

## Comparative evaluation of two doses of pregabalin as oral premedication for laparoscopic sterilisation with respect to analgesic efficacy and time to discharge

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### Abstract

**Introduction:** Pain management plays a very important role in recovery after ambulatory surgery and any delay in the time to discharge may lead to logistic problems associated with increased hospital stay for a day care procedure. A higher dose of opioid may be needed for better analgesia which may lead to complications such as respiratory depression, nausea, vomiting. Newer drugs and agents are being used to prevent such complications and decrease hospital stay post procedure. We present a study where preemptive use of two doses of Pregabalin, 75mg and 150mg was evaluated not only for its analgesic efficacy but also to ascertain comparative effects on the time to discharge in patients undergoing laparoscopic sterilisation.

**Observations and Results:** Hundred patients included in the study, were comparable with respect to age, ASA physical status, educational status and body mass index. The VAS score at rest at 2,3 and 4hours post-surgery was significantly less in the P150 group as analyzed by the Mann Whitney test (p value of 0.001 for each recording). We found that 150 mg pregabalin delays the need for first rescue analgesic administration even though clinically both doses were comparable. The time to discharge between the two groups as per the Post Anaesthesia discharge scoring system (PADSS) was comparable.

**Conclusion:** The multimodal approach to analgesia especially in day care surgeries have not only reduced the time to discharge but also improved patient outcome. This has become possible by using certain adjuvant drugs with analgesic effects that have proven to be beneficial in preventing central sensitisation. We report that Preemptive Pregabalin 150mg has a better VAS scores for pain at rest and mobilisation after laparoscopic sterilisation and also did not delay the time to discharge.

### Introduction

Provision of effective analgesia for the surgical patient is one of the most important aspects of anaesthesiology practice. An increasing percentage of surgical procedures are being performed on an outpatient basis, as ambulatory surgery can offer a number of advantages for patients, health care providers, third party payers and even hospitals.

Laparoscopy, being minimally invasive involves insufflation of the abdomen by gas, so that an endoscope is introduced through one or more ports to view the intra-abdominal contents without being in direct contact with the viscera or tissues. Laparoscopic tubal ligation is one of the most common gynaecologic operative procedure performed on an outpatient basis. Pain which occurs after this procedure is significantly less and of shorter duration than that caused by laparotomy. Nevertheless, pain intensity may be significant and is multifactorial. The three methods used for laparoscopic sterilization are tubal diathermy, ring or loop occlusion and clips. All the three methods have been associated with considerable postoperative pain especially due to pelvic spasm that mimics the colicky pain of dysmenorrhoea.<sup>1</sup>

Multimodal analgesia is now recommended to prevent and treat post laparoscopy pain.<sup>2</sup> Many clinical studies suggest that the intensity of acute postoperative pain is a significant predictor of chronic postoperative pain.<sup>3</sup> Thus, control of perioperative pain and the fashion in which it is implemented (e.g. multimodal) may be important in facilitating short and long-term patient convalescence after surgery. We need to balance between an early discharge and effective pain relief; wherein multimodal analgesia is becoming increasingly popular for postoperative pain relief.

Noxious stimuli release inflammatory mediators from peripheral nociceptors and are transmitted by A delta and C fibers. After complex modulating influences in the spinal cord, some impulses pass to the ventral and ventrolateral horns. This will initiate segmental (spinal) reflex responses, while others are transmitted to higher centers where they induce suprasegmental and cortical responses (central sensitization) to ultimately produce the perception of pain.<sup>4</sup>

Pre-emptive analgesia includes medication (oral, parenteral, epidural, peripheral nerve block etc.) that is administered before the surgical incision is given. This prevents the establishment of central sensitization resulting

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from incisional and inflammatory injury during the perioperative period<sup>5</sup> and thereby providing superior analgesia.<sup>6</sup> A number of drugs like gabapentin, clonidine and dexmedetomidine have been used as premedication in attenuation of post-operative pain. Gabapentin has antiallodynic and anti-hyperalgesic properties<sup>7</sup> and reduces the hyperexcitability of dorsal horn neurons induced by tissue injury.<sup>8</sup> Reduction in central sensitization by an anti-hyperalgesic drug like gabapentin may reduce acute postoperative pain.

Postoperative pain has been found to be a major factor complicating recovery and delaying discharge after ambulatory surgery.<sup>9</sup> Opioids, regional analgesic techniques and peripheral regional analgesia all fail to deliver in such a setting as a result of their associated adverse effects, need for patient monitoring and delay in the discharge. With an increase in number and complexity of outpatient surgeries, discharge criteria have been amended by various authors and the PADSS (post anaesthesia discharge score) continues to evolve. The current version is based on 5 criteria: vital signs, ambulation, nausea and vomiting, pain and surgical bleeding and a score of 9 or greater are considered fit for discharge<sup>10</sup> (Refer to Table 1).

Preoperative oral gabapentin has been shown to decrease pain scores and other analgesic consumption in the post-operative period.<sup>11,12</sup> Pregabalin, a drug similar to gabapentin, was introduced in 2005 for the treatment of epilepsy, diabetic neuropathic pain and post herpetic neuralgia. It has a more favorable pharmacokinetic profile than that of gabapentin with lesser side effects. Optimization of perioperative analgesia may decrease complications and facilitate recovery during the immediate postoperative period<sup>13</sup> and even after discharge from the hospital.<sup>14</sup>

Pregabalin as an oral premedication in anesthesia has been used in doses ranging from 50 mg to 300 mg.<sup>15</sup> A few randomized controlled trials have compared different dosages of preemptive Pregabalin in laparoscopic surgeries for post-operative pain relief.<sup>21</sup> Hence, this study was conducted to compare and evaluate the efficacy of two doses of pregabalin (75mg and 150mg) as an oral premedication in day care gynecological laparoscopic surgeries. The parameters recorded were Visual analogue score, Ramsay sedation score, Time to first rescue analgesic administration (T<sub>1</sub>), incidence of postoperative nausea and vomiting and other side effects if any and time to discharge using post anesthesia discharge scoring system (T<sub>2</sub>).

### Patients and Methods

After obtaining the approval from the institutional review board and ethics committee, this prospective, double blind, randomized study was conducted in the Department of Anesthesiology and Intensive Care of Maulana Azad Medical College and Associated Lok Nayak hospital.

100 ASA grade I and II females between the age group of 18-45 years undergoing elective laparoscopic tubal ligation were recruited for the study and were randomly allocated by a computer-generated random table to one of the 2 groups: Group P75 (75 mg pregabalin) and Group

P150 (150mg pregabalin). The observer recording parameters in postoperative period was blinded to the dose of the drug being administered to the patient.

Patients with a long standing medical or psychiatric illness, BMI>25, known hypersensitivity to pregabalin, previous laparotomy and those who refused were excluded from the study.

After a detailed preanesthetic evaluation, the patients were explained about the visual analogue scale and their weight and BMI was recorded. They were kept NPO overnight and were given the allocated dose 1 hour before the laparoscopy with sips of water. The Ramsey sedation score was assessed 1 hour after the drug administration before induction of anesthesia. Standard anesthesia protocol was followed with routine monitoring of HR, SpO<sub>2</sub>, EtCO<sub>2</sub>, NIBP and an intravenous line was established. All patients were premedicated with IV fentanyl 1.5 µg kg<sup>-1</sup>, IV ranitidine 50mg and IV metoclopramide 10 mg and induced with IV propofol 2.0 mg kg<sup>-1</sup> with inhalational agent 1.2% isoflurane and 66% nitrous oxide in oxygen. The adequacy of depth of anaesthesia was assessed by the loss of jaw tone. A pre checked and prepared Proseal LMA of appropriate size was inserted using the prescribed standard technique. Anaesthesia was maintained with isoflurane (1-1.5%) and 66% nitrous oxide in oxygen. Vital parameters (heart rate, NIBP, SpO<sub>2</sub>, EtCO<sub>2</sub>) were recorded in the intraoperative period. Patients were maintained on spontaneous respiration. At the end of the procedure administration of the inhalational anaesthetic agent was stopped. The patient was administered 100% oxygen and Proseal LMA removed when the patient regained consciousness.

Patients in whom either the duration of surgery exceeded 1 hour, or needed intubation due to unsuccessful Proseal placement or had any other complication like uterine perforation were to be excluded from the statistical analysis but no such incidents were observed in our study.

Ramsay sedation scores were recorded as soon as the patient was shifted to the post anaesthesia care unit and then hourly till the patient reached a score of 2 or less. Visual analogue score on a scale of 0 to 10 was recorded at 30 min, 1 hour, 2 hours, 3 hours and 4 hours post-surgery. At each time the VAS was recorded at rest (static) and after coughing (dynamic). The rescue analgesic was administered when the patient had a VAS of more than 3. The rescue analgesic was IV diclofenac 1.5 mg kg<sup>-1</sup>. The time to administration of first rescue analgesic was recorded and time (T<sub>1</sub>) was calculated from the time pregabalin was given to the administration of the rescue analgesic. Severity of post-operative nausea and vomiting was graded on a three-point scale (0- No nausea or vomiting; 1- Nausea; 2 - Vomiting). The rescue anti emetic was injection ondansetron 0.1 mg kg<sup>-1</sup> IV.

Patients who achieved a PADSS score of 9 or more were considered fit to be discharged. Time to discharge (T<sub>2</sub>) was calculated from the time patient was administered Pregabalin to the time the patient achieved a post anesthesia discharge score of 9 or more.

All data was statistically analyzed using Statistical Package for the Social Sciences (SPSS-17) statistical software.  $P < 0.05$  was considered significant with a sample size of 100 (50 in each group) giving the power of the study to be 80%. Qualitative data were analyzed using Chi-Square test or Fisher Exact test. Quantitative data between groups were analyzed using t test, Mann Whitney U Test.

### Results and Observations

Hundred patients included in the study, were comparable with respect to age, ASA physical status, educational status and body mass index (Table 2). The type and duration of surgery was also comparable in both the groups.

The post-operative recordings on pain and sedation were recorded at 30 min, 1 hour, 2 hours, 3 hours and 4 hours post-surgery. The VAS score at rest (Table 3) at 2, 3- and 4-hours post-surgery was significantly less in the P150 group as analyzed by the Mann Whitney test (p value of 0.001 for each recording). The VAS score on coughing (Table 4) was also significantly less in the P150 group at 30 min, 2 hours, 3 hours and 4 hours post-surgery as analyzed by the Mann Whitney test (p values of 0.044, 0.010, 0.003 and 0.008 respectively).

The need for rescue analgesia with IV diclofenac was observed in only 36% of the patients in P75 group and 30%

of patients in P150 group. In these patients, the time to first rescue analgesic administration was 121 and 131.6 minute respectively. We derived the actual analgesia time post-surgery to be 34 min and 44 min post-surgery in the two groups respectively. Even though clinically both doses were comparable, this time difference was statistically significant ( $p < 0.05$ ) and indicates that 150 mg pregabalin delays the need for first rescue analgesic administration (Table 5). Statistical significance was calculated using the t test.

There was no statistically significant difference in the Ramsay sedation scores of the two groups (p value = 0.198). All patients reached a sedation score of 2 after two hours post-surgery, which was the end point for assessing sedation score in the post-operative period. Statistical significance was calculated using the Fishers exact test.

The incidence of nausea and vomiting was comparable in both groups with a higher dose not causing an increased incidence of PONV.

The time to discharge using the post anesthesia discharge scoring system is shown in Table 6. There was no difference in the time required to achieve the criteria for discharge which was a score of 9 and above, between the two groups (p = 1).

**Table 1:** Modified Post anesthesia discharge scoring (PADS) System

| Category          | Description of status               | PADSS Score |
|-------------------|-------------------------------------|-------------|
| Vital Signs       | Within 20% of pre-operative value   | 2           |
|                   | 20 - 40% of the pre-operative value | 1           |
|                   | > 40% of the pre-operative value    | 0           |
| Ambulation        | Steady gait/no dizziness            | 2           |
|                   | With assistance                     | 1           |
|                   | No ambulation/dizziness             | 0           |
| Nausea & Vomiting | Minimal                             | 2           |
|                   | Moderate                            | 1           |
|                   | Severe                              | 0           |
| Pain              | Minimal                             | 2           |
|                   | Moderate                            | 1           |
|                   | Severe                              | 0           |
| Surgical bleeding | Minimal                             | 2           |
|                   | Moderate                            | 1           |
|                   | Severe                              | 0           |

**Table 2:** Patient characteristics

| Group (n=50) | Age (yrs) Mean $\pm$ SD | ASA Class |   | Educational Status |         |           |            | BMI kg/m <sup>2</sup> Mean $\pm$ SD |
|--------------|-------------------------|-----------|---|--------------------|---------|-----------|------------|-------------------------------------|
|              |                         | 1         | 2 | Illiterate         | Primary | secondary | >secondary |                                     |
| Group P75    | 28 $\pm$ 3.48           | 50(100%)  | 0 | 17(34%)            | 21(42%) | 5(10%)    | 7(14%)     | 21.04 $\pm$ 2.06                    |
| Group P150   | 28.72 $\pm$ 4.25        | 50(100%)  | 0 | 18(36%)            | 17(34%) | 11(22%)   | 4(8%)      | 21.09 $\pm$ 1.99                    |
| p value      | 0.357                   | -         |   | 0.318              |         |           |            | 0.895                               |

**Table 3:** Visual analogue score (VAS): At rest

| Group<br>n=50 | VAS at Rest (Mean $\pm$ Std Deviation) |                  |                  |                  |                  |
|---------------|----------------------------------------|------------------|------------------|------------------|------------------|
|               | 30 min                                 | 1 hour           | 2 hours          | 3 hours          | 4 hours          |
| Group P75     | 3.14 $\pm$ 1.604                       | 2.77 $\pm$ 0.864 | 2.50 $\pm$ 0.544 | 2.26 $\pm$ 0.487 | 2.24 $\pm$ 0.476 |
| Group P150    | 2.78 $\pm$ 1.475                       | 2.48 $\pm$ 0.995 | 2.14 $\pm$ 0.833 | 1.90 $\pm$ 0.463 | 1.88 $\pm$ 0.435 |
| P value       | 0.147                                  | 0.055            | 0.001            | 0.001            | 0.001            |

**Table 4:** Visual analogue score (VAS): On coughing

| Group<br>n = 50 | Vas on Coughing (mean $\pm$ std deviation) |                  |                  |                  |                  |
|-----------------|--------------------------------------------|------------------|------------------|------------------|------------------|
|                 | 30 min                                     | 1hr.             | 2hr.             | 3hr.             | 4hr.             |
| Gp P75          | 3.41 $\pm$ 1.564                           | 2.86 $\pm$ 0.881 | 2.58 $\pm$ 0.538 | 2.38 $\pm$ 0.490 | 2.32 $\pm$ 0.471 |
| Gp P150         | 2.94 $\pm$ 1.557                           | 2.66 $\pm$ 1.061 | 2.30 $\pm$ 0.839 | 2.06 $\pm$ 0.512 | 2.06 $\pm$ 0.550 |
| P value         | 0.044                                      | 0.096            | 0.010            | 0.003            | 0.008            |

**Table 5:** Time to administration of rescue analgesic (T<sub>1</sub>) in patients who demanded

| Group<br>n = 50          | Rescue Analgesic<br>Required | Rescue Analgesic Not<br>Required | Time to rescue (T <sub>1</sub> min)<br>(Mean $\pm$ Std Deviation) |
|--------------------------|------------------------------|----------------------------------|-------------------------------------------------------------------|
| Gp P75<br>(Count, %age)  | 18<br>36%                    | 32<br>64%                        | 121 $\pm$ 12.11                                                   |
| Gp P150<br>(Count, %age) | 15<br>30%                    | 35<br>70%                        | 131.67 $\pm$ 15.99                                                |
| P value                  | 0.523                        |                                  | <b>0.037</b>                                                      |

**Table 6:** Time to discharge (T<sub>2</sub>) using post anesthesia discharge score (PADSS) was similar in both groups, with no prolongation on giving higher dose of Pregabalin

| Group n=50 | Time to discharge (T <sub>2</sub> ) in minutes, Mean $\pm$ Std Deviation |
|------------|--------------------------------------------------------------------------|
| Group 75   | 221.20 $\pm$ 10.32                                                       |
| Group 150  | 221.20 $\pm$ 13.30                                                       |
| P value    | 1                                                                        |

## Discussion

Surgery produces tissue injury and the continuous release of inflammatory mediators in the periphery sensitizes functional nociceptors and activates dormant ones. Such noxious input may lead to functional changes in the dorsal horn of the spinal cord and other consequences that may later cause postoperative pain to be perceived as more painful than it would otherwise have been. Uncontrolled postoperative pain has a range of detrimental effects on all organ systems. The multimodal approach to pain management especially in day care surgeries have not only reduced the time to discharge but also improved patient outcome. This has become possible by using certain adjuvant drugs, whose analgesic effects have proven to be very beneficial in preventing central sensitisation.

Pregabalin, a newer gabapentinoid was shown to be effective in neuropathic pain and also effective in treatment of generalized anxiety disorder. The main site of action appears to be on the  $\alpha 2\delta$  subunit of presynaptic voltage dependent calcium channels.<sup>16</sup> It is rapidly absorbed with peak blood concentration within 1 hour and bioavailability exceeding 90%. Unlike gabapentin, absorption of pregabalin is not saturable, resulting in a linear pharmacokinetic profile. Elimination half time is 5.5 to 6.7 hours and is renally excreted in an essentially unchanged form. No clinically relevant pharmacokinetic drug interactions have

been identified. Pregabalin is well tolerated and its adverse effects are mild and usually transient.

Pregabalin has been used as premedication in various types of surgeries like dental extractions, spinal fusion, laparoscopic cholecystectomy, gynecological surgeries (both laparoscopic and open) and orthopedic surgeries in different studies.<sup>17-19,21</sup>

This randomized double-blind study was conducted to compare two doses of pregabalin for postoperative pain relief. The primary outcome variable of our study was the visual analogue score (VAS) for pain and the opioid sparing effect of the premedication. There was no difference in the VAS in the first hour post-surgery which could be due to the residual analgesic effect of fentanyl that was used in the intraoperative period. The pain scores at 2, 3 and 4 hours after surgery, were significantly less in the 150 mg pregabalin group both at rest and on coughing. Even though a statistically significant difference was observed in the time to first rescue analgesic administration in the 150 mg Pregabalin group, the duration of post-operative analgesia was comparable in both the groups.

The incidence of PONV was comparable in both the study groups which is in concordance with a study reported by Paul F White et al<sup>20</sup> in which they compared the effect of 75, 150 and 300 mg pregabalin on sedation in day care and short stay procedures. Hence both dosages were well

tolerated by patients, and a higher dose does not result in a higher incidence of PONV.

It was observed that the average mean time to discharge to ward after surgery was 134 mins in both the groups. Thus, suggesting that adjuvant drugs even at higher doses unlike opioids do not have an effect on delaying the discharge. Going through the literature on day care procedures, we did not find any study where PADSS was used as a discharge-criteria to assess the efficacy of preemptive pregabalin in early ambulation to the ward.

### Conclusion

The objective of this study was to compare two doses of pregabalin and find out which is more suitable as a premedication for ambulatory surgery. We found no statistically significant difference in the sedation scores, side effect profile and the time to achieve fitness to discharge between the two doses, but superior analgesia with 150mg of pregabalin was observed. Thus, we recommend a preemptive dose of 150mg pregabalin as a suitable choice for better post-operative analgesia in patients undergoing laparoscopic tubal ligation without leading to any delay in discharge.

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