ORIGINAL ARTICLE

A Prospective, Randomized, Placebo-Controlled, Trial Comparing the Effectiveness of Gabapentin, Ondansetron & Dexamethasone in Prevention of Nausea &Vomiting after Laparoscopic Cholecystectomy

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Abstract

Gabapentin is an anticonvulsant drug that has been shown useful in postoperative nausea and vomiting (PONV). AIM: We compared the effects of gabapentin on PONV with ondansetron, dexamethasone and placebo in patients undergoing laparoscopic cholecystectomy under general anesthesia. One-hundred-twenty patients undergoing elective laparoscopic cholecystectomy were randomly assigned to one of the following four groups: gabapentin group (G) received 600mg oral gabapentin capsule two hours before surgery +IV 2ml saline 10-15 minutes before surgery; ondansetron group (O) received an oral placebo two hours before surgery +IV 4mg ondansetron 10-15 minutes before surgery; dexamethasone group (D) received oral placebo two hours before surgery +IV 8mg dexamethasone 10-15 minutes before surgery and placebo group (P) received oral placebo two hours before surgery +IV 2ml saline 10-15 minutes before surgery. Granisetron IV 1mg was used as rescue medication for emesis. Nausea and vomiting were assessed by direct questioning of the patients at 1, 2, 6, 12 and 24 hours after surgery. RESULTS: We found that the incidence of PONV (by simple yes or no) in first 24 hours was significantly lower in gabapentin (40%) dexamethasone (30%) and ondansetron group (36.7%) as compared to placebo group (66.7%) ($P<0.05$). The number of patients requiring rescue antiemetics was significantly decreased in gabapentin (30%), dexamethasone (26.7%) and ondansetron (26.7%) group versus placebo group (60%) ($P<0.05$). Gabapentin is as effective as ondansetron and dexamethasone as an antiemetic in laparoscopic cholecystectomy patients.

Key Words

Gabapentin, Antiemetic, Postoperative nausea, Vomiting

Introduction

Postoperative nausea and vomiting are distressing and one of the commonest complications following anesthesia and surgery with an overall incidence of 25-30%. (1-3) It is one of the most common reasons for poor patient satisfaction (4) and may adversely affect the patient and surgical outcomes. As many as 70% to 80% of patients at risk may be affected. (5) With the increasing trend in minimally invasive surgeries, laparoscopic cholecystectomy has become common and popular in the management of cholelithiasis but it is associated with appreciably high rate of PONV; 53-72% of patients require antiemetic therapy after laparoscopic cholecystectomy; and such a high incidence of PONV remains a major cause of morbidity. Gabapentin, (1-(amino methyl) cyclohexane acetic acid, is a structural analogue of the inhibitory neurotransmitter gamma-amino

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butyric acid (GABA). Gabapentin has no affinity for GABAA or GABAB receptors. Instead, it has a high affinity for the voltage gated calcium channels but its exact mechanism of action is complex and not fully understood. Gabapentin is available only as oral preparations and its absorption is dose-dependent due to a saturable L-amino acid transport mechanism in the intestine. (6) After a single oral dose of 300mg, mean maximum plasma concentrations are attained in 2-3hr. The oral bioavailability of a single 300mg oral dose of gabapentin is 60% and varies inversely with dose. It does not bind to plasma proteins (7) and is not metabolized in humans. Elimination rate constant, plasma clearance and renal clearance are linearly related to creatinine clearance. In patients with normal renal function the elimination half-life of gabapentin when administered as monotherapy is between 4.8 and 8.7 hr. (8) Gabapentin has been studied as an antiemetic in perioperative setting and has been shown to effectively suppress nausea and vomiting in patients of laparoscopic cholecystectomy.(9) We performed a randomized placebo-controlled study to evaluate antiemetic effect of gabapentin compared with ondansetron and dexamethasone in preventing PONV in patients of laparoscopic cholecystectomy.

Materials And Methods

This randomized placebo-controlled comparative study was conducted jointly in the departments of General Surgery and Anesthesiology of SMHS hospital (associated hospital of Govt. medical college, Srinagar). The protocol was approved by the institutional authorities and informed consent was obtained from each patient. Patients with USG diagnosed cholelithiasis scheduled for laparoscopic cholecystectomy under general anesthesia were included in the study. Total of 140 patients, both sexes, of ASA physical status I and II, were enrolled, 120 of these were finally eligible for study. The exclusion criteria were: patients with < 18 or > 60 years of age; unable to cooperate or epileptic; impaired kidney or liver functions; history of hypersensitivity to any drug; history of peptic ulcer disease; patients on psychotropic drugs, calcium channel blockers or antidepressants; patients on whom laparoscopic cholecystectomy was converted into open cholecystectomy (*Fig 1*).

Before the study, patients provided detailed medical histories and demographic information; preanesthesia assessment was done and the study protocol was explained. Patients were randomly assigned to one of the four groups of 30 patients each using the table of random numbers. The four groups of patients received the medications as follows: gabapentin group (G) received 600mg oral gabapentin with sips of water 2 hrs before surgery + IV 2ml saline 10-15 min before surgery. Dose of gabapentin was decided from previous available studies (9,10). Ondansetron group (O) received an oral placebo (capsule similar to gabapentin), 2 hrs before surgery and IV 4mg ondansetron 10-15 minutes before surgery. Dexamethasone group (D) received oral placebo 2 hrs

Table 1. Demographic profile of study patients

	Gabapentin (n=30)	Ondansetron (n=30)	Dexamethasone (n=30)	Placebo (n=30)
Age (in years, Mean±SD)	42.2±9.7	42.8±8.2	43.9±10.4	39.6±8.6
Weight (Mean±SD)	58.1±7.7	60.4±7.1	57.9±8.0	60.3±8.6
Gender Male(n) Female(n)	6 24	9 21	7 23	11 19
Duration of surgery (in min, Mean±SD)	63.0±16.1	64.8±15.1	65.8±15	65.6±10.7
Duration of anesthesia (in min,±SD)	76.0±16.0	75.2±14.8	75.5±15.6	79.4±11.5
ASA Score 1/11 (Mean±SD)	21/9	24/6	23/7	24/6
Co_2 Insufflation time (in min, Mean±SD)	51.4±13.9	51.2±13.1	57.3±15.7	55.2±11.4

Fig.1. STUDY FLOW DIAGRAM
(Prospective, Randomized, Placebo-controlled, Comparative Parallel Study)

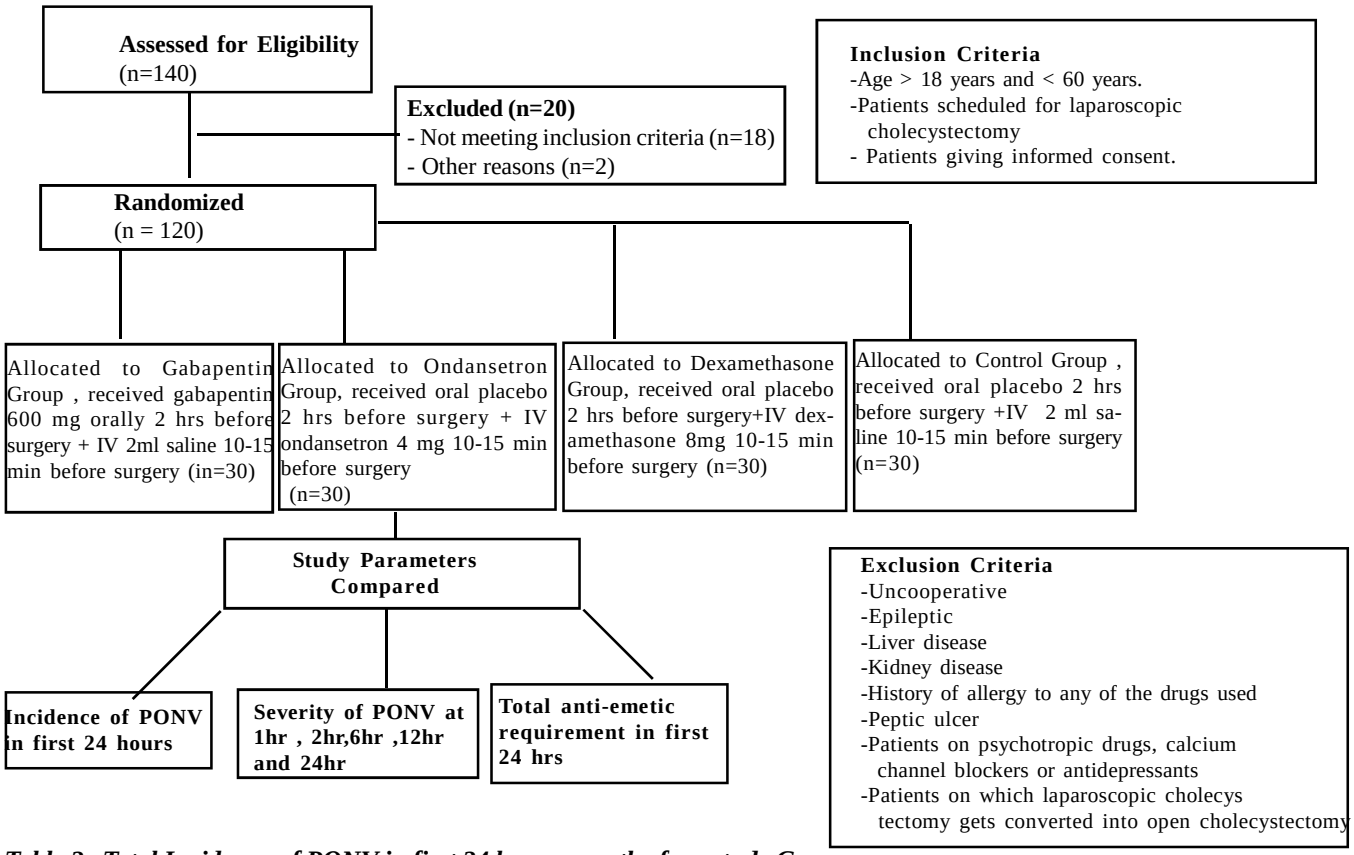

Table 2. Total Incidence of PONV in first 24 hrs among the four study Groups

Incidence of PONV	Gabapentin		Ondansetron		Dexamethasone		Placebo	
	n	%	n	%	n	%	n	%
Yes	12	40.0	11	36.7	9	30.0	20	66.7
No	18	60.0	19	63.3	21	70.0	10	33.3

Z test (Mann Whitney U test), Kruskal Wallis test

Table 3. Total Antiemetic requirement in the first 24 hrs among the four Study Groups

Anti-emetic	Gabapentin		Ondansetron		Dexamethasone		Placebo	
	n	%	n	%	n	%	n	%
Yes	9	30.0	8	26.7	8	26.7	18	60.0
No	21	70.0	22	73.3	22	73.3	12	39.2

Z test (Mann Whitney U test), Kruskal Wallis test

before surgery + IV 8mg dexamethasone 10-15 minutes before surgery. Placebo group (P) received oral placebo 2 hrs before surgery + IV 2 ml saline 10-15 minutes before surgery.

Anesthesia was induced with propofol 2mg/kg. Intubation of trachea was facilitated with suxamethonium 2mg/kg.Anesthesia was maintained with N2O:O2:Isoflurane. Intraoperative muscle relaxation was obtained with injection atracurium besylate 0.5mg/kg initially. After tracheal intubation a nasogastric tube was passed to keep stomach empty; the tube was removed at the end of the surgery before tracheal extubation. During the surgery patients were kept in reverse trendelenburg position with the right side of the table elevated. The abdomen was insufflated with carbon dioxide (CO2) to an intra-abdominal pressure of 10-14mmHg. Duration of anesthesia, surgery and CO2 insufflation was also recorded in each patient as per the proforma. After completion of the surgery, neuromuscular blockade was reversed with a standard mixture of neostigmine and atropine (2.5mg:1.2mg) and patients were extubated and when adequate spontaneous ventilation was established, patients were transferred to Recovery. After arrival in the Recovery, postoperative data was collected at 1, 2, 6, 12 and 24 hrs.

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 incidence of PONV in first 24 hrs was recorded in all the four arms. Granisetron 1mg IV was kept as rescue antiemetic and total antiemetic requirement in first 24 hrs was noted. The severity of PONV was graded as follows. (9)

No PONV : Absence of any emetic episode or nausea.

Mild PONV: Mild nausea or one emetic episode or short lasting nausea of any severity of less than 10 minutes triggered by exogenous stimulus and no antiemetic drug required.

*Moderate PONV:*1-2 emetic episodes or moderate or severe nausea without exogenous stimulus and antiemetic therapy required once.

*Severe PONV:*More than two emetic episodes or patient nauseated more than twice and administration of at least one antiemetic required.

Statistical Methods

Data was expressed as mean ± standard deviation and percentage. The intergroup comparison of the parametric data was done by Student's 't' test and Analysis of Variance (ANOVA). The non parametric data was analyzed by Mann Whitney U test, Chi Square analysis and Kruscal Wallis test. P value < 0.05 was considered significant. The software used was Statistical Package for Social Sciences (SPSS) and Microsoft Excel.

Results

There were no differences among the four groups with respect to age, weight, gender, ASA score, duration of surgery and Co2 insufflation time (*Table 1*).

Total incidence of PONV in the four groups during first 24 hours after surgery are reported in *table 2*.

The overall incidence of PONV was significantly more($P<0.05$) in the placebo group (66.7%) compared with the other three groups (40.0% in group G, 36.7% in group O and 30.0% in group D. However, gabapentin did not decrease the severity of PONV. Moreover, the antiemetic requirement was significantly less in group G (30.0%), group O (26.7%) and group G (26.7%) compared with placebo group P (60.0%) ($p<0.05$); but there were no significant differences in antiemetic requirement between the first three treatment groups ($P>0.05$) (*Table 3*)

Discussion

Our study shows that prophylactic gabapentin 600mg is more effective than placebo and is as effective as 8mg ondansetron and 10 mg dexamethasone for the prevention of nausea and vomiting associated with laparoscopic cholecystectomy. Gabapentin is available as oral preparation only. Ondansetron 4mg and dexamethasone 8mg were used intravenously. To overcome this limitation regarding 'route of administration' double dummy idea was utilized. Gabapentin group received 2ml IV saline as placebo, ondansetron and dexamethasone group received oral placebo 2 hrs before surgery and placebo group was given oral placebo 2 hrs before surgery plus 2ml IV saline 10-15 minutes before surgery.

The etiology of PONV is complex and multifactorial and depends upon patient, medical and surgery related factors. General anesthesia is associated with increased

likelihood of PONV by 11 times compared to other types of anesthesia and longer the duration of anesthesia more is the likelihood of PONV (11). Guttoso et al observed antiemetic effect of gabapentin in breast cancer patients (12) and mitigation of tachykinin neurotransmitter activity has been postulated to be useful (13). Tachykinin activity has a role in the pathogenesis of chemotherapy- induced emesis in ferrets and a selective tachykinins receptor antagonist improves chemotherapy induced nausea and vomiting. Antagonism of tachykinin activity may be one probable mechanism for prevention of PONV by gabapentin.Gabapentin has been shown to be useful in other acute perioperative conditions as well (postoperative analgesia (14,15), postoperative delirium (16), pressor response to direct laryngoscopy and tracheal intubation(17), postoperative anxiety (18).

Conclusion

In conclusion, our study demonstrates that preemptive use of 600mg oral gabapentin effectively suppresses nausea and vomiting in laparoscopic cholecystectomy and is as effective as ondansetron and dexamethasone. Thus important areas of perioperative anesthesia care might be taken care of by this single drug.

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