



## Effect of premedication with oral pregabalin in patients posted for lower limb orthopedic surgeries under spinal anesthesia: A prospective, double-blind, randomized study

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### Abstract

**Background:** Pregabalin which is a GABA analogue when administered orally in preoperative period has been reported to prolong the blockade of spinal anaesthesia and reduce acute postoperative pain. So we designed the study to evaluate the efficacy of a single dose of oral pregabalin in terms of duration of spinal blockade and need for rescue analgesia.

**Materials and Methods:** A prospective, randomised, double blind study was carried out on 50 patients with ASA physical status I & II aged between 18–50 years. Both the groups received tablets 1 hour prior to spinal anaesthesia. Group C (control group)- received colour matched placebo, while Group P (pregabalin group)– received 150mg of oral pregabalin. Spinal anaesthesia was administered to the patients in sitting position in L3-L4 space with Inj. Bupivacaine heavy (0.5%) at a dose of 0.3mg/kg body weight using 25 gauge spinal needle. Rescue analgesia was provided with using Inj. Diclofenac 1.5 mg/kg intramuscular.

**Results:** The duration of sensory and motor blockade was significantly prolonged in group P patients when compared with that in group C patients, and the VAS scores at postoperative 6 and 24 hours were significantly lower in group P patients. Requests for analgesics during the first postoperative 24 hours were lower among group P patients.

**Conclusion:** Premedication with a single dose of 150mg oral pregabalin 1 hr before surgery promoted the efficacy of spinal anaesthesia and improved postoperative analgesia in patients undergoing for lower limb orthopedic surgery under spinal anesthesia.

**Keywords:** oral pregabalin, spinal anaesthesia, post-operative pain, visual analogue scale.

### Introduction

Postoperative pain has significant impact on the surgery outcome due to many adverse effects like tachycardia, hypertension, ischemia, reduced alveolar ventilation, poor wound healing and patient discomfort<sup>[1]</sup>. Hence, the alleviation of pain has been the priority of the medical

profession and health authorities since time immemorial. Currently a multimodal approach is followed for treating postoperative pain which includes NSAIDs and opioids. A better understanding of the pain pathways and physiology led to the emergence of a new regimen known as preemptive analgesia. Preemptive

analgesia was a concept developed by Crile and is a method of administration of medications before surgery in order to prevent the establishment of central sensitization of pain, thus reducing the intensity and duration of postoperative pain<sup>[2]</sup>. GABA analogues like pregabalin and its developmental precursor gabapentin are being used as preemptive analgesics<sup>[3-5]</sup>. Pregabalin has been effective in the treatment of neuropathic pain, incisional pain, and inflammatory pain. Pregabalin plays its role in treatment of acute post-operative pain by decreasing the excitability of dorsal horn neurons caused by tissue damage<sup>[6]</sup>. Moreover, since most patients are afflicted with stress and emotion pre-operatively, the anti-excitement effects of pregabalin can be effective<sup>[7]</sup>. In several studies, pregabalin has been used to reduce the need for opioids<sup>[8]</sup> treatment of dental pains<sup>[9]</sup>, the treatment of pain after spinal fusion surgery<sup>[10]</sup>, and treatment of pain after laparoscopic cholecystectomy<sup>[11-16]</sup>. In this study we hypothesized that single dose 150mg pregabalin premedication would prolong the sensory and motor blockade of spinal anesthesia in orthopedic surgery. A secondary objective of this study was to determine if premedication with pregabalin also reduces the need for medication to relieve postoperative pain.

### Materials and Methods

After getting ethical committee approval a prospective, randomised, double blind study was conducted at tertiary care hospital on 50 patients of ASA grade I & II of either sex, between 15-50 years of age and 45 to 70 kg weight who were scheduled for elective lower limb orthopedic surgeries under spinal anaesthesia were enrolled in the study. The exclusion criteria were patients with known drug allergy to pregabalin or gabapentin, uncontrolled hypertension, diabetes

mellitus, ischemic heart disease, cerebrovascular disease, renal and hepatic disease, history of alcohol and drug abuse. Patients with any general contraindications for spinal anaesthesia were also excluded from the study. Patients with chronic pain, neurological disorders and patients on NSAID's and on other analgesics were excluded from study. A detailed pre anaesthetic assessment was done one day prior to the scheduled surgery. All the patients were provided with written information sheet about the drug and the anaesthesia technique. After obtaining written informed consent from the patient, they were educated about 0-10 centimeters of VAS (Visual Analogue Scale) which was to be used for pain assessment in the postoperative period<sup>[17]</sup>. All patients were kept nil by mouth (NBM) for ten hours prior to the surgery. They were premedicated with Tab. Ranitidine 150mg and Tab. Alprazolam 0.25mg at night on the day before surgery. The patients were randomly allocated into two groups based on computer generated random number table. The patients were divided in two groups and they were unaware as to which group they belonged to. Group C (control group)- which received colour matched placebo capsules 1 hour prior to spinal anaesthesia. While Group P (pregabalin group)- received 150mg of oral pregabalin 1 hour prior to spinal anaesthesia. The anaesthesia technique was standardised for both the groups. Baseline Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), mean Arterial Blood Pressure (MAP) and SpO<sub>2</sub> were recorded. All the patients were preloaded with Ringer Lactate 10 mL/kg IV and Inj. Ondansetron 0.08/kg IV was administered. Spinal anaesthesia was given in sitting position in L3-L4 interspace with Inj. Bupivacaine heavy (0.5%) at a dose of 0.3mg/kg body weight with

using 25 gauge spinal needle. All the patients were catheterized with appropriate sized Foley's urine catheter to monitor the urine output. All patients were administered oxygen via facemask at 4 liters/min. The study follow-up was done by another resident anaesthesia who was unaware of patients allocation to different group. The patients were monitored during the course of the study for any incidence of bradycardia (HR < 50bpm) which was treated with a dose of Inj. Atropine 0.6 mg IV, fall in the blood pressure (SBP < 20% of baseline), requiring bolus doses of Inj. Mephentermine 3mg IV and sensory blockade was assessed using a pinprick test in at the midaxillary line on both sides of the chest. Pinprick tests were performed every 1 minute until maximum sensory blockade was achieved in the relevant body segment and subsequently every 5minutes for the next 30minutes. Thereafter, assessments were performed every 15 minutes until recovery of sensation in the L2 segment. The time to T10 sensory block, peak sensory level, and time from the injection to the peak level were recorded. We defined the recovery time from the sensory blockade as a 2 dermatome regression of anesthesia from the maximum level. In addition, immediately after sensory block assessment, the motor block was evaluated using a modified Bromage scale as reported in previous studies (grade 0: no paralysis; grade 1: unable to raise an extended leg but able to move the knees and ankles; grade 2: unable to flex knees, can flex ankle, grade 3: no movement) <sup>[18]</sup>. The time to reach Bromage 1 was recorded. Motor block duration was defined as the time for return to Bromage 2. Postoperative pain was controlled by rescue analgesics administered by hospital personnel without patient-controlled analgesia. Postoperative pain was assessed by the patient using the visual analog scale (VAS, 0=no pain;

10=worst possible pain) at 6 and 24 hours after the operation. Patients with a VAS score of 4 or more received 75mg diclofenac intramuscularly. The times of the first request for postoperative analgesia and the number of injections were recorded. The detailed data was entered into the Microsoft excel sheet and subsequently analyzed by using appropriate statistical tests. Graphical display was done for better visual inspection.

## Results

When the 2 groups were compared in terms of age, gender, height, weight, and operation duration, no significant differences were found (Table 1).

**Table 1:** Demographic characteristics and duration of surgery.Ta

Parameters	Control group	Pregabalin group	P value
Age ( yrs)	50±15	53±15	0.616
male/female	14/16	17/13	0.32
Height (cm)	164.4±7.9	167.2±6.6	0.307
Weight (kg)	66.9±9.4	70.1±11.1	0.783
Operation duration (min)	93.58±31.32	101.36±36.14	0.14
Dose of Bupivacaine (mg)	18.31 ± 1.62	18.67 ± 1.22	0.244

Table 2 shows that the mean time of onset for T10 sensory blockade was similar between the 2 groups. The time to reach Bromage score 1 motor block was not significantly different (P= 0.106), and the maximum level was similar in both groups. The mean duration of 2-dermatome regression from peak sensory block levels in group P (88.8±13.1 minutes) was significantly longer than in group C (67.1±10.9 minutes) (P= 0.000). The time for regression to L2 sensory block levels was significantly prolonged in group P as well. In addition, the regression time from Bromage 1 to Bromage 2 was prolonged in group

P (198±16.8 minutes) than group C (168.2±31.6 minutes) (P=0.000).

**Table 2:** Onset time and duration of sensory and motor blocks

Variables, min	Control group	Pregabalin group	P value
Time to T10 sensory block (min)	5.0±1.0	4.9±1.3	0.790
Time to Bromage 1 block (min)	8.1±1.4	7.3±1.4	0.106
Mean of maximal sensory level	T8	T8	
Time of 2-segment regression (min)	67.1±10.9	88.8±13.1	0.000
Time for regression to L2 (min)	130.0±16.7	156.0±14.5	0.000
Time for regression to Bromage 2 (min)	168.2±31.6	198.1±16.8	0.000

Table 3 shows that the postoperative 6hr and 24hr VAS pain scores were decreased in group P. The time to the first request for postoperative supplemental analgesia was significantly prolonged in group P (404.0±123.2 minutes) when compared with group C (204.8±37.6 minutes) (P=0.000). The total rescue dosages of diclofenac were lower in group P (P=0.000)

**Table 3:** VAS score, time to first dose of rescue analgesic and total dose of inj diclofenac request during the first 24 hours

Variables, min	Control group	Pregabalin group	P value
VAS score at 6 h postop	4.2±1.0	3.1±1.2	0.002
VAS score at 24h postop	2.2±0.7	1.6±0.7	0.005
Time for first rescue analgesia request (min)	204.8±37.6	404.0±123.2	0.000
Total dose of Diclofenac (mg)	111.60 ± 36.615	177.91 ± 39.694	< 0.05

## Discussion

Postoperative pain is a severe nociceptive stimulus associated hyperalgesia and allodynia which can exacerbate the existing pain by wind up phenomenon in dorsal column of spinal cord. Pregabalin is a lipophilic GABA analogue approved by FDA for clinical use. It is superior to other routinely used analgesics in that it reduces the anxiousness of the patient, is effective against neuropathic component of pain and is available at a reasonable cost. Pregabalin binds to the  $\alpha 2\text{-}\delta$  subunit of voltage-gated calcium channels and modulate the release of several excitatory neurotransmitters such as glutamate, norepinephrine and substance P. Hence pregabalin reduces the hyperexcitability of the dorsal horn neurons of spinal cord that is induced by tissue damage and thereby decreases perception of acute postoperative pain. Use of pregabalin as preemptive analgesia helps in the control of postoperative pain by its anti allodynic and antihyperalgesic activity. We investigated whether pregabalin premedication prolonged the duration of a sensory and motor block as well as the time to the first rescue analgesic postoperatively. This study showed that oral pregabalin administered 1 hour before spinal anesthesia prolongs both sensory and motor blocks. The time to the first request for postoperative rescue analgesics was delayed, and lower rescue analgesic requirements were observed during the early postoperative 24 hours. The length of the delay to the first request for postoperative analgesics was significantly related to the total dose of postoperative analgesics required. Bon Sebastian et al<sup>(19)</sup>, studied oral pregabalin is effective preemptive analgesic in undergoing lower limb orthopedic surgeries under spinal anaesthesia. Few studies use pregabalin in various doses for gynaecological laproscopic surgeries and laparoscopic

cholecystectomy and found that preemptive oral pregabalin significantly decreases the postoperative pain as well as reduces analgesic requirement [20,21,22]. Few studies showed that a single preoperative oral dose of pregabalin 150mg is an effective method for reducing postoperative pain, opioid and NSAIDs consumption in patients undergoing orthopedic and abdominal hysterectomy surgeries [23,24,25].

### Conclusion

We concluded that the preoperative administration of single dose 150mg pregabalin 1 hour before spinal anesthesia demonstrated the prolonged the duration of both sensory and motor blocks, the mean time for the need of first rescue analgesic request was delayed and the dosage of postoperative analgesics was significantly decreased in the first 24 hours following orthopedic surgery. So oral pregabalin 150mg administered 1hr before the spinal anaesthesia can be an effective tool for patients posted for lower limb orthopedic surgeries.

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