**POST-OPERATIVE ANALGESIC AND OPIOID-SPARING EFFECT OF A SINGLE DOSE PRE-OPERATIVE ORAL PREGABALIN IN GYNAECOLOGICAL SURGERIES**

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**Abstract**

**Background:** Postoperative pain treatment is a major challenge in our environment. Opioids may cause respiratory depression postoperatively. Therefore, any combination of opioid and non-opioid analgesics that provides quality postoperative pain control and reduces opioid consumption with its attendant side effects will be highly desirable.

**Objective:** Evaluation of analgesic benefits and opioid-sparing effects of preoperative oral pregabalin in patients who undergo abdominal gynaecological surgeries.

**Methodology: A** prospective randomized double-blind placebo controlled study carried out at University of Ilorin Teaching Hospital, Kwara State. Eighty-two patients scheduled for gynaecological surgeries were randomized into two equal groups. The patients in the control and study groups received a placebo drug and oral pregabalin 150mg respectively one hour before induction of general anaesthesia. Postoperative pain intensity using a five-point Verbal Rating Scale (VRS), time to first request for analgesia, and 24 hours postoperative pethidine consumptions were assessed. Mean values were compared using the student’s t-test. Categorical data were compared with the chi-square test. Level of significance was set at 5% (0.05) and power of the study was 80%.

**Results:** Demographic characteristics were comparable between the two groups. The median pain score was 0 to 2 (no pain – moderate pain) throughout the study. Post-operative static and dynamic pain scores at 1, 4 and 12 hours were significantly higher in the placebo group (<0.001). Twenty-four hours post-operatively, there were no significant differences in static and dynamic pain scores between the two groups (p=0.131 and p=0.384 respectively).

Time to first analgesic requirement and total pethidine consumed within 24 hours postoperative were 47±19 vs 258±137mins (p=0.001) and 326.19±62.70mg vs 192.86±55.84mg (p=0.001) in the control and study groups respectively. The preoperative use of pregabalin reduced postoperative opioid requirement by 40.9% in the study group. Nausea and vomiting were more common in the placebo group while dizziness, blurring of vision and sedation were more common in the pregabalin group.

**Conclusion:** A single preoperative dose of 150mg oral pregabalin had significantly greater analgesic effects compared to placebo and reduced post-operative opioid requirements in patients undergoing myomectomy or total abdominal hysterectomy. It should be considered an adjuvant in multimodal pain management regimens following gynaecological surgeries.

**Keywords**: Postoperative pain, Multimodal analgesia, Gynaecological surgeries, Pregabalin.

**Introduction**

Postoperative pain control remains a significant problem following surgical operations in our environment.1 Poorly managed postoperative pain can result in decreased vital capacity, tachycardia, hypertension, myocardial ischaemia, and transition to chronic pain.2Recent advances in the pathophysiology of pain have suggested that it is possible to prevent or attenuate the central neural hyper-excitability that contributes to enhanced postoperative pain.3

Traditionally, opioids are the mainstay of the treatment of postoperative pain. However, opioids are associated with numerous side effects such as nausea, vomiting, constipation and respiratory depression. The use of oral non-opioid analgesics in the practice of multimodal analgesic technique has gained attention over the years. Newer agents for postoperative pain control with pre-emptive analgesic effect like pregabalin create possibilities for better combinations in multimodal analgesia. This has led to the development of newer pharmaceutical products that have pre-emptive analgesic effects in multimodal postoperative pain control.4

Pregabalin is a gabapentinoid and a structural analogue of the inhibitory neurotransmitter, gamma-aminobutyric acid.5 The oral bioavailability is 90%, and elimination half-life is 5.5-6.7 hours independent of dose and repeated administration.6 It does not undergo hepatic metabolism and is not bound to plasma proteins. It is generally well tolerated but associated with transient mild to moderate adverse effects such as dizziness, somnolence, dry mouth, blurred vision and inability to concentrate, which are dose dependent.7 It has been used in the multimodal management of postoperative pain because of its analgesic effect.8

Studies on the effectiveness of perioperative oral pregabalin in the treatment of postoperative pain have yielded promising results by reducing postoperative pain and opioids consumption.4,9Evidence supporting the analgesic effect of pregabalin includes the treatment of neuropathic pain and postoperative pain after breast surgery.10 However, the results of a study have questioned the role of pregabalin in postoperative pain management.6

This study aimed at evaluating the analgesic benefit and opioid-sparing effects of a single dose preoperative 150mg oral pregabalin on the postoperative pain intensity and 24 hours pethidine consumption on patients who had abdominal gynaecological surgeries under general anaesthesia.

**Methods**

Following institutional ethical review committee approval, this prospective, double-blind, and placebo-controlled study was carried out on 82 ASA (American Society of Anaesthesiologists) physical status I and II adult patients aged 18 to 65 years who had open myomectomy or total abdominal hysterectomy under general anaesthesia at the University of Ilorin Teaching Hospital. Patients were recruited after admission to the ward. The study was explained to them by the researchers with the use of the information sheet and consent obtained.

The sample size was calculated using the formula for comparing means,11 and time to first request for analgesia as the primary outcome. Level of significance was set at 5% (0.05) and power of the study was 80%. In a previous study,12the standard deviation for the time to first analgesia request in the placebo group was 10.97; with a difference of 7.5 minutes between the means set as being of clinical significance, a sample size of 34 was obtained for each group. To allow for a possible attrition rate of 20% the sample size for each group was increased to 41.

Patients with chronic pain syndromes on analgesics, those with impaired kidney or liver functions, history of drug or alcohol abuse, as well as those who took non-steroidal anti-inflammatory drugs within 24 hours before surgery were excluded from the study. Diabetics, hypertensives and patients with mental health challenges were also not enrolled into the study. The study was carried out over a period of 10 months (May 2017 – March 2018).

The patients were trained on the use of the verbal rating scale13 (VRS) pain scoring method which had been validated in the local language.13 The score was assigned as 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain, 4 = excruciating pain. Patient’s weight, height and body mass index were measured and recorded.

They were randomly assigned into two groups of 41 each using simple random sampling techniques. The randomization was done by balloting, with patients picking from a ballot box containing 41 ballot papers labeled A and 41 papers labeled B by the hospital pharmacy. Patients in group A received a placebo (an empty shell of pregabalin capsule which contained no active agent, prepared by the hospital pharmacy), while those in group B received pregabalin 150mg. The medications were administered to patients orally 1 hour before induction of anaesthesia with sips of water by a research assistant who was not involved in the study. All the medications were the same brand (Lyrica, Pfizer®, Lot No: H64117). The key to the coding was revealed to the investigator by the hospital pharmacy after data analysis.

Anaesthesia technique was standardized in all the groups. In the operating suite, patients were connected to multi-parameter patient monitor and baseline vital signs such as heart rate (HR), blood pressure (BP), respiratory rate (RR), temperature, peripheral arterial oxygen saturation (SPO2), and electrocardiogram (ECG) were measured and recorded. Patients were pre-oxygenated for 3 minutes and a loading dose of intravenous fentanyl at 2µg/kg was given. Anaesthesia was induced with intravenous propofol 2mg/kg and intravenous suxamethonium 1mg/kg was immediately administered to facilitate excellent intubating condition. Laryngoscopy was done and patient’s trachea was intubated with an appropriate size cuffed endotracheal tube. Correct tube placement was confirmed with auscultation of the chest for equal air entry and with capnography. Anaesthesia was maintained with 0.5-1% Isoflurane with oxygen as carrier gas. Muscle relaxation was maintained with intravenous pancuronium 0.1mg/kg. The BP was subsequently monitored and measured at 5-minute intervals; RR, SPO2, temperature, and ECG were monitored continuously until the end of surgery.

Intravenous fentanyl at 1µg/kgwas repeated every 45 minutes until the end of surgery to maintain intraoperative analgesia. At the end of surgery, Isoflurane was discontinued, and residual neuromuscular paralysis was reversed with intravenous atropine 0.02mg/kg and neostigmine 0.05mg/kg. Patients’ trachea was extubated when fully awake and they were transferred to the post anaesthesia care unit (PACU). Monitoring of vital signs, fluid administration, pain assessment and oxygen supplementation were continued. An hour after admission to the PACU, all patients were discharged to the ward. Paracetamol infusion 1g every six hours starting from when the first intraoperative dose was given at induction of anaesthesia was continued postoperatively for 48 hours.

Static and dynamic pain intensity were assessed using the verbal rating scale in the PACU 1 hour after surgery when patients were fully awake and at 4, 12, and 24 hours postoperatively on the ward. Rescue analgesia was provided with intramuscular pethidine 1 mg/kg, administered 4 hourly and only when the pain score exceeded moderate (>2). The opioid consumption in the placebo and study groups 24 hours after surgery was determined and opioid-sparing effect of pregabalin calculated. The time to first request for analgesia was noted in both groups. Nausea and vomiting were treated with intravenous ondansetron 4 mg. Ramsay Sedation Scale14 was used to assess the level of sedation and incidence of dizziness was noted in both groups.

Data were analyzed using IBM SPSS Statistics for windows, version 20 (Armonk, NY: IBM Corp). Results were presented as frequency, proportion, mean, and standard deviation. Mean values were compared using the student’s t-test. Categorical data were compared with the chi-square test (or Fisher’s exact test, where applicable). Mann-Whitney u-test was used for comparison of pain scores which were presented in range and a p-value of <0.05 was considered statistically significant.

**Results**



















A total of 82 patients were recruited into the study, out of which 41 subjects, (Group A, placebo group) received placebo, and the other 41 subjects, (Group B study group) received pregabalin after randomization. All eighty-two patients completed the study.

**Table 1**

There were no significant differences, between the two groups, in their mean ages, heights, weights and BMI’s. The proportions of patients in ASA classes I and II between the two groups were not significantly different and neither were the proportions that had myomectomy or total abdominal hysterectomy performed.

**Table 2**

The mean duration of surgery in groups A and B were not significantly different (193±73 minutes and 184±92 minutes respectively, p = 0.634). The time to first request for analgesia was significantly shorter for the placebo compared to the study group, (47±19 minutes versus 258±137 minutes respectively, p<0.001).Twenty-four hours after surgery the total amount of pethidine consumed by patients in the placebo group was significantly greater than that consumed by those in the study group, (326.19±62.70 mg versus 192.86±55.84 mg respectively, p=0.001). The 24-hour postoperative opioid-sparing effect of preoperative oral 150 mg pregabalin was 40.9% (ie 133.33 X 100/326.19).

**Table 3**

The median pain score was 0 to 2 (no pain – moderate pain) throughout the study. Four hours postoperatively, patients in the placebo group had a pain score ranging from no pain to excruciating pain both at static and dynamic states, likewise at 12hrs in the dynamic state. Pain score in the study group ranged from no pain (VRS 0) to moderate (VRS 2) at static state, and severe pain (VRS 3) at dynamic state at 4hrs and 12hrs postoperatively. Pain scores in the placebo group were significantly higher than those in the study group at 1, 4 and 12 hours postoperatively (p<0.001). Twenty-four hours post-operatively there were no significant differences in the pain scores between the two groups in the static and dynamic states (p=0.131 and p=0.384 respectively).

**Table 4**

The Ramsay sedation scores at 1 hour and 4 hours after surgery showed significantly higher proportions of patients in the study group with deeper levels of sedation compared with patients in the placebo group (p=0.001). The sedation scores were not significantly different between the groups at 12 and 24 hours postoperatively (p = 1.000).

**Table 5**

The incidence of side effects is shown in this table. Nausea and vomiting were significantly more common in patients who had the placebo whilst dizziness and blurred vision were significantly more common in the study group patients (p<0.001).

**Discussion**

This study showed that pre-operative single-dose oral pregabalin 150 mg administered an hour before induction of general anaesthesia in patients who had abdominal gynaecological surgeries reduced both the static and dynamic pain intensity within the first 12 hours postoperatively. Furthermore, time to first request for analgesia was significantly prolonged in the pregabalin group with resultant significant reduction in the pethidine consumption within 24 hours after the surgery. However, patients in the pregabalin group experienced greater prevalence of side effects such as dizziness and blurring of vision.

Postoperative pain control was significantly better in the study group at 1 hour, 4 hours, and 12 hours both at static and dynamic states than the control group. However, after this period, there was no significant difference in pain scores between the groups. The results of the present study agree with the findings of improved postoperative pain control reported by Agarwal et al,12 Kim et al,15 and Ghai et al.16 Agarwal and co-workers12 observed a lower postoperative VAS scores in the pregabalin group compared with the placebo group. The similarity in the results might be explained by the fact that similar doses of 150mg of pregabalin were given to patients in the two studies.

A single dose of 150mg of pregabalin lasted for 12 hours in this study and which is in accordance with the pharmacokinetic profile of pregabalin after a single dose with duration of action lasting 7-12 hours. Given these pharmacokinetic characteristics, a second dose of pregabalin for the sustenance of the postoperative analgesic effect would have been appropriate except that it might be associated with more side effects.7,17 The fact that the drug is only available in oral formulation also makes repeat administration after abdominal surgeries impractical.

Though several studies4,18 have demonstrated the perioperative analgesic effects of pregabalin, findings of some studies6,19 failed to support this assertion. Paech et al,20 concluded that preoperative single dose of 100mg pregabalin to patients who had minor uterine surgery like dilatation and curettage did not reduce postoperative pain severity or improve their recovery. The use of doses lower than 150mg of pregabalin for perioperative pain control has been shown to produce no benefit.8 Thus, administration of 100mg pregabalin to patients enrolled by Paech et al, compared with the 150mg used in the other studies4,15 could explain the failure to demonstrate analgesic effect in their study.

The time to first request for analgesia in our study was significantly longer in the study group compared to the control group. This is consistent with the findings of Bindu et al21 and Ghai et al.16 Bindu and co-workers15 studied the effects of preoperative pregabalin on postoperative analgesia after thyroidectomy. They reported a longer mean time to request for rescue postoperative analgesia in the pregabalin group compared with the morphine group (322.07±69.11minutes vs 256.33±111.99 minutes respectively). Despite the fact that pain intensity expected in thyroidectomy may not be as severe as in abdominal gynaecological surgeries, pregabalin premedication was shown to prolong the time to first request for analgesia in their study.

As reported in our study, Ghai et al16 also found a significantly longer mean time to first request for analgesia in the pregabalin group in comparison with gabapentin group after abdominal hysterectomy under general anaesthesia. However, 300mg of pregabalin was administered by Ghai and colleagues in their study. No comparative advantage has been found in the use of 150mg or 300mg of pregabalin for postoperative pain management.22

This study demonstrated that preoperative use of pregabalin significantly reduced the total 24-hour postoperative pethidine consumption by 40.9% when compared with the placebo group. In a study by Mathiesen et al,23 a preoperative dose of 300mg pregabalin resulted in a 50% reduction in 24-hour morphine consumption in patients who had hip alloplastic surgery. Also similar to our finding, Agarwal et al4 reported a reduction of 73.1% in the 24-hour intravenous fentanyl patient-controlled analgesia (PCA) in the pregabalin group compared with the placebo group and this was coroborated by Ittichaikulthol et al22 and Cabrera Schulmeyer et al24 in their studies.

In spite of its analgesic and opioid-sparing benefits, dizziness was the leading side effect of pregabalin in the present study. Baidya et al25 reported that dizziness and somnolence were the most frequent side effects of pregabalin (22-29%). The incidence of dizziness was reported by studies3,26 that used higher doses than 150 mg of pregabalin. Interestingly, the pharmacodynamic mechanism of dizziness by pregabalin is not understood.

Consistent with the finding of Alimian et al,27 our study revealed higher incidence of sedation among the patients in the pregabalin group. This could be due to the sedative property of pregabalin.8 Our study also observed higher incidence of nausea and vomiting in the control group than the pregabalin group. This finding could be as a result of the opioid-sparing effects of pregabalin in the study group, and this corroborates the finding of a meta-analysis that reported a reduced incidence of postoperative nausea and vomiting (PONV).28,29

The limitation of this study is that it was confined to gynaecological abdominal surgeries and therefore the findings may not be generalized to other abdominal surgical procedures.

**Conclusion**

This study showed that preoperative oral administration of 150 mg pregabalin effectively reduced postoperative static and dynamic pain, prolonged time to first request for analgesia, and reduced 24-hour pethidine consumption and opioid-related adverse effects after abdominal gynaecological surgeries. However, pregabalin use was associated with greater incidence of dizziness, blurring of vision and sedation. It should be considered an adjuvant in multimodal pain management regimens following gynaecological surgeries.

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