

# Preemptive use of oral gabapentin or pregabalin for acute postoperative pain following lower limb orthopaedic surgery under spinal anaesthesia

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## Abstract

**Background:** Postoperative pain is a major cause of perioperative morbidity and functional impairment. Preemptive analgesia is an analgesia regimen instituted before the surgery, to desensitize the pain pathways. Pregabalin and gabapentin have been claimed to be effective in reducing postoperative pain without significant alterations in hemodynamics.

**Objectives:** This study was conducted to compare the effectiveness of pregabalin and gabapentin in reducing postoperative pain, total opioid consumption, postoperative nausea and vomiting and sedation in patients undergoing lower limb orthopaedic surgeries under spinal anaesthesia.

**Methodology:** Eighty patients undergoing lower limb orthopaedic surgeries under spinal anaesthesia were divided into two groups, to either receive 300mg gabapentin or 150mg pregabalin, one hour before surgery. The patients were evaluated at one, two, six, 12 and 24 hours postoperatively and Visual Analogue Scale score for pain, postoperative nausea vomiting, and sedation score were monitored. Tramadol 50 mg was used as rescue analgesic and total consumption over 24 hours was recorded.

**Results:** The mean duration of postoperative analgesia was significantly higher with pregabalin (282±106 minutes versus 234 ± 97minutes, p=0.009). The sedation score was significantly higher with pregabalin in the first hour (p=0.001). The total tramadol consumption was higher with gabapentin; however, it was statistically insignificant. The occurrence of postoperative nausea and vomiting was comparable between the groups. Minor adverse effects such as dizziness, sedation and headache were observed in both groups.

**Conclusion:** Pregabalin 150 mg orally significantly increases the duration of postoperative analgesia than gabapentin 300mg following lower limb orthopaedic surgeries. Although sedation is frequently observed, it doesn't alter the hemodynamics and thus, may be used safely.

**Key words:** Gabapentin; Pre-emptive analgesia; Pregabalin

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## INTRODUCTION

Postoperative pain is a major cause of perioperative morbidity and functional impairment. Preemptive analgesia involves the introduction of an analgesic regimen before the onset of noxious stimuli, with the goal of preventing sensitization of the nervous system to subsequent stimuli that could amplify pain<sup>1</sup>. Pregabalin

and gabapentin have been claimed to be effective in reducing the magnitude of postoperative pain, without significant alterations in hemodynamics.

In addition to the distress and discomfort, acute pain elicits a consistent and well defined metabolic response involving release of various neuroendocrine hormones and cytokines that lead to a myriad of detrimental effects<sup>2</sup>. The rationale behind pre-emptive analgesia is that anti-nociceptive treatment started before surgery is more effective in reducing postoperative pain than treatment started in the early postoperative period<sup>3</sup>.

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Considering that the most common adverse effects of pregabalin, somnolence and dizziness, occur more frequently at higher doses, it is valuable to reduce the dose of pregabalin while maintaining its analgesic efficacy<sup>4</sup>.

Since multimodal approach is considered to provide optimal pain control in surgical patients, use of drugs like pregabalin and gabapentin can be expected not only to provide pre-emptive analgesia but also prevent the development of postsurgical chronic pain. Till date various studies have been undertaken to determine the effectiveness of pregabalin as well as gabapentin in control of post-operative pain, either as pre-emptive analgesics or preventive analgesics. Our study was undertaken to compare the effectiveness of gabapentin and pregabalin in low dose as postoperative analgesics following their preemptive use.

## METHODOLOGY

This was a prospective, randomized, double blinded, clinical study. The study was undertaken over a period of one year, from July 16, 2015 to July 15, 2016. Ethical approval was obtained from the Institutional Review Committee of B.P. Koirala Institute of Health Sciences. Patients of either sex, aged 18-65, of American Society of Anaesthesiologists (ASA) Physical Status I or II, undergoing lower extremity orthopaedic surgery under spinal anaesthesia were enrolled in the study after obtaining an informed written consent. The patients were randomly assigned into two groups of 40 patients each.

**Group A** patients received capsule Gabapentin 300 mg orally, approximately one hour before surgery.

**Group B** patients received capsule Pregabalin 150 mg orally, approximately one hour before surgery

During the pre-anesthetic checkup (PAC), the patients were familiarized and explained about the Visual Analogue Scale (VAS) score for pain assessment in a simple, understandable language. On the night before surgery, the patients received lorazepam 1-2mg (20-40mcg/kg) orally as a premedicant for anxiolysis. In the operation theatre, non-invasive blood pressure (NIBP) cuff, electrocardiography (ECG) leads and pulse oximetry (SPO<sub>2</sub>) probe were attached to the patient and the baseline ECG, NIBP, respiratory rate (RR), heart rate (HR) and SPO<sub>2</sub> were monitored.

Spinal anaesthesia was administered in sitting or lateral position using 2.5-3.0 ml of 0.5% hyperbaric bupivacaine.

After spinal anaesthesia, all patients received oxygen supplementation at the rate of two liters per minute via nasal prongs. By using a sterile needle, the level of sensory block was assessed. After ascertaining adequate block, the surgery was commenced. During the intraoperative period, RR, HR., systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and SPO<sub>2</sub> was monitored and recorded at 5, 10, 20, 30, 45 and 60 minutes.

The pain intensity was measured immediately after the patient was transferred to post anaesthesia care unit (PACU) and then at one, two, six, 12 and 24 hours respectively, using a 10cm (100mm) VAS score. Asking the patient to grade the severity of pain he/she felt, we assessed the intensity of pain. Post-operative sedation was assessed by the Ramsay sedation scale (RSS). The severity of postoperative nausea and vomiting (PONV) was graded on a four-point ordinal scale.

When the severity of pain was four or more in the scale, or when the patient asked for analgesia, tramadol 50mg was given intravenously. The time of first administration of analgesic on demand was considered as the time of termination of the postoperative analgesic effect of the study drug. When PONV score was two or more, ondansetron 4mg was given intravenously. The total consumption of ondansetron in 24 hours following surgery was also noted.

The data collected was analysed using the Statistical Package for Social Sciences (SPSS) software version 11.5 for Windows. Shapiro-Wilk test was used to see the normality of distribution. Normally distributed data were analysed using Student's T test and data not having normal distribution were analysed using Man Whitney U test. Categorical data were analyzed using Chi Square test. The 'p-value' thus calculated using these tools were considered statistically significant if less than 0.05.

## RESULTS

Overall, the demographic characteristics of the patients were comparable among the two groups. The two groups were statistically comparable in terms of baseline vital parameters. The Heart Rate at any given time point between the two groups were comparable. However, a drop in the heart rate was observed in both the groups over one hour after spinal anaesthesia.

The MAP was found to decline over 60 mins after spinal anaesthesia, and the change in MAP was significant in both the groups (p=0.001). However, the MAP was comparable among the groups at any given time.

The comparison of duration of post-operative analgesia was the primary objective of our study. We considered the duration from transfer of the patient to PACU to the first requirement of the rescue analgesic as the duration of effective post-operative analgesia. The mean duration of effective post-operative analgesia in the Group A was  $234 \pm 97$  minutes and in Group B was  $282 \pm 106$  minutes, which was statistically significant ( $p=0.009$ ). The total tramadol consumed over 24 hours was compared in between the two groups. The total opioid consumption in Group A was more than that of Group B. However, the difference was not statistically significant. Also, the mean duration of surgery was comparable and statistically insignificant among the two groups. We observed that the VAS at given time over 24 hours was comparable between the two groups (Table 1).

Among the 80 patients, 30 patients had to be given ondansetron as a rescue antiemetic. Thirteen patients in Group A and 17 patients in Group B required ondansetron. Out of these, three patients in Group B and one patient in Group A required a second dose of antiemetic over 24 hours. However, these data were statistically insignificant. The sedation score was significantly higher in the pregabalin group during the first postoperative hour than the gabapentin group ( $p=0.001$ ). The sedation scores were comparable among the two groups at other given points of time (Table 2).

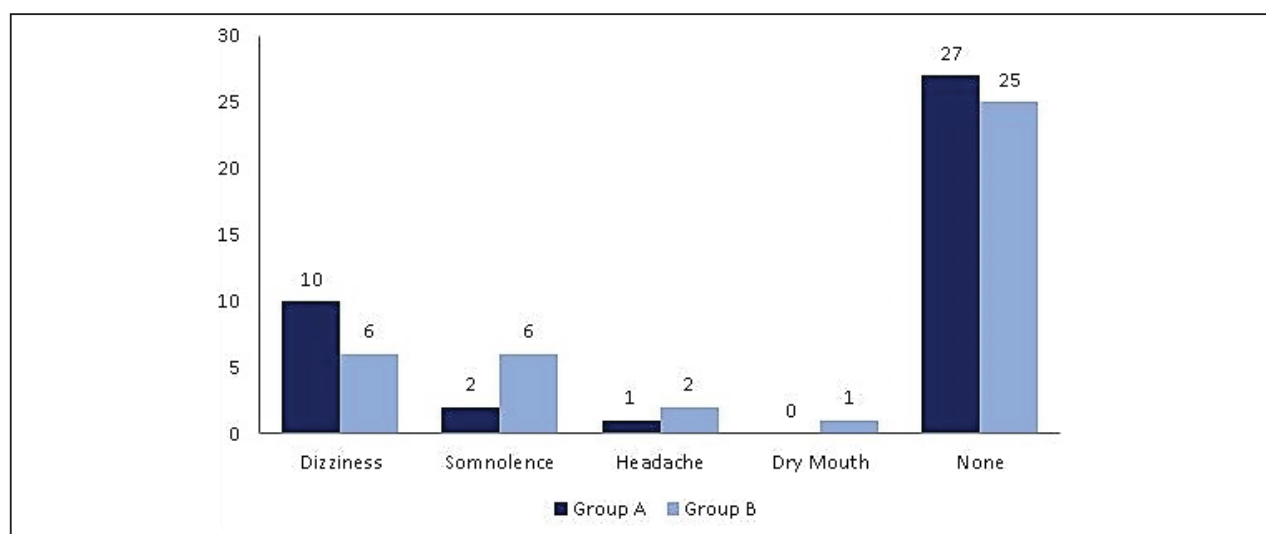
The common adverse effects observed during the study were dizziness, somnolence, headache and dry mouth. These adverse effects were observed in both the study groups (Figure 1).

**Table 1: Summary of observations**

Observations	Group A (n=40)	Group B (n=40)	p-value
Duration of Surgery (minutes)	$88.38 \pm 41.25$	$86.30 \pm 37.09$	0.814
Duration of Postoperative analgesia (minutes)	$234 \pm 97$	$282 \pm 106$	<b>0.009</b>
Total tramadol consumption (mg)	$75.00 \pm 29.96$	$66.25 \pm 28.62$	0.199

**Table 2: Ramsay sedation scale score over 24 hours**

Duration post-surgery	Group A	Group B	p-value
1 h	$2.12 \pm 0.49$	$3.48 \pm 0.89$	0.001
2 h	$2.22 \pm 0.27$	$2.16 \pm 0.38$	0.179
6 h	$2.00 \pm 0$	$2.08 \pm 0.22$	0.155
12 h	$1.68 \pm 0.27$	$2.11 \pm 0.16$	0.308
24 h	$1.96 \pm 0.22$	$2.38 \pm 0.16$	0.559



**Figure 1: Adverse effects observed between the two groups**

(Group A patients received capsule Gabapentin 300 mg orally, approximately one hour before surgery. Group B patients received capsule Pregabalin 150 mg orally, approximately one hour before surgery)

## DISCUSSION

Proper pain relief is a major concern and area of focus today. Pain is also one of the primary concerns of the surgeon because of its close ties with clinical outcome and acute postoperative patient well-being. Studies have indicated such negative clinical outcomes to include decreases in vital capacity and alveolar ventilation, pneumonia, tachycardia, hypertension, myocardial ischemia, myocardial infarction, transition to chronic pain, poor wound healing, and insomnia<sup>5</sup>.

The demographic profiles were comparable between the two groups, justifying proper randomization. The baseline hemodynamic parameters and the mean duration of surgery were also comparable. Decline in arterial blood pressure was observed during the intraoperative period, however no episode of hypotension or bradycardia was observed. Bafna et. al., also observed in their study that both pregabalin and gabapentin maintained stable hemodynamics throughout the perioperative period, when used for pre-emptive analgesia in patients undergoing gynecological surgeries<sup>6</sup>. This was further supported by Khetarpal et. al., and concluded that pregabalin and gabapentin increase the duration of postoperative analgesia without altering the haemodynamics<sup>7</sup>.

The present study has demonstrated significant postoperative analgesia with the use of 150 mg oral pregabalin (282±106 mins) for pre-emptive analgesia compared to 300 mg gabapentin (234 ± 97 mins), when administered approximately one hour before surgery. This supports the study done by Basavareddy et. al. where preoperative single dose of pregabalin (300 mg) resulted in significant postoperative analgesia compared to gabapentin (900 mg) and placebo in infraumbilical surgeries under spinal anaesthesia<sup>8</sup>. They concluded that both the drugs were better than placebo for postoperative analgesia.

Bafna et.al<sup>6</sup> also observed significantly longer mean duration of effective postoperative analgesia with 150 mg pregabalin (535.16 ± 32.86 min) when compared to 600 mg gabapentin (302.00 ± 24.26 min) and placebo (151.83 ± 16.21 min), in patients undergoing gynecological surgeries under spinal anaesthesia. The duration of postoperative analgesia with pregabalin was much more than we observed in our study, albeit with the same dose. This difference could be explained by the fact that our patients had undergone orthopedic surgeries, and most of them were already in severe pain before the administration of the drugs; on the contrary, the patients observed in their study had undergone

gynecological surgeries and did not have any pain in the preoperative period. However, the duration of analgesia observed with gabapentin was similar to that observed in our study, considering the higher dose used in their study.

We also observed that the mean consumption of tramadol for rescue analgesia over 24 hours in Gabapentin group was more than that in pregabalin. Similar differences were observed in the study of Basavareddy et.al<sup>8</sup>. In contrast to our study, the consumption of analgesic was observed over 72 hours following surgery, where patients receiving pregabalin consumed less tramadol than those receiving gabapentin and placebo. Akhavanakbari et.al, also observed less postoperative opioid consumption and concluded that a single pre-operative oral dose of pregabalin 150 mg is an effective method for reducing postoperative pain and opioid consumption in patients undergoing orthopaedic surgery<sup>9</sup>.

The incidence of postoperative sedation was found to be more with pregabalin than with gabapentin during the first postoperative hour. At other points of time, however, the scores were comparable between the groups. The findings of Sebastian et.al, in their study also showed increased sedation scores with pregabalin when compared to control, in terms of the proportion of patients having a higher Ramsay sedation score<sup>10</sup>.

While assessing for PONV, we found that 37% of the patients required ondansetron within 24 hours of surgery. The PONV scores at any given point of time over 24 hours were comparable. Similar results were observed in another study conducted by Mathiesen et.al, in which neither pregabalin alone or in combination with dexamethasone were associated with a reduced incidence of nausea or vomiting<sup>11</sup>.

## CONCLUSION

A single preoperative dose of 150 mg pregabalin is more effective than a single dose of 300 mg gabapentin for postoperative analgesia following lower limb orthopedic surgeries under spinal anaesthesia. Neither of these drugs reduced the incidence of PONV. Furthermore, pregabalin is associated with significant sedation during the immediate postoperative period. Both pregabalin and gabapentin maintain stable hemodynamics throughout the intraoperative period as well as postoperative period. To conclude, a single preoperative dose of pregabalin 150 mg can be used as an effective drug for preemptive analgesia for the management of postoperative pain in lower limb orthopaedic surgeries.

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