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The Role Of Pregabalin In Pre-Operative Anxiety And Post-Operative Pain In Spine Surgery Patients- A Randomised Controlled Trial

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Abstract

Background: Pregabalin is a gabapentinoid which has been shown to possess analgesic and anxiolytic properties. The present study was conducted to assess the effect of pregabalin premedication on preoperative anxiety and post operative pain scores and opioid consumption in patients operated for lumbar laminectomy and discectomy. **Method:** A total of 75 patients were randomised equally into three groups- Group A: received placebo (B-complex); Group B: received pregabalin 150mg and group C: received pregabalin 300mg. **Results:**TheVAS anxiety score was significantly lower in Group B (17.96±5.08) and Group C (13.40±2.65) compared to Group A (45.08±10.12), ($p<0.05$).The HR, SBP, DBP and MAP levels in Group A and B were significantly higher compared to Group C from 30 mins till150 mins post induction, ($p<0.05$). The mean intra-operative (210.40±3.47ml vs. 150.44±3.74ml vs.167.76±3.97ml) and post-operative fentanyl consumption (339.12±3.36 ml vs. 212.16±3.59 ml vs. 189.64±3.78 ml) was significantly higher in GroupA compared to Group B and C. The mean VAS scores for pain at rest and in pain on movement in first 5hrs was significantly higher in Group A compared to Group B and C, ($p<0.05$). **Conclusion**: Pregabalin in both the doses of 150 and 300mg given prior to surgery can significantly reduce preoperative anxiety and intraoperative requirement of fentanyl compared to placebo. Pregabalin 300mg significantly decreased postoperative pain VAS scores at rest and on movement during the first 5 h after surgery. Therefore, the single use of pregabalin in doses between 150 and 300 mg is both safe and effective for reducing preoperative anxiety with a favourable postoperative analgesic profile.

Keywords: Pregabalin, Gabapentinoid, Preoperative anxiety, VAS score: Laminectomy and Discectomy

Introduction

Lumbar laminectomy and discectomy surgeries are associated with moderate to extreme pain at hospital discharge, thus hampering recovery. Appropriate pain control is a prerequisite to promoting early mobilization and functional recovery after spine surgery. Although pain control is an essential part of perioperative care, postoperative pain is still a difficult and undertreated problem. More than 80% of the 73 million patients undergoing surgery annually experience postoperative pain and over 85% of these experience mode rate, severe, or extreme pain [1,2].

Although opioids are important component of postoperative pain management, they are associated with side effects [3], and so, the multimodal analgesic approach has been recommended for the management of acute postoperative pain [4,5]. Experimental models of neuropathic pain and inflammatory hyperalgesia have shown that γ-amino butyric acid analogues, such as gabapentin and

pregabalin, have antinociceptive and antihyperalgesic properties. It has been suggested that central neuronal sensitisation may result in amplification of postoperative pain [6], and that preoperative administration of gabapentin, before inflammatory trauma or surgical stimulation, may reduce the degree of central sensitisation [7]. Compared with gabapentin, pregabalin has better pharmacokinetic properties and fewer drug interactions, due to an absence of hepatic metabolism [8]. Apart from its analgesic potency, pregabalin possesses anxiolytic properties [9].
Hence the present study was done at our tertiary care centre to assess the effect of pregabalin premedication on preoperative anxiety, evaluate the effect of pregabalin pre medication on post operative pain scores (both stationery and movement related) and opioid consumption in patients operated for lumbar laminectomy and discectomy.

Material and Method:
After obtaining Institutional Ethical Committee approval and written informed consent from all the patients, this prospective, randomized, single blind study was conducted in 75 patients of age between 18 to 65 years, ASA status I and II with symptoms of nerve root compression and who undergoing elective lumbar laminectomy and discectomy (admitted in orthopaedics ward) at our Tertiary care Hospital. These patients were randomized equally to following 3 groups using pre-designed, computer generated random allocation plan:

- Group A: 25 patients received placebo (B-complex)
- Group B: 25 patients received pregabalin 150mg.
- Group C: 25 patients received pregabalin 300mg.

Patients who were unable to assess and comprehend 100 point VAS score to assess self-score pain, patients with known allergy to pregabalin/gabapentin and/or fentanyl, any history of drug and/or alcohol abuse, intake of nonsteroidal anti-inflammatory drugs (NSAIDs) within 24 h prior to operation, impaired kidney function and patients taking sedatives or anticonvulsants and pregnant females were excluded from the study.
A thorough history and physical examination was done as per proforma. All patients received 0.2 mg glycopyrrolate intramuscularly, 1h before surgery. Patients' anxiety level was assessed by 100 mm VAS, before administration of the study drug. Assessment of the score was repeated in the preinduction room and in the operating room (OR). In the OR, patients' baseline pain intensity at rest and during movement (from supine to lateral position) was assessed using VAS for pain. Simultaneously, baseline values of heart rate (HR), mean arterial blood pressure (MABP), BIS, respiratory rate (RR) and oxygen saturation (SpO2) were noted. Anesthesia was induced with fentanyl 2 μg/kg, propofol 1.5-2 mg/kg and tracheal intubation facilitated with rocuronium 1 mg/kg. Anesthesia was maintained with nitrous oxide and oxygen in 2:1 ratio with isoflurane (end tidal 0.8%–1.2%) and intermittent doses of rocuronium. Fentanyl was repeated as per requirement, at the discretion of the attending anesthesiologist. Mechanical ventilation was adjusted to keep the end-tidal CO2 concentration between 36 and 38 mmHg. Lactated Ringer's solution was used for maintenance requirements of fluids throughout the surgery.
Continuous electrocardiogram, HR, SpO2, NIBP, airway pressure, temperature and end-tidal anesthetic concentrations were monitored during anesthesia. All parameters were recorded at 15 min interval. Under proper aseptic precaution, the surgical site was infiltrated with lignocaine 1% with adrenaline (1:200,000). At the end of the surgery, patients were turned supine. Neostigmine 50 μg/kg and glycopyrrolate 10 μg/kg were given to reverse the residual neuromuscular blockade. Trachea was extubated when the patient was fully awake. On arrival to the intensive care unit, patient's pain intensity at rest and during movement was assessed using pain VAS. Simultaneously, values of HR, MABP, RR and SpO2 were noted and taken as the values at 0 h. Then, the measurements were repeated at hourly intervals until 8 h. Pain medications were converted to oral NSAIDs after the study period. Patients were given a bolus dose of fentanyl 1 μg/kg. The incremental dose was set at 0.25–0.5 μg/kg and titrated according to requirement. All patients received oxygen through face mask with a flow of 3 L/min throughout the study period.

A single observer recorded all the measurements. Total dose of fentanyl consumed intra- and postoperatively over the 8 h period was noted. Sedation was assessed using Ramsay 5-point sedation score at every 2h up to 8h. Adverse effects such as postoperative nausea and vomiting (PONV), dizziness, headache and visual blurring were noted.

Statistical Analysis

Quantitative data is presented with the help of Mean and Standard deviation. Comparison among the study groups is done with the help of unpaired t test as per results of normality test. Qualitative data is presented with the help of frequency and percentage table. Association among the study groups is assessed with the help of Anova and Chi-Square test. 'p' value less than 0.05 is taken as significant.

Observations and Results

A total of 75 patients were enrolled in the study and randomly divided into 3 equal groups: Group A received placebo (B-complex), Group B patients received pregabalin 150mg and Group C received pregabalin 300mg. All three groups were comparable and found no significant difference with respect to demographic profile of the patients as shown in Table 1.

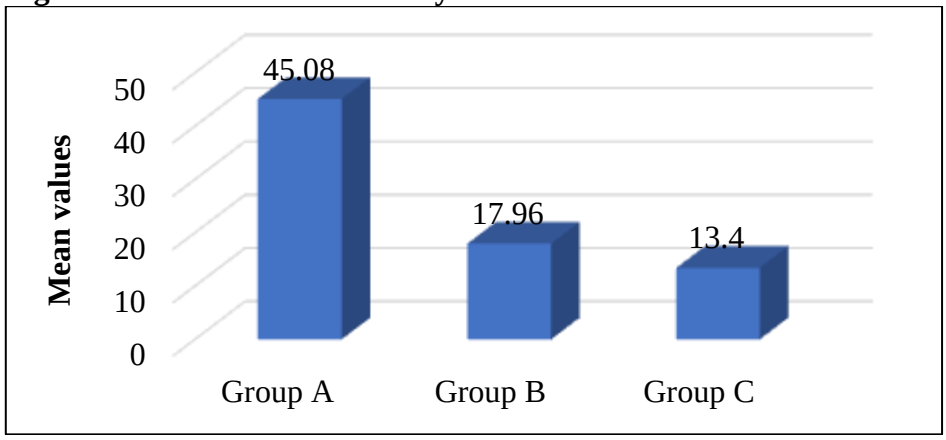
The mean duration of anaesthesia was comparable between the groups (171.44±39.26 mins vs. 174.64±37.63 mins vs. 172.16±35.04 mins) and statistically not significant as per ANOVA test ($p>0.05$).

Table 1: Distribution of patients according to demographic data

Demographic data		Group A	Group B	Group C	P value
Age (years)	18-30	6 (24%)	4(20%)	6(24%)	p>0.05
	31-40	4(16%)	8(32%)	4(16%)	
	14-50	9(38%)	7(28%)	7(28%)	
	51-60	5(20%)	4(16%)	7(28%)	
	61-65	1(4%)	2(8%)	1(4%)	
Gender	Male	14(56%)	16(64%)	13(52%)	p>0.05
	Female	11(44%)	9(38%)	12(48%)	
ASA	I	19(76%)	18(72%)	16(64%)	p>0.05
	II	6(24%)	7(28%)	9(36%)	
BMI (kg/m2)	Normal	12(48%)	9(36%)	10(40%)	p>0.05
	Overweight	10(40%)	14(56%)	11(44%)	
	Obese	3(12%)	2(8%)	4(16%)	

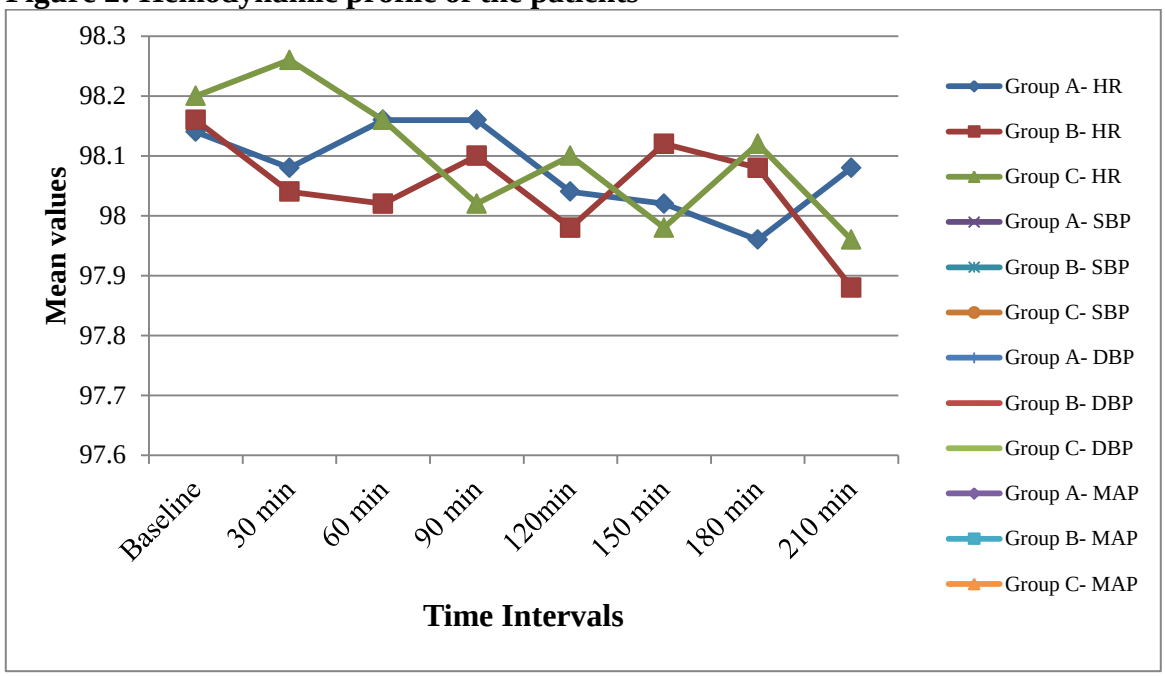
The VAS anxiety score was significantly lower in Group B and Group C compared to Group A as per ANOVA test ($p<0.05$) as depicted in figure 1.

Figure 1: VAS scores for anxiety



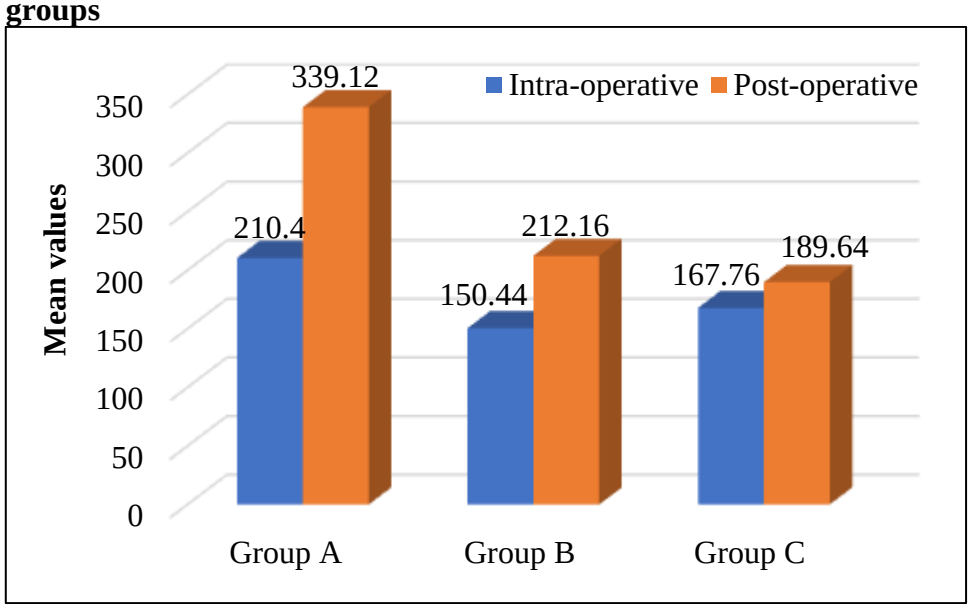
The heart rate values (HR), SBP, DBP and MAP levels in Group A and Group B were significantly higher compared to Group C from 30 mins till 150 minutes post induction as per ANOVA test (**p<0.05**). From 180 minutes post induction, HR, SBP, DBP and MAP values in all 3 groups was comparable and statistically not significant (p>0.05), (Figure 2). However the SpO2 levels were comparable between the groups and statistically not significant as per Student t-test (p>0.05).

Figure 2: Hemodynamic profile of the patients



The mean intra-operative and post-operative fentanyl consumption was significantly higher in Group A compared to Group B and Group C, (p<0.05), (Figure 3).

Figure 3: Comparison of intra-operative and post-operative fentanyl consumption between groups



The mean VAS scores for pain at rest and pain on movement in first 5 hours was significantly higher in Group A compared to Group B and Group C as per ANOVA test (p<0.05) as shown in table 2.

Table 2: Comparison of VAS score for pain at rest and pain on movement between groups

VAS score		Group A	Group B	Group C	P value
VAS score for Pain at Rest	1 hour	51.84±11.63	47.56±14.84	48.44±15.13	<0.05 (ANOVA test)
	2 hours	42.40±12.03	18.60±5.52	19.44±5.87	
	3 hours	41.72±13.23	21.88±5.23	20.56±5.16	
	4 hours	39.12±12.16	17.64±4.58	18.52±5.92	
	5 hours	44.12±11.82	22.16±5.69	23.16±4.78	
VAS score for Pain on Movement	1 hour	61.40±4.87	62.44±4.33	64.12±3.67	<0.05 (ANOVA test)
	2 hours	53.32±10.21	27.88±4.58	26.28±3.03	
	3 hours	51.48±12.23	21.64±5.33	22.44±4.59	
	4 hours	54.44±8.87	23.04±4.83	21.60±5.22	
	5 hours	58.20±7.33	24.12±3.80	24.28±3.61	

The incidence of post-operative nausea and vomiting (PONV) was significantly higher in Group A compared to Group B and Group C. The incidence of dizziness and blurring of vision were significantly higher in Group C compared to Group A and Group B as per Chi-Square test ($p<0.05$), (Table 3).

Table 3: Distribution of patients according to side effects

Side effects	Group A	Group B	Group C
PONV	14 (56%)	04 (16%)	03 (12%)
Dizziness	03 (12%)	03 (12%)	12 (48%)
Blurring of vision	02 (8%)	03 (12%)	10 (40%)
P value	P<0.05		

Discussion

In the present study, all three groups were comparable and found no significant difference with respect to demographic profile of the patients and duration of anaesthesia which is comparable with the study done by Yadav R et al [10].

Anxiety is an unpleasant emotion and most patients awaiting elective surgery experience preoperative anxiety. It may also adversely influence anesthetic induction and patient recovery, as well as decrease patient satisfaction with the perioperative experience. In the current study, the VAS anxiety score was significantly lower in Group B and Group C compared to Group A ($p<0.05$). This finding is similar to the study conducted by Yadav R et al [10], Shimony N et al [11], and White PF et al [12].

In the present study, the heart rate values (HR), SBP, DBP and MAP levels in Group A and Group B were significantly higher compared to Group C from 30 mins till 150 minutes post induction as per ANOVA test (p0.05). The SpO2 levels were comparable between the groups and statistically not significant as per Student t-test ($p>0.05$). These findings are correlated with the study conducted by Yadav R et al [10].

However, the mean intra-operative (210.40±3.47 ml vs. 150.44±3.74 ml vs. 167.76±3.97 ml) and post-operative fentanyl consumption (339.12±3.36 ml vs. 212.16±3.59 ml vs. 189.64±3.78 ml) was significantly higher in Group A compared to Group B and Group C demonstrating that both 150 and 300 mg doses of pregabalin resulted in significantly less consumption of fentanyl postoperatively. This is concordant to the other studies [10, 13-15].

It was observed in the present study that the mean VAS scores for pain at rest and pain on movement in first 5 hours was significantly higher in Group A compared to Group B and Group C suggesting that pregabalin effectively alleviates pain and significant finding here is that pregabalin causes reduction in movement-evoked pain. Similar observations were noted in the studies of Yadav R et al [10] and Mishriky BM et al [14].

Pregabalin has analgesic properties,12- opioid-sparing effects 13 and relieves anxiety.14 Pregabalin probably reduces or modulates the release of excitatory neurotransmitters,16 leading to reduction in the level of anxiety and pain. It has been observed that pregabalin displays a linear pharmacokinetics, and the time to peak plasma concentration is within 1 to 2 h. The decision to administer pregabalin prior to induction of anesthesia is primarily to ensure that the peak plasma effect of pregabalin has been achieved at the time of assessing anxiety prior to induction of anesthesia. Hence, the true protective effect of pregabalin could be revealed by comparing the analgesic outcome in the treatment and placebo groups.
The incidence of post-operative nausea and vomiting (PONV) was significantly higher in Group A compared to Group B and Group C. The incidence of dizziness and blurring of vision were significantly higher in Group C compared to Group A and Group B as per Chi-Square test ($p<0.05$). Similar finding is reported in study conducted by Yadav R et al [10].

Conclusions

Pregabalin in both the doses of 150mg and 300mg given prior to surgery can significantly reduce preoperative anxiety and intraoperative requirement of fentanyl compared to placebo. Pregabalin 300mg significantly decreased postoperative pain VAS scores at rest and on movement during the first 5 h after surgery but with an increased incidence of sedation, dizziness and visual blurring while reduced incidence of PONV was seen with Pregabalin 300mg dose. Therefore, the single use of pregabalin in doses between 150 and 300 mg is both safe and effective for reducing preoperative anxiety with a favourable postoperative analgesic profile.

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