ORIGINAL ARTICLE

A Randomized, Double Blind, Placebo Controlled Study Evaluating Preventive Role of Gabapentin for PONV in Patients Undergoing Laparascopic Cholecystectomy

Farhana Bashir, Kharat Mohd, Shigufta Qazi, A.M. Hashia

Abstract

A double blind, prospective, randomized placebo controlled study was carried out to evaluate the antiemetic efficacy of Gabapentin on incidence and severity of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy under general anaesthesia. One hundred patients of ASA grade I & II randomly assigned equally in two groups were given 600mg of gabapentin or matching placebo orally two hours before surgery. A complete response (no nausea and vomiting) was observed in 60% patients in gabapentin group as compared to 38.2% in Placebo group. The difference was statiscally significant (P = 0.028). In addition use of rescue antiemetics was reduced in gabapentin group to 34% (17 patients) compared to placebo group 54% (27 patients) with a statistically significant difference (P = 0.044). However, there was no difference of severity of PONV amongst two groups; 1st, 2nd, 6th, 12th and 24th. hour of surgery. The study reveals that gabapentin, an anticonvulsant and analgesic may prove to be multimodal when further research is conducted to prove its efficacy as antiemetic.

Key Words

Gabapentin, Postoperative Nausea, Vomiting, Anaesthesia, Laparoscopic,Cholecystectomy

Introduction

Postoperative nausea and vomiting (PONV) continues to present a vexing challenge to anesthesia providers (1) and till date remains one of the commonest complications following anesthesia and research is continuously onto prove the efficacy of various antiemetic agents. The etiology of PONV is complex and is dependent on many factors including the technique of anesthesia, patient characteristics, the nature of underlying disease, the type of surgical procedure as well as the post operative care. Laparoscopic Cholecystectomy has now-a-days almost replaced the traditional open cholecystectomy & it is reported that nearly of 53-72% of patients undergoing this procedure require antiematics after surgery (2).

Persistent vomiting leads poor patient satisfaction, electrolyte disturbances, delayed wound healing and wound dehiscence and sometimes life threatening aspiration. A return to status quo in all surgical patients may be delayed and hospital stay may be prolonged.The drugs used so far for prevention of PONV have been prokinetics, dopaminegic antagonist, 5HT3 antagonists, butyrophenones, anticholinergies, phenothiazines, antihistaminics, benzamides and steroids alone or in combination with other antiemetics (3-8) recently an open clinical study demonstrated the antiemetic effect of Gabapentin in Chemotherapy induced acute (within 24 hrs) and delayed onset (days 2-5) of nausea and vomiting in breast cancer (9).

Again several studies in which gabapentin was used to study its postoperative analgesic effects showed tendency towards a lower incidence of PONV(10-13). Hence,the present study was carried to find the role of gabapentin being for its role as an agent that prevents PONV apart from being an analgesic (10).

Material & Methods

This prospective, randomized, double blind study was conducted in the department of Anesthesiology of SKIMS, Srinagar, J&K from June 2006 to May 2008 after seeking clearance from ethical committee. In this

From the PG Department of Anaesthesiology, SKIMS, Srinagar, Kashmir, India.
Correspondence to : Dr. Kharat Mohammad Bhat, Asso Professor, PG Department of Anaesthesiology, SKIMS, Srinagar Kashmir, India

study 100 patients of American Society of Anesthesiology (ASA) status I & II, of both sexes and in age range of 20 to 60 years scheduled for elective laparascopic cholecystectomy were selected. Patient with body weight more than 20% of ideal body weight, patients older than 60 years and younger than 18 year, smokers, substance addicts or alcoholics, those with history of hypersensitivity to any drug, patients with history of peptic ulcer disease, bleeding diathesis or taking antacids, patients with impaired liver and kidney function, patients already on some antiemetic, menstruating, pregnant or lactating females, patient with history of motion sickness, history of previous PONV, patients on antidepressants or Ca++ channel blockers and patient converted to open cholecystectomy were all excluded from the study.The placebo capsule similar to gabapentin capsule was taken for the study. It was a B-complex capsule which would have no antiemetic property and shall have no deleterious effect on patients.One day prior to surgery patients were clinically evaluated, assessed and investigated and explained the study protocol. After obtaining the written informed consent the patient were prescribed 0.5mg of oral alprozolam evening define the operation. The patients were randomly allocated to two groups of 50 patients each. The drug or placebo was given to the patient by the surgical doctor on duty two hours before operation orally with a sip of water. Patients enrolled in gabapentin group received 600 mg gabapentin and those in the placebo group received similar capsule. The identity of the capsule used in two groups was blinded from the anaesthetist who observed the patient postoperatively. In order to minimize the interference with interpretation of study data risk factors of PONV like female sex, long period of CO2 insufflation, gall bladder surgery and anesthesia technique was controlled in the study. The anesthesia was standardized.

Anaesthesia was induced with injection propofol 2 mg/kg wt. and injection morphine 100 micro gm/kg wt Intubation of trachea was facilitated with injection vecuronium bromide 100ug/kg wt. Anesthesia was maintained with 60 % nitrous oxide in oxygen. Propofol infusion of 100-200 kg/kg wt. and intermittent vecuronium bromide when indicated. After tracheal intubation nasogastric tube was placed to promote baseline emptying of stomach of air and gastric secretions. Nasogastric tube was removed at the end of surgery before extubation Intermittent positive pressure ventilation was used which was controlled mechanically. During the surgery patient was positioned in the reverse Trendlenburg position with right side of the table elevated. The abdomen was insufflated with Carbon dioxide to an intra abdominal pressure of 10-14 mmHg. Intraoperative monitoring included ECG, pulse oximetry, systolic, diastolic and mean blood pressure which were recorded every three minutes. After the completion of surgery, neuromuscular block was reversed with atropine 0.02 mg/kg wt and neostigimine 0.04mg/kg and patients were extubated when adequate spontaneous respiration was established .In postoperative period patients were observed for a period of 24 hours for PONV and the amount of rescue antiemetics consumed by the patients. The PONV was defined as the subjective unpleasant sensation associated with awareness of urge to vomit (nausea retching or vomiting was grouped together). The incidence of nausea, vomiting was recorded at 1st , 2nd, 12th & 24th hour by direct questioning the patients or his attendants by the same anesthetist. The severity of PONV was graded as follows Wilson (6):-

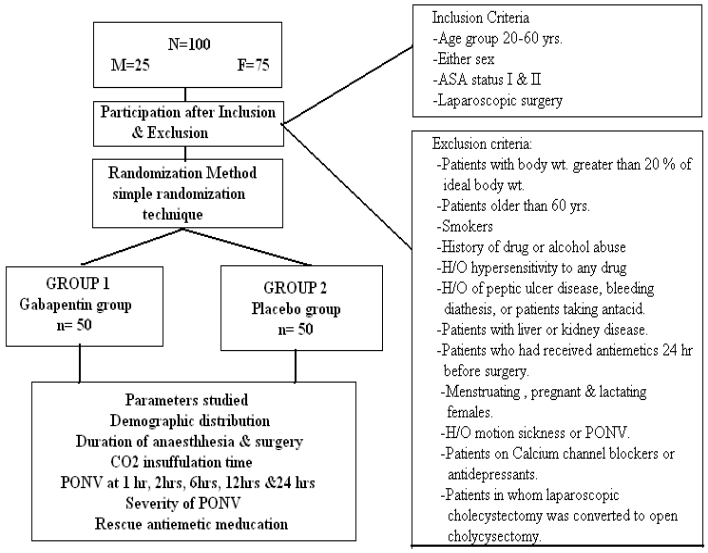
*1.**No PONV**: Absence of any emesis or nausea.*

*2.**Mild PONV**: Patient having only mild nausea, or one emetic episode or nausea lasting for less than 10 minutes and where no antiemetic is required.*

*3.**Moderate PONV**: Patient has 1-2 emetic episodes or moderate to severe nausea and antiemetic therapy is required.*

*4.**Severe PONV**: Patient has more than 2 emetic episodes or is nauseated more than twice & more than*

Fig 1. A Randomized, Double blind, Placebo Controlled Study of Prophylaxis with Gabapentin for Prevention of PONV in Patients Undergoing Laparascopic Cholecystectomy



one antiemetic required. Patients received ondansterone 0.1mg/kg wt. i/v as rescue antiemetic.

Statistical Analysis

Students 'T-Test' was used for statistical evaluation of the following:-Effect of age, weight, gender and ASA.

Table I (a) Dmographic Distribution

Age (yrs)	N	GP %	P N	%	Results
20-29	11	22	10	20	
30-39	15	30	21	42	
40-49	12	24	13	26	P=0.364
50-59	12	24	6	12	(NS)

Table I (b) Dmographic Distribution

ender distribution of the Studied Subjects					
ender	Gabapentin n	%	Placebo n	%	Result
lale	15	30	10	20	p=0.250(NS)
emale	35	70	40	80	

Table 2. Incidence of PONV in 24 hours in the Studies Subjects

	Gabapentin		Placebo		
PONV	N	%	N	%	Result
Yes	20	40.0	31	62.0	P=0.028 (Sig.)
No	30	66.0	19	38.0	OR=2.4

Table.3 Rescue Antiemetic Required in the Studied Group

e ietic	Gaba pentin N	%	Placebo N	%	Result	ARR (%)	RRR (%)
	17	34.0	27	54.0	P= 0.044 (Sig.)	26.0	39.4
	30	66.0	19	46.0			

Table 4. Severity of PONV 24 hrs After Surgery in the Studied Subject

PONV After 24 hrs.	Gabapentin N	%	Placebo N	%	Result
Mild	1	2.0	1	1	
Moderate	0	0.0	0	0	
Severe	0	0.0	0	0	P=1.000 (N.S)
No	49	98.0	49	98.0	

Results

Physical status: Two groups had comparable number of patients in two groups and showed insignificant variation (P>0. 0.5) *table I(a) & I(b).*Mean duration of anesthesia and surgery in gabapentin group was 74.7 + minutes and 79.5 + 13. 5 minutes in placebo group with a mean of 59. 1 + 14.6 minutes and 64.2 + 12.5 minutes respectively (statistically insignificant difference P> 0.05).The Mean duration of CO2 insufflation in two groups was 46.7 + 12.3 minutes and 51.3 + 11.6 minutes respectively (statistically insignificant difference P> 0.05).*Postoperative Nasusea and Vomiting (PONV)*:A complete response (no nausea and vomiting was observed in 60% of patients in gabapentin group compared to 38% in Placebo group which is a statistically significant difference (P= 0.028) *table 2*. Again rescue antiemetic medication was used in 17 (34%) patients in gabapentin group compared to 27 (54%) in placebo group which is a statistically significant difference (P=0.044) (*Table-3*). However, severity of PONV which was observed in 1st hour, 2nd hour, 12th hour and 24 hour showed statistically insignificant difference (P=0.239) in both groups (*Table: 4*).

Discussion

Postoperative nausea and vomiting is area of concern as nearby 53-72% of patients require antiemetic therapy after laparoscopy cholecystectomy (Naginb *et al* (2), Wang *et al* (5)). In our study conducted on 100 patients who underwent laparoscopic cholecystectomy and were given oral gabapentin (50 patients) and placebo (50 patients) it was observed that 60% of patients had no postoperative nausea and vomiting compared to placebo (38% of patients), a statistically significant difference (P= 0.028) which is quite encouraging. Again rescue antiemetic in postoperative period was required in 17 patients (34%) in gabapentin group and 27 patients (54%)

in placebo group (significant difference P=0.044).The idea of gabapentin being an antiemetic came from various studies where this drug was used as an analgesic in the treatment of various malignancies. In the study by Guttuso *et al* (9). Also in studies (10-13) where gabapentin was studied as postoperative analgesic there was a significant tendency towards lower incidence of postoperative nausea and vomiting. Although precise mechanism of gabapentin being antiemetic is not clear, it is postulated that mechanism could be mitigation of tachykinin neurotransmitter activity. There is an evidence that tachykinin activity is a part of pathogenesis of chemotherapy induced emesis and a selective tacykinin receptor antagonist improves both acute and delayed nausea and emesis induced by chemotherapy (9,14, 15). Our results of significant decrease in incidence of postoperative nausea and vomiting (P=0.028) and also the statistically significant reduction in the use of rescue antiemetic compared to placebo (P=0.044) is comparable and in agreement with Guttuso *et al* (9); Rosarius *et al* (11); Turan *et al* (12); Pandey *et al* (10) and Ole Metheisan (13) who observed as follows.

Guttossu *et al* (9) - six out of nine patients had improvement in nausea and three patients had complete resolution of nausea while being given chemotherapy and gabapentin 300 mg thrice daily.

Rosarius *et al* (11) used gabapentin 1200 mg orally preoperative to prevent postoperative pain after vaginal Hysterectomy and with decrease in postoperative pain noticed significant decrease in postoperative nausea vomiting.Turan *et al* (12) studied the use of oral gabapentin given preoperatively in patients of spinal surgery noticed significant reduction in incidence of vomiting (P<0.05) compared to placebo.

Pandey *et al* (10) in a study similar to ours found that preoperative use of 600 mg oral Gabapentin reduced the incidence of nausea and vomiting in 60% of patients compared to placebo where the incidence was 37.8% (P=0.04).Metheison *et al* (13) found out considerable improvement in nausea with gabapentin after abnormal Hysterectomy in twenty three trails with 1529 pateints.

Conclusion

The preoperative use of oral gabapentin can be a simple and effective tool in the armentarium of anaesthesia practice for prevention of postoperative nausea and vomiting. But this multimodal drug needs further research and more clinical trials before it is put in regular practice for the safe conduct of Anaesthesia.

Refereneces

1. Lake CL, Johnson JO, McLoughlin TM. Prophylaxis and treatment of postoperative nausea and vomiting. *Advances Anesthesia* 2004;22: 61-95.
2. Naguib M, el Bakry AK, Khoshim MH, *et al* . Prophylactic antiemetic therapy with ondansetron, tropisetron, granisetron and Metoclopramide in patients undergoing laparoscopic cholecystectomy:a randomized, double blind comparison with placebo. *Can J Anaesth* 1996;43:226-31.
3. Sikka R, Kaul T,Grewal A, Satija A.Postoperative nausea and vomiting. *J Anesth Clin Pharmacology* 2007;23 (4):341-56.
4. Kothari1 SN, Boyd1 WC, Bottcher1ML,Lambert PJ.Antiemetic efficacy of prophylactic dimenhydrinate (Dramamine) vs ondansetron (Zofran). *J Surg Endoscopy* 2000; 14(10):926-29.
5. Wang JJ, Ho ST, Liu YH, *et al* . Dexamethasone reduces nausea and vomiting after laparoscopic cholecystectomy. *Br J Anaesth* 1999; 83:772-75.
6. Wilson EB, Bass CS, Abrameit W, Roberson R, Smith RW. Metoclopramide versus ondensetron in prophylaxis of nausea and vomiting for laparoscopic cholycystectomy. *Am J Surg* 2001;181:138-41.
7. Madej TH, Simpson KH. Comparison of the use of domperidone, droperidol, and metoclopramide in the prevention of nausea and vomiting following gynaecological surgery. *Br J Anaesth* 1986; 56:879-83.
8. Kotelko DM, Rottman RL, Wright WC,*et al*. Transdermal scopolamine decreases nausea and vomiting following cesarean section in patients receiving epidural morphine. *Anesthesiology* 1989; 71: 675-78.
9. Guttuso T Jr, Roscoe J, Griggs J. Effect of gabapentin on nausea induced by chemotherapy in patients with breast cancer. *Lancet* 2003; 361:1703-05.
10. Pandey CK,Priye, Ambesh SP *et al*. A Randomized, double blind, Placebo-Controlled study of Prophylactic gabapentin for prevention of postoperative nausea and vomiting in patients undergoing Laparoscopic Cholecystectomy. Postgraduate. *J Anaesthesia* 2006, 52 (2), 97-100.
11. Rosarius M, Mennander S, Suominen P, *et al*. Gabapentin for the prevention of postoperative pain after vaginal hysterectomy. *Pain* 110(1 - 2)175 - 81.
12. Turan A, Karamanlio B, Memi D, Hamamcioglu MK, Tükenmez B, Pamukçu Z, Kurt I. Analgesic effects of gabapentin after spinal surgery. *Anesthesiology* 2004 ;100(4):935-38.
13. Mathiesen O, Møiniche S, Dahl JB. Gabapentin and postoperative pain: a qualitative and quantitative systematic review, with focus on procedure. *BMC Anesthesiology* 2007;7:2253-57.
14. Kong VKF, Irwin MG. Gabapentin multimodal Perioperative drug? *Br J Anaesth* 2007, 99(6); 775-86.