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Original Research Article

PREMEDICATION WITH TWO DIFFERENT DOSES OF PREGABALIN FOR POSTOPERATIVE ANALGESIA AFTER LAPAROSCOPIC CHOLECYSTECTOMY

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ABSTRACT

Background & Methods: the aim of the study is to compare premedication with two different doses of pregabalin for postoperative analgesia after laparoscopic cholecystectomy. After approval written informed consent was taken from patients for participation in study.90 patients of both sexes aged 18 – 60 years ASA Grade 1 & 2 scheduled for elective laparoscopic cholecystectomy under general anesthesia were randomly divided into three groups of 30 each (n=30).

Results: In our study, there was a significant reduction in VAS in group A and B in comparison to group C at different time points & the total number of rescue analgesia given was significantly ($p<0.001$) higher in placebo group (group C) than pregabalin group (B) and least among three in group A The patients in group A were significantly remained drowsy as compared to group B and group C ($P <0.001$)

Conclusion: The single preoperative dose administration of pregabalin (150 or 300 mg) had a significant opioid sparing effect in first 2-4h after surgery. A single oral dose of pregabalin 150mg in patients undergoing laparoscopic cholecystectomy was effective in reducing postoperative pain, tramadol consumption as well as nausea & vomiting without any untoward side effects.

Keyword: laparoscopic cholecystectomy, pregabalin, VAS, tramadol

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INTRODUCTION

Laparoscopic cholecystectomy is a gold standard treatment for symptomatic gall stones as it provides edges over open cholecystectomy in terms of less pain shorter recovery time and shorter stay[1]. Pain in laparoscopic cholecystectomy is mainly visceral pain due to stretching of the intra-abdominal cavity, peritoneal inflammation followed by shoulder tip due to phrenic nerve irritation caused by residual carbon dioxide in peritoneal cavity. Postoperatively common location of the pain is right upper quadrant and port sites. Pain management is an integral component of caring for the postoperative patient.

Pre-emptive analgesia is analgesic administration that precedes the painful stimulus, thus improving postoperative pain control[2]. It is an anti-nociceptive treatment that prevents the establishment of altered processing of afferent input, which amplifies postoperative pain. This technique is utilised in acute postsurgical pain management to improve the efficacy of analgesics and thereby reduce the requirement for opioids[3]. Various drugs have been used pre-emptively to relieve postoperative pain and these include ketamine, ketorolac, diclofenac sodium, morphine, dexamethasone, gabapentin and so on but consistent delivery of peri/postoperative analgesia is still a major challenge. Hence there is a need for an ideal analgesic drug which provides good pain relief in the postoperative period with minimal or no side effects[4].

Pregabalin an amino acid derivative of gamma aminobutyric acid (GABA analog) is six times more potent successor to gabapentin. It has been used as a pre-emptive and postoperative analgesic in laparoscopic surgeries with variable results. Low dose pregabalin has shown only limited analgesia benefits. High dose pregabalin though provides good analgesia but is associated with an increased incidence of side effects. Pregabalin is the structural derivatives of the inhibitory neurotransmitter γ-aminobutyric acid. Their main site of action is α2-δ ligand that has analgesic, anticonvulsant, anxiolytic and sleep-modulating activities[5]. Pregabalin binds potently to the α2-δ subunit of calcium channels, resulting in a reduction in the release of several neurotransmitters including glutamate, noradrenaline, serotonin, dopamine, and substance P.

Pregabalin is several times more potent than gabapentin. It is rapidly absorbed orally and achieves peak plasma levels within one hour. The elimination half-life of pregabalin ranges from 6.5 to 8 hours and is independent of dose and repeated dose administration. Pregabalin has side effects with the most common events being drowsiness and dizziness[6-8].

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AIMS & OBJECTIVES

AIM:

To assess and compare the premedication with pregabalin 150mg versus 300mg for postoperative analgesia after laparoscopic cholecystectomy.

OBJECTIVES:

To determine the difference in mean total number of rescue analgesia in first 24 hour, postoperatively in all three groups.

To determine the difference in mean VAS score at different intervals post operatively in 3 groups.

To determine hemodynamics at different time interval postoperatively 24 hours.

To determine the proportion of cases with complications.

MATERIAL & METHODS:

STUDY DESIGN:

Hospital based Randomized double-blind comparative study.

SAMPLE SIZE:

Sample size was calculated and 30 cases in each group were adequate for each of the 3 groups at 95% confidence and 80%power. So, for the study purpose 30 cases were taken in each group.

ELIGIBILITY CRITERIA:

Inclusion criteria	Exclusion criteria
Patients of either sex.	**History of allergy to opioids or pregabalin**
Age group of 18 to 60 years.	**Patient already taking gabapentinoids.**
ASA grade I & II	**History of drug abuse**

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Weight (40Kg-75kg)	**Morbidly obese patients i.e., BMI >35kg/m^2**
Undergoing laparoscopic cholecystectomy under general anesthesia.	**Patients having renal or hepatic insufficiency, neurologic and psychiatric disease or communication difficulties.**
Patients willing to participate in the study.	**If laparoscopic cholecystectomy converted to open cholecystectomy.**

The study was conducted in the following three groups of patients:

- **Group A: Patients received 300mg of pregabalin orally 1hour before surgery with sip of water. (n=30)**
- **Group B: Patients received 150mg of pregabalin orally 1hour before surgery with sip of water. n=30**
- **Group C: Patients received similar looking capsule orally 1hour before surgery with sip of water. n=30**

RANDOMIZATION:

In this study randomization done by opaque sealed envelope technique.

BLINDING:

This trial was so planned that neither the doctor nor the patient were aware of the groups and the drug used. The Anesthesiologist who would give anesthesia would be different from the Anesthesiologist who would record study variables.

PROCEDURE

After obtained Institutional Ethics Committee approval and written informed consent, 90 patients undergone laparoscopic cholecystectomy under General Anesthesia and which follow inclusion criteria were included in this study. Upon arrival in operation theatre, the written informed consent, PAC, and nil per oral status confirmed. Tablet alprazolam 0.5 mg was given for all patients orally one night before surgery. Study population (90) were randomly divided into three groups by opaque sealed envelope technique. Group A (n=30) received pregabalin 300mg and Group B (n=30) received pregabalin 150mg and Group C (n=30) received placebo

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orally with a sip of water one hour before surgery. After arrival in the operating room, an 18G/20G peripheral intravenous catheter was inserted into patient forearm and IV fluid Ringer lactate was started. Routine monitors attached and baseline vital parameters were recorded. Standard monitoring was used throughout the procedure including heart rate, non-invasive blood pressure (NIBP), electrocardiograph (ECG), and pulse oximetry (SPO2).Pre-medication was given with intravenous glycopyrrolate 0.02mg, ondansetron 0.1mg/kg, midazolam 0.01 mg/kg, fentanyl 2 μg/kg. All patients were pre-oxygenated with 100% oxygen for 3 minutes and anesthesia induced with intravenous propofol 2 mg/kg in slow incremental dose and adequacy of mask ventilation noted.After confirming adequate mask ventilation, succinylcholine 2mg/kg was administered for neuromuscular blockade. Under direct laryngoscopy oral endotracheal intubation with appropriate tube size was done, bilateral equal air entry was checked and then cuff was inflated. After then, the tube was connected to the breathing circuit and fixed with adhesive tape. Effective ventilation was confirmed by bilateral thoracic movements and square capnography waveform. For maintenance of anesthesia loading dose of Inj. Atracurium 0.5 mg/kg as bolus with mixture of O_2 + Isoflurane 0.4-0.6% and then Inj. Atracurium 0.1 mg/kg as supplemental dose was given. Ventilation was adjusted to maintain EtCO2 between 35-40 mmHg pneumoperitoneum created with CO2 with 12-14mmHg pressure, intraoperative vital parameters (HR, SBP, DBP, MAP, and SPO_2) were recorded at different intervals.

At the end of surgery, all anesthetic agent discontinued and patient taken on 100% O2. At the completion of surgery residual neuromuscular blockade was reversed with inj. neostigmine 0.05mg/kg + inj. glycopyrrolate 0.005mg/kg. Tracheal extubation was performed after proper suctioning of oropharynx. After extubation vitals parameters (HR, SBP, DBP, MAP & SPO2) were recorded and then transferred to the post-operative unit.

In Postoperative period (24 hours):

Following parameters were recorded

- **HR, BP in 1hour, 2hour, 4hour ,8hour, 12hour and 24hours.**
- **VAS score**

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- **Total number of rescue analgesia (tramadol) in postoperatively 24 hours.**
- **Any side effects.**

RESULTS AND OBSERVATIONS

Table 1: DEMOGRAPHIC VARIABLES

DEMOGRAPHIC VARIABLES	GROUP A	GROUP B	GROUP C	P VALUE
AGE	44.2 ± 14.45	40.67 ± 11.81	42.07 ± 12.17	0.229(NS)
WEIGHT(In kgs)	62.37 ± 7.27	60.77 ± 4.88	61.23 ± 4.99	0.551(NS)
GENDER				P = 0.679(NS)
MALE	10	8	7	
FEMALE	20	22	23	
ASA				P = 0.830(NS)
GRADE 1	22	23	24	
GRADE 2	8	7	6	
DURATION OF SURGERY	47.33 ± 8.83	50.33 ± 10.7	48.13 ± 9.58	0.409(NS)

Table 2: Comparison of post op mean VAS Score among study groups

Time	Group A	Group B	Group C	P value
1 hr	1.27 ± 1.2	2.3 ± 1.12	2.77 ± 1.22	<0.001 (S)
2 hrs	1.57 ± 1.28	2.57 ± 1.48	3 ± 1.44	0.041 (S)
4 hrs	2.03 ± 1.61	2.87 ± 1.2	2.83 ± 1.46	0.043 (S)
8 hrs	2.87 ± 1.36	1.5 ± 1.17	1.67 ± 0.84	0.001 (S)
12 hrs	1.57 ± 0.86	2.03 ± 0.85	2 ± 1.44	0.184 (NS)
24 hrs	0.5 ± 0.57	1.03 ± 0.76	1.23 ± 0.76	0.005 (S)

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Table depicts the mean visual analog scale score for pain postoperatively within 24 hours. VAS score was significantly higher in Group C than group B and lesser in group A at 2hr, 4hr, 24hr and highly significant at 1hr. But at 8 hours the VAS score was high in group A than group B with P <0.001(highly significant) however there was no as such significant difference observed further and at 12hr the difference in mean score among all three groups were statistically nonsignificant.

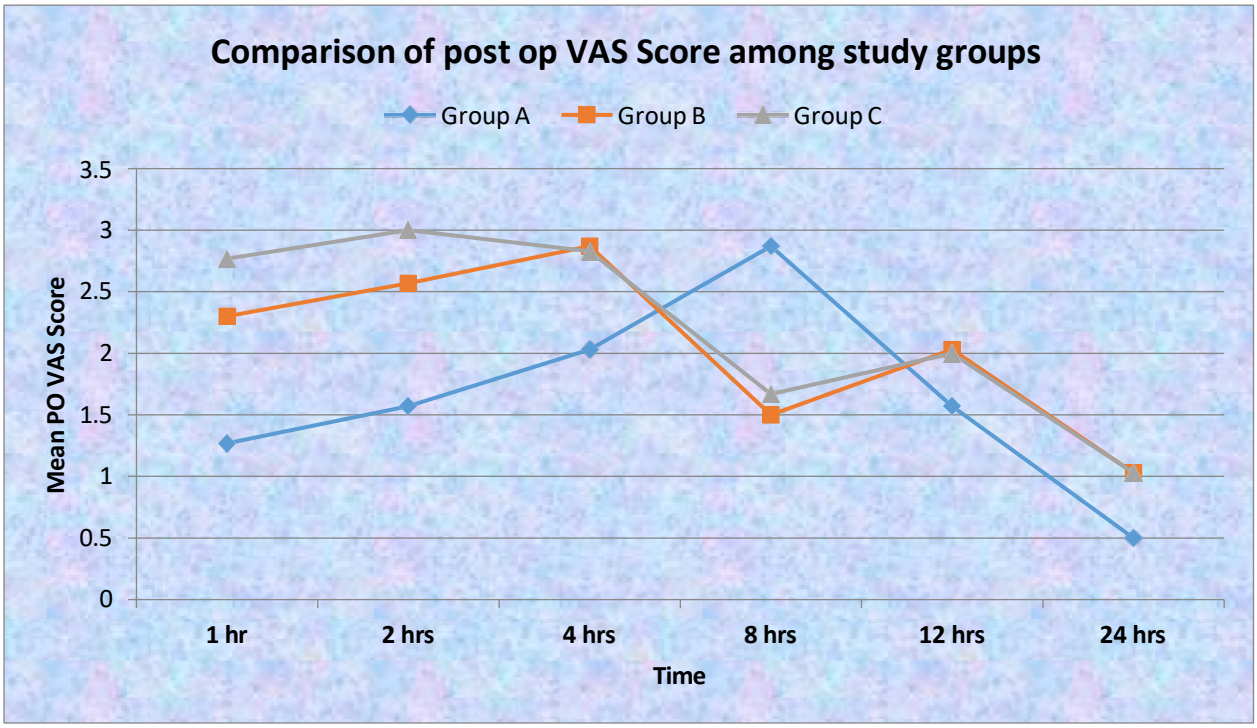

Table 3: Comparison of total number of rescue analgesia (tramadol) in postoperative 24 hours among study groups

total dose	Group A		Group B		Group C	
	N	%	N	%	N	%
1 dose	9	30.0	6	20.0	2	6.7
2 doses	17	56.7	14	46.7	12	40.0
3 doses	4	13.3	10	33.3	16	53.3
Total	30	100	30	100	30	100
Chi-square = 12.437 with 4 degrees of freedom; P = 0.014 (S)						

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Table reveals the number of rescue analgesics required in first 24 hours post operatively. In group A, 13.3% of patients required 3 doses of rescue analgesia, 56.7% patient's required 2 doses of rescue analgesia and the rest 30% required one dose of rescue analgesia within 24 hours postoperatively

In group B, 33.3% of patients required 3 doses of rescue analgesia, 46.7% patient's required 2 doses of rescue analgesia and the rest 20% required one dose of rescue analgesia within 24 hours postoperatively

Whereas in Group C, 53.3% of patients required 3 doses of rescue analgesia, 40% required 2 doses of rescue analgesia and rest the remaining 6.7 % required 1 dose in 24 hours postoperative duration. Thus, groups A & B patients had significant longer duration of postoperative analgesia and the requirement of additional analgesics was significantly reduced ($p < 0.05$: significant).

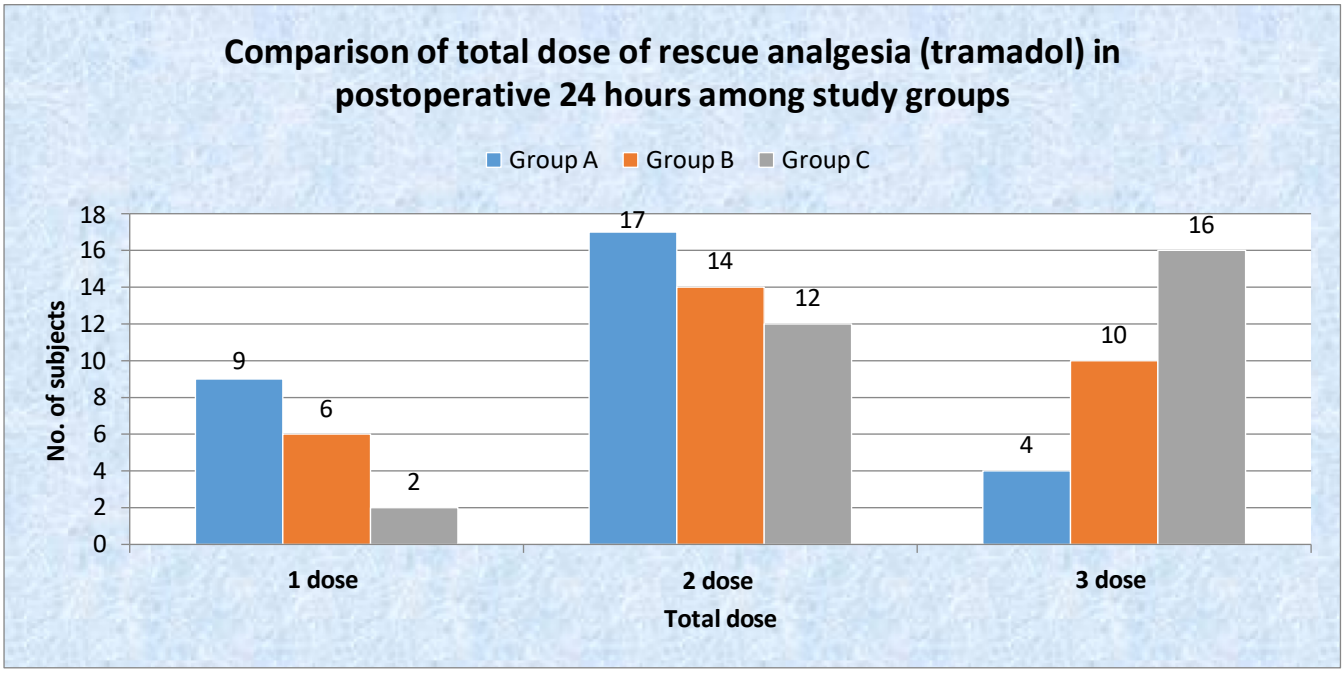

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Table 4: Comparison of post op Heart rate (beats/min) among study groups

Time	Group A	Group B	Group C	P value
After extubation (0 hr)	85.4 ± 12.72	87.9 ± 9.81	89.03 ± 8.25	0.390
1 hr	79.73 ± 13.71	83.23 ± 8.63	88.2 ± 9.49	0.012(S)
2 hrs	82.47 ± 15.9	86.23 ± 7.99	88.47 ± 8.95	0.202
4 hrs	88.8 ± 14.21	90.13 ± 9.44	96.5 ± 9.83	0.023 (S)
8 hrs	83.33 ± 11.72	84.97 ± 10.13	85.53 ± 4.36	0.637
12 hrs	82.53 ± 11.66	80.17 ± 7.56	85.97 ± 8.72	0.064
24 hrs	76.23 ± 11.52	78.13 ± 6.94	80.47 ± 9.4	0.227

S = Significant; NS = Non Significant

Table shows postoperative mean heart rate with standard deviation at various intervals upto 24hours and was found that there was significant decrease in the mean heart rate in the group A and B compared to group C 1h and 4h postoperatively as shown the table(P <0.001). There was no significant difference in the mean heart rate between the three groups 8h postoperatively.

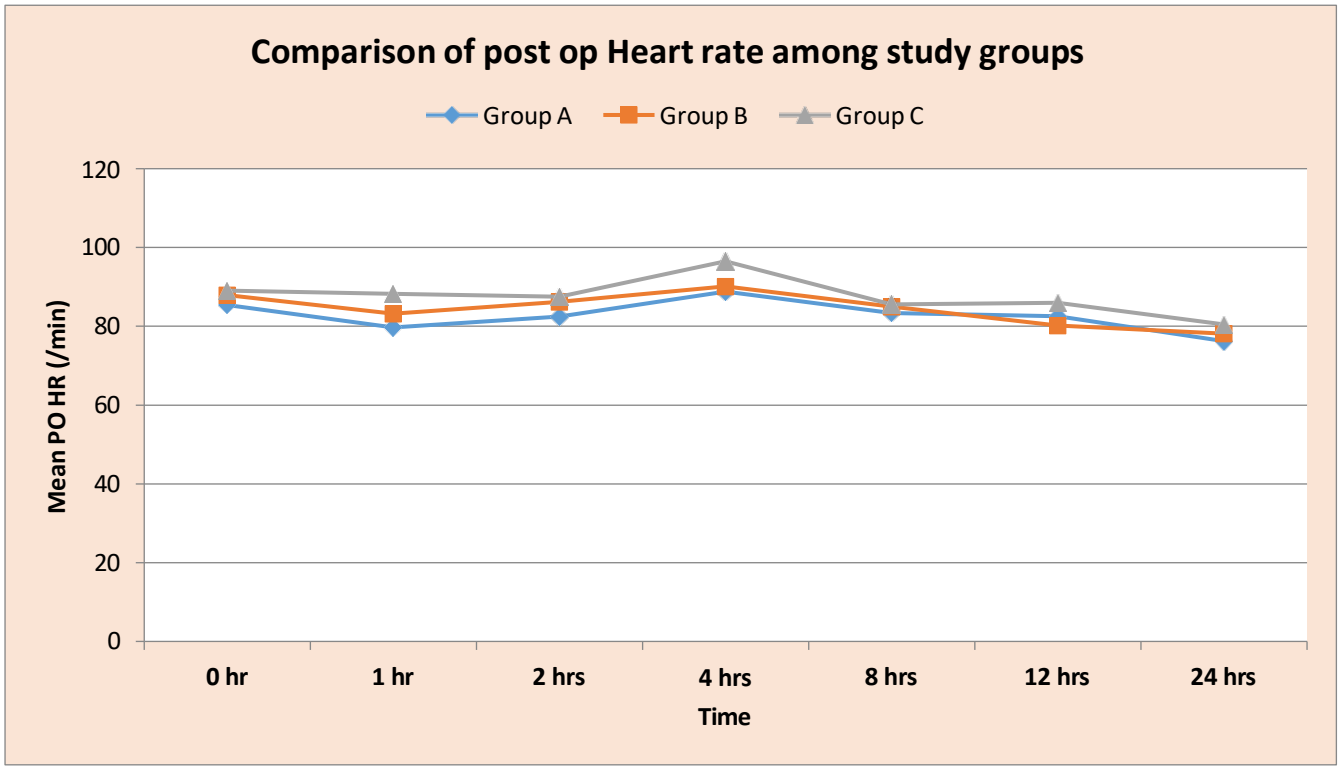

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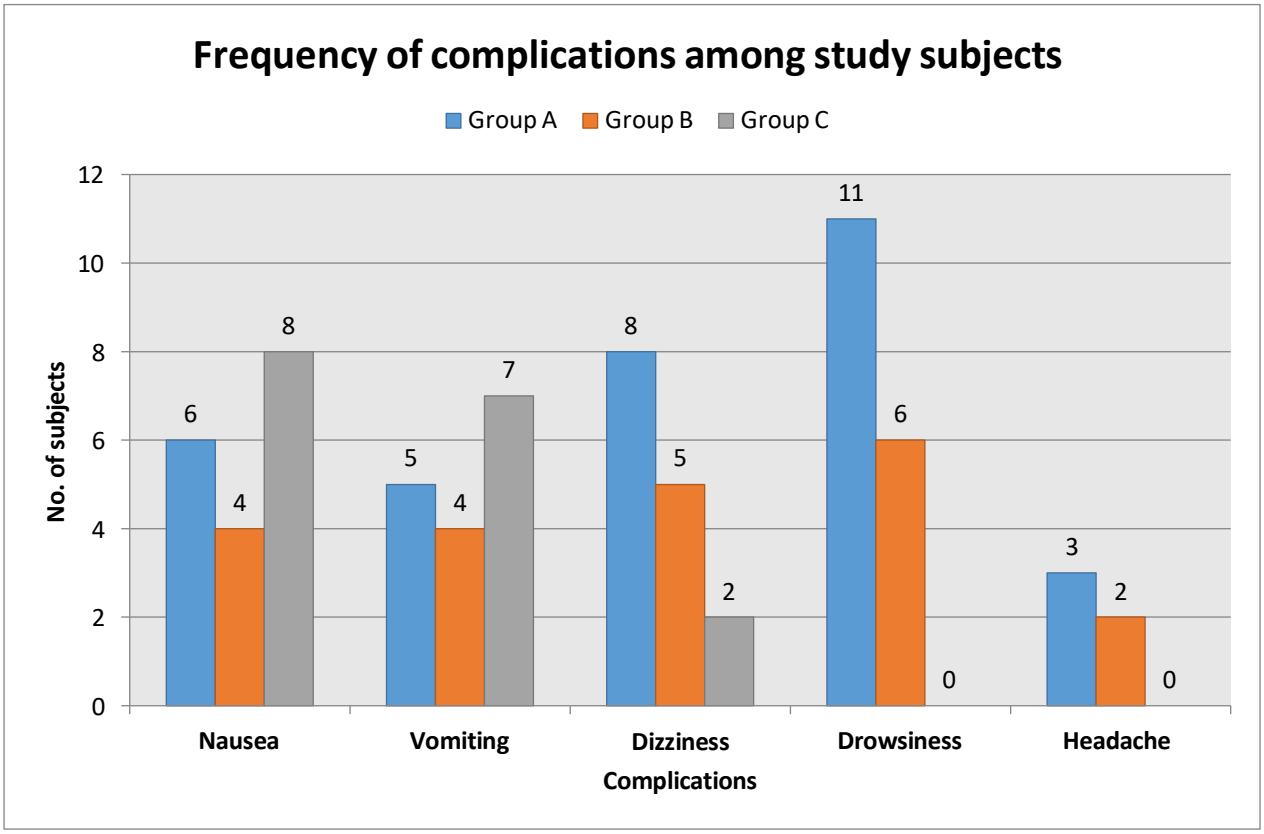
Table 5: Frequency of complications among study subjects

Complications	Group A		Group B		Group C		P value
	N	%	N	%	N	%	
Nausea	6	20	4	13.3	8	26.6	0.435
Vomiting	5	16.6	4	13.3	7	23.3	0.587
Dizziness	8	26.7	5	16.7	2	6.7	0.115
Drowsiness	11	36.7	6	20	0	0	0.001 (S)
Headache	3	10	2	6.7	0	0	0.227

Table shows the distribution of postoperative complications between the study groups. The patients in group A were significantly remained drowsy as compared to group B and group C (P <0.001). There was no statistically significant difference between the three groups with regards to postoperative complications i.e. nausea, vomiting, dizziness and headache.



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DISCUSSION

Pain after laparoscopic cholecystectomy is definitely significantly decreased compared with the open cholecystectomy, but pain control after laparoscopic cholecystectomy still remains a clinical challenge. The ideal method for pain relief should be simple to perform, inexpensive and causes minimal morbidity[9].

Pregabalin has some proven role in the control of anxiety and postoperative pain either singly or in combination with other antinociceptive drug for synergistic effects; various clinical studies with the drugs for postoperative analgesia and analgesic consumption have shown promising results as per Jokela R et al[10].

Hill et al were the first to report on the use of pregabalin for treating pain after surgery whereas Gajraj NM postulated pregabalin used in pain management having analgesic and anxiolytic properties but there is no consensus on the optimum dose of pregabalin. Analgesic efficacy with dose ranges from 50 to 300 mg of pregabalin has been established. Evidence suggests that doses below 150mg are sedative and anxiolytic but not good analgesic. Higher doses (>300mg) have however been associated with side effects such as drowsiness, dizziness. Hence the present study was undertaken to compare the two doses of pregabalin along with the control (placebo) group.

In this study patients belonging to American Society of Anesthesiologists (ASA) physical status I or II aged between 18 and 60 years scheduled for laparoscopic cholecystectomy after obtaining written informed consent divided into group A, group B and group C and received oral tablet pregabalin 300mg , 150mg and placebo 1 hour before surgery respectively.
All 3 groups were comparable in terms of demographic data like Age, Sex, ASA status, weight. The duration of surgery was comparable and statistically nonsignificant among all the 3 groups. Various parameters were observed in post-operative period upto 24 hours, postoperative pain assessment by visual analog scale, haemodynamic vitals, side effects (if any) and total number of rescue analgesic (tramadol) requirement.

Postoperative pain was assessed by visual analog score (VAS) similar to Gupta P et al. Patients were provided rescue analgesia (i.e tramadol) when VAS ≥3 and time for first postoperative rescue analgesia was recorded similar to Gupta P et al.

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There was a significant reduction in VAS in group A and B in comparison to group C at different time points. The VAS scores statistically significant at 1, 2 and 4hr ($p<0.001$) and thereafter at 24hours ($p<0.05$) which were lower in pregabalin groups (A & B) compared with placebo (group C) similar to Agarwal A et al[11].

At 8 hours postoperatively, the mean VAS score in group A was more than group C and least in group B explains that elimination of the drug pregabalin of dose 300mg as per pharmacokinetics of pregabalin by Bockbrader et al and thus requiring the rescue analgesia. Whereas at 12 hours the difference in VAS scores in all the three groups were found non-significant.

In our study, the total number of rescue analgesia given was significantly ($p<0.001$) higher in placebo group (group C) than pregabalin group (B) and least among three in group A similar to study by Gupta P et al and Anand LK et al. 53.3% of group C required 3 doses, whereas 56.7% of group A and 46.7% of group B patients got relieved from pain by 2 doses of analgesia in 24 hours postoperatively. Hence 24hours after surgery, tramadol consumption was significantly less in pregabalin groups (A & B) than the placebo group(C). These findings are supported by studies of Agarwal et al that pregabalin reduces the opioid consumption after laparoscopic cholecystectomy.

Tissue damage due to surgery and peripheral sensitization with several chemical mediators produced, will trigger a neuroendocrine response sympathoadrenal activation with consequent including heart rate and blood pressure (systolic) and mean arterial pressure increases. In this study it was found that heart rate was higher in the control group compared with the two groups given preemptive pregabalin postoperatively. In statistical tests are significant differences between the three groups in the 1 hour postoperative similar to the study done by Esmat IM et al and Lalenoh et al.

At 4 hours interval in our study we observed that the mean heart rate in group A was lower than group B and highest in Group C statistically significant (P value <0.05), the results were similar to study conducted by Esmat IM et al and Peng W et al. Lower heart rates recorded explained the antinociception and analgesic properties of pregabalin as it reduces the hyper excitability of neurons and the glutamate and substance P levels as per Lalenoh et al.

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In our study patients were observed for complications like drowsiness, dizziness, nausea and vomiting. There was more incidence of drowsiness in group A than group B than control group C and this finding of ours was in consonance with the studies done by Saraswat V et al. Patients were less apprehensive and well sedated in group A than in B as compared to placebo (group C) similar to Gupta P et al.

3 patients in group A and 2 patients in group B also complained of headache.
Similarly the incidence of dizziness was also found out to be higher in pregabalin groups 8 patients in group A, 5 patients in group B and 2 patient in placebo complained of dizziness similar to study by Kohli M et al, Gajraj NM et al reviewed the pharmacology of pregabalin and found that it is associated with common side effects like headache and dizziness. The side effects of pregabalin are dose dependent, mild to moderate and are usually transient. Hence the side effects were lesser in group B than in group A as observed by Agarwal et al and Balaban F et al who evaluated that higher and multiple doses of pregabalin are associated with increased sedation, headache, dizziness or visual disturbances[12]. Hill et al, Chang et al had evaluated postoperatively the undesirable side effects of preoperative 300mg eg. excessive sedation, blurring of vision, drowsiness, dizziness.
PONV (postoperative nausea and vomiting) is a usual complication of surgery and anesthesia. Although it is rarely fatal, it is unpleasant associated with patient discomfort and dissatisfaction with perioperative management. The nausea and vomiting were less in pregabalin groups (A&B) as compared with the placebo, same reported by White PF et al and Anand LK et al[13]. This may be explained on the association of greater VAS score in the placebo group C with increased demand of rescue opioid analgesics. There was no significant arrhythmias noted on ECG in all the three groups.

CONCLUSION

The single preoperative dose administration of pregabalin (150 or 300 mg) had a significant opioid sparing effect in first 2-4h after surgery. The postoperative undesirable side effects of preoperative oral pregabalin 300mg e.g. excessive sedation, drowsiness headache and postoperative nausea vomiting were significantly common. The use of preoperative oral pregabalin 150mg was an effective and a safe adjuvant for acute pain after surgery. Hence present study showed that a single oral dose of pregabalin 150mg in patients undergoing

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laparoscopic cholecystectomy was effective in reducing postoperative pain, tramadol consumption as well as nausea & vomiting without any untoward side effects.

LIMITATIONS

Long-term follow-up was not carried out. In this study follow-up was done for 24hrs. We did not evaluate the dose response or the effect of continuation of therapy beyond 24 hours. In addition to the resting pain, pain on movement and other tools for assessment of quality of analgesia should be included. In our study we didn't evaluate recovery time, sedation score satisfaction score and opioid related symptom distress scale after surgery. Our smaller sample size and particular surgery inclusion, make it unable to impose outcome results on different type of surgery.

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