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Evaluation of the Effect of Preemptive Oral Pregabalin in the Attenuation of Cardiovascular Response to Direct Laryngoscopy and Endotracheal Intubation during General Anesthesia: A Randomized Placebo-Controlled Trial

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Abstract

Background: Pregabalin ameliorates neuro humoral stress response by inhibitory modulation of neuronal excitation. The primary objective of this study was to evaluate the effect of pre-emptively administered oral Pregabalin (150mg) in attenuating the pressor response to laryngoscopy and endotracheal intubation and secondary objective to evaluate its' safety profile. **Methods:** Following institutional ethics committee approval, 80 patients of ASA grade I and II aged 20- 50 years of either sex undergoing surgeries under general anesthesia were allocated randomly into two groups of 40 each in this prospective randomized, double-blinded, placebo-controlled study. Group I and II received oral capsules of Pregabalin 150mg and Vitamin respectively, with sips of water, 90 minutes before induction of general anesthesia. All patients were anesthetized using standard anesthesia protocol. Hemodynamic parameters were observed at baseline, pre-induction, and 1,2,4,6,8,10 and 15 minutes following laryngoscopy and intubation. **Results:** Demographic parameters were comparable between groups. The mean heart rate, blood pressures were higher in group II compared to group I, following intubation ($p<0.001$). The maximum magnitude of increase in heart rate [Group I 15.67 ± 1.54 (95% CI 15.4 – 16.1), group II 29.7 ± 2.5 (95% CI 28.9 – 30.5) ($P<<0.001$)], systolic [group I (5.95 ± 1.63, 95% CI 5.45 to 6.46), group II (24.75 ± 2.21, 95% CI 24.1 to 25.4) ($p<0.001$)], diastolic [group I (5.45 ± 0.87, 95% CI 5.18 to 5.72), group II (22.45 ± 1.42, 95% CI 22 to 22.9) ($p<0.001$)] and mean arterial pressures [Group I (5.33 ± 1.02, 95% CI 5.01 to 5.65), group II (24.15 ± 3.87, 95% CI 22.9 to 25.3), ($p<0.001$)] were greater in group II compared to group I. The incidence of tachycardia was higher in group II ($p<0.001$). **Conclusion:** Administration of pre-emptive oral Pregabalin 150 mg, 90 minutes prior to induction of general anesthesia effectively attenuates the hemodynamic stress response to laryngoscopy and intubation without significant adverse effects.

Keywords: Endotracheal Intubation, Hemodynamic Response, Laryngoscopy, Pregabalin

1. Introduction

Direct laryngoscopy and endotracheal intubation, integral components of airway management during general anesthesia is associated with hemodynamic perturbations such as tachycardia, hypertension, and cardiac dysrhythmias are not desirable and essentially preventable[1]. These are essentially the outcomes of hypothalamic stimulation and reflex sympathetic discharge, which results in tachycardia, hypertension

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and elevated norepinephrine concentrations[2,3]. Heart Rate (HR), Blood Pressure (BP), and the Rate Pressure Product (RPP), serve as non-invasive surrogates of this hemodynamic response and myocardial oxygen consumption[4-6]. Systemic hypertension and tachycardia are dynamic predictors of perioperative cardiac morbidity and can predispose to complications like increased intraocular pressures, development of pulmonary edema, intracranial hemorrhage, cerebrovascular accident, precipitation of acute left ventricular failure, and intra-operative myocardial infarction in patients with end-organ dysfunction[7-9]. Amelioration of hemodynamic responses to laryngo-tracheal stimulation play a key role in safe peri-operative care. Numerous interventions namely, increase in the anesthetic depth, topical anesthesia of the airway, oropharyngeal lidocaine instillation, pretreatment with opioids, magnesium, vasoactive and anti adrenergic drugs, calcium channel antagonists, dexmedetomidine and gabapentin are proven as effective attenuators of hemodynamic stress response to airway instrumentation under general anesthesia[10-18]. However, these drugs have their limitations[19,20]. Pregabalin is a novel gabapentinoid with analgesic, anticonvulsant and anxiolytic effects, by virtue of its effect on cerebral voltage gated calcium channels[21] Literature concerning the cardiovascular effects of Pregabalin in surgical patients is limited. The primary objective of our study was to assess the efficacy of oral pre-emptive Pregabalin of 150 mg in attenuation of hemodynamic stress response to laryngoscopy and endotracheal intubation for elective surgeries, while our secondary objective was to assess its sedative, analgesic, and safety profile.

2. Methods

This prospective randomized, placebo-controlled, single-center trial was conducted on 80 patients admitted to our hospital from November 2012 to May 2014 after approval from the Institutional Ethics Committee. Forty Patients belonging to ASA physical status Grade I and II, aged between 20 to 50 years of either sex, weighing between 50 to 70kgs. undergoing elective surgeries under general anesthesia not exceeding 2 hours were included for the study. Patients with anticipated difficult airway and obesity, those on treatment with sedatives, hypnotics, antidepressants, antipsychotic, and anti hypertensive medications, and those with systemic and endocrine disorders were excluded from the study.

The patients were randomly allocated into two groups sequentially based on computer-generated random numbers. The study medicines were masked by packing them in opaque plastic papers labeled with the randomization numbers and the drug's expiry date, by an anaesthesiologist not involved in the study. Each patient received a consecutive pack containing medications. The patient and the anesthesia provider were blinded about the drug administered. The randomization code was not opened until the survey was completed. The primary investigator performed a detailed pre-anesthetic assessment of the patients scheduled for surgery under general anesthesia was done on the day before the surgery. Written informed consent for general anesthesia and study participation was obtained from all the eligible consenting patients. The patients were advised fasting for 6 hours before surgery and administered Ranitidine Hydrochloride 150mg orally during the previous night of the surgery. The baseline HR and systolic (SBP), diastolic (DBP) and Mean Arterial Pressure (MAP) were recorded before giving the study drugs. The respective study drug was then given to the patient 90 minutes before induction. The study participants were randomly divided into two groups. Group I (n=40): Pregabalin group, Group II (n=40): Control group. Group I received capsule Pregabalin 150mg, and Group II received Vitamin capsule as a placebo, orally with sips of water about 90 minutes before induction of general anesthesia. After receiving the patient in the Operating Room (OR), Electro-Cardio-Gram (ECG), pulseoximetry (SpO2), and Non Invasive Blood Pressure (NIBP) monitors were connected and intravenous (IV) ringer lactate infusion of 6-8ml/kg was started. The patient's pre-induction HR, SBP, DBP, MAP, SpO2 and Ramsay Sedation Score (RSS) were used to assess sedation level. All patients were premedicated with IV Inj. Glycopyrrolate 0.005mg/kg, Inj. Midazolam 0.03mg/kg, Inj. Fentanyl Citrate 2mcg/kg and Inj. Ondansetron 4mg. After pre-oxygenation for 3 minutes, anesthesia was induced with IV Inj. Thiopentone sodium 5mg/kg. After successful trial of ventilation, IV Inj.Vecuronium Bromide 0.1mg/kg was given to facilitate laryngoscopy and intubation. Patients were mask ventilated for 3 minutes with 60 % nitrous oxide (N2O), 40 % oxygen (O2), and 0.4 % Isoflurane. At the end of 3 minutes, direct laryngoscopy was performed using an appropriately sized curved Macintosh blade (No. 3 or 4). Endotracheal intubation was done with an appropriately sized cuffed oral endotracheal tube (7.5 mm internal diameter for females and 8.5 mm internal diameter for males). Laryngoscopy and intubation time was taken care not to exceed 20seconds. If laryngoscopy time exceeded 20 seconds, case was omitted from statistical analysis.

The HR, SBP, DBP, MAP was noted at 1, 2, 4, 6, 8, 10, 15 minutes after intubation, and the corresponding RPP calculated using the formula HR multiplied by SBP. After confirmation of tracheal tube position with capnography, the cuff was inflated, tube fixed, and connected to the ventilator. Surgery commenced at the end of 15 minutes after laryngoscopy and intubation, with no stimulus applied during the study period. Anesthesia was maintained using closed circuit of anesthesia workstation with N2O: O2 (60%:40%), Isoflurane to achieve Minimum Alveolar Concentration of 1. Rest of the anaesthetic management was done as per discretion of the attending anaesthesiologists. IV Inj. Vecuronium Bromide for muscle paralysis maintenance based on neuromuscular monitoring by Train Of Four (TOF) and Double Burst Stimulation (DBS) and fentanyl top ups as required were administered as required. Post intubation, patients were observed for complications like hypotension, hypertension, tachycardia, bradycardia, arrhythmias, bronchospasm and treated accordingly. Post-operative follow-up for 24 hours for studying the investigational drug's side-effects, if any, were recorded and treated appropriately.

We hypothesized that pregabalin resulted in lesser increase in blood pressure compared to placebo. By keeping the power of study as 80% and the confidence limit at 95%, assuming standard deviation of 20.5, to detect a minimum of 10% difference in SBP at 1 min following intubation, the minimum sample size required was 25 in each group. We included 40 patients in each group for better validation of results.

Descriptive and inferential statistical analysis was carried out in the present study. Results on continuous measurements were presented on Mean + SD, and results on categorical measurements are presented in Number (%). Significance was assessed at 5% level of significance. Dependent variables were normally distributed. Samples drawn from the population were random cases of the samples were independent. Student t-test (two-tailed, independent) was used to find the significance of study parameters on a continuous scale between two groups (Intergroup analysis) on measured parameters, and paired 't' test was used for intra-group comparison. Chi-square/ Fisher Exact test was used to find the significance of study parameters on a categorical scale between two groups. The findings were considered as significant if p-value was less than 0.05. The Statistical software, namely SAS 9.2, SPSS 15.0, Stata 10.1, Med Calc 9.0.1, Systat 12.0, and R environment ver.2.11.1, were used for data analysis.

3. Results

A total of 80 patients who underwent surgeries under general anesthesia during the study period at our hospital were studied. All patients received intervention and completed the study, there were no drop outs. Baseline demographic parameters were similar in both groups (Table 1).

Table 1. Demographic profiles in both groups

Variable	Group I	Group II	P-Value
(mean ± SD)	33.03±8.58	32.95±9.81	0.971
Gender [Male: Female]	18:22	17:23	0.822
(mean ± SD)	60.35±6.62	58.78±6.71	0.294
(mean ± SD)	160.68±6.95	158.80±7.46	0.248
(mean ± SD)	23.47±3.11	23.42±3.17	0.936
ASA I: ASA II	35:5	36:4	0.745

* BMI: Body mass index; † ASA: American Physical Status

The predominant surgery in both groups was laparoscopic cholecystectomies (21/40 in group I and 23/40 in Group II). Other surgeries were orthopedic (9 versus 8 in groups I and II respectively), gynecological (5 versus 4 in groups I and II respectively), and ear nose throat surgeries (5 in each group). The mean duration of intubation in group I and II were similar, with 16.28±2.32 and 15.93±1.67 seconds, respectively (p-value > 0.05).

Baseline and pre-induction HR were similar between the groups (p = 0.143 and 0.176 respectively). The maximum clinical elevation in HR from pre-induction levels occurred at the first-minute post-intubation in both groups, and mean ± SD increase was 15.67 ± 1.54 (95% CI 15.4 – 16.1) and 29.7 ± 2.5 (95% CI 28.9 – 30.5) (P<<0.001) beats per min in groups I and II, respectively. The increases in HR at 1, 2, 4, 6, 8, 10, and 15 minutes were significantly greater in group II than group I (p<0.001). The magnitude of the HR rise was lower and falling to less than the basal value by 10 minutes in the Pregabalin group. However, the increase in HR in the control group was sustained and had not reached the basal value even by 15 minutes post-intubation (Table 2).

Table 2. Comparison of heart rate (bpm) in two groups of patients

(mean ± SD)	Group I	Group II	P value
Basal	86.45±7.46	83.85±8.24	0.143
Pre induction	92.73±7.98	90.23±8.39	0.176
1 min	102.13±7.96	113.55±8.67	<0.001**
2 min	99.43±7.38	112.03±8.03	<0.001**
4 min	92.48±8.13	106.10±9.00	<0.001**
6 min	88.00±9.32	102.20±10.03	<0.001**
8 min	85.93±9.47	98.60±9.69	<0.001**
10 min	83.60±9.25	94.95±9.62	<0.001**
15 min	80.28±8.89	89.75±9.94	<0.001**

The HR changes in the Pregabalin group, at pre-induction, and up to 4 minutes after intubation, were significantly greater when compared to baseline ($p < 0.01$), but the HR at 6 and 8 minutes were statistically not significant ($p > 0.05$) and clinically close to the baseline value. HR changes at 10 and 15 minutes were significantly lower ($p<0.01$) than the baseline value. In Group II (control), the HR at all times, even up to 15minutes after intubation, was more than the basal value and statistically more significant ($p<0.01$).

In Group I (Pregabalin), the SBP rise at 1 and 2 minutes was statistically significant ($p<0.01$), but at 4 and 6 minutes, they were statistically not significant ($p>0.05$) and thus comparable to basal values. At 8, 10, and 15 minutes, SBP was significantly lesser than the baseline value ($p<0.01$). In Group II (control), the SBP at all times was significantly greater than the baseline value up to 15minutes post-intubation ($p< 0.01$).

Both the groups were comparable in the basal and pre-induction systolic BP. There was a statistically significant rise ($p<0.01$) in SBP in both the groups at 1, 2 minutes post-intubation, which was greater in the control group (Table 3).

The magnitude of the rise in SBP was maximum at 2nd minute post intubation in both groups. The magnitude of rise was cinically and statistically higher in group II (24.75 ± 2.21, 95% CI 24.1 to 25.4) compared to group I (5.95 ± 1.63, 95% CI 5.45 to 6.46) ($p<0.001$) and found to be falling to less than the basal value by 8 minutes in the Pregabalin group. However, the rise in SBP in the control group was sustained and had not reached the basal value even by 15 minutes following laryngoscopy and intubation.

In Group I (Pregabalin), the mean DBP changes at 1 and 2 minutes after laryngoscopy and intubation were greater than the basal value and statistically significant ($p < 0.01$). After 4minutes post-intubation, it was significantly lower than the baseline value ($p < 0.01$). In Group II (control), the mean DBP was significantly greater than the baseline values at all times post-intubation ($p<0.01$) and did not reach the baseline value. The mean DBP was at all times significantly lower ($p<0.01$) in the Pregabalin group compared to the control group. The magnitude of maximum rise in DBP in group II (22.45 ± 1.42, 95% CI 22 to 22.9) was higher than group I (5.45 ± 0.87, 95% CI 5.18 to 5.72) ($p<0.001$) (Table 3).

In group I (Pregabalin), MAP increased from baseline for first 2 minutes after intubation ($p<0.01$) and then fell below baseline for 15 minutes ($p<0.01$). In group II (control), the mean MAP at all times post-intubation was significantly greater than the baseline value ($p<0.01$) and did not reach the baseline value. The mean MAP at baseline and pre-induction are comparable in both groups ($p>0.05$). Mean MAP at all times post-intubation was significantly lower in the group I compared to group II ($p<0.01$) (Table 3). The maximum increase in MAP was noted at 1 min following intubation in group I (5.33 ± 1.02, 95% CI 5.01 to 5.65) and at 2 min in group II (24.15 ± 3.87, 95% CI 22.9 to 25.3), the increase was greater in group II compared to group I ($p<0.001$). The maximum fall in MAP from baseline in group I was noted at 15th min (13.67 ± 2.34), where as in group II the MAP was always higher from baseline (Table 3).

The baseline and pre-induction RPP were comparable in both groups. The mean RPP was clinically lower and statistically significant ($p<0.01$) in the Pregabalin group when compared to the control group (Figure 1). In group I (Pregabalin), the RPP rise at 1, 2, and 4 minutes though was statistically highly significant ($p<0.01$), the RPP at 6 and 8 minutes were comparable to baseline values. At 10 and 15 minutes, RPP dropped to a significantly lower value than baseline ($p<0.01$). In group II (control), the RPP changes were significantly greater at all times following intubation ($p <0.01$) and did not reach the baseline values even by 15 minutes, unlike the Pregabalin group (Figure 1).

Table 3. Comparison of blood pressure (mm Hg) in two groups

SBP (mm Hg)	Group I	Group II	P value
Basal	116.50±7.13	117.30±6.68	0.606
Pre induction	116.35±6.58	119.00±6.61	0.076
1 min	121.60±6.06	141.00±8.00	<0.001**
2 min	122.45±5.70	142.05±8.79	<0.001**
4 min	117.35±5.77	137.25±9.81	<0.001**
6 min	115.15±6.04	133.58±10.21	<0.001**
8 min	113.20±5.73	129.80±9.69	<0.001**
10 min	113.20±5.73	126.75±10.16	<0.001**
15 min	107.05±5.42	121.05±9.79	<0.001**

DBP (mm Hg)	Group I	Group II	P value
Basal	80.85±8.10	80.05±8.15	0.661
Pre induction	80.20±8.18	80.10±8.53	0.957
1 min	86.30±7.86	102.50±6.73	<0.001**
2 min	85.00±7.47	103.90±6.82	<0.001**
4 min	76.08±9.64	99.60±6.78	<0.001**
6 min	72.18±8.58	95.35±6.58	<0.001**
8 min	69.33±7.91	92.45±7.01	<0.001**
10 min	67.23±6.59	87.90±7.25	<0.001**
15 min	65.98±7.10	83.55±6.98	<0.001**

MAP (mm Hg)	Group I	Group II	P value
Basal	92.73±6.65	92.47±6.32	0.855
Pre induction	92.25±6.51	93.07±6.42	0.574
1 min	98.07±6.31	115.33±5.92	<0.001**
2 min	97.48±5.84	116.62±6.32	<0.001**
4 min	89.83±6.91	112.15±6.51	<0.001**
6 min	86.50±6.15	108.09±6.49	<0.001**
8 min	83.95±5.96	104.90±6.79	<0.001**
10 min	81.70±5.14	100.85±6.89	<0.001**
15 min	79.67±5.58	96.05±6.69	<0.001**

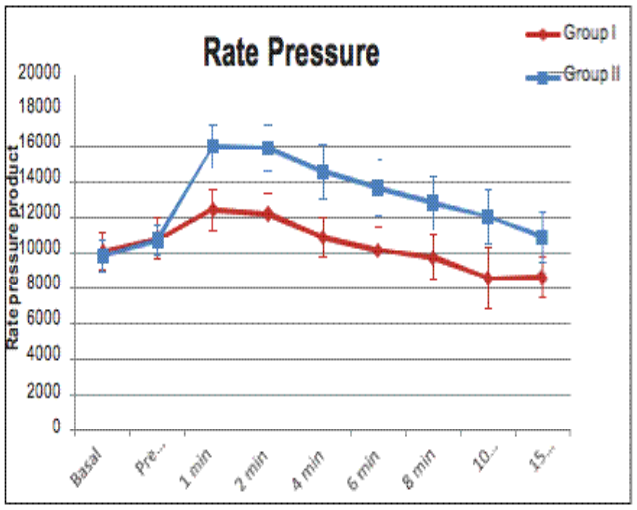

Figure 1. Intergroup comparison of mean rate pressure product with error bars showing standard deviation.

The pre-induction RSS in both groups was statistically significant (p<0.001), and the score was better in the Pregabalin group than the control group. The change in postoperative RSS compared to the pre-induction score was greater in the Pregabalin group than the control group (Table 4). None of the patients had deep sedation or respiratory distress in the peroperative or post operative period. Bradycardia was noted in 4 patient in group I, where as incidence of tachycardia was higher in group II (group I- 2 patients, group II – 14 patients, p<0.001) hypotension was noted in 5 patients in group I and hypertension in 7 patients in group II, from the time of premedication to 15 min post intubation (p–0.51). Postoperatively, during the first 24 hours, two patients in each group had nausea (p=1.000). Three patients in the control group had shivering (p= 0.241).

Table 4. Demographic profiles in both groups

Sedation score	Group I	Group II	P value
Pre induction	1.90±0.44	1.10±0.30	<0.001**
Immediate Post op	3.00±0.00	1.48±0.51	<0.001**
30 min Post op	3.00±0.00	1.00±0.00	-
60 min Post op	2.00±0.00	1.00±0.00	-
120 min Post op	2.00±0.00	1.00±0.00	-

4. Discussion

The present study showed that preoperative administration of oral pregabalin 150 mg, 90 min before induction of anaesthesia resulted in lesser increases in heart rate and blood pressure following intubation compared to placebo. There was reduction in the incidence of tachycardia. Pregabalin binds to the alpha-2-delta site of cerebral voltage-gated calcium channels, facilitates inhibitory modulation of neuronal excitability with attenuation of excitatory neurotransmitters release like glutamate, noradrenaline, and substance P[22-24].

Various researchers have used oral Pregabalin for blunting hemodynamic responses to laryngoscopy and intubation in different doses and found 150 mg more effective than 75 mg and hence the dose of 150 mg was chosen for the present study[25]. Pregabalin is rapidly absorbed following oral administration, with peak plasma concentrations occurring between 0.7 and 1.3 hours. Pregabalin oral bioavailability is approximately 90% and is independent of dose and frequency of administration[26].

Ali *et al*., observed that administration of gabapen tinoids did not affect basal plasma catecholamine (epine phrine and norepinephrine) concentrations before intub ation, also failed to attenuate the catecholamine response to intubation and conversely, enhanced the increase of plasma norepinephrine concentration[27].

Memis and co-workers reported that the inhibitions of Ca^{2+} efflux from muscle cells with a consequent inhibition of smooth muscle relaxation might explain the effectiveness of gabapentinoids in the relaxation of laryngoscopy[28]. A systematic review assessing the various benefits of pregabalin found its effective role in neuropathic pain, partial epilepsy and management of anxiety disorders[29].

Several studies conducted earlier have shown beneficial effect of pregabalin on hemodynamic response following laryngoscopy and intubation and in most of the studies the timing of premedication was between 60 to 90 min[27,30-32]. However, the magnitude of change in heart rate and blood pressure varied between studies, which may be attributable to concomitant drugs such as beta blockers taken preoperatively[39]. In contrast to the observations of an earlier study, the mean arterial pressure dropped below baseline after 4th min of intubation in patients receiving pregabalin, which may be due to concomitant administration of isoflurane during mask ventilation[27]. Its remains unknown if there are any synergistic effect of volatile agents with pregabalin on blood pressure. However, there is low level evidence, that regular intake of pregabalin may worsen heart failure[33].

RPP value > 20,000 correlates with a predisposition to myocardial ischemia. In the present study, at first-minute post-intubation, the mean RPP rose from 10067 and 9816 to a maximum of 12419 and 15986 in the Pregabalin and control groups, respectively. The increase in RPP in the control group was significantly greater than the Pregabalin group ($p<0.01$) at all times post-intubation up to 15 minutes.

Patients receiving pregabalin were better sedated in the present study, but were easily arousable. As RSS was assessed two hours postoperatively, higher score were observed in the present study than Sundar *et al*[30]. who assessed it six hours postoperatively. Both studies were done in different surgical populations, and the duration of CABG may be more than two hours, which is the duration of surgeries in the present study. Considering that Pregabalin was given 90 minutes preoperatively and the elimination half-life is 6.3 hours, the sedation may not last for more than 6 hours.

Pregabalin has antiemetic and analgesic properties attributable to inhibition of tachykinin activity and opioid-sparing action as postulated by Guttuso[34] in their study on the effect of gabapentin on chemotherapy-induced nausea in breast cancer patients. However, the beneficial effect of pregabalin on Post operative nausea and vomiting was not noted in the present study, which may be due to smaller sample size.

The present study has few limitations. The dose-response effect of Pregabalin was not evaluated. Plasma catecholamine levels, if measured, could have given greater credibility to the study findings.

5. Conclusion

Oral Pregabalin (150mg) given ninety minutes preoperatively attenuates the hemodynamic response associated with laryngoscopy and endotracheal intubation, which is more prominent with BP than HR. Pregabalin's sedative and analgesic properties were evidenced by calm and non-anxious patients at pre-induction and two hours postoperatively, with no significant side effects. However, larger sampled studies are needed to derive a definite conclusion.

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