

# A Comparative Study of Oral Pregabalin versus Gabapentin on Hemodynamic Responses to Laryngoscopy and Endotracheal Intubation under General Anaesthesia

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**Abstract:** *Background and Aim-* Laryngoscopy and endotracheal intubation are potent stimuli that can induce increased sympathetic activity leading to tachycardia, hypertension and dysrhythmias. Various drugs and methods have been tried to obtund this response. To obtain ideal drugs, studies still continue. We compared the efficacy of pregabalin and gabapentin to attenuate the pressor response during laryngoscopy and intubation. *Method:* Total 120 patients of ASA grade I&II scheduled for elective surgery under general anaesthesia, were randomized into three groups. Group A received oral pregabalin 150mg 2 hrs prior to surgery, group B received oral gabapentin 800mg 2 hrs prior to surgery and group C received oral placebo 2 hrs prior to surgery. Heart rate and blood pressure (SBP, DBP &MAP) were recorded at baseline, before induction, before intubation, during laryngoscopy, 0, 1, 3, 5, and 10 minutes after intubation. *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 was better than gabapentin in suppressing the pressor response. *Conclusion:* Pregabalin appears to be better than Gabapentin for control of haemodynamic response to laryngoscopy and intubation. Both drugs have anti-nociceptive effects that may be beneficial for controlling post-operative pain.

**Keywords:** Pregabalin, Gabapentin, hemodynamic changes and endotracheal intubation

## 1. Introduction

Endotracheal intubation is considered to be the gold standard in airway management during general anaesthesia and in critical care settings. As such endotracheal intubation is a safe and common practice in modern day anaesthesia but it can induce increased sympathetic activity leading to tachycardia, hypertension and dysarrhythmias. When laryngoscopy and intubation is carried out, there is mechanical irritation of stretch receptors situated in the respiratory tract leading to reflex hemodynamic responses through a sympathetic reflex. The pressor response to laryngoscopy and endotracheal intubation has been described by Reid and Brace in 1940.<sup>1</sup> Tracheal intubation causes a reflex increase in sympathetic activity that may result in hypertension, tachycardia, and arrhythmia. A change in plasma catecholamine concentrations also has been demonstrated to be a part of the stress response. This autonomic changes are variable, transitory, unpredictable and well tolerated in ASA I & II patients, but it may be detrimental in patients with pre-existing hypertension, Cardiac disease, and cerebral pathologies.<sup>2,3</sup>

Various non-pharmacological methods like smooth & gentle intubation with a shorter duration of laryngoscopy, insertion of LMA in place of endotracheal intubation has been tried.<sup>4</sup> In pharmacological methods a number of drugs have been used. These include lidocaine spray, IV lignocaine and Opioids, Propranolol, isosorbidedinitrate, Calcium channel blockers, Esmolol, fentanyl, Magnesium sulphate, Clonidine, Pregabalin, Gabapentin, and dexmedetomidine.<sup>5</sup>

<sup>18</sup>None of the above approaches or agents has been proved to be ideal so the need for an ideal agent to obtund the stress responses to laryngoscopy & intubation is still continuing.

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 pregabalin as premedication to attenuate pressor response to laryngoscopy and intubation.

## 2. Subject and Methods

After approval from the institutional ethical committee 120 patients with study eligibility of ASA grade I and II, aged 30–60 years, weighing 40 to 70 kg, posted for elective surgery under general anaesthesia were selected and randomly allocated into three groups of 40 patients each by using 'Chit in box' technique.

**Group (A) (n=40)** - patients have received oral tab Pregabalin 150mg 2 hrs prior to surgery.

**Group (B) (n=40)** - patients have received oral tab. Gabapentin 800mg 2 hrs prior to surgery.

**Group (C) = Control group (n=40)** - patients have received oral tab. Placebo 2 hrs prior to surgery.

Patient with major organ dysfunction (hypertension, cerebrovascular disease, ischemic heart disease, arrhythmias, shock), on medications (like hypnotics, narcotic analgesics,

$\alpha_2$  agonists, calcium channel blockers,  $\beta$  blockers) and with reactive airway diseases, having known allergy to anaesthetic agents used in study, with anticipated difficult intubation, pregnancy/ lactation and in whom intubation was done after more than 1 attempt or more than 20 seconds were excluded from the study.

Pre-anaesthetic checkup was done in all patients as per institutional protocol. Written informed consent was taken for performance of general anaesthesia after complete explanation about the study protocol. 120 patients were randomly allocated into 3 groups of 40 each. Group A received Pregabalin 150mg, Group B received Gabapentin 800mg and Group C received placebo orally with sips of water as premedication 2 hours prior to induction of general anaesthesia. Anaesthesiologist who was not aware of the study protocol and was not participating in study was the observer.

On arrival in the operation theatre fasting status, written informed consent and PAC was checked. All the routine monitors were attached and the preoperative baseline vitals i.e heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP), SpO<sub>2</sub> & ECG were noted. Intravenous line was secured, and i.v. fluid Ringer Lactate started.

**Premedication**-Patients were premedicated with inj Midazolam 1mg iv, inj. Glycopyrolate 0.2mg iv, and inj. ondansetron 4mg iv, Inj. Fentanyl 2 mcg/kg iv prior to induction.

Patients were pre oxygenated with 100 % O<sub>2</sub> for three minutes. Induction was done with inj. Propofol 2mg/kg iv followed by inj. atracurium 0.5 mg/kg iv and ventilated with 100% oxygen for 3 minutes. Data were collected just before intubation. Direct laryngoscopy was done and patient was intubated with appropriate size endotracheal tube. Bilateral air entry was checked. Tube was fixed at the angle of mouth by durapore. Patients intubated after more than 1 attempt or more than 20 seconds duration were excluded from the study.

Data were collected at baseline, before induction, before intubation, during laryngoscopy, 0, 1, 3, 5, and 10 minutes after intubation.

**Maintenance**-Surgery was allowed to commence after 10 minutes of intubation & anaesthesia was maintained with 60% Nitrous Oxide and 40% Oxygen, 0.6-1% isoflurane and inj. Atracurium 0.1 mg/kg i.v. SOS.

**Reversal**- At the end of the surgery patient was reversed with Inj. Neostigmine (0.05mg/kg i.v.) and Inj. Glycopyrrolate (0.01mg/kg i.v.). Extubation was done after proper suction, and when patient was fulfilling the criteria for extubation. Patient was shifted to recovery room. In recovery room patient was observed for any side effects.

### 3. Statistical Analysis

Statistical analysis was performed with the SPSS, version 21 for Windows statistical software package (SPSS inc., Chicago, IL, USA). All the quantitative data were summarized in the form of Mean  $\pm$  SD. The Categorical data was presented as numbers (percent) and were compared among groups using Chi square test. The quantitative data was presented as mean and standard deviation and were compared by students t-test. The levels of significance and  $\alpha$  - error were kept 95% and 5% respectively, for all statistical analyses. P values <0.05 were considered as Significant (S) and P value > 0.05 as statistically Non Significant (NS).

### 4. Results

A total 120 patients were induced into the study. There were no statistically significant differences in the demographic parameters such as Age, Sex, Weight, Height, ASA physical status, Mallampatti grading and duration of laryngoscopy among the study groups. The patients were in the age group of 30-60yrs, in weight group of 40-70kgs. In our study, there was slight male preponderance.

**Table 1: Demographic parameters**

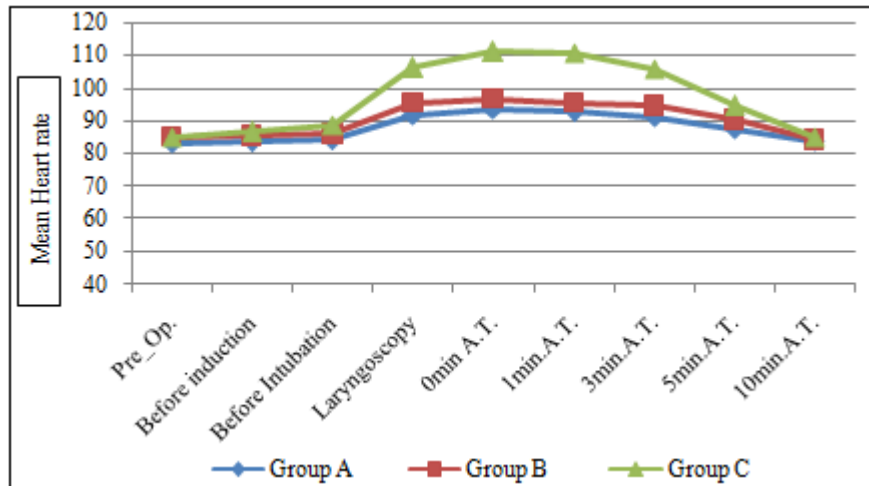
Particulars	Group A	Group B	Group C	P value
Age(years) (Mean $\pm$ SD)	39.98 $\pm$ 8.73	43.95 $\pm$ 11.77	43.58 $\pm$ 7.80	0.127 (NS)
Sex(male:female)	23:17	27:13	25:15	0.109(NS)
Weight(kg) (Mean $\pm$ SD)	55.80 $\pm$ 7.03	59.18 $\pm$ 7.26	58.93 $\pm$ 7.16	0.067(NS)
Mallampatti grading(I:II)	38:2	39:1	38:2	0.815 (NS)
ASA(I:II)	37:3	36:4	38:2	0.702 (NS)
LaryngoScopy time sec (Mean $\pm$ SD)	17.17 $\pm$ 1.61	17.12 $\pm$ 1.75	16.87 $\pm$ 1.82	0.710 (NS)

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-93.42, Group B-96.65 and Group C-111.02 was seen at 0 min and maximum MAP was 100.32, 102.4 and 110.17 in Group A, B and C respectively at 0 min.

The difference between the control and the gabapentin and pregabalin was found to be significant with a p value of <0.05 at 0, 1, 3 and 5 min after 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 laryngoscopy but was not statistically significant.

**Table 2: Mean Heart Rate at Various Time Intervals**

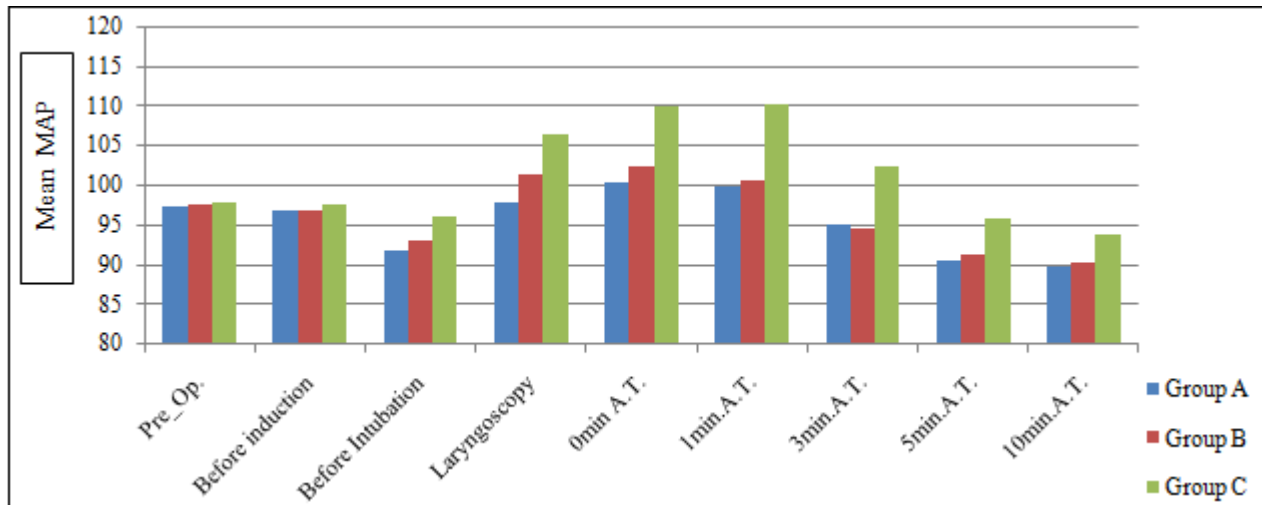
Time interval	Group A	Group B	Group C	P value
	Mean±SD	Mean±SD	Mean±SD	
Pre_Op.	83.07±12.46	84.85±7.24	85.07±7.39	0.579 (NS)
Before Induction	83.52±11.95	85.32±7.13	86.5±7.51	0.344 (NS)
Before Intubation	84.02±11.63	85.92±7.13	88.7±6.88	0.062 (NS)
Laryngoscopy	91.72±13.41	95.4±8.35	106.1±8.18	0.0003 (S)
0 min. post intubation	93.42±11.82	96.65±5.30	111.02±7.62	0.0003 (S)
1 min. post intubation	92.65±10.47	95.32±5.47	110.72±8.18	0.0002(S)
3 min. post intubation	91.17±12.56	94.5±7.52	106.00±8.02	0.0002 (S)
5 min. post intubation	87.5±16.38	90.22±7.73	94.4±8.51	0.029 (S)
10 min. post intubation	83.57±12.24	84.00±7.14	84.95±7.20	0.790 (NS)



**Figure 2: Mean Heart Rate at Various Time Interval**

**Table 3: Mean MAP at Various Time Interval**

Time interval	Group A	Group B	Group C	P value
	Mean±SD	Mean±SD	Mean±SD	
Pre_Op.	97.3±4.38	97.45±3.21	97.8±7.42	0.911 (NS)
Before Induction	96.75±4.62	96.87±3.02	97.5±7.68	0.805 (NS)
Before Intubation	91.65±8.83	93.1±5.79	96.12±6.85	0.022 (S)
Laryngoscopy	97.75±4.18	101.47±11.23	106.47±6.46	0.0003 (S)
0 min. post intubation	100.32±4.15	102.4±10.08	109.82±7.78	0.0003 (S)
1 min. post intubation	99.75±3.93	100.65±10.61	110.17±7.38	0.0002 (S)
3 min. post intubation	95.0±4.18	94.47±8.92	102.3±10.25	0.0003 (S)
5 min. post intubation	90.55±9.01	91.37±9.68	95.8±9.00	0.026 (S)
10 min. post intubation	89.85±8.61	90.17±8.67	93.9±9.00	0.045 (S)



**Figure 3: Mean MAP at Various Time Intervals**

The mean oxygen saturation remained above 98% in these groups at all the point of study. There were no significant

differences in oxygen saturation among these groups. There was no respiratory depression in these groups. There was no drop in oxygen saturation in these groups.

There was no incidence of ECG abnormality, hypotension, bradycardia in all groups but unsteadiness and nausea were found in 5% of case in pregabalin group post-op.

Thus pregabalin & gabapentin were found to be effective in controlling HR, SBP, DBP, & MAP as compared to control group.

## 5. Discussion

Most of the general anaesthesia procedures in modern anaesthesia practice are carried out with endotracheal intubation. The sympathoadrenal activation associated with laryngoscopy and tracheal intubation causes the rise in arterial blood pressure, tachycardia and dysrhythmias. It may have deleterious respiratory, neurological and cardiovascular effects and is more marked in hypertensive patients<sup>1-3,10</sup>. If no measure are taken to prevent haemodynamic response then heart rate may increase 26-66% & SBP can increase from 36-45%. The achievement of a smooth induction with minimal reflex haemodynamic response during laryngoscopy and endotracheal intubation remains an important anaesthetic goal. To obtund these adverse effects by various pharmacological and non-pharmacological methods is main concern of anaesthesiologist.

In various studies, pregabalin and gabapentin have been compared with other drugs separately and there are very few studies indicating comparison of pregabalin and gabapentin, therefore present study was undertaken to evaluate and compare both the drugs in attenuating the haemodynamic response to laryngoscopy and endotracheal intubation in normotensive patients undergoing elective surgery.

We have done this study to compare the effects of pregabalin and gabapentin on haemodynamic responses to endotracheal intubation to find a better drug in this respect.

**Pregabalin** binds to  $\alpha 2\delta$  (alpha-2-delta) subunit of the voltage-dependent calcium channel in the central nervous system. Pregabalin decreases the release of neurotransmitters including glutamate norepinephrine, substance P and calcitonin gene-related peptide. However, unlike anxiolytic compounds (e.g., benzodiazepines) which exert their therapeutic effects through binding to GABA, pregabalin neither binds directly to these receptors nor augments GABA currents or affects GABA metabolism. The half-life for pregabalin is 6.3 hours.

Similarly, **Gabapentin** which is a structural analogue of the neurotransmitter gamma-aminobutyric acid is being used since 1993 as an anticonvulsant drug is also effective in controlling neuropathic pain. It acts by selective activation of heterodimeric GABA<sub>B</sub> receptors. The peak onset of action is 2-4 hours; elimination half life is 5-7 hours and is unaltered by single dose<sup>18,26</sup> or following multiple dosing.<sup>17</sup>

In our study both Pregabalin & Gabapentin were found to be effective in controlling **Heart rate** to laryngoscopy & intubation as compared to control group. During laryngoscopy there was increased heart rate in all groups. It increased from 84.85  $\pm$  7.24 bpm to 95.4  $\pm$  8.35 bpm (12.43%) in group B as compared to group A in which it increased from 83.07  $\pm$  12.46 bpm to 91.72  $\pm$  13.41 bpm (10.41%), whereas in control group it increased from 85.07  $\pm$  7.39 bpm to 106.1  $\pm$  8.18 bpm (24.72%). When compared to gabapentin, pregabalin had very slight rise in HR to laryngoscopy but was not statistically significant. Increase in HR from baseline was significant in these groups after intubation. In control group rise was 30.50% at 0 min. post intubation as compared to group A (12.45%) & group B (13.90%) which was significant (p<0.05) but not significant between group A & group B (p>0.05). The heart rate was below base line at 10 min. post intubation.

In our study also the effect of pregabalin (150gm) on HR was similar to the study done by **Namratha et al.**<sup>29</sup> **Mimis D & colleagues**<sup>19</sup> observed complete attenuation of HR with gabapentin 800mg given 1 hr before surgery. While another author Fassoulakiet al<sup>20</sup> didn't observe any effect on change in HR but attenuation of pressor response to laryngoscopy even with higher dose (1600mg) of gabapentin, this was due to divided dose.

The **SBP** elevation at laryngoscopy & intubation was significantly less than that compared to control group (<0.05). Both groups (group A & B) were comparable & there was no significant difference between them. The difference was significant in both pregabalin & control group and gabapentin & control group. Hence both pregabalin and gabapentin are found to be effective in controlling the SBP as compared to control group. Our results are similar to the study of **Indira Kumari et al**<sup>25</sup> and **Mrashi SM et al.**<sup>24</sup>

The **DBP** elevation was comparable in both groups & there was no significant difference between group A and B. The DBP elevation was controlled in group A and B compared to control group (<0.05) at laryngoscopy & intubation. There was significant difference between group A & control group and group B & control group. Hence both pregabalin and gabapentin are effective in controlling the DBP as compared to control group. Our results are similar to the study of **K Gupta et al**<sup>27,28</sup> and **Archana Raichurkar et al.**<sup>30</sup>

The **MAP** elevation was significantly less than that compared to control group (<0.05) at laryngoscopy & intubation. During laryngoscopy it increased from 97.30  $\pm$  4.38 mmHg to 97.75  $\pm$  4.18 mmHg (0.46%) in group A as compared to group B in which it increased from 97.45  $\pm$  3.21 mmHg to 101.47  $\pm$  11.23 mmHg (4.12%) whereas in group C it increased 97.8  $\pm$  7.42 mmHg to 106.47  $\pm$  6.46 mmHg (8.86%). When compared to gabapentin, pregabalin had very slight rise in MAP to laryngoscopy. After intubation there was increase in MAP in group A & group B at 0, 1 min. and in group C at 0, 1, 3 min. In control group rise was 11.26% at 0 min. post intubation as compared to group A (2.51%) & group B (3.28%) which was significant (p<0.05). The MAP was near baseline at 3 min. post intubation in all groups. Our results are similar to the study of **Kiran S et al**<sup>23</sup> and **Faheim SM et al.**<sup>22</sup>

Thus pregabalin & gabapentin were found to be effective in controlling HR, SBP, DBP, & MAP.

## 6. Conclusion

It is concluded from our study that oral Pregabalin (150mg) and Gabapentin (800mg) administered 2 hrs prior to surgery controls the haemodynamic response to laryngoscopy and endotracheal intubation. Pregabalin is better than gabapentin in attenuating pressor response. These drugs are safe, simple, effective, economical, easy to administer & no side effects. Both drugs have anti-nociceptive effects that may be beneficial for controlling post-operative pain.

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