Original Research Paper

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COMPARISON OF EFFICACY OF ORAL PREGABALIN VERSUS GABAPENTIN IN THE ATTENUATION OF HEMODYNAMIC STRESS RESPONSE IN PATIENTS UNDER GENERAL ANAESTHESIA: A PROSPECTIVE RANDOMIZED DOUBLE BLIND STUDY.

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ABSTRACT

INTRODUCTION: Laryngoscopy and tracheal intubation induces changes in circulating catecholamine levels significantly. This can result in detrimental effects including myocardial ischemia, infarction, cardiac dysrhythmia, premature ventricular complexes, cardiac failure, raised ICP and intracranial haemorrhage especially in high risk patients. Pregabalin and Gabapentin are two agents that have been used to prevent this pressor response. So, the present study is undertaken to compare the efficacy of oral Pregabalin and Gabapentin in attenuating hemodynamic response to laryngoscopy and intubation.

OBJECTIVES: The present study compares the efficacy of oral Pregabalin and Gabapentin in attenuating hemodynamic response to laryngoscopy and intubation.

Haemodynamic responses were compared in both the groups by measuring at different time points:

1. Heart Rate (HR) 2. Mean Arterial Pressure (MAP)

METHODS: After institutional ethical committee clearance, a prospective randomized control study was conducted. A total of 80 patients of ASA grade 1 and 2 of age groups 18-60 years undergoing elective surgeries under general anaesthesia were included.

Group P (n=40), was the pregabalin group and Group G (n=40), was the gabapentin group. Patients in both groups received oral pregabalin and gabapentin respectively one hour prior to surgery. Patients underwent general anaesthesia with induction of propofol 2mg/kg IV and muscle relaxation with succinyl choline 2mg/kg IV. The airways were secured with endotracheal intubation. Anaesthesia was maintained with Sevoflurane 1%.

RESULTS: Statistical analysis using students t-test showed that there is no statistically significant difference between heart rate of the two groups (P>0.05). The mean arterial (MAP) pressure at different time intervals was measured and showed no significant difference (p >0.05).

CONCLUSION: A single oral dose of Pregabalin 150mg or Gabapentin 600mg administered one hour prior to surgery are equally effective in reducing hemodynamic response to laryngoscopy and intubation.

KEYWORDS : Pregabalin, Gabapentin, Laryngoscopy, Intubation.

INTRODUCTION:

Endotracheal intubation has become an integral part of anaesthesia and critical care. Laryngoscopy and tracheal intubation induces changes in circulating catecholamine levels significantly. As early as 1951, King et al. first described the circulatory responses to laryngeal and tracheal stimulation following direct laryngoscopy and tracheal intubation, as a reflex sympatho-adrenal response.[1,2,3]

Even though the elevation in blood pressure and heart rate due to laryngoscopy and intubation are brief, they may have detrimental effects including myocardial ischemia, infarction, cardiac dysrhythmia, premature ventricular complexes, cardiac failure, raised ICP and intracranial haemorrhage especially in high risk patients.[4]

Hence it is important to find an effective means of attenuating sympathetic responses to laryngoscopy and tracheal intubation. Pregabalin and Gabapentin are relatively new drugs which were originally introduced as antiepileptics. Pregabalin is a synthetic molecule and a structural derivative of the inhibitory neurotransmitter γ-aminobutyric acid. It has analgesic, anticonvulsant, anxiolytic, and sleep-modulating activities. Pregabalin has been emerging as an effective oral premedication drug with safe and multimodal drug profile with hemodynamic stability.[5,6,7,8,9]

Gabapentin is effective at relieving allodynia and hyperalgesia. It has been shown to be efficacious in a wide variety of pain syndromes. More recently gabapentin has been used in randomized controlled trails to treat acute post operative pain and to reduce post operative opioid requirements.[10,11]

Hence, the present study is undertaken to compare the efficacy of oral Pregabalin and Gabapentin in attenuating hemodynamic response to laryngoscopy and intubation.

MATERIALS AND METHODS

The present hospital based prospective interventional randomized double blind study was carried out in 80 randomly selected ASA class I and class II patients undergoing elective surgeries under general anaesthesia in Karnataka Institute of Medical Sciences, Hubballi. Due permission from institutional ethical committee was taken.

The adult patients of either sex aged between 18yrs-60yrs weighing 50-70kgs posted for elective surgeries belonging to ASA grade I & II under general anaesthesia were included in our study. Patients with difficult airway, Patients on antiepileptic medications, Pregnant or breast feeding females, Patients who were taking pregabalin or gabapentin prior to study were excluded from the study.

Preoperative assessment was done for each patient and relevant investigations were sought and an informed written consent was obtained from all patients participating in the study the day before the surgery.

The study population was randomly allocated using computer generated randomization into 2 groups of 40 patients in each group. Group P (n=40), was the pregabalin 150mg dose group. Group G (n=40), was the gabapentin 600mg dose group.

All the patients of the two groups, with their informed consent, were kept nil per oral 6 hours for solids and two hours for clear fluids. Group G patients were given capsule gabapentin 600mg orally one hour prior to induction. Group P patients were given 150mg pregabalin capsule orally one hour prior to induction with sips of water.

On arrival in the operation room, all the patients were connected to non-invasive monitoring – pulse oximetry (SPO2), Non Invasive Blood Pressure (NIBP) and electrocardiography (ECG) using multiparameter monitor. 18G intravenous cannula was secured on the non-dominant hand and infusion of Ringer Lactate was started. Patients were premedicated with midazolam 0.05mg/kg IV, glycopyrrolate 0.01 mg/kg IV, fentanyl 2mcg/kg IV, ondansetron 0.1 mg/kg IV and ranitidine 1mg/kg IV. After preoxygenation for 3 min with 100% oxygen, general anaesthesia was induced with Propofol

2mg/kg IV. Pain on injection with Propofol was prevented by using IV injection of 1.5 mg/kg body weight of preservative free 2% lignocaine given 30 seconds before Propofol. The end point of induction was taken as loss of eye lash reflex and noted. Suxamethonium 2 mg /kg IV was used for intubation in all the patients. All the patients were intubated with appropriate sized cuffed endotracheal tubes by experienced anaesthesiologist who was blinded about the premedication given with gentle laryngoscopy and tracheal position of the tube confirmed by end tidal carbon dioxide (EtCO2). Anaesthesia was maintained with Oxygen+ Nitrous oxide+ sevoflurane 1%+ Inj.Vecuronium 0.1mg/kg. After the surgical procedure, patients of all the groups were reversed with Neostigmine 0.05mg/kg IV and Inj glycopyrrolate 0.01 mg/kg given IV and extubated and observed in the post anaesthetic care unit for 6hrs.

- **PARAMETERS MONITORED**

Haemodynamic responses were compared in both the groups by measuring

1. Heart Rate (HR)
2. Systolic Blood Pressure (SBP)
3. Diastolic Blood Pressure (DBP)
4. Mean Arterial Pressure (MAP)

These parameters are measured using automatic Multiparameter monitor Before induction, Immediately after induction, Immediately after endotracheal Intubation and cuff inflation (1 min), 3 Minutes, 5 Minutes, 10 minutes, every 15 min till the end of the surgery.

STATISTICALANALYSIS:

Mean arterial pressure among both the groups at one minute after endotracheal intubation was taken as the measure of interest for the purpose of sample size calculation. The sample size of 40 in each group was decided with a power of 90% with 99% confidence interval with 1% precision/error. Data was analysed and compared with students t test, chi square test. The statistical software namely SPSS 21 .0 was used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc. The value of P <0.05 was considered significant.

RESULTS:

Both the groups were comparable with respect to age, sex, weight and ASA physical status. There were no significant differences in demographic profile among the three groups (p>0.05). The heart rate at different time intervals between the two groups was measured. Statistical analysis using students t-test shows that there is no statistically significant difference between heart rate of the two groups before induction, after induction 1,3,5,10,15 minutes after intubation and also post operatively (P>0.05).

The mean arterial (MAP) pressure at different time intervals was measured between the two groups. Statistical analysis using students t-test shows that there is no statistically significant difference between the (MAP) readings of the both groups at any point of time (p >0.05).

Table 1: Comparison Of Two Study Group (p And G) With Heart Rate At Different Time Points By T Test

Time points	Group P		Group G		t-value	p-value
	Mean	SD	Mean	SD		
Basal	83.85	10.27	81.35	11.83	1.0091	0.3160
post induct	82.55	12.43	80.40	12.03	0.7860	0.4342
1minute	82.60	11.51	85.90	15.60	-1.0765	0.2850
3minutes	82.30	11.22	82.75	13.82	-0.1599	0.8734
5minutes	80.20	10.61	80.15	11.15	0.0205	0.9837
10minutes	78.58	8.90	77.58	9.36	0.4895	0.6259
15minutes	76.93	9.95	77.18	8.98	-0.1179	0.9064
Post op	77.43	10.33	77.33	9.37	0.0453	0.9640

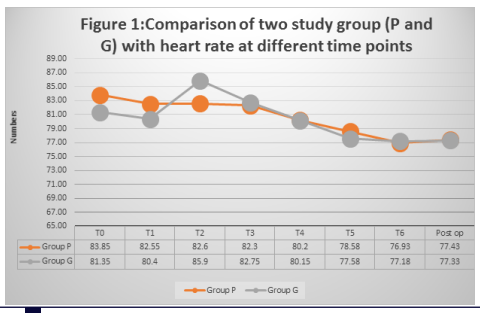
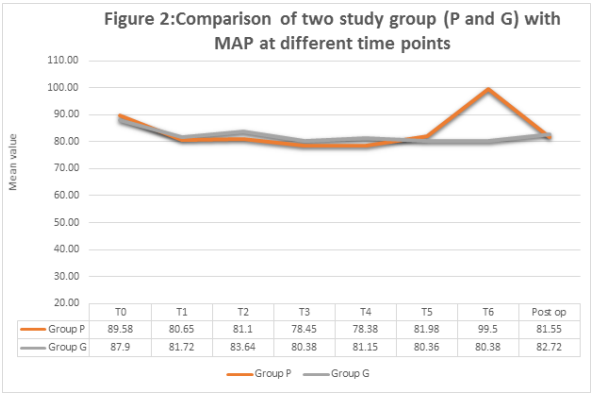


TABLE 2: COMPARISON OF TWO STUDY GROUP (P AND G) WITH MAP AT DIFFERENT TIME POINTS BY T TEST

Time points	Group P		Group G		t-value	p-value
	Mean	SD	Mean	SD		
Basal	89.58	7.83	87.90	9.28	0.8688	0.3877
post induct	80.65	8.32	81.72	10.13	-0.5127	0.6096
1minute	81.10	8.62	83.64	12.58	-1.0499	0.2970
3minutes	78.45	8.93	80.38	11.54	-0.8344	0.4066
5minutes	78.38	8.84	81.15	9.34	-1.3585	0.1783
10minutes	81.98	9.29	80.36	10.24	0.7348	0.4647
15minutes	99.50	110.03	80.38	9.13	1.0811	0.2830
Post op	81.55	8.54	82.72	10.40	-0.5462	0.5865

CHART 2:



DISCUSSION:

Endotracheal intubation has remained a gold standard method of securing airway since the time of its introduction. Laryngoscopy and tracheal intubation alters respiratory and cardiovascular physiology via reflex responses and by the physical presence of endotracheal tube. Changes in plasma catecholamine concentration during endotracheal intubation has been observed and it was found out that there were both nor adrenergic and adrenergic responses suggesting an increase in sympathetic activity.[12]

The necessity to attenuate stress response to laryngoscopy and intubation is apparent and well established. Many drugs effectively attenuate this response, which are aimed at different levels of reflex arc[13],such as, block of peripheral sensory receptors and afferent input – topical application and infiltration of local anaesthetic, block of central mechanism of integration and sensory output-opioids, block of efferent pathway and effector sites –beta blockers, CCBs, IV lignocaine, including anaesthetics, analgesics, adrenergic blocking agents and vasodilators. This has been a potential area for clinical investigations paving room to numerous studies which modify and reduce haemodynamic response to intubation.

Pregabalin is a member of a unique class of compounds characterized by its high-affinity binding to the alpha 2-delta protein, of presynaptic[5], voltage dependent calcium channels[14]Binding at this site has been shown to reduce depolarization-induced calcium influx at nerve terminals, which reduces the release of several excitatory neurotransmitters, including glutamate and norepinephrine[15]. Pregabalin also modulates the release of sensory neuropeptide substance P and calcitonin gene-related peptide from rat spinal tissues[15].

Gabapentin originally introduced as antiepileptic, is effective in neuropathic pain and most recently has been evaluated as analgesic, anti-hyperalgesic, or both, perioperatively. Gabapentin also has voltage dependent calcium channel blocking property.[16]

In our study, the groups were comparable with respect to their demographic variables and their baseline values of HR and MAP. The mean basal heart rate in Group P before induction was 83.85±10.27 /min and 81.35 ±11.83/min in Group G (p>0.05). There was no significant difference in the heart rate among the two groups before induction. Hence both groups were comparable. No tachycardia or bradycardia was seen at any point of time in both the groups. This observation correlated with the study conducted by Bhashyam et al [17], which evaluated the efficacy of preoperative oral Gabapentin (600mg) and Pregabalin (150mg) in attenuation of stress response, sedation and anxiolysis. There was no significant difference in HR in both groups one hour after premedication and induction. Post induction, the mean

heart rate in group P was 82.55±12.43/min and Group G was 80.40 ±12.03/min (p >0.05). There was no significant difference in the heart rate among groups after induction. This observation correlated with the study conducted by Bhashyam at al [17] and Namratha et al[18].

At one minute after intubation, there was slight increase in mean heart rate in Group G 85.90 ± 15.60 /min compared Group P 82.60±11.51/min, but statistically not significant (p>0.05). At 3,5,10 and 15 mins of intubation, the mean heart rate among both the groups remained same with no statistical significant difference (p>0.05). Namratha et al[18] compared gabapentin and pregabalin in dose of 800mg and 150mg respectively as premedication for attenuation of pressure response which found that compared to gabapentin, pregabalin had very slight rise in HR to laryngoscopy which was statistically not significant.

However in a study by Bhashyam et al[17] there was increase in the HR and MAP in both Pregabalin and Gabapentin group after intubation, but on comparing both the groups, the attenuation of HR was significantly high in Pregabalin group (p<0.001) unlike our study. 10 mins after intubation, HR almost reached baseline value and there was no significant difference in both the groups (p=1.00).

In our study, no precipitous severe tachycardia was noted that required intervention. Even after laryngoscopy and intubation the mean heart rate among both the groups remained close to baseline value. Slight decrease in HR post induction in both groups may be attributable to Propofol induction.

In our study mean arterial pressure (MAP) before induction was 89.58±7.83 mmHg in group P and 87.90± 9.28 mmHg in group G (p>0.05). There was no significant difference in the Mean Arterial Pressure (MAP) among groups before and after induction. Decrease in MAP was observed in both the groups after induction compared to baseline.

At 1 min after intubation mean MAP increased in both group P and group G compared to post induction value but did not increase more than the basal value.

At all points of time (1, 3, 5, 10 mins after intubation) mean MAP remained similar in both the groups and within normal range. At 15 mins after intubation there was increase in mean MAP in group P 99.5±11.3 mmHg compared to 80.38 ±9.31 mmHg in group G but was statistically not significant.

Namratha et al.[18] compared gabapentin and pregabalin in dose of 800mg and 150mg respectively as premedication for attenuation of pressor response. When compared to gabapentin, pregabalin had very slight rise in heart rate and MAP to laryngoscopy which was not statistically significant. This observation was in consensus with our study.

Bhashyam et al[17] compared oral gabapentin and pregabalin premedication for anxiolysis, sedation and attenuation of pressor response to endotracheal intubation in doses of 600mg of gabapentin and 150 mg of pregabalin. There was no significant difference in baseline (P=0.533), one hour after premedication and after induction in HR and MAP values among both groups our study was in consensus with these findings. During laryngoscopy and immediately after intubation attenuation MAP was significantly high in group P than Group G (p<0.001). However in our study, statistical analysis showed no significant difference between two drugs to attenuation of pressor response.

A comparative study of oral pregabalin and oral gabapentin in the attenuation of hemodynamic response to laryngoscopy and intubation by Doddaiha et al[19] wherein the patients were given oral pregabalin 150 mg, oral gabapentin 800 mg, or oral placebo capsules according to their respective groups 90 min before surgery. There was a statistically significant decrease in mean arterial pressure (MAP) in pregabalin group when compared to gabapentin group at 1 and 10 min with P < 0.06 and P < 0.07, respectively. But the study stated that there was some reduction in HR, SBP, DBP, and MAP between gabapentin and pregabalin groups, but it was not statistically significant.

In our study no patient of either group suffered from bradycardia, hypotension, or postoperative respiratory depression or postoperative excessive sedation.

LIMITATIONS

The laryngoscopy period was restricted to <15 s, but the duration of laryngoscopy was not measured. The stress mediators (catecholamine levels) in plasma were not measured. Sedation was not scored in our study; which can be considered as a limitation. It could have been included in the study if the administration of Pregabalin/Gabapentin reduced the induction dose of Propofol.

CONCLUSION:

A single oral dose of Pregabalin 150mg or Gabapentin 600mg administered one hour prior to surgery reduces hemodynamic response to laryngoscopy and intubation. Both the drugs are equally effective, safe, cost effective and without significant side effects and either of the drug can be used.

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