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Comparative Evaluation of Oral Gabapentin and Pregabalin Premedication for Attenuation of Pressor Response to Endotracheal Intubation under General Anaesthesia

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Abstract: ***Purpose: Laryngoscopy and tracheal intubation causes severe noxious stimuli that induce an intense sympathetic hemodynamic response. This study aims to investigate the effect and safety of oral gabapentin and pregabalin in attenuating these responses.Methods: This is a prospective, randomized, double blind, placebo controlled study in which 90 adult ASA I and II patients undergoing elective surgery of both sexes were divided into three groups. Group A received placebo, Group B received oral gabapentin 800mg and Group C received pregabalin 150mg orally. Base line heart rate (HR), mean arterial pressure (MAP) and before induction, after induction, at the time of laryngoscopy and at the end of 0, 1, 3, 5 and 10min were recorded. Sedation score of all the 3 groups were recorded.Results: When compared to gabapentin and pregabalin, there was a significant increase in HR and MAP in control group after laryngoscopy and tracheal intubation. Pregabalin being more sedative than gabapentin is better than gabapentin in suppressing the pressor response.Conclusion: Oral gabapentin and pregabalin is a safe, simple and economical method in attenuating the pressor response to laryngoscopy and tracheal intubation.***

Keywords: Gabapentin, Pregabalin, Laryngoscopy, Pressor response, Tracheal intubation

1. Introduction

Laryngoscopy and tracheal intubation are an essential part of general anaesthesia causing severe noxious stimuli that induce an intense sympathetic hemodynamic response, the 'pressorresponse'[1]. Tachycardia and hypertension cause an imbalance in myocardial oxygen demand and supply, predisposing it to ischemia, infarction and heart failure. While this sympathetic response can normally be tolerated by healthy adults, it can be quite hazardous in patients having compromised cardiovascular function. The search for an ideal drug to attenuate the pressor response to intubation has been going on since few decades. Some of those are intubation in a deeper plane of anaesthesia, topical anaesthesia of the upper respiratory tract prior to laryngoscopy with lignocaine, pre-treatment with vasodilators, beta blockers, calcium channel blockers and opiods[2]-[3]. But, no single drug has been proven to be the drug of choice.

Gabapentin and pregabalin apart from its use in the treatment of epilepsy, alleviating neuropathic pain, acute post-operative pain relief, it also decreases pre-operative anxiety and attenuates perioperative stress response. This study was designed to evaluate oral gabapentin and pregabalinhas premedication to attenuate pressor response to laryngoscopy and intubation.

2. Methods

A prospective, randomized, double blind, placebo controlled study was carried out. Ninety normotensive patients of both sexes in ASA I and II physical status, between the age group of 18-60yrs, who were posted for elective surgery under general anaesthesia were included in this study. Institutional ethical committee approval and written informed consent was obtained. They were divided into three groups.

Group A – Control group
Group B – Gabapentin group
Group C – Pregabalin group

The exclusion criteria:

- Anticipated difficult intubation
- ASA III or greater
- Cardiac, pulmonary or renal disease
- Obesity
- Sensitive to any drugs involved in the study
- On antihypertensives, sedatives, hypnotics
- Second attempt for intubation
- Duration of laryngoscopy exceeding 20 sec
- Pregnancy / lactation
- Intubation other than orotracheal

In the preoperative visit, the patients were examined and investigated appropriately. Informed consent was obtained and 90 patients were randomly allocated into 3 groups of 30 each. Group A is the control group who received placebo. Group B received Gabapentin 800mg and Group C received Pregabalin 150mg orally with sips of water as premedication 2hours prior to induction of general anaesthesia. Anaesthesiologist who was not aware of the study protocol and was not participating in study was the observer. In the operating room patient was connected to three lead ECG, non-invasive blood pressure and arterial oxygen saturation. Baseline heart rate, systolic, diastolic, mean arterial pressure and oxygen saturation were recorded. The pre-operative level of sedation was assessed by the Ramsay sedation scale[4]: 1. Anxious, agitated or restless 2.Co-operative, oriented or restless 3.Responds to command, 4.Asleep with brisk response to stimulus 5.Asleep with sluggish response to

stimulus 6.Asleep with no response. A 20 gauge intravenous catheter was secured and Ringer lactate was started at a rate of 6-7ml/kg. A uniform anaesthetic technique was used in all three groups. They were premedicated with InjGlycopyrolate 0.2mg, Inj Midazolam 1mg, InjEmeset 4mg, Inj Fentanyl 2µgm/kg intravenously prior to induction. They were preoxygenated with 100% oxygen for 3min, induced with Injpropofol 2mg/kg and paralysed with Injvecuronium 0.1mg/kg. Patients were ventilated with 50% N_20 and 50% o_2 and Isoflurane 1% for 3min after which larynogoscopy and tracheal intubation was performed by a senior anesthesiologist. The duration of intubation was limited to as minimum as possible.Anaesthesia was maintained with oxygen and 60% of nitrous oxide and 0.4-0.6% of isoflurane using controlled ventilation. Normocapnia of 35-40mmHg was maintained throughout the procedure. Heart rate and blood pressure were recorded prior to induction, after induction, during laryngoscopy and at the end of 0, 1, 3, 5 and 10min following intubation and thereafter every 5min interval till the end of the surgery. At the end of the procedure residual neuromuscular blockade was reversed with Inj neostigmine 0.05mg/kg and Injglycopyrolate 0.01mg/kg and extubated once the patient was breathing adequately. Intraoperatively monitored for any complication like hypotension, hypertension, arrhythmias and hypoxemia.

3. Statistical Methods

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Analysis of variance (ANOVA) has been used to find the significance of study parameters between three groups of patients. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Significant figures
+ Suggestive significance (P value: 0.05<P<0.10)
* Moderately significant (P value:0.01<P ≤ 0.05)
**Strongly significant (P value : P≤0.01)

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

4. Results

A total of 90 patients were inducted into the study. Laryngoscopy which took >20sec and second attempt for intubation were excluded from the statistical analysis, leaving 25 patients in each group. In this study all the three groups were comparable with respect to demographic characteristics – Age, sex, weight, ASA grading, Mallampattigrading, duration of laryngoscopy, duration and type of surgical procedures and anaesthesiatechniques.

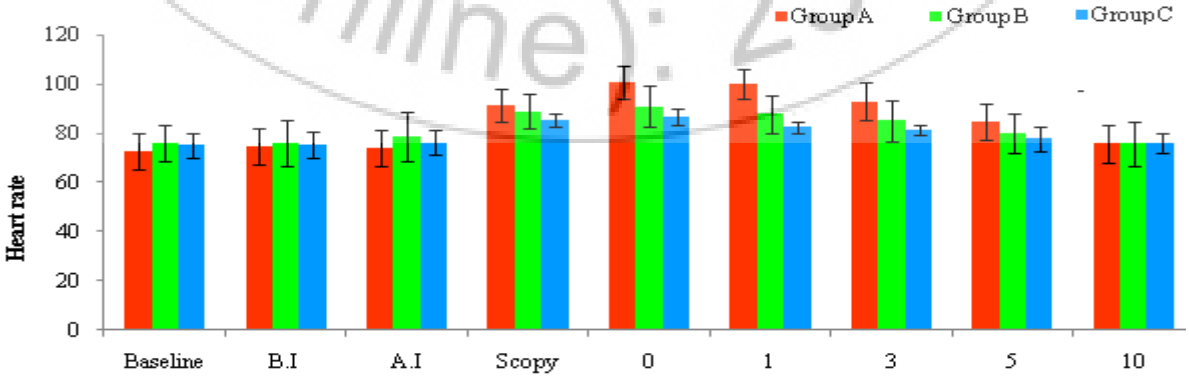
Table 1: Demographic parameters

Demographic parameters	*Group A*	*Group B*	*Group C*
Age (years)	35.08±11.50	34.60±13.83	32.88±11.12
Sex (M:F)	12:13	9:16	11:14
Weight(Kgs)	55.96±7.03	55.08±8.38	53.04±8.37
ASA (I:II)	21:4	19:6	20:5
Mallampatti (I:II)	20:5	17:8	18:7
Scopy timing (sec)	18.08±1.41	16.04±1.64	17.00±1.38

The initial baseline heart rate and Mean arterial pressure were similar in all the 3 groups. An increase in heart rate and MAP was seen from the time of laryngoscopy upto 5 minutes after intubation. Maximum heart rate and MAP was seen at 0 min of intubation. The average maximum heart rate in the study Group A-100.56, Group B-90.96 and Group C-86.64 was seen at 0 min and maximum MAP was 106.34, 98.62 and 95.0 in Group A, B and Crespectively at 0 min. The difference between the control and the gabapentin and pregabalin was found to be highly significant with a p value of <0.001 at 0, 1, 3 and 5 minafter intubation. Thereafter the heart rate and MAP started declining towards baseline by the end of 10min. When compared to gabapentin, pregabalin had very slight rise in HR and MAP to larynogoscopy but was not statistically significant.

Table 2: Comparison of heart rate (BPM)

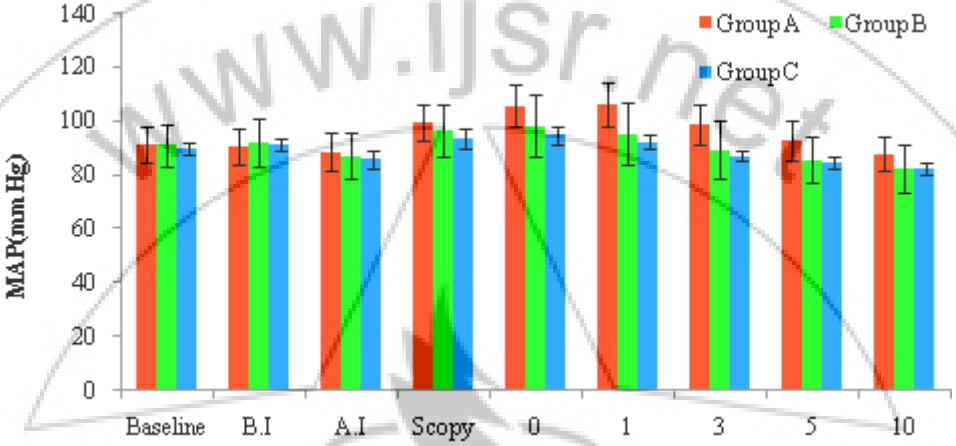
Heart rate	*Group A*	*Group B*	*Group C*	*P value*
Baseline	72.72±7.46	76.00±7.50	75.08±5.00	0.216
B.I	74.56±7.27	76.16±9.29	75.24±5.39	0.751
A.I	74.04±7.06	78.72±10.21	76.20±4.98	0.108
Scopy	91.36±6.99	88.96±7.16	85.40±2.90	0.003**
0	100.56±6.72	90.96±8.22	86.64±3.29	<0.001**
1	100.16±6.00	87.72±7.81	82.44±2.47	<0.001**
3	92.92±7.57	85.04±8.40	81.64±2.00	<0.001**
5	84.80±7.40	79.96±8.17	77.84±5.11	0.003**
10	75.88±7.65	75.88±8.90	75.88±4.02	1.000



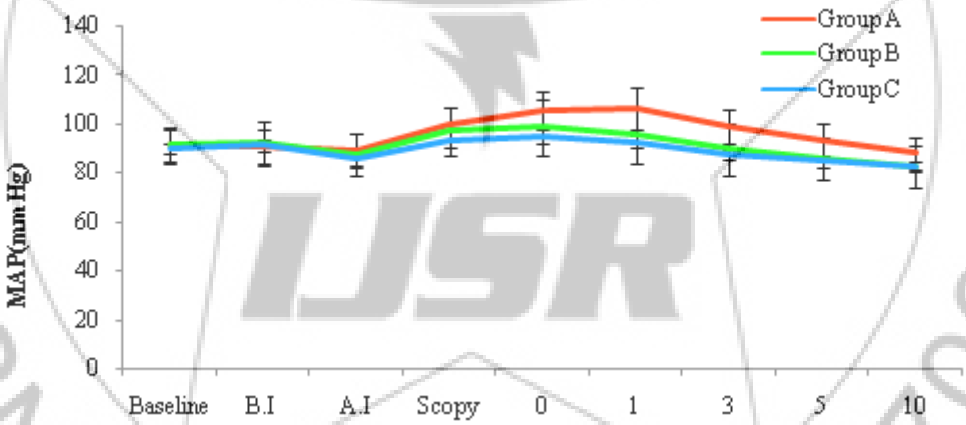
Graph 1: Comparison of Heart rate (BPM)

Table 3: Comparison of MAP (mm Hg)

MAP	*Group A*	*Group B*	*Group C*	*P value*
Baseline	91.24±6.80	91.23±7.70	90.16±2.06	0.769
B.I	90.69±6.73	92.13±8.74	91.28±2.15	0.732
A.I	88.96±6.80	87.31±8.45	86.12±3.36	0.313
Scopy	99.76±6.70	96.98±9.65	93.68±3.44	0.013*
0	105.79±7.88	98.62±11.59	95.00±3.19	<0.001**
1	106.34±8.52	95.52±11.58	92.56±2.35	<0.001**
3	98.93±7.11	89.65±10.53	87.44±1.98	<0.001**
5	93.15±7.34	85.67±8.45	84.80±2.25	<0.001**
10	88.00±6.44	82.64±8.73	82.48±2.08	0.004**



Graph 2: Comparison of MAP (mm of Hg)



None of the patient in the present study developed severe hypotension, only 1 patient in gabapentin and 2 patients in pregabalin group had transient hypotension (MAP < 80mmHg for <1min), which did not require any vasopressors. No incidence of bradycardia, tachycardia, arrhythmia or ST segment alterations were observed during the study. Sedation was significantly higher in the pregabalin group than in the gabapentin group at the time of induction. Onset of action for level II sedation was seen by 30 min in pregabalin group and by 60 min in gabapentin group. By 90 min, 20 patients in pregabalin group had reached level II sedation with no effect on 5 patients. By 120 min, 15 patients in gabapentin group had reached levelII sedation with no effect on 10 patients. There was no respiratory depression in both the groups. Drop in oxygen saturation in 2 patientsupto 95% in pregabalin group was observed. During emergence and recovery, there were no cases of delayed recovery in all the 3 groups and were extubated when fully awake and alert.

Table 4 : Sedation score (n)

Time (min)	*Group A*	*Group B*	*Group C*
30	-	-	2 (8%)
60	-	3 (12%)	8 (32%)
90	-	5 (20%)	10(40%)
120	-	7 (28%)	-
No effect	25 (100%)	10 (40%)	5 (20%)

5. Discussion

Laryngoscopy and tracheal intubation are associated with hypertension, tachycardia and increased catecholamines[5] – [7]. Haemodynamic changes are usually transient and without any sequelae. However, in patients with pre-existing coronary artery disease, hypertension or cerebrovascular disease, these changes may precipitate myocardial ischaemia, arrhythmias, myocardial infarction and cerebral hemorrhage. To attenuate this pressor response to laryngoscopy and intubation, oral gabapentin 800mg and pregabalin 150mg was administered as premedication. Gabapentin, [8]-[15] 2-[1-

(aminomethyl) cyclohexyl] acetic acid, is a structural analogue of the neurotransmitter gamma amino butyricacid. It acts by selective activation of GABA – B receptors and enhancement of NMDA current at GABAergic interneurons. It is used in epilepsy, chronic pain condition, pre emptive analgesia, preoperative anxiolysis, post operative analgesia, attenuation of hemodynamic response to laryngoscopy and intubation and in post operative nausea and vomiting. It is well absorbed from the GIT, with a peak plasma concentration of 2-3hrs. Not metabolized and eliminated unchanged in urine.

Pregabalin, (s)-3-(amino methyl)-5-methyl hexanoic acid is a lipophilic analogue of GABA. Although pregabalin is structurally related to GABA, it is inactive at GABA receptors and does not appear to mimic GABA physiologically. It acts by decreasing the synthesis of neurotransmitter glutamate to act on the central nervous system. It exhibits potent anticonvulsant, analgesic and anxiolytic activity[16]-[20]and is effective in preventing neuropathic component of acute nociceptive pain of surgery. It is well absorbed after oral administration, with maximal plasma concentration occurringwith in 1hr. It undergoes negligible metabolism and is excreted virtually unchanged by the kidneys.

The patients were in the age group of 18-60yrs. The majority of the patients were in the range of 21-40yrs, with a mean age of 34yrs. Most of the other studies of gabapentin involve a similar age group. They claimed that older patients could have confounding factors such as comorbid diseases, medications, and the physiologic changes associated with age itself could alter their responses to stress during laryngoscopy and intubation.

In our study, there was slight female preponderance. However, this was not found to be statistically significant. No other studies have quoted any confounding factors related to gender, and gender does not seem to have any effects on the stress response.

The patients were found to have an average weight of 55kgs. Patient weighing more than 70kgs or less than 40kgs were excluded from the study. Since a single dose of gabapentin and pregabalin was given to all patients, extremes of age were expected to alter the pharmacokinetics and plasma concentration achieved. Also over weight patients tend to have associated cardiovascular conditions, difficult airways and more often pose difficulties in intubation. They all belonged to ASA physical status I and II having a Mallampatti airway grading of I andII. The anaesthetic technique was kept uniform in all the three groups.The surgical procedures lasted not more than 2hrs. The present study demonstrated that a single oral dose of 800mg of gabapentin and 150mg of pregabalin given 2hrs prior to surgery caused a significant reduction in Pressor response to tracheal intubation when compared to the control group in adults with some sedative effect. Pregabalin was found to be more effecitve in reducing the pressor response due to its more sedative effect than Gabapentin. There was no significant side effect in all the three groups. The oral route of administration of these drugs has a bioavailability of 60% for gabapentin and >90% for pregabalin. Two hours prior to surgery both the drugs can be safely administered to the patient with sips of water. Paramedics may also administer the drug to the patients and it does not necessitate the need of intense monitoring. The lack of need for intravenous access is another factor increasing its patient compliance. Another important aspect of the use of gabapentin and pregabalin is the cost-effectiveness. Either gabapentin or pregabalin can be used for attenuating the pressor response as they do not produce any acute change in hemodynamics.

6. Conclusion

A single oral dose of 800mg of gabapentin and 150mg of pregabalin administered 2 hrs prior to surgery effectively reduces the hemodynamic response to laryngoscopy and endotracheal intubation even though not completely attenuated which is due to its analgesic and sedative effect. So it is a safe, simple and economical technique with good patient comfort and compliance.

7. Future Implications

As this study was conducted on patients with ASA physical status I and II, patients with uncontrolled hypertension and coronary insufficiency who do not tolerate pressor response further studies has to be conducted on that group.

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