiemetic (ondansetron, i.v.) consumed in Group I was 2.0 ± 0.46 mg and in Group II was 2.2 ± 0.61 mg ($p = 0.79$) (Table 3 and Figure 2). The difference in antiemetic requirement was not significant.

DISCUSSION

This study did not find significant reduction in PONV score and antiemetic consumption in gabapentin group when compared to a placebo for a period of 24 hrs. Our findings are in contradiction to a study, which has shown gabapentin in a dose of 600 mg, given 2 hrs before surgery to be effective in reducing PONV and antiemetic consumption in patients undergoing laparoscopic cholecystectomy over a period of 24 hrs post-operatively.¹² The present and the above said study used same premedication and anesthetics. The difference in our results might be due to the fact that the above said study used fentanyl for pain relief in the post-operative period and opioid use is well-known to be one of the causes of PONV. Moreover, our study had only 20 patients in each group, whereas there were 125 patients in each group in the above study. This study was underpowered as compared to the above mentioned study to bring to light any difference in PONV if it existed. Moreover, the present study excluded patients who had motion sickness or were smokers, both of which are well-known to cause increased PONV. The role of gabapentin per se in reduction of PONV has been questioned and reduction of opioid use for pain relief has been suggested as an explanation to reduced PONV in the gabapentin group.¹⁸ Using larger number of patients in surgery with use of emetogenic anaesthetics and post-operative medicines that increase PONV might bring out the real efficacy if it exists.

Another study done in patients undergoing laparoscopic cholecystectomy found substantial increase in the incidence of PONV in the gabapentin group.¹⁹ However, there are studies that have not shown gabapentin to be effective in PONV in other type of surgeries also.²⁰ Thus substantiating the results of our study.

Table 2: Post-operative nausea and vomiting score on 0 to 3 PONV scale in Group I (gabapentin) and Group II (placebo) groups.

| Group | 1 hr | 4 hrs | 8 hrs | 12 hrs | 24 hrs |
|----------------|-----------|-----------|-----------|-----------|--------|
| I (Gabapentin) | 0.85±0.19 | 0.8±0.19 | 0.15±0.08 | 0.05±0.05 | 0 |
| II (Placebo) | 0.95±0.17 | 0.95±0.18 | 0.15±0.08 | 0.1±0.06 | 0 |

PONV: Post-operative nausea and vomiting

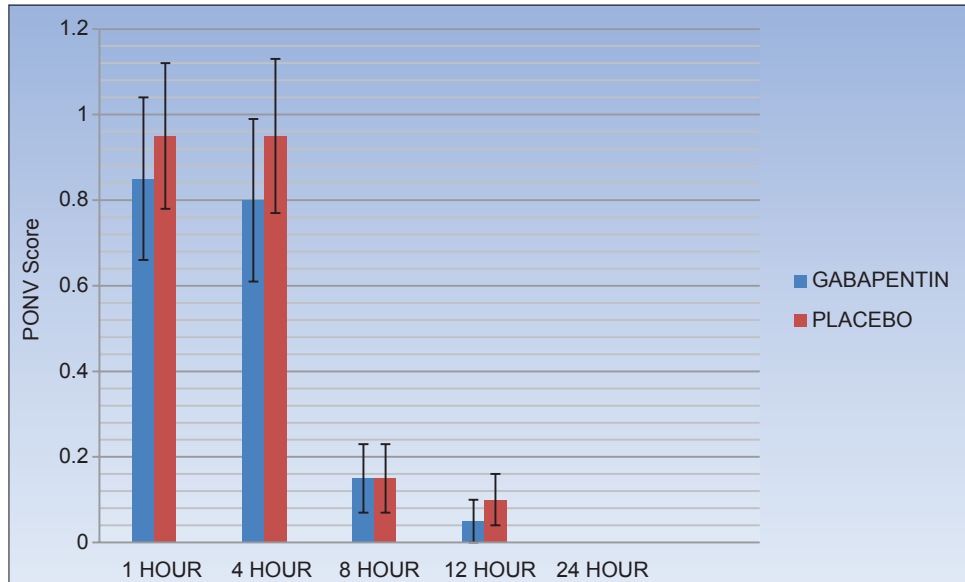


Figure 1: Comparison of post-operative nausea and vomiting scores on 0-3 post-operative nausea and vomiting scale at different time intervals in gabapentin and placebo groups.

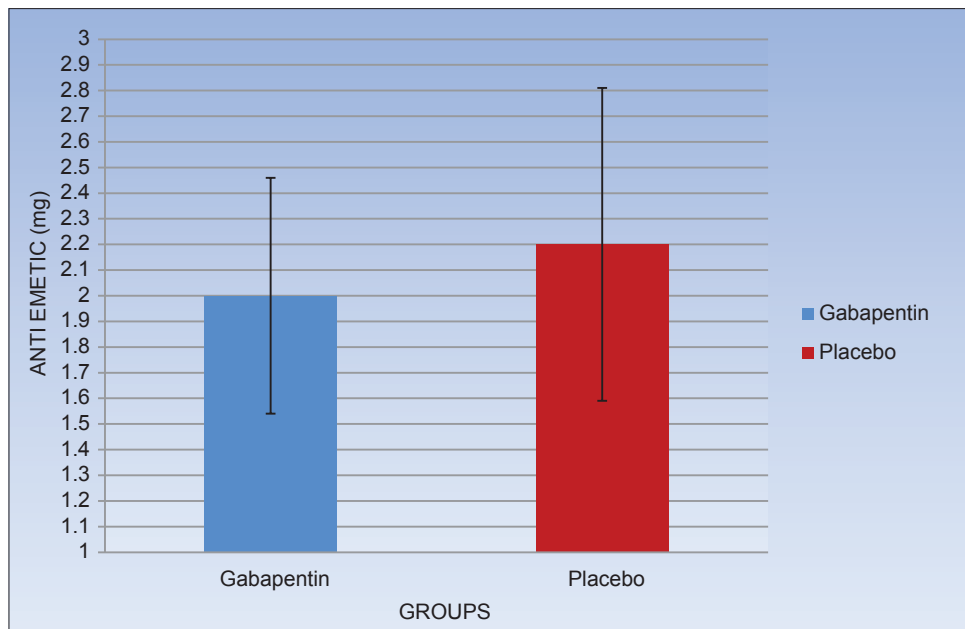


Figure 2: Comparison of additional antiemetic (Ondansetron, i.v) consumption in (mg) during 24 hr post-operative period in gabapentin and placebo groups.

There are other studies not related to PONV where gabapentin has been shown to reduce nausea and vomiting. In an anecdotal report gabapentin 300 mg thrice daily resolved all nausea and vomiting associated with Chemo therapy (doxorubicin and cyclophosphamide) given for

newly diagnosed breast cancer. Then, an open-label trial with gabapentin 300 mg TDS was done to see the effect on chemotherapy induced nausea and vomiting in nine patients with breast cancer who had not taken chemotherapy and was found to be useful.¹¹

Table 3: Additional antiemetic consumption (mg) in 24 hr post-operative period in Group I (gabapentin) and Group II (placebo) groups.

| Group | Additional antiemetic consumption (ondansetron, i.v) (mg) |
|----------------|---|
| I (Gabapentin) | 2.0±0.46 |
| II (Placebo) | 2.2±0.61 |

The present study shows a trend for little improvement in PONV as patients in gabapentin needed lesser antiemetic. There is some interest in the effectiveness of gabapentin in nausea and vomiting of different origins.¹¹ The present results obtained were challenged on many counts thus making gabapentin an unfavorable candidate for use in nausea and vomiting specially in PONV. This needs further investigations in light of controversial yet suggestive findings.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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