A COMPARATIVE EVALUATION OF PRE-EMPTIVE DOSES OF GABAPENTIN AND PREGABALIN FOR POSTOPERATIVE RELIEF OF PAIN IN PATIENTS SCHEDULED FOR SURGERY UNDER GENERAL ANAESTHESIA

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ABSTRACT

OBJECTIVE

To evaluate the comparative pre-emptive effects of gabapentin and pregabalin on postoperative pain in patients scheduled for surgery under general anaesthesia.

MATERIAL AND METHODS

90 patients of ASA grade I and II posted for elective surgeries under general anaesthesia were randomised into 3 groups (Group G, P and C of 30 patients each). One and a half hour before surgery, the drug selected for the study was given blindly with a sip of water. Group G - Received 600 mg Gabapentin capsule; Group P - Received 300 mg of pregabalin capsule; Group C - Received identical placebo capsule. Pain (Visual analogue score) and side effects assessments were performed immediately and then at 15 mins., 30 mins., 45 mins., 60 mins., 90 mins., 120 mins. and at 180 mins. postoperatively.

RESULTS

The mean (±SD) of VAS score was 5.86±0.34 in group C, 5.10±0.84 in group G and 4.96±1.03 in group P. VAS score were significantly lower in both groups G and P as compared to group C. Time for analgesic requirement is more with oral pregabalin than gabapentin and control group. The mean (±SD) TRA-I was 38.40±24.61 in group C, 44.03±8.94 in group G and 58.69±25.21 in group P. Pregabalin causes more sedation than gabapentin. No significant difference was observed among the three groups regarding side effects during the study period.

CONCLUSION

Our study demonstrated that pre-emptive oral pregabalin 300 mg and oral gabapentin 600 mg significantly decreases the severity of pain postoperatively in patients posted for surgery under general anaesthesia. Oral pregabalin produces higher degree of sedation as compared to oral gabapentin.

KEYWORDS

Gabapentin, Pregabalin, General Anaesthesia.

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INTRODUCTION

The most common and distressing symptom, which follows anaesthesia and surgery is pain.[1] The aim of postoperative pain treatment is to minimise patient discomfort, facilitate early mobilisation and functional recovery, and prevent acute pain developing into chronic pain.[2] The use of opioids by patient controlled analgesia is popular, but limited by side effects.

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Because of the multiplicity of the mechanisms involved in postoperative pain, a multimodal analgesia regimen with a combination of opioid and non-opioid analgesic drugs is often used to enhance analgesic efficacy and reduce opioid requirements and side effects. In this context, gabapentin and pregabalin have been used as pre-emptive analgesics.[3]

Pre-emptive analgesia is a treatment that is initiated before the surgical procedure in order to reduce sensitisation. Gabapentin, is 1-aminomethyl cyclohexane acetic acid, is used as an anticonvulsant drug. It prevents partial seizures and generalised tonic-clonic seizures both in add on and monotherapy. Gabapentin is structurally related to the neurotransmitter GABA (Gamma aminobutyric acid), but it does not modify GABAA or GABAB radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. Gabapentin has an alternative mechanism of action in CNS, it acts by decreasing the synthesis of neurotransmitter glutamate and by binding to the $\alpha 2\delta$

subunits of voltage dependent calcium channels.[4] It is suggested that the antihyperalgesic action of gabapentin is due to its binding to this site on the voltage-gated calcium channel. Pregabalin also a structural analogue of GABA binds potently to the $\alpha 2\delta$ subunit of presynaptic voltage dependent calcium channels and modulates calcium influx at nerve terminals, and thereby reduces the release of several neurotransmitters including glutamate, noradrenaline, serotonin, dopamine and substance P. binding affinity for the $\alpha 2\delta$ subunit, and potency is six times more than that of gabapentin.[5]

The aim of this study was to compare the effect of gabapentin and pregabalin with the control group on the postoperative pain in patients scheduled for surgery under general anaesthesia.

MATERIAL AND METHODS

After Ethical Committee approval and written informed consent this double-blind, randomised, prospective clinical study was carried out in 90 patients of ASA grade I or II of either sex, aged 18-50 years scheduled for elective surgeries under general anaesthesia. Exclusion criteria included known allergy or sensitivity to the drugs, psychiatric illness, history of neurological, hepatic, renal, cardiovascular, respiratory diseases, hypertension, peptic ulcer diseases, diabetes mellitus, bleeding or clotting disorders. Menstruating, pregnant or lactating females were also excluded from the study. Ninety patients who fulfilled the eligibility criteria were chosen, explained about the procedure and written consent was taken. Patients were subsequently randomised into three groups of 30 each. Group C (n=30) – received a placebo orally one and a half hours prior to surgery.

Group G (n=30) – received gabapentin 600 mg orally one and a half hours prior to surgery.

Group P (n=30) – received pregabalin 300 mg orally one and a half hours prior to surgery.

One and a half hour before surgery vital parameters including pulse rate, Blood Pressure (BP) and Electrocardiography (ECG) of all the patients were recorded in pre-anaesthetic room and then the drug selected for the study was given with a sip of water. Anaesthesia technique was standardised in all the groups. In the operating room, Intravenous (IV) line was secured by using 18-gauge cannula and preoperative vitals (pulse, BP, respiratory rate, SpO2) were recorded. The patients were premedicated with Inj. Glycopyrrolate 0.02 mg/kg I/M 30 minutes before surgery and Inj. Pentazocine 0.5 mg/kg IV on OT Table.

After pre-oxygenation for three minutes, anaesthesia was induced with Inj. Thiopentone sodium 5 mg/kg IV and Inj. Succinylcholine 1.5 mg/kg IV. Intubation was done with appropriate size endotracheal tube and anaesthesia was maintained on oxygen (33%), nitrous oxide (67%) along with intermittent doses of Inj. Atracurium besylate 0.5 mg/kg body weight, initially followed by increments of 0.1 mg/kg body weight and halothane (0.75%) under controlled ventilation.

After completion of the surgery, neuromuscular blockade was reversed with Inj. Glycopyrrolate 0.4 mg/kg+. Inj. Neostigmine 0.08 mg/kg body weight IV, and once adequate reversal was obtained the patient was shifted to postoperative ward for further monitoring.

Postoperative

Pulse rate, blood pressure, respiratory rate and severity of pain on VAS scale was noted immediate postoperatively and then at 15 mins., 30 mins., 45 mins., 60 mins., 90 mins., 120 mins. and at 180 mins.

Assessment of Postoperative Pain

Postoperative pain was assessed using a visual analogue score scale, which consisted of a 10 cm horizontal scale with gradations marked as '0' means no pain at all and '10' means unbearable pain Inj. Tramadol 2 mg/kg body weight IV was given as rescue analgesic whenever the subject requests for analgesia.

Sedation Score

Sedation was assessed on the basis of Modified Ramsay sedation score.[6]

Indication	Score
Anxious, agitated, restless	1
Awake, cooperative, oriented, tranquil	2
Semi-asleep but responds to commands	3
Asleep but responds briskly to glabellar tap or loud auditory stimulus	4
Asleep with sluggish or decreased response to glabellar tap or loud auditory stimulus	5
No response can be elicited	6

The occurrence of side effects such as nausea and vomiting, respiratory depression, dizziness, sedation, headache and shivering were recorded.

All data were collected and analysed with the SPSS, version 17.0 for Windows Statistical Software Package (SPSS Inc., Chicago, IL, USA). Quantitative data were analysed by student t-test. P-value < .05 was considered statistically significant.

RESULTS

A total of 90 patients were recruited and studied. The three groups were comparable with respect to age, sex, weight and duration of surgery (Table 1).

On haemodynamic parameters, there was no significant changes (P value) were present in pulse rate, systolic blood pressure, diastolic blood pressure and respiratory rate among three groups ($P > 0.05$).

The mean (±SD) of VAS score was 5.86±0.34 in group C, 5.10±0.84 in group G and 4.96±1.03 in group P. VAS score was significantly lower in both groups G and P as compared to group C. VAS score in group P was highly significantly lower ($p<0.01$) as compared to group G and group C (group P> group G> group C) at all the points of observations (Table 2).

The mean (±SD) TRA-I was 38.40±24.61 in group C, 44.03±8.94 in group G and 58.69±25.21 in group P. TRA-I was significantly lower in both groups G and P as compared to group C. TRA-I in group P was lower in highly significant values ($p < 0.01$) as compared to group G and group C (group P > group G > group C) at all the points of observations (Table 3).

In group C none of the patients had sedation, in group G 43.33% patients had sedation score 2, while in group P 6.66% patients had sedation score 2, 16.66% patients had

sedation score 3, 43.33% patients had sedation score 4. Thus, it was found that Pregabalin causes more sedation than Gabapentin (Table 4).

None of the patients in all the three groups had respiratory depression.

Characteristic	Group 'C'	Group 'G'	Group 'P'
Age (Years)	34.20 (±8.80)	37.53 (±9.31)	34.60 (±9.33)
Sex (M:F)	10:20	14:16	13:17
Weight (Kgs)	56.10 (±6.65)	59 (±6.96)	58.3 (±4.11)
Duration of Procedure (Minutes)	105.83 (±45.45)	106.33 (±33.44)	110 (±40.95)

Table 1

Sl. No.	Time in Min.	Group- C (Mean±SD)	Group-G (Mean±SD)	Group-P (Mean±SD)
1	PO_i	5.86±0.34	5.10±0.84	4.96±1.03
2	PO_{15}	5.60±0.49	5.06±0.98	4.93±1.14
3	PO_{30}	5.20±0.48	4.60±1.27	4.63±1.09
4	PO_{45}	5.03±0.66	4.40±1.24	4.43±1.04
5	PO_{60}	4.90±0.40	4.10±1.24	4.03±1.03
6	PO_{90}	4.70±1.02	4.00±1.28	3.56±1.43
7	PO_{120}	4.86±1.07	4.03±1.47	3.50±1.52
8	PO_{180}	4.86±0.97	4.00±1.33	3.36±1.49

Table 2: Statistical Analysis of Visual Analog Score in Three Study Groups

	Group – C	Group – G	Group – P
Mean	38.40	44.03	58.69
± SD	24.61	8.94	25.21

Table 3: Comparison between Tramadol – I of the Groups

Sedation Score	Group-C		Group-G		Group-P	
	(n)	(%)	(n)	(%)	(n)	(%)
1	30	100	17	56.66	10	33.33
2	0	0	13	43.33	2	6.66
3	0	0	0	0	5	16.66
4	0	0	0	0	13	43.33
5	0	0	0	0	0	0
6	0	0	0	0	0	0

Table 4: Showing Distribution of Sedation Score among Three Groups

DISCUSSION

The findings of this study indicate that pre-emptive oral Pregabalin 300 mg and oral Gabapentin 600 mg significantly decreases the severity of pain postoperatively as compared to placebo in patients posted for surgery under general anaesthesia. We also observed that time for analgesic requirement is more with oral Pregabalin than oral Gabapentin, although no significant difference was observed in VAS, this could be because of variation in subjective assessment on VAS.

We used Gabapentin in a dose of 600 mg and Pregabalin in a dose of 300 mg, one and a half hours prior to surgery. The doses were chosen after careful consideration of the oral bioavailability of the drugs as well as a few previous trials done on similar lines.

In comparison to the control group, patients in the gabapentin and pregabalin group had significantly lower VAS scores in all time intervals during the study period. The mean (±SD) TRA-I was 38.40±24.61 in group C, 44.03±8.946 in group G and 58.69±25.21 in group P. Time for rescue analgesia is more with oral Pregabalin than oral Gabapentin, although no significant difference was observed on VAS.

Gabapentin and pregabalin both are gamma-aminobutyric acid and binds to $\alpha 2\delta$ subunit of presynaptic voltage dependent calcium channels and reduces the calcium influx at nerve terminals and decrease the release of their neurotransmitters and produces analgesia and their synergistic effect with opioid reduces the analgesic requirement.

Pandey C. K. et al[7] also found that Gabapentin significantly decreases postoperative pain and rescue analgesic requirement in laparoscopic cholecystectomy. Similar results were obtained from other studies.[3,8,9,10,11,12,13,14]

Eskandar A. M. et al[15] found that oral 300 mg pregabalin decreases VAS score significantly and total consumption of nalbuphine also decreased.

Alimian M. et al[16] and Alimian M. et al[17] in their respective studies also observed that postoperative pain intensity level were lower in patients who received oral 300 mg Pregabalin an hour before surgery. Opioid consumption were also lower in the Pregabalin group than the placebo group. Similar conclusions have been reported from other studies.[12,15,18]

Table 4 shows that in group C none of the patients had sedation, in group G 43.33% patients had sedation score 2, while in group P 6.66% patients had sedation score 2, 16.66% patients had sedation score 3, 43.33% patients had sedation score 4. Thus, it was found that Pregabalin causes more sedation than Gabapentin. Similar results were obtained from other studies.[7,15,19]

CONCLUSION

This clinical study demonstrated that pre-emptive oral Pregabalin 300 mg and oral Gabapentin 600 mg significantly decreases the severity of pain postoperatively as compared to placebo in patients posted for surgery under general anaesthesia.

Time for analgesic requirement is more with oral Pregabalin than oral Gabapentin, although no significant difference was observed in VAS. This could be because of variation in subjective assessment on VAS. Oral Pregabalin produces higher degree of sedation as compared to oral Gabapentin.

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