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# A PROSPECTIVE RANDOMIZED CONTROLLED STUDY COMPARING THE EFFICACY OF PREOPERATIVE ORAL PREGABALIN 100mg vs 200mg FOR POSTOPERATIVE PAIN CONTROL IN INFRA UMBILICAL SURGERIES UNDER SPINAL ANAESTHESIA

**Anaesthesiology**

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## ABSTRACT

**Background** – Pain is a personal, subjective experience that involve sensory, emotional and behavioral factors. Prevention and treatment of post-operative pain continues to be a major challenge in post-operative care. One of the methods used for management of postoperative pain is pre-emptive analgesia –blockade of afferent nerve fiber before surgical stimulus. The objective of the study is to compare the quality of post-operative analgesia provided by two different doses (200mg & 100mg) of oral pregabalin given pre-operatively. **Materials And Methods –** After institutional ethical committee approval, a prospective randomized controlled. Study is done on 90 patients of ASA I & II physical status aged between 18-60 yrs who were posted for elective surgeries under spinal anaesthesia. Subjects are randomly divided into three groups of thirty each by envelope method. Oral Pregabalin 200mg; Pregabalin 100mg and Placebo is given 1 hr prior to surgery to the respective groups. The following parameters are recorded both intraoperatively and postoperatively. Hemodynamic parameters, onset and level of block achieved, time to 2 segment regression, duration of motor blockade, sedation score using Ramsay sedation Scale, Pain using Visual Analgoue Scale, Adverse events, as well as rescue analgesia if used is recorded. **Result -** The total rescue analgesia (tramadol) consumption requirement over 24hrs of post-operative period is significantly lower in pregabalin 200mg; (72.4mg) compared to pregabalin 100mg and control group which were (128mg) and (146mg) respectively. The sedation in Pregabalin group is better than that of control group, as evidenced higher mean ramsay sedation score postoperatively. The study did not show any serious side effects with the test groups. **Conclusion -** A preoperative oral dose of pregabalin 200mg is more effective than 100mg for reducing postoperative pain in patients undergoing lower abdominal surgeries. However both 100mg and 200mg produce a prolonged postoperative analgesia compared to the placebo.

## KEYWORDS

Pregabalin, Post operating nausea and vomiting (PONV), Pre-emptive analgesia, Postoperative pain, Visual Analogue Scale (VAS)

## INTRODUCTION

Surgical incision has been known to induce hyperalgesia, which can contribute to persistent pain after surgery. The intensity of pain in the acute postoperative period is an important risk factor for functional improvement in the long term and it is the primary reason for prolonged hospital stay after surgery, overall well-being and patient satisfaction.

An ideal premedication drug should relieve anxiety, produce amnesia and sedation, decrease secretions, prevent nausea and vomiting and most importantly reduce post-operative pain.

The major goal in the management of postoperative pain is to minimize the dose of medications to lessen side effects and provide adequate analgesia.

One of the methods used for management of postoperative pain is pre-emptive analgesia -blockade of afferent nerve fiber before surgical stimulus.

Presently opioids form the basis for postoperative pain attenuation and because of their known side effects, a lot of effort is made to reduce their usage.

Pregabalin is a new gabapentinoid with favorable pharmacological profilewhich acts by reducing calcium entry into the nerve terminals of central nervous system and lowers substance P, glutamate and noradrenaline levels which play a role in creating the sense of pain.

Studies have been done with varying doses of pregabalin in mitigating post-operative pain, but optimal dose to attenuate post-operative pain while preventing development of adverse effects is still unknown.

## METHODOLOGY:

After clearance from the Institutional Ethics Committee and obtaining written informed consent, A total of 90 patients were enrolled in the study as per American Society of Anesthesiologists (ASA) classes I and II. The patients were randomly allocated into three groups of 30 each.

### Inclusion Criteria

1) Patients who give informed written consent.
2) Patients above 18 years of age.
3) Patients belonging to ASA Grade I and Grade II.
4) Patients posted for infra-umbilical surgeries under sub-arachnoid block.

### Exclusion Criteria

1) Patients who refuse to give informed written consent**.**
2) Patients with systemic disorders- uncontrolled hypertension, ischemic heart disease, cerebrovascular disease, uncontrolled diabetes mellitus, renal and hepatic disease, bronchial asthma.
3) Patients taking sedatives, antidepressants, anxiolytics, anticonvulsants or any other contraindication for the use of patient controlled analgesia.
4) Patients with known history of allergy to any drugs.
5) History of chronic pain and chronic daily intake of analgesics.
6) Patients with history of smoking, alcohol and drug abuse.

Patients were recruited following their preoperative assessment and randomly assigned into three groups by asking them to pick up sealed envelopes (each envelope indicates to which group they belong to).

One hour prior to spinal anaesthesia, patients were familiarized with Visual Analogue Scale and given
GROUP-A oral pregabalin 200mg.
GROUP-B oral pregabalin 100mg.
GROUP-C placebo.

### Anesthetic Technique:

On arrival in the operating room, standard anesthesia monitors were attached and baseline vitals- HR, Systolic BP, Diastolic BP, Mean Arterial Pressure, and oxygen saturation recorded.

All patients were preloaded with IV Fluid RL 6-8ml/kg, followed by Inj Ondansetron 0.08mg/kg.

O2 was administered with facemask at 4lts/min.

The patients were then administered spinal anaesthesia under aseptic precautions in sitting position at L3-L4 level with Inj Hyperbaric Bupivacaine (Heavy) – 0.5%, at a dose of 0.3mg/kg.

### Statistical Method And Software-

The parameters recorded were entered on a computer and compared between the three groups using one way ANOVA test for continuous variables and P ≤ 0.05 is deemed significant using SPSS 25.0.

## RESULTS

The statistical analysis of the values is represented as the tables and graphs below.

Here, the patients administered with Pregabalin 200mg are noted as group A. Pregabalin 100mg and the control group are represented as Group B and C respectively.

**Table 1: Age In Years- Frequency Distribution In Three Groups Of Patients Studied**

| Age in Years | Group A | Group B | Group C |
|---|---|---|---|
| <30 | 04 (13.3%) | 2 (6.67%) | 3 (10 %) |
| 30-40 | 18 (60%) | 17 (56.67%) | 18 (60%) |
| >40 | 08 (26.7%) | 10 (33.33%) | 9 (30%) |
| Average age | 36.27±6.95 | 36.17±1.57 | 35.67±4.24 |
| Male | 22 (73.3%) | 21 (70%) | 21 (70%) |
| Female | 08 (26.7%) | 09 (30%) | 09 (30%) |
| Average BMI | 25.55±4.65 | 26.08±5.1 | 25.24±3.56 |

There was no significant difference in the demographic details between the three groups.

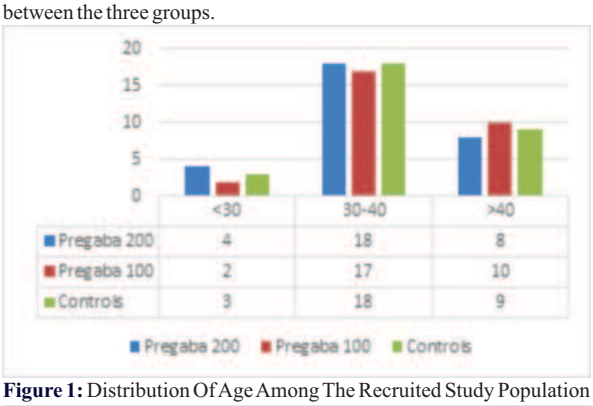


**Figure 1:** Distribution Of Age Among The Recruited Study Population

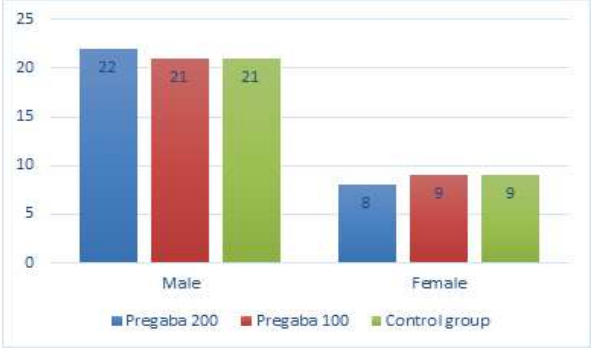


**Figure 2:** Distribution Of Gender In The Three Groups

**Table 2: ASA GRADE- Frequency Distribution In Three Groups Of Patients Studied**

| ASA GRADE | Group A | Group B | Group C |
|---|---|---|---|
| 1 | 22(73.3%) | 21 (70%) | 21 (70%) |
| 2 | 8(26.7%) | 9 (30%) | 09 (30%) |

Majority of the patients in all the three group belong to ASA 1 accounting for 22(73.3%), 21 (70%) and 21 (70%), in Group A, Group B and Group C group respectively. The ASA distribution of patients among the three study groups were comparable.

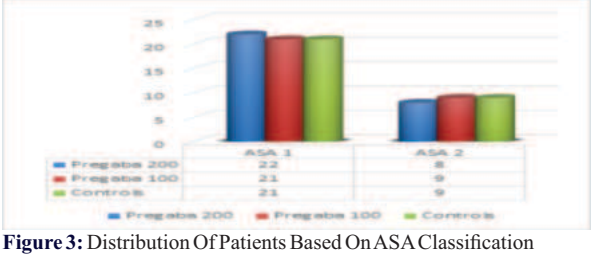


**Figure 3:** Distribution Of Patients Based On ASA Classification

**Table 3: Heart Rate (bpm)- Comparison In Three Groups Of Patients Studied**

| HR (per/min) | Group A | Group B | Group C | Total | P Value |
|---|---|---|---|---|---|
| Basal | 82.43± 19.1 | 92.47± 20.84 | 91.87± 17.61 | 91.26± 19.06 | <0.001 |
| 1min | 82.23± 20.18 | 89.77± 16.14 | 92.63± 23.89 | 89.88± 20.21 | <0.001 |
| 5min | 78.9±12.6 9 | 81.6±13.2 7 | 92.1±10.7 6 | 81.53±12. 34 | <0.001 |
| 20min | 73.97±14. 17 | 74.8±14.0 1 | 82.33±10. 71 | 76.7±13.3 3 | <0.001 |
| 30min | 68.67±11. 84 | 70.97±13. 63 | 83.43±12. 73 | 70.26±12. 71 | <0.001 |
| 60min | 68.84±10. 5 | 71.3±12.8 | 81.31±10. 9 | 72.4±10.9 | <0.001 |
| 90min | 68.91±8.5 4 | 72.89±10. 4 | 80.6±11.3 | 74.5±12.1 | <0.001 |
| 2 hours | 69.38±10. 54 | 73.13±11. 2 | 81.62±12. 1 | 80.5±11.6 | <0.001 |
| 6 hours | 72.85±12. 1 | 73.1±12.4 | 80.53±12. 4 | 81.6±12.5 | <0.001 |
| 12 hours | 72.8±11.9 | 73.16±11. 8 | 83.87±11. 6 | 81.37±10. 1 | <0.001 |
| 24 hours | 76.67±11. 84 | 79.67±13. 63 | 82.43±12. 73 | 80.26±12. 71 | 0.21 |

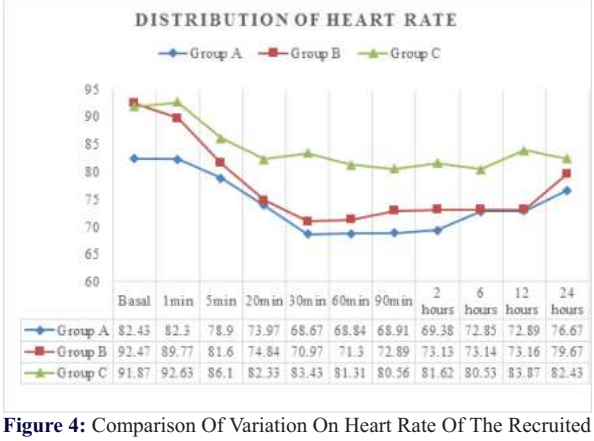


**Figure 4:** Comparison Of Variation On Heart Rate Of The Recruited Study Population In Three Groups

Group A patients had statistically significant($p < 0.01$) effect on heart rate at all times for a period of up to 12 hrs following which the heart rate was comparable among the three study groups.

**Table 4: Systolic BP (mm Hg)- Comparison In Three Groups Of Patients Studied**

| SBP (mm Hg) | Group A | Group B | Group C | Total | P Value |
|---|---|---|---|---|---|
| Basal | 108.4±8.5 9 | 112.37±14 .69 | 120.64±14 .67 | 117.68±8. 8 | <0.001 |
| 1min | 108.53±6. 71 | 112.03±20 .64 | 118.8±16. 2 | 117.43±8. 91 | <0.001 |
| 5min | 105.7±8.1 6 | 109.03±13 .16 | 112.5±14. 82 | 114.56±9. 4 | <0.001 |
| 20min | 105.1±11. 69 | 110.47±11 .31 | 112.4±12. 5 | 114.48±10 .3 | <0.001 |
| 30min | 104.63±7. 6 | 109.87±11 .51 | 111.4±10. 58 | 114.56±11 .1 | <0.001 |
| 60min | 104.97±9. 67 | 110.87±13 .5 | 112.84±11 .07 | 112.45±10 .9 | <0.001 |
| 90min | 106.85±12 .1 | 112.36±12 .8 | 111.56±13 .1 | 112.34±8. 8 | <0.001 |
| 2 hours | 106.91±10 .8 | 111.48±12 .4 | 113.82±11 .5 | 112.1±10. 2 | <0.001 |
| 6 hours | 106.39±8. 1 | 110.56±11 .6 | 113.45±10 .32 | 111.54±8. 9 | <0.001 |
| 12 hours | 107.84±7. 2 | 111.15±10 .23 | 112.6±8.5 8 | 116.56±9. 2 | <0.001 |

| | | | | | |
|---|---|---|---|---|---|
| 24 hours | 108.48±7.43 | 109.32±10.18 | 111.91±8.49 | 117.56±12.8 | 0.11 |

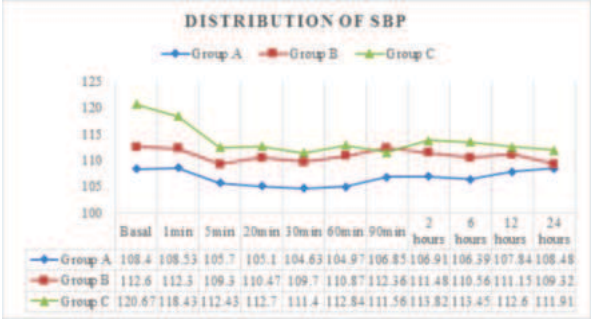


**Figure 5:** Comparison of variation in Systolic BP between three groups

The above table 4 and the figure 5 illustrates the comparison of distribution of Systolic BP between the three groups. We found that there is drastic reduction in systolic BP of Group A compared to other two groups from baseline data and following the procedure. The reduction in systolic BP is observed throughout the procedure but there was no need for rescue vasopressors. At the 24th hour, there was no significant difference in the systolic BP as observed from the above table.

**Table 5: Diastolic BP (mm Hg)- Comparison In Three Groups Of Patients Studied**

| DBP | Group A | Group B | Group C | Total | P Value |
|---|---|---|---|---|---|
| Basal | 64.77±8.5 | 72.2±12.8 | 74.07±6.61 | 84.01±10.8 | <0.001 |
| 1min | 62.27±6.98 | 71.6±11.74 | 73.97±6.57 | 83.61±8.99 | <0.001 |
| 5min | 59.53±12.57 | 65.77±10.6 | 70.67±13.85 | 75.32±12.66 | <0.001 |
| 20min | 60.83 ±7.6 | 66.07±11.07 | 69.17±12.33 | 61.69±10.91 | <0.001 |
| 30min | 61.63±7.59 | 67.87±7.73 | 70.53±11.55 | 60.68±9.27 | <0.001 |
| 60min | 62.57±8.04 | 68.23±13.89 | 72.23±4.96 | 69.01±10.75 | <0.001 |
| 90min | 60.91±10.23 | 69.31±11.2 | 73.42±9.81 | 78.14±10.82 | <0.001 |
| 2 hours | 60.23±9.81 | 70.18±3.98 | 72.14±7.23 | 77.91±4.56 | <0.001 |
| 6 hours | 61.48±3.7 | 69.32±8.1 | 71.11±9.1 | 75.69±10.5 | <0.001 |
| 12 hours | 63.51±11.2 | 69.14±7.41 | 72.35±8.45 | 75.63±11.42 | <0.001 |
| 24 hours | 66.23±8.91 | 68.32±6.93 | 70.32±7.91 | 70.15±8.17 | <0.001 |

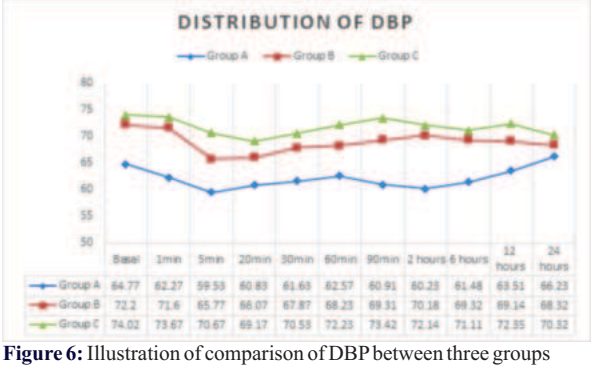


**Figure 6:** Illustration of comparison of DBP between three groups

The above table 5 and figure 6 illustrates the comparison of distribution of diastolic BP between the three groups. We observed a drastic reduction in diastolic BP of Group A subjects compared to the other two groups from the start of spinal, the same trend is observed even after the procedure. This statistically significant reduction in diastolic BP was observed throughout the procedure in Group A and B but there was no need for rescue vasopressors. Similar to systolic BP, there was no significant difference observed in the average diastolic BP values at the end of 24 hours.

**Table 6: Mean Arterial Pressure (mm Hg)- Comparison In Three Groups Of Patients Studied**

| MAP | Group A | Group B | Group C | Total | P Value |
|---|---|---|---|---|---|
| 1min | 92.43±7.28 | 97.2±12.99 | 99.17±8.74 | 102.57±11.36 | <0.001 |
| 5min | 85.73±5.21 | 89.27±14.18 | 102.13±8.01 | 102.13±10.35 | <0.001 |
| 20min | 84.03±10.73 | 89.53±11.02 | 102.7±12.78 | 100.76±12.45 | <0.001 |
| 30min | 86.17±9.47 | 91.6±8.14 | 100.87±12.51 | 98.88±10.47 | <0.001 |
| 60min | 88.4±5.97 | 94.07±7.73 | 100.83±11.18 | 96.77±8.64 | <0.001 |
| 90min | 91.07±7.57 | 95.1±13.01 | 99.13±5.2 | 92.43±10.23 | <0.001 |
| 2 hours | 92.83±7.83 | 94.56±9.85 | 98.71±6.8 | 88.91±11.1 | <0.001 |
| 6 hours | 94.25±6.91 | 97.16±7.86 | 99.38±9.45 | 87.92±10.6 | <0.001 |
| 12 hours | 91.38±7.82 | 93.13±10.1 | 98.81±8.8 | 87.34±11.3 | <0.001 |
| 24 hours | 90.14±9.1 | 92.56±9.3 | 97.34±7.9 | 91.83±10.2 | 0.12 |

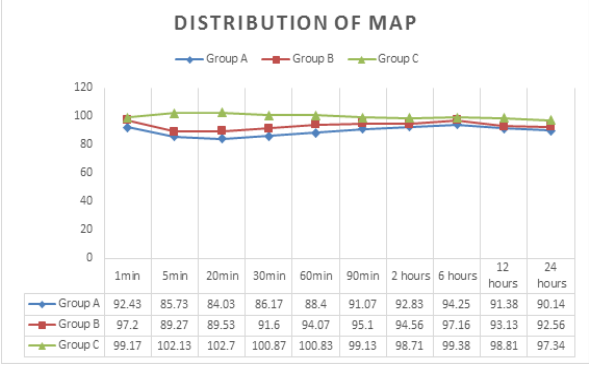


**Figure 7:** Illustration of comparison of Mean Arterial Pressure between three groups

The above table 6 and the figure 7 illustrates the comparison of distribution of mean BP between the three groups. We found that a drastic reduction in Group A compared to the other two study groups from the baseline values till the end of procedure. The statistically significant reduction in mean BP was observed throughout the procedure but there was no need for rescue vasopressors as the reduction in BP was not clinically significant. There was no difference in MAP at the end of 24 hours.

**Table 7: Maximum Sensory Level- Comparison In Three Groups Of Patients Studied**

| Maximum sensory level | Group A | Group B | Group C |
|---|---|---|---|
| T8 | 4 (13.3%) | 5 (16.7%) | 5 (16.7%) |
| T4 | 4 (13.3%) | 4 (13.3%) | 4 (13.3%) |
| T6 | 22 (73.3%) | 21 (70%) | 21 (70%) |

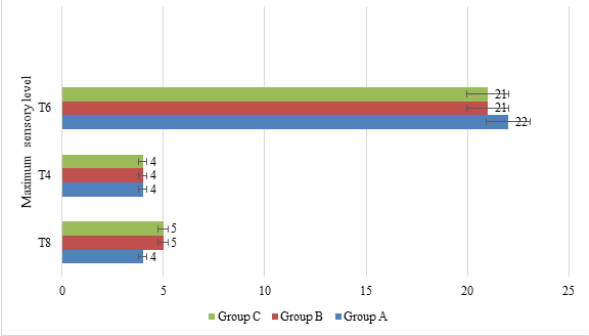


**Figure 8:** Maximum Sensory Level Attained

Maximum sensory level attained is similar between the groups. Majority of the patients attained a maximum sensory level of T6. A slightly higher number of patients had attained maximum sensory level of T8 but inter group variation is similar as oberserved from the the above table.

**Table 8: Ramsay Sedation Score At The End Of Surgery- Comparison In Three Groups Of Patients Studied**

| Sedation score at end of surgery | Group A | Group B | Group C |
|---|---|---|---|
| 1 | 0 | 0 | 0 |
| 2 | 20 | 19 | 20 |
| 3 | 10 | 11 | 10 |

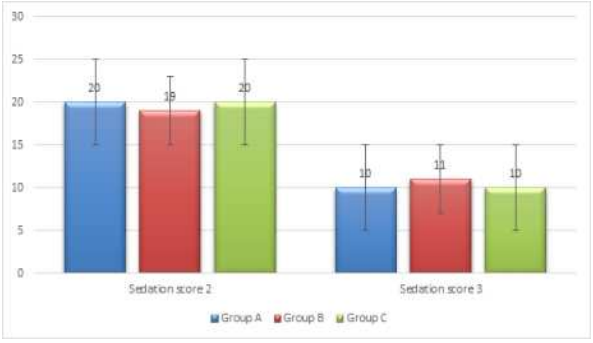


**Figure 9:** Comparison Of Sedation Score Between Three Groups

Group A and C had 20 patients in each and 19 patients in Group B had a sedation score 2. Whereas 10 patients in group A and C had ramsay sedation score 3 and 11 patients in group B had a sedation score of 3. The score was better in Pregabalin 200mg group than Pregabalin 100mg group.

**Table 9: Comparison Of Study Variables – In Three Groups Of Patients Studied**

| Variables | Group A | Group B | Group C | Total | P Value |
|---|---|---|---|---|---|
| Time to max sensory level (mins) | 8.73±1.17 | 7.43±1.77 | 6.67±2.11 | 6.94±2.12 | 0.35 |
| Total duration of surgery (mins) | 143.5±55.39 | 144±43.08 | 140.03±34.37 | 139.51±53.44 | 0.52 |
| Time to 2 segment regression(mins) | 77.83±11.48 | 69.17±11.23 | 65.33±20.54 | 73.78±15.2 | <0.001 |
| Duration of motor blockade (mins) | 190.83±30.26 | 170±45.18 | 163±33.85 | 174.61±31.45 | 0.013* |
| Total duration of sensory block | 220.83±30.26 | 190±45.18 | 135±33.85 | 187.34±42.23 | <0.01* |
| Total duration of analgesia | 435.83±30.26 | 352±45.18 | 249±33.85 | 279.68±51.13 | <0.01* |

We observed that time to 2 segment regression was significantly higher in Group A.

Total duration of sensory block and total duration of analgesia were statistically significant and higher in Group A compared to Group B and control groups

**Table 10: Post-Operative Average VAS Scoring**

| VAS | GROUP A | GROUP B | CONTROL | P-VALUE |
|---|---|---|---|---|
| 0Hrs | 0 | 0 | 0 | - |
| 1hrs | 0 | 0 | 0 | - |
| 2hrs | 0 | 1.24±0.9 | 2±0.5 | <0.001 |
| 3hrs | 1.2±0.8 | 1.83±0.6 | 2.03±1.1 | <0.001 |
| 4hrs | 1.83±0.78 | 2.96±1.32 | 3.96±2.1 | <0.001 |
| 6hrs | 3.43±1.2 | 4.3±2.7 | 5.7±1.97 | <0.001 |
| 9hrs | 2.83±1.8 | 3.96±2.3 | 3.43±2.9 | <0.001 |
| 12hrs | 3.96±3.1 | 3.43±1.9 | 5.4±3.5 | <0.001 |
| 24hrs | 3.2±1.5 | 3.2±1.1 | 3.4±5.2 | 0.34 |

There is significantly lesser VAS scoring from 2 hours after the procedure till the end of 12 hours in the test groups compared to control group.

There is no significant difference observed at the end of 24 hours.

**Table 11: Total Dose Of Tramadol Administered In 24 Hrs Post-surgery**

| | GROUP A | GROUP B | CONTROL | P-VALUE |
|---|---|---|---|---|
| Tramadol | 72.4±12.5mg | 128±42mg | 146±10.8mg | <0.001 |

We observed that there was significantly lesser total rescue analgesia (Tramadol) consumption during initial 24hrs of postoperative period in Pragabalin 200 group.

**Table 12: Adverse Events**

| Adverse Events | Group A | Group B | Group C | Total |
|---|---|---|---|---|
| YES Nausea | 1(3.3%) | 0(0%) | 0(0%) | 0(0%) |

Only one patient of pregabalin 200mg group developed nausea which was statistically significant.

## DISCUSSION

In our study, post-operative VAS score and rescue analgesia consumption were significantly lower in Pregabalin 200mg group compared to Pregabalin 100mg and control groups.

Our observation is supported by the study conducted by A.Agarwal[1] et al done on 6o patients, divided into placebo group and Pregabalin 150mg posted for laparoscopic cholecystectomy, they concluded that a single dose Pregabalin 150mg was effective in reducing post-operative pain after laparoscopic hysterectomy.

Incidence of nausea and vomiting showed no significant difference between the groups which correlated with the study conducted by R.Jokela[2] et al done on 91 patients; they concluded that pregabalin 300mg was safe and effective with insignificant side-effects.

V Saraswat[3] et al in their study done on 60 patients, who were given pre-emptive gabapentin 1200mg (group G) and pregabalin 300mg (group P) reported total postoperative analgesic time of 8.98h in Group G whereas 14.17h in Group P (P< 0.001) and concluded that gabapentin and pregabalin, both have been effective in prolongation of post-spinal analgesia.

## CONCLUSION

Pre-emptive Pregabalin provides better analgesia post operatively than placebo group. Pregabalin 200mg produces longer duration of analgesia and reduces the total dose requirement of rescue analgesia. Ramsay sedation score was higher in Pregabalin 200mg group as evidenced by non-anxious patients in the immediate post-operative period.

There was no significant changes in the intraoperative hemodynamics, and the incidence of side-effects was not significant.

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