

Study of Different Doses of Gabapentin for Post-Operative Pain Relief after Laparoscopic Cholecystectomy

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Abstract: This is a prospective, randomized, double blind, placebo controlled study conducted at Yashoda Superspeciality Hospital, Secunderabad, Telangana, India over 160 patients who underwent elective lap cholecystectomy during the period of 1st September 2015 – 30th May2016. Hospital Ethical Committee approval was taken prior to start this study. Sample size was calculated basing on the pilot study and keeping dropouts in mind total sample was decided 40 in each group. Sample size of 40 patients each, randomly allocated into four groups, using computer generated random number list. They were given tab. gabapentin 2hrs before surgery with sips of water. Group 1(Placebo), Group 2(GP-100mg), Group3 (GP-200mg), Group 4 (GP-300mg). Oral Gabapentin 300 mg may be the optimal preoperative dose to reduce the severity of postoperative pain and has an opioid sparing effect after laparoscopic cholecystectomy. At this dose it is well tolerated and may be used as part of multimodal analgesia to improve the quality of postoperative pain relief.

Keywords: lap cholecystectomy, post-operative pain.

INTRODUCTION

Acute pain after laparoscopic cholecystectomy is complex in nature and does not resemble pain after other laparoscopic procedures [1-3]. In laparoscopic cholecystectomy, overall pain is a conglomerate of three different and clinically separate components [2]: incisional pain (somatic pain), visceral pain (deep intraabdominal pain), and shoulder pain (presumably referred visceral pain).

Postoperative pain is reduced compared with open traditional cholecystectomy [4] but effective analgesic treatment after laparoscopic cholecystectomy has remained a clinical challenge [5]. In 17–41% of the patients, pain is the main reason for staying overnight in the hospital on the day of surgery [5-8] and pain is the dominating complaint and the primary reason for prolonged convalescence after laparoscopic cholecystectomy [1, 9]. Moreover, it has been hypothesized that intense acute pain after laparoscopic cholecystectomy may predict development of chronic pain [10]. Characteristically, pain after laparoscopic cholecystectomy carries a high inter-individual variability in intensity and duration and is largely unpredictable [2]. Pain is most intense on the day of surgery and on the following day and subsequently declines to low levels within 3–4 days. However, pain may remain severe in approximately 13% of patients throughout the first week after laparoscopic cholecystectomy [2]. The fact that acute pain after

laparoscopic cholecystectomy is complex in nature and does not resemble pain after other laparoscopic procedures [1,2] suggests that effective analgesic treatment should be multimodal.

In preclinical and clinical studies, gabapentin, an antiepileptic drug, has been found to be an effective potent antihyperalgesic that works centrally by reducing the release of monoamine neurotransmitters [11]. In patients undergoing breast surgery [12, 13], spinal surgery [14] and after abdominal hysterectomy [15] gabapentin had clinically important effects on postoperative pain and morphine consumption. However, there is no consensus on the optimal dose of gabapentin and there has been a wide variability in the dose of gabapentin and the results [16-18]. Pandey *et al.* [19] conducted a randomized placebo controlled trial to evaluate the optimal preoperative dose of gabapentin for postoperative pain relief and found that gabapentin 600 mg is an optimal dose for postoperative pain relief

following lumbar discectomy [19]. The lowest dose of gabapentin evaluated in Pandey *et al.* study [19] was 300 mg and even at this dose it was associated with a higher incidence of sedation, nausea, retching and vomiting [19,20]. It is not known if lowering the dose of gabapentin further, will reduce the incidence of side effects while decreasing the postoperative pain scores and opioid requirement. Dose response studies of the analgesic efficacy of gabapentin are warranted in laparoscopic cholecystectomy before this treatment can be recommended as routine. Hence, the present study was designed to evaluate effects of different doses of gabapentin as a pre-emptive analgesic contributing to postoperative analgesia in patients undergoing laparoscopic cholecystectomy.

OBJECTIVES

Primary objective

To assess and compare the efficacy of three different doses of prophylactic gabapentin in reducing postoperative pain in patients undergoing laparoscopic cholecystectomy as measured by visual analogue scale (VAS) scores.

Secondary objectives

- To assess and compare the efficacy of three different doses of prophylactic gabapentin in reducing the 24 hour cumulative opioid (tramadol) consumption after laparoscopic cholecystectomy.
- To assess and compare the time of first request of tramadol.
- To assess the side effects if any (sedation)
- To assess and compare the post-operative nausea and vomiting (PONV).
- To assess and compare the patient's overall satisfaction with postoperative analgesia.

MATERIALS AND METHODS

This is a prospective, randomized, double blind, placebo controlled study conducted at YASHODA SUPERSPECIALITY HOSPITAL, Secunderabad, Telangana, India over 160 patients who underwent elective lap cholecystectomy during the period of 1st September 2015 – 30th May 2016. Hospital Ethical Committee approval was taken prior to start this study. Sample size was calculated basing on the pilot study and keeping dropouts in mind total sample was decided 40 in each group. Sample size of 40 patients each, randomly allocated into four groups, using computer generated random number list.

Inclusion criteria

Patient belonging to following

- American Society of Anaesthesiologists grade I and II physical status.
- Patients of either sex between 18-60 years.
- Elective laparoscopic cholecystectomy.
- Capable of giving informed consent.

Exclusion criteria

- Patients allergic to gabapentin or pregabalin.
- Patients with uncontrolled systemic medical illnesses,
- Chronic use of any analgesic or gabapentin, associated pancreatitis,
- BMI >30.
- Indications of cholecystectomy other than cholelithiasis.
- Patients on antiepileptic medications.
- Uncontrolled anxiety and Schizophrenia or bipolar disorder.
- Have impaired liver or kidney function.

Allocation concealment

Group allocation was concealed in sealed, opaque envelopes.

Blinding

A pain nurse who had undergone prior education in assessment of postoperative analgesia and who was unaware of group assignment collected data on each patient. Thus the observer was blinded.

Procedure

After obtaining well informed written consent from the patient they were given tab.gabapentin 2hrs before surgery with sips of water.

Group 1(Placebo) patients were received the placebo.

Group 2(GP-100mg) patients were received 100mg of gabapentin.

Group3 (GP-200mg) patients were received 200mg of gabapentin.

Group 4 (GP-300mg) patients were received 300mg of gabapentin .

The “duration of effective analgesia” was considered to be the time interval between the end of anesthesia (extubating) and the time of first requirement of tramadol dose at VAS ≥ 4 . The postoperative pain was assessed using VAS scores, at 0min, 2ndhr, 4thhr, 8thhr, 12thhr, 16thhr, 20thhr & 24thhr after surgery at rest by the pain nurse blinded to group allocation. Patient's hemodynamic stability, sedation by ram say sedation score, nausea vomiting scale, time of first rescue analgesia and its total dose, overall satisfaction scores were also recorded. In all the four groups, postoperative analgesia was provided with intravenous tramadol 50-100mg boluses up to a maximum of 400mg per day was given along with rescue antiemetic injection ondansetron 0.1mg/kg and also be instructed to request pain medication from the nurse whenever they required pain relief & not to wait for their next scheduled pain assessment.

ASSESSMENT OF SEDATION

Ramsay sedation score

- Patient is anxious and agitated or both
- Patient is cooperative, oriented and tranquil
- Patient responds to commands only
- Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
- Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
- Patient exhibits no response to light glabellar tap or loud auditory stimulus

ASSESSMENT OF NAUSEA

Categorical scoring system

0- None ; 1- Mild ; 2- Moderate ; 3- Severe

ASSESSMENT OF PATIENTS' SATISFACTION

Likert- type satisfaction scale

1- Very satisfied; 2- satisfied; 3- moderate; 4-poor

OUTCOME MEASURES- Postoperatively,

- VAS pain scores at rest and movement in 24hrs postoperatively.
- Total dose of tramadol received in the first 24hrs postoperatively.
- Time of request for tramadol after completion of surgery.
- Post-operative nausea and vomiting (PONV).
- Any adverse effect of gabapentin (Sedation).
- Overall satisfaction scores of the patients for analgesia.

STATISTICAL ANALYSIS

Statistical Methods

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean + SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Significance levels (ascending order): * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$

The following assumptions on data are made:

- Dependent variables should be normally distributed.
- Samples drawn from the population should be random, and cases of the samples should be independent.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale among four groups (Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test and ANOVA (analysis of variance test) has been used to find the significance of study parameters on categorical scale between two or more groups.

Statistical software

The Statistical software namely SPSS version 17 was used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

OBSERVATION AND RESULTS

A total of 160 patients were included in this study and were randomized into four groups of 40 patients each. Group 1(Placebo),Group 2(GP-100mg),Group 3(GP-200mg),Group 4(GP-300mg).Results were presented under Demographic data, VAS score , sedation score, nausea vomiting scale, time to first request of tramadol postoperatively, total dosage of tramadol requirements in 24hrs, patient satisfaction scores were compared between the Group 1, Group 2, Group 3 and Group 4.

Demographic variables

There were no statistically significant differences among four groups in the patient's demographic characteristics including age, gender, height, weight and ASA grading.

Age distribution in four groups

The mean age of patient in Group 1 (Placebo) was 48.05+8.28 years, Group 2 (GP – 100mg) was 46.9+8.92, Group 3 (GP – 200mg) was 50.77+7.30, Group 4 (GP – 300mg) was 47.55+9.49 years. The P value was 0.193 which signifies that the four groups were comparable with regards to age.

Gender distribution in four groups

Among 160 patients, 95 patients are females and 65 patients are males. There was no statistically significant difference in gender among the four study groups. ($p=0.92277$)

Weight distribution in four groups

For Male, the mean weight of patients in Group 1 (Placebo) was 70.20+9.28 kgs, Group 2 (GP – 100mg) was 70+8.57 kgs, Group 3 (GP – 200mg) was 71.61+9.08 Kgs, and Group 4 (GP – 300mg) was 66.75 + 3.57 Kgs. For Female, the mean weight of patients in Group 1 (Placebo) was 68.72+8.85 kgs, Group 2 (GP – 100mg) was 69.54+10.53 kgs, Group 3 (GP – 200mg) was 67.86+9.08 Kgs, Group 4 (GP – 300mg) was 67.25+4.58 Kgs The P value was > 0.05 which is not significant, showing that the groups are comparable with regards to weight.

Height distribution in four groups

For Male, the mean weight of patients in Group 1 (Placebo) was 159.60+5.90 Cms, Group 2 (GP – 100mg) was 158.88+3.84 Cms, Group 3 (GP – 200mg) was 156.39+3.84 Cms, and Group 4 (GP – 300mg) was 158.13 + 4.41 Cms. For Female, the mean weight of patients in Group 1 (Placebo) was 158.24+7.42 Cms, Group 2 GP – 100mg) was 155.25+4.46 Cms, Group 3 (GP – 200mg) was

158.32±5.45 Cms, Group 4 (GP – 300mg) was 158.29±4.64 Cms. The P value was > 0.05 which is not significant showing that the groups are comparable with regards to height.

ASAG distribution in the four groups

The four study groups were comparable with regard to ASA physical status grade distribution. (p=0.919) .The ASA score was nearly similar in all four groups where in Group 1(Placebo) 22 patients had an ASA I, 18 patients had an ASA II score. In Group 2 (GP-100mg) 24 patients had ASA I score, 16 patients had ASA II. In Group 3 (GP-200 mg) 21 had patients

ASA I score, 19 patients with ASA II score. In Group 4 (GP-300 mg) 23 patients with ASA I and 17 patients had ASA II scores. P Value=0.63 shows no statistical significance among all four groups.

Comparison of post-operative VAS scores in four groups

Visual analouge scale

Visual analouge scale (VAS) scores were recorded at 0 hr,2hr, 4th hr, 8th , 12th hr and at 24 hrs. ANOVA was applied for statistical analysis of VAS scores in the two groups over the various time intervals.

Table-1: VAS scores in four groups studied

	PLACEBO (Mean±SD)	GP 100mg (Mean±SD)	GP 200mg (Mean±SD)	GP 300mg (Mean±SD)	F value	P value
0 HR	0.0	0.0	0.0	0.0	-	-
2 HR	2.175±2.06	0	0	0	-	-
4HR	4.83±1.26	1.80±1.62	2.25±2.11	0.25±0.59	64.141	P<0.001
8HR	4.53±0.91	3.25±1.69	3.38±0.90	1.48±1.41	39.134	P<0.001
12HR	5.225±1.27	3.825±1.11	2.775±1.25	1.525±1.04	72.044	P<0.001
16 HR	4.93±0.86	3.43±0.84	3.25±0.93	1.85±1.39	59.769	P<0.001
S20HR	5.175±0.81	4.25±1.10	4.025±1.21	1.525±1.06	87.232	P<0.001
24HR	3.7±1.11	5.4±0.93	4.15±1.42	1.15±1.14	93.659	P<0.001

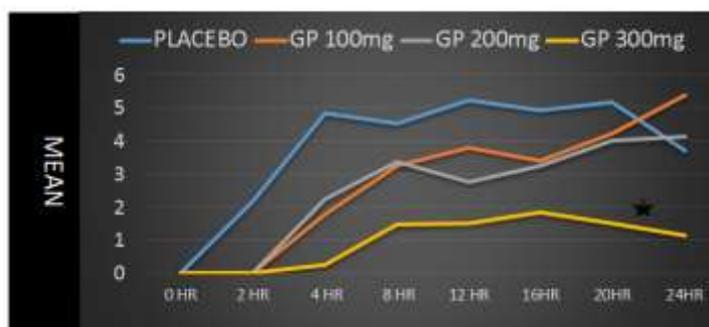


Fig-1: VAS score among all four groups

The mean static pain score on VAS in Group 1 (Placebo), Group 2 (GP-100mg), Group 3 (GP-200mg), and Group 4 (GP-300 mg) was 2.175±2.06, 0.00±0.00, 0.00±0.00 and 0.00 ± 0.00 respectively at 2nd hr of surgery (table 1). The difference in four groups was statistically significant (p value <0.001).The mean static pain score on VAS in Group 1 (Placebo), Group 2 (GP-100mg), Group 3 (GP-200mg), and Group 4 (GP-300 mg) was 4.83±1.26, 1.80±1.62, 2.25±2.11 and 0.25±0.59 respectively at 4th hr of post-operative period (table 6). The difference in four groups was statistically significant (p value <0.001).The mean static pain score on VAS in Group 1 (Placebo), Group 2 (GP-100mg), Group 3 (GP-200mg), and Group 4 (GP-300 mg) was 4.53±0.91, 3.25±1.69, 3.38±0.90 and 1.48±1.41 respectively at 8th hr of surgery (table 6). The difference in four groups was statistically significant (p value <0.001).The mean static pain score on VAS in Group 1 (Placebo), Group 2 (GP-100mg), Group 3 (GP-200mg), and Group 4 (GP-300 mg) was 5.225±1.27, 3.825±1.11, 2.775±1.25 and 1.525±1.04 respectively at 12th hr of surgery (table 6). The difference in four groups was statistically significant (p value <0.001).The mean static pain score on VAS in Group 1 (Placebo), Group 2 (GP-100mg), Group 3 (GP-200mg), and Group 4 (GP-300 mg) was 4.93±0.86, 3.43±0.84, 3.25±0.93 and 1.85±1.39 respectively at 16th hr of surgery (table 1, figure 1). The difference in four groups was statistically significant (p value <0.001).The mean static pain score on VAS in Group 1 (Placebo), Group 2 (GP-100mg), Group 3 (GP-200mg), Group 4 (GP-300mg) was 5.175±0.81, 4.25±1.10, 4.025±1.21 and 1.525±1.06 respectively at 20th hr of surgery (table 1, figure 1). The difference in four groups was statistically significant (p value <0.001).The mean static pain score on VAS in Group 1 (Placebo), Group 2 (GP-100mg), Group 3 (GP-200mg), and Group 4 (GP-300 mg) was 3.7±1.11, 5.4±0.93, 4.15±1.42 and 1.15±1.14 respectively at 24th hr of surgery (table 6, figure 9). The

5.225±1.27, 3.825±1.11, 2.775±1.25 and 1.525±1.04 respectively at 12th hr of surgery (table 6). The difference in four groups was statistically significant (p value <0.001).The mean static pain score on VAS in Group 1 (Placebo), Group 2 (GP-100mg), Group 3 (GP-200mg), and Group 4 (GP-300 mg) was 4.93±0.86, 3.43±0.84, 3.25±0.93 and 1.85±1.39 respectively at 16th hr of surgery (table 1, figure 1). The difference in four groups was statistically significant (p value <0.001).The mean static pain score on VAS in Group 1 (Placebo), Group 2 (GP-100mg), Group 3 (GP-200mg), Group 4 (GP-300mg) was 5.175±0.81, 4.25±1.10, 4.025±1.21 and 1.525±1.06 respectively at 20th hr of surgery (table 1, figure 1). The difference in four groups was statistically significant (p value <0.001).The mean static pain score on VAS in Group 1 (Placebo), Group 2 (GP-100mg), Group 3 (GP-200mg), and Group 4 (GP-300 mg) was 3.7±1.11, 5.4±0.93, 4.15±1.42 and 1.15±1.14 respectively at 24th hr of surgery (table 6, figure 9). The

difference in four groups was statistically significant (p value <0.001).

The overall pain scores are significantly lower in Group 4(GP-300mg) compared to other three groups.

Total dose of tramadol in the four groups

Table-2: Total dose of tramadol (mg) given in the four groups studied

	N	Mean	Std.Deviation	F value	P value
PLACEBO	40	283.75	58.164	189.625	<0.05 (SIGNIFICANT)
GABAPENTIN 100mg	40	110.00	32.423		
GABAPENTIN 200mg	40	95.00	50.383		
GABAPENTIN 300mg	40	73.75	29.930		

The postoperative 24hr tramadol consumption in Group1 (Placebo) was 283.75± 58.164 and Group2 (gp-200MG) was 110.00±32.42, Group3 (GP300mg) was 95.00±50.38, Group4 (GP-300mg) was 73.75±29.93 mg (Table 2). There was statistically significant differences between four groups (p<0.005). In our present study GP-300mg group required significantly lower rescue doses of tramadol compared to other three groups.

Time of first tramadol in the four groups

The time of first request of tramadol in Group1 (Placebo) was 2.75±1.104 min, Group2 (GP-100mg) was 5.05±1.28, Group3 (200mg) was 5.2±1.09, Group4 (300mg) was 10.3±3.12 min. There was statistically significant difference among the four groups (p value< 0.05) the requirement of first dose of tramadol is longer in Group4 (GP-300mg) patients compared to other groups. In Placebo group, 18 patients needed first dose of tramadol from 0 to 4th hour of post-operative period.

Comparison of PONV in four study groups

Table-3: Comparison of PONV in four study groups studied

GROUPNAME	Nausea n Vomiting	Frequency	Percent
GABAPENTIN 100mg	0	1	2.5
	1	15	37.5
	2	15	37.5
	3	9	22.5
GABAPENTIN 200mg	0	19	47.5
	1	18	45.0
	2	2	5.0
	3	1	2.5
GABAPENTIN 300mg	0	15	37.5
	1	19	47.5
	2	4	10.0
	3	2	5.0
PLACEBO	0	4	10.0
	1	4	10.0
	3	9	22.5
	4	10	25.0
	5	6	15.0
	6	7	17.5

Anova for Nausea and vomiting is significant. Nausea vomiting scale in placebo group is significantly higher compared to Group 3(GP-200mg) & Group4 (GP-300mg). Around 10 patients have nausea

&vomiting greater than 4. Mean value Group1 (Placebo) is 3.575±1.86 and in Group4 (GP-300mg) the mean value of nausea vomiting is 0.825±0.81.

Comparison of post-operative sedation in four groups
SEDATION SCALE

Table-4: Comparison of sedation score in four groups studied

	GABAPENTIN 100mg (Mean±SD)	GABAPENTIN 200mg (Mean±SD)	GABAPENTIN 300mg (Mean±SD)	PLACEBO (Mean±SD)	FValue	P value
0HR	2.08±0.417	2.37±0.49	2.58±0.594	2.25±0.543	6.677	P<0.001
2 HR	2.18±0.446	2.57±0.594	3.05±0.597	2.05±0.597	25.737	P<0.001
4 HR	1.85±0.533	2.85±0.736	3.17±0.446	2.18±0.385	50.267	P<0.001
8 HR	2.1±0.379	2±0.599	2.6±0.744	1.97±0.48	10.642	P<0.001
12HR	2.15±0.362	2.18±0.549	2.73±0.716	1.82±0.501	18.646	P<0.001
16HR	2.23±0.423	2.05±0.221	2.25±0.439	2.25±0.439	2.437	P>0.05
20HR	2.2±0.464	2.05±0.221	2.05±0.221	2.3±0.464	4.544	P<0.05
24HR	2.18±0.385	2	2	2.03±0.357	4.112	P<0.05

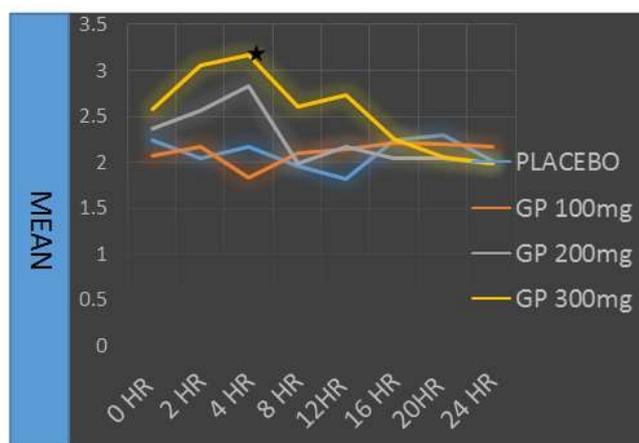


Fig-2: sedation given in the four groups studied

In our present study the mean sedation scores at 2nd hr for Group1 (Placebo) was 2.05±0.597, Group2 (GP-100mg) was 2.18±0.446, Group3 (GP-200mg) was 2.57±0.594, Group4 (GP300mg) was 3.05±0.597 (P<0.001). At 4th hr the mean sedation scores were 2.18±0.385, 1.85±0.533, 2.85±0.736, 3.17±0.446 for Group1(Placebo), Group2(GP-100mg), Group3(GP-200mg), Group4(GP300mg) respectively (P<0.001). At 8th hr the mean sedation scores were 1.97±0.48, 2.1±0.379, 2±0.599, 2.6±0.744 for Group1(Placebo), Group2(GP-100mg), Group3(GP-

200mg), Group4(GP300mg) respectively (P<0.001). At 12th hr the mean sedation scores were 1.82±0.501, 2.15±0.362, 2.18±0.549, 2.73±0.716 for Group1(Placebo), Group2(GP-100mg), Group3(GP-200mg), Group4(GP300mg) respectively (P<0.001). Group 4(GP300mg) patients have significantly higher sedation compared to other three groups. At 24th hr all groups have almost similar sedation scores.

PT Satisfaction scale in the four groups

Table-5: PT Satisfaction scale in the four groups studied

GROUPNAME	Frequency	Percent
GABAPENTIN 100mg	2	6
	3	25
	4	9
GABAPENTIN 200mg	1	4
	2	24
	3	12
GABAPENTIN 300mg	1	25
	2	14
	3	1
PLACEBO	2	16
	3	12
	4	12

Group 4(GP-300MG) were more satisfied with pain relief compared to other three groups and this was found to be statistically significant. Group 4 (GP-300mg) 1.40 ± 0.54 vs Group 1 (Placebo) 2.90 ± 0.84 , Group 2 (GP-100mg) 3.07 ± 0.60 , Group 3 (GP-200mg) 2.20 ± 0.60 ($p < 0.05$)

DISCUSSION

In our study we attempted to determine whether reducing the dose of gabapentin below 300mg reduces the side effect profile while maintaining the analgesic efficacy. Our results suggest that decreasing the dose of gabapentin below 300 mg decreased the incidence of sedation but caused no further decrease in VAS scores or in tramadol consumption.

VAS Scores

In our study, we observed that patients who received gabapentin 300mg (GP-300) had significantly lower VAS scores in the first 24 hrs post operatively and thus better quality of analgesia compared to gabapentin 100mg (GP-100), gabapentin 200mg (GP-200), and placebo groups suggesting that the preoperative administration of gabapentin 300mg has a more prolonged analgesic effect. Anti hyperalgesic drugs such as gabapentin may have a role in post-operative pain, and the combination with other rant nociceptive drugs may produce synergistic analgesia effects [21, 22]. Significantly low VAS scores in the immediate postoperative period in the gabapentin group may suggest the synergistic effect of gabapentin with intraoperative fentanyl. A decreased rescue analgesic requirement in the gabapentin group also suggests the synergistic effect of gabapentin with Tramadol.

Our results were similar to the results from systemic reviews and meta-analysis done by Seib MA *et al.* [23, 24] where they found better quality of post-operative analgesia and low VAS scores with preoperative use of oral gabapentin.

Total dose of opioid consumption

In our study we observed that gabapentin decreased the total opioid consumption in the first 24 hours postoperatively compared to placebo suggesting an opioid sparing effect of gabapentin. The mean tramadol requirement was significantly lower in gabapentin 300 mg group compared to other groups [placebo (283.75mg) vs GP-100 (110 mg) vs GP-200(95mg) vs GP- 300(73.75 mg) with $p < 0.05$]. This suggests that oral preoperative gabapentin in a dose of 300 mg is more effective than 100mg and 200 mg respectively in reducing opioid requirements. A reduction in tramadol requirement may have contributed the lower incidence of side effects such as nausea and vomiting observed in our study.

Our results were similar to the results of previous studies [19, 25] who also found a decreased

need for rescue analgesics in patients undergoing laparoscopic cholecystectomy in the post-operative period when gabapentin 600mg was given in the preoperative period.

First dose of rescue analgesic

In our study the time to first request for rescue analgesic was significantly later in the postoperative period in 300mg gabapentin group compared with other groups. This could suggest that gabapentin in a dose of 300 mg has a better synergistic analgesic effect with intraoperative fentanyl compared with lower doses of gabapentin. Although it can be debated that the higher incidence of sedation in the gabapentin 300mg group may have attributed to the later request for rescue analgesia.

Sedation scores

Gabapentin has been studied extensively in surgical populations that were given general anesthesia as the primary anesthetic modality. One of the major concerns for health care providers is the incidence of sedation that has been reported in several studies [16, 19, 20]. In our study we found that the mean sedation scores were higher in the gabapentin groups compared with the placebo group. However, patients in the gabapentin 300mg group had significantly higher mean sedation scores throughout the observation period compared to GP-100, GP-200 and placebo groups. When comparing the mean sedations.

*cores amongst the four groups, the difference was very highly significant ($p < 0.001$) during the first 12 postoperative hours. Though patients in the gabapentin group showed sedation, none of the patients had episodes of desaturation ($SpO_2 < 95\%$) and did not require any further intervention. Our findings correlate with previous randomised controlled trials and meta-analysis [19, 20, 24].

Post-operative nausea and vomiting

T-he aetiology of PONV following laparoscopic cholecystectomy remains unclear, but is probably associated with operative factors. These include the effect of intra-peritoneal CO_2 insufflation on residual stretching and irritation of the peritoneum [26]. Factors like use of opioids for pain management and elective surgical procedures also influence the incidence of PONV. Gabapentin has been reported to be effective in the treatment of emesis in patients receiving cytotoxic drugs [27]. The precise mechanism of gabapentin in the prevention of nausea and vomiting induced by cytotoxic drugs is not known but mitigation of tachykinin neurotransmitter activity has been postulated to be useful [27]. The etiology of PONV in patients undergoing laparoscopic cholecystectomy is not identical to that in patients receiving cytotoxic drugs but we assume that it may be one probable mechanism for prevention of PONV by gabapentin. In our study patients who received gabapentin 300mg preoperatively

had a lower incidence of PONV compared to lower doses of gabapentin or a placebo. This may be attributed to better quality of analgesia and therefore a lower requirement of tramadol or a direct effect on tachykinin activity. Our results correlate with previous studies [25, 26, 28].

Patient satisfaction scale

The patient satisfaction rates were better in the 300mg gabapentin group compared to Gabapentin 100mg, Gabapentin 200mg and placebo group. The higher mean patient satisfaction rates could be attributed to the combined effects of lower postoperative pain scores, lower requirement of opioids, decreased PONV and decreased agitation.

Limitations of the study

- The study was conducted in laparoscopic surgery only. The extent of pain and analgesic effects are procedure specific and are influenced by many factors including but not limited to the site of surgery, duration of surgery, the extent of surgery, and open versus laparoscopic surgery. Therefore the results cannot be extrapolated to other surgeries.
- In our study all the surgeries were performed by a single surgeon with a vast experience with laparoscopic cholecystectomy. So, factors such as the time taken to operate and tissue handling by surgeons, which could potentially play a role in the degree of pain experienced, have not been addressed in our study.
- Pain was assessed only at rest. The assessment of the intensity of acute pain at rest after surgery is important for making the patient comfortable in bed. However, adequate relief of dynamic pain during mobilization, deep breathing, and coughing is more important for reducing risks of cardiopulmonary and thromboembolic complications after surgery. Therefore, the results of the study may not have revealed the real difference in pain between the groups studied.

CONCLUSIONS

- Gabapentin in a dose of 300mg orally given preoperatively not only reduces the severity of postoperative pain and the 24 hour tramadol requirement but also delays the time to first request for rescue analgesic and reduces the incidence of PONV after laparoscopic cholecystectomy compared to placebo, gabapentin 100mg and gabapentin 200mg.
- Reducing the dose of gabapentin below 300mg does not confer analgesic benefits.
- Further studies are required to determine the efficacy of gabapentin in different surgical populations

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