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Prophylactic Gabapentin for Prevention of Postoperative Nausea and Vomiting in Patients Undergoing Laparoscopic Surgery

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Abstract
Context: *Prevention and treatment of postoperative nausea and vomiting continues to be a major challenge in postoperative care. Gabapentin is an antiepileptic drug .Its antiepileptic action is demonstrated in chemotherapy-induced acute and delayed onset of nausea and vomiting in breast cancer patient.*
Aims: *The aim of this study was to evaluate the antiemetic effect of gabapentin on incidence and severity of postoperative nausea and vomiting in laparoscopic surgery.*
Methods and Material: *Sixty adult patients of ASA grade I & II scheduled for laparoscopic surgeries like lap appendicectomy, lap cholecystectomy, lap hernia repair were randomly assigned into two equal groups to receive 600 mg gabapentin (Group G, n=30) or matching placebo (Group P, n= 30) two hours prior to surgery. Conventional anaesthesia technique was applied to every patient. Ondansetron 4mg was used intravenously as rescue medication for emesis.*
Statistical analysis used: *Incidence and severity of postoperative nausea and vomiting (PONV) were compared between the study groups in the next 12 hours.*
Results: *Demographic data and the duration of anaesthesia were not significantly different between the two study groups .Six patients in group G had PONV in 12 hours compared with 18 patients in group P (P<0.05). Eighteen patients (60%) in group G had no incidence of PONV in comparison with twelve patients (40%) in group P (P<0.05).*
Conclusions: *Administration of oral gabapentin before laparoscopic surgery effectively suppresses nausea and vomiting.*
Keywords: *Antiemetic, gabapentin, postoperative nausea, vomiting.*

I. Introduction

Postoperative nausea and vomiting are commonly occurring complications following anaesthesia and surgery [1,2]. Prevention and treatment of PONV continues to be a major challenge in postoperative care and plays an important role in well-being of the surgical patients. Several factors are responsible for the etiology of PONV including the technique of anaesthesia, type and site of surgery, gender. Now-a-days laparoscopic procedure has become more popular compared to conventional open technique. Incidence of PONV is more in laparoscopic operation than open technique. It is seen that nearly 53-72% of patients require antiemetic therapy after laparoscopic surgery, whereas the incidence of PONV in patients undergoing general anaesthesia for conventional surgery is 30% [3, 4].

The probable cause of PONV in laparoscopic surgery is peritoneal stretching due to intraperitoneal CO_2 insufflation Gabapentin is an anticonvulsant that has antinociceptive and antihyperalgesic properties. It is a structural analog of gamma amino butyric acid (GABA). It does not bind with plasma proteins and is not metabolized in humans. After a single oral dose of 300 mg, mean maximum plasma concentrations attained in 2-3 hours. Absorption kinetics of gabapentin is dose-dependent, due to a saturable transport system. The bioavailability of a single 300mg oral dose of gabapentin is 60% and decreases with increasing dose. Elimination of gabapentin is by renal clearance and elimination half-life is about 5-7 hour after a single oral dose of 200-400mg. [5, 6, 7].

Recently it is reported the anti-emetic effect of gabapentin in chemotherapy-induced acute (within 24 hour) and delayed onset (2-5 days) of nausea and vomiting in breast cancer [8]. In this study, we have evaluated the antiemetic effect of gabapentin on the incidence and severity of PONV in patients who underwent laparoscopic surgery.

There are several drugs used to prevent PONV like metoclopramide, ondansetron etc.They deserve some severe adverse effects like extra-pyramidal symptoms etc. On the other hand, they do not decrease post-operative rescue analgesic requirement.

In the study by Pandey et al. [3] on 250 patients scheduled for laparoscopic cholecystectomy, gabapentin as premedication effectively suppresses nausea and vomiting and post-operative rescue analgesic requirement. Therefore, we designed a placebo-controlled study to test the hypothesis that oral gabapentin 600mg as premedication, would decrease the incidence and severity of PONV in laparoscopic surgery.

II. Subjects And Methods

This clinical trial was performed from January 2016 to April 2016.After taking approval from the Institutional Ethical Committee, written informed consent was taken from each patient separately. We recruited 60 patients of ASA physical status 1 &2, of both sexes scheduled for elective laparoscopic surgery for a double-blind, prospective, randomized and placebo-controlled study.

The patients whose body weight more than 20% of ideal body weight, who had impaired liver or kidney function, received antiemetic within 24 hours, who were menstruating ,pregnant or lactating women, history of motion sickness or on an antidepressant or converted to open techniques were excluded from the study. The patients were randomly allocated into two equal groups. The patients of group G received oral gabapentin 600mg (n=30) and the patients of group P received matching placebo (n=30) 2 hour before surgery. Randomization was based on computer generated codes that were concealed until interactions were assigned. Tablet alprazolam (0.5) was given to every patient in the night before surgery and on arrival in the operating room, standard anaesthesia monitors were applied. Anaesthesia was induced with propofol 2mg/kg, tramadol 1mg/kg. Tracheal intubation was facilitated with rocuronium bromide 0.9mg/kg. Anaesthesia was maintained with propofol infusion at the rate of 100 microgram/kg/min and 70% nitrous oxide in oxygen and intermittent vecuronium bromide when indicated. At the end of operation, neuromuscular blockade was reversed with glycopyrolate (0.01mg/kg) and neostigmine (0.04mg/kg) and extubation was done. Patients were shifted to post-anaesthesia care unit (PACU) for 6 hour and then shifted to their respective wards. A resident doctor, who was blind to the type of medication the patients had received, recorded PONV at 1, 3, 6 &12 hours. Intravenous tramadol was used if the pain score was >3 (VAS score) or on patient demand within 12 hours. Any adverse effect was also noted. Intra &postoperative BP, pulse, spO_2 were noted for all the patients of both the groups.

III. Statistical Analysis

The arithmetic means and the standard error of means (mean ± SEM) of percentage (%) of type of nausea &vomiting in each of the treated (Group G) and Placebo (Group P) groups were calculated. The data were analyzed by one way analysis of variance (ANOVA),where F values indicated significance and means were compared by a post-hoc multiple range test with $P<0.05$ taken as the statistically significant threshold.

IV. Results

All patients in both groups were comparable according to age, body weight, ASA status, duration of surgey and duration of anaesthesia (Table I). There was no statistically significant difference regarding the type of operation between the two study groups (Table 2).Intraoperative and postoperative vital parameters were more or less same in both groups. The difference was not statistically significant(Table 3).The incidence of PONV during first 12 hour in patients after laparoscopic surgery was significantly lower in gabapentin group then placebo group regarding no vomiting, mild vomiting and moderate vomiting and the result is statistically significant($P<0.05$). But there was no statistically significant difference in the severity of PONV amongst the two groups (Table 4 & Table 5 & Figure 1).

The total number of patients (4/30) requiring 1st dose of rescue antiemetic was much less than placebo group (30/30). The difference in both groups was statistically significant ($P<0.05$) (Table 6 & Figure 2).Regarding 2nd dose rescue antiemetic, it was nil in GrG whereas 18 patients (60%) of Group P received 2nd dose of antiemetic ($P<0.05$) (Table 6).The patients of placebo group consumed significantly higher amount ondansetron as antiemetic ($P<0.05$) and tramadol as analgesic compared to the patients of Gabapentin group (Table 7 & 8).

The incidence of side effects in both the groups was similar and few. Drowsiness and headache was observed in a very few patients of Group G. The result was not statistically significant (Table 9).

V. Discussion

Gabapentin is mainly used as an analgesic. Gabapentin has been demonstrated to decrease opioids consumption in postoperative as well as painful neuropathic conditions [9,10,11,12].

Antihyperalgesic properties of gabapentin are by reducing central sensitization, a pre-requisite for postoperative hyperalgesia. It binds with the alpha2δ subunit of voltage dependent calcium channels and blocks the development of hyperalgesia and controls sensitization[13, 14].

PONV was defined as the subjective unpleasant sensation associated with awareness of urge to vomit (nausea, retching, vomiting had been grouped together). The severity of PONV was graded as follows:-

No Ponv

Absence of any emetic episode or nausea

Mild Ponv

The patient had only mild nausea or one emetic episode or short lasting nausea of any severity of less than 10 minutes which triggered by exogenous stimulus no antiemetic drug was required.

Moderate ponv

The patient had 1-2 emetic episodes or moderate or severe nausea without exogenous stimulus and patient required antiemetic therapy once.

Severe ponv

The patient had more than two emetic episodes or was nauseated more than twice and administration of at least one antiemetic was required. Recently gabapentin has been reported to be effective in the treatment of nausea &vomiting in patient receiving cytotoxic drugs [8].Although the etiology of PONV in patient undergoing laparoscopic surgery is not same as that in patients receiving cytotoxic drugs, in our study we found that there was lower incidence of PONV during first 12 hour after laparoscopic surgery in the group of patient who received prophylactic Gabapentin 600mg two hours before surgery than those who received placebo. In a study by Pandey et al. [3] it was found that incidence of postoperative nausea and vomiting within 24 hour after laparoscopic cholecystectomy was significantly lower in gabapentin group than in the placebo group(P=0.04). But Sussan Soltani and Mirsadegh [15] showed in their study that oral gabapentin 300 mg 1hour before surgery was effective in reducing postoperative nausea but not vomiting.

In our study we found that more than 80% of patients of group G have no vomiting and a few percentage of patients have been suffering from mild & moderate type of vomiting (P<0.05).This is correlated with the study of Pandey et al [3].

Probably the cause of ineffective vomiting control in the study of Sussan Soltani and Mirsadegh [15] is due to low dose of gabapentin and early ambulation.

The mechanism of gabapentin in the prevention of PONV is unknown but it could possibly be due to the indirect effect of opioid sparing or a direct effect on tachykinin activity [16].

Study by Bashir et al [17] showed that the additional use of rescue antiemetics was reduced in that group treated with gabapentin (34%) compared to placebo group (54%) (P<0.05). Our study also showed that only 4 patients (13.33%) of Gr G received first dose antiemetic drug compared to Gr P where all patients received first dose of antiemetic .This difference is statistically significant (P<0.05%). Second dose of antiemetic was not required in Gr G. But 60% of patients in Gr P received second dose of antiemetic. This difference is statistically significant(P<0.05).It is also shown that the total dose of antiemetic was also markedly reduced in Gr G as compared to GrP.This is also confirmed in the studies by different authors [3,18].

In our study in the patients of Gr G received lower amount of analgesic postoperatively than those the patients of Gr P (P<0.05).This observation was same as the observation of different authors [9, 10, 11].

Gabapentin was well tolerated with no significant side effects in this study. A few patients (6/30), however, suffered from headache of moderate intensity postoperatively.

VI. Conclusion

To conclude, a single dose of gabapentin 600mg as premedication decreases PONV significantly. It also reduces postoperative oral analgesic consumption. Further studies however are required to investigate the efficacy of this drug alone or in combination with other antiemetic.

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Table 1: Demographic and Perioperative data
Values are expressed Values are expressed as mean±SD

Characteristics	Group G	Group P
Age(years)	30±6.4	30±6.1
Weight(Kg)	67.7+_9.4	68.1+_10.3
ASA(I/II)	24/6	25/5
Duration of surgery (mins)	51.8±9.6	52.1±9.3
Anaesthesia time (mins)	56.5±3	57.4±5

Table 2: Types of operation

No. of patients	Group G (n=30)	Group P (n=30)
Lap. Appendicectomy	8	9
Lap. Cholecystectomy	14	13
Lap. Hernia repair	3	4
Lap. Ovarian cystectomy	5	4
Total	30	30

Table 3: Intra and postoperative vital parameters

Characteristics	Group G		Group P	
Period	Intra op	post op	Intra op	post op
Heart rate	80.3±6.2	74 ±4.6	78.5 ± 5.4	76.4±3.4
Mean Blood Pressure (mm Hg)	102.5±8.1	96.8±10.6	101.4±7.8	98.4 ±9.8
Respiratory rate	18.3±3.6	16.6±3.4	17.6±2.8	17.2±2.5
SpO_2	99.3± 0.5	99.1±0.8	99.2±0.4	99.4 ±0.2

Values are expressed as mean ± SD

Table 4: Postoperative Nausea and Vomiting (PONV)

Group	Group G (N=30)				Group P (N=30)			
Time (hrs)	No Vomiting	Mild Vomiting	Moderate Vomiting	Severe Vomiting	No Vomiting	Mild Vomiting	Moderate Vomiting	Severe Vomiting
1	24/30 (80%)	5/30 (16.66%)	1/30 (3.33%)	0/30 (0%)	0/30 (0%)	9/30 (30%)	18/30 (60%)	3/30 (10%)
3	24/30 (80%)	2/30 (6.66%)	4/30 (13.33%)	0/30 (0%0	1/30 (3.33%)	10/30 (33.33%)	18/30 (60%)	1/30 (3.33%)
6	29/30 (96.66%)	1/30 (3.33%)	0/30 (0%)	0/30 (0%)	5/30 (16.66%)	15/30 (50%)	10/30 (33.33%)	0/30 (0%)
12	28/30 (93.66%)	2/30 (6.66%)	0/30 (0%)	0/30 (0%)	10/30 (33.33%)	20/30 (66.66)	0/30 (0%)	0/30 (0%)

Table 5: Postoperative Nausea and Vomiting (PONV) - *P* Values

Hour	No Vomiting	Mild Vomiting	Moderate Vomiting	Severe Vomiting
1	*P*<0.05	*P*<0.05	*P*<0.05	NS
3	*P*<0.01	*P*<0.05	*P*<0.05	NS
6	*P*<0.05	*P*<0.05	*P*<0.05	NS
12	*P*<0.05	*P*<0.05	NS	NS

Table 6: Total number of patients requiring ondansetron as rescue antiemetic

Dose	Group G(n=30)	Group P(n=30)	*P* Value
First dose	4/30(13.33%)	30/30(100%)	*P*<0.05
Second dose	0/30(0%)	18/30(60%)	*P*<0.05

Table 7: Requirement of rescue analgesic

Hour	Group G(n=30)	Group P(n=30)	*P* Value
1	3/30(10%)	30/30(100%)	*P*<0.05
3	5/30(16.66%)	30/30(100%)	*P*<0.05
6	6/30(20%)	30/30(100%)	*P*<0.05
12	3030(100%)	30/30(100%)	*P*<0.05

Table 8: Total dose of antiemetic (ondansetron) and total dose of analgesic (tramadol) required

Drug	Group G(n=30)	Group P(n=30)	*P* Value
Total dose of ondansetron(mg)	20±10	150±10	*P*<0.05
Total dose of tramadol(mg)	100±10	150±30	*P*<0.05

Table 9: adverse effects

Adverse effects	Group G(n=30)	Group P(n=30)	P Value
Drowsiness	2/30(6.66%)	0/30(0%)	NS
Itching	0/30(0%)	0/30(0%)	NS
Somnolence	1/30(3.33%)	0/30(0%)	NS
Headache	6/30(20%)	0/30(0%)	NS

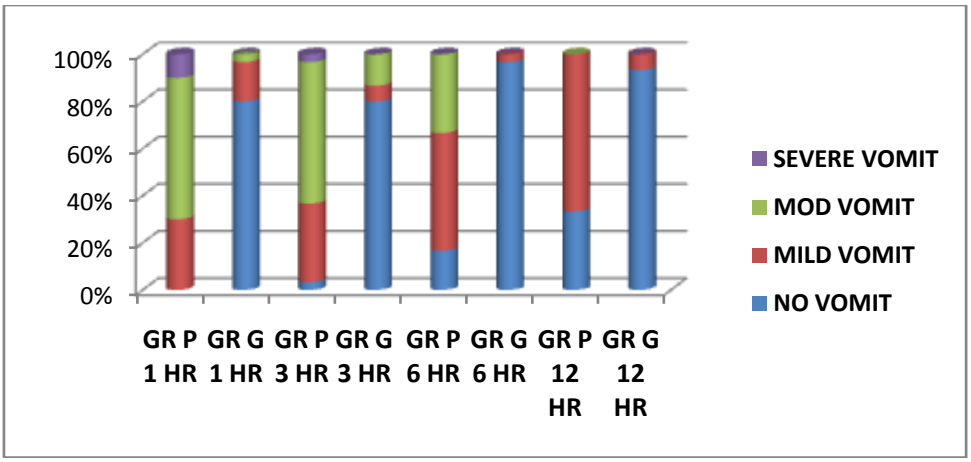

Figure 1: Distribution of no, mild, moderate, severe vomiting among the two groups at 1, 3, 6 & 12 hour

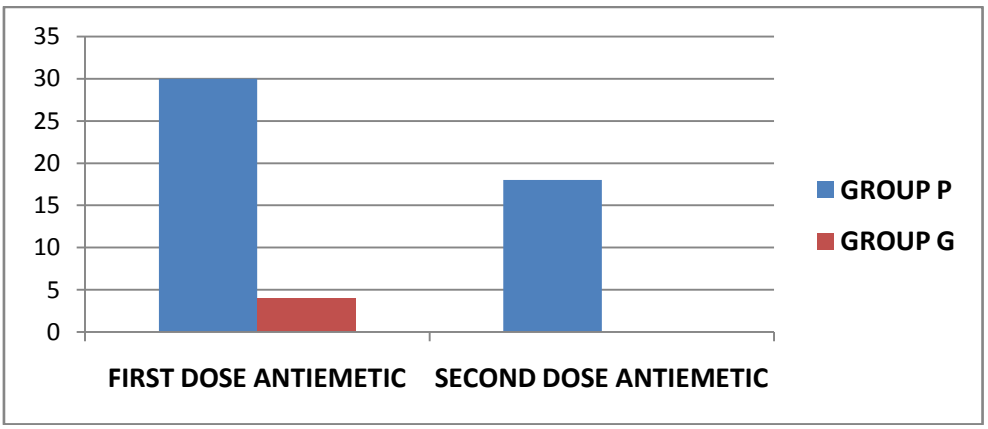

Figure 2: Total number of patients requiring ondansetron as rescue antiemetic

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