

THE ANALGESIC EFFECT OF GABAPENTIN VERSUS PREGABALIN IN POSTOPERATIVE PAIN MANAGEMENT OF MAJOR LOWER LIMB ORTHOPAEDIC SURGERIES

¹Dr. Kalu EBE, ^{*2}Dr. Nnaji, Chimaobi TIM and ³Dr. Okoli Chinwe EDITH

¹Consultant Anaesthetist, Department of Anaesthesia, Federal Medical Centre, Owerri, Imo State, Nigeria.

²Chief Consultant Anaesthetist, Department of Anaesthesia, Federal Medical Centre, Owerri, Imo State, Nigeria.

³Chief Consultant Anaesthetist, Department of Anaesthesia, Federal Medical Centre, Umuahia, Abia State, Nigeria.

*Corresponding Author: Dr. Nnaji, Chimaobi TIM

Chief Consultant Anaesthetist, Department of Anaesthesia, Federal Medical Centre, Owerri, Imo State, Nigeria.

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ABSTRACT

Background: Postoperative pain is of significant concern to patients undergoing lower limb surgery. Several pharmacological agents have been used to manage postoperative pain following lower limb orthopaedic surgery with variable results. However, only a few studies compared pregabalin and gabapentin for postoperative pain management of lower limb orthopaedic surgery. **Aim:** This study evaluated the postoperative analgesic effect of preoperatively administered oral gabapentin and pregabalin in lower limb orthopaedic surgery. **Method:** Approval for this study was obtained from the Health Research and Ethics Committee of Federal Medical Centre Owerri, Imo State, Nigeria. Written informed consent was obtained from each patient before enrolment into the study. A total of 90 patients between the ages of 18 – 65 years, ASA I and II physical status, scheduled for elective lower limb surgery were recruited for this study. They were randomized into three groups to receive either 300mg gabapentin in group G (n = 30), 150mg of pregabalin in group P (n=30), or placebo in group C (n=30). The pain scores, duration of analgesia, total opioid consumption, and side effects of the study drugs were assessed and documented. Data were collected and analysed using Statistical Package for Social Sciences (SPSS) version 20. A p-value of < 0.05 was considered statistically significant. **Results:** Ninety patients completed the study. The mean VAS score at 1st hour was significantly lower in Group P (1.33±0.48), compared with Group G (2.17±0.83) and Group C (3.67±1.61), (p < 0.01). Moreover, the mean duration of analgesia was significantly prolonged in Group P (422.00±39.934 min), compared with Group G (272.07±55.08 min) and Group C (194.27±23.22 min), p<0.01. Nevertheless, the mean total analgesic consumption was significantly higher in Group C (180.23±34.07 mg), compared to Group G (126.10±41.88 mg) and Group P (102.13±32.78 mg), p<0.01. However, the incidence of hypotension was more in Group C (20%), compared with Group P (13.3%) and Group G (10%). **Conclusion:** This study showed that single preoperative oral pregabalin 150mg provided prolonged duration of analgesia, reduced pain score, and reduced postoperative pethidine consumption, compared with preoperative oral gabapentin in patients that received spinal anaesthesia for lower limb orthopaedic surgery.

KEYWORDS: Postoperative pain relief, gabapentin, pregabalin.

INTRODUCTION

Effective postoperative pain control is an essential component of surgical patients' care. The advantages include patient comfort and satisfaction, early mobilization, fewer pulmonary and cardiac complications, reduced risk of deep vein thrombosis, and faster recovery.^[1] Pain is described by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage".^[2]

Patients undergoing lower limb orthopaedic surgery are usually characterized by musculoskeletal dysfunctions such as unstable fractures, deformities, joint disorders, infected or necrotic tissues, trauma or tumours. Common surgical procedures include open reduction with internal fixation and closed reduction with external fixation of fractures, arthroplasty, joint replacement, meniscectomy, and amputations.^[3] These are well suited for regional anaesthetic techniques. Regional anaesthesia like spinal and epidural anaesthesia may reduce perioperative complications compared with general anaesthesia.^[4] The goal of surgery is to improve limb function, recover movement and stability in addition to alleviating pain and incapacity.^[3] The degree of postoperative pain is

usually moderate to severe following lower limb surgery.^[5] Thus, establishing the need to identify a means of effectively managing postoperative pain following lower limb orthopaedic surgery.

Studies.^[6,7] have shown that pharmacological and non-pharmacological techniques can be used to manage postoperative pain. Cooks et al.^[8] in a review study showed that drugs such as local anesthetics, opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors, gabapentin, pregabalin, clonidine and dexmedetomidine are beneficial in managing postoperative pain. They also noted the value of non-pharmacological interventions like patient education, cognitive behavioural therapy, distraction techniques, aromatherapy, canine therapy, and virtual reality aiding management of postoperative pain.

Some studies.^[5,9] established that pregabalin and gabapentin reduced postoperative pain, prolonged the duration of analgesia, reduced analgesic consumption, and improved patient satisfaction. Gabapentin and pregabalin have been known to also reduce movement evoked pain, and this can lead to enhanced recovery of function postoperatively.^[10] Gabapentin,^[11] is a structural analogue of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), such that it is soluble in water, basic and acidic aqueous solutions. It is highly charged at physiological pH. Pregabalin,^[12] is a lipophilic GABA analogue, absorbed in the small intestine by a combination of diffusion and facilitated transport. The average bioavailability is greater than 90% independent of the dose and its elimination half-life is 5.5 – 6.7 hours. Both drugs are available only in oral preparation and are excreted unchanged in urine.

This study aimed to compare the postoperative analgesic effect of gabapentin and pregabalin administered preoperatively for lower limb orthopaedic surgery. The primary outcome will be to determine the mean duration of analgesia of preoperatively administered gabapentin and pregabalin, while the secondary outcomes will be to determine the mean pain scores, postoperative analgesic requirement, haemodynamic differences and side effects among the groups for 24 hours.

MATERIALS AND METHODS

Ethical approval for this prospective, randomized double-blind controlled study was obtained from the Ethics and Research Committee of Federal Medical Centre, Owerri, Imo State, in Nigeria (FMC/OW/HREC/VOL.1). Written informed consent was obtained from each patient scheduled for elective lower limb orthopaedic surgery before enrolment into the study. We recruited ASA I or II, 18 – 65 years old male and female adult patients, who were to have their surgery under spinal anaesthesia and allocated them into Groups G (n=30), P (n=30) and C (n=30), by using a computer-derived random number sequence in an opaque envelope, to receive any of the study agents. The investigators were

not aware of the group allotment until the patients had been randomized. Sample size of 30 in each of the groups was derived using the formula for comparison of the mean by Raveedran and Gitanjali 1997.^[13]

Patients who refused to consent for the study, undergoing general anaesthesia, with evidence of uncontrolled clinically important neurological, renal, hepatic, cardiovascular, metabolic, or endocrine dysfunction, on anticoagulants, allergic to the study agents or ASA class more than II, whose body mass index more than 30kg/m², age is less than 18 and more than 65 years, pregnant or booked as an emergency were excluded from the study.

The patients booked for elective lower limb orthopaedic surgery were preoperatively evaluated day from surgery in the orthopaedic ward, to establish rapport and fitness for anaesthesia and surgery. Preoperative anxiolysis was achieved overnight with oral diazepam 5mg. The patients were counselled for 6 hours preoperative fasting for solid food and 2 hours for clear fluid.

Patients in Group G (n=30) were given a single dose of gabapentin 300mg, in Group P (n=30) pregabalin 150mg was administered, while in Group C (n=30) a placebo similar to the study drugs in shape and colour was given via the oral route with 30 ml of water, one hour prior to administration of spinal anaesthesia, by a research assistant.

Preanaesthetic check was done, intravenous access was secured with a 16 gauge cannula, and the patients were preloaded with warm normal saline 10ml/kg over 20 minutes. The patients were placed in the sitting position on the surgical table with the help of a research assistant, legs placed on a stool to allow enough arching of the spine, and arms rested on a pillow. The back of the patient was cleaned with swabs and antiseptic solutions and draped. Subarachnoid block was performed at L₃ - L₄ interspace through a midline approach using a 25 Gauge Quincke spinal needle. A dose of 15mg (3ml) of 0.5% hyperbaric bupivacaine (Marcaine Spinal 0.5% AstraZeneca) was injected into the subarachnoid space after confirming a clear, and free flow of cerebrospinal fluid and the patient was immediately returned to the supine position with the head and shoulders supported on a pillow.

The pulse rate (PR), systolic, diastolic, and mean arterial blood pressures (SBP, DBP, MAP), peripheral oxygen saturation (SpO₂), level of sensory block, and degree of motor block, were monitored until the sensory and motor blocks reached an acceptable level for surgery. A Modified Bromage Scoring System^[9] was used to assess the extent of motor block, and a 10cm visual analogue scale (VAS), was used to assess pain. The level of sensory block was assessed using a piece of cotton wool soaked in alcohol (methylated spirit) to touch the patients extending to higher dermatomal levels, the highest

dermatomal level was recorded. Having achieved the desired level of sensory block (T_{10}), the surgical site preparation and surgery was commenced.

Intra-operatively, the PR, SpO_2 , heart rhythm, intraoperative blood loss estimation, and temperature were monitored continuously, while the SBP, DBP, and MAP were monitored every 3 minutes in the first 15 minutes, and every 5 minutes till the end of surgery. Ephedrine was used to manage hypotension and documented. Hypothermia was prevented and managed by giving warm intravenous fluids and keeping the surgical theatre environmental temperature at $25^\circ C$.

At the end of the surgery, the patients were transferred to the Post Anaesthesia Care Unit (PACU). The HR, SBP, DBP, MAP, and SpO_2 were monitored and recorded at 0 (on arrival in PACU), 15 and 30 minutes, 1, 2, 3, and 4th hour following recovery by a PACU staff. Regression of motor block of the lower limbs was assessed using the modified Bromage's score. Pain was assessed with VAS score at 0, 1, 2, 3, 4, 8, 12, 16, 20, and 24 hr. Patients with a pain score >3 received rescue analgesia (intravenous Pethidine 1mg/kg), which were documented.

The duration of analgesia was taken as the interval between intrathecal injection of spinal bupivacaine to the time of first request for analgesia (VAS >3). While the duration of motor blockade it was taken as the interval between intrathecal injection of hyperbaric bupivacaine 0.5% to complete recovery of motor block (modified Bromage's score 0). Sedation was assessed with the Ramsay sedation scale⁹. Time to micturition and ambulation were not documented because patients were non-ambulant and had urethral catheter drains.

RESULTS

Ninety patients were recruited for this study; 30 patients in Group G, 30 patients in Group P, and 30 patients in Group C, and they all completed the study.

Table I shows the comparison of demographic characteristics among groups. The mean ages among Groups G, P, and C were not statistically significant ($p = 0.99$). Furthermore, there were no statistical differences ($p = 0.45$, $p = 0.93$, and $p = 0.50$) in the mean weight, mean height, and mean BMI as well as the gender distribution ($p=1.00$).

Table II compares the perioperative characteristics between groups. There was no statistical significance ($p=1.00$) in ASA I/II grading among Group G (21/9), Group P (22/8), and Group C (24/6). The mean duration of surgery was the same among the groups ($p=0.80$). However, the mean total analgesic consumption was significantly lesser in Group P (102.13 \pm 32.78 mg), compared to Group G (126.10 \pm 41.88 mg) and Group C (180.23 \pm 34.07 mg), $p<0.01$.

The mean onset time of sensory block was the same among the Groups ($p=0.64$), as well as the mean onset time of the motor block ($p = 0.11$). The mean duration of motor block was prolonged in Group P (158.23 \pm 15.32 min) compared with Group G (156.33 \pm 9.96 min) and Group C (151.33 \pm 10.83 min), but this was not statistically significant ($p = 0.85$). However, the mean duration of analgesia was significantly prolonged in Group P (422.00 \pm 39.934 min), compared with Group G (272.07 \pm 55.08 min) and Group C (194.27 \pm 23.22 min), $p<0.01$, as shown in Table III.

The change in mean lowest PR was statistically significant ($p = 0.01$), and the reduction was more in Group C (65.90 \pm 3.25 bpm), compared with Group P (67.73 \pm 3.52 bpm) and Group G (68.53 \pm 2.98 bpm). However, the changes in the mean highest PR among the groups were not statistically significant ($p=0.56$). The changes in the mean lowest SBP and mean highest SBP among the groups were respectively, not statistically significant ($p = 0.37$ and $p = 0.24$), as well as the changes in the mean lowest DBP and mean highest DBP ($p=0.18$ and $p=0.74$). The changes in the mean lowest MAP and mean highest MAP remained the same with $p = 0.85$ and $p=0.83$, respectively, as shown in Table IV.

Table V compares the mean VAS scores among groups G, P and C. The difference in mean VAS score among the groups at 0 hr was not statistically significant ($p = 0.21$). Nevertheless, at 1 hr, the mean VAS score became significantly higher in Group C (3.67 \pm 1.61), compared with Group G (2.17 \pm 0.83) and Group P (1.33 \pm 0.48), $p < 0.01$. At 2nd hr, the mean VAS score remained significantly higher in Group C (2.90 \pm 0.83), compared with Group G (2.40 \pm 1.04) and Group P (1.50 \pm 0.57), $p<0.01$. However, at the 3rd hr, the change in mean VAS score was not statistically significant ($p=0.29$). At the 4th hour, the mean VAS score was significantly lower in G (2.13 \pm 0.93), compared with Group C (2.83 \pm 0.65), and Group P (2.47 \pm 0.97), $p = 0.01$. However, at the 8th hr, the mean VAS score became significantly lower in Group P (1.83 \pm 1.18), compared to Group G (2.43 \pm 0.68) and Group C (3.00 \pm 0.98), $p < 0.01$. However, at the 12th hr, the mean pain score in Group G dropped to 2.30 \pm 1.06, while Group P and Group C increased to 3.00 \pm 1.11 and 3.90 \pm 0.89 respectively. The difference observed was statistically significant ($p < 0.01$). At the 16th hr, it was observed that the difference in mean pain scores was not statistically significant, $p=0.13$. Group P (2.07 \pm 0.87) remained lower at the 20thhr, compared with Group C (2.53 \pm 0.86) and Group G (2.67 \pm 0.88), and the difference observed were statistically significant ($p = 0.02$). The value of mean pain score at the 24th hour was the same among the Groups ($p = 0.68$).

Table VI compares the mean VAS scores between the gabapentin and pregabalin groups. The mean VAS score at 0 hr was lower in Group P (1.17 \pm 0.38), compared with Group G (1.43 \pm 0.68) and the differences was not statistically significant ($p = 0.52$). However, at 1 hr and

2nd hr, the mean VAS scores remained lower in Group P (1.33±0.48 and 1.50±0.57) compared with Group G (2.17±0.83 and 2.40±1.04) and the difference were statistically significant ($p < 0.01$ and $p < 0.01$). At the 3rd hr, the mean VAS score remained lower in Group P (1.83±0.38), compared with Group G (2.13±0.98). However, the difference was not statistically significant ($p=0.10$). At the 4th hour, the mean VAS score became higher in Group P (2.83±0.65), compared with Group G (2.13±0.93), but the difference was not statistically significant ($p = 0.16$). At the 8th and 12thhr, the mean VAS scores were significantly reduced in Group P (1.83±1.18 and 2.36±1.06), compared to Group G (2.43±0.68 and 3.00±1.11), $p < 0.01$ and $p=0.02$ respectively. However, at the 16thhr, it was observed that the mean VAS scores in Group G and Group P reduced to 2.23±1.04 and 2.00±1.15, and the difference was not statistically significant ($p=0.26$). The mean VAS scores remained significantly lower in Group P (2.07±0.87), compared with Group G (2.67±0.88) at the 20thhr, $p = 0.01$. At the 24thhr, the mean VAS score remained the same between Group P (2.23±0.72) and Group G (2.23±0.57), $p = 0.55$.

Table VII compares the mean VAS scores between Group G and Group C. The mean VAS score at 0 hr was not statistically significant ($p = 0.52$). At 1st and 2ndhr, the mean VAS score was significantly higher in Group C (3.67±1.61 and 2.90±0.83), compared with Group G (2.17±0.83 and 2.40±1.04) and the difference was statistically significant ($p < 0.01$ and $p < 0.01$). At the 3rdhr, the mean VAS score was not statistically significant ($p=0.32$). However, at the 4th, 8th, and 12th hour, the mean VAS scores were significantly lower in G (2.13±0.93, 2.43±0.68 and 2.30±1.06), compared with Group C (2.83±0.65, 3.00±0.98 and 3.00±1.11), $p =$

0.02, $p=0.03$ and $p=0.003$ respectively. At the 16th, 20th, and 24th hr, the mean VAS score was not statistically significant ($p = 0.3$, $p=0.37$, and $p=0.73$ respectively).

The comparison of the mean VAS scores among groups P and C shows that at 0 hr the difference was not statistically significant ($p = 0.49$). At 1 hr, the mean VAS score was higher in Group C (3.67±1.61), compared with Group P (1.33±0.48), and the difference was statistically significant ($p < 0.01$). At the 2nd hr, the mean VAS score was higher in Group C (2.90±0.83), compared with Group P (1.50±0.57), and the difference was statistically significant ($p < 0.01$). At the 3rd and 4th hr, the mean VAS score was not statistically significant ($p=0.31$ and $p=0.14$ respectively). At the 8th and 12thhr, the mean VAS score was significantly lower in Group P (1.83±1.18 and 2.36±1.06), compared to Group C (3.00±0.98 and 3.90±0.89), $p < 0.01$ and $p < 0.01$ respectively. At the 16th, 20th, and 24th hr, it was observed that the mean VAS was, respectively, not statistically significant ($p=0.06$, $p=0.05$, and $p = 0.88$), as shown in Table VIII.

The distribution of the types of orthopaedic surgery done is shown in Figure 1, while Figure 2 shows the distribution of side effects among the groups. Hypotension was more in Group C (20%), compared with Group P (13.3%) and Group G (10%). Group P (6.7%) and Group C (6.7%) had the same incidence rate of nausea. However, this was lower in Group G (3.3%). Dizziness 6.7% in Group P and 3.3% in Group G. There was no incidence of dizziness in Group C. The incidence of somnolence was 3.3% in Group G and 3.3% in Group P, while Group C patients did not observe any somnolence. Shivering was more in Group C (23.3%), compared to Group P (16.7%) and Group G (10%).

Table I: Demographic characteristics of the patients in the Gabapentin, Pregabalin, and Control groups.

Variables	Group G (n=30) mean±SD, N (%)	Group P (n=30) mean±SD, N (%)	Group C (n=30) mean±SD, N (%)	p value
Age (Yr)	40.90±13.18	40.90±14.50	41.30±12.65	0.99
Weight (kg)	66.77±6.50	70.87±20.87	67.63±6.58	0.45
Height (cm)	164.13±7.12	164.53±6.43	163.87±6.58	0.93
BM1 (kg/m ²)	24.79±1.90	26.18±7.45	25.20±2.16	0.49
Gender (M/F)	16(53%)/14(47%)	17(57%)/13(43%)	17(57%)/13(43%)	1.00

Table II: Perioperative characteristics of the Gabapentin, Pregabalin, and Control groups.

Variables	Group G (n=30) mean±SD, N (%)	Group P (n=30) mean±SD, N (%)	Group C (n=30) mean±SD, N (%)	p value
ASA I/II grading	21(70%)/9(30%)	22(73%)/8(27%)	24(80%)/6 (20%)	--
Duration of Surgery (min)	109.13±13.89	110.70±13.28	108.33±14.24	0.80
Total analgesic consumption (mg)	126.10±41.88	102.13±32.78	180.23±34.07	<0.01*

* $p < 0.05$ = significant

Table III: Sensory and motor block characteristics of the Gabapentin, Pregabalin, and Control groups.

Variables	Group G (n=30) mean±SD	Group P (n=30) mean±SD	Group C (n=30) mean±SD	p value
Onset of sensory block (min)	2.60±0.26	2.62±0.26	2.65±0.22	0.64

Onset of motor block (min)	3.19±0.35	3.33±0.22	3.30±0.20	0.11
Duration of motor (min)	156.33±9.96	158.23±15.32	151.33±10.83	0.85
Duration of analgesia (min)	272.07±55.08	422.00±39.34	194.27±23.22	<0.01*

* p<0.05 = significant

Table IV: Intraoperative haemodynamic changes of the Gabapentin, Pregabalin, and Control groups.

Variables	Group G (n=30) mean±SD	Group P (n=30) mean±SD	Group C (n=30) mean±SD	p value
Lowest PR (bpm)	68.53±2.98	67.73±3.52	65.90±3.25	0.01*
Highest PR (bpm)	88.17±3.80	87.72±3.34	87.20±3.15	0.56
Lowest SBP (mmHg)	106.7±7.65	108.27±7.30	103.66±7.30	0.37
Highest SBP (mmHg)	130.47±4.15	131.0±5.15	129.00±4.60	0.24
Lowest DBP (mmHg)	63.31±7.45	64.10±7.44	60.60±7.78	0.18
Highest DBP (mmHg)	80.53±4.96	81.43±5.20	80.70±4.04	0.74
Lowest MAP (mmHg)	77.70±7.67	78.80±6.55	74.34±7.58	0.85
Highest MAP (mmHg)	98.09±3.71	98.70±3.71	98.46±3.22	0.83

* p<0.05 = significant

Table V: Mean VAS scores of the Gabapentin, Pregabalin, and Control groups.

Variables	Group G (n=30) mean±SD	Group P (n=30) mean±SD	Group C (n=30) mean±SD	p value
0hr	1.43±0.68	1.17±0.38	1.33±0.67	0.21
1 hr	2.17±0.48	1.33±0.48	3.67±1.61	< 0.01*
2 hr	2.40 ± 1.04	1.50 ± 0.57	2.90 ± 0.83	<0.01*
3 hr	2.13±0.98	1.83±0.38	2.17±1.11	0.29
4 hr	2.13±0.93	2.47±0.97	2.83±0.65	0.01*
8 hr	2.43±0.68	1.83±1.18	3.00±0.98	< 0.01*
12 hr	3.00±1.16	2.36±1.06	3.90±0.89	<0.01*
16 hr	2.23±1.04	2.00±1.15	2.60±1.22	0.13
20 hr	2.67±0.88	2.07±0.87	2.53±0.86	0.02*
24 hr	2.23±0.57	2.37±0.72	2.23±0.73	0.68

* p<0.05 = significant

Table VI: Mean VAS scores between Gabapentin and Pregabalin groups.

Time	Group G (n=30) (Mean±SD)	Group P (n=30) (Mean±SD)	p value
0 hr	1.43±0.68	1.17±0.38	0.522
1 hr	2.17±0.48	1.33±0.48	0.002*
2 hr	2.40±1.04	1.50±0.57	< 0.01*
3 hr	2.13±0.97	1.83±0.38	0.10
4 hr	2.13±0.93	2.47±0.97	0.159
8 hr	2.43±0.68	1.83±1.18	0.012*
12 hr	3.00±1.16	2.36±1.06	0.021*
16 hr	2.23±1.04	2.00±1.15	0.263
20 hr	2.67±0.88	2.07±0.87	0.013*
24 hr	2.23±0.57	2.23±0.72	0.549

* p<0.05 = significant

Table VII: Mean VAS scores between Control and Gabapentin groups.

Time	Group C (n=30) (Mean±SD)	Group G (n=30) (Mean±SD)	p value
0 hr	1.33±0.67	1.43±0.68	0.522
1 hr	3.67±1.61	2.17±0.83	<0.001*
2 hr	2.90±0.83	2.40±1.04	<0.001*
3 hr	2.17 ± 1.11	2.13 ± 0.97	0.32
4 hr	2.83±0.65	2.13±0.93	0.021*
8 hr	3.00±0.98	2.43±0.68	0.033*
12 hr	3.90±0.89	3.00±1.16	0.003*
16 hr	2.60±1.22	2.23±1.04	0.312

20 hr	2.53±0.86	2.67±0.88	0.368
24 hr	2.23±0.73	2.23±0.57	0.728

* p<0.05 = significant

Table VIII: Mean VAS scores between Control and Pregabalin groups.

Time	Group C (n=30) (Mean±SD)	Group P (n=30) (Mean±SD)	p value
0 hr	1.33±0.67	1.17±0.38	0.490
1 hr	3.67±1.61	1.33±0.48	<0.001*
2 hr	1.50±0.57	2.90±0.83	<0.01*
3 hr	1.83±0.38	2.17±1.11	0.32
4 hr	2.83±0.65	2.47±0.97	0.142
8 hr	3.00±0.98	1.83±1.18	0.001*
12 hr	3.90±0.89	2.36±1.06	<0.001*
16 hr	2.60±1.22	2.00±1.15	0.057
20 hr	2.53±0.86	2.07±0.87	0.053
24 hr	2.23±0.73	2.37±0.72	0.880

* p<0.05 = significant

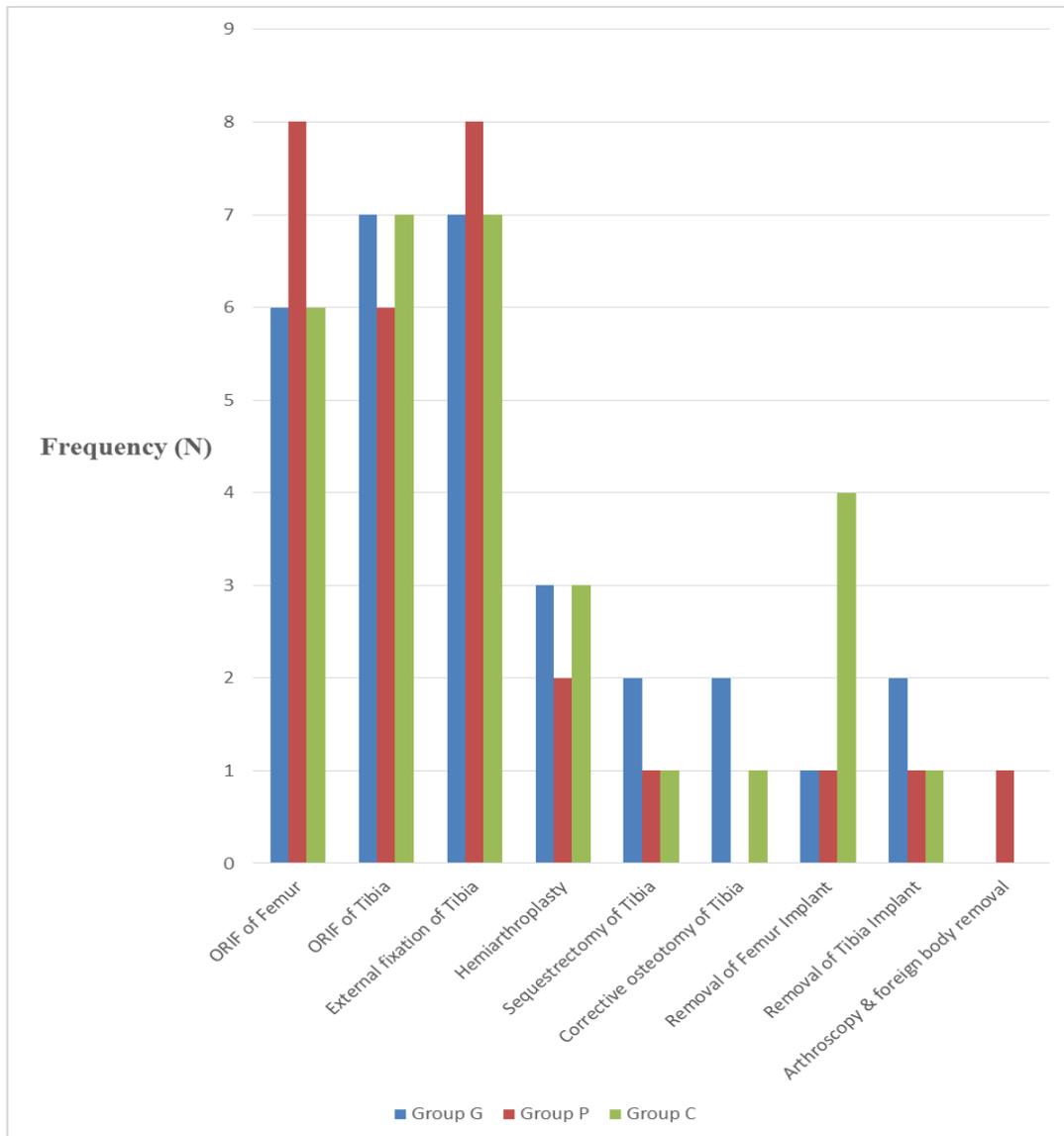


Figure 1: The distribution of the types of orthopaedic surgery among the study groups.

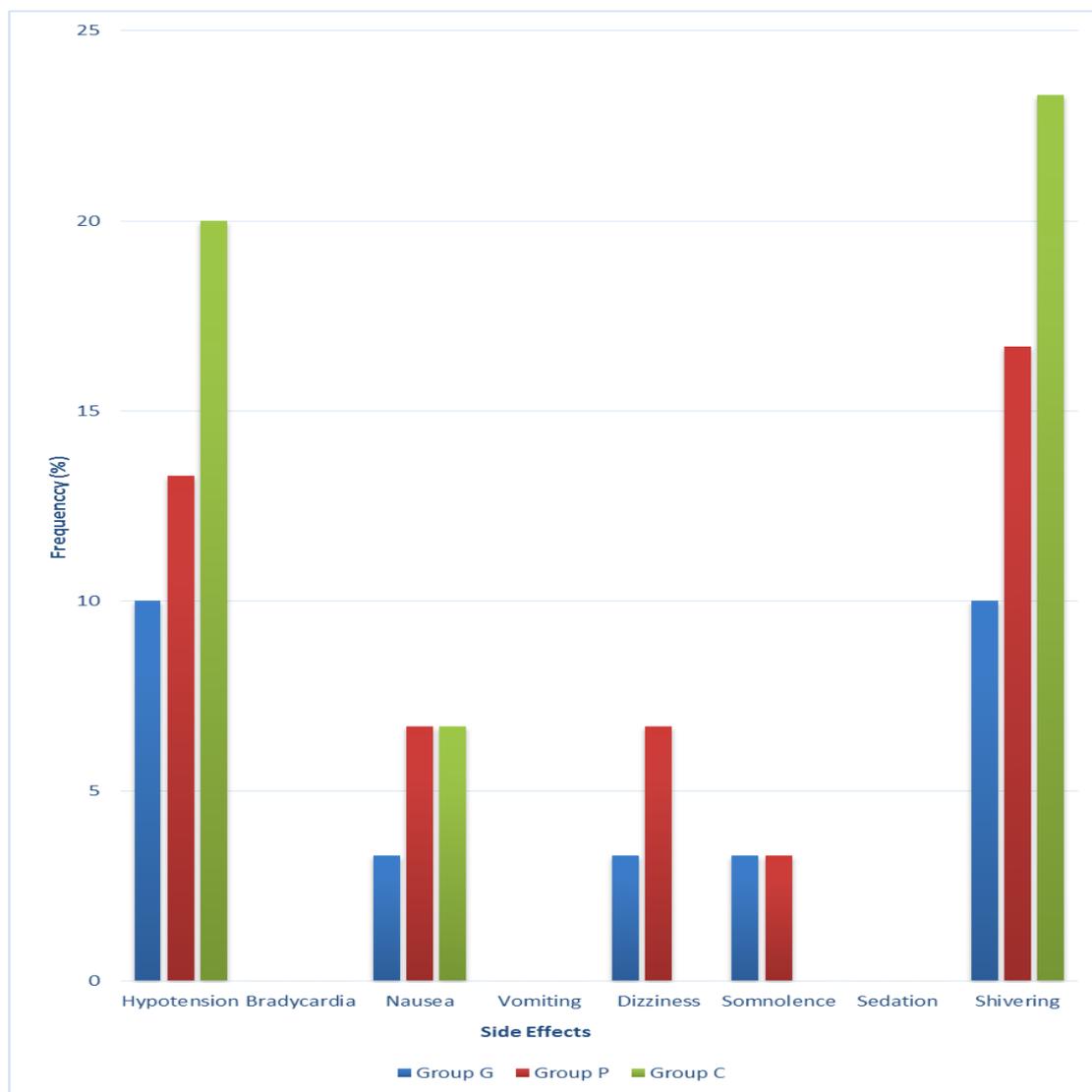


Figure 2: The distribution of the side effects among Groups G, P and C.

DISCUSSION

This study has shown that single-dose preoperative oral pregabalin 150 mg provided prolonged postoperative analgesia and reduced postoperative pethidine consumption than single-dose preoperative oral gabapentin 300mg and placebo in patients that had lower limb orthopaedic surgery.

The duration of analgesia was significantly prolonged in the pregabalin group, irrespective of the similarities in demographic characteristics of the groups. This finding is similar to that of other studies that used similar doses, as well as higher doses of the study drugs. Sabastian et al.^[14] in their study used pregabalin 150 mg and observed that the time for the first request of postoperative analgesics was prolonged. Saraswat et al.^[5] and Khetarpal et al.^[9] used pregabalin 300mg and observed that the time taken for the request of the first postoperative analgesic was prolonged.

Spinal anaesthesia provides adequate intraoperative analgesia and at times can provide good immediate postoperative analgesia in patients undergoing lower limb orthopaedic procedures.^[15,14] Spinal anaesthesia has a duration of up to 245 - 298 minutes,^[15] however, it has been suggested that when an additive is combined with spinal injection or preoperative medication is given prior to the administration of spinal anaesthesia, it can eliminate pain in the intraoperative, as well as during the postoperative period.^[15,16] The addition of preoperative pregabalin to spinal anaesthesia provided pain relief for lower limb orthopaedic surgery that extended into the postoperative period than in patients that received preoperative gabapentin or placebo.

The duration of analgesia in patients that received preoperative pregabalin in this study (7.03 hours) did not corroborate with that observed by Abdou et al.^[17](8.13 hours) and Saraswat et al.^[5] (14 hours) studies. The disparity between the present study and that of Abdou et al.^[17] despite the use of the same dose of pregabalin (150mg), could be explained by the complexity and

degree of the surgery. Abdou *et al.*^[17] evaluated only patients undergoing fixation of a tibial fracture, while the present study evaluated different arrays of surgeries including femoral fracture fixation, and hemiarthroplasty. In a study conducted by Tong,^[18] in the United States, he identified the degree of surgery and extent of injury as a predicting factor in the causation of postoperative pain. The prolonged duration of analgesia found in Saraswat *et al.*^[5] (14 hours) irrespective of the use of the same dose of spinal bupivacaine (15 mg) could be due to, the use of a higher dose of pregabalin (300mg). Piyapolrungrroj *et al.*^[19] and Schulze-Bonhage²⁰ reported that pregabalin demonstrates linear uptake without transporter saturation at therapeutic concentrations, as it is absorbed throughout the small intestine. Thus, this might demonstrate increased efficacy and prolonged postoperative analgesia in situations where higher doses are used.

In our study, we evaluated the duration of postoperative analgesia in patients that received preoperative oral gabapentin 300mg, one hour prior to spinal anesthesia for lower limb orthopaedic surgery. It was observed that gabapentin prolonged the duration of postoperative analgesia relative to the patients that received placebo. Khetarpal *et al.*^[9] reported a longer duration of analgesia in patients that received gabapentin, in comparison with those that received placebo in lower limb orthopaedic surgery. This is also similar to Panah *et al.*^[16] and Gogna *et al.*^[21] findings. In this study, the dose of gabapentin 300mg was used and it was noted that the duration of analgesia was 4.5 hours. This is consistent with the duration of analgesia that was reported in the studies of Panah *et al.*^[16] (4 hours) who used the dose of gabapentin 300mg and Gogna *et al.*^[21] (4.8 hours) who used the dose of gabapentin 600mg. Bockbrader *et al.*^[22] reported that gabapentin bioavailability varies inversely with its dose, and with increasing the dose of gabapentin, the absorption remains nonlinear and the bioavailability decreases. This could explain the duration of analgesia observed in Gogna *et al.*^[21] study, irrespective of the increase in the dose used.

The placebo group had the lowest duration of analgesia in the present study. This finding corroborates the report of Khetarpal *et al.*^[9] that placebo compared with gabapentin and pregabalin did not affect postoperative analgesia. Gupta *et al.*^[23] reported that placebo effects are genuine psychobiological phenomena attributable to the overall therapeutic context.

The analgesic intensity and quality of pain relief of lower limb orthopaedic surgery in the present study was observed to be adequate in patients that received preoperative gabapentin, pregabalin and placebo. When VAS score was used to compare postoperative pain in all three groups of patients, it was observed that the patients that received pregabalin reported lesser pain throughout the study, those that received gabapentin also reported lesser pain until 12 hours, but from 1 hour the patients

that received preoperative placebo reported pain. Subsequently, the pain scores remained lower in all groups due to the provision of adequate pain relief. This finding is similar to the report of Khetarpal *et al.*^[9] and Rajendran *et al.*^[23] that patients in both pregabalin and gabapentin groups reported less pain than patients in the placebo group in the postoperative hours in their various studies.

The present study has also demonstrated that there is synergism with the administration of gabapentin with spinal anaesthesia in reducing pain score. When placebo administration was compared with gabapentin in patients that received spinal anaesthesia, it was demonstrated that placebo did not improve the pain score beyond one hour after surgery; and those that received gabapentin did not report of pain until 12 hours. This finding corroborates with Panah *et al.*^[16] report that noted that when gabapentin was administered before spinal anaesthesia, pain reduction was observed at the second hour after surgery; however, it did not show any effect on the pain at the 12th and 24th hour after surgery in comparison with the placebo. This further augments Gogna *et al.*^[21] finding that subjects who received gabapentin preoperatively before spinal anaesthesia and incision had significantly lower pain scores at all points of time compared to placebo.

Reports from literature on the effect of preoperative administered pregabalin 150mg in patients receiving intrathecal bupivacaine in reducing pain scores are consistent with our findings.^[13,25] When pregabalin 150mg was administered before spinal anaesthesia in our study, it showed that the patients reported low pain score in comparison with controls. Sabastian *et al.*^[13] found that pre-emptive oral pregabalin 150mg significantly decreases the postoperative pain score. Akhavanakbari *et al.*^[25] in a study of sixty patients showed that 150mg dose preoperative pregabalin is a reliable method in reducing pain.

When patients that received pregabalin was compared with those that received gabapentin, it was noted that pregabalin significantly improved pain scores better than gabapentin. However, the study on the effect of preoperative administration of pregabalin or gabapentin in addition to intrathecal bupivacaine were conflicting. While some reports claim that preoperative administered pregabalin improved pain scores better than preoperative administered gabapentin,^[24,26] others report the contrary.^[26] Khetarpal *et al.*^[9] also noted that the pain scores in the pregabalin group decreased more postoperatively compared to the gabapentin group. On the contrary, Usama *et al.*^[26] reported that, there was no significant difference between pregabalin and gabapentin in the postoperative pain score.

The amount of postoperative pethidine consumed can be summated as an index of the quality of pain relief by the study drugs. This was found to be higher in patients that

received preoperative placebo before spinal anaesthesia, in comparison with those that received preoperative gabapentin and pregabalin. The postoperative analgesic consumption was lowest in the pregabalin group. Our result corroborates with those of Sabastian et al.^[14] and Montazeri et al.^[27] findings, as well as that reported by Khetarpal et al.^[9] despite the use of different doses of gabapentin and pregabalin.

Significant changes in heart rate and blood pressure can be observed in patients receiving spinal anaesthesia. Bradycardia and hypotension due to spinal anaesthesia are proportional to the height of block. Hypotension is caused by the denervation of the sympathetic outflow tract, leading to dilatation of resistance and capacitance vessels.^[28,29] Bradycardia following intrathecal local anaesthetic administration results from the blockade of sympathetic cardiac accelerator fibers and decreased venous return to the heart,^[28,29] No patient in the three groups had bradycardia.

Other adverse effects observed in this present study are somnolence, dizziness, nausea, and shivering. Different studies have reported adverse effects of pregabalin and gabapentin such as somnolence, dizziness, confusion, headache, ataxia, nausea, sedation, shivering, and weight gain.^[5,17] However, these adverse effects were reported for long-term use and increased dose. Common adverse effects of single oral therapy for postoperative pain management were dizziness, somnolence, and sedation. The findings of dizziness, somnolence, and nausea are consistent with those of other studies.^[5,9,24] that evaluated the analgesic effect of pregabalin and gabapentin, although the incidence rate differs.

Times for ambulation and micturition were not evaluated because patients were non-ambulant and on urethral drain postoperatively. Delay in ambulation could result from motor weakness that follows spinal anaesthesia. Urinary retention following spinal anaesthesia can be caused by sympathectomy and unopposed action of the parasympathetic nervous system.^[30] We had the limitation of not being able to assess the effect of pregabalin and gabapentin on micturition and ambulation, because the patients were catheterized perioperatively and immobilized due to lower limb fracture treatment.

CONCLUSION

This study showed that single preoperative oral pregabalin 150mg provides prolonged duration of analgesia, reduced pain score, and postoperative pethidine consumption, compared with preoperative oral gabapentin 300mg in patients that received spinal anaesthesia for lower limb orthopaedic surgery.

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