

Post-operative Analgesic and Opioid-sparing Effect of a Single-dose Pre-operative Oral Pregabalin in Gynaecological Surgeries

Abstract

Background: Post-operative pain treatment is a major challenge in our environment. Opioids may cause respiratory depression post-operatively. Therefore, any combination of opioid and non-opioid analgesics that provides quality post-operative pain control and reduces opioid consumption with its attendant side effects will be highly desirable. **Objectives:** The aim of this article is to evaluate analgesic benefits and opioid-sparing effects of pre-operative oral pregabalin in patients who undergo abdominal gynaecological surgeries. **Materials and Methods:** A prospective randomized double-blind placebo-controlled study is carried out at University of Ilorin Teaching Hospital, Kwara State, Nigeria. 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 150 mg, respectively, 1 h before induction of general anaesthesia. Post-operative pain intensity using a five-point Verbal Rating Scale, time to first request for analgesia, and 24 h post-operative pethidine consumptions were assessed. Mean values were compared using Student's *t*-test. Categorical data were compared with the χ^2 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 0–2 (no pain–moderate pain) throughout the study. Post-operative static and dynamic pain scores at 1, 4, and 12 h were significantly higher in the placebo group ($P < 0.001$). 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 h post-operative were 47 ± 19 vs. 258 ± 137 min ($P = 0.001$) and 326.19 ± 62.70 vs. 192.86 ± 55.84 mg ($P = 0.001$) in the control and study groups, respectively. The pre-operative use of pregabalin reduced post-operative opioid requirement by 40.9% in the study group. Nausea and vomiting were more common in the placebo group, whereas dizziness, blurring of vision, and sedation were more common in the pregabalin group. **Conclusion:** A single pre-operative dose of 150 mg oral pregabalin had significantly greater analgesic effects compared with 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: Gynaecological surgeries, multimodal analgesia, postoperative pain, pregabalin

Introduction

Post-operative pain control remains a significant problem following surgical operations in our environment.^[1] Poorly managed post-operative pain can result in decreased vital capacity, tachycardia, hypertension, myocardial ischaemia, and transition to chronic pain.^[2] Recent 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 post-operative pain.^[3]

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Traditionally, opioids are the mainstay of the treatment of post-operative 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 post-operative pain control with pre-emptive analgesic effects 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]

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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 h 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 post-operative pain because of its analgesic effect.^[8]

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

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

Materials and 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 18–65 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,^[12] the standard deviation for the time to first analgesia request in the placebo group was 10.97; with a difference of 7.5 min 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 h 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 scale^[13] (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. Patients' 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 labelled A and 41 papers labelled 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), whereas those in group B received pregabalin 150 mg. The medications were administered to patients orally 1 h 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 a multi-parameter patient monitor and baseline vital signs such as heart rate, 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 min and a loading dose of intravenous fentanyl at 2 µg/kg was given. Anaesthesia was induced with intravenous propofol 2 mg/kg, and intravenous suxamethonium 1 mg/kg was immediately administered to facilitate excellent intubating condition. Laryngoscopy was done and patients' 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 0.1 mg/kg. The BP was subsequently monitored and measured at 5-min intervals; RR, SPO₂, temperature, and ECG were monitored continuously until the end of surgery.

Intravenous fentanyl at 1 µg/kg was repeated every 45 min until the end of surgery to maintain intra-operative analgesia. At the end of surgery, isoflurane was discontinued, and residual neuromuscular paralysis was reversed with intravenous atropine 0.02 mg/kg and neostigmine 0.05 mg/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 1 g every 6 h starting from when the first intra-operative dose was given at induction of anaesthesia was continued post-operatively for 48 h.

Static and dynamic pain intensities were assessed using the VRS in the PACU 1 h after surgery when patients were fully awake and at 4, 12, and 24 h post-operatively 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 h 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. The Ramsay Sedation Scale^[14] was used to assess the level of sedation, and incidence of dizziness was noted in both groups.

Data were analysed using IBM SPSS Statistics for windows, version 20 (Armonk, NY, USA: IBM Corp). Results were presented as frequency, proportion, mean, and standard deviation. Mean values were compared using Student's *t*-test. Categorical data were compared with the χ^2 test (or Fisher's exact test, where applicable). The Mann-Whitney *U*-test was used for comparison of pain scores which were presented in range, and a *P*-value of less than 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 82 patients completed the study [Table 1 and Figure 1].

There were no significant differences between the two groups in their mean ages, heights, weights, and body mass index (BMI). The proportions of patients in ASA classes I and II between the two groups were not significantly different and nor were the proportions that had myomectomy or total abdominal hysterectomy performed [Table 2].

The mean duration of surgery in groups A and B was not significantly different (193 ± 73 and 184 ± 92 min, respectively, $P = 0.634$). The time to first request for analgesia was significantly shorter for the placebo compared with the study group (47 ± 19 vs. 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 vs. 192.86 ± 55.84 mg, respectively, $P = 0.001$). The 24-h post-operative opioid-sparing effect of pre-operative oral 150 mg pregabalin was 40.9% (i.e., $133.33 \times 100/326.19$) [Table 3].

The median pain score was 0–2 (no pain–moderate pain) throughout the study. Four hours post-operatively, patients in the placebo group had a pain score ranging from no pain to excruciating pain both at static and dynamic states, likewise at 12 h 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 4 and 12 h post-operatively. Pain scores in the placebo group were significantly higher than those in the study group at 1, 4, and 12 h post-operatively ($P < 0.001$). Twenty-four hours post-operatively, there were no significant differences

Table 1: Demographic variables, ASA classification, and the type of surgery in the control and study groups

Variables	Number of patients, <i>n</i> (%)			<i>P</i> -value
	Group A (<i>n</i> = 41)	Group B (<i>n</i> = 41)	Total (<i>n</i> = 82)	
Age group				
≤ 30	7 (17.1)	10 (24.4)	17 (20.7)	0.323
31–35	10 (24.4)	12 (29.3)	22 (26.8)	
36–40	11 (26.8)	7 (17.1)	18 (22.0)	
41–45	3 (7.3)	7 (17.1)	10 (12.2)	
> 45	10 (24.4)	5 (12.2)	15 (18.3)	
Mean ± SD	39.14 ± 9.16	36.83 ± 7.95		0.220
Weight (kg)				
Mean ± SD	63.86 ± 9.34	61.86 ± 9.88		0.343
Height (m)				
Mean ± SD	1.62 ± 0.06	1.63 ± 0.06		0.653
BMI (kg/m ²)				
Mean ± SD	24.33 ± 3.13	23.44 ± 3.51		0.222
ASA classification				
I	36 (87.8)	37 (90.2)	73 (89.0)	1.000
II	5 (12.2)	4 (9.8)	9 (11.0)	
Type of operation				
Myomectomy	30 (73.2)	32 (78.0)	62 (75.6)	0.608
TAH	11 (26.8)	9 (22.0)	20 (24.4)	

ASA = American Society of Anesthesiologists Physical Status Grading, *n* = number of patients, TAH = total abdominal hysterectomy, BMI = body mass index

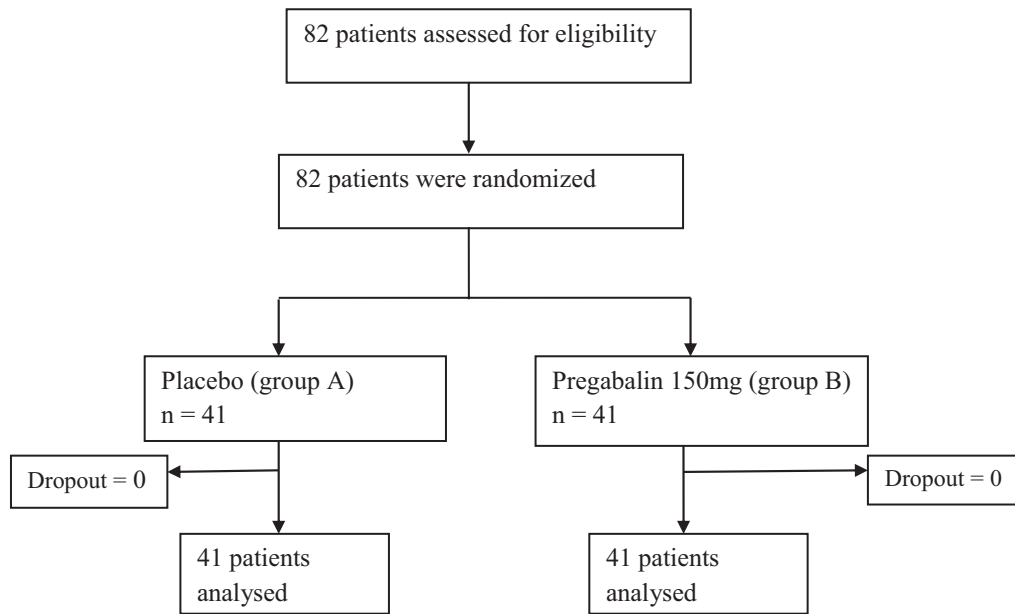


Figure 1: Flowchart

Table 2: Duration of surgery, time to first request for analgesia, and 24-h pethidine consumption in the control and study groups

Variables	Group A, n = 41	Group B, n = 41	P-value
Duration of surgery (min)			
Mean $\pm$ SD	193 $\pm$ 73	184 $\pm$ 92	0.634
Time to first request for analgesia (min)			
Mean $\pm$ SD	47 $\pm$ 19	258 $\pm$ 137	<0.001
Total amount of pethidine consumed (mg)			
Mean $\pm$ SD	326.19 $\pm$ 62.70	192.86 $\pm$ 55.84	<0.001

SD = standard deviation

Table 3: Post-operative VRS pain scores in both groups at static and dynamic states

Pain score	Groups, N = 82	Median	Range	P-value
VRS 1 h static	Group A	1 0	0–3	0.001
	Group B		0–2	
VRS 1 h dynamic	Group A	1 0	0–3	0.000
	Group B		0–2	
VRS 4 h static	Group A	2 1	0–4	0.000
	Group B		0–2	
VRS 4 h dynamic	Group A	2 2	0–4	0.000
	Group B		0–3	
VRS 12 h static	Group A	2 1	1–3	0.000
	Group B		0–2	
VRS 12 h dynamic	Group A	2 2	1–4	0.000
	Group B		1–3	
VRS 24 h static	Group A	1 1	1–3	0.131
	Group B		1–2	
VRS 24 h dynamic	Group A	2 2	1–3	0.384
	Group B		1–3	

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 and 4 h after surgery showed significantly higher proportions of patients in the study group with deeper levels of sedation compared with

Table 4: Post-operative sedation Ramsay scores in the control and study groups

Sedation score	Number of patients, <i>n</i> (%)		<i>P</i> -value
	Group A, <i>n</i> = 41	Group B, <i>n</i> = 41	Total, <i>n</i> = 82
1 h			
Anxious/agitated/restless	0 (0.0)	1 (2.4)	1 (1.2)
Cooperative	16 (39.0)	33 (80.5)	49 (59.8)
Responding to command	25 (61.0)	7 (17.1)	32 (39.0)
4 h			
Anxious/agitated/restless	0 (0.0)	0 (0.0)	0 (0.0)
Cooperative	2 (4.9)	14 (33.1)	16 (19.5)
Responding to command	39 (95.1)	27 (65.9)	66 (80.5)
12 h			
Anxious/agitated/restless	0 (0.0)	0 (0.0)	0 (0.0)
Cooperative	0 (0.0)	0 (0.0)	0 (0.0)
Responding to command	41 (100.0)	41 (100.0)	82 (100.0)
24 h			
Anxious/agitated/restless	0 (0.0)	0 (0.0)	0 (0.0)
Cooperative	1 (2.4)	0 (0.0)	1 (1.2)
Responding to command	40 (97.6)	41 (100.0)	81 (98.8)

Table 5: Side effects observed in patients in the control and study groups

	Number of patients, <i>n</i> (%)		<i>P</i> -value
	Group A, <i>n</i> = 41	Group B, <i>n</i> = 41	Total, <i>n</i> = 82
Nausea			
Yes	28 (68.3)	1 (2.4)	29 (35.4)
Vomiting			
Yes	11 (26.8)	0 (0.0)	11 (13.4)
Dizziness			
Yes	0 (0.0)	23 (56.1)	23 (28.0)
Blurring of vision			
Yes	0 (0.0)	11 (26.8)	11 (13.4)

patients in the placebo group ($P=0.001$). The sedation scores were not significantly different between the groups at 12 and 24 h post-operatively ($P = 1.000$) [Table 5].

The incidence of side effects is shown in this table. Nausea and vomiting were significantly more common in patients who had placebo, whereas 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 h post-operatively. Furthermore, time to first request for analgesia was significantly prolonged in the pregabalin group with resultant significant reduction in the pethidine consumption within 24 h after the surgery. However, patients in the pregabalin group experienced greater prevalence of side effects such as dizziness and blurring of vision.

Post-operative pain control was significantly better in the study group at 1, 4, and 12 h 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 post-operative pain control reported by Eman *et al.*,^[12] Kim *et al.*,^[15] and Ghai *et al.*^[16] Eman *et al.*^[12] observed a lower post-operative VAS score in the pregabalin group compared with the placebo group. The similarity in the results might be explained by the fact that similar doses of 150 mg of pregabalin were given to patients in the two studies.

A single dose of 150 mg of pregabalin lasted for 12 h 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 h. Given these pharmacokinetic characteristics, a second dose of pregabalin for the sustenance of the post-operative 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 studies^[4,18] have demonstrated the perioperative analgesic effects of pregabalin, findings of some studies^[6,19] failed to support this assertion. Paech *et al.*^[20] concluded that pre-operative single dose of 100 mg pregabalin to patients who had minor uterine surgery such as dilatation and curettage did not reduce post-operative pain severity or improve their recovery. The use of doses lower than 150 mg of pregabalin for perioperative pain control has been shown to produce no benefit.^[8] Thus, administration of 100 mg pregabalin to patients enrolled by Paech *et al.*, compared with the 150 mg used in the other studies,^[4,15] 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 when compared with the control group. This is consistent with the findings of Bindu *et al.*^[21] and Ghai *et al.*^[16] Bindu and co-workers^[15] studied the effects of pre-operative pregabalin on post-operative analgesia after thyroidectomy. They reported a longer mean time to request for rescue post-operative analgesia in the pregabalin group compared with the morphine group (322.07 ± 69.11 vs. 256.33 ± 111.99 min, 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 al.*^[16] also found a significantly longer mean time to first request for analgesia in the pregabalin group in comparison with the gabapentin group after abdominal hysterectomy under general anaesthesia. However, 300 mg of pregabalin was administered by Ghai *et al.* in their study. No comparative advantage has been found in the use of 150 or 300 mg of pregabalin for post-operative pain management.^[22]

This study demonstrated that pre-operative use of pregabalin significantly reduced the total 24-h post-operative pethidine consumption by 40.9% when compared with the placebo group. In a study by Mathiesen *et al.*,^[23] a pre-operative dose of 300 mg pregabalin resulted in a 50% reduction in 24-h morphine consumption in patients who had hip alloplastic surgery. Also similar to our finding, Agarwal *et al.*^[4] reported a reduction of 73.1% in the 24-h intravenous fentanyl patient-controlled analgesia in the pregabalin group compared with the placebo group and this was corroborated by Ittichaikulthol *et al.*^[22] and Cabrera Schulmeyer *et al.*^[24] 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 al.*^[25] reported that dizziness and somnolence were the most frequent side effects of pregabalin (22–29%). The incidence of dizziness was reported by studies^[3,26] 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 in 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 post-operative nausea and vomiting.^[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 pre-operative oral administration of 150 mg pregabalin effectively reduced post-operative static and dynamic pain, prolonged time to first request for analgesia, and reduced 24-h 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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Conflicts of interest

There are no conflicts of interest.

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