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EFFECTS OF PREOPERATIVE PREGABALIN ON OUTCOME OF SPINAL ANAESTHESIA FOR PATIENTS UNDERGOING OPEN MYOMECTOMY

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ABSTRACT

Background: Preoperative oral administration of pregabalin has been reported to significantly reduce immediate postoperative pain and reduce opioid consumption. However, there are some reported cases of very prolonged duration of spinal anaesthesia beyond the surgery period. **Objectives:** To evaluate the possible prolongation of spinal anaesthesia; delayed ambulation; balance and gait abnormality and other side effects of preoperative single oral pregabalin for myomectomies during the first 24 hours after the surgery. **Methodology:** A prospective, randomized and double-blinded study was designed. Seventy-two women scheduled for myomectomy were randomly allocated to 2 groups (A and B). Group A received orally 150 mg pregabalin 1 hour before surgery while group B received orally placebo 1 hour before surgery. **Results:** The duration of sensory and motor blockades was significantly more prolonged in group A patients than in group B patients, and the pain scores at 2^{nd}, 3^{rd}, 8^{th}, 14^{th} and 24^{th} hours postoperatively were significantly higher in group A patients than in group B patients. The total analgesics consumed within the first 24 hours postoperatively were significantly higher in group B patients than group A patients. There was significantly more delay in time to first ambulate postoperatively in group A patients than group B patients. **Conclusion:** A single oral dose of 150mg pregabalin administered before surgery optimized the efficacy of intrathecal bupivacaine and improved postoperative analgesia in patients that underwent open myomectomy under spinal anesthesia but delayed their postoperative ambulation.

KEYWORDS: Ambulation, Myomectomy, Pregabalin, Spinal anaesthesia.

INTRODUCTION

The increase in the desire of the patients to have their surgeries under spinal anaesthesia was demonstrated by Stern.[1] This might not be unconnected with associated fear of general anaesthesia. However, the duration of the subarachnoid blockade may not sustain some surgeries lasting for a long period. This might result in converting spinal anaesthesia to general anaesthesia which was originally the anaesthetic technique not preferred. This necessitated the introduction of adjuvants with the aim of prolonging the duration of spinal anaesthesia.

The use of intrathecal adjuvants has become increasingly popular as some have proven to have the ability to prolong the duration of the block, improving the quality of the block, and improving patients' satisfaction.[2] The concern about the side effects of these adjuvants has led to the trial of many agents. Despite its proven efficacy, concerns have continued to be raised over spinal opioid-induced side effects. These side effects include delayed respiratory depression, pruritus, and postoperative nausea and vomiting.[3] This has motivated a search for other novel alternatives with α2 adrenergic receptor agonists like clonidine,[4] and dexmedetomidine,[5] N-methyl D-aspartate receptor antagonists like ketamine,[6] and magnesium sulphate,[2] anticholinesterases like neostigmine,[7] benzodiazepines like midazolam,[8] and pregabalin.[9] A novel alternative will invariably validate the surgeons' undisguised choice for regional anaesthesia during surgeries amenable to regional anaesthesia as shown by Arati and colleagues.[10] These surgeries

include abdominal surgeries like cholecystectomies, laparotomies and myomectomies.

The removal of fibroids from the uterus by surgical procedures is called myomectomy. It is usually carried out abdominally through open laparotomy. It might be done laparoscopically with minimal surgical incisions and occasionally through the vagina using the hysteroscope. Abdominal myomectomy may be complicated with increased intraoperative blood loss, post-operative pain and a longer hospital stay.[11] Myomectomy may be done under general anaesthesia or regional anaesthesia but neuraxial blockade has recently become the preferred mode of anaesthesia because of the obvious advantages.[12] Such advantages include cost-effectiveness, reduced blood loss, reduced risk of deep venous thrombosis, reduced stress of the surgery, postoperative analgesia and no general anaesthesia induced adverse effects.[12]

It has long been found that immediate postoperative ambulation necessitates quick recovery.

Early ambulation after surgery significantly reduces the incidence of perioperative complications, shortens the duration of in-hospital stay and contributes to improved perioperative functional status especially in the elderly patients.[13]

Therefore, we studied the effect of a single oral dose of preoperative pregabalin on the duration of spinal anaesthesia; balance and gait after recovering; early ambulation and other immediate postoperative side effects for patients that underwent myomectomies.

METHODOLOGY

This randomized and double-blinded study was conducted in a tertiary hospital centre at Nnewi, Nigeria. The study was carried out within a period of twelve months (July 2017 to June 2018) after obtaining ethical clearance from the hospital ethics and research committee. Routine biodata and American Society of Anesthesiology (ASA) physical grading of the patients were done at the time of pre-anaesthetic review. They were provided with written informed consent.

Patients with a history of cognitive impairment; drug abuse; chronic pain; known allergy to pregabalin; chronic use of pregabalin; intraoperative use of breakthrough analgesics and sedation; conversion to general anaesthesia, impairment of gait and balance were excluded from the study.

Consecutive patients diagnosed with uterine fibroid, scheduled for open myomectomy under spinal anaesthesia were recruited for the study. Using the balloting method, they were randomly allocated into two equal groups using the balloting method. Pregabalin group (A) received 150 mg of pregabalin-containing capsules orally (Lyrica®, Pfizer), while a matching placebo group (B) received an empty capsule orally 1 hour before the induction of anesthesia with sips of water. Both the patient and the researcher were double-blinded to the treatment, and all records were done by an anaesthetist blinded to group allocation.

Upon arrival at the operating room, electrocardiography, blood pressure, and oxygen saturation were monitored and subsequently every 5 minutes with ongoing intravenous normal saline. The patients were positioned in sitting positions with their feet resting on a stool, head flexed and forearms rested on their thighs and their skin at the back prepared with the appropriate antiseptics. The suitable L_{3-4} intervertebral space was located by palpating the spinous process at the level of a line joining the iliac crests. Subcutaneous infiltrations were done with 2mls of 2% plain lidocaine at the L_{3-4} intervertebral space. The spinal injection was done with a 25 gauge Quincke needle and 0.21mg/kg of 0.5% bupivacaine was administered. Sterile gauze was plastered at the site after the withdrawal of the spinal needle. Patients were subsequently placed in a supine position with head elevation using a pillow.

The onset of the spinal block was noted from the time of spinal injection to loss of sensation at the shin bilaterally (L_4); the level of the spinal block was assessed bilaterally upwards at the mid-clavicular line every 2 minutes until it was constant for two consecutive assessments with methylated spirit impregnated cotton wool and the maximum height of block noted.

Bilateral motor block was assessed with the Modified Bromage Scale:
Grade III- inability to move leg or feet.
Grade II- able to move feet only.
Grade I- just able to flex the knee and full flexion of feet possible.
Grade 0- full flexion of knee and feet, able to lift legs.

The time from the injection into the sub-arachnoid space to the point when the patient was unable to flex the knee was noted as the onset of motor block. Onset time of 2 segments regression of maximum height of spinal blockade was the duration of sensory block, which was checked every 15minutes. The time from the onset of motor block to the regression of motor blockade to Bromage grade 0 was noted as the duration of motor block. The time from the spinal injection to the time of return to the grade 0 Bromage scale was the duration of spinal anaesthesia.

Non-invasive Blood Pressure, Mean arterial Blood Pressure, Heart Rate and Arterial Oxygen Saturation were noted every 3 minutes after spinal injection until 20minutes, then every 5minutes until the surgery was over and at the postoperative anaesthesia care unit. Systolic blood pressure 20% below baseline or less than 90mmHg was treated with an intravenous bolus of 10ml/kg normal saline followed by intermittent boluses

of intravenous ephedrine 5mg, if no improvement. When the heart rate was less than 60 beats per minute, intravenous atropine 0.6mg was given. Fluid maintenance was achieved with normal saline and blood loss was replaced with three units of crystalloid for each unit of blood loss and blood transfusion commenced if necessary. All fluid was warmed to reduce the risk of hypothermia and shivering. Nausea and vomiting were treated with intravenous metoclopramide 10mg. Breakthrough pain was treated with 1mg/kg of intravenous tramadol and such patients excluded from the study. Patients that were anxious intra-operatively were sedated with 0.015mg/kg of intravenous midazolam and they were excluded from the study.

The patients' level of pain were assessed using the Numerical Rating Scale (NRS). It was done at the end of the surgery (last stitch). Then, postoperatively every hour for the first 6 hours, two-hourly for the next 12 hours and at 24hours postoperatively. For the pain score of more than 3, intravenous rescue analgesia was given using intravenous tramadol 1mg/kg. The occurrence of nausea, vomiting, dizziness, sedation, respiratory depression and other untoward effects were noted and recorded.

The time of the first request for analgesia at the ward was recorded and the patient was given intravenous tramadol 1mg/kg. Subsequently, the patient received the same intravenous tramadol 1mg/kg every 4 hours for post-operative analgesia during the first 24 hours after the surgery and total dose consumed noted.

Prior to the surgery, all patients were evaluated using the Tinetti balance and gait test chart and those with abnormal balance and gait excluded from the study. The test was done again 1 hour after the postoperative first ambulation. The Tinetti test assesses balance and gait in two main categories using 16 questions: The first nine questions are about balance, and the subsequent seven questions are about gait. The total score received from the first nine questions indicates the balance score and the total score received from the subsequent seven questions indicates the gait score. The 16 questions represent the totality of the movements made during daily life activities. Scoring is based on observation and defined as follows: 2 points if the specified movement is performed correctly, 1 point if the specified movement is performed with adaptations, 0 points if there is an inability to perform the specified movement. A total score of 18 or below shows a high risk of falling, a total score between 19 and 24 shows a moderate risk of falling and a total score of 24 or above shows a low risk of falling.

The time to first ambulate after the surgery was noted and recorded as the time of postoperative ambulation. The presence of any of the following possible complications during the first 24 hours postoperative was recorded by the attending nurses: drowsiness (no eye-opening in response to verbal command), dizziness, dry mouth, and nausea/vomiting.

Statistical analysis was performed with the SPSS, version 24.0 for Windows Statistical Software Package (SPSS Inc., Chicago, IL, USA). The data were presented as frequency tables and figures. Continuous data were represented as mean and standard deviations (SD) and their mean differences compared using Student's t-test, while dichotomous categorical data were analyzed using Pearson Chi-square and/or Fisher's Exact test where appropriate. Statistical significance was inferred at P-value of ≤ 0.05

RESULTS

Sixty-eight patients, aged 25-50 years, of ASA physical status I and II completed the study according to the protocol and were included in the analysis. Four patients received general anesthesia when the initial spinal anaesthesia effect wore off following prolonged surgery and were excluded from the study. When the 2 groups were compared in terms of age, height, weight, ASA physical status, parity and the duration of surgery, no significant differences were found (Table 1). All surgical procedures were completed without complications.

The mean duration of 2 segment regression from peak sensory block levels in group A (145.47±9.13 minutes) was significantly longer than in group B (123.35±8.21 minutes) (P=0.001) but there is no significant difference between the groups in the onset time and time to achieve the maximum sensory level of the block (Table 2). The mean duration of motor block in group B (184.59.38±11.14 minutes) was significantly shorter than in group A (212.57±12.54 minutes), (P=0.001) but no significant difference between the groups in the onset time of the motor block. The maximum level of the block was similar in both groups.

The time to first analgesic requirement was significantly prolonged in group A (246.00±4.24 minutes) than group B (206.45±5.82 minutes), (P=0.001). The total analgesics (tramadol) consumed within the first 24 hours was significantly higher in group B (447.26±15.61 mg) than group A (372.51±18.31 mg), (P=0.001). The time to first ambulate (Table 3) was significantly delayed in group A (221.15±09.45 minutes) than in group B (190.13±12.31 minutes), (P=0.001). Although 8.83% of patients in group A (Table 4) showed features of falling, while none in group B showed any feature of falling, the difference was not statistically significant (P=0.891).

The postoperative NRS pain scores were all decreased in group A than group B (Figure I) but statistically significant differences were noted at 2^{nd}, 3^{rd}, 8^{th}, 14^{th} and 24^{th} hours, (P=0.001).

There was significant dry mouth noted in 14.71 % of patients in group A while none was observed in group B, (P=0.039). The patients got better with a few drops of

saline into their mouths. No other differences were observed in the other postoperative adverse effects between the 2 groups during the first 24 hours after the surgery (Table 5) and intraoperative hemodynamic variables did not differ between the two groups.

Table 1: Demographic Characteristics and Duration of The Surgeries.

	Control group (n=34)	Pregabalin group (n=34)	*P*
Age (years)	34.86±3.43	33.53±4.23	0.067
Weight (kg)	70.21±2.75	72.41±4.20	0.543
Height (cm)	165.34±4.53	166.24±4.84	0.077
Duration of surgery (min)	132.33±7.30	133.63±5.32	0.313
ASA physical status			
I N (%)	27(79.41)	26(76.47)	0.740
II N (%)	7(20.59)	8(23.53)	0.740
Parity			
Nulliparous (%)	30(88.24)	29(85.29)	0.820
Parity[1] (%)	4(11.76)	5(14.71)	0.790

Data are mean ± standard deviation, Parity[1]: One previous pregnancy

Table 2: Characteristics of Spinal Block.

BLOCK SENSORY	Control group (n=34)	Pregabalin group (n=34)	*P*
Mean onset time (min)	3.26±0.05	3.32±0.09	0.057
Mean time to ach.	8.91±1.16	9.02±0.87	0.273
max. sensory lev (min)			
Mean time for 2	123.35±8.21	145.47±9.13	0.001
segment reg. (min)			
Mean Max level of block	$T_{6.08}$	$T_{6.11}$	1.000
MOTOR			
Mean onset time (min)	7.43±0.68	7.71±0.72	0.122
Mean duration (min)	184.59.38±11.14	212.57±12.54	0.001

LEGEND: ach- achieve, lev: level, reg: regression, max: maximum, min: minutes

Table 3: Post-operative analgesia and time to first ambulate.

	Control group (n=34)	Pregabalin (n=34)	*P*
Time (min) of spinal injection to	206.45±5.82	246.00±4.24	0.001
1st dose of supplemental analgesia			
Pain Scores at the 1st dose of	3.12±0.48	3.15±0.67	0.724
supplemental analgesia			
Total analgesics consumed in	447.26±15.61	372.51±18.31	0.001
24 hours (tramadol in mg)			
Time to first ambulate (min)	190.13±12.31	221.15±09.45	0.001

Table 4: Tinetti Balance and Gait Test.

	Control group (n=34)	Pregabalin group (n=34)	*P*
Preoperative scores			
Above 24: N (%)	34 (100)	34(100)	1.000
Postoperative scores			
Above 24: N (%)	34 (100)	31 (91.17)	0.943
Between 18-24: N (%)	0	3(8.83)	0.891

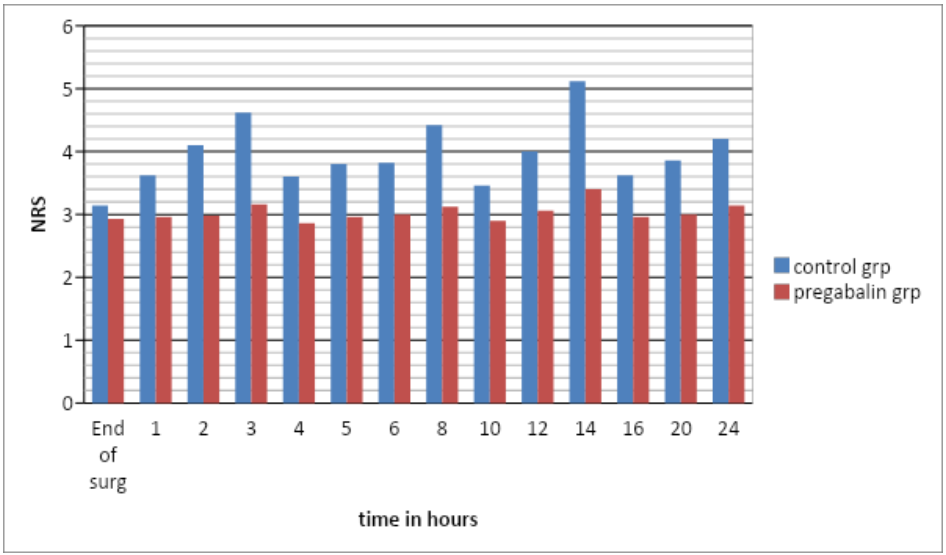

Figure I: Mean Pain Scores Using Numerical Rating Scale.

Table 5: Postoperative Adverse Effects During The First 24 Hours.

Variables	Control group (n=34)	Pregabalin group (n=34)	*P*
Dizziness (N%)	4(11.76)	7(20.58)	0.867
Drowsiness (N%)	3(8.82)	6(17.65)	0.821
Dry mouth (N%)	0	5(14.71)	0.039
Nausea/Vomiting (N%)	2(5.88)	4(11.76)	0.093

DISCUSSION

In this study, the oral administration of pregabalin an hour prior to spinal anesthesia prolonged both sensory and motor blocks induced by spinal bupivacaine anesthesia. The time to the first request for postoperative analgesics was delayed, and lower rescue analgesic requirements were observed during the first 24 hours postoperatively. The study also showed the delayed time to postoperative ambulation and associated dry mouth within the first 24 hours.

A meta-analysis conducted by Ong *et al*,[14] demonstrated the ability of preemptive analgesic interventions with pregabalin to attenuate postoperative pain scores, decrease supplemental postoperative analgesic requirements, and prolong time to first rescue analgesic. Elmansouri *et al*,[15] also revealed reduced postoperative pain and analgesics in those that received preoperative pregabalin during laparoscopic cholecystectomy. However, the efficacy of preoperative pregabalin in regional anaesthesia has not been extensively studied,[16] and the effect of a single oral dose of preoperative pregabalin on postoperative ambulation has not been well reported in the literature. Park and his colleague showed in their study,[17] similar ability of preoperative pregabalin to attenuate postoperative pain scores, decrease supplemental postoperative analgesic requirements, and prolonged time to first rescue analgesic in patients who underwent spinal anaesthesia for urinary bladder and prostate surgeries. In their study,[17] there was 158 minutes more delay to the first analgesics request in the pregabalin group compared to our study. This might have arisen because of different surgeries their study patients had undergone compared to our patients that had myomectomies. Different surgeries most often have different tissue handling with ensuing different pain perception and analgesic requirements.[18]

Pregabalin binds to the α-2-δ subunit of voltage-gated calcium channels reducing the release of several excitatory neurotransmitters like glutamate and blocking the development of hyperalgesia.[19] In so doing, it inhibits central sensitization and pain progression.[20]

In view of the multiplicity of the mechanisms involved in post-operative pain, rnultimodal analgesic techniques utilizing several drugs acting on different analgesic mechanisms are becoming increasingly advocated and popular.[21] Pregabalin with its mode of action through central sensitization inhibition,[19] has a role in the multimodal analgesic techniques for acute pain management.

However, this study reported a significantly delayed time to first ambulation postoperatively compared to the control. Early ambulation after surgery has been demonstrated to reduce complications and decrease patient length of hospital stay.[22] Myhre *et al*,[23] also found that perioperative pregabalin significantly negatively affected subdomains of executive functioning, including inhibition, and working memory compared to placebo. Therefore, risk-benefit assessment should be evaluated using pregabalin as part of multimodal analgesic techniques. Çağlar-Okur *et al*,[24] evaluated the effect of preoperative pregabalin on balance and gait.

The study[24] showed that Tinetti total test scores (23.2 ± 3.9) in the first (p=.001) week were significantly lower in the pregabalin group but there was no significant difference between the Tinetti test scores (balance, gait, and total scores) at baseline and in the 12th week (p>.001). In this study, there were 8.83% of study patients that had scores 18-24; with features of possible fall. Even though the difference was not statistically significant between the two groups, there is a concern for further studies as the initial therapy in the study by Çağlar-Okur *et al*,[24] revealed a low Tinetti score during the first week of pregabalin therapy with increased risk of poor balance and falling. Tolerance might have account for no difference in the chronic use.

The most common adverse effects of the pregabalin were sedation and dizziness.[25] In this study, there was significant dry mouth in the study group compared to the control group but sedation, dizziness, drowsiness, nausea and vomiting were not significant between the two groups.

CONCLUSIONS

This study showed that preoperative single oral pregabalin attenuated postoperative pain scores, decrease supplemental postoperative analgesic requirements, prolong time to first rescue analgesia and delayed time to postoperative ambulation. However, further studies are needed concerning its noted effects on delayed postoperative ambulation and balance. This becomes very imperative especially for patients with other risks for deep venous thrombosis.

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