# EFFICACY OF PREGABALIN AS PREEMPTIVE ANALGESIC IN LAPAROSCOPIC CHOLECYSTECTOMY

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## ABSTRACT

### Introduction

Different pharmacological approach for preemptive analgesia have been tried with varying degree of success. Preemptive analgesia results in decrease in postoperative opioid requirement and hence decreases opioid related complication.

### Objectives

This study aims to evaluate pregabalin as preemptive analgesic in scheduled cases.

### Methodology

Fourty ASA I and II patients posted for elective laparoscopic cholecystectomy under general anesthesia were divided into two groups of twenty. Group A received pregabalin 300 mg, two hours before induction of anesthesia but group B were not given any medication. Postoperative VAS Score, Ramsay Sedation Score, postoperative nausea and vomiting and postoperative opioid requirement in two groups were observed over 48 hours and noted.

### Result

The mean VAS scores were higher in control group whereas the mean Ramsay score was higher in group pregabalin in the first six hours in the post operative period which was statistically significant. The mean Ramsay sedation score was same (2) in both the group after twelve post operative period. Postoperative nausea and vomiting was lower in the pregabalin group. Requirement of post operative analgesia was higher in the control group.

### Conclusion

Preemptive use of Pregabalin decreases postoperateive pain, postoperative opioid requirement and increases postoperative sedation.

## KEYWARDS

*Pain, preemptive analgesic, pregabalin, postoperative*

## INTRODUCTION

The international society for study of pain has defined pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Early postoperative pain is the most common cause of overnight hospital stay after any surgery. Intense postoperative pain after any surgery can develop into chronic pain such as in post laparoscopic cholecystectomy syndrome.[1] Recent advanced studies on pathophysiology of pain suggests the possibility of prevention of such phenomenon by attenuating the central neuroaxialhy per excitability that contributes to enhanced postoperative pain which is now commonly pronounced as preemptive analgesia.[2] Different agents have been employed for preemptive analgesia such as nonsteroidal anti-inflammatory drugs, NMDA antagonists and gama amino butyric acid analogues.[3] One of the gama amino butyric acid analogues is pregabalin. Pregabalin, though not functionally related, it is a structural analogue of the inhibitory neuro transmitter g-aminobutyric acid. Pregabalin similar to gabapentin, binds to the a-2-dsubunit of voltage-gated calcium channels which results in reduction of the release of excitatory neurotransmitters and thus inhibit the development of central sensitization. This property of pregabalin can be used preoperatively for preemptive analgesia as well.[4] Pregabalin has been approved for the treatment of partial seizure, pain fuldiabetic neuropathy, post herpetic neuralgia and fibromyalgia. Pregabalin has also been shown to be effective for generalized anxiety and social anxiety disorders.[5] Interestingly it has been found that Pregabalin has a significant effect in attenuating cardiovascular responses during laryngoscopy and tracheal intubation.[6] Since Pregabalin is now known to inhibit the development of central sensitization and thus attenuate postoperative pain and decrease analgesic consumption, the present study was therefore designed to evaluate the role of a preoperative single oral dose of pregabalin (300 mg) as preemptive analgesic.

## METHODOLOGY

After approval from institutional review committee (IRC) and consent from all the participants, this prospective trial was conducted in the Department of Anesthesiology, College of Medical Sciences, Bharatpur, Chitwan, Nepal on July and August 2019. Fourty ASA I and II patients aged 18 – 45 years old, posted for elective laparoscopic cholecystectomy under general anesthesia were included. Patients who were ASA more than II, aged less than 18 or more than 60 years, predicted difficult laryngoscopy and intubation, posted for emergency surgery, heart rate more than 100 or less than 50, grade III hypertension or blood pressure less than 90/60 mmHg were excluded from the study. Prolongation of surgical duration of more than one hour, unanticipated difficult intubation and unusual delay in extubation were also criteria for exclusion from the study. Primary outcomes were severity of postoperative pain and postoperative fentanyl requirement. Secondary outcomes were incidence and severity of side-effects such as postoperative nausea and vomiting (PONV), headache, sedation, and respiratory depression if any.

Sample size calculation was based on the study by Dhakal et al.[7] Standard deviation (1.16) and difference between the means (1.4) were taken from the visual analogue scale at 48 hours postoperative time. The sample size in each group comes to be > 10.72. We decided to take 20 patients in each group. So the total sample size would be 40.

Patients were randomly assigned into two equal groups of 20 patients (n=20) by lottery method. Group A received pregabalin 300 mg two hours before induction of anesthesia but group B were not given any medication. Preoxygenation with 100 percent oxygen for three minutes was done in both the groups followed by induction with intravenous midazolam (0.05 mg/kg), fentanyl (2 mcg/kg) and Propofol (2 mg/Kg). Induction time was taken as the time in seconds from the start of injection to disappearance of eyelashes reflex. In all patients after induction (loss of eye lashes reflex) tracheal intubation was facilitated using Rocuronium 1mg/kg. All the patients were intubated after 90 seconds of injecting Rocuronium with appropriate size tube. Exaggerated response to intubation i.e fluctuation of heart rate and mean arterial pressure greater than or less than 20 from baseline value were managed with deepening anesthesia with intravenous Propofol and intravenous Esmolol 0.25 mg/kg if required. Patients who had exaggerated response were excluded from the study. Anesthesia was maintained with oxygen and Isoflurane. Whenever required, Fentanyl for analgesia and Vecuronium or Rocuronium for muscle relaxation was added intraoperatively.

Assessment of pain was done by a 10 cm visual analogue scale (VAS). VAS was recorded at 0,2,4,6,12,24 and 48$^{th}$ postoperative hours. Zero hour was the time when the patient was received in the post-anesthesia care unit. Rescue analgesic was given when VAS score was six or above and on patient demand. Injection fentanyl 0.5 mcg/kg intravenously was given as rescue analgesia. In the postoperative period, all the patients received intravenous injection of tramadol (1 mg/kg) and intravenous injection of paracetamol (1 gram) three times a day.

Any complication like nausea, vomiting, pruritus, sedation, dizziness or others were recorded. These verity of PONV was graded on a four-point ordinal scale(0, no nausea or vomiting; 1, mild nausea; 2, moderate nausea; and 3, severe nausea with vomiting). Rescue antiemetic ondansetron 4 mg i.v. was given to all patients with PONV of grade 2 or more. The Ramsay sedation scale (awake levels were: 1, anxious, agitated, or restless; 2, cooperative, oriented, and tranquil; 3, responds to command; asleep levels were dependent on patient's response to a light glabellar tap or loud auditory stimulus; 4, brisk response; 5, a sluggish response; and 6, no response) was used to assess the sedation. Respiratory depression was defined as ventilatory frequency 8 bpm and oxygen saturation 90% without oxygen supplementation. Statistical analysis was done using IBM

SPSS statistics version 20 software. Patient demography were analysed with independent sample t test and frequency. The VAS pain scores and ramsay scores were analysed with both Mann–Whitney U-test and independent sample t test.

## RESULTS

There were total of 40 participants in the study who were equally divided into two groups of 20. There was no significant difference between age, sex and ASA in two groups (table no.1). The mean VAS scores were higher in control group when compared to pregabalin group throughout the post operative period which was statistically significant (table no.2). The mean RAMSAY score was higher in group pregabalin in the first six hours in the post operative period which was statistically significant (table no.3). However, the mean RAMSAY score was 2 in both the group after twelve post operative period. Requirement of post operative analgesia was higher in the control group as compared to pregabalin group. Rescue analgesia was also required up to 12th postoperative period in the control group (table no.4). Postoperative nausea and vomiting was lower in the pregabalin group as compared to control group(table no.5).

**Table 1:** Demographical distribution of participants

| | Pregabalin group | Control group |
|---|---|---|
| Age | 40±9.97 | 38.80±6.56 |
| Sex (M:F) | 6:14 | 7:13 |
| ASA (I:II) | 7:13 | 11:9 |

**Table 2:** VAS Score of the participants over forty eight postoperative hours.

| | Group Pregabalin (cm) | Group Control (cm) | |
|---|---|---|---|
| POST OP Hours | Mean ± SD | Mean ± SD | Mann whitney U test |
| 0 | 4.60±1.04 | 6.45±1.31 | U= 60, p< 0.001 |
| 2 | 4.50±0.51 | 5.30±0.65 | U= 80, p< 0.001 |
| 4 | 4.20±0.41 | 5.40±0.68 | U=40, p< 0.001 |
| 6 | 4.30±0.47 | 5.20±0.52 | U=55, p< 0.001 |
| 12 | 4.05±0.39 | 4.60±0.59 | U=104, p=0.002 |
| 24 | 3±0.79 | 4.45±1.09 | U=57, p< 0.001 |
| 48 | 1.95±0.82 | 3.45±1.05 | U=61, p< 0.001 |

**Table 3:** RAMSAY Score of participants over forty eight postoperative hours.

| POST OP Hours | Pregabalin | Control |
|---|---|---|
| 0 | 3(15%) | 14 (70%) |
| 2 | 2 (10%) | 8 (40%) |
| 4 | 3 (15%) | 10 (50%) |
| 6 | 3 (15%) | 5 (25%) |
| 12 | 0 | 3 15%) |
| 24 | 0 | 0 |
| 48 | 0 | 0 |

**Table 4 :** Prevalence of requirement of rescue analgesics in the postoperative hours

| POST OP Hours | Pregabalin | Control |
|---|---|---|
| 0 | 3(15%) | 14 (70%) |
| 2 | 2 (10%) | 8 (40%) |
| 4 | 3 (15%) | 10 (50%) |
| 6 | 3 (15%) | 5 (25%) |
| 12 | 0 | 3 15%) |
| 24 | 0 | 0 |
| 48 | 0 | 0 |

Table 5: Incidence and severity of postoperative nausea and vomiting.

| Group | Frequency | Percentage | Grade I | Grade II | Grade III |
|---|---|---|---|---|---|
| Pregabalin | 3 | 15% | 2 | 1 | 0 |
| Control | 5 | 25% | 3 | 2 | 0 |

## DISCUSSION

First introduced by Crile in 1913, the concept of prevention of pain was further developed by Wall and Woolf who suggested that the timing of treatment had profound effects on postoperative pain.[8,9] The concept of preemptive analgesia was first paved by Woolf in 1983 who suggested the involvement of central component in development of hypersensitivity in experimental studies.[10] Preemptive analgesia is now defined as a treatment thatis initiated before surgery to prevent the development of central sensitization due to the incisional and inflammatory injuries inflected during surgery and the experience of severe magnitude of pain in the early postoperative period.[11,12] To preemptive cure pain, a wide variety of agents and techniques have been employed such as parenteral or oral nonsteroidal anti-inflammatory drugs (NSAIDs), Sublingual and intravenous (IV) opioids, Parenteral NMDA receptor antagonists, Local anesthetics (LA) for neuraxial administration, peripheral blocks, wound infiltrations, and intraperitoneal instillations, and Systemic antiepileptics (GABA (gamma-amino butyricacid) analogues).[3] Pregabalin have been found to have satisfactory antinociceptive effect and even reduced postoperative opioid requirement when given as a premedication before a number of surgical procedures. Single dose premedication of pregabalin have been observed to reduceanalgesic requirement during differentcatagories of surgeries (tonsillectomy, hysterectomy, laparoscopic cholecystectomy and spinal surgery).[13-16] In a review of 22 RCTs, it was observed dose of that decrease in opioid consumption in first 24 h postoperative period was not dependent on gabapentin dose, concluding that increasing the dose of gabapentin (1200 mg) and pregabalin (300 mg) for premedication before surgery only increases the adverse effects.[17] Pregabalin is structurally similar to the major inhibitory neurotransmitter gabaaminobutyric acid. Similar to its predecessor, gabapentin, it acts by binding to the a-2-d subunit of voltage gated calcium channels in the presynaptic end and reduces the release of excitatory neurotransmitters.[18] Advantage of pregabalin over gabapentin is that it is more

potent and has lesser side effects. Pregabalin was designed as a lipophilic GABA analog to facilitate diffusion across the blood-brain barrier. It is rapidly absorbed orally with more than ninghty percent bioavailability. It achieves peak plasma levels within 30 minutes to 2 hours and shows linear pharmacokinetics. Apparent volume of distribution after oral administration is 0.5l/kg. Pregabalin does not bind to plasma proteins. Pregabalin undergoes negligible metabolism and ninty percentage of the dose is recoveredin the urine as parent compound. The N-methylated derivative of Pregabalin is the major metabolite which is found in the urine and accounted for 0.9 % of the dose. Half life of pregabalin is 6.3 hrs. In healthy subjects, renal clearance is 67.0 – 80.9 ml/min. Dizziness and somnolence are the most common adverse effects of pregabalin. Pregabalin has no effect on arterial blood pressure or heart rate.[19]

Zhang et al[18]in their meta- analysis observed that the VAS score in the first 24 hours after surgery was not reduced by perioperative pregabalin administration. Agarwal et al[20] observed that pregabalin group had lower VAS Score in the postoperative period as compared to placebo group. In our study, we observed that postoperative VAS score was lower in patients who received preoperative pregabalin as compared to control group. Lam et al[21] in their meta-analysis observed decreased opioid consumption in the post surgical period. They concluded that there was 30% reduction in consumption of opioid for post surgical pain. However, Surana et al[22]suggested that there was no significant difference between control and pregabalin group. It is suggested that the difference in results of VAS scores and Opioid consumption in different studies is due to difference in dose of pregabalin and type of studies. We observed decreased requirement of rescue analgesia in pregabalin group.Esmatet al[23] reported that there is increase in incidence of sedation in postoperative period in patients receiving preoperative pregabalin. Sebastian et al[24] in their study observed that there was increased RAMSAY score in the perioperative period in patients who received preoperative pregabalin during orthopedic surgery under spinal anesthesia. We also observed higher RAMSAY sedation score in pregabalin group.Sebastian et al[24] They concluded that there was 30% reduction in consumption of opioid for post surgical pain and hence reduction in opioid related adverse events such as PONV. We also observed decreased incidence of PONV in pregabalin group

## CONCLUSION

The study concludes that preoperative pregabalin is effective in reducing immediate postoperative pain and opioid consumption and is devoid of any major side effects. However, pain being a subjective emotion and due to use of other analgesics in the postoperative period we do not suggest to completely rely on single dose of preoperative pregabalin as a standard preemptive analgesic. A study with larger sample size is required to establish the efficacy of pregabalin as a preemptive analgesic.

## LIMITATIONS OF THE STUDY

Dose of study drug was not prescribed on the basis of weight. Response to continuation of therapy was not evaluated. Use of other analgesics in the postoperative period. The sample size is small.

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