



## Effect of Oral Pregabalin on Hemodynamic Stress Response to Laryngoscopy and Endotracheal intubation

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### Abstract

**Background:** Direct laryngoscopy and endotracheal intubation are potent stimuli that initiate a hemodynamic response leading to increase in heart rate and blood pressure. This response can be attenuated by appropriate premedication, smooth induction and rapid intubation. The present study evaluated the efficacy of oral pregabalin in attenuation of hemodynamic stress response.

**Materials and Methods:** A total of 60 patients belonging to ASA PS 1 and 2 categories were divided into two equal groups. Group I received pregabalin 150mg capsule and group II received placebo one hour prior to surgery and were assessed for preoperative sedation, hemodynamic changes after laryngoscopy and endotracheal intubation along with post-operative side effects.

**Results:** Pre-operative sedation levels were higher in group I and caused statistically significant reduction in heart rate and mean arterial pressure at 1,3,5 and 10 minutes after laryngoscopy and endotracheal intubation. The systolic blood pressure values recorded at 1, 3 and 5 minutes post intubation in the pregabalin group was significantly lower than that in the control group. Diastolic blood pressure recorded at 1 min after intubation was significantly lower than the control group, although no difference was observed at 3 and 5 minutes after intubation.

**Conclusion:** 150 mg of oral pregabalin administered one hour before surgery is a simple and safe method for the attenuation of the hemodynamic response to laryngoscopy and intubation.

**Keywords:** Hemodynamic response, intubation, laryngoscopy, pregabalin, sedation.

### Introduction

Laryngoscopy and endotracheal intubation are associated with a transient hemodynamic stress response characterized by hypertension and tachycardia. In 1940, Reid and Brace first described the hemodynamic stress response to

laryngoscopy and intubation.<sup>1</sup> The intensity of this response varies with depth of anesthesia, duration of laryngoscopy and intubation and patient factors.<sup>2,3,4</sup> The effect is transient, occurring 30 sec after initiation and lasting for less than 10 minutes<sup>5</sup>. An increase in systolic blood pressure

(SBP), mean arterial pressure (MAP) and heart rate (HR) is documented.<sup>5,6</sup> These changes are deleterious to patients with co-morbidities leading to myocardial ischemia, infarction, cardiac failure, pulmonary edema and cerebral hemorrhage (Kovac<sup>7</sup> Hassen<sup>8</sup> and Stone et al<sup>9</sup>).

Methods employed to attenuate the response include deepening the plane of anesthesia, treatment with vasodilators<sup>10,11</sup> adrenergic receptor blockers<sup>9</sup>, calcium channel blockers<sup>10</sup> and opioids.<sup>12,13</sup> Conventionally, IV lignocaine 1.5mg/kg administered 90 sec before intubation is employed. Recent studies have indicated that oral pregabalin may be effective in attenuating the hemodynamic response. Originally introduced as an antiepileptic drug, it possesses analgesic, anticonvulsant and anxiolytic effect.<sup>14,15,16,17</sup> The aim of the present study was to determine the efficacy and safety of pregabalin in preventing hemodynamic changes during laryngoscopy and endotracheal intubation.

### Materials and Methods

This prospective randomized single-blind study was carried out on 60 patients of both genders who were posted for elective surgery under general anesthesia with endotracheal intubation. Approval of the Institutional Ethical Committee was obtained and informed consent was taken from the participants prior to the procedure. Patients with ASA PS1 and 2 in the age group of 18-60 years posted for elective surgery were included. Those with anticipated difficult intubation, uncontrolled hypertension, hypotension, heart rate of <50/min, body mass index of >25 and consumption of antidepressants, sedatives and hypnotics were excluded from the study.

After routine pre-anesthetic checkup, eligible patients were randomly allocated to either of the two groups. Patients were kept nil per orally 8 hours prior to the surgery. Both groups received T. alprazolam 0.25mg and T. pantoprazole 40mg at 10 pm on the previous day and 6 am on the day of surgery.

In the premedication room, baseline values of B.P and heart rate were recorded. One hour before anesthesia, group I patients were administered 150mg oral pregabalin and group II was given the vitamin B capsule (control). Patients were monitored in the premedication room and assessed at 15, 30, 45 and 60 minutes for the level of sedation using Ramsay scale.<sup>18</sup>

One hour after giving the oral drug, patients were taken to the operation theatre and monitors attached – ECG, noninvasive blood pressure monitors and pulse oximeter. Heart rate and blood pressure values were recorded. Intravenous access was obtained and crystalloid infusion started.

All patients were anaesthetized using the standard anesthetic procedure. Patients were administered inj. midazolam 1mg IV, inj glycopyrrolate 0.2mg IV, inj. ondansetron 0.08 mg/kg IV and inj morphine 0.1mg/kg IV. Preoxygenation was done with 100% oxygen for 3 min and then induced with IV propofol 2mg/kg. Both groups were administered IV vecuronium 0.1 mg/kg. Bag and mask ventilation was given for 3 min with 100% O<sub>2</sub> and 0.6% isoflurane. Preservative free 2% lignocaine 1.5mg/kg was administered IV to both groups 90 seconds prior to intubation.

Direct laryngoscopy was done by a senior anesthetist using MacIntosh laryngoscope and appropriate sized cuffed endotracheal tube was introduced and the position confirmed and tube secured. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were recorded at 1, 3, 5 and 10 min after intubation. Intermittent positive pressure ventilation was given using nitrous oxide and oxygen in 4:2 ratios. No other drug was administered for the next 10 min. The surgical procedure was allowed to start only after 10 minutes.

Muscle relaxation was maintained with intravenous vecuronium and anaesthesia supplemented with isoflurane. Rescue doses of ephedrine and atropine were kept ready to tackle hypotension and bradycardia respectively.

At the end of surgery, patients were reversed using inj. neostigmine 0.05 mg/kg and inj. glycopyrrolate 0.01mg/kg IV. On recovery, patients were shifted to the recovery room and monitored for next 4 hrs. They were also observed for side effects like bradycardia (HR < 20% baseline), hypotension (BP < 20% base line), nausea, vomiting, dizziness, respiratory depression, headache and visual disturbance.

**Statistical Analysis**

The data was entered in Microsoft Excel and statistical analysis done in SPSS version 17.0. Quantitative variables were described using means, standard deviation, median and interquartile range. Qualitative variables were described using percentage distribution. Between groups comparison of quantitative variables were analysed using chi-squared test. P value of 0.05 was taken as the level of significance.

**Results**

The baseline characteristics of the two groups were comparable.

**Heart rate:** The pregabalin group had a significantly lower heart rate (Table 1). At 1 min after intubation, the mean HR of the pregabalin and control groups was 83.8 and 107.3 respectively. The difference was highly significant. The HR was also lower at 3, 5 and 10 min

**Table 1.** Comparison of effectiveness on heart rate and SBP

|          | Heart rate |             | P value | SBP         |             | P value |
|----------|------------|-------------|---------|-------------|-------------|---------|
|          | Group 1    | Group 2     |         | Group 1     | Group 2     |         |
| Baseline | 80.7 ±7.2  | 79.5± 5.6   | 0.486   | 131.7 ±9.9  | 130.9 ±11.6 | 0.785   |
| 1 min    | 83.8 ±7.6  | 107.3 ±9.6  | 0.000   | 132.2 ±13.8 | 148.4 ±15.3 | 0.000   |
| 3 min    | 84.2 ±6.6  | 105.6 ±10.6 | 0.000   | 122.1 ±11.6 | 135.7 ±17.1 | 0.001   |
| 5 min    | 82.0 ±6.9  | 94.2± 6.3   | 0.000   | 119.0 ±11.9 | 125.8 ±12.5 | 0.0034  |

after intubation in the study group. The mean value at 10 min was lower than basal value in the study group whereas it was higher in the control group. This shows that pregabalin effectively attenuated the HR response to laryngoscopy and intubation.

**SBP:** The baseline SBP was comparable in the two groups. The post intubation rise in SBP was significantly lower with pregabalin at 1, 3 and 5 min. Table 1 shows that the SBP was below basal level at 3, 5 and 10 min after intubation. In the control group, the mean values were higher or near basal level.

**DBP:** Mean basal DBP was the same in both groups (Table 2).The post- intubation rise of DBP was significantly lower in pregabalin group at 1 min (P value=0.000) However, there was no statistically significant difference between DBP values at 3, 5 and 10 min.

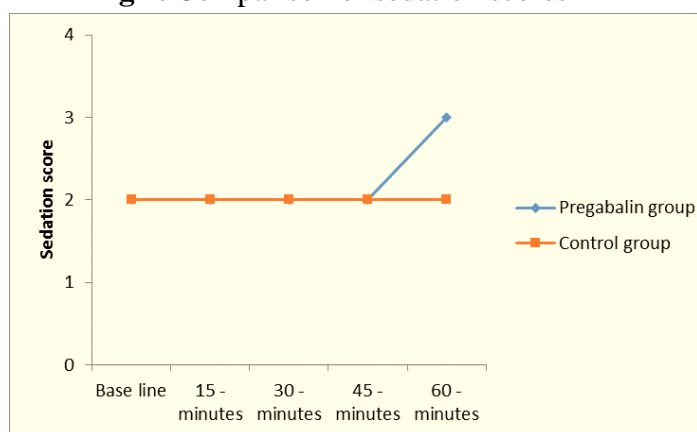
**MAP:** Baseline values of MAP were similar (Table 2). The MAP was lower in the pregabalin group at 1, 3, 5 and 10 min post intubation compared to the controls. The differences were highly significant at 1 and3 min (P=0.000) and significant at 5 and 10 min. The rise in MAP after intubation is thus attenuated.

**Sedation scores:** The patients in the pregabalin group were better sedated than the control group (Fig 1).

|        |           |           |       |             |             |       |
|--------|-----------|-----------|-------|-------------|-------------|-------|
| 10 min | 80.3 ±6.6 | 88.8± 4.9 | 0.000 | 116.7 ±12.1 | 120.5 ±10.1 | 0.193 |
|--------|-----------|-----------|-------|-------------|-------------|-------|

**Table 2.** Comparison of effectiveness on DBP and MAP

|          | DBP       |            | P value | MAP       |            | P value |
|----------|-----------|------------|---------|-----------|------------|---------|
|          | Group 1   | Group 2    |         | Group 1   | Group 2    |         |
| Baseline | 78.1± 6.8 | 78.6±5 .7  | 0.760   | 95.2± 6.7 | 95.8±6 .9  | 0.766   |
| 1 min    | 77.7± 7.8 | 87.1±6 .7  | 0.000   | 95.6± 8.3 | 107.5± 8.1 | 0.000   |
| 3 min    | 73.4± 7.9 | 78.3±1 5.2 | 0.129   | 89.5± 8.0 | 98.9±9 .4  | 0.000   |
| 5 min    | 70.4± 8.2 | 74.6±7 .9  | 0.052   | 86.6± 7.9 | 91.4±8 .5  | 0.026   |
| 10 min   | 68.5± 6.7 | 73.0±7 .0  | 0.014   | 84.4± 7.2 | 88.8±6 .8  | 0.016   |

**Fig 1.** Comparison of sedation scores

## Discussion

Laryngoscopy and endotracheal intubation are an essential part of general anesthesia. They arouse stimuli that induce an intense sympathetic hemodynamic response - an increase in HR and blood pressure, which cause an imbalance in myocardial oxygen demand and supply predisposing to ischemia, infarction and heart failure. While this sympathetic response can normally be tolerated by healthy adults, it may be quite hazardous in patients with compromised cardiovascular function.<sup>19</sup> The necessity to attenuate this response is therefore imperative for safety. Pregabalin is structurally related to the inhibitory mediator GABA and is used in the management of epilepsy, relief of neuropathic pain and post-operative pain.

One of the obvious finding in our study was the sedative effect of pregabalin. Ramsay sedation score showed that patients in the pregabalin group were better sedated at 60 min after administration, compared to the control group.

Bhawna et al achieved a better preoperative sedation with 150 mg pregabalin.<sup>15</sup> A similar study in patients undergoing off-pump coronary bypass graft surgery, did not provide significant difference in the consumption of fentanyl during surgery.<sup>16</sup> In a comparative study on the effect of oral premedication with 150 mg of pregabalin or 200µg of clonidine, the former provided better sedation.<sup>20</sup>

Better sedation reduces psychic stress and this leads to reduction in impulse traffic from the

trachea which might help to reduce the severity of hemodynamic response to intubation. Premedication with pregabalin in our study was found to be effective in preventing the adverse hemodynamic responses to laryngoscopy and intubation. Basal mean levels of HR were the same in control and treatment group. HR of patients who received 150mg pregabalin was significantly lower than the control at 1, 3, 5 and 10 min after intubation. Even at 10 min, HR level remained above basal levels in the control group.

The results of a study by Sunder et al concurred with our findings.<sup>16</sup> Pregabalin 150 mg was given 1 hr before intubation and the HR were lower than that of the control group. Gupta et al also conclude that 150mg of pregabalin attenuates the effect of laryngoscopy and intubation on HR.<sup>20</sup> Bhawna et al however did not observe any advantage for pregabalin regarding HR.<sup>15</sup>

At 1, 3 and 5 min post-intubation, significant lower SBP was recorded in the treatment group. At 10 min, the difference was not significant which might indicate the transient nature of the response. DBP was also modified by pregabalin. At 1 min post-intubation, the DBP was significantly lower than the control group ( $P=0.000$ ). At 3 and 5 min, there was no statistically significant difference.

No rise in MAP was noted for the pregabalin group. The difference of MAP between the control and pregabalin group was highly significant at 1 min ( $P=0.000$ ) and significant at 3, 5 and 10 min after intubation.

Pregabalin thus attenuates the pressor response to laryngoscopy. SBP and MAP are more responsive and DBP response may be very transient and soon returns to normal.

Similar results have been obtained in other studies. Bhawna et al observed a significant reduction in DBP and MAP in subjects given 150mg of pregabalin.<sup>15</sup> There was no change in HR response in the pregabalin group. Patients undergoing laparoscopic cholecystectomy who received pregabalin 1 hour prior to intubation

showed reduction in hemodynamic response.<sup>20</sup> Namratha et al also reported similar effects.<sup>17</sup> The precise mechanism of the hemodynamic response to laryngoscopy and intubation is elusive, but sympathetic nervous system seems to be involved in this response. This results in an increase in HR and blood pressure. The increase in HR occurs during laryngoscopy and intubation while the increase in blood pressure occurs during laryngoscopy.

The hemodynamic response should be attenuated due to the associated risk like myocardial ischemia and cerebral hemorrhage. Tachycardia increases the workload on the heart and its oxygen requirement. Concomitantly diastolic period shortens and coronary perfusion falls.<sup>21</sup> This imbalance may result in ischemia and its consequences especially in those with compromised myocardial function. Myocardial oxygen demand is determined by myocardial wall tension, contractility and heart rate.<sup>22</sup> If MAP is high, the ventricular work increases. If associated with an increase in oxygen demand, strongly contracting myocardium compresses the coronary vessels and reduces perfusion and oxygen availability, contributing to myocardial ischemia.<sup>23</sup>

The period during which intubation is performed is crucial.<sup>21,23,24</sup> Slogoff and Keats<sup>24</sup> reported that most ischemic episodes during anesthesia are associated with intubation and surgical stimulation. Our study confirms that administration of pregabalin attenuates both the increase in heart rate and the pressor response to laryngoscopy and intubation.

Pregabalin is chemically (S) 3 (amino methyl) 5 methyl hexanoic acid. Attenuation of the cardio acceleratory and pressor responses may be related to inhibition of release of inhibitory neurotransmitters in the medullary cardiovascular centres and/or at peripheral nerve endings. The effect on sedation may also be related to inhibition of neurotransmitter release in the sleep related area of the brain.

Pregabalin does not bind to GABA receptors and is superior to many other pharmacological agents

with respect to attenuation of hemodynamic responses to laryngoscopy and intubation. IV lignocaine will occasionally blunt the pressor response, but not the HR response.<sup>14</sup> Topical routes have been tried, but few studies have shown convincing benefit.<sup>25</sup> High doses of fentanyl completely blunts the response but is associated with significant side effects.<sup>7</sup> In some studies, though the pressor response was attenuated with smaller doses, there was no change in HR.<sup>12,26</sup> Alpha 2 agonists like clonidine given 60-90 minutes prior to surgery can be beneficial, but the risk of bradycardia was always present. Gupta et al who compared the effect of 200 ug of clonidine and pregabalin recorded that although clonidine attenuated the hemodynamic response, it was less sedative.<sup>20</sup>

In our study, four patients in the pregabalin group developed hypotension and dizziness. There was no bradycardia, respiratory depression, headache or visual disturbances in any of the patients during the first four hours after recovery from anesthesia. An added advantage was its adequate absorption by oral route.

**In conclusion**, pregabalin could be an answer to the long search as safe agent to attenuate the adverse hemodynamic effects to laryngoscopy and intubation. Further studies to look into its effect on cardio respiratory function is in order. Interaction with anesthetic drugs and dose-effect relationship could also be studied.

## References

1. Reid L C, Brace D.E Irritation of the respiratory tract and its reflex effect upon the heart. *Sur Gynaec Obstet.* 1940; 70: 157-162.
2. Vohra A, Kumar S, Charlton . Effects of diabetes on the cardiovascular responses in induction of anesthesia and tracheal intubation *Br. J Anaesth* 1993 Aug, 71(2): 258-61
3. Low JM, Harvey JT, Prys -Roberts. Studies of anesthesia in relation to hypertension VII: Adrenergic responses to



- laryngoscopy. Br. J Anaesth. 1986 May; 58: 471-7.
4. King BD, Harris LC. Reflex circulatory responses to direct laryngoscopy and tracheal intubation performed during general anesthesia. *Anesthesiology* 1951 Sep 12: 556-66
  5. Gupta A, Wakhloo. R, Gupta V, Kapoor B. Comparison of Esmolol and Lignocaine for Attenuation of Cardiovascular Stress response to Laryngoscopy and Endotracheal Intubation 2009 ;11: (2):0-3.
  6. Perkins ZB, Gunning M Crilly. J Lokey D, O' Brien B. The hemodynamic response to prehospital RSI in injured patients. *Injury Elsevier Ltd.* 2013; 44:(5)618 -23.
  7. Kovac L. Controlling the hemodynamic response to laryngoscopy and endotracheal intubation. *J. Clin Anesth.* 1996 Feb 8(1): 63-79.
  8. Hassan HG, El Sharkawy, Renk H, Mansour G. Fouda A. Hemodynamic and catecholamine stress response to laryngoscopy with Vs without endotracheal intubation. *Acta Anesthesiology Scand.* 1991;35:442-7.
  9. Stone JG, Foex P, Sear JW, Johnson LL, Kamebatta H, Triner L. Myocardial Ischemia in untreated hypertension patients. Effect of a single dose of beta adrenergic blocking agent. *Anesthesiology* 1988; 8:495-500.
  10. James MF, Beer RE, Esser JD. Intravenous magnesium sulfate inhibits catecholamine release associated with tracheal intubation, *Anesth.Analg.*1989; 68(6):772-6.
  11. Puri GD, Marudhachalam KS, Chari P, Suri RK. Effect of magnesium sulfate on hemodynamics and its efficacy in attenuating the response to endotracheal intubation in patients with Coronary Artery disease. *Anesth Analg* 1998; 87:4;808-11.
  12. Kautto UM. Attenuation of the circulatory response to laryngoscopy and intubation by fentanyl. *Acta Anaesthesiol, Scand,* 1982; 26(3) 217-21.
  13. Song H. Small dose Fentanyl optimal time of injection for blunting the circulatory response to tracheal intubation. *Anesth Analg* 1998, 86: 658-61.
  14. Miller CD, Warren SJ. IV lignocaine fails to attenuate the cardiovascular response to laryngoscopy and intracheal intubation. *Br.J. Anaesth.* 1990 Aug 65(2):216-9.
  15. Rastogi B, Gupta K, Gupta PK, Agarwal S, Jain M, Chauhan H. Oral pregabalin premedication for attenuation of haemodynamic pressor response of airway instrumentation during general anaesthesia: a dose response study *Indian J. Anaesth,* 2012, 56(1): 49-54
  16. Sundar AS, Kodali R, Sulaiman S. The effect of preemptive pregabalin on attenuation of stress response to endotracheal intubation and opioid – sparing effect in patients undergoing off pump coronary artery bypass grafting. *Annals of Cardiac Anaesthesia* 2012; 15: 18-25
  17. Namratha S, Shobha D,. Comparative evaluation of oral gabapentin and pregabalin premedication for attenuation of pressor response to endotracheal intubation under general anaesthesia, *Int. Journal of Science and Research* 2014;3(11) 654.
  18. Ramsay MA, Savege TM, Simpson BR, Goodwin R: Controlled sedation with alphaxalone-alphadolone. *BMJ* 1974, 2:656- 659.
  19. Gupta K, Sharma D, Gupta PK. Oral premedication with pregabalin or clonidine for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy: A comparative evaluation. *Saudi J. Anaesth. (Internet)* 2011Apr 5: 179-84.
  20. Fox EJ, GS, Hill CH, Vilanueva P, King BD. Complications related to the pressor response to endotracheal intubation. *Anesthesiology.* 1977; 47:524-5.

21. Kleinmann B, Henkin RE, Glisson S et al. Qualitative evaluation of coronary flow during anaesthetic thalium 201 perfusion scans. *Anaesthesiology* 1986; 64: 157-64.
22. Dinardo JA, Zvara DA. Quoted in *Anesthesia for cardiac surgery* 3<sup>rd</sup> edition.
23. Moffit EA, Sethna DH, Brussel JA, Raymond MJ, Matloff JM, Gray RJ. Effect of intubation on coronary blood flow and myocardial oxygenation. *Can Anaesth Soc J*. 1985; 32:105-11.
24. Slogoff S, Keats AS. Does perioperative myocardial ischemia lead to postoperative myocardial infraction. *Anaesthesiology* 1985; 62: 107-14.
25. Hamill JF, Bedford RF, Weaver DC, Colohan AR. Ligocaine before endotracheal intubation: Intravenous or laryngotracheal?. *Anesthesiology* 1981;55:578-81.
26. Feng CK, Chan KH, Liu KN, Or CH, Lee TY. A comparison of lidocaine fentanyl and esmolol for attenuation of cardiovascular response to laryngoscopy and tracheal intubation. *Acta Anaesthesiol*. 1996; 34(2) 61-7.