

# Preemptive Gabapentin vs Pregabalin for Acute Postoperative Pain in Women Undergoing Cesarean Section Under Spinal Anesthesia: A Prospective Randomized Double-blind Study

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## Abstract

**Background:** Appropriate management of pain is needed during the postpartum hospitalization period for preventing cesarean section (CS) related complications. Gabapentin and pregabalin have been used in treatment of neuropathic pain as well as postoperative pain with good results. However, there is paucity of studies in comparison with each other. The aim of current study was to compare the analgesic efficacy with respect to increase in duration of analgesia, reduction in total postoperative requirements of analgesics and study side effects and complications. **Methods:** A randomized, double-blind, placebo-controlled study was conducted in 90 women undergoing cesarean section who were anesthetized in a standardized fashion. Patients received 300 mg pregabalin, 600 mg gabapentin or placebo, 2 hours prior to surgery. Postoperative analgesia was given at visual analogue scale (VAS)  $\geq 3$ . The primary outcome of present study was consumption of analgesic over 24 hours and patients were followed for time to rescue analgesia, pain scores, and side effects as secondary outcomes. **Results:** The consumption of diclofenac was statistically significant between both pregabalin and control groups, and gabapentin and control groups; however, pregabalin and gabapentin groups were comparable. Patients in pregabalin and gabapentin groups had lower pain scores in the initial hour of recovery. However, pain scores were subsequently similar in all the groups. Time to first request for analgesia was longer in pregabalin group followed by gabapentin and control groups. **Conclusion:** Prior to CS, a single dose of 300 mg pregabalin given 2 hours is equally effective to 600 mg gabapentin but superior to placebo. Both the drugs are better than placebo.

**Keywords:** Cesarean Section; Gabapentin; Postoperative pain; Pregabalin.

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## Introduction

Adequate postoperative analgesia after cesarean section (CS) is necessary since these patients have a unique surgical recovery requirement which

include breastfeeding and care of the newborn. Post-CS analgesic management should be efficient without impacting the ability of a mother to take care of the neonate and with minimum drug transfer through breast milk. Although multimodal

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approaches have been there for proper pain relief yet they are inadequate and unsatisfactory in many patients.<sup>1</sup> Inadequate pain management can result in increased morbidity due to thromboembolic events, inappropriate neonatal care and delay in discharge which makes postoperative pain control in this group of patients is more challenging than other surgeries.<sup>2</sup> Post-partum pain management in women undergoing CS differs among different regions based on facilities available at the center or region.

Pregabalin and its precursor, gabapentin, are structural analogs of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA). These compounds have anticonvulsant, antihyperalgesic, and anxiolytic effects, and both bind to the alpha 2-delta ( $\alpha 2-\delta$ ) protein subunit of presynaptic, voltage-gated calcium channels extensively distributed in the both central and peripheral system. This inhibits calcium influx and reduces excitatory neurotransmitter (e.g., glutamate, substance P, calcitonin, noradrenaline, gene-related peptide) release in pain pathways.<sup>3,4</sup> Pregabalin is considered pharmacologically superior to gabapentin due to higher bioavailability (90% vs. 33%–66%), more rapid absorption (peak plasma level: 1-hour vs 3–4 hours), fewer drug interactions due to the absence of hepatic metabolism and linear increase in plasma concentrations when its dose is increased.<sup>5,6</sup> The lower doses of pregabalin required for its analgesic effect, compared to gabapentin, result in better tolerance and fewer side effects, making its use more advantageous.<sup>7,8</sup>

Pregabalin use as an analgesic in postoperative pain is still restricted to randomized control trials in patients of dental pain, hysterectomy, minor and day-case gynecological surgery and hip arthroplasty. To the best of our knowledge, there are no trials comparing pregabalin and gabapentin in postoperative pain in women undergoing cesarean section in the available literature. Thus, the study was undertaken to know whether the preoperative use of gabapentin and pregabalin will reduce the consumption of analgesics after cesarean section and to compare their efficacy and side effects with that of placebo.

## Materials and Methods

After getting written informed consent from each participant, ninety women in the age group of 20–35, undergoing cesarean section, were enrolled. The inclusion criteria were ASA I and II with no contraindications to the use of gabapentinoids.

Exclusion criteria were women of age more than 35; having history of central nervous system disorders, sedatives, chronic pain, using regular analgesics, anticonvulsants, impaired renal functions and 20% more than the ideal body weight.

The study was a randomized, double-blind and placebo controlled. A list of random numbers was generated by block randomization schedule using random number generator by a statistician and was handed over to the hospital pharmacist. Masking of study drugs was done by pharmacist by packing drugs in identical looking gelatine capsules. These capsules were further packed and sealed in an opaque envelope and labeled with study name, investigator name, and randomization number. Participants were assigned to their group according to their randomization number. The allocation sequence and enrollment of the patients was done by the same anesthetists who were involved in intraoperative and postoperative data collection. None was aware of allotted group till every woman was included and the assessments were done. Ninety women were allocated by sealed opaque envelopes bearing a code to each of the three groups to receive pregabalin 300 mg (Group P), gabapentin 600 mg (Group G) or a matching placebo (Group C) ( $n=30$  each) prepared by pharmacy. The study drug was given orally 2 hours prior to surgery and no other sedative premedication was given. Patients were told how to use of a 10 cm linear visual analogue scale (VAS) for pain, where 0 denotes “no pain” and 10 denotes “worst imaginable pain”, before surgery. In the operating room, electrocardiogram (ECG), noninvasive blood pressure (NIBP), peripheral oxygen saturation ( $SpO_2$ ) and heart rate (HR) were monitored (Philips Intellivue MP70). Using an aseptic procedure, a 26-gauge Quincke needle was inserted intrathecally via a midline approach at the L3–4 interspace by the same anesthetist, who was unaware of allotted group. Following a successful dural puncture, the anesthetic solution (2.2 mL hyperbaric bupivacaine 0.5%) was injected. After completion of CS, all the patients were transferred to post-anesthesia care unit (PACU).

The primary outcomes of this study were to evaluate the time to the first requirement of analgesic and the total analgesic consumption in the first 24 postoperative hours. In this study, postoperative analgesia was defined as the time from the intrathecal injection of anesthetic solution to the first requirement of analgesic supplement. The pain intensity of patients was evaluated at the end of anesthesia in recovery room, then at 2, 4, 6, 8, 12, 18 and 24 hours after surgery. Rescue analgesia was given at  $VAS \geq 3$  with intramuscular diclofenac sodium 1 mg/kg.

The secondary outcome of this study included the assessment of sedation level and the incidence of vomiting. The sedation level of patients after surgery was measured according to modified Ramsay sedation score<sup>9</sup> using a 3-point scale with 1=anxious, 2=calm and oriented, 3=calm and drowsiness.

Any side effects like nausea, vomiting, skin rash, headache, dizziness, visual disturbances, peripheral edema and respiratory depression (sedation score > 2 and respiratory rate < 10 breaths/minute) were noted. Injection ondansetron 0.1 mg/kg was given when required.

Sample size was decided in consultation with a statistician. Sample size was calculated using a power of 90% and an  $\alpha$  value of 0.05. Based on preliminary results from our department, the anticipated consumption of diclofenac sodium was 175 mg (standard deviation = 40 mg) in gabapentin group and a reduction in pregabalin group by 20% was considered significant. Based on these assumptions and sample size of previous trial also into consideration, a sample size of 30 per group was taken.<sup>10</sup> No adjustment to the Type 1 error rate was made to accommodate the multiple analyses associated with the secondary outcome measures. One-way analysis of variance (ANOVA) was used for comparison of total analgesic consumption over 24 hours and the time intervals to first analgesic.

## Results

Ninety patients were enrolled in, completed the study protocol and were included in the data analysis. Failed spinal anesthesia and conversion to general anesthesia were encountered in one case from control group (C) which were replaced by another case to complete the sample size. Demographic characteristics in all three groups did not show any statistically significant difference ( $p$  value > 0.05) (Table 1). Time to first request for analgesia was  $24.32 \pm 9.2$  minutes in pregabalin group, followed by  $19.13 \pm 14.2$  minutes in gabapentin ( $p = 0.0983$ ) and  $9.00 \pm 3.2$  minutes in control group.

(Table 2). Sedation score analysis revealed significance in control group in comparison to P and G groups ( $p < 0.001$ ) at all measured times. Sedation scores are shown in Table 3. The common side effects in the study were nausea, vomiting and dizziness with no difference in the incidence of side effects between pregabalin and gabapentin groups.

Twenty-eight patients in the control group had nausea and vomiting in comparison to 13 in pregabalin group and 20 patients in gabapentin group ( $p < 0.001$ ). Five patients reported dizziness in pregabalin group, nine in gabapentin group and one in control group. The incidence of sedation was 30% in pregabalin group, 40% in gabapentin group, 6.6% in control group. The incidence of headache, blurred vision, and skin rash was comparable in all the

**Table 1:** The demographic profile of patients in the three groups.

Demographic profile	Group P	Group G	Group C	$p$ value
Age (yrs)	28.3 $\pm$ 5.2	27.8 $\pm$ 5.1	29.2 $\pm$ 4.2	0.529
Weight (Kg)	75.1 $\pm$ 12.4	76.5 $\pm$ 14.2	78.4 $\pm$ 12.1	0.613
Height (cm)	158.5 $\pm$ 4.6	157.4 $\pm$ 5.3	157.6 $\pm$ 3.4	0.662
Gestational age (week)	38.4 $\pm$ 1.2	38.2 $\pm$ 1.0	38.3 $\pm$ 1.1	0.782

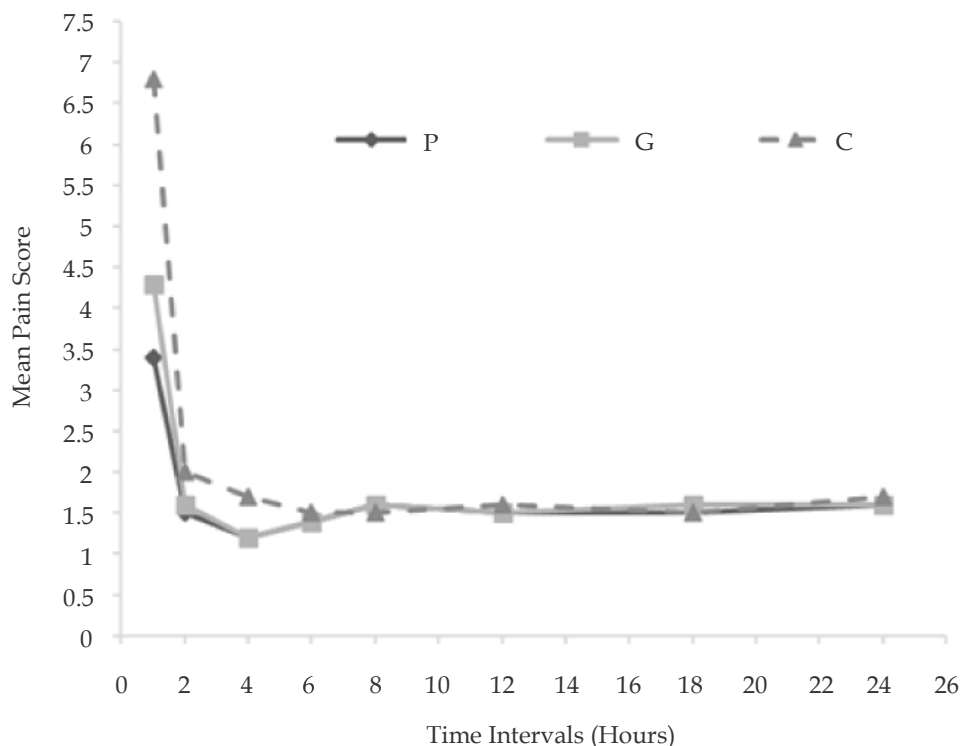
Numerical data were expressed as mean  $\pm$  SD.  $p$  value > 0.05 was considered insignificant.

**Table 2:** Time to first analgesic and requirement of rescue analgesic (mean  $\pm$  SD)

Group	Time interval (minutes)	Diclofenac sodium (mg)
P	24.32 $\pm$ 9.2	162.32 $\pm$ 35.34
G	19.13 $\pm$ 14.2	171.21 $\pm$ 38.2
C	9.00 $\pm$ 3.2	200.00 $\pm$ 35.4

**Table 3:** Sedation score at different time intervals postoperatively (mean  $\pm$  SD)

Group	1 hour	2 hour	6 hour	12 hour
P	1.98 $\pm$ 0.24	1.99 $\pm$ 0.12	1.92 $\pm$ 0.26	1.29 $\pm$ 0.42
G	1.87 $\pm$ 0.35	1.97 $\pm$ 0.18	1.90 $\pm$ 0.31	1.37 $\pm$ 0.43
C	1.45 $\pm$ 0.572	1.49 $\pm$ 0.46	0.88 $\pm$ 0.38	0.35 $\pm$ 0.27



**Fig. 1:** Visual analogue scale (VAS) scores for pain at rest postoperatively in different time intervals. Time 0 is taken as admission to the recovery. Results are expressed as mean (SD). Patients in pregabalin and gabapentin groups had lower mean pain scores in the initial hour of recovery than placebo group. However, pain scores were subsequently similar in all the groups

groups. Figures 1 display postoperative pain scores over time. Patients in pregabalin and gabapentin groups had lower mean pain scores than placebo in the initial hour of recovery. However, pain scores were subsequently similar in every group.

## Discussion

The study reveals that pregabalin 300 mg and gabapentin 600 mg, given orally 2 hours before LSCS significantly reduced postoperative analgesic requirement compared with placebo. This finding is in agreement with the pharmacokinetic profile of both the study drugs as they have short elimination life (6–8 hours) after a single dose. Their administration 2 hours prior to surgery appeared rational in order to attain maximal plasma concentration at the time of surgical stimuli though pregabalin is rapidly absorbed (peak: within 30 minutes to 2 hours) and gabapentin is slowly absorbed (peak: 2 hours). Two hours lapsed easily by the time patient received the drug and skin incision was given, which gave sufficient time to achieve peak effect of both the drugs.

In a study of patients undergoing infraumbilical surgery, it was found that gabapentin and

pregabalin when given preoperatively in absence of an opioid or nonopioid analgesic, prolong the analgesic effects of spinal analgesia, which far exceeds the normal duration of spinal analgesia. The analgesic effect is longer lasting following pregabalin as compared to gabapentin (8.98 hr in Gabapentin vs 14.17 hr in Pregabalin group).<sup>8</sup> There are many studies showing that gabapentin in postoperative pain relief in various surgical procedures, but there is very little data regarding placebo-controlled studies of pregabalin in acute pain states. In comparison to the above studies, premedication with 150 and 300 mg pregabalin reduced analgesic consumption in laparoscopic hysterectomy.<sup>10</sup>

Mean pain scores was reduced with a preoperative dose of gabapentin and pregabalin in the initial hour of recovery in this study which is consistent with previous studies.<sup>11,12</sup> There was no difference after the initial hour. It may be due to the reason that gabapentin and pregabalin have a relatively short half-life and were given as a single preoperative dose. The incidence of side effects did not differ among all the groups except sedation and vomiting. Sedation with their use has been reported in previous studies also, but it had no effect on ambulation and discharge.<sup>11,12</sup>

Gabapentin and pregabalin also reduce movement-evoked pain which may cause enhanced functional postoperative recovery.<sup>13</sup> Postoperative opioid sparing is of questionable relevance since few trials have shown reduced opioid-related adverse effects. In one study by Jesper *et al.*<sup>13</sup> showed substantial reduction in movement-related pain 2 and 4 h after radical mastectomy after a single dose of 1,200 mg oral gabapentin administered preoperatively but reduction was not significant at rest. This could be explained by prevention or reduction of the development of central neuronal hyperexcitability induced by the surgical procedure as only evoked pain during movement was significantly decreased, in contrast to pain at rest.

Sedation and dizziness are the two most common side effects associated with gabapentin and pregabalin. The incidence reported in present study is similar to earlier studies.<sup>11</sup> This is usually not disabling and antianxiety effect has been found to be favorable in some studies.<sup>14</sup>

The limitation of the present study is that single dose of gabapentin and pregabalin has been used. The half-life of gabapentinoids is 5–7 hours and conclusions about the optimal dose and duration of the treatment cannot be made. Though no major difference was seen in pregabalin and gabapentin in the present study, further studies are needed to determine the long-term benefits, if any, of perioperative gabapentin and pregabalin comprehensively.

To conclude, postoperative analgesia was better with 600 mg gabapentin and 300 mg pregabalin than placebo during the early recovery after LSCS. Gabapentinoids like pregabalin and gabapentin are an effective drug in the treatment of postoperative pain.

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