Section: Anaesthesiology and Critical Care

Original Research Article

EFFECTS OF PRE-EMPTIVE GABAPENTIN VERSUS PREGABALIN ON ACUTE POST-OPERATIVE PAIN AFTER SURGERY UNDER SPINAL ANAESTHESIA

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Abstract

Background: Many studies indicated the importance of Pregabalin and Gabapentin as analgesics for the Prevention and management of pain following abdominal surgery. The study aimed to compare the effect of Pregabalin and Gabapentin as pre-emptive analgesics in elective gynaecological surgeries. **Materials and Methods:** Ninety patients aged 20 to 60 years undergoing elective gynaecological surgeries under spinal anaesthesia were randomly allocated into three groups. An hour before spinal anaesthesia, the patients received Group G (n=30) – Gabapentin 600mg, Group P (n=30) – Pregabalin 150mg, and Group C (n=30) – Identical placebo respectively with a sip of water. Time to first rescue analgesia with VAS score, level of sensory block at 5min and 10 min intervals, onset of motor block, total duration of analgesia, number of rescue analgesics received and side effects were noted in all groups. **Result:** The total duration of analgesia was 316.76 ± 15.86 minutes in Group G; 538.73 ± 28.89 min in Group P and 155.57 ± 8.45 min in Group C ($P < 0.001$). The total number of rescue analgesics in the first 24 hr was 4.00 ± 0.80 in Group G; 2.37 ± 0.85 in Group P and 4.70 ± 0.65 in Group C ($P < 0.001$). VAS score at first rescue analgesic was 2.9 ± 0.80 in gr G; 2.37 ± 0.85 in gr P and 3.10 ± 0.75 in gr C ($P = 0.002$). Dizziness; somnolence and nausea or vomiting were noticed in three groups ($P > 0.005$). **Conclusion:** The Pregabalin group had the longest duration of analgesia with the least number of rescue analgesia compared to the Gabapentin and placebo groups.

INTRODUCTION

Pain is a public health concern throughout the world.[1] Effective postoperative analgesia is necessary to provide subjective comfort and alleviate the suffering in patients undergoing surgery. Prevention and treatment of postoperative pain remain a major challenge in post-operative care and play an important role in the early mobilisation and well-being of the patient. The control of postoperative pain also increases the quality of anaesthesia.[2] Although opioids are extensively utilized for postoperative analgesia they have unfavourable side effects, that might edge their utilization.[3] A drug that has analgesic properties, opioid-sparing effect, possibly reduced opioid tolerance,[4] anti-anxiety and not associated with adverse effects, typical for the traditional analgesic, would be an attractive adjuvant for postoperative pain management.[2,5] The traditional approach to post-operative analgesia is to begin therapy at the end of surgery but it has been observed that intense nociceptive stimuli can cause sensitization of the central nervous system leading to the perception of pain in response to less noxious stimuli (hyperalgesia) or even non-noxious stimuli (allodynia).[6] Such stimulation can subsequently lead to functional changes in the dorsal horn of the spinal cord that may cause post-operative pain to be perceived as even more painful than it would have been otherwise.[4,6] There is growing interest in the recent concept of pre-emptive analgesia which is defined as an anti-nociceptive treatment that prevents the establishment of altered central processing of afferent input, which amplifies postoperative pain and consequently decreases the incidence of hyperalgesia and allodynia after surgery.[7] Various drugs such as local anaesthetics, opioids, non-steroidal anti-inflammatory drugs,[8] NMDA receptor antagonist,[9] gabapentin and pregabalin have been used as pre-emptive analgesics.[10-13]

Large placebo-controlled, double-blind trials confirmed the effectiveness of (Gabapentinoids) gabapentin and pregabalin in relieving neuropathic post-herpetic pain and reflex sympathetic dystrophy.[14,15] Gabapentinoids effectively reduce

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postoperative pain by inhibiting calcium influx and reducing excitatory neurotransmitter release in pain pathways,[16] they also reduce opioid consumption and opioid-related adverse effects after surgery. These properties may also be beneficial in postoperative pain.[5]

We therefore, performed a prospective, randomised, placebo-controlled, double-blinded study to investigate the pre-emptive use of oral gabapentin 600 mg and pregabalin 150 mg for acute post-operative analgesia in lower abdominal surgeries performed under spinal anaesthesia.

MATERIALS AND METHODS

After the approval of the Ethical Committee of the Regional Institute of Medical Sciences, Imphal and obtaining informed consent from participants, this prospective, randomized, placebo-controlled study was conducted at the Regional Institute of Medical Sciences, Imphal over a period of two years. Patients of ASA grade I or II, aged 20-60 years, scheduled for elective gynaecological and abdominal surgeries under spinal anaesthesia using 0.5% bupivacaine heavy were included in the study. Patients with contraindications to spinal anaesthesia or major neurological, cardiovascular, metabolic, respiratory, renal disease, or coagulation abnormalities were excluded.

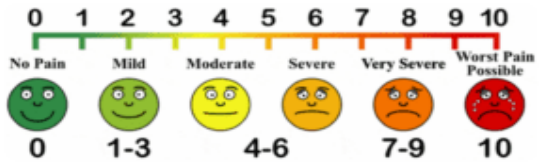
The sample size calculation was based on the study done by Induja R et al17 using 24.06 hours and 20.76 hours as the means of effective analgesia and common standard deviation of 5 for pregabalin and gabapentin respectively, and assuming alpha error was 0.05 and the power of the study was 80%. Thus, the calculated sample size for each group was 30 patients in each.

Randomization

Computer-generated randomization was performed. Each patient received an appropriate randomized number and was allocated to their group according to the number. The patients were divided into three groups of thirty each to receive either pregabalin 150 mg (Gr-P), gabapentin 600 mg (Gr-G) or an identical placebo (Gr-C).

Study Tools

1. Modified Bromage scale for intensity of motor block.[10]
2. Visual Analogue Scale for pain assessment.[10]



3. Rescue analgesic (Injection tramadol 100 mg intramuscular).
4. Study drugs: Gabapentin, Pregabalin and Identical Placebo.
5. Duration of analgesia was measured as time from intrathecal drug administration to the patient's first request for analgesia (VAS > 7).

A uniform Pre anaesthetic assessment was carried out a day before the surgery. An hour before surgery, the identically packed study drug was given orally to the patient by an unaware anaesthetist as per group allocation with a sip of water. Then intravenous (IV) line was secured over the hand and preloaded with ringer lactate at 10ml/kg. Patients were familiarized with the use of a 10 cm linear Visual Analogue Scale (VAS) for pain, which ranges from 0 (no pain) to 10 (worst imaginable pain). In the operation theatre, pulse oximeter, heart rate, non-invasive blood pressure and electrocardiogram (ECG) were monitored. Standardized spinal anaesthesia with 15mg of Anawin Heavy was administered in all patients while intravenous fluids were continued intraoperatively. The level of sensory block was assessed using a blunt 26 G needle in the midline and recorded as loss of sensation to pinprick, checking in a caudal to cephalic direction. The motor block was recorded according to the Modified Bromage scale.[10] Immediately after surgery, patients were assessed for pain by VAS and the assessment was continued at 2-hour intervals in the wards for 24 hrs by a trained nurse and medical student. When the VAS score was more than 7, the patient received injection tramadol 100 mg intramuscularly over the gluteal region and was noted. Time for the first dose of rescue analgesia and total doses of rescue analgesia in 24 hours were recorded and considered as the primary outcome. Any side effects like dizziness, somnolence, nausea, vomiting, diplopia and ataxia during the 24 hours were noted.

Statistical analysis: Data were analyzed using IBM SPSS Statistics 21 for Windows (IBM Corp. 1995, 2012). Descriptive data were presented using percentages and in terms of mean standard deviation for VAS. One-way analysis of variance (ANOVA) was used to compare total analgesic consumption over 24 hours and time intervals to the first analgesic. Post hock Bonferroni test was used for intergroup comparison. Non-parametric Krushal Wallis test was used for comparing sedation scores over 24 hours. The chi-square test was used to find the association between side effects and the study drug. Descriptive variables were expressed as mean ± SD. P value <0.05 was taken as statistically significant.

RESULTS

Demographic profiles of the three study groups were comparable and found statistically insignificant [Table 1].

Intergroup comparison on duration of surgery in all the groups was found statistically insignificant (P > 0.05). Sensory levels at 5th and 10th minute intervals among the groups and inter-groups were comparable and found statistically not significant (P > 0.05). Group and intergroup comparisons on the onset of motor block in all the study groups were found statistically insignificant (P > 0.05).

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Group and Intergroup comparisons of the total duration of analgesia among the study groups were found statistically significant (P < 0.001), [Table 2].
The total number of rescue analgesic consumption in group and intergroup among the three groups were comparable and found statistically significant (P < 0.001), [Table 3]

Groups and Intergroups distribution and comparison of VAS score at first rescue analgesic in the three study groups were also found statistically significant (P < 0.001), [Table 4].
The incidence of dizziness, somnolence, nausea, vomiting, diplopia and ataxia are presented in [Table 5] and found statistically not significant (P > 0.05).

Table 1: Demographic profiles of three study groups

Parameters	**Group C Mean ±SD N=30**	**Group G Mean ±S N=30**	**Group P Mean ±SD N=30**	**Statistical test value**	**'P' value**
Age in years	44.17±8.02	46.07±8.87	46.10±7.96	0.53	0.58
Weight in Kg	48.93±4.11	49.80±2.21	50.87±4.18	2.14	0.12
Height in cm	152.30±6.54	155.57±6.9	152.47±5.09	2.61	0.08
Duration of Surgery	54.43 ± 3.99	52.23 ± 7.53	53.70 ± 9.31	0.34	0.71
ASA (I:II)	27:3	26:4	27:3	Chi-square value of 0.26	0.89

Table 2: Groups and Intergroups comparison of the total duration of analgesia among the study groups.

Groups comparison of the total duration of analgesia among the study groups					
	Group C (Control) N=30	**Group G (Gabapentin) N=30**	**Group P (Pregabalin) N=30**	**Statistical test value**	**'P' value**
Time (Min) (Mean±SD)	155.57±8.45	316.76±15.86	538.73±28.89	2877	0.000
Intergroups comparison of the total duration of analgesia among the study groups					
		Statistical test value		'P' value	
Gr C vs Gr G		'T' test value of 49.06		0.000	
Gr G vs Gr P		'T' test value of 36.90		0.000	
Gr C vs Gr P		'T' test value of 69.72		0.000	

Table 3: Groups and Intergroups comparison of the total number of rescue analgesic consumption in the three groups

Groups comparison of the total number of rescue analgesic consumption					
	Group C (Control) N=30	**Group G (Gabapentin) N=30**	**Group P (Pregabalin) N=30**	**Statistical test value**	**'P' value**
No of rescue (Mean±SD)	4.70±0.65	4.00±0.80	2.37±0.85	79.16	0.000
Intergroups comparison of the total number of rescue analgesic consumption					
Intergroup		Statistical test value		'P' value	
Gr C Vs Gr G		'T' test value of 4.03		0.000	
Gr G Vs Gr P		'T' test value of 8.14		0.000	
Gr C Vs GR P		'T' test value of 11.93		0.000	

Table 4: Groups and Intergroups distribution and comparison of VAS score at first rescue analgesic in the three groups

Groups distribution and comparison of VAS score at first rescue analgesic in the three groups					
	Group C (Control) N=30	**Group G (Gabapentin) N=30**	**Group P (Pregabalin) N=30**	**Statistical test value**	**'P' value**
VAS Score in cm (Mean±SD)	3.10±0.75	2.9±0.80	2.37±0.85	6.65	0.002
Intergroups distribution and comparison of VAS score at first rescue analgesic in the three groups					
Intergroup		Statistical test value		'P' value	
Gr C Vs Gr G		'T' test value of 0.99		0.32	
Gr G Vs Gr P		'T' test value of 2.50		0.01	
Gr C Vs GR P		'T' test value of 3.52		0.01	

Table 5: Distribution and Comparison of side effects in the groups

Parameters	**Group C**	**Group G**	**Group P**	**Chi-square value**	**'P' Value**
Dizziness	1	2	1	0.52	0.77
Somnolence	1	3	2	1.07	0.58
Nausea /vomiting	2	4	2	1.09	0.57
Diplopia	0	0	0	-	Not Significant
Ataxia	0	0	0	-	Not Significant

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DISCUSSION

Administration of pregabalin 150 mg and gabapentin 600 mg 1 to 2 hours before surgery appeared rational to attain maximal plasma concentration at the time of surgical stimuli though pregabalin is rapidly absorbed (30 min-2 hours) and gabapentin is slowly absorbed (2 hrs).[18] Pregabalin is approximately 2.5 times more potent than gabapentin.16,19 In this study pregabalin 150 mg and gabapentin 600 mg were administered orally one hour before scheduled operation to attain maximal plasma concentration.

In this study, we compared the effect of pre-emptive oral pregabalin 150 mg (group P), gabapentin 600mg (group G) and placebo (group C) for postoperative analgesia in 90 patients undergoing gynaecological surgeries. The average age in placebo (group C) was 44.17±8.02 years, gabapentin (group G) was 46.07±8.87 years and pregabalin (group P) was 46.10±7.96 years. In case of weight, group C was 48.93±4.11 kg while group G was 49.80±2.21 kg and group P was 50.87±4.18 kg. Regarding height, it was 152.30±6.54 cm in pregabalin, 155.57±6.9 cm in gabapentin and 152.47±5.09 cm in the placebo group. The difference in the means observed among the three groups was found to be statistically insignificant (P = 0.58). Similarly, ASA physical status of all patients in the three groups was comparable. The duration of surgery in group C was (54.43±3.99) minutes, in group G (52.23±7.53) minutes and in group P (53.70±9.31) minutes which was found to be statistically insignificant (P= 0.71).

In our study, the total duration of analgesia was more in pregabalin (group P) 538.73±28.89 minutes compared to gabapentin (group G) 316.76±15.86 minutes and placebo (group C) 155.57±8.45 minutes which was statistically significant (P=0.000). Our findings in this study conform to that of the study conducted by Bafna et al,[2] where the total duration of analgesia in pregabalin (group P) was 535.16 ± 32.86 minutes, gabapentin (group P) 302.00 ± 24.26 minutes and placebo (group C) 151.83 ± 16.21 minutes. In our study, we observed a significant reduction of rescue analgesia consumptions (in terms of number of doses) in pregabalin (group P), i.e. 2.37±0.85 followed by gabapentin (group G) 4.00±0.80 and then placebo (4.70±0.65). Similarly, better VAS score at first rescue analgesia was observed in pregabalin (group P) 2.37±0.85 followed by gabapentin (group G) 2.9±0.80 and placebo (group C) 3.10±0.75 (P= 0.002). Gabapentin (group G) had a better VAS score than placebo (group C) though not statistically significant (P= 0.32).

Time to first rescue analgesia was longest in pregabalin (group P) which could be explained due to its quicker onset of action than gabapentin [Table 2]. Several studies on the alleviation of post-operative pain after surgery under spinal anaesthesia had been conducted with the pre-emptive use of pregabalin and gabapentin orally.[5,7,10,14,16] In the study done by Bafna et al10 pre-emptive use of pregabalin and gabapentin showed better VAS scores when compared to placebo, i.e. 2.3±0.7, 2.4±0.05, 2.8±0.6 respectively (P<0.005). Similarly, the mean number of doses of rescue analgesia in the first 24 hours in the pregabalin group was 3.97±0.614, gabapentin group was 4.1±0.66 and placebo group was 4.7±0.65 which was found to be statistically significant among this group (p<0.001). Our study results are in concurrence with their finding.

In the study done by Induja et al,[17] they observed a statistically significant decrease in rescue analgesic consumption in the pregabalin and gabapentin group compared to control (p<0.001). Similarly, initial VAS scores were lower in pregabalin (3.2 ± 0.4) and gabapentin (3.63 ± 0.32) when compared to placebo (6.60 ± 0.77) and were statistically significant (P < 0.001). This study supports the findings of our present study. However, they observed a longer duration of analgesia than our present study which may be due to the higher dose of pregabalin 300 mg and gabapentin 900 mg used in their study. This may also be due to the possibility of lesser stress responses elicited by the trauma of the surgical procedures included in their study.[20]

As the dose of gabapentin increases, bioavailability decreases.[10] So, we have chosen 600 mg of gabapentin for pretreatment in our study. In one meta-regression analysis, it was also suggested that the gabapentin induced reduction in the 24-hour opioids consumption was not significantly dependent on the gabapentin dose. The most common adverse effects of the gabapentinoids were sedation and dizziness.5 Pregabalin has been used in doses ranging from 75-300 mg but the higher doses of pregabalin were associated with more incidence of side-effects.6 Therefore, we chose 150 mg of pregabalin in our study and the side-effects were not significant.

Kelly DJ et al,[21] have done a review study of pre-emptive analgesia and their recent advances and current trends. The variable patient characteristics and timing of pre-emptive analgesia to surgical noxious input require individualization of the technique(s) chosen.

In this study, the mean time of onset of analgesia was taken when sensory block reached the level of T5 or T6 and the mean onset of motor block was considered adequate when the Modified Bromage score was 1 in all the groups which reduced the chances of disparity in assessing the outcome of the results. It can be concluded that pre-emptive use of pregabalin is better than gabapentin in controlling post-operative pain under spinal anaesthesia but the scope for further discussion is still at large.

CONCLUSION

It is concluded that pre-treatment with oral pregabalin 150 mg significantly reduced the incidence and intensity of postoperative pain compared to oral gabapentin 600 mg and placebo group without significant adverse effects.

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Limitation: We did not investigate varied pregabalin doses, larger or lesser than 150 mg. However, we were concerned that larger doses would cause sedation and central depression. Further, studies with varying doses of the study drug with varying intervals of pre-treatment duration in various surgeries need evaluation to come to a definitive conclusion.

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