A Comparative Evaluation of Oral Pregabalin with Placebo in Atteneuation of Pressor Response during Direct Laryngoscopy and Intubation in Patients of General Surgical Procedures under General Anaesthesia

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ABSTRACT

Introduction: Laryngoscopy and endotracheal intubation is generally related with exaggerated haemodynamic response. Tracheal intubation and direct laryngoscopy result in increased heart rate and blood pressure the so called 'pressor response'. In extreme cases this might result in cardiac failure, myocardial ischemia, intracranial haemorrhage and increased intracranial pressure. Hence, we aim to observe the effect of Pregabalin in attenuating this haemodynamic response.

Material and methods: In this prospective randomized double blinded study 40 adult patients of ASA I/II undergoing surgery were included. They were allocated randomly into two groups, group-PG received 150mg oral Pregabalin and group-PL received oral Placebo as sugar tablets one hour before surgery. Systolic blood pressure (SBP), Heart rate (HR), diastolic blood pressure (DBP), mean arterial pressure (MAP) were evaluated.

Results: In both groups there was significant increase in HR, SBP, DBP, and MAP at the time just after intubation and 1st and 3rd minutes after intubation. Attenuation of SBP, DBP, and MAP was significantly high in Group-PG than Group-PL ($p<0.001$) whereas HR changes were insignificant.

Conclusion: Oral Pregabalin 150 mg when used as premedication one hour prior to induction of anesthesia was found to be more effective in significant attenuation of hemodynamic pressor response to laryngoscopy and endotracheal intubation with acceptable levels of sedation and negligible side effects.

Keywords: Pregabalin, Pressor Response,Sedation, Laryngoscopy, Intubation, Haemodynamic Changes.

INTRODUCTION

In patients undergoing surgery under general anaesthesia endotracheal intubation is the gold standard for securing the airway. However, the procedure may cause activation of the sympathetic nervous system and release of catecholamines resulting in a haemodynamic response that precipitates an increase in Heart Rate (HR) and Mean Arterial Pressure (MAP). This response does not cause problems in most patients, however in high-risk patient groups with pre existing cardiovascular disease it may increase the risk of myocardial ischaemia, myocardial infarction and mortality.[1,2] Attenuation of circulatory response to these stimuli is usually done by several methods and medications. Several pharmacological agents like benzodiazepines, opioids, local anesthetics, calcium channel blockers, beta blockers and alpha agonists etc., have been used to reduce anxiety, produce sedation and attenuate pressor responses.[3]

Pregabalin is a lipophilic Gamma-Aminobutyric acid (GABA) analogue with anticonvulsant, anxiolytic, analgesic and sleep modulating properties. It binds to the alfa 2 – delta subunit of pre synaptic, voltage-dependent calcium channels that are widely distributed throughout the central and peripheral nervous system and results in decreased synthesis and release of several neurotransmitters like Glutamate, Norepinephrine, Serotonin, Dopamine, and substance 'P'. Pregabalin is well absorbed after oral administration and its oral bioavailability is 90%. Peak plasma concentrations are achieved within 1 to 1.5 hours of oral administration and half-life is approximately 6 hours. It undergoes negligible metabolism and approximately 90% of the administered dose is recovered in the urine as unchanged Pregabalin.[4]

Dose response relationship calculated allows Pregabalin 150mg/day dose with no need for titration. This drug finds its application as anticonvulsant, analgesic, anxiolytic, treatment of neuropathic pain, partial seizures and fibromyalgia. The adverse effects of Pregabalin are transient with somnolence and dizziness being most common.[1,4]

Hence in this prospective, randomized, double-blinded and comparative study, we aimed to compare the oral Pregabalin with placebo in attenuation of pressor response during direct laryngoscopy and intubation in patients of general surgery under general anaesthesia.

MATERIAL AND METHODS

The present study was conducted in Department of Anaesthesiology, Career Institute of Medical Sciences, Lucknow. After the approval from ethical committee of the

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institution a total of 40 patients belonging to ASA grade I and II between the age group 20 to 60 years, scheduled for elective general surgery, were enrolled for the study. The present study will be conducted in a prospective, randomized manner and it is a double blind study.

Inclusion Criteria

Patients who were included into: 1.ASA grade I and II belonging to American Society of Anaesthesiologists (ASA). 2. Age group 20 to 60 years of either sex. 3. Patients undergoing general surgery requiring direct laryngoscopy and intubation. 4. Willing to give consent.

Exclusion Criteria

- Patients who were excluded from the study:
- Anticipated difficult intubation (Mallampati-grade 3-4) e.g. short neck, buck teeth, micrognathia.
- Oropharyngeal pathology e.g. haematoma, abscess, tumors and tissue disruption.
- Low pulmonary compliance or high airway resistance e.g. chronic bronchitis, bronchial asthma, interstitial disease.
- History of cardiovascular disease e.g. ischaemic heart disease, hypertension.
- Known drug allergy.
- Chronic renal failure.
- Alcohol or drug abuse.
- Pregnancy.
- Edentulous patient and patient with loose teeth.
- Risk of regurgitation and aspiration e.g. H/O gastro-esophageal reflux and hiatus hernia.
- Drugs- Antihypertensives, Pregabalin, Gabapentin, sedatives or antidepressant drugs.
- Athletes.
- Known neurological disease and autonomic neuropathy.
- BMI $\geq$ 30 kg/m^2.

Patients were divided into groups of 20 each.

- **Group PL:** Comprising of 20 patients received oral Placebo in the form of sugar tablets one hour before intubation.
- **Group PG:** Comprising of 20 patients received oral Pregabalin (Tab. Gabanext 150 mg, Glenmark) one hour before intubation.
- The premedication, induction agent and muscle relaxant to facilitate intubation was standardized for both the groups. Ringer Lactate infusion was given for surgery with 18G cannula. Patients were preoxygenated with 100% oxygen for 3 minutes and attached to Non invasive Blood Pressure Monitor, Electrocardiographic leads and Pulse Oxymeter probe. Ondansetron 4 mg was given intravenously just before induction. Patients were induced by injection Propofol (2mg/kg body weight) followed by Succinyl choline 2 mg /Kg. All patients in both PG and PL group were ventilated with 100% Oxygen for 60 Seconds before intubation. The time taken for intubation was not allowed to exceed 20 seconds (those needed more than 20 seconds were excluded from the study).Anaesthesia was maintained with Injection Vecuronium bromide 0.1mg/kg top-up doses.Intermittent positive pressure ventilation with nitrous oxide and oxygen was used in the ratio of 66.0%: 33.0%. All patients were under circle absorber system connected to the Drager Fabius plus workstation.
- Surgery was not allowed to commence till the recordings was completed which would be around ten minutes. After the surgical procedure was over, patient was reversed as per calculated doses of injection Neostigmine (0.05mg/kg) and Glycopyrrolate (0.01mg/kg).All the patients were followed in the post-operative period.
- Duration of the study was 1 year and was self funded. Informed consent for the study was obtained from the subjects.

The parameters recorded

1. Heart Rate.
2. Systolic Blood Pressure.
3. Diastolic Blood Pressure.
4. Mean Arterial Pressure.
5. Oxygen Saturation.

The recordings noted were- Pre-Operative (Basal value) just before the study drug, Just after premedication, Just after Intubation and then 1, 3, 5 8 and 10 minutes after intubation.

STATISTICAL ANALYSIS

All data were presented as mean±standard deviation and were analysed by student's 't' test (independent samples 't' test),Chi-square test and Fisher's exact test whenever applicable. A 'P' value <0.05 was considered statistically significant. The package SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

RESULT

The demographics like age, gender and ASA grades were comparable in both the groups (p>0.05) (Table 1). The increase in HR was found to be insignificant in both groups but the increase in HR was lesser in Pregabalin 150 mg group (Table 2). A significant attenuation in mean SBP, DBP and MAP were observed in Group-PG immediately after intubation, at 1 and 3 minutes. The mean SBP, DBP and MAP were returned to their baseline value significantly earlier in Group PG (3 min) when compared to Group PL (5min) (Table 3,4,5).

Parameters	Group PL (n=20)	Group PG (n=20)	p-value
Mean Age in years	39.5±7.21	37.8±5.84	0.319
Gender (M/F)	9/11	12/08	0.584
ASA (I/II)	12/08	13/07	0.592
Mean Duration of intubation (seconds)	15.32±11.1	16.4±10.5	0.700

Table-1: Demographic profile and duration of intubation

Time Interval	Group PL (n=20)	Group PG (n=20)	p-value
Baseline	84.36±10.48	84.03±9.87	0.901
Just after premedication	86.5±10.23	84.7±8.49	0.461
Just after intubation	93.6±9.7	92.4±9.1	0.623
At 1 min	94.9±8.6	93.2±7.7	0.423
At 3 min	92.9±8.8	90.4±7.9	0.252
At 5 min	89.6±7.1	87.9±6.3	0.331
At 8 min	83.7±6.3	82.4±5.2	0.387
At 10 min	81.1±5.9	79.6±4.7	0.281

Table-2: Comparison of mean HR (bpm) in two groups

Time Interval	Group PL (n=20)	Group PG (n=20)	p-value
Baseline	124.3±8.8	122.4±7.6	0.374
Just after premedication	119.7±7.9	119.2±6.5	0.789
Just after intubation	135.3±9.7	129.6±7.3	0.013
At 1 min	129.8±7.5	126.1±6.2	0.041
At 3 min	125.7±6.1	122.2±5.1	0.019
At 5 min	122.6±5.8	121.1±4.8	0.279
At 8 min	119.5±4.9	118.4±4.3	0.359
At 10 min	119.8±3.6	119.1±3.1	0.423

Table-3:- Comparison of mean SBP (mmHg) in two groups

Time Interval	Group PL (n=20)	Group PG (n=20)	p-value
Baseline	79.6±7.3	78.8±6.4	0.653
Just after premedication	81.3±6.4	79.1±5.3	0.152
Just after intubation	89.2±6.9	84.7±4.8	0.004
At 1 min	84.3±5.2	82.1±4.2	0.045
At 3 min	81.8±5.0	79.2±4.1	0.031
At 5 min	78.3±4.6	77.9±3.4	0.703
At 8 min	77.1±4.1	76.4±3.7	0.490
At 10 min	76.7±3.6	76.9±3.9	0.837

Table-4: Comparison of mean DBP (mmHg) in two groups

Time Interval	Group PL (n=20)	Group PG (n=20)	p-value
Baseline	94.8±6.9	93.9±5.8	0.575
Just after premedication	95.4±6.4	94.3±5.4	0.474
Just after intubation	104.3±7.1	98.5±5.9	0.001
At 1 min	101.1±6.2	96.7±5.1	0.004
At 3 min	96.6±5.4	94.4±4.7	0.097
At 5 min	93.3±4.8	92.6±4.2	0.550
At 8 min	91.4±4.2	90.6±3.9	0.447
At 10 min	90.3±3.8	90.1±3.6	0.835

Table-5: Comparison of mean MAP in two groups

DISCUSSION

Attenuation of the hemodynamic response to laryngoscopy, intubation, anxiolysis and peri-operative sedation require different pharmacological agents for each individual action.[5] GABA analogs such as Pregabalin and Gabapentin are known for their multimodal effects like anxiolysis, sedation peri-operative analgesia, attenuation of hemodynamic responses to laryngoscopy and intubation etc. in various clinical studies.[6] Pregabalin is structurally related to GABA which inactivates GABA receptors and acts by decreasing the synthesis of the neurotransmitter Glutamate.Thus it acts as an analgesic, anxiolytic, anticonvulsant, and maintains hemodynamic stability throughout perioperative period.[7]

In our study although the increase in HR was found to be insignificant in both groups but the increase was lesser in Pregabalin 150 mg group which showed that Pregabalin 150 mg provided an adequate anxiolysis and analgesia with acceptable levels of sedation which prevent the rise of mean HR during laryngoscopy and endotracheal intubation and immediately thereafter. Our results are in concordance with the study of Rastogi B et al[8] who compared placebo (Group-I), Pregabalin 75 mg (Group-II) and Pregabalin 150 mg (Group-III), given 1h before the induction of anaesthesia and they observed that HR was increased in all groups

immediately after laryngoscopy and intubation, but increase was least in Pregabalin 150 mg ($p>0.05$) while statistically significant attenuation of MAP was seen in Pregabalin 150 mg. It might be because of effective analgesia and the adequate sedation by Pregabalin 150 mg. A previous study by Gupta K et al[9] showed statistically significant attenuation of MAP with oral Pregabalin 150 mg 1h prior to the surgery with no significant change in HR. Our findings are different from Eren G et al[10] in which there was a significant decrease in HR and MAP in Pregabalin 150 mg after laryngoscopy and intubation. The probable reason might be the use of different premedicants in their study. However, in contrast Meena R et al[11] reported the significant increase in heart rate after the airway instrumentation in the Pregabalin 150 mg group.

A significant attenuation in mean SBP, DBP and MAP were observed in Group-PG immediately after intubation at 1 and 3 min. The mean SBP, DBP and MAP were returned to their baseline value significantly earlier in Group PG (3 min) when compared to Group PL (5min). Our findings are similar to study conducted by Bhandari G et al[12]and Chakraborty R et al[13] who compared the oral Pregabalin 150 mg and placebo received 1 h prior to the surgery and they observed the significant attenuation of SBP, DBP and MAP in Pregabalin 150 mg group following the laryngoscopy and endotracheal intubation. Although increase in HR was less in Pregabalin group during laryngoscopy and intubation but it was in significant. Salman E et al[14] compared oral Pregabalin 150 mg and placebo received 1 h prior to surgery showed statistically significant attenuation in SBP, DBP and MAP in Pregabalin 150 mg group after induction, at intubation and 1 min post intubation. No significant difference in HR was noted at any time interval between two groups. Allu H et al[1] also observed the similar trends of changes in SBP, DBP and MAP who compared Pregabalin 150 mg and placebo given 1 h prior to induction of anaesthesia.

The effect of Pregabalin on the hemodynamic response to laryngoscopy and tracheal intubation might be explained by its inhibitory effects on membrane voltage gated calcium channels. Pregabalin, binds strongly and selectively to the alpha 2 delta subunit of hyper excited voltage gated calcium channels. It modulates the release of excitatory neurotransmitters in hyperexcited neurons and restoring them to normal physiologic state by reducing calcium influx at nerve terminals.

CONCLUSION

Oral Pregabalin in a dose of 150mg one hour prior to the surgery is safe and effective premedicant in attenuating the pressor response among the patients requiring laryngoscopy and intubation. The effect is more prominent with blood pressure components of hemodynamic response than heart rate. However, rise in the heart rate is lower with Pregabalin than placebo and trend of heart rate response is much better and predictable with Pregabalin.

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