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Attenuation of Haemodynamic Responses to Tracheal Intubation with Oral Pregabalin Premedication – A Randomized Controlled Trial.

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Abstract

Background

Haemodynamic response to laryngoscopy and intubation can result in deleterious effects in susceptible individuals. Various techniques and measures have been tried to attenuate this response but are not able to fully control it. Some recent study have highlighted the effectiveness of oral pregabalin in attenuation of these responses.

Aims

The aim of our study was to determine the effects of haemodynamic response to laryngoscopy and intubation and other side effects with oral pregabalin premedication.

Methods

The study was a prospective, randomized, controlled one in which 76 patients of either sex, aged between 20-60 years, ASA I & II were randomly divided into two groups as Group A- to receive 150 mg of oral pregabalin and Group B- to receive oral placebo capsule 60 minutes before the induction. Heart rate, blood pressure, SPO_2 were recorded before and after induction, immediately after intubation and 1, 3, 5 and 10 min, thereafter at every 5 min interval till the end of surgery.

Results

The demographic parameters such as age, weight, sex and ASA were comparable in the two groups. The heart rate showed reduced value at all time points. Significant reduction in the systolic blood pressure at all the time intervals was recorded in the pregabalin group. There were no incidence of side effects like sedation, dizziness, nausea and vomiting in both the groups.

Conclusion

Pregabalin effectively reduced the haemodynamic responses to laryngoscopy and tracheal intubation.

Key words: *Pregabalin, laryngoscopy and intubation, hemodynamic response*

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I. Introduction

Haemodynamic response to laryngoscopy and intubation is generally transient and unpredictable. Such transient cardiovascular changes are of no consequences and well tolerated in healthy individuals but are of great concern in susceptible individuals particularly those with systemic hypertension, coronary artery disease, leaking abdominal aneurysm, intracranial aneurysm and recent myocardial infarction. In such patients these transient changes can result in potentially deleterious effects such as myocardial ischaemia (left ventricular failure as a result of increased myocardial oxygen demand) and cerebral haemorrhage.[1,2]

The appropriate premedication, smooth induction and rapid intubation would prevent the associated risk and complication of the hemodynamic pressor responses.[3]Several techniques have been proposed to prevent or attenuate these hemodynamic responses such as deepening the plane of anaesthesia, pretreatment with vasodilators, beta blockers, calcium channel blockers and opioids[4,5], but are not able to relieve it fully. Recent

studies have indicated the effectiveness of oral pregabalin in attenuating the hemodynamic response with desirable post-operative analgesic with higher patient satisfaction.[6-9] Pregabalin, a gabapentinoid, has been found to posses antiepileptic, analgesic, anticonvulsant and anxiolytic effect. It acts by decreasing synthesis of glutamate which acts on central nervous system and is well absorbed and tolerated after oral administration, with peak plasma concentration occurring within 1 hr. Oral pregabalin is used in the range of 75- 300mg and higher doses of pregabalin were associated with increased incidence of dizziness.[7] Side effects include nausea, headache, dizziness and drowsiness.[10] In literature, we found that there is paucity of work evaluating the hemodynamic effect of pregabalin on tracheal intubation. For this reason, we planned a study design to evaluate and compare the efficacy of pregabalin in attenuating the hemodynamic responses related to tracheal intubation.

II. Aims And Objects

The aims of our study was to study the effects of haemodynamic response to laryngoscopy and intubation and other side effects with oral pregabalin premedication

III. Materials And Methods

The study was a prospective, randomised, controlled, double blind one, conducted at a Tertiary care centre, Imphal, Manipur, between August 2016 to August 2018, over a period of two years. After getting approval from the Institutional Ethics committee and written informed consent from 76 patients of either sex, aged between 20-60 years, ASA I and II physical status, scheduled to undergo elective surgery under general anaesthesia were enrolled in the study. Patients with history of allergy to pregabalin, narcotic dependent patients, patients with history of cerebrovascular, neurologic, respiratory, renal and hepatic dysfunction, patients with anticipated difficult intubation and when duration of laryngoscopy exceeds 22 seconds, or a second attempt for intubation is needed were excluded from the study.

All patients were examined a day before surgery, and were kept overnight fasting after 10:00 pm and received Tab. Alprazolam 0.5 mg orally and Tab. Ranitidine 150 mg as premedication on the night before surgery. Patients were given oral capsule of pregabalin 150 mg or oral placebo capsules with sips of water according to their respective groups determined by computer generated randomization, 60 minutes before induction of general anaesthesia as Group "A" received - Cap. Pregabalin 150 mg and Group "B" received – Placebo capsules.

On arrival in the operation theatre, monitors were attached and baseline heat rate, systolic and diastolic and mean arterial blood pressure were recorded. The pre-operative sedation level were assessed by Ramsay sedation scale[11.] An uniform anaesthetic techniques was advocated for all the patients. After preoxygenation for 3 minutes with 100% oxygen, anaesthesia was induced with propofol(2mg/kg body weight) and fentanyl(1.5 mcg/kg body weight). The direct laryngoscopy and intubation was facilitated with rocuronium(0.9mg/kg) after 90 seconds, Anaesthesia was maintained with isoflurane and nitrous oxide 60% in oxygen and were mechanically ventilated to maintain the normocapnia (Carbon dioxide between 35 and 40 mmHg). The supplemental neuromuscular blockade was achieved with rocuronium 0.1 mg/kg. After completion of surgery, residual neuromuscular block was reversed with appropriate doses of neostigemine(0.05 mg/kg) and glycopyrolate(0.01 mg/kg) and the extubation was done when respiration was adequate. Intraoperatively, the heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure, electrocardiography, pulse oximeter(SpO_2) and $EtCO_2$ levels were continuously monitored and recorded before and after induction, immediately after intubation and 1, 3, 5 and 10 min, thereafter at every 5 min interval till end of surgery. Patients were observed for complications like hypotension, hypertension, arrhythmias, hypoxemia and bronchospasm, and thereafter transferred to post anaesthesia care unit and monitored for at least 3 hours, or until there were no signs of any drug induced effects such as nausea, vomiting, any respiratory inadequacy or hemodynamic instability. Sample size was calculated based on a previous study of Bhawna R et al.[7] Data were entered in IBM SPSS Statistics 21 for Windows (IBM Corp. 1995, 2012) and summarised using appropriate statistical test and a P-value of less than 0.05 was considered significant.

IV. Results And Observation

The demographic parameters such as age, weight, sex and ASA were comparable in both the groups as shown in table 1 and will not affect the study outcome.

Table 1. showing the demographic profile of group A & group B

Parameters	**Group A**	**Group B**	P-value
Age(years) (Mean±SD)	37.48 ± 10.91	42.20 ± 11.57	0.10
Weight(Kg.)(Mean±SD)	56.78 ± 12.08	59.58± 11.34	0.29
M:F	11:29	9:31	0.61
ASA I:II	37:3	36:4	1.00

P<0.05 is significant

The increase in the heart rate from the baseline value, as shown in table 2, was more in the control group as compared with the pregabalin group at all the time points eventhough it was statistically significant at 1minute

Table 2: Heart Rate (bpm)-Comparison in two groups of patients studied

Heart Rate (bpm)	Group A	Group B	P value
Baseline	86.80±11.32	87.45±14.04	0.820
1min	89.50±12.03	97.33±17.95	0.025*
3min	85.63±11.65	89.70±16.75	0.210
5min	85.60±12.02	85.48±12.62	0.964
10min	85.15±11.79	83.15±12.52	0.464
15min	84.43±11.69	81.88±11.30	0.324
30min	82.61±10.25	81.32±11.67	0.625
45min	80.92±9.73	84.41±10.00	0.322
60min	76.00±7.48	86.70±15.30	0.135
After extubation	97.13±11.10	97.48±14.34	0.903

P<0.05 is significant

The systolic blood pressure recorded significant reduction in the pregabalin group at 1 min, 3 min, 5 min, 10 min, 15 min, 30 min, 60 min and after extubation as compared with the control group(Table 3).

Table 3. SBP (mm Hg)- Comparison in two groups of patients studied

SBP (mm Hg)	**Group A**	**Group B**	**P value**
Baseline	126.68±14.98	127.25±15.03	0.864
1min	125.68±19.11	150.30±26.88	<0.001*
3min	122.70±15.86	138.58±19.76	<0.001*
5min	123.05±15.07	134.10±17.03	0.003*
10min	125.00±15.26	134.75±16.52	0.008*
15min	126.73±15.15	136.13±20.93	0.024*
30min	125.03±13.86	134.97±16.16	0.008*
45min	127.23±13.70	136.30±15.53	0.088
60min	117.17±14.41	138.40±18.48	0.031*
After extubation	136.78±12.25	153.85±16.39	<0.001*

P<0.05 is significant

The diastolic blood pressure, as shown in table 4 also followed the same trend as that of heart rate with reduced values in the pregabalin group at all time points and also significant at 1 minute.

Table 4: DBP (mm Hg)- Comparison in two groups of patients studied

DBP (mm Hg)	**Group A**	**Group B**	**P value**
Baseline	81.03±7.27	81.90±8.01	0.610
1min	83.50±13.22	92.90±15.14	0.004*
3min	83.23±14.07	85.35±12.90	0.484
5min	80.68±10.80	83.78±10.69	0.201
10min	83.93±12.17	83.78±10.49	0.953
15min	83.90±12.97	85.05±10.92	0.669
30min	83.61±10.40	86.41±10.34	0.264
45min	86.08±14.27	85.32±10.67	0.859
60min	78.17±11.69	84.10±9.64	0.289
After extubation	86.58±8.63	95.20±7.67	<0.001*

P<0.05 is significant

The preoperative sedation score after the study drugs were comparable with a score of "2" in both the groups. There were no incidence of side effects like bradycardia, respiratory depression, visual disturbances, etc in both the groups at any time points during the study period.

V. Discussion

Laryngoscopy and tracheal intubation is associated with increased level of circulating catecholamines like norepinephrine, epinephrine, and vasopressin which is the reason for tachycardia and increase in blood pressure.[2] Therefore it is very much essential to attenuate this hemodynamic response to laryngoscpy and tracheal intubation in high risk patients with history of coronary artery disease, hypertension and cerebrovascular diseases.[8]Many therapeutic agents and methods have been recommended and used till date but none of them has evolved as the drug of choice yet.[12]

Many pharmacological techniques were introduced and evaluated either in the premedication or during induction to attenuate the haemodynamic pressor response to airway instrumentation.[13] More attention is given

to the use of selective beta‑adrenergic blockers to prevent the reflex sympatho-adrenal discharge mediated tachycardia and hypertension during laryngoscopy and intubation.[4] Hypotensive agents, including sodium nitroprusside, nitroglycerine, adrenoreceptor blockers, calcium channel blockers and opioids, have been used effectively to attenuate these haemodynamic responses.[14,15] The intravenous lidocaine (1.5 mg/kg) prevented the increase in mean arterial pressure with no effect on heart rate.[5] Among opioids, remifentanil(1 µg/kg), alfentanil (10–20 µg/kg) or fentanyl (0.5–1 µg/kg) have been used successfully to attenuate haemodynamic pressor response to laryngoscopy and tracheal intubation, but these are associated with bradycardia, hypotension and post‑operative respiratory depression.[16,17] However, all the above drugs and measures cannot fully control the pressor response.

There was no significant difference in heart rate before and after premedication. Baseline heart rates were comparable in both the groups ($p > 0.05$). In our study the heart rate (HR) at 1 minute post intubation it was significantly lower for pregabalin group than the placebo group. Though statistically insignificant the heart rate in pregabalin group (group A)was also lower at 3,5,10,15,30,45,60 minutes and after extubation. These findings are consistent to the studies done by Dhanya PR et al,[18] Doddaiah et al[19] and Singh G et al.[20]

Contrary to our findings, there was significant rise in heart rate post intubation in pregabalin group in the study done by Rastogi et al [7]. They used butorphanol as premedication which is a less potent analgesic as compared to fentanyl, used in our study. This implies that pregabalin is more effective in attenuation of haemodynamic responses when used with fentanyl and similar findings were found by Singh G et al.[20]

There was no significant difference in systolic blood pressure before and after premedication. Baseline systolic blood pressure was comparable in both the groups ($p > 0.05$). The systolic blood pressure (SBP) was found to be significantly lower for pregabalin group upto 60 minutes and even after extubation(P=<.05). This finding is consistent to studies done by Bhandari G et al,[21] Dhanya PR et al[18] and Kiran S et al.[22] Baseline diastolic blood pressure was comparable in both the groups ($p > 0.05$). In pregabalin group, there was significant reduction in diastolic blood pressure at 1 minute(Group A=83.50±13.22, Group B=92.90±15.14, P<.0.05)but no significant difference was seen thereafter. Similar to our study findings Dhanya et al[18] reported diastolic blood pressure to be significantly lower at 1 minute in pregabalin group as compared to placebo group (P=<0.001). Rastogi B et al[7] also obtained similar findings.

The mechanism by which pregabalin attenuates the hemodynamic response to airway instrumentation remains elusive. In our present study, the attenuation of pressor response to laryngoscopy and tracheal intubation with near stable hemodynamic variables and no postoperative complications were indication of clinically effective and safe analgesia with oral pregabalin (150 mg) premedication. Several mechanisms may contribute to the beneficial effects, which includes the modulation of visceral pain and central sensitization.[10] Pregabalin has inhibitory effects on membrane voltage gated calcium channels. It binds potently and selectively to the alpha 2 delta subunit of hyper-excited voltage gated calcium channels. It modulates the release of excitatory neurotransmitters in hyper-excited neurons, restoring them to normal physiologic state, by reducing calcium influx at nerve terminals.[23] It will be appropriate at this juncture to put forward that the favourable pharmacokinetics of pregabalin make it a valuable premedicant for attenuation of haemodynamic pressor response to laryngoscopy and tracheal intubation during general anaesthesia.[24,25]

Sedation score for all participants in both group remained the same, i.e at 2, co-operative, oriented and tranquil. On the contrary, Ghai A et al,[26] in their study achieved an increased level of sedation before and after surgery in the study group which could be possibly due to the higher dose of pregabalin (300 mg) in their study. Our study also did not find any side effects like bradycardia, respiratory depression, headache or visual disturbances in any of the patients in both the groups.

Limitations of our study:

1. Measurement of stress mediators in plasma(catecholamines) during intubation was not done.
2. Dose related study is needed to confirm the optimal dose of pregabalin per kg of body weight.

VI. Conclusion

Pregabalin administered as a pre-medicant are safe and effective measures in attenuating the haemodynamic responses to tracheal intubation, an effect which may be useful in patients suffering from coronary insufficiency.

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