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Pregabalin for postoperative pain in patients undergoing spinal surgery: a dose ranging randomized clinical study

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Abstract

Background: *the efficacy of pregabalin in acute post-surgical pain management is well demonstrated. As, the use of pregabalin is officially not approved and hence, there is no dosing guideline as well.*

Aim: *to determine whether single preoperative administration of different doses of pregabalin (150 mg to 300 mg) could decrease postoperative pain intensity following spinal surgery.*

Materials and Method: *in this prospective, randomized double-blinded study, a total of 60 patients undergoing spinal surgery were selected and randomly assigned to any of these four groups of 15 each; group A (received placebo drug), group B (received pregabalin 150 mg), group C (received pregabalin 200 mg), and group D (received pregabalin 300 mg). All the groups received the said drugs (coded as it was double-blinded study) in the same manner and two hours prior to operation. The patients were followed for pain scores on visual analogue scale (VAS), time to rescue analgesia and side effects as secondary outcomes.*

Results: *patients in pregabalin dose ranging groups had lower pain in the initial hour of recovery. However, the pain scores subsequently decreased and became similar in all groups. Time for the requirement for analgesic was longer in pregabalin 300 mg group when compared with other study groups.*

Conclusion: *a single dose of 300 mg pregabalin given 1–2 hours prior to surgery is superior to placebo after spinal surgery.*

Key words*: pain management, pregabalin, spinal surgery, visual analogue scale (VAS)*

Introduction

Pain manage ment after spinal surgeries is essential for decreasing postoperative complications such as unfavourable circumstances for the patient and extended hospital stay. The traditional way of pain treatment with opioids has been associated with undesirable side effects such as nausea, vomiting, constipation, urinary retention resulting in increased frustration among the patients.[1, 2]

Numerous studies over time have demonstrated the efficacy of pregabalin in acute post-surgical pain; however, its adverse effects remain uncertain. Pregabalin is a gamma-amino butyric acid analogue, a new synthetic

molecule that binds to $\alpha_2\delta$ subunits of the voltage-gated calcium channels. It was synthesized in 1991 and was introduces into acute pain management in 2001. Pregabalin and gabapentin, also known as gabapentinoids share a similar mechanism of action. And like gabapentin, Pregabalin also has hyperalgesic properties. The hyperexcitability of dorsal horn neurons induced by tissue damage could be reduced by use of Pregabalin and hence it has been found useful in post-surgical pain prevention.[3,4]

Since, the use of pregabalin is officially not approved as the effect of pregabalin on preventing acute postoperative pain is inconclusive; hence, there is no dosing guideline as well. The current study aims to investigate the preoperative use of pregabalin used doses ranging from 150 mg to 300 mg.

Aim & Objective

To determine whether single preoperative administration of different doses of pregabalin (150 mg to 300mg) could decrease postoperative pain intensity following spinal surgery.

Materials & Method

This prospective, randomized double-blinded study was conducted at Jaipur National University Institute for Medical Sciences and Research Centre, Jaipur, Rajasthan. The ethical clearance certificate was requested and received from the University's Ethics committee before the present study was conducted. Patients/care-givers provided informed consent for the study. For the current study, patients were excluded if they were known to be allergic to pregabalin, had any clinically significant medical or psychiatric conditions, were pregnant or lactating, had a history of alcohol or drug abuse within the past 6 months, or were taking opioid-containing pain or sedative medications on a long-term basis. Thus, a total of 60 patients undergoing spinal surgery were selected and randomly assigned to any of these four groups of 15 each; group A (received placebo drug), group B (received pregabalin 150 mg), group C (received pregabalin 200 mg), and group D (received pregabalin 300 mg). All the groups received the said drugs (coded as it was double-blinded study) in the same manner and two hours prior to operation.

Procedure: IV cannulation general anaesthesia was induced with thiopental sodium (5 mg/kg), fentanyl (2 mcg/kg), and vecuronium (0.01 to 0.015 mg/kg) and maintained with sevoflurane and 60 % nitrous oxide after initial monitoring. Sevoflurane concentration was adjusted to maintain adequate anaesthesia. Fentanyl infusion (1–2 mcg/kg/min) was continued during the surgery. Along with this, a combination of ondansetron, 4mg IV and dexamethasone, 8 mg IV were given intraoperative to prevent postoperative discomfort. At the end of surgery sevoflurane was stopped and oxygen flow was increased. Residual neuromuscular blockade was reversed with neostigmine, 40 mcg/kg and Glycopyrrolate, 5 mcg/kg IV. After extubation patients were transferred to post anaesthesia care unit (PACU).

In PACU, the patients were asked to express the level of pain they experienced using 11 point visual analogue scale (VAS), with 0 indicating no pain at all and 10 indicating worst possible pain. Fentanyl, 25–50 mcg IV, boluses were given to reduce acute postoperative pain when the patient complained of moderate to severe pain. Anxiety scores, vital signs, Numeric Sedation Scores (NSS; 1 = completely awake, 2 = awake but drowsy, 3 = asleep but responsive to verbal commands, 4 = asleep but responsive to tactile stimulus, 5 = asleep and not responsive to any stimuli), fentanyl consumption and adverse effects such as nausea and vomiting were recorded. Recovery time to oral fluid intake and start of normal diet as well as first bowel movement were recorded.

No financial assistance was taken and there was no conflict of interest. Patient's demographics, clinical data and laboratory values were collected by the investigator. The collected data was recorded and evaluated.

Statistical analysis: a sample size of 15 patients in each group will be sufficient to detect a 30 % difference in the incidence of postoperative pain between the study group assuming power of 90 % and a significant level of 0.05. The recorded data was evaluated and presented using descriptive statistics expressed in mean ± SD. One-way analysis of variance (ANOVA) was used for comparison of pain scores over 24 hours and the time intervals to first analgesic, sedation scores over 12 hours. The chi-square test was applied to test the association between side effects (vomiting and nausea) and the study drug. All the analysis were performed on SPSS software.

Results

The current dose ranging randomised clinical study was conducted at JNUIMSRC, Jaipur, Rajasthan. A total of 60 patients, randomly assigned to four groups of 15 each (Placebo group, Pregabalin 150 mg group, Pregabalin 200 mg group, and Pregabalin 300 mg group). Based on the study sample, the patient characteristics

and demographics are depicted in Table 1. Postoperative sedation scores are depicted in Table 2 and were analysed. The difference in postoperative sedation score was significant among group at 2 hour between placebo group and pregabalin 150 mg group and between placebo group and pregabalin 300 mg group (P < 0.05) and at 6 hour between placebo group and pregabalin 150 mg group, between placebo group and pregabalin 300 mg group and between pregabalin 200 mg and pregabalin 300 mg group (P < 0.001). The post-operative side effects of vomiting and nausea are depicted in Table 3 and Table 4 respectively, there was no significant difference in

Table 1. Descriptive statistics of demographic variables

	Placebo group (N = 15)	Pregabalin 150 mg group (N = 15)	Pregabalin 200 mg group (N = 15)	Pregabalin 300 mg group (N = 15)
Age (years)	45.41 ± 12.64	54.91 ± 13.51	40.28 ± 12.61	44.51 ± 11.74
Weight (kg)	58.9 ± 13.16	62.93 ± 11.6	59.95 ± 11.32	55.26 ± 14.64
Duration of surgery (min)	121 ± 5.9	120 ± 5.63	121 ± 5.74	120 ± 6.04

Data are expressed in mean ± SD

Table 2. Sedation score postoperatively (Mean ± SD)

	1 hour	2 hour	6 hour	12 hour
Placebo group	2.06 ± 0.45	2.33 ± 0.74	1.86 ± 0.74	1.13 ± 0.51
Pregabalin 150 mg group	1.66 ± 0.72	1.6 ± 0.50	1.86 ± 0.63	1.06 ± 0.70
Pregabalin 200 mg group	1.53 ± 0.63	1.86 ± 0.63	1.26 ± 0.45	0.73 ± 0.79
Pregabalin 300 mg group	1.6 ± 0.50	1.4 ± 0.63	0.86 ± 0.63	0.53 ± 0.51

the incidence of these side effects among study groups. Figure 1 shows the visual analogue scale (VAS) for post operative pain at different time intervals. Patients in dose ranging pregabalin groups displayed low mean pain scores, which were statistically at 2 hour between placebo group and pregabalin 150 mg group and between pregabalin 150 mg group and pregabalin 200 mg group (P < 0.05); between placebo group and pregabalin 200 mg group, and between placebo group and pregabalin 200 mg group, and between placebo group and pre-

Table 3. Distribution of postoperative vomiting in dose ranging study groups

	Postoperative Vomiting		p — value
	Yes	No	
Placebo group	10 (66.7)*	5 (33.3)*	0.505
Pregabalin 150 mg group	8 (53.3)*	7 (46.7)*	
Pregabalin 200 mg group	6 (40)*	9 (60)*	
Pregabalin 300 mg group	7 (46.7)*	8 (53.3)*	

Expressed in numbers (%): chi-square test, $\chi 2$ (3, N = 15) = 2.33 ; p > 0.05 and hence, the results are not significant*

Table 4. Distribution of postoperative nausea in dose ranging study groups

	Postoperative Nausea		p — value
	Yes	*No*	
Placebo group	11 (73.3)*	4 (26.7)*	0.321
Pregabalin 150 mg group	8 (53.3)*	7 (46.7)*	
Pregabalin 200 mg group	8 (53.3)*	7 (46.7)*	
Pregabalin 300 mg group	3 (20)*	12 (80)*	

Expressed in numbers (%): chi-square test, $\chi 2$ (3, N = 15) = 8.8 ; p>0.05 and hence, the results are not significant

gabalin 300 mg group (P < 0.001). The pain scores were also statistically significant at 6 hour between placebo group and pregabalin 150 mg (P < 0.05) and between placebo group and pregabalin 300 mg group (P < 0.001) and statistically significant at 24 hour between placebo group and pregabalin 150 mg (P < 0.05), between placebo group and pregabalin 200 mg group (P < 0.001) and between placebo group and pregabalin 300 mg group (P < 0.01). Table 5 depicts consumption of fentanyl (analgesic) postoperatively among study groups. The difference in the time for request of analgesic was statistically significant between pregabalin 150 mg group and placebo group (P < 0.001), pregabalin 200 mg group and placebo group (P < 0.001), pregabalin 300 mg group and placebo group (P < 0.001), pregabalin 150 mg group and pregabalin 300 mg group (P < 0.001) and pregabalin 200 mg and pregabalin 300 mg group (P < 0.001).

Discussion

Postoperative pain after surgery is normally perceived as nociceptive pain. Pain, indeed is one of the three most common medical causes of delayed discharge post-surgery, the other two being nausea and vomiting. Pregabalin is classified as an anti-epileptic drug along with gabapentin and both are widely used analgesics to reduce post operative pain. Thus, the present study was conducted to determine whether single preoperative administration of different doses of pregabalin (150 mg to 300 mg) could decrease postoperative pain intensity following spinal surgery. The study sample consisted a total of 60 patients, randomly assigned to four groups of 15 each (Placebo group, Pregabalin 150 mg group, Pregabalin 200 mg group and Pregabalin 300 mg group).

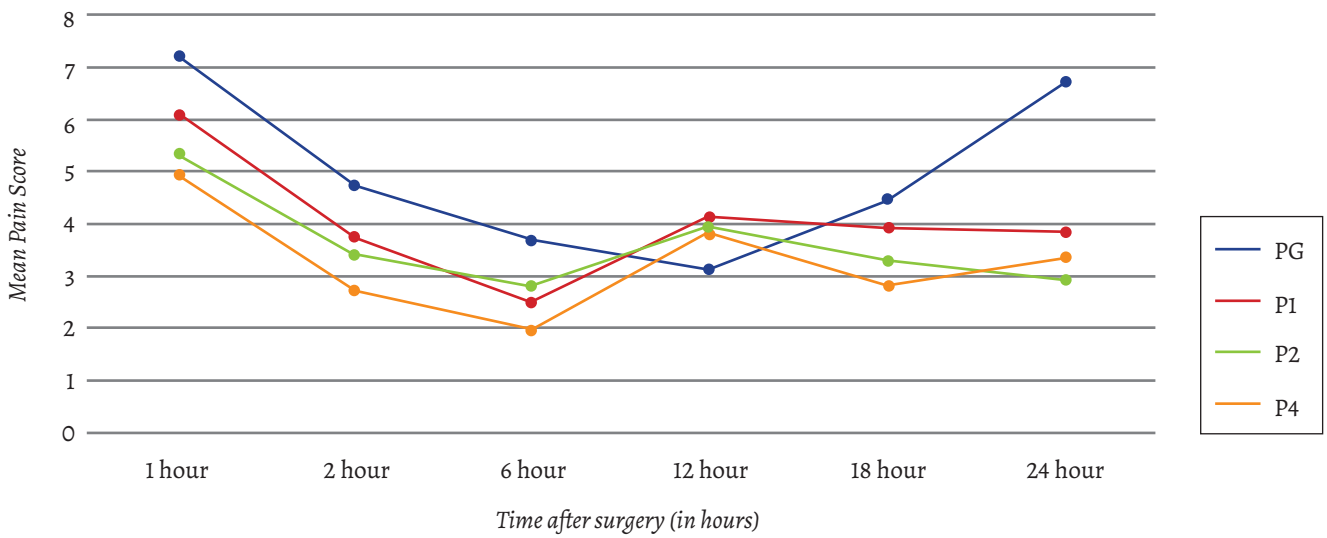

Fig. 1: Visual analogue scale (VAS) scores for pain post-operatively in different time intervals

Table 5: Mean consumption of fentanyl in mcg (opioid) postoperatively in study groups

	Time Interval (in minutes)	Fentanyl (mcg)
Placebo group	7.4 ± 1.64	43.33 ± 11.44
Pregabalin 150 mg group	14.9 ± 4.02	30 ± 10.35
Pregabalin 200 mg group	17.73 ± 4.71	23.33 ± 17.59
Pregabalin 300 mg group	23.93 ± 5.33	16.66 ± 12.19

Data are expressed in mean ± SD

The results of this study revealed that pain decreased in Pregabalin 300 mg Group-The most when compared to other study groups over time. Several studies have explored the effectiveness of pregabalin in post-operative pain reduction. However, our study is one among the first few studies to report a dose ranging effectiveness of pregabalin. Ghai et al. also reported lower pain scores in pregabalin group in the initial hour of recovery.[5]

The aim of our study was to find the difference in efficacy of Pregabalin doses ranging from 150 mg to 300 mg. Based on the above observations, we found reduced pain scores in Pregabalin 300 mg group when compared to other study groups. However, the pain scores became subsequently similar in all groups in later hours. We also found that the pain score did not reduce much among pregabalin 150 mg group and pregabalin 200 mg group. The results on our study are supported by other studies.[5, 6, 7]

One among the most common postoperative concerns are nausea and vomiting. We found of patients required treatment for nausea and vomiting after spinal surgery. The number of cases of nausea and vomiting in the pregabalin 300 mg group were lower when compared to the other three groups, and were highest in the placebo group. Hill et al.[8] in a similar study found Pregabalin 300 mg to be more effective than pregabalin 50 mg or ibuprofen 400 mg in reducing pain post dental extraction. In another similar study by Mathiesen et al. it was found that pregabalin resulted in reduction of pain but it was not associated with reduced incidence of vomiting or nausea.[9] studies also reported use of pregabalin resulting in decreased postoperative pain in the initial hour of recovery.[10, 11]

We also reported the requirement for analgesic (fentanyl) consumption postoperatively in all study groups and found that it was the highest in placebo group and lowest in the Pregabalin 300 mg group. Also, additionally in the placebo Group-The analgesic (fentanyl) was required in the mean time lapse of few minutes while the other study groups required it several minutes later. The difference in the time for request of analgesic was statistically significant between all study groups while not significant between Pregabalin 150 mg group and Pregabalin 200 mg group. We found pregabalin 300 mg to be more effective than pregabalin 150 mg and pregabalin 200 mg in the current study, however more controlled studies like ours are needed to define clear benefits and side effects of different dosages of pregabalin in pain management.

Conclusion

A single dose of 300 mg pregabalin given 1–2 hours prior to surgery is superior to placebo after spinal surgery and its usage was associated with decreased analgesic consumption.

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Прегабалін для лікування післяопераційного болю у пацієнтів, які перенесли операцію на хребті: рандомізоване клінічне дослідження з діапазоном доз

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Анотація

Довідкова інформація: *ефективність прегабаліну в лікуванні гострого післяхірургічного болю добре доведена. Оскільки використання прегабаліну офіційно не схвалено, то відсутні й відповідні рекомендації щодо дозування.*

Мета: *визначити, чи може одноразове передопераційне введення різних доз прегабаліну (від 150 мг до 300 мг) зменшити інтенсивність післяопераційного болю після операції на хребті.*

Матеріали та методи: *у цьому проспективному, рандомізованому подвійному сліпому дослідженні було відібрано загалом 60 пацієнтів, які перенесли операцію на хребті. Їх випадковим чином розподілено до будь-якої з цих чотирьох груп по 15 у кожній; група A (отримала препарат плацебо), група B (отримала прегабалін 150 мг), група C (отримала прегабалін 200 мг) і група D (отримала прегабалін 300 мг). Усі групи отримували зазначені препарати (закодовані як подвійне сліпе дослідження) однаково за дві години до операції. Пацієнтів спостерігали по балах болю за візуальною аналоговою шкалою (VAS), часом до рятівної анальгезії, та побічних ефектах як вторинних результатах.*

Результати. *Пацієнти в групах із різними дозами прегабаліну мали менший біль у першу годину після операції. Однак бали болю згодом зменшилися і стали однаковими в усіх групах. Час для потреби в анальгетиках був довшим у групі прегабаліну 300 мг порівняно з іншими групами дослідження.*

Висновок: *одноразова доза 300 мг прегабаліну, введена за 1–2 години до операції, перевершує плацебо після операції на хребті.*

Ключові слова: *лікування болю, прегабалін, хірургія хребта, візуальна аналогова шкала (VAS)*