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Original Research Article

Pregabalin for Post-Cholecystectomy Pain Relief- A Study on the Response of Two Different Doses

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ABSTRACT

Objectives: Many studies have demonstrated the role of pregabalin as a pre-emptic analgesic in the multimodal therapy for acute postoperative pain management. However, there are limited trials regarding its use in more painful operative procedures like open cholecystectomy and determination of its dose response effect. So, the present study was undertaken to evaluate the effectiveness of a single dose of preoperative oral pregabalin in attenuating the postoperative pain and to determine the quality of analgesia with two different doses of pregabalin.

Materials & methods: In this randomized, controlled, prospective and double blinded study, 120 patients (ASA I & II, age 18-55 years and of both sexes) undergoing open cholecystectomy under GA were divided into three equal groups (n=40) to receive oral pregabalin 150mg or 300 mg or placebo 1 hour before the surgery. Intraoperative haemodynamic variables, postoperative VAS score, sedation score, analgesic free time intervals, total dose of rescue analgesic, side effects, etc. were recorded and compared for the first 24 hours postoperative.

Results: VAS score distributions within the 24 hours were comparable in the two pregabalin groups (P>0.05) but higher in the control group (P<0.05). The analgesia free time interval and the number of rescue analgesic(inj. Tramadol 50mg) in the pregabalin 150mg, 300 mg and control groups were 11.31± 0.75, 11.16 ±0.73 & 0.09 ±0.11hours and 1.08± 0.27, 1.13± 0.33 &3.25± 0.40 times respectively(P<.05). Sedation and side effects like visual disturbances & dizziness were more with the pregabalin 300mg (P<.05)

Conclusion: Pregabalin 150 mg will be the ideal dose for controlling post-cholecystectomy pain. Pregabalin 300mg provides equal analgesic quality but at the cost of increased sedation and side effects.

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 in17-41% 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 anaesthetics, 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 gabalin 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 α_2-δ (type I) receptor in the central nervous system. Binding of pregabalin to the α_2-δ (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 neurotransmitter 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]

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 gabapentin [5] 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 surgery [6], spinal fusion surgery [7], laparoscopic hysterectomy, day case gynaecological laparoscopic surgery [8], laparoscopic cholecystectomy [9] etc. None of these trials have investigated the role of pre-operative administration of pregabalin in attenuating post-operative pain and its dose response effect in more painful operative procedure like open cholecystectomy, which is one of most common operations performed in our Institute. The present study was, therefore, designed to evaluate the effects of two different doses of pre-operative oral pregabalin in attenuating the post-operative pain and thereby reduce 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 Anaesthesiology, at a tertiary care centre, Imphal from October 2011 to February 2013. After getting approval from the Institutional Ethics Committee and written informed consent for participation of the study from the patients, one hundred and twenty (120) 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) inscision of about 2 inches under general anaesthesia patients were randomly allocated by computer generated randomization schedule in the three groups of 40 patients each, which were blinded to both the patient and anaesthesiologist as: -

Group C (Control)– received oral placebo capsule one hour before the surgery.

Group P1 (Study) – received oral Pregabalin capsule 150 mg one hour before
the surgery.

Group P2 (Study– received oral Pregabalin capsule 300 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. associated with the study.

Pain was assessed by Visual Analogue Scale (VAS) score [10] and sedation by Ramsay sedation score [11] 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.

A uniform anaesthetic technique was maintained in all the patients. All the patients were premedicated with oral tab. alprazolam 0.5mg and tab. ranitidine 150mg on the night before the surgery. In the pre-operative room, either a placebo capsule or a pregabalin capsule 150mg or 300mg was administered orally, one hour before the induction of anaesthesia with sips of water by a person who were not involved in the study. 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. Anaethesia was induced with Inj propofol (2mg/kg) and laryngoscopy and intubation was facilitated with intravenous bolus inj.suxamethonium (1.5mg/kg) and anaesthesia maintained on oxygen with nitrous oxide (40:60) along with Inj. propofol infusion (100µg/kg/min). Intermittent positive pressure ventilation was used for ventilation and inj vecuronium as muscle relaxant intraoperatively.

The intra-operative parameters such as heart rate, blood pressure and SPO_2 were recorded for every 5 minutes for the first 15 minutes, then at intervals of 10 minutes till the end of surgery and the duration of surgery was noted. Neuromuscular paralysis was antagonized with intravenous Inj. neostigmine 0.05mg/kg and Inj. glycopyrrolate 0.01mg/kg and after satisfactory recovery; patients were extubated and shifted to the post-anaesthetic care unit (PACU) for observation.

The Visual Analogue Scale (VAS) score and Ramsay's sedation score were recorded in the PACU 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 such as nausea, vomiting, headache, dizziness, somnolence, peripheral edema, etc. if any, were also recorded.

Sample size calculation was calculated based on two independent similar studies with the use of preoperative pregabalin 150mg and 300mg for controlling postoperative pain, conducted by Agarwal A et al [9] and Saraswat V et al [12] respectively. For the results to be statistically significant with α=0.05 and power of 80% we need to recruit 35 patients in each group. Considering any dropouts, we had enrolled 40 patients in each group. The parameters recorded were entered on a computer and compared between the three groups using one way ANOVA test for continuous variables, χ^2 test for categorical variables, Student's 't' test for continuous variables in between any of the two groups, etc and $P \leq 0.05$ is deemed significant. Statistical Package for Social Sciences (SPSS) version 19.0 software for Windows was used for statistical analysis.

RESULTS

A total of 120 patients, 40 patients in each group were included and analysed for the study. There were no significant differences in age, weight, sex, ASA status, duration of surgery in the three groups and were comparable(P>0.05).(Table 1) The intraoperative haemodynamics parameter such as mean arterial pressure, heart rate and percentage saturation of oxygen were also comparable in the three groups (P>0.05).

Table 1 showing the distribution and comparison of patients demographic profile, ASA and duration of surgery in the three groups.

Parameter	Control(n=40)	Pregabalin 150mg (n=40)	Pregabalin 300mg (n=40)	Statistical test value	P value
Age in years (Mean±SD)	35.47±7.54	35.17±7.13	36.55±7.14	F value of 0.40	0.67
Weight in Kgs (Mean±SD)	49.53±5.89	50.50±5.21	49.95±5.27	F value of 0.32	0.73
Sex	Male=10(25%) Female=30(75%)	Male=9(23%) Female=31(77%)	Male=10(25%) Female=30(75%)	χ^2 value of 0.09	0.96
ASA	I=37(93%) II=3(7%)	I=36(90%) II=4(10%)	I=36(90%) II=4(10%)	χ^2 value of 0.20	0.91
Duration of surgery (in minutes)	39.70±2.07	39.80±2.16	40.25±2.23	F value of 0.74	0.48

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

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	P 300 (n=40) (M±SD) Static	P 300 (n=40) (M±SD) Dynamic	F value Static	F value Dynamic	P value
0 hour	5.65±0.58	6.65±0.58	0.00±0.00	0.08±0.27	0.05±0.22	0.05±0.22	3801	3809	0.000*
1 hour	5.23±0.62	6.23±0.62	0.00±0.00	0.45±0.51	0.05±0.22	0.55±0.50	2844	1471	0.000*
2 hours	4.98±0.48	5.98±0.48	0.20±0.45	0.88±0.72	0.28±0.45	1.05±0.75	1500	765	0.000*
4 hours	4.83±0.45	5.82±0.45	0.63±0.45	1.55±0.60	0.73±0.45	1.70±0.52	1070	858	0.000*
6 hours	4.78±0.43	5.78±0.42	1.05±0.27	2.05±0.39	1.08±0.27	2.10±0.30	1374	1296	0.000*
8 hours	4.70±0.46	5.70±0.46	1.30±0.49	2.28±0.51	1.38±0.49	2.38±0.49	626	640	0.000*
12 hours	4.49±0.51	5.50±0.55	1.63±0.46	2.63±0.54	1.80±0.46	2.80±0.46	401	382	0.000*
18 hours	4.20±0.56	5.23±0.58	1.70±0.36	2.68±0.53	1.85±0.36	2.83±0.38	329	324	0.000*
24 hours	3.60±0.63	4.63±0.63	0.78±0.46	1.63±0.59	0.88±0.46	1.73±0.51	344	350	0.000*

*= Highly significant

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 two pregabalin

groups recorded comparable insignificant lower VAS score with mean range score of 0 to 1cm and 0 to 3 cms for static and dynamic VAS respectively. (Table 2)

The sedation score as measured by Ramsay sedation score (RSS) at different time points recorded least (mean score range of 1 to 1.25) in the control group followed by pregabalin 150mg group with a mean score range of 2 to 2.28, whereas it is highest in the pregabalin 300mgs group (mean score range of 2.55 to 4) which decreases gradually in due course of time ($P<0.05$). However, as the control and pregabalin 150 mgs groups have lower RS score, pregabalin 150 mgs does not produce any significant clinical sedation. (Table 3)

Table 3 showing the distribution & comparison of postoperative Ramsay sedation score at different time points in the three groups (score from 1 to 6).

Time intervals	Control (n=40) (Mean±SD)	Pregabalin 150mg(n=40) (Mean±SD)	Pregabalin 300mg(n=40) (Mean±SD)	F value	P value
0 hour	1.25±0.44	2.28±0.45	4.00±0.00	584.1	0.000*
1 hour	1.05±0.22	2.03±0.16	4.00±0.00	11160	0.000*
2 hours	1.05±0.22	2.00±0.00	3.40±0.50	708.5	0.000*
4 hours	1.05±0.22	2.00±0.00	3.03±0.16	4921	0.000*
6 hours	1.05±0.22	2.05±0.22	3.00±0.00	1171	0.000*
8 hours	1.05±0.22	2.05±0.22	3.00±0.00	1171	0.000*
12 hours	1.05±0.22	2.05±0.22	3.00±0.00	1171	0.000*
18 hours	1.05±0.22	2.05±0.22	3.00±0.00	1171	0.000*
24 hours	1.05±0.22	2.05±0.22	2.55±0.82	291.91	0.000*

*= Highly significant

Table 4 showing the distribution and comparison of analgesic free time interval and number of rescue analgesic in the three groups.

	Control (n=40) (Mean±SD)	Pregabalin 150mg(n=40) (Mean±SD)	Pregabalin 300mg(n=40) (Mean±SD)	F value	P value
Analgesic free time interval (in hours)	0.09±0.11	11.31±0.75	11.16±0.73	4457	0.000*
Number of rescue analgesic	3.25±0.44	1.08±0.27	1.13±0.33	492.4	0.000*

*= Significant

Table 5 showing the distribution and comparison of side effects in the three groups postoperatively

Side effects	Control (n=40) (Mean±SD)	Pregabalin 150mg(n=40) (Mean±SD)	Pregabalin 300mg(n=40) (Mean±SD)	χ^2 value	P value
Vomiting	Yes=10(25%) No=30(75%)	Yes=2(5%) No=38(95%)	Yes=3(7.5%) No=37(92.5%)	8.69	0.01*
Nausea	Yes=12(30%) No=28(70%)	Yes=3(7.5%) No=37(92.5%	Yes=2(5%) No=38(95%)	12.47	0.002*
Dizziness & Headache	Yes=2(5%) No=38(95%)	Yes=8(20%) No=32(80%)	Yes=18(45%) No=22(55%)	18.26	0.000*
Visual disturbances	Yes=0(0%) No=40(100%)	Yes=6(15%) No=34(85%)	Yes=17(42.55% No=23(57.5%)	24	0.000*

*= Significant

The mean postoperative rescue analgesic free time interval in the control group was 0.09±0.11 hours as compared with pregabalin 150mgs and pregabalin 300 mgs which recorded insignificant($P>0.05$) comparable maximum time interval of 11.31±0.75 hours and11.16±0.73 hours respectively.(Table 4) The control group also recorded significant maximum number of postoperative rescue analgesic (3.25±0.44) as compared with the two pregabalin groups which recorded least number of rescue analgesics with 1.08±0.27 and 1.13±0.33 respectively and the two groups are comparable ($P>0.05$).

The control groups recorded more significant number of patients with nausea and vomiting than the two pregabalin groups

which recorded comparable lower number of patients.(Table 5) However, Pregabalin 300 mgs group recorded highest number of 18(45%) patients with postoperative dizziness and headache, followed by pregabalin 150mgs group (8,20%) and least in the control group (2,5%) (χ^2=18.26 and P value of 0.000). Also, the control group did not have any patients with postoperative visual disturbances whereas the two pregabalin groups had got 6(15%) and 17(42.55%) patients with such disorder in the 150 and 300mgs groups respectively (χ^2=24 and P value of 0.000). The intergroup comparison between any two groups also showed significant differences (P<0.05).

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. [13] 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][14,18]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][18] The conformational changes induced by this binding inhibit 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 three 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 pregabalin groups were compared with the control group. However, the two pregabalin groups showed comparable VAS score with no significant differences at different time points 24 hours post-operatively. This finding of pregabalin groups having significant lower VAS score as compared with the control are in agreement with the studies conducted by Agarwal A et al[9] with 150 mg of pregabalin for post laparoscopic cholecystectomy pain control, Hill CM et al [6] with 50 and 300 mg pregabalin in dental pain model, Kim SY et al [15] with 150 mg of pregabalin in robot

assisted thyroidectomy, Wichai I et al [14] with 300 mg of pregabalin and Kholi M et al [17] with 150 mg and 300 mg of the drug in lower abdominal surgeries. Contradictory results were reported by Mathiesen O et al [19], 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 [20], which 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 al [21] 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 two pregabalin groups were significantly longer than the control group(<1 hour). The numbers of rescue analgesic were also comparable in the two pregabalin groups and significantly lesser than the control group (F=4457 and P=0.000). These findings are supported by studies of Sahu S et al [16] (7.6 hours) and Saraswat V et al [12] (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.

The sedation score, as measured with the Ramsay sedation score was least with the control group and maximum with the pregabalin 300 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] So, pregabalin 300 mg(mean RS score range of 2.5 to 4) was associated with increased significant sedation than 150 mg group (P<0.05), even though they had comparable VAS score distribution. These findings are corroborated with that of independent studies involving 150 mg and 300 mg of pregabalin by Jokela R et al [8], Paul FW et al [21], Kholi M et al [17], etc.

The haemodynamic changes in the three groups were comparable and statistically not significant. Our findings are consistent with that of the independent studies conducted by Kholi M et al [17], Ruben SS et al [7], Buvanendren A et al [23], etc, 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 haemodynamic 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 two pregabalin groups as compared with the control which recorded increase incidence, and the same had been reported on different independent studies of Paul FW et al [21], Wichai I et al[14], etc. This may be explained on the association of greater VAS score in the control group with increased demand of rescue opoid analgesic. However, comparable incidence of nausea and vomiting episodes were reported in the two pregabalin groups.

Pregabalin 300 mg group was associated with significant increased incidence of dizziness, headache and blurred vision than the 150 mg group (P<0.00), and was negligible in the control group. These findings were in accordance with that of studies done by Jokela R et al [8], Kholi M et al [17], Paul FW et al [21], etc which used the same 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. [18]

Our study recorded comparable VAS score in both the pregabalin groups, which is in contrast to the study conducted by Jokela R et al [8] and Kholi M et al [17] where they found that 300mg of pregabalin was more effective than 150mg at the cost of increased sedation and side effects. 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.

CONCLUSION

We can safely conclude that oral pregabalin when administered 1 hour before surgery proved to be effective and adequate for postoperative analgesia in the immediate 24 hours postoperatively with lesser requirement of rescue analgesic thereby produced less opoids related side effects and without any significant haemodynamic and other systemic changes. The pregabalin 300 mg group was associated with more of its side effects than the 150 mg group significantly, even though they had comparable analgesic quality and duration. Thus, pregabalin 150 mg can be considered as a safe and ideal dose for controlling post-cholecystectomy pain.

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