Original Article

Comparison of Two Preoperative Doses of Pregabalin for Attenuation of Postoperative Pain after Laparoscopic Cholecystectomy

Pratibha S[1], Ranjan Ramakrishna[1], Sunil Vasudeva Rao[1*]

Abstract

Background: Pregabalin is a novel drug used as an adjunct to multimodal analgesia for reducing post-operative pain. We aimed to compare the efficacy and side effects of two different pre-emptive doses of pregabalin (75 mg vs. 150 mg) for attenuation of postoperative pain following laparoscopic cholecystectomy.

Materials and Methods: This was a prospective randomized study where 70 patients planned for elective laparoscopic cholecystectomy (LC) were enrolled and received a pre-emptive dose of oral pregabalin. Group A received 75 mg and Group B received 150 mg of Pregabalin (PGB) 1 hour before surgery. Assessment of static and dynamic pain was done at 0, 0-4, 4-8, 8-12, 12-16, 16-24 hours post-surgery using Visual Analog Scale (VAS) Score. Adverse effects like postoperative nausea and vomiting (0-6 hr), headache, sedation, and respiratory depression (0-24 hr) were assessed at regular intervals.

Results: There was no significant difference in static and dynamic pain perception at different timed intervals between the two groups. Even the total analgesic requirement in both groups was comparable. The incidence of Postoperative Nausea Vomiting (PONV) (p-value 0.04) and headache (P-value 0.034) were statistically significant in Group B when compared to Group A.

Conclusion: Preemptive PGB (75 mg) had a lesser incidence of PONV and headache. Therefore, from our results, we can conclude that a lower dose of PGB has lesser adverse effects, although the analgesic effects are comparable.

Keywords: Pregabalin, Laparoscopic cholecystectomy, Pre-emptive dose, Post-operative pain

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Introduction

Great progress was made in the direction of understanding the pathology and pharmacology of acute pain along with the improvement of surgical techniques. Pregabalin was initially approved for chronic neuropathic pain and partial seizure, but in the year 2001 beneficial effect of pregabalin for acute pain

was first published (1). Acute postoperative pain is still inadequately treated in nearly 20% of all surgical patients within the first 24 hours (2).

A multimodal approach can provide significant benefits including reductions in pain intensity, opioid requirements, and opioid-related adverse events (3). With the invention of laparoscopic surgeries, the Patients often experience lesser pain and scarring, a speedy recovery with LC when compared to traditional open surgery. Pre-emptive analgesia is initiated before surgery to prevent the establishment of central sensitization evoked by the traumatic and inflammatory injuries occurring during surgery and in the early postoperative period (4).

Pain in LC is a conglomeration of somatic pain caused by incision, deep intra-abdominal visceral pain, and referred shoulder pain (5). The postoperative neuropathic pain generated is probably due to the elevated temperatures of electrical scalpels and intraoperative nervous fiber dissection (6). Therefore, nociceptive, inflammatory, and neuropathic mechanisms mediate the perception of postoperative pain. The mechanisms of pain vary between individuals and different operative procedures (7).

Various analgesic regimens and techniques are employed in multimodal opioid-sparing analgesia which targets multiple central and peripheral pain pathways. They act synergistically to enhance the analgesic requirement and minimize the dose of any single analgesic agent (8).

Unlike other laparoscopic procedures, pain in LC is quite complex requiring multimodal analgesia. As a part of a multimodal analgesic regimen, Pregabalin (PGB) has been proposed as an adjunct in multimodal postoperative analgesia management (9). PGB inhibits the neurotransmitter gamma-aminobutyric acid (GABA) (10). The tissue damage causes increased excitability of dorsal root neurons which is reduced with gabapentinoids (11). The α2δ1 subunit of calcium channels which are voltage-gated is bound by PGB and Gabapentin, which is a predecessor of PGB (10). It is expeditiously and extensively absorbed following oral intake, with maximum plasma concentration at one hour following solitary or multiple doses. The oral bioavailability is 90% and is not related to the dosage.

Most anesthesiologists and surgeons lately, rely on multimodal analgesia to manage postoperative pain effectively. Various research studies have been conducted in the past to explore the effectiveness of high-dose PGB in LC. Even though there have been positive outcomes, studies were hindered due to the high incidence of adverse effects like headache, dizziness, and sedation to name a few. There are very few studies available to prove the efficacy of low-dose PGB for attenuation of pain following LC. Henceforth, we conducted a research study to analyze the effective dose of PGB to which patients are more amenable.

Methods

After obtaining approval from Ethical Committee, Kasturba Medical College, Mangaluru (Coded IEC KMC MLR 10-17/211, October 17, 2017), and written informed consent from the patients, the prospective randomized clinical study was carried out on 70 patients admitted to a tertiary health care center to undergo laparoscopic cholecystectomy from September 2017 to June 2019, based on the CONSORT patient flow chart (Figure 1).

The sample size was selected with 95% confidence level and 90% power regarding P75 duration of the surgery, with the mean difference with the relative risk of 10%, sample size comes to be 35 per group i.e. 70.

$$\eta = \frac{(Z\alpha)^2\sigma^2}{d^2}$$

Zα= 1.96 at 95% confidence interval,
σ= combined SD,
d= mean difference with the relative risk of 10%

At the end of the study, all data were compiled systematically and analyzed using mean, the standard deviation was estimated, cross-tabulations were done. The categorical variable was analyzed using the Chi-square test and the Continuous variable was calculated using the Student t-test using SPSS 17.0 (SPSS Inc. 233 South Wacker Drive, 11th Floor, Chicago, IL 60606-6412) for windows. Value of $P<0.05$ is considered significant and $P<0.0001$ is highly significant.

70 cases are randomized into two equal groups A and B of 35 each who fulfill the inclusion-exclusion

criteria was done using a sealed envelope system. The inclusion criteria included: ASA physical status (PS) grade I and II, 18-60 years of age, patients of either sex and patients scheduled to undergo elective LC. However, exclusion criteria included patients belonging to ASA PS grade III and above, patients with hepatic or renal derangements, patients on anti-epileptic treatment, patients already on chronic NSAID medication, patients who refuse the study, or have known allergy and pregnant and pediatric patients.

Thorough pre-anesthetic evaluation, baseline vitals of pulse, blood pressure, respiratory rate, body mass index, and the result of routine investigations were noted. The planned anesthetic and induction techniques were detailed to the patient. Nil per oral orders was advised as per standard guidelines, after taking written and informed consent. Pre-medication with 150 mg oral ranitidine was given a night before surgery. In group A, 75 mg oral PGB was given 1 hour before surgery. In group B, 150 mg oral PGB was given 1 hour before surgery, respectively. Static and dynamic pain was evaluated at 0, 0-4, 4-8, 8-12, 12-16, 16-24 hours after surgery using VAS Score. Patients with pain corresponding to a score equal to or greater than 4mm at rest were provided rescue analgesia with injecting. Paracetamol (PCT) 1g over 15 to 20 minutes intravenously, followed by TID dose. The episode of PONV at 0-6 hours was treated with an injection, using 4 mg IV Ondansetron as rescue antiemetic. Headache, respiratory depression, and sedation as per Ramsay's sedation score were assessed for 0-24 hours.

Results

The mean age, sex, ASA status, and body mass index in Group A and B were comparable. The mean duration of surgery in Group A was 102.1 minutes and Group B 104.4 minutes. The p-value was 0.454, statistically not significant. The mean intraoperative intravenous fentanyl consumption in Group A was 127.86 mcg, which was comparable to Group B, 128.57 mcg, with a standard deviation of 34.18 and 23.59. The T-test p-value was 0.919, which is statistically not significant.

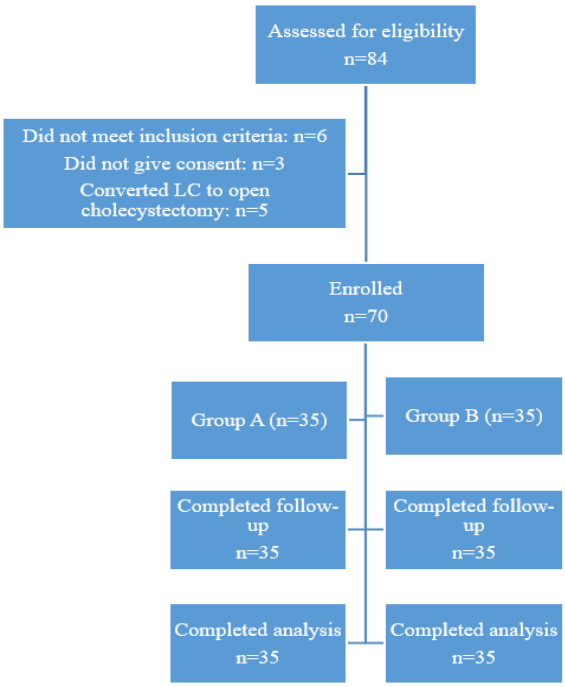

Figure 1. CONSORT Flow Chart depicting the study selection process.

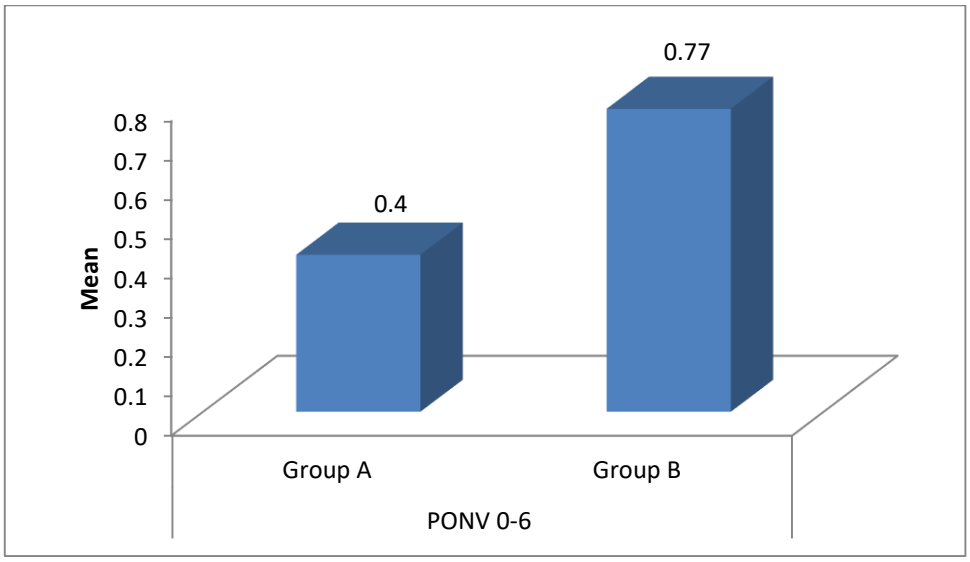

Figure 2. Incidence of PONV in the patients.

The VAS scores at rest i.e., Static measured at the end of 0, 0-4, 4-8, 8-12, 12-16, 16-24 hours, the highest mean score of 3.09 and 3.06 were at 0-4 hours before the administration of analgesic. The p-value was 0.703, comparable, between the groups and statistically not significant. The trend of VAS score between the two groups was comparable at respective time intervals.

The VAS scores on coughing i.e., Dynamic measured at the end of 0, 0-4, 4-8, 8-12, 12-16, 16-24 hours, the highest mean score of 4.06 and 3.91 were at 0-4 hours before the administration of analgesic. The p-value was 0.424, comparable between the groups and statistically not significant. The trend of VAS score amongst the two groups was comparable at respective time intervals. Intravenous paracetamol consumption was congruent between the groups with the mean value of 3.37 and 3.2g. It was statistically not significant with a p-value of 0.679.

The incidence of PONV at 0-6 hours was higher in Group B when compared to Group A with a mean of 0.77 and 0.40. It was statistically significant (Mannwhitney's test, P-value= 0.04; Figure 2).

40% of Group B patients complained of a headache when compared to 17% in Group A. This was statistically significant (Chi-square test, P-value=

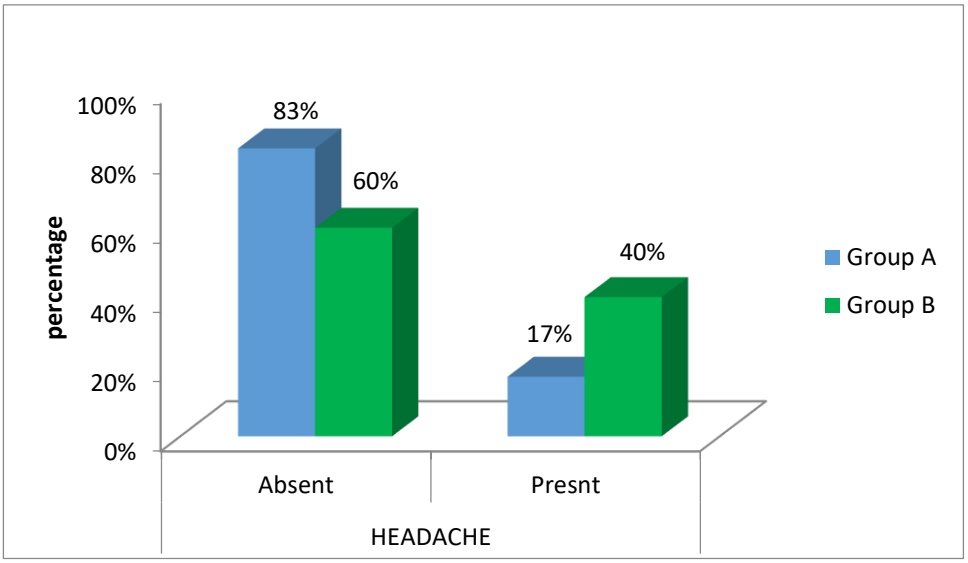

Figure 3. Headache in the patients.

0.034, Figure 3).

Ramsay sedation scores in the majority of the patients of both the groups were 2, i.e., cooperative, oriented with a mean of 82.86% in Group A and 62.86% in Group B. 8.57% of patients in either group were anxious and restless with a score of 1. 22.86% patients in group B responded to commands only when compared to 8.57% in Group A (Ramsay score 3). Only 5.71% of patients in Group B and none in Group A had a quick response to light tap over the glabella or loud sound (Ramsay score 4). Mann-Whitney's test p-value was 0.148, which was statistically not significant. Only 2.9% of patients (1 patient) in Group B had respiratory depression with no significance established with a p-value of 0.10.

Discussion

Laparoscopically executed surgeries have attained popularity in the recent few decades. According to numerous reports, LC offers remarkable advantages when compared to open cholecystectomy, and is the imminent standard operation for symptomatic gallstone disease. Studies have proved to show that there is a marked decrease in the span of hospitalization, the duration of recovery, and also the expenditure (12).

The incision preceded by pre-emptive analgesia pivots the postoperative pain management including a reduction in the consumption of analgesics, along with potent neuroprotective characteristics (12, 13). The purpose of multimodal analgesia is to enhance the level of analgesia and even to decrease opioid-related adverse effects (14). PGB has been known to have antihyperalgesic effects and decrements in central and peripheral sensitization following tissue or nerve injury (15, 16).

Our research study demonstrates the efficacy of two different pre-emptive doses of oral PGB 75mg (group A) and 150mg (group B) on the postoperative pain and analgesic requirement following elective LC under general anesthesia. It even elucidates the dose-related adverse effects of PGB. In our study, the highest VAS score at rest (static) of 3.09 was seen in group A patients between 0-4 hours which was comparable to group B with a static VAS of 3.06 at 0-4 hours. It was statistically not significant (p=0.703). Similarly, the VAS score on coughing (Dynamic) was highest at 0-4 hours in both the groups with scores of 4.06 and 3.91, respectively. As the p-value was 0.424, it did not show significance.

This accords with the research study conducted by Agarwal et al in 2008 where the single pre-emptive dose of 150 mg oral PGB reduced both static and dynamic pain post LC when compared with placebo, with the highest VAS score recorded at 0-4 hours. It was statistically significant (13). Peng et al performed a research study to analyze the effects of low-dose PGB in patients undergoing LC. When compared to the placebo and PGB 50mg groups, static and dynamic pain scores after surgery were lesser in the first 45 minutes and 90 minutes respectively, with PGB 75mg group (12). In contrast, Jokela et al found that static dynamic VAS scores for pain were lesser in the initial recovery following premedication with PGB 150mg when compared to PGB 75mg or diazepam 5mg, all combined with ibuprofen 800mg after gynecological laparoscopic surgery. VAS scale far pain was lesser in PGB 150 mg and statistically significant (14).

The mean total intravenous paracetamol consumption in Group A was 2.02g with a standard deviation of 0.8 when compared to 1.9g in Group B with a standard deviation of 0.72. It was statistically not significant (p=0.79). Agarwal et al demonstrated the decremented patient-controlled consumption of fentanyl with oral PGB 150mg in comparison with the placebo group which showed statistical significance ($p<0.05$) (13).

Even in the systematic review designed by Zhang et al to evaluate the efficacy of PGB in acute post-surgical pain, they found a significant reduction in opioid usage due to PGB administration in the first 24hours following surgery (17). In contrast, Hu et al who steered a research study to analyze the efficiency of one single dose of pre-emptive PGB and gabapentin in acute post-surgical analgesia management, found that there was a consistent decrease in 24- hour opioid consumption with an augmented dose of PGB and gabapentin. A higher dose (>150mg) of PGB was strikingly efficient in reducing pain score compared to 75mg for a 24-hour static pain score.

The occurrence of PONV was significant in Group B with a P-value of 0.04 (18). Likewise,

Agarwal et al found that the occurrence and grade of PONV and even the size of patients requiring anti-emetics were comparable among PGB 150mg and placebo group, p-value > 0.05 (13). Furthermore, Hu J et al had similar findings in their studies where the overall occurrence of PONV was decremented in the PGB group contrary to the control group and Gabapentin group. Nevertheless, PGB 150 mg had a higher incidence of PONV when compared to PGB 75mg, but it was statistically not significant (18).

The occurrence of headache was remarkably high in group B in contrast to Group A, with a p-value of 0.034. Similarly, Chang S.H et al found that the incidence of headache was more in PGB 150 mg compared to the placebo group (15). Whereas Jokela R et al found the incidence of a headache to be higher in PGB 75mg when compared to PGB 150mg but it was statistically not significant (14).

The incidence of respiratory depression, sedation was comparable between both groups A and B. Peng P.W.H, et al also found that occurrences of blurred vision and sedative effect were more in the PGB group 50mg as well as 75mg compared to the placebo group (12).

It was a single-blind study; Therefore, observer bias may play a vital role in assessing the clinical assays. There was considerable dependence on the patient to assess various clinical parameters, which might add to bias.

Conclusion

Pre-emptive doses of PGB 75 mg and 150 mg did not have any significant difference in VAS score for attenuation of pain post LC. PGB 75mg had lesser side effects of PONV and headache. Therefore, from our results, we can conclude that a lower dose of PGB has lesser adverse effects, although the analgesic effects are comparable.

Acknowledgment

None.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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