

ORIGINAL ARTICLE

A RANDOMIZED PLACEBO CONTROLLED STUDY OF PREOPERATIVE PREGABALIN ON POSTCHOLECYSTECTOMY PAIN RELIEF

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ABSTRACT: There are studies that have demonstrated the role of pregabalin as a pre-emptic analgesic in the multimodal therapy for acute postoperative pain management. However, its use in more painful operative procedures like open cholecystectomy are limited and hence the present study was undertaken to evaluate the effectiveness of a single dose of preoperative oral pregabalin in attenuating the postoperative pain. In this randomized, controlled, prospective and double blind study, 80 patients (ASA I & II, aged 18-55 years and of both sexes) undergoing open cholecystectomy under GA were divided into two equal groups (n=40 each) to receive either oral pregabalin 150mg or placebo 1 hour before the surgery. Intraoperative hemodynamic variables, postoperative VAS scores, sedation scores, analgesic free time intervals, total dose of rescue analgesic, side effects etc. were recorded and compared for the first 24 hours postoperatively. VAS score distribution in the first 24 hours were significantly lower in the pregabalin group than the control group (P<0.05). The analgesia free time interval was longer and the number of rescue analgesic(inj. tramadol 50mg) was lesser in the pregabalin 150mg (P<.05). Preoperative pregabalin 150 mg administered 1 hour prior to surgery attenuates the postoperative pain thereby reducing opioid consumption.

KEYWORDS: Pregabalin, open cholecystectomy, pre-emptic analgesia and postoperative pain.

INTRODUCTION: Post-operative pain is the most common clinical problem in hospitals among surgical patients and is the main reason for overnight hospital stay in 17-41% of surgical day care patients.¹ It has been managed with varieties of drugs and techniques such as combination of opioids, non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol, small dose ketamine, peri-operative administration of local anesthetics, interventional techniques like epidural and nerve blocks etc. which are associated with potential risks of serious complications. Thus, with the emerging concepts of pre-emptive analgesia, a drug that has analgesic properties, opioid sparing effects, possibly reduces opioid tolerance, relieves anxiety and is not associated with adverse effects typical for the traditional analgesic would be an attractive adjuvant for post-operative pain management.²

Pregabalin and its developmental predecessor gabapentin were originally developed as spasmolytic agents and adjuncts for the management of generalized or partial epileptic seizures resistant to conventional therapies. Pregabalin, like gabapentin is an amino-acid derivative of gamma amino butyric acid. It binds to the $\alpha_2\text{-}\delta$ (type I) receptor in the central nervous system. Binding of pregabalin to the $\alpha_2\text{-}\delta$ (type I) subunit of voltage gated calcium channels alter the kinetic and voltage dependence of calcium current. By reducing calcium influx at the nerve terminal pregabalin reduces the release of several neurotransmitters including glutamate, substance-P, noradrenaline and calcitonin gene related peptide. This accounts for the analgesic activity of pregabalin which is six times more potent than gabapentin.³

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Gabapentin has been found to be useful for neuropathic pain and post-operative pain after breast surgery, spinal surgery and laparoscopic cholecystectomy.⁴ Similarly, pregabalin which has a better pharmacological profile than gabapentin⁵ has a proven role in treating neuropathic pain; however, evidence supporting the post-operative analgesic efficacy of pregabalin is limited to randomized control trials in patients undergoing dental surgery⁶, spinal fusion surgery⁷, laparoscopic hysterectomy, day case gynecological laparoscopic surgery⁸, laparoscopic cholecystectomy⁹ etc. None of these trials have investigated the role of pre-operative administration of pregabalin in attenuating post-operative pain in more painful operative procedures like open cholecystectomy which is one of most common operations performed in our Institute. The present study was, therefore, designed to evaluate the effect of a single dose of pre-operative oral pregabalin 150mgs in attenuating the post-operative pain and thereby reducing the post-operative analgesic consumption.

MATERIALS AND METHODS: The study was a prospective, randomized, double blinded and placebo controlled one conducted in the Department of Anesthesiology, at a tertiary care center, After getting approval from the Institutional Ethics Committee and written informed consent, consecutive eighty (80) patients, between 18-55 years of age and of both sexes belonging to ASA I and II, scheduled for open cholecystectomy with right subcostal (Kocher's) incision of about 2 inches under general anesthesia were included and randomly allocated by computer generated randomization schedule in the two groups of 40 patients each, which were blinded to both the patient and anesthesiologist as: -
Group C (Control) – those receiving oral placebo capsules one hour before the surgery.
Group P (Study) – those receiving oral pregabalin capsules 150 mg one hour before the surgery.

Patients allergic to the study medications, pregnant and lactating women, patients with impaired kidney or liver function, history of drug or alcohol abuse, history of chronic pain or daily intake of analgesics, uncontrolled medical diseases (diabetes mellitus, hypertension etc.), history of intake of non-steroidal anti-inflammatory drugs within 24 hours before surgery, history of chronic use of central nervous system depressant drugs and anti-convulsants, patients with impaired mental status who were not able to communicate, obese patients etc. were excluded from the study.

Primary outcomes of the study were the severity of pain, analgesic free time interval, rescue inj. tramadol requirement and sedation score in the postoperative period. Secondary outcomes included the incidence of side effects of pregabalin such as nausea, vomiting, headache, dizziness, somnolence, peripheral edema, etc.

Pain was assessed by Visual Analogue Scale (VAS) score¹⁰ and sedation by Ramsay sedation score¹¹ as follows:-

- a. Visual Analogue Scale (VAS) score for both static and dynamic pain score with 10 cms Visual analogue scale; 0= No pain and 10=Worst imaginable pain. Static and dynamic pain score were assessed at rest and during coughing respectively.
- b. Ramsay sedation score: Score 1 = anxious, agitated or restless, Score 2 = co-operative, oriented and tranquil, Score 3 = responds to command, Score 4 = asleep but has a brisk response to light glabellar tap or loud auditory stimulus, Score 5 = asleep but has a sluggish response to light glabellar tap or loud auditory stimulus and Score 6 = asleep, no response.

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All the patients were premedicated with oral tab. alprazolam 0.5mg and tab. ranitidine 150mg on the night before the surgery. Inj. glycopyrrolate 0.004mg/kg intramuscular and inj. ondansetron 4mg intravenous were given to all the patients 45 minutes before the induction. This was followed by slow intravenous inj. tramadol hydrochloride (1.5mg/kg) 15 minutes before the induction. A uniform general anesthetic technique was maintained in all the patients. The intra-operative parameters such as heart rate, NIBP and SPO₂ were recorded for every 5 minutes for the first 15 minutes, then at intervals of 10 minutes till the end of surgery. The duration of surgery was noted and all the patients are shifted to the post-anesthetic care unit (PACU) for observation.

The Visual Analogue Scale (VAS) score and Ramsay sedation scores were recorded at 0 hour, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours and 24 hours. Rescue analgesic in the form of slow intravenous Inj. tramadol hydrochloride (1mg/kg) were given at any point of time with VAS score of static greater than 4 and dynamic greater than 5 or if the patient demands so. The rescue analgesic free time interval and the total dose of rescue analgesic were noted. Other associated side effects were also recorded.

Statistical Package for Social Sciences (SPSS) version 19.0 software for Windows was used for statistical analysis. Chi square test, for categorical variables, and Students' 't' test for continuous variables were used to compare the data, and $P \leq 0.05$ was deemed significant.

RESULTS: A total of 80 patients, 40 patients in each group were included and analyzed for the study. There were no significant differences in age, weight, sex, ASA status, duration of surgery in the two groups and were comparable ($P > 0.05$) (Table 1). The intraoperative hemodynamics parameter such as mean arterial pressure, heart rate and percentage saturation of oxygen were also comparable in the two groups ($P > 0.05$).

The postoperative visual analog scale (VAS) score within the first 24 hours recorded increased values for both static and dynamic in the control group with mean range score of 3 to 6 cms and 4 to 7 cms respectively. However, the pregabalin group recorded significant lower VAS score with mean range score of 0 to 1cm for static and dynamic VAS respectively. (Table 2)

The sedation score as measured by Ramsay sedation score (RSS) at different time points recorded lower score (mean score range of 1 to 1.25) in the control group than the pregabalin 150mg group with a mean score range of 2 to 2.28, which decreased gradually in due course of time ($P < 0.05$). (Figure 1)

The mean postoperative rescue analgesic free time interval in the control group was 0.09 ± 0.11 hours as compared with pregabalin 150mgs of 11.31 ± 0.75 hours which was longer ($t = 93$ & $P = 0.000$). The control group also recorded significant maximum number of postoperative rescue analgesic (3.25 ± 0.44) as compared with the pregabalin group which recorded least number of rescue analgesics with 1.08 ± 0.27 ($t = 26.8$ & $P = 0.000$). (Table 3)

The control group recorded more significant number of patients with nausea and vomiting than the pregabalin group which recorded lower number of patients ($P < 0.05$). However, pregabalin 150mgs group has got more (8, 20%) patients with dizziness and headache than the control group (2, 5%) ($\chi^2 = 4.11$ and P value of 0.04). Also, the control group did not have any patients with postoperative visual disturbances whereas the pregabalin group had got 6(15%) patients with such disorder ($\chi^2 = 6.49$ and P value of 0.01). (Table 4).

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DISCUSSION: Effective postoperative analgesia is necessary to provide subjective comfort and alleviate the suffering in patients undergoing surgery. Surgical stimulation or mechanical hyperalgesia in postoperative wounds appear to share a common mechanism with heat induced experimental secondary hyperalgesia which leads to sensitization of dorsal horn neurons and subsequently to central neuronal sensitization which are associated with augmentation of postoperative pain.¹² Postoperative pain is typically regarded as a type of pain with peripheral mechanoreceptors stimulation involving inflammatory neurogenic and visceral mechanism, with a transient reversible type of neuropathic pain.

The invention of newer generation of potent and safe pharmacological agents has opened up a lot of options and multimodal approach for providing adequate pain relief in post-surgical patients. The choice of such an agent is guided by factors such as efficacy, convenience of administration, cost-effectiveness, safety profile and additional advantage associated with the outcome variable relative to a standard analgesic regimen.

Anti-hyperalgesia drug such as pregabalin has some proven role in the control of postoperative pain either singly or in combination with other antinociceptive drug for synergistic effects; and various clinical studies with the drugs for postoperative analgesia have shown promising results.^{8, 13-17} The proposed mechanism of action of pregabalin is to limit the short-duration wind-up component of central sensitization by binding to the pre-synaptic alpha-2-delta subunit of voltage gated calcium channels which are distributed widely in the spinal cord and brain.^{3, 17} The conformational changes induced by this binding inhibits abnormally intense neuronal activity by reducing the synaptic release of glutamate and other neurotransmitter. Experimental studies with animal models and healthy volunteers have shown that pregabalin reduces nociceptive responses, particularly in condition involving central sensitization. However, pregabalin has shown efficacy against acute somatic pain and it may be less effective in visceral pain model.^{6, 7}

The relative efficacy analysis with comparison between the two groups demonstrated that the changes in VAS score, both static and dynamic, across different time points in the post-operative period during 0-24 hours was found to be highly significant when compared with the control group. The pregabalin group showed significant lower VAS score at different time points 24 hours post-operatively. This finding of pregabalin group having significant lower VAS score as compared with the control are in agreement with the studies of Agarwal A et al⁹ with 150 mg of pregabalin for post laparoscopic cholecystectomy pain control, Kim SY et al¹⁴ with 150 mg of pregabalin in robot assisted thyroidectomy and Kholi M et al¹⁶ with 150 mg and 300 mg of the drug in lower abdominal surgeries. Contradictory results were reported by Mathiesen O et al¹⁸ on a study of 300 mg of pregabalin in abdominal hysterectomy which showed no significant effect on the VAS score. This finding is also supported by Peach MJ et al,¹⁹ who opined that lower pain score in the placebo groups, underpowered study and evaluation of analgesia in visceral pain model were responsible for the negative results. Likewise, on a study with 75, 150, and 300 mg of pregabalin on various surgeries, Paul FW et al²⁰ concluded that there were no improvement in pain score in all the groups and sedation increased with increasing dose of the drug.

The analgesic free time intervals of 11 hours in the pregabalin group were significantly longer than the control group (<1 hour). The numbers of rescue analgesic were also significantly lesser than the control group. Our findings are supported by studies of Sahu S et al¹⁵ (7.6 hours) and Saraswat V

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et al²¹ (14.17 hours) on different doses and different types of rescue analgesic treatment regimen; and the plasma half-life of the drug which is 4.6 to 6.8 hours.¹⁷

The sedation score as measured with the Ramsay sedation score was least with the control group and maximum with the pregabalin 150 mg group and statistically significant. Even though the mean sedation score of 2 was recorded in pregabalin 150mg group as compared with a significant mean score of 1 in the control group it did not produce clinical sedation as also reported by Kim SY et al.²² These findings are corroborated with that of independent studies involving 150 mg and 300 mg of pregabalin by Jokela R et al,⁸ Paul F et al²¹, KholiM et al¹⁶ etc.

The hemodynamic changes in the two groups were comparable and statistically not significant. Our findings are consistent with that of the independent studies conducted by Kholi M et al,¹⁶ Ruben SS et al,⁷ Buvanendren A et al²³etc, thus, supporting the findings that pregabalin has no action on arterial pressure or heart rate. However, in two independent studies conducted by Gupta K et al,^{24, 25} the role of pregabalin in attenuating hemodynamic response to laryngoscopy and intubation has been highlighted which may due to the increased sedation rather than the actual inhibition of sympatho-adrenal axis.

The incidence of side effects such as nausea and vomiting were minimal in the pregabalin group as compared with the control which recorded increase incidence and the same had been reported on different independent studies of Paul F et al,²¹ Wichai I et al¹³ etc. This may be explained on the association of greater VAS score in the control group with increased demand of rescue opioid analgesic.

Pregabalin 150 mg group was associated with significant increased incidence of dizziness, headache and blurred vision than the control group ($P < 0.00$). However, these side effects were not significant clinically as the study is underpowered for side effects. These findings were in accordance with that of studies done by Jokela R et al⁸, Kholi M et al,¹⁶ Paul W et al²¹etc which used two pregabalin doses and stated that these side effects increased with increasing dose of the drug; and these were also reported in the pharmacology of pregabalin by Garaj M et al.¹⁷ Considering the above facts and discussion, pregabalin 150 mg will be an ideal dose in controlling post cholecystectomy pain relief with negligible side effects.

The study is not without its limitation. Patient controlled analgesia pump could have been incorporated for accurate determination of rescue analgesic consumption. Quality of analgesia should have been assessed by tools other than VAS such as Mc Gill pain questionnaire and patient satisfaction level should have been assessed. Study period should have extended beyond 24 hours as pregabalin attain steady state plasma concentration after 24 hours. Further studies may also be needed to determine its exact dose response effect.

CONCLUSION: It may be safely concluded that oral pregabalin 150 mgs administered 1 hour prior to surgery provided effective and adequate analgesia in the immediate 24 hours postoperatively. It also reduced the opioid related side effects without significant hemodynamic and systemic changes.

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Parameter	Control (n=40)	Pregabalin 150mg (n=40)	Statistical test value	P value
Age in years (Mean±SD)	35.47±7.54	35.17±7.13	t value of 0.18	0.86
Weight in Kgs (Mean±SD)	49.53±5.89	50.50±5.21	t value of 0.78	0.43
Sex	Male=10(25%) Female=30(75%)	Male=9(23%) Female=31(77%)	χ ² value of 0.07	0.79
ASA	I=37(93%) II=3(7%)	I=36(90%) II=4(10%)	χ ² value of 0.16	0.69
Duration of surgery (in minutes)	39.70±2.07	39.80±2.16	t value of 0.21	0.83

Table 1: Showing the distribution and comparison of patient's demographic profile, ASA and duration of surgery in the two groups

Time intervals	Control (n=40) (M±SD) Static	Control (n=40) (M±SD) Dynamic	P150 (n=40) (M±SD) Static	P150 (n=40) (M±SD) Dynamic	t value Static	t value Dynamic	P value
0 hour	5.65±0.58	6.65±0.58	0.00±0.00	0.08±0.27	61.65	65.18	0.000*
1 hour	5.23±0.62	6.23±0.62	0.00±0.00	0.45±0.51	53.32	45.73	0.000*

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2 hours	4.98±0.48	5.98±0.48	0.20±0.45	0.88±0.72	48.10	37.18	0.000*
4 hours	4.83±0.45	5.82±0.45	0.63±0.45	1.55±0.60	40.06	36.29	0.000*
6 hours	4.78±0.43	5.78±0.42	1.05±0.27	2.05±0.39	41.00	41.00	0.000*
8 hours	4.70±0.46	5.70±0.46	1.30±0.49	2.28±0.51	30.97	31.56	0.000*
12 hours	4.49±0.51	5.50±0.55	1.63±0.46	2.63±0.54	24.36	23.49	0.000*
18 hours	4.20±0.56	5.23±0.58	1.70±0.36	2.68±0.53	20.68	20.67	0.000*
24 hours	3.60±0.63	4.63±0.63	0.78±0.46	1.63±0.59	21.64	22.10	0.000*

Table 2: Showing the distribution and comparison of postoperative static and dynamic visual analog scale (VAS) score at different time points in the two groups(Score from 0 to 10cms)

*= Highly significant

	Control (n=40) (Mean±SD)	Pregabalin 150mg(n=40) (Mean±SD)	t value	P value
Analgesic free time interval (in hours)	0.09±0.11	11.31±0.75	93.00	0.000*
Number of rescue analgesic	3.25±0.44	1.08±0.27	26.80	0.000*

Table 3: Showing the distribution and comparison of analgesic free time interval and number of rescue analgesic in the two groups

*= Significant

Side effects	Control (n=40) (Mean±SD)	Pregabalin 150mg(n=40) (Mean±SD)	X² value	P value
Vomiting	Yes=10(25%) No=30(75%)	Yes=2(5%) No=38(95%)	6.28	0.01*
Nausea	Yes=12(30%) No=28(70%)	Yes=3(7.5%) No=37(92.5%)	6.64	0.01*
Dizziness & Headache	Yes=2(5%) No=38(95%)	Yes=8(20%) No=32(80%)	4.11	0.04*
Visual disturbances	Yes=0(0%) No=40(100%)	Yes=6(15%) No=34(85%)	6.49	0.01*

Table 4: Showing the distribution and comparison of side effects in the two groups postoperatively

*= Significant

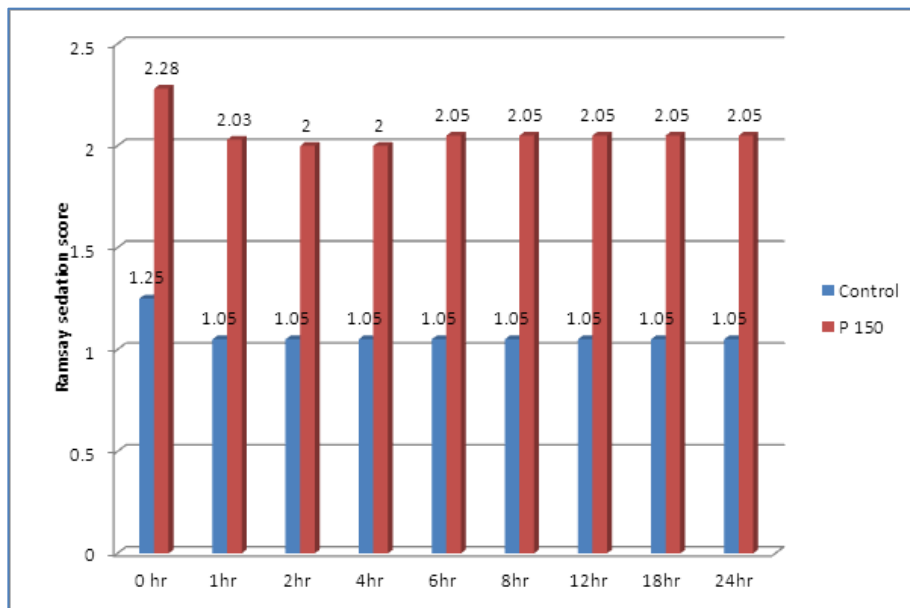


Fig 1: showing the distribution of Ramsay sedation score in the two groups at different time points

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