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# EVALUATION OF A SINGLE PREOPERATIVE ORAL DOSE OF PREGABALIN FOR ATTENUATION OF POST OPERATIVE PAIN AFTER LAPAROSCOPIC CHOLECYSTECTOMY (A STUDY OF 80 CASES)

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**ABSTRACT**

Post-operative pain is one of the major problem in laparoscopic surgeries, wherein lack of control on it has many side-effects such as tachycardia, hypertension, myocardial ischemia, decreased alveolar ventilation, and prolong hospital stay.We have evaluated the efficacy of a single preoperative dose of Pregabalin for attenuating postoperative pain and diclofenac consumption after laparoscopic cholecystectomy. Eighty adults (18–70 yr), ASA risk I and II, of either sex undergoing elective laparoscopic cholecystectomy were included in this prospective, randomized placebo controlled, double-blind study. Subjects were divided into two groups of 40 each to receive either a matching placebo or Pregabalin 150 mg, administered orally 1 h before surgery. Post-operative pain was assessed at 0, 1, 2, 3, 4, 8, 12, 16, 20 and 24 hours period post operatively Postoperative pain (static and dynamic) was assessed by a 10 cm visual analogue scale, where 0, no pain; 10, worst imaginable pain. Post-Operative Nausea Vomiting (PONV) score along with hemodynamic variables (Systolic and diastolic blood pressure and pulse rate) were also observed post operatively. Subjects received i.v. diclofenac analgesia during the postoperative period if VAS score more than 4. Data analysis was done using Epi Info 7.0 software Results were analysed by Anova test. Postoperative pain and postoperative diclofenac consumption were reduced in the Pregabalin group compared with the Placebo group ($P$<0.05). Side-effects were similar in both groups. A single preoperative oral dose of Pregabalin 150 mg is an effective method for reducing postoperative pain and diclofenac consumption in patients undergoing laparoscopic cholecystectomy.

**Key words:** Visual analogue scale, Pregabalin, Analgesia, nonopioid, Laparoscopic Cholecystectomy.

## INTRODUCTION

Pain is thought to be inadequately treated in one-half of all surgical procedures. Recent advances in the pathophysiology of pain have suggested that it is possible to prevent or attenuate the central neural hyperexcitability that contributes to enhanced postoperative pain [1]. Early postoperative pain is the most common complaint after elective laparoscopic cholecy stectomy [1,2,7,12]. Pain is the main reason for overnight hospital stay after day care surgery. Postoperative pain is the dominating complaint and the primary reason for prolonged convalescence after laparoscopic cholecystectomy [1,2]. Intense acute pain after laparoscopic cholecystectomy might predict the

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development of chronic pain (e.g. post-laparoscopic cholecystectomy syndrome). Pregabalin originally developed for the management of generalized or partial epileptic seizures resistant to conventional therapies [3,4]. Pregabalin reduces hyper excitability of dorsal horn neurons induced by tissue damage rather than reduce the afferent input from the site of tissue injury [3]. It binds to alpha$_2$-delta subunit of voltage gated calcium channels, reducing the release of several excitatory neurotransmitters and blocking the development of hyperalgesia and central sensitization [3,5]. This medicine is $\delta^{-2}$ α ligand having anesthetic, anticonvulsant, anti-excitement, and sleep movement moderating effects[3,5]. Pregabalin has a proven role in treating neuropathic pain; however, evidence supporting the postoperative analgesic efficacy of Pregabalin is limited to randomized controlled trials in patients undergoing dental surgery, spinal fusion surgery, laparoscopic hysterectomy and day-case gynaecological laparoscopic surgery. None of these trials has investigated the role of preoperative single-dose administration of Pregabalin in attenuating postoperative pain after laparoscopic cholecystectomy. The present study was therefore designed to evaluate the role of preoperative single dose of Pregabalin for attenuating postoperative pain and analgesic consumption in patients undergoing laparoscopic cholecystectomy [6,11-15].

## METHODS

This prospective, randomized, double-blind, and placebo controlled clinical study was designed to include 80 adult patients (18–70 yr) of either sex, ASA risk I and II, undergoing laparoscopic cholecystectomy under general anaesthesia. The study protocol was approved from the institutional ethical committee and written informed consent was obtained from all the patients. Patients with impaired kidney function, history of drug or alcohol abuse, history of chronic pain or daily intake of analgesics, allergic to Pregabalin or diclofenac, uncontrolled medical disease (diabetes mellitus and hypertension), history of intake of non-steroidal anti-inflammatory drugs or steroids within 24 h before surgery were excluded from the study.

Patients meeting the inclusion criteria during the pre-anaesthetic evaluation were randomly assigned into two groups of 40 each with the help of a computer-generated table of random numbers, to receive either a matching placebo or Pregabalin 150 mg. All the medications were provided by hospital pharmacy, were identical, and were administered orally, 1 h before the induction of anaesthesia with sips of water by a staff nurse who was not involved in the study.

Anaesthesia technique was standardized in all the groups. Patients were induced with fentanyl 2 µg kg$^{-1}$ and Thiopentone sodium 2.5% 5-7 mg kg$^{-1}$ Followed by Succinylcholine 2 mg kg$^{-1}$ ; Orotracheal intubation was done and neuromuscular relaxant Vecuronium 0.08 µg kg$^{-1}$ given. Anaesthesia was maintained with Vecuronium, Sevoflurane and 50% Nitrous oxide in Oxygen. At the end of surgery, residual neuromuscular paralysis was antagonized with Neostigmine 0.05 mg kg$^{-1}$ and Glycopyrrolate 0.008 mg kg$^{-1}$. After satisfactory recovery, the patients were extubated and shifted to the post-anaesthesia care unit (PACU). In the PACU, patients received i.v. diclofenac as a rescue analgesic in a dose of 2mg kg$^{-1}$ if VAS score more than 4.

Primary outcomes were severity of postoperative pain and postoperative diclofenac requirement. Secondary outcomes were incidence and severity of side-effects such as postoperative nausea and vomiting (PONV). Both these outcomes were assessed by an independent anaesthesia registrar (S.K.G.) blinded to group allocation.

Assessment of pain was done by a 10 cm visual analogue scale (VAS); 0, no pain; 10, worst imaginable pain. Assessment of pain was done on arrival of patient to the PACU (0) and then 1,2,3,4,8,12,16,20,24 h till the end of the study, that is, 24 h after operation. From these data, the maximum pain scores at different time intervals (0, 0–4, 4–8, 8–12, and 12–24 h) for each patient were considered for statistical analysis. The severity 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. Calculation of sample size was based on the presumption that postoperative VAS scores after preoperative administration of Pregabalin 150 mg would be 3 cm when compared with 4.5cm in the placebo group with a standard deviation of 2 cm at all-time points. For the results to be of statistical significance with $\alpha$=0.05 and $\beta$=0.80, one needed to recruit 25 patients in each group. To take care of any drop outs, we enrolled 40 patients in each group. The method of analysis was decided prospectively and incorporated the intention-to-treat principle. Patient characteristic data were analysed with one-way anova for continuous variables. Postoperative diclofenac consumption was analysed with Student's *t*-test. Data analysis was done using Epi Info 7.0 software. $P$<0.05 was considered significant.

**Table 1. Demographic Data**

| Group | Age (Mean+/- SD) (Years) | Gender (M/F) | Weight (Mean+/- SD) (kg) | Duration of Surgery(min) |
|---|---|---|---|---|
| A(Pregabalin) | 43.6+/-5.8 | 7/33 | 55+/-6.7 | 91.3 (22.9) |
| B(Placebo) | 44.1+/-7.58 | 8/32 | 54+/-6.6 | 88.7 (22.7) |

As shown in Table-1 Demographic data like age, gender, weight,duration of surgery are statistically comparable between two groups.

**Table 2. VAS immediately after extubation**

| Group | VAS (Mean+/-SD) | p- Value |
|---|---|---|
| A(Pregabalin) | 1.30+/-0.56 | p<0.001 |
| B(placebo) | 3.30+/-1.24 | |

As from the data shown in table-2, mean VAS in Group A is less than VAS in Group B and there is statistical significance (p<0.05) in pain scores between two groups immediately after extubation.

**Table 3. VAS post-operative period**

| Group | VAS (Mean+/-SD) | p- Value |
|---|---|---|
| A(Pregabalin) | 1.30+/-0.56 | p<0.001 |
| B(placebo) | 3.30+/-1.24 | |

As from the data shown in table-3, mean VAS in Group A is less than VAS in Group B and there is statistical significance (p<0.05) in pain scores between two groups immediately after extubation.

**Table 4. VAS post-operative period**

| Group | VAS (Mean+/-SD) at interval (hours) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 8 | 12 | 16 | 20 | 24 |
| A | 1.52 +/- 0.68 | 1.70 +/- 0.76 | 2.25 +/- 0.63 | 2.68 +/- 0.73 | 3.25 +/- 0.74 | 3.12 +/- 0.79 | 2.95 +/- 0.96 | 3.18 +/- 0.90 | 2.95 +/- 0.90 |
| B | 2.48 +/- 0.55 | 3.20 +/- 0.94 | 2.98 +/- 0.70 | 2.98 +/- 0.58 | 3.68 +/- 0.97 | 3.20 +/- 0.85 | 3.52 +/- 0.85 | 3.52 +/- 0.78 | 3.68 +/- 1.0 |
| p value | <0.001 | <0.001 | <0.001 | <0.004 | <0.03 | >0.05 | <0.005 | >0.05 | <0.001 |

**Table 5. Post-Operative Analgesic Requirement**

| Group | Analgesic profile | |
|---|---|---|
| | Time to first analgesic dose(hours) (Mean+/-SD) | Number of total dose (Mean+/-SD) |
| A(Pregabalin) | 9.55+/-4.08 | 2.10+/-0.5 |
| B(placebo) | 1.60+/-1.39 | 3.28+/-0.55 |
| | p<0.0001 | p<0.0001 |

As shown in Table-5, mean duration at which first analgesic dose required after surgery is significantly long in Group A than Group B and mean of total number of analgesic doses required in Group A is lesser than Group B and both are statistically significant (p<0.05).

**Table 6. Analgesic requirement**

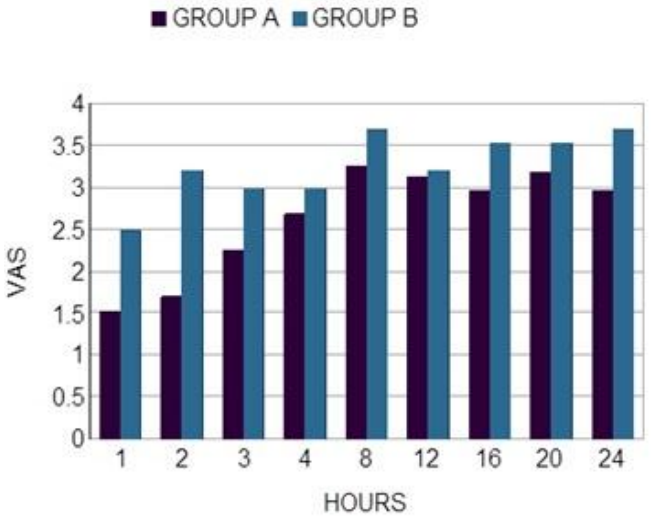
| Group | Number of Doses of Systemic analgesics required in 24 hour post-operative period | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| A(Pregabalin) | 3 | 30 | 7 | 0 |
| B(Placebo) | 0 | 2 | 25 | 13 |

**Table 7. Post-operative complications**

| Complications | Group A | Group B |
|---|---|---|
| PONV | | |
| No | 24 | 23 |
| Mild | 5 | 5 |
| Moderate | 6 | 5 |
| Severe | 5 | 7 |
| TOTAL | 11 (27%) | 12 (30%) |

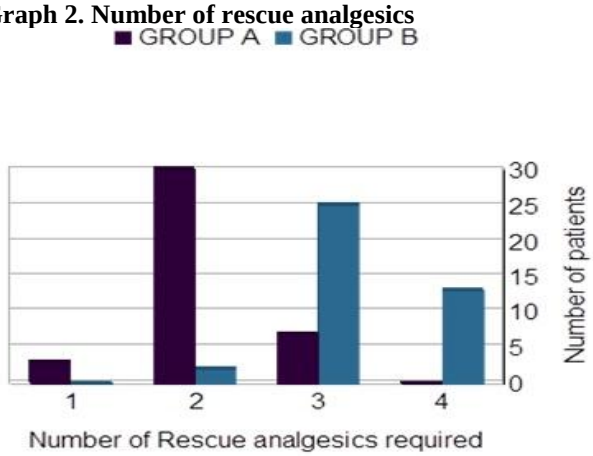
As shown in above data (Table-7), post-operative complications like nausea and vomiting are similar in Group A and Group B.

**Graph 1. VAS- post operative period**




As seen from the above data (Table-4, Graph-1), mean VAS score in Group A(Pregabalin) is significantly less than Group B(placebo) up to 8 hours post operatively and it is statistically significant(p value<0.005).

**Graph 2. Number of rescue analgesics**




As shown in above data (Table-6 and Graph-2), in Group A, 3(7.5%) patients required only one rescue analgesic dose in the post-operative period, 30(75%) patients required 2 doses, only 7(17.5%) patients required 3 rescue analgesic doses and No patient required 4 doses. While in Group B No patient satisfied with one rescue analgesic dose in the post-operative period, 2(5%) patients required 2 doses, 25(62.5%) patient required 3 rescue analgesic doses and 13(31%) patients required 4 rescue analgesic doses.

## DISCUSSION

We observed that preoperative single-dose Pregabalin (150 mg) was effective in reducing postoperative pain along with postoperative diclofenac consumption in subjects undergoing laparoscopic cholecystectomy.

Experimental models of neuropathic pain and inflammatory hyperalgesia have shown that γ-aminobutyric acid analogues such as Gabapentin and Pregabalin have antinociceptive and antihyperalgesic properties. The pharmacological effects of Pregabalin are believed to result from its action as a ligand at the alpha-2-delta binding site, which is associated with the voltage-gated calcium channels in the central nervous system. Potent binding of Pregabalin at alpha-2-delta site has been shown to reduce the depolarization-induced calcium influx at nerve terminals with a consequential reduction in the release of several excitatory neurotransmitters, including glutamate, norepinephrine, substance P, and CGRP. It is probable that this modulation of neurotransmitter release by Pregabalin contributes to the drug's anticonvulsant, analgesic, and anxiolytic effects. However, Pregabalin appears to be a better option when compared with Gabapentin, as it exhibits greater analgesic efficacy in rodent models of neuropathic pain and better pharmacokinetic profile across its therapeutic dose range with low inter-subject variability. The side-effect profile of Pregabalin is also very promising with the most common adverse events being dizziness and somnolence; in addition, Pregabalin has no effect on arterial pressure or heart rate.

Pregabalin is rapidly and extensively absorbed after oral dosing in the fasted state(>90%), with maximal plasma concentration occurring ~1 h after single or multiple doses, and steady state being achieved within 24–48 h after repeated administration. It can be started at an effective dose of 150 mg $day^{-1}$, the dose of Pregabalin used in the present study. The oral bioavailability of Pregabalin is high at ≥90% and is independent of dose.

The use of Pregabalin in acute postoperative pain management has been evaluated in recent studies. These studies sought to determine whether perioperative Pregabalin was effective in reducing postoperative pain and whether it had opioid-sparing effects. However, differences in the Pregabalin dosages and types of surgery have yielded contrasting results. A study investigating pain relief after dental extraction showed that 400 mg Pregabalin administered after operation was more effective than ibuprofen in attenuating acute post-procedural pain. In another clinical trial, Jokela and colleagues observed that perioperative administration of Pregabalin 300 mg before and after laparoscopic hysterectomy decreases oxycodone consumption, but is associated with an increased incidence of adverse effects. Jokela and colleagues in another study observed that analgesia was better after premedication with Pregabalin 150 mg in patients undergoing day-case gynaecological laparoscopic surgery. Agarwal A and his collegue conducted study in 2008 and observed that postoperative pain and postoperative patient-controlled fentanyl consumption were reduced in the Pregabalin group compared with the placebo group. Dauri M in 2009 conducted 8 Pregabalin (707 patients) RCTs and 7 meta-analysis were involved in this review and concluded that Pregabalin provided better post-operative analgesia and rescue analgesics sparing than placebo in two of the three RCTs that evaluated the effects of Pregabalin alone vs. placebo. Sarakatsianou C and his collegue conducted study in 2013 and concluded Postoperative patient-controlled

morphine consumption was significantly less in the Pregabalin group compared with the placebo group.

On the contrary, in a recently published article, Paech and colleagues reported that a single preoperative dose of 100 mg Pregabalin was ineffective in reducing acute postoperative pain or improving recovery after minor surgery involving only the uterus. The difference in the results from our study could possibly be because Paech and colleagues administered a smaller dose (100 mg) against the recommended starting dose of 150 mg or because of the difference in the nature of surgery. Limitations of the present study are that we did not evaluate the dose–response or the effect of continuation of therapy. Further studies are suggested in these areas.

In conclusion, oral Pregabalin 150 mg administered before operation was effective in reducing postoperative pain and postoperative patient-controlled diclofenac requirement in patients undergoing laparoscopic cholecystectomy. The side-effect profiles were similar in both the groups. We therefore suggest that oral preoperative single dose of Pregabalin 150 mg is an effective method for reducing postoperative pain and diclofenac consumption in patients undergoing laparoscopic cholecystectomy.

**REFERENCES**


1. Bisgaard T, Klarskov B, Rosenberg J, Kehlet H. Characteristics and prediction of early pain after laparoscopic cholecystectomy. *Pain*, 90, 2001, 261–69.
2. Joris J.Cigarini, Legrand M, Jacquet N, Franchiment P, Lamy M. Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy. *British J Anaesth*, 69, 1992, 341-45.
3. Arikkath J, Campbell KP. Auxillary subunits, Essential components of the voltage-gated calcium channel complex. *Curr Opin Neurobiology*, 13, 2003, 298–307.
4. Dahl JB, Mathiesen O, Moiniche S. 'Protective Premedication', an option with gabapentin and related drugs A review of gabapentin and Pregabalin in the treatment of post-operative pain. *Acta Anaesthesiol Scand*, 48, 2004, 1130-6.
5. Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. *Epilepsia*, 45, 2004, 13-8.
6. Shneker BF, McAuley JW Pregabalin as a new neuromodulator with broad therapeutic indications. *Ann Pharmacother*, 39, 2005, 2029-37.
7. Louizos AA, Hadzilia SJ, Leandros E, Kouroukli IK, Georgiou LG, Bramis JP. Post-operative pain after laparoscopic Cholecystectomy. *Surg Ebdose*, 19, 1503-1506.
8. Gan TJ, Habib AS. Gabapentin and postoperative pain-a systematic review of randomized controlled trials. *Pain*, 126, 2006, 91-101.
9. Freedman BM, O'Hara E. Pregabalin has opioid-sparing effects following augmentation mammaplasty. *Aesthet Surg J*, 28, 2008, 421.
10. Jokela R, Ahonen J, Tallgren M, Haanpaa M, Korttila K. Premedication with Pregabalin 75 or 150 mg with ibuprofen to control pain after day-case gynaecological laparoscopic surgery. *Br J Anaesth*, 100, 2008, 834-40.
11. Agarwal A, Gautam S, Gupta D, Agarwal S, Singh PK, Singh U. Evaluation of a single preoperative dose of Pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. *Br J Anaesth*, 101, 2008, 700-04.
12. Lau H, Brooks DC. Predictive factors for unanticipated admissions after ambulatory laparoscopic cholecystectomy. *Arch Surg*, 136, 2001, 1150–53.
13. Dauri M, Faria S, Gatti A, Celidonio L, Carpenedo R, Sabato AF Gabapentin and Pregabalin for the acute post-operative pain management. A systematic-narrative review of the recent clinical evidences. *Curr Drug Targets*, 10, 2009, 716-33.
14. Chang SH, Lee HW, Kim HK, Kim SH, Kim DK. An evaluation of perioperative Pregabalin for prevention and attenuation of postoperative shoulder pain after laparoscopic cholecystectomy. *Anesth Analg*, 109, 2009, 1284-86.
15. Cabrera Schulmeyer MC, de la Maza J, Ovalle C, Farias C, Vives I Analgesic effects of a single preoperative dose of Pregabalin after laparoscopic sleeve gastrectomy. *Obes Surg*, 20, 2010, 1678-81.