Effect of Pregabalin Premedication on the Requirement of Anesthetic and Analgesic Drugs in Laparoscopic Cholecystectomy: Randomized Comparison of Two Doses

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Background: Preoperative medication has a vital role in anesthesia. Pregabalin (PG) is a newer drug of gabapentinoid class and is six times more potent than gabapentin. Our study was designed to evaluate the effect of PG as premedication on the perioperative anesthetic requirement and analgesia. Materials and Methods: The study was conducted on ninety patients of American Society of Anesthesiologists Grade I and II of age group 20–60 years, allocated to one of the three groups of thirty patients each. Group I received tablet diazepam 10 mg HS and 5 mg 1 h before surgery, Group II received capsule PG 75 mg HS and 150 mg 1 h before surgery, and Group III received capsule PG 75 mg HS and 300 mg 1 h before surgery. Patients were induced with injection fentanyl citrate, thiopentone sodium, and rocuronium bromide and maintained by 66% N₂O + 33% O₂ gas mixture with sevoflurane and intermittent boluses of fentanyl. Results: Perioperative consumption of thiopentone sodium was 5.59 ± 0.49 mg/kg in Group I, 4.29 ± 0.53 mg/kg in Group II, and 4.06 ± 0.59 mg/kg in Group III; fentanyl was 1.55 ± 0.42 μg/kg in Group I, 1.00 ± 0.00 μg/kg in Group II, and 1.05 ± 0.20 μg/kg in Group III; sevoflurane (%) was 1.20 ± 0.31 in Group I, 0.933 ± 0.25 in Group II, and 1.00 ± 0.00 in Group III. Perioperative requirement of thiopentone sodium, opioid, and inhalational agent was significantly less in Group II and III when compared with Group I. Maximum number of patients required postoperative rescue analgesia within 0–2 h of surgery in Group I, 2–4 h of surgery in Group II, and 6–8 h after surgery in Group III. Patients were more comfortable and asleep with a longer pain-free postoperative period in PG groups. Conclusion: PG premedication effectively reduced the consumption of all anesthetic agents during induction and maintenance of anesthesia as compared to diazepam. Patient’s postoperative comfort and pain-free duration were also greater with PG 300 mg as compared to PG 150 mg.

Keywords: Anesthetic drugs sparing, laparoscopic surgery, pregabalin premedication
Materials and Methods
After clearance from the Institutional Ethics Committee and written informed consent from all subjects, a double-blind randomized controlled trial was conducted on ninety American Society of Anesthesiologists I/II patients aged 20–60 years, scheduled for laparoscopic cholecystectomy under general anesthesia. Patients with impaired hepatic and renal function, cardiovascular disorders, on calcium channel blockers, antidepressants and oral hypoglycemic agents, drug allergy, and pregnant were excluded from the study. Randomization was done using random number table generated from computer software. Random drug/placebo assignment in three groups was placed in serially numbered, opaque, sealed, and identical envelopes by one of the senior anesthesiologists who was not involved with the study. For external uniformity of drugs, diazepam tablets were put inside empty capsules. The anesthesiologist administering drug/conducting anesthesia was blinded to drug administered patients were equally divided into three groups and were premedicated as per group allotted:

- **Group I (Diaz):** Tablet diazepam 10 mg HS and 5 mg 1 h before surgery
- **Group II (PG 150):** Capsule PG 75 mg HS and 150 mg 1 h before surgery
- **Group III (PG 300):** Capsule PG 75 mg HS and 300 mg 1 h before surgery.

General anesthesia was induced with fentanyl citrate (1 μg/kg), thiopentone sodium (till abolition of eyelash reflex), and rocuronium bromide (1 mg/kg). Laryngoscopy and intubation were done after 90 s and hemodynamic parameters recorded. No surgical intervention was allowed till 15 min after intubation. N₂O (66%), O₂ (33%), sevoflurane (1%), and injection rocuronium (0.2 mg/kg) were used for maintenance of anesthesia. An increase in pulse rate and blood pressure (>20%), lacrimation and sweating in the presence of normal end-tidal carbon dioxide were treated with additional dose of fentanyl (0.5 μg/kg). Response was checked after 10 min; nonresponders were managed by incremental increase of sevoflurane till hemodynamic normalization. Patients were reversed and extubated at the end of surgery. Sevoflurane concentration which was needed constantly for more than 50% duration of surgery was taken as concentration needed for intraoperative period. Perioperative consumption of anesthetic drugs was noted.

Preoperative and postoperative sedation was assessed in all the three groups using five-point scale [Table 1]. Heart rate and blood pressure (systolic, diastolic, and mean arterial pressure) were recorded before premedication, at induction, immediately (0 min) and 1, 3, 5, 10, and 15 min after laryngoscopy, at skin incision, start of pneumoperitoneum, and every 15 min thereafter till completion of surgery. Electrocardiogram, oxygen saturation, and end-tidal carbon dioxide were also monitored continuously throughout the procedure.

Postoperative pain was assessed by visual analog score (VAS). Patients were provided rescue analgesia when VAS was ≥6. Time for first postoperative rescue analgesia was recorded.

Assuming a 5% dropout rate, the final sample size was set at ninety patients which would permit a type I error of α to be 5%, with a type II error of β to be 50%, and power of 80%. The results obtained were presented in tabulated form, and statistical analysis was performed using the IBM Statistical Package for Social Sciences (SPSS), Windows version 20. Data were analyzed using Mann–Whitney, Chi-square, ANOVA, Kruskal–Wallis, and t-tests as appropriate. *P < 0.05 was considered statistically significant and *P < 0.01 as highly significant. The failure rate of drug was defined as >30% increase in hemodynamic parameters from the baseline values.

Results
Demographic data, duration of laryngoscopy, and duration of surgery were comparable [Table 2]. Although female patients dominated in all the three groups, sex distribution was comparable.

Preoperative and postoperative sedation levels were lowest in Group III followed by Group II and highest in Group I; difference was statistically significant with *P < 0.001 and *P < 0.01, respectively [Table 3].

| Table 1: Five-point sedation scale |
|-----------------------------------|
| Score 1 (barely arousable): Asleep, needs shaking or shouting to arise |
| Score 2 (asleep): Eyes closed, arousable with soft voice or light touch |
| Score 3 (sleepy): Eyes opened, less active, and responsive |
| Score 4: Awake |
| Score 5: Agitated |

| Table 2: Patient characteristics |
|---------------------------------|
| Group I | Group II | Group III | *P* |
| Age (years) | 34.97±11.95 | 35.50±9.46 | 36.97±8.22 | 0.73 |
| Weight (kg) | 53.47±12.32 | 53.83±9.79 | 58.33±10.91 | 0.17 |
| Sex (female/male) | 29/1 | 27/3 | 25/5 | 0.23 |
| Duration of laryngoscopy (s) | 10.10±1.73 | 10.40±1.59 | 10.30±1.68 | 0.46 |
| Duration of surgery (min) | 67.33±30.33 | 68.33±29.49 | 71.67±27.92 | 0.91 |

| Table 3: Preoperative and postoperative sedation scores |
|-------------------------------------------------------|
| Sedation score | Group I | Group II | Group III | *P* |
| Preoperative Range | 4-4 | 3-4 | 2-4 | 0.000 |
| Mean±SD | 4.00±0.00 | 3.37±0.49 | 2.77±0.73 |
| Postoperative Range | 2-5 | 2-5 | 2-4 |
| Mean±SD | 4.17±0.37 | 4.17±0.37 | 3.03±0.71 | 0.000 |

SD=Standard deviation
Consumption of all anesthetic agents used in the study, i.e., thiopentone, fentanyl, and sevoflurane was less in PG groups (II and III) as compared to diazepam group. This decreased consumption was highly statistically significant when Group II and III were compared to Group I, and statistically insignificant when Group II was compared to Group III [Table 4].

Maximum patients (80%) who received diazepam required rescue analgesia in <2 h. In PG 150 and 300 group, majority require rescue in 2–4 h (43.3%) and 6–8 h (33.3%), respectively [Table 5].

Only one patient in PG 150 group and two patients in PG 300 group suffered dizziness which was statistically insignificant.

**DISCUSSION**

PG is a new synthetic molecule and a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid. It is an \(\alpha_2-\delta\) ligand that has analgesic, anticonvulsant, anxiolytic, and sleep-modulating activities. PG binds potently to the \(\alpha_2-\delta\) subunit of calcium channels, resulting in a reduction in the release of several neurotransmitters including glutamate, noradrenaline, serotonin, dopamin, and substance P.[3]

PG as premedication has been previously studied in attenuating the laryngoscopy response and prolongation of postoperative analgesia. There is no consensus on the optimum dose of PG.

**Table 4: Drugs administered for anesthesia**

| Drug          | Range (mg/kg) | Mean±SD | \(P\)   |
|---------------|---------------|---------|---------|
| Thiopentone   |               |         |         |
| Group I       | 5-6.8         | 5.59±0.49 | 0.000   |
| Group II      | 3.7-5.8       | 4.29±0.53 | 0.000   |
| Group III     | 3.2-5.8       | 4.06±0.59 | 0.095   |
| Fentanyl      |               |         |         |
| Group I       | 1-2           | 1.55±0.42 | 0.000   |
| Group II      | 1-2           | 1.00±0.00 | 0.000   |
| Group III     | 1-2           | 1.05±0.20 | 0.000   |
| Sevoflurane   |               |         |         |
| Group I       | 1-2           | 1.20±0.31 | 0.000   |
| Group II      | 0-1           | 0.933±0.25 | 0.001  |
| Group III     | 0-1           | 1.00±0.00 | 0.000   |

SD=Standard deviation

**Table 5: Requirement of rescue analgesia in various groups during immediate postoperative period**

| Range (h) | Number of patients (%) |
|-----------|-------------------------|
|           | Group I | Group II | Group III |
| 0-2       | 24 (80) | 5 (16.6) | 2 (6.6)   |
| 2-4       | 6 (20)  | 13 (43.3)| 2 (6.6)   |
| 4-6       | 0       | 7 (23.3) | 7 (23.3)  |
| 6-8       | 0       | 3 (10)   | 10 (33.3) |

Analgesc efficacy with dose ranges from 50 to 300 mg of PG has been established. Evidence suggests that doses below 150 mg are sedative and anxiolytic but not good analgesic.[4] Higher doses (>300 mg) have however been associated with side effects such as dizziness and lightheadedness. Thus, we used 75 mg night before surgery and 150 and 300 mg on the day of surgery.[5]

The present study was undertaken to evaluate the anesthetic dose-sparing effect of two different doses of PG 150 and 300 mg as premedication, as compared to diazepam. There were no significant differences between the three groups with respect to mean age, weight, and sex of patients. The duration of laryngoscopy and duration of surgery were comparable and statistically nonsignificant among all the three groups.

Consumption of intraoperative anesthetic drugs showed interesting trends. Thiopentone consumption (mg/kg) was 5.59±0.49 in Group I, 4.29±0.53 in Group II, and 4.06±0.59 in Group III. Intraoperative consumption of fentanyl was 1.55±0.42 µg/kg, 1.00±0.00 µg/kg, and 1.05±0.20 µg/kg in Group I, II, and III, respectively. Furthermore, sevoflurane (%) consumption (Group I = 1.20±0.31, Group II = 0.933±0.25, and Group III = 1.00±0.00) was more in diazepam group as compare to PG groups which were statistically significant.

The number of patients requiring postoperative rescue analgesia was maximum within 0–2 h of surgery in Group I, 2–4 h in Group II, and 6–8 h in Group III. This was statistically as well as clinically highly significant. Many workers have studied and reported the postoperative analgesic property of PG. Our results have similar findings with that of Jokela et al.,[6] Saraswat and Arora,[7] Peng et al.,[8] Patricia et al.,[9] Kim et al.,[10] Mathiesen et al.,[11] and Burke and Shorten.[12] All of them have reported the analgesic property of PG. All these findings suggest that oral PG reduces opioid consumption during intra- and post-operative period because of its anxiolytic, antinociceptive, and morphine-like activity. This effect is mainly because of central neuronal sensitization. PG’s antihyperalgesic effect result from its action on \(\alpha_2-\delta\) subunit of voltage-gated calcium channels, which are upregulated in dorsal root ganglia and spinal cord after peripheral injury.[13] Furthermore, PG causes modulation of both visceral sensitization and affective component of pain.

Sedation includes the whole spectrum of anxiety, amnesia, and hypnosis. There is very narrow margin between anxiety and sedation. Hence, we did not measure anxiety separately, and sedation was measured using a five-point sedation score. Patients were less apprehensive and well sedated in Group II (mean score = 3.37±0.490) and Group III (mean score = 2.77±0.728) as compared to Group I (mean score = 4.00±0.00) in preoperative period. The difference between Group II and Group III were also highly statistically significant (\(P<0.005\)).
The postoperative sedation scores immediately after extubation were $4.17 \pm 0.37$ in Group I, $3.53 \pm 0.62$ in Group II, and $3.03 \pm 0.71$ in Group III. These differences were highly significant in Group II and Group III as compared to Group I and also between Group II and Group III. This shows patient were more comfortable and asleep in PG groups (PG 300 > PG 150) as compared to Group I in which more number of patients were awake and agitated. These differences were significant statistically as well as clinically. In our study, we specifically observed that patients who received PG were very comfortable, well oriented, and responding to verbal commands with good recovery. Our results are in comparison with studies conducted by Pande et al.\textsuperscript{[14]} and Gonano et al.\textsuperscript{[15]} who studied the effect of oral PG on social anxiety disorder and on patients undergoing minor orthopedic surgery. Both of them concluded that PG reduces anxiety in an effective and well-tolerated manner.

Side effects in the form of dizziness, lightheadedness, confusion, and ataxia are described with PG in literature. However, in our study, only one patient in PG 150 group and two patients in PG 300 group suffered dizziness which was statistically insignificant.

**Conclusion**

Perioperative anesthetic drug consumption is reduced in a comparable manner by both the doses of PG, i.e., 150 and 300 mg. However, we recommend premedication with 75 mg of PG the night before and 300 mg 1 h before surgery as it significantly decreases postoperative analgesic consumption without causing any statistically significant rise in adverse effects. Ability to provide anxiolytic/sedation, reduction in perioperative anesthetic drug requirement and postoperative analgesic action was significantly greater with PG as compared to diazepam.

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**Conflicts of interest**

There are no conflicts of interest.