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Original Article

Anaesthesia Section

Effects of Pregabalin versus Gabapentin on their Opioid Sparing Effects among Patients Undergoing Laproscopic Cholecystectomy: A Randomised Controlled Study

KISHORE KUMAR ARORA[1], SUSHMA HANDATTU[2], DEEPALI VALECHA[3], NIDHI SHARMA[4]

ABSTRACT

Introduction: Gabapentin and pregabalin were earlier used as antiepileptics. These have been also found to have analgesic, anticonvulsant and anxiolytic effects.

Aim: To compare the pre-emptive use of pregabalin and gabapentin on their opioid sparing effects among patients undergoing laparoscopic cholecystectomy.

Materials and Methods: This randomised controlled, single-blind study was conducted in Department of Anaesthesiology at Mahatma Gandhi Medical College and M.Y Hospital Indore, Madhya Pradesh, India, from August 2020 to August 2021. The study included 90 patients of American Society of Anaesthesiologists (ASA) physical status class I/II, undergoing elective laparoscopic cholecystectomy. Patients were allocated randomly into three groups, 30 patients each. Group P receiving tablet oral pregabalin 150 mg, group G receiving oral gabapentin 600 mg and group C receiving tablet multivitamin (control group), before induction of anaethesia. Intraoperative requirement of opioids, sedation score, Visual Analogue Scale (VAS) score, and postoperatively analgesia requirement in the form of opioid were noted. Association between two non parametric variables was done using Pearson Chi-square test. Comparison of means between three groups was done using One-way Analysis of Variance (ANOVA) followed by Post-hoc Turkey test. Statistical Package for Social Sciences (SPSS) version 20.0 software was used.

Results: The mean age in group P, C and G was 39.73±13.55, 38.67±13.33 and 41.03±5.62 (p-value=0.726). The mean intraoperative requirement of opioid in pregabalin group was 100 µg, in gabapentin group was 100 µg when compared to control group 150 µg. Postoperative requirement of analgesic was later in pregabalin group (7.23±0.64 hours) compared to gabapentin group (5.78±0.49 hours) and control group (4.37±0.47 hours).

Conclusion: Pregabalin and gabapentin have opioid-sparing effect intraoperatively and postoperatively and can be used pre-emptively as an attractive choice.

Keywords: Anxiolytic, Pre-emptive analgesia, Sedation score

INTRODUCTION

Pre-emptive analgesia is described as an antinociceptive treatment which averts the establishment of altered central processing of afferent input, which increases postoperative pain [1]. Pre-emptive analgesia is given to lessen postoperative pain and the concept was found on a series of successful animal experimental studies that revealed central nervous system plasticity and sensitisation after nociception [2-4].

Various interventions have been used to achieve a noticeable preemptive effect, such as epidural analgesia, peripheral local anaesthetic infiltrations, systemic N-methyl d-aspartate receptor antagonists, systemic non steroidal anti-inflammatory drugs and systemic opioids [5,6].

Gabapentinoids (gabapentin and pregabalin) are relatively new drugs, which were preliminarily used as antiepileptics, has been also found to have analgesic, anticonvulsant, and anxiolytic effects. These drugs are well tolerated by patients and are known to have limited side-effects. Pregabalin is structurally alike to Gamma Aminobutyric Acid (GABA). It presynaptically binds to the α-2-λ subunit of voltage-gated calcium channels that are widely dispersed in the spinal cord and brain [7].

Pregabalin lessens or regulates the release of several excitatory neurotransmitters, including glutamate, norepinephrine, substance P, and calcitonin gene-related peptide by changing calcium currents, producing inhibitory modulation of "overexcited" neurons and returning the neurons to a "normal" state, thus pregabalin lessen the hyperexcitability of dorsal horn neurons that is produced by tissue damage [8]. Peak plasma concentration of pregabalin is usually attained within one hour after being absorbed rapidly through oral rote. Bioavailability exceeds 90% and the elimination half-life is 5.5-6.7 hours. Undergoes renal excretion and 98% of the absorbed dose is excreted unchanged in the urine [9]. Pregabalin is known to be useful in neuropathic pain, diabetic neuropathy, postherpetic neuralgia, reflex sympathetic dystrophy, acute postoperative pain and in reducing the postoperative opioid requirements.

Gabapentin is analogous to gamma-aminobutyric acid. Though it is a GABA analogue it is neither an agonist nor antagonist. It acts by binding to α2d subunit of the calcium channels which are voltage gated and results in decrease release of certain excitatory neurotransmitters [10].

Pre-emptive use of gabapentinoids is known to effectively reduce the opioid consumption intraoperatively and postoperatively. Limited studies are available, in which pregabalin and gabapentin were used preemptively to know the opioid sparing effect intraoperative and postoperatively [11]. Most of the studies compares the use of pregabalin and gabapentin pre-emptively to reduce the postoperative pain [12,13]. In these studies, pregabalin had a better opioid sparing effect or lesser need of analgesic in postoperative period. So, focusing to fill this breach,the present study aimed to assess the opioid sparing effects of pregabalin and gabapentin both intraoperatively and postoperatively. The primary outcome measures of the study was the dose of opioid required. Secondary outcome measure was the assessment of need of postoperative analgesia and the duration for the need of the drug.

MATERIALS AND METHODS

This randomised controlled, single-blind study was conducted in Department of Anaesthesiology at Mahatma Gandhi Medical College and M.Y Hospital Indore, Madhya Pradesh, India, from August 2020 to August 2021. The Institutional Ethics and Scientific review Committee IEC was obtained (EC/MGM/Feb-20133).

Sample size calculation: Sample size estimation was done using the formula = a^2x2xS^2/D^2

a= Coefficient of difference

S= Previous study value [14]

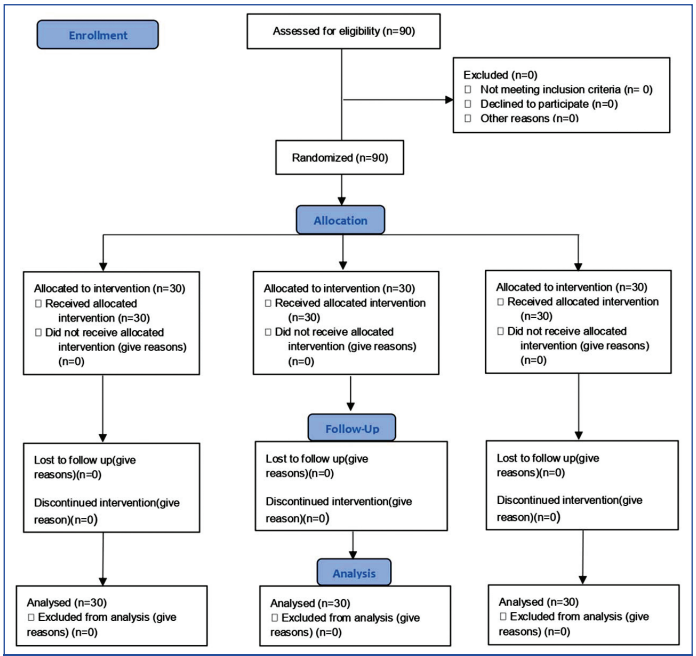
d= degree of differentiation

N=(1.96)2x(0.34)2/(0.10)2

D=10 percentage

S=0.34

A total of 90 patients were considered in the study. Informed consent was taken from all the 90 patients [Table/Fig-1].



[Table/Fig-1]: CONSORT flow chart.

Inclusion criteria: All the patients with age between 18-65 years, American Society of Anaesthesiologist (ASA) I and II, either sex, patient undergoing laparoscopic cholecystectomy under general anaesthesia were included in the study.

Exclusion criteria: All patients who refused to participate in the study, known hypersensitivity to pregabalin and gabapentin, patients on chronic neuroleptic medications, tricyclic antidepressants, serotonin and nor epinephrine reuptake inhibitor were excluded from the study.

After a thorough preanaesthetic evaluation, 90 patients who were planned for elective laproscopic cholecystectomy under general anaesthesia were randomly allocated in to three groups by chit method:

- Group P (n=30): receiving tablet oral pregabalin 150 mg,
- Group G (n=30): receiving oral gabapentin 600 mg
- Group C (n=30): receiving tablet multivitamin

All patients were given their respective tablets 90 min before surgery orally. Vitals were noted for every 30 min in the preoperative room.

Study Procedure

Upon arriving in the operative room, intravenous cannula 18G was inserted in a peripheral vein and ringers lactate solution was started at 10 mL per kg. Baseline parameters such as pulse rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, oxygen saturation and electrocardiogram were recorded. Patients were induced with inj. propofol 2 µg/kg until loss of verbal commands. Inj. fentanyl 100 µg was given. Endotracheal Intubation was done with a suitable sized cuffed endotracheal tube with Inj. atracurium 0.5 mg/kg. Respiratory rate and tidal volume were adjusted accordingly to body weight to maintain normocapnia. Maintanence was done with oxygen/nitrous oxide in ratio of (40:60), isoflurane and Inj. atracurium 0.1 mg/kg maintanence dose. Intraopertaive requirement of injection fentanyl was noted. At the end of surgery, residual blockade was reversed with inj. neostigmine 0.05 mg/kg and inj. glycopyrolate 0.01 mg/kg and patient was intubated.

- **Sedation score:** The sedation score was measured using (Ramsay sedation score) postoperatively at 30 min, 1 hour and 3 hour.
- **Visual Analogue Scale (VAS):** Postoperatively Inj. tramadol 50 mg was given on demand or whenever VAS was four or more and the time was noted.

STATISTICAL ANALYSIS

The data was initially expressed in the customised proforma and then transferred to Microsoft excel for analysis. Descriptive statistics was depicted in the form of numbers and percentages. Statistical Package for Social Sciences (SPSS) version 20.0 IBM software was used. Association between two non parametric variables was done using Pearson Chi-square test. Comparison of means between three groups was done using one-way ANOVA followed by Post-hoc Tukey test. A p-value of <0.05 was taken as statistically significant.

RESULTS

The groups were comparable with respect to age, sex and ASA physical status [Table/Fig-2]. Comparison of mean sedation and mean VAS between the three groups at different time intervals are presented in [Table/Fig-3,4]. The intraoperative requirement of opioid in pregabalin was (100 µg), in gabapentin group was (100 µg) when compared to control group (150 µg) [Table/Fig-5].

The Ramsay sedation score postoperatively was comparable in Pregabalin and Gabapentin (p-value=0.667; p-value=0.764) at 30 min and 1 hours, respectively. The VAS score was lowest in pregabalin group in comparison to gabapentin group and control group and it was statistically significant (p-value=0.001) at 1 hour, 6 hours and 12 hours. Both pregabalin and gabapentin had better opioid sparing effect compared to control group. The requirement of first dose of rescue analgesia postoperatively in the form of inj. tramadol 50 mg was earliest in control group (4.37 hour) and latest in pregabalin group (7.23 hours) and in gabapentin group (5.78 hours).

Parameters	Group P	Group G	Group C	p-value
Mean age (years)	39.73±13.55	38.67±13.33	41.03±5.62	0.726
Gender				
Male	20%	23.3%	26.7%	0.830
Female	80%	76.7%	73.3%	
American Society of Anaesthesiologist (ASA) physical status				
Grade I	80%	90%	73.3%	0.252
Grade II	20%	10%	26.7%	

[Table/Fig-2]: Comparison of age, sex, ASA grade between the three groups.

DISCUSSION

Peripheral sensitisation and central sensitisation is evoked by the peripheral tissue injury. It causes postinjury pain hypersensitivity state which exhibits as an increase in the responsiveness to noxious stimuli and a decrease in the pain threshold, at the site of injury and also at the surrounding uninjured tissue [15].

Time interval	Group	Sedation score (Mean±SD)	F-value	p-value	Post-hoc Tukey (p-value)		
					Group P and G	Group P and C	Group G and C
0 min	Group P	3.97±0.18	841.00	0.001*	0.001*	0.001*	1
	Group G	3.00±0.00					
	Group C	3.00±0.00					
30 min	Group P	2.90±0.31	90.332	0.001*	0.667	0.001*	0.001*
	Group G	2.83±0.38					
	Group C	1.97±0.18					
1 hour	Group P	2.10±0.48	59.797	0.001*	0.764	0.001*	0.001*
	Group G	2.03±0.18					
	Group C	1.17±0.38					
3 hours	Group P	1.57±0.50	73.892	0.001*	0.001*	0.001*	0.001*
	Group G	1.97±0.18					
	Group C	1.00±0.00					

[Table/Fig-3]: Comparison of mean sedation between the three groups at different time intervals.
*p-value <0.05 statistically significant

Time interval	Group	VAS score (Mean±SD)	F-value	p-value	Post-hoc Tukey (p-value)		
					Group P and G	Group P and C	Group G and C
1 hour	Group P	2.13±0.43	1245.72	0.001*	0.001*	0.001*	0.001*
	Group G	3.00±0.00					
	Group C	6.67±0.48					
6 hours	Group P	3.20±0.66	319.56	0.001*	0.001*	0.001*	0.001*
	Group G	4.00±0.00					
	Group C	6.27±0.52					
12 hours	Group P	3.00±0.37	273.66	0.001*	0.001*	0.001*	0.001*
	Group G	3.60±0.49					
	Group C	5.63±0.49					
24 hours	Group P	2.63±0.49	277.91	0.001*	0.857	0.001*	0.001*
	Group G	2.70±0.47					
	Group C	5.23±0.50					

[Table/Fig-4]: Comparison of mean VAS between the three groups at different time intervals.

Fentanyl requirement	Fentanyl Requirement (Mean±SD) (µg)	Time to first requirement of tramadol (hrs) (Mean±SD)	F-value	p-value	Post-hoc Tukey (p-value)		
					Group P and G	Group P and C	Group G and C
Group P	100.00±0.00	7.23±0.64	213.00	0.001*	0.001*	0.001*	0.001*
Group G	100.00±0.00	5.78±0.49					
Group C	150.00±0.00	4.37±0.47					

[Table/Fig-5]: Comparison of mean fentanyl requirement and time for first requirement of tramadol at different time intervals.

In order to relieve postoperative pain and reduce drug side-effects multimodal approach is used. Taking in to account that surgical stimulation is related with peripheral and central sensitisation, antihyperalgesic drugs can be used to treat postoperative pain by preventing central nervous system pain hypersensitivity. Gabapentin and pregabalin, which are antiseizure, antihyperalgesic and antianxiety drugs, are used to reduce pain. These drugs bind to the α2-δ-1 subunit of voltage-dependent calcium channels found in the central nervous system. Pregabalin is structurally alike to gabapentin but have a greater analgesic effect in the case of neuropathic pain, diabetic peripheral neuropathy, and postherpetic neuralgia than gabapentin. Pregabalin is more efficacious than the gabapentin as the bioavailability is increased (90% vs 33%-66%), more rapid absorption, and a linear increase in blood concentration with increases in dose [12].

This study aimed to assess the opioid sparing effect of pregabalin and gabapentin in patients undergoing laparoscopic cholecystectomy.

Intraoperative opioid requirement: The requirement of fentanyl was more in group C in comparison to group P and group G. The result is similar to study done by Agrawal A et al.,where oral pregabalin (150 mg) was administered before operation and it was effective in reducing postoperative pain and postoperative patient-controlled fentanyl requirement in patients undergoing laparoscopic cholecystectomy [11]. The result also correlates with the study by Eidy M et al., where they found that single dose of gabapentin or pregabalin decreased postoperative pain opioid consumption after laparoscopic cholecystectomy [12].

Requirement of rescue analgesia postoperatively: The mean time for first requirement of rescue analgesia was later in group P compared to group G and group C which was statistically significant. This is in accordance to study done by Sharma A et al., where the time of requirement of first analgesic was lowest for placebo group with as early as 76 minutes succeeded by gabapentin group with 93 minutes. Subjects in the pregabalin group had the first analgesic request at the later duration of time with 136.5 minutes. The VAS score was remarkably lower in the Pregabalin group at 0,2,3,6,9,12 and 24 hours after surgery [13]. Study done by Pandey CK et al., also found that the preemptive use of gabapentin in laparoscopic

cholecystectomy significantly lessen the postoperative pain and rescue analgesic requirement [15].

Sedation score: The mean sedation score was highest in group P and group G and lowest in group C. This is similar to study done by Chakraborthy R et al., where they found that the preoperative and postoperative sedation scores were relatively higher after pregabalin premedication than the control group [16].

Limitation(s)

This was a single-centre study. Only fixed dose of drugs were used, and the dosage was not based on body weight. Side-effects of the drugs were not considered.

CONCLUSION(S)

Pregabalin and gabapentin both have better opioid sparing effect than the control group. The sedation score postoperatively was comparable in pregabalin and gabapentin group and was least in case of control group. The VAS score was lowest in pregnable group in comparison to gabapentin group and control group. The requirement of first dose of rescue analgesia was earliest in control group, followed by gabapentin group and lastly in pregabalin group. Hence, this study found that pregabalin and gabapentin have an opioid sparing effect intraoperatively and postoperatively.

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PARTICULARS OF CONTRIBUTORS:
1. Professor and Head, Department of Anaesthesiology, Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh, India.
2. Resident, Department of Anaesthesiology, Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh, India.
3. Assistant Professor, Department of Anaesthesiology, Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh, India.
4. Assistant Professor, Department of Anaesthesiology, Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Nidhi Sharma,
28-A, Lalaram Nagar, Near Water Tank Garden,
Behind Geeta Bhawan, Indore, Madhya Pradesh, India.
E-mail: drnidhisharma1004@gmail.com

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