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Comparison of Gabapentin and Pregabalin in Attenuating the Stress Response to Laryngoscopy and Intubation

Dr Chethanananda T. N[1], Dr Muhammad Raoof VK[2], Dr. Srudhi Estherin Koshy[3]

[1]Professor and HOD, Departments of Anaesthesiology Adichunchanagiri Institute of Medical Sciences, B. G. Nagara, Bellur, Mandya, Karnataka, India
[2]Juniour Resident, Departments of Anaesthesiology Adichunchanagiri Institute of Medical Sciences, B. G. Nagara, Bellur, Mandya, Karnataka, India
[3]Juniour Resident, Departments of Anaesthesiology Adichunchanagiri Institute of Medical Sciences, B. G. Nagara, Bellur, Mandya, Karnataka, India

Abstract: ***Background: The airway instrumentation of direct laryngoscopy and tracheal intubation are powerful noxious stimuli that should be attenuated by appropriate premedication, smooth induction and rapid intubation. This study compared the efficacy of oral Gabapentin and oral pregabalin to attenuate the stress response of laryngoscopy and endotracheal intubation. Methods: A total of 70 normotensive adult consented patients aged 20–50 years, ASA grade I and II of both gender were randomized into two treatment groups of 35 patients each. Group A received oral Gabapentin 600 mg, Group B oral pregabalin 150 mg, 1 h prior to induction. Anaesthetic technique was standardized and all groups were assessed for pre-operative sedation, haemodynamic changes after the premedication, before and after induction, after laryngoscopy and intubation, along with intraoperative haemodynamic stability and post-operative side-effects. Results: In both the groups, all the haemodynamic parameters were maintained within (20% of baseline values) throughout the study period. There was no statistically significant difference in MAP between two groups (P > 0.05). Conclusion: Oral Gabapentin and pregabalin can attenuate the haemodynamic stress responses of laryngoscopy and endotracheal intubation without significant differences in MAP between two groups.***

Keywords: Haemodynamic pressor response, intubation, laryngoscopy, gabapentin pregabalin

1. Introduction

Induction of general anaesthesia, laryngoscopy, tracheal intubation, and extubation are associated with various haemodynamic changes. Laryngoscopy and tracheal intubation may be associated with sympathetic stimulation and lead to tachycardia and hypertension. These haemodynamic changes may predispose to myocardial ischaemia. [1]

Therefore, there is a need to blunt these noxious responses effectively. Various drug combinations have been used with variable success to attenuate the sympathetic responses during laryngoscopy and intubation (L‑I).

Premedication is usually administered to reduce anxiety, easy parental separation, amnesia and to reduce anaesthetic requirements. An ideal premedication should have anxiolytic sedative, analgesic andantisialagogue property. It preferably should be short acting, rapid onset, administered non‑parenterally and devoid of any adverse haemodynamic or respiratory effect. [2]

Gabapentin is a structural analogue of the neurotransmitter, γ–aminobutyric acid (GABA) that was introduced as an antiepileptic drug.7 It was proved to be effective in controlling neuropathic pain and acute postoperative pain with a reduction of postoperative opioid requirements.8 It has been used to attenuate the pressor response to laryngoscopy and endotracheal intubation. [3, 4]

Pregabalin, a gabapentinoid compound, is described structurally as (S)-3 aminomethyl-5 – methylhexanoic acid. Pregabalin is structurally related to the inhibitory neurotransmitter gamma‑aminobutyric acid (GABA), but is not functionally related to it. It acts by decreasing the synthesis of neurotransmitter glutamate to act on the central nervous system, and possesses analgesic, anticonvulsant and anxiolytic activity and is effective in preventing neuropathic component of acute nociceptive pain of surgery. [5] It is well absorbed and tolerated after oral administration, with peak plasma concentrations occurring within 1 h. It undergoes negligible hepatic metabolism. It is non‑narcotic, with clinically important reduction in pain and adverse haemodynamic response.

We planned to compare gabapentin and pregabalin to attenuateof haemodynamic pressor response of airway instrumentation with pre‑operative sedation and perioperative haemodynamic stability.

2. Methods

After hospital ethics committee approval a total of 70 patients (20 to 60 years) of either sex belonging to American Society of Anaesthesiologists (ASA) physical status I or II, were allocated randomly to the gabapentin or the pregabalin group. Patients with a history of hypertension, anticipated difficult intubation, having hiatus hernia or history of gestroesophageal reflux, on drugs which are likely to interfere with cardiovascular variables (e. g. calcium channel blockers and beta-blocker), on antacid therapy preoperatively, obese, pregnant and lactating females were excluded. Group A (n=35) patients received gabapentin 600 mg1hour prior to induction of anaesthesia. Group B (n=35)

patients received pregabalin 150 mg tablet 1hour prior to induction of anaesthesia.

On arrival in the operating room, monitors were attached and baseline heart rate and systolic, diastolic and mean arterial blood pressure were recorded. The pre-operative level of sedation was assessed by the Ramsay sedation scale: 1, anxious, agitated or restless; 2, co-operative, oriented and tranquil; 3, responds to command; 4, asleep with brisk response to stimulus; 5, asleep with sluggish response to stimulus; 6, asleep with no response.

A crystalloid intravenous infusion of 6–8 ml/kg was started and all patients were premedicated with glycopyrrolate (0.2 mg), midazolam (1 mg). After pre-oxygenation for 3 min with 100% oxygen, anaesthesia was induced with propofol (2 mg/kg) or in a dose sufficient for loss of verbal commands. The direct laryngoscopy and intubation was facilitated with succinylcholine, and of minimum possible duration. [5, 6] It was being similar to all patients Anaesthesia was maintained with isoflurane and nitrous oxide 60% in oxygen by gas monitoring on Datex Ohmeda Cardiocap 5 monitor. The patients were mechanically ventilated to maintain the normocapnia (CO2 between 35 and 40 mmHg). The supplemental neuromuscular blockade was achieved with vecuronium 0.1 mg/kg. After completion of surgery, residual neuromuscular block was antagonized with appropriate doses of neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg), and the extubation was performed when respiration was adequate.

Intraoperatively, the heart rate, mean arterial blood pressure, electrocardiography, pulse oximeter (SpO2) and EtCO2 levels were continuously monitored and recorded before and after induction, immediately after intubation and 1, 3, 5 and 10 min, thereafter at every 5-min interval till end of surgery. Patients were observed for complications like hypotension, hypertension, arrhythmias, hypoxemia and bronchospasm, and treated as required. Tachycardia was defined as heart rate greater than 100 beats/min and hypertension when systolic blood pressure was more than 180 mmHg. Autonomic or somatic signs of insufficient anaesthesia included lacrimation, sweating and flushing, which were treated by increasing the inhaled concentration of isoflurane and supplemental bolus doses of fentanyl (0.5 mg/kg). Hypotension was defined as fall in mean arterial pressure by more than 20% from baseline, and was treated by increasing the intravenous infusion and, additionally, with vasoactive drugs. Bradycardia was defined as reduction in heart rate less than 60 beats/min, and was treated with intravenous atropine (0.01 mg/kg).

Anaesthetic and surgical techniques were standardized for all patients. All groups were assessed for pre-operative sedation and changes in heart rate and mean arterial blood pressure after induction and airway instrumentation intraoperatively. The patients were transferred to the post-anaesthesia care unit and monitored for at least 3 h, or until there were no signs of any drug-induced effects such as nausea, vomiting, any respiratory inadequacy or haemodynamic instability in form of hypotension/ hypertension or tachycardia/bradycardia. If any side-effects were noted, they were treated accordingly.

A pilot study was conducted to calculate the sample size on the basis of difference in MAP between the two groups in post intubation period with standard deviation of 15 mmHg. It was calculated that 35 subjects were required per group in order to detect difference of 10 mmHg in MAP with 80% power and 5% type‑1 error probability. Sample size calculation was done by nMaster 2.0 software

3. Statistical Analysis

Statistical analysis was done by using Statistica version 6 [Tulsa, Oklahoma: StatSoft Inc., 2001] and GraphPad Prism version 5 [San Diego, California: GraphPad Software Inc., 2007]. All the numerical variables in the descriptive statistics were normally distributed (by Kolmogorov-Smirnov goodness‑of‑fit test), except RSS and SpO2 values. For statistical analysis, RSS score 2 (awake, oriented and cooperative) was considered as satisfactory.

Comparisons of numerical variables between two groups were analyzed by Student's unpaired *t* test for normally distributed data, and by Mann‑Whitney U test for skewed data. Intergroup comparison was done by repeated measures analysis of variance (ANOVA) followed by Tukey's test as a *post hoc* test, if normally distributed, and for skewed data by Friedman's analysis of variance (ANOVA) followed by Dunn's test as a *post hoc* test. A *P* value <0.05 was considered as significant.

4. Results

70 patients were randomised for assessment and none of these patients was lost during the follow up. The groups were well matched for their demographicdata. The baseline haemodynamic parameters were similar in both the groups [Table 1]. All the patients of both groups were alert and awake at the beginning of the study (RSS2).

No significant differences were found among them with respect to age, sex, weight, time between oral premedication of pregabalin administration to anaesthetic induction, type of urgical procedures, duration of laryngoscopy and anaesthesia [Table1].

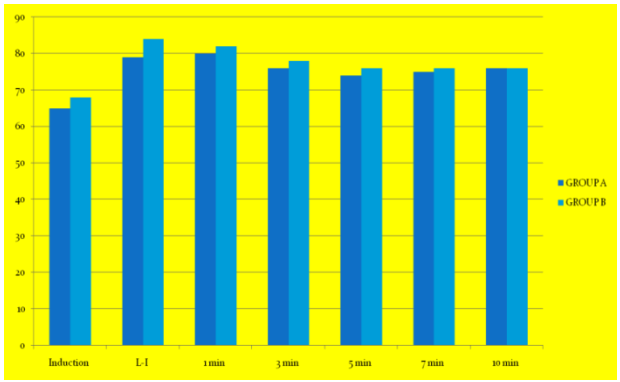
	GROUP A	GROUP B	P VALUE
SEX(M/F)	19/16	22/13	0.64
Weight in kg	61.03±7.35	60±6.89	0.54
Height in meter	1.62±0.06	1.62±0.07	0.89
BMI in kg/m2	23.10±2.38	22.75±1.70	0.98
SBP in mm of Hg	126.94±10	128.20±11	0.63
DBP in mm of Hg	78.74±8.96	79.74±7.59	0.61
MAP in mm of Hg	93.06±9.36	94.63±8.12	0.45
Heart Rate in beats/min	82.43±8.46	87.06±11.33	0.05

Considering the sedation status, most of the patients (57.1%) in group A and B remained in RSS stage II [(oriented, cooperative, tranquil),].

Comparison of Heart Rate

In post-intubation period, HR was slightly higher in the group Bthan group A. During intergroup comparison, statistically significant difference in HR between two groups was found only during L-I ($P < 0.05$). None of the patient in both groups had clinically significant tachycardia during the study period

	GROUP A	GROUP B	P VALUE
pInduction	65±5.77	68±9.77	0.12
L-I	79±5.88	84±9.11	0
1 min	80±5.77	8265±5.77	0.41
3 min	7665±6.77	78±9.97	0.24
5 min	74±5.37	76±9.66	0.33
7 min	75±5.88	76±9.67	0.6
10 min	76±5.77	76±9.47	0.72



Time in minute

Comparison of SBP

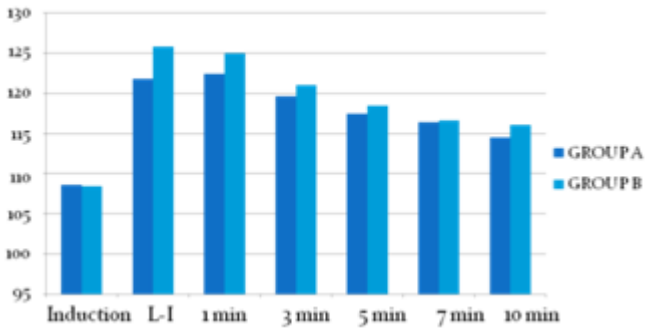
After L-I

Group B SBP, DBP and MAP all were slightly higher than group A.

There was no statistical significant differences in BP in post-intubation period during intergroup comparison ($P > 0.05$). None of the patient in both groups had clinically significant hypertension during the study period.

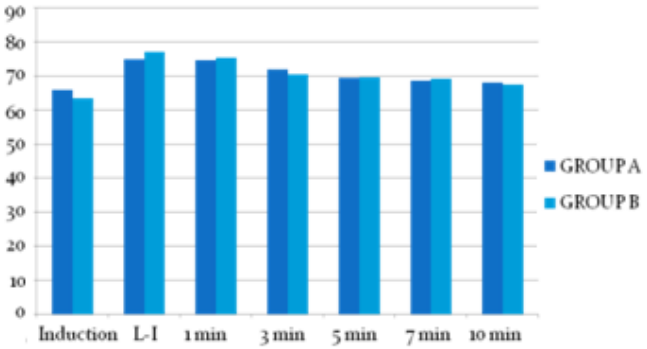
	GROUP A	GROUP B	P value
Induction	108.63±8.95	108.46±9.20	0.93
L-I	121.83±9.20	125.83±8.74	0.06
1 min	122.43±8.99	124.97±1.33	0.3
3 min	119.66±9.75	121.03±11.15	0.58
5 min	117.46±9.40	118.51±11.04	0.66
7 min	116.40±9.21	116.63±10.94	0.92
10 min	114.51±8.80	116.09±10.28	0.49

SBP



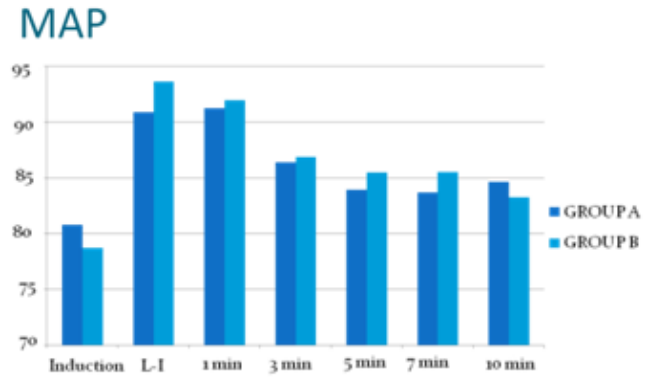
DBP

	GROUP A	GROUP B	P value
Induction	66.03±7.99	63.49±6.42	0.14
L-I	75.03±8.23	77.09±7.48	0.27
1 min	74.74±7.75	75.43±6.81	0.69
3 min	72.00±7.45	70.60±6.68	0.53
5 min	69.54±7.47	69.66±6.20	0.32
7 min	68.71±7.16	69.26±6.56	0.3
10 min	68.14±7.10	67.54±5.70	0.69



MAP

	GROUP A	GROUP B	P value
Induction	80.80±8.14	78.74±6.41	0.24
L-I	90.91±8.33	93.63±7.08	0.14
1 min	91.26±6.85	91.97±7.83	0.68
3 min	86.40±7.53	86.89±7.69	0.79
5 min	83.97±6.64	85.49±7.08	0.36
7 min	83.71±6.09	85.54±6.63	0.23
10 min	84.66±7.55	83.26±5.61	0.38



- There was no incidence of significant heart rate and BP in either group.
- None of the patients experienced nausea, vomiting or respiratory depression in the study period.

5. Discussion

Attenuation of laryngoscopic stress response is a major challenge for anaesthesiologist. The satisfactory role of preoperative Gabapentin and pregabalin for attenuation of laryngoscopic stress responses is well established. In the present study, we compared the efficacy of oral gabapentin and pregabalin on the stress responses of L-I.

From this study it was found that oral gabapentin 600Mgwas administered as premedication 60 min before induction, the effect was comparable with preoperative oral pregabalin 150 mg for the prevention of stress responses of L-I. Both oralgabapentin and pregabalin attenuated successfully the laryngoscopic stress responses without significant hypertension and tachycardia. In both the groups, all the haemodynamic parameters (HR, SBP, DBP, MAP) were maintained in normal limit (±20% of basal values) before and during L-I.

Our observation are in accordance with of Memis et al (2006) who reported compleate attenuation of reflex increase in heart rate and MAP after laryngoscopy and intubation with 600mg Gabapentine when given one hour before surgery. [7] However in another study done by Fassoulaki et al (2006) they reported that Gabapentine attenuated increase in blood pressure but not the tachycardia response to laryngoscopy and intubation. [8] The mechanism by which Gabapentine attenuates the pressor response to laryngoscopy and intubation is unknown. Although the molecular targets of gabapentine remain unknown, the inhibition of calcium flux in muscle cells with a consequent inhibtion of smooth muscle contraction might explain the effectiveness of Gabapentine in attenuation of the pressor response to laryngoscopy. Our study results are also similar to Kong VKF and Irwin MG 2007 who concluded preoperative Gabapentine is efficacious for not only post operative analgesia, post operative nausea and vomiting but also for attenuation of pressor response. [9]

The haemodynamic pressor response during laryngoscopy and intubation, in the form of tachycardia and hypertension, occurs frequently. [10] Shribman *et al.* reported that laryngoscopy alone or with tracheal intubation increases the arterial blood pressure and catecholamine levels, while intubation significantly increases heart rate. [11] Reid *et al.* and Hassan *et al.* reported high incidences of cardiac arrhythmias, myocardial ischemia, acute left ventricular failure and cerebrovascular accidents following intubation in hypertensive patients. [12, 13] These physiological changes are due to variation in the balance of sympathetic and parasympathetic outflow or receptor hypersensitivity. Specific measures should be taken to prevent these changes as hypertension may affect perioperative morbidity through the extent of end organ damage, like myocardial ischemia or cerebral haemorrhage. [14] Aronson and Fontes stated that rise in pulse pressure as little as 10 mmHg in both normotensive and hypertensive persons is associated with a 20% or more increased risk of renal failure, coronary events and cerebral stroke. [15]

6. Conclusion

Pregabalin and Gabapentin is emerging as an effective and safe drug as it leads to sedation, analgesia and haemodynamic stability. A single, oral dose of 150 mg of pregabalin, Gabapentin 600 mg premedication seems to be effective in attenuating the haemodynamic response to orotracheal intubation after the first attempt, an effect which may be useful in patients suffering from coronary insufficiency. Therefore both of this drugs can be used as a safer alternative premedication for adequate control of haemodynamic responses (MAP)]during laryngoscopy and endotracheal intubation.

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