Pre-emptive Use of Oral Pregabalin Attenuates the Pressor Response of Laryngoscopy and Endotracheal Intubation: A Double Blind Randomized Placebo Controlled Study.

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ABSTRACT

Background: Laryngoscopy and intubation may cause undesirable increase in blood pressure and heart rate. The aim of the present study was to investigate the effect of Pregabalin premedication on hemodynamic responses to laryngoscopy and intubation. **Methods:** Sixty ASA physical status I or II patients undergoing elective surgery under general anesthesia were randomly allocated into two equal groups who received either oral Pregabalin 150 mg (Group PB)or placebo (Group PL)1 hour prior to surgery. Heart rate, Systolic, Diastolic and Mean arterial blood pressures were recorded preoperative, at laryngoscopy and 0,1,3,5 and 10 minutes after tracheal intubation. **Results:** Demographic data and base-line values for Heart rate, Systolic, Diastolic and Mean arterial blood pressures were comparable between groups. During laryngoscopy and intubation there was significant attenuation of SBP, DBP and MBP in PB group as compared to PL group. Although increase in heart rate was less in pregabalin group during laryngoscopy and intubation but it was not statistically significant. **Conclusion:** In the present study design, oral Pregabalin premedication at a dose of 150 mg one hour prior to surgery attenuates pressor response associated with laryngoscopy and endotracheal intubation but not the tachycardia significantly.

Keywords: Haemodynamic response, Intubation, Laryngoscopy, Pregabalin.

INTRODUCTION

Haemodynamic pressor response to airway instrumentation is often a hazardous complication of general anaesthesia. It can provoke a marked sympathetic response manifested as tachycardia and hypertension, which is well tolerated by normal patients but can lead to disastrous events in hypertensive patients.[1,2] High incidences of cardiac arrhythmias, myocardial ischemia, acute left ventricular failure and cerebrovascular accidents are reported following intubation in hypertensive patients.[3-5] Many pharmacological techniques were evaluated either in the premedication or during the induction to attenuate these adverse haemodynamic responses to airway instrumentation.

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Omitting cholinergic premedication, pre-treatment with beta blockers,[6] calcium channel blockers,[7] nitroglycerine,[8] opioids,[9] gabapentin,[10] dexmedetomidine, [11] and clonidine[12] are common practices with variable results. Efficacy of oral pregabalin postoperative analgesia and reduction of parenteral analgesics has been demonstrated in several studies.[13,14] Only few data are published in literature about the cardiovascular effects of pregabalin on the patients undergoing surgery.[15,16] The aim of the present study was to investigate the effect of pregabalin on changes in blood pressure and heart rate observed during laryngoscopy and endotracheal intubation and perioperative hemodynamic stability.

MATERIALS AND METHODS

Informed consent was taken from all patients after approval from ethics committee.

This prospective, randomized, double blind and placebo controlled study was performed on sixty patients, age group of 18 to 60 years, ASA grade I and II, undergoing elective surgery under general anaesthesia. Patients were divided into groups of 30 each. Group PL received oral placebo in the form sugar tablets and Group PB received pregabalin tablet one hour before Surgery. Patients were explained about Ramsay sedation scale (RSS) for sedation. Patients with anticipated difficult intubation, Gastroesophageal reflux disease, history of cardiopulmonary or renal disease, obesity (BMI >35), allergy to any anaesthetic medication and taking sedatives, hypnotics or antihypertensive medication were excluded. We also excluded cases where duration of laryngoscopy exceeded 30 sec, or a third attempt for intubation was taken.

On arrival in the operating room, monitors were attached and baseline heart rate along with systolic, diastolic and mean arterial blood pressure were recorded. The pre-operative level of sedation was assessed by the Ramsay sedation scale(RSS).A crystalloid intravenous infusion of 6-8 ml/kg was started and all patients were pre-medicated with intravenous Ranitidine (1 mg kg^{-1}),Metoclopramide (0.15 mg kg^{-1}), Glycopyrrolate (0.01 mg kg^{-1}) and Pentazocine (0.6 mg kg^{-1}). After pre-oxygenation for 3 min with 100% oxygen, anaesthesia was induced with Propofol (2 mg kg^{-1}) or in a dose sufficient for loss of verbal commands. The direct laryngoscopy and intubation was facilitated with Vecuronium 0.1 mg kg^{-1} after 4 minutes, and of minimum possible duration by an anesthetist having at least 500 previous experiences of laryngoscopy and intubation. Anaesthesia was maintained with isoflurane and nitrous oxide 60% in oxygen. Patients were mechanically ventilated to maintain the normocapnia. After completion of surgery, residual neuromuscular block was antagonized with appropriate doses of Neostigmine (0.05 mg kg^{-1}) with Glycopyrrolate (0.01 mg kg^{-1}) and extubation was performed when respiration and airway reflexes were adequate.

Heart rate, systolic BP, diastolic BP, mean arterial blood pressure before and after induction, immediately after intubation and 1, 3, 5 and 10 min. thereafter were monitored and recorded by an observer blind to nature of the drug used. Patients were observed for complications like hypotension, hypertension, arrhythmias, hypoxemia and bronchospasm. After tracheal extubation and on awakening from anaesthesia, patients were assessed for postoperative sedation using RSS at 0, 1, 6, 12 and 24 hours.

RESULTS

Data was analyzed on computer software SPSS 21. Study population was calculated by power analysis (power 80% & α error 0.05).Characteristics of the patients between two groups were compared with student *t*- tests and *chi-square* test as appropriate. Changes in HR, SBP, DBP,MBP and sedation score between the two groups were compared with student *t*- tests. P –value < 0.05 was considered significant. It was found that the two study groups were comparable with respect to age, sex, height, weight and ASA status [Table 1]. The baseline values of heart rate [Table 2], systolic BP [Table 3], diastolic BP [Table 4], mean BP [Table 5] were comparable in both the groups. At laryngoscopy and intubation SBP, DBP and MBP rises in both groups in similar fashion at laryngoscopy (AL) and at 1 min, 3 min after laryngoscopy but settled down towards baseline after 3 min in both groups. HR increased in both groups at AL and at 1 min after laryngoscopy. Even though increase was less in PB group at 3 min, 5 min and 10 min after laryngoscopy but the differences were not statistically significant. The sedation scores [Table 6] in the present study were significantly higher in the group PB at 30 min (P=0.018) and 60 min (P=0.020) preoperatively and immediate postoperatively (P=0.02).

Table 1: Demographic characteristics in each group.

	Group PB (n=30)	Group PL (n=30)	P -Value
Age(years) mean±SD	45.30(±10.96)	40.40(±13.17)	0.123
Height(cm)mean±SD	163.73 (±8.93)	162.97 (±8.62)	0.736
Weight(kg) mean±SD	55.63±11.76	54.13±9.15	0.584
Sex (male: female)	7:23	8:22	0.766
ASA I/II	20/10	25/5	0.136

Table 2: HR baseline(BL), at laryngoscopy (AL) and at 1,3,5,10 min after tracheal intubation and Cuff inflation in the pregabalin and the placebo group.

Variable	Groups	PRE-OP BL	INTRAOPAL	INTRA OP AI 1 min	INTRA OP AI-3 min	INTRAOP AI-5 min	INTRA OP AI 10 min
HR	PB n=30	88.23 ± 18.48	93.80 ± 17.46	91.90 ± 18.76	86.57 ± 19.62	83.90 ± 16.30	78.57 ± 13.24
	PL n=30	86.77 ±15.25	90.10 ± 18.15	93.17 ± 18.45	89.03 ± 16.90	85.80 ± 15.88	78.13 ± 15.94
P- value		0.734	0.424	0.793	0.604	0.649	0.909

Table 3: SBP baseline (BL), at laryngoscopy (AL) and at 1,3,5,10 min after tracheal intubation and Cuff inflation in the pregabalin and the placebo group.

Variable	Groups	PRE-OP BL	INTRAOP AL	INTRA OP AI 1 min	INTRA OP AI-3 min	INTRA OP AI-5 min	INTRA OP AI 10 min
SBP	PB n=30	129.53 ± 9.63	137.30 ± 9.67	141.07 ± 9.44	143.73 ± 9.35	139.23 ± 9.91	134.43 ± 9.84
	PL n=30	129.06 ± 10.52	148.57 ± 10.23	154.60 ± 10.40	159.97 ± 10.39	154.20 ± 10.55	150.03 ± 10.30
	P -value	0.858	0.001	0.001	0.001	0.001	0.001

Table 4: DBP baseline(BL), at laryngoscopy (AL) and at 1,3,5,10 min after tracheal intubation and Cuff inflation in the pregabalin and the placebo group

Variable	Groups	PRE-OP BL	INTRAOP AL	INTRA OP AI -1MIN	INTRA OP AI-3 min	INTRA OP AI-5 min	INTRA OP AI-10 min
DBP	PB n=30	83.87 ± 8.05	88.93 ± 8.14	90.97 ± 8.14	92.97 ± 8.14	89.63 ± 8.02	86.57 ± 7.93
	PL n=30	84.37 ± 7.51	94.43 ± 8.10	100.43 ± 8.22	104.80 ± 8.74	101.03 ± 8.32	97.00 ± 8.11
	P -value	0.804	0.011	0.001	0.001	0.001	0.001

Table 5: MBP baseline (BL), at laryngoscopy (AL) and at 1,3,5,10 min after tracheal intubation and Cuff inflation in the pregabalin and the placebo group

Variable	Groups	PRE-OP BL	INTRAOP AL	INTRA OP AI -1 min	INTRA OP AI-3 min	INTRAOP AI-5 min	INTRA OP AI-10 min
MBP	PB n=30	99.09 ± 7.61	105.06 ± 7.75	107.67 ± 7.73	109.89 ± 7.67	106.17 ± 7.92	102.52 ± 7.73
	PL n=30	99.27 ± 7.03	112.48 ± 7.03	118.49 ± 7.12	123.19 ± 7.18	118.76 ± 6.87	114.68 ± 6.75
	P- value	0.925	0.001	0.001	0.001	0.001	0.001

Table 6: Comparison of mean ramsay sedation score in the groups at pre-operative and post operative period

RAMSAY SEDATION SCORE	GROUPPB (n=30)	GROUPPL (n=30)	
PRE-OP	**Mean ± SD**	**Mean ± SD**	**P* VALUE**
T 0	1.47 ± 0.51	1.53 ± 0.51	0.613
T 30 min	1.73 ± 0.45	1.43 ± 0.50	0.018
T 60 min	1.67 ± 0.48	1.37 ±0.49	0.020
POST OP	**Mean ± SD**	**Mean ± SD**	**P* VALUE**
T 0	3.33 ± 0.55	3.03 ± 0.41	0.020
T 1 hr	2.80 ± 0.55	2.83 ± 0.46	0.800
T 6 hr	2.33 ± 0.55	2.10 ± 0.40	0.065
T 12 hr	1.93 ± 0.25	1.80 ± 0.45	0.128
T 24 hr	1.47 ± 0.51	1.57 ± 0.50	0.447

*Significant (p<0.05)

DISCUSSION

Tracheal intubation is a noxious stimulus, tending to provoke a marked sympathetic response manifested as tachycardia and hypertension which is potentially deleterious in some patients.[1-,3] Various agents, including anaesthetics, analgesics, adrenergic blocking agents and vasodilators effectively attenuate this response.[6-12] This has been a fertile area for clinical investigation, spawning numerous studies of the various techniques which might be expected to modify the haemodynamic response to intubation. Even a transient hyper-dynamic response may cause serious complication in patients with symptomatic aortic aneurysm, recent myocardial infarction, cerebral aneurysm, or intracranial hypertension, known or suspected ischaemic heart disease is by far the most common indication for modifying the haemodynamic response to intubation. Myocardial ischaemia is a frequent consequence of induction and intubation especially if tachycardia occurs. Perioperative myocardial ischaemia has been associated with postoperative myocardial infarction, and a causal relationship has been postulated.[8,10] Therefore, elimination of ischaemia at the time of intubation might prevent infarction. Modification of the haemodynamic response to intubaton is a laudable objective and is clearly indicated in a small subgroup of patients in whom a single hyper-dynamic episode may cause a catastrophe.

A variety of drugs have been used to control this haemodynamic response. Recently, Pregabalin was found to be effective in attenuating the pressor response to tracheal intubation in various studies**.** In previous conducted studies it was noticed that 150 mg of Pregabalin, administered orally 1 hour before the surgery, was found to be effective in reducing the noxious stimuli to laryngoscopy and intubation, there by attenuating the hemodynamic response adequately.[17-19]With this background, in our study, 150 mg of Pregabalin was given one hour before intubation and results were analyzed.

A previous study by Gupta et al showed statistically significant attenuation of mean arterial pressure with oral Pregabalin (*P*<0.007) 150 mg 1 hr prior surgery with no significant change in heart rate.[17] In a similar study conducted on 90 patients, randomized into three groups, Group I received oral placebo, Group II oral pregabalin 75 mg and Group III oral pregabalin 150 mg 1 hour prior to induction. Significant increase in heart rate and mean arterial pressure was observed in Groups I and II after airway instrumentation, while statistically significant attenuation of mean arterial pressure was seen in Group III. No significant decrease in heart rate was observed in any group.[18] In another study by Salman et al, patients receiving 150 mg Pregabalin showed significant decrease in SBP after anesthesia induction, at intubation and one minute post intubation. Heart rate did not differ between groups at any time.[19]

In the present study, the comparison of MB Preadings in both the groups revealed similar finding [Table 5]. The baseline values were similar in both the groups i.e 99.09 mmHg in group PB and 99.27 mmHg in group PL. Laryngoscopy led to an increase in MBP followed by a consistent decrease towards the baseline values after 3 min. Inter group comparison was significant at all time points in comparison to the previous study in which group PB showed significantly lower MBP values at induction and at intubation.[19]

The baseline heart rate was again comparable in both the groups in the present study [Table 2]. There was an apparent increase in heart rate in both the groups after laryngoscopy and intubation, although increase in heart rate was less in group PB at all times but it was not statistically significant. These findings are markedly different from previous study where there was a significant decrease in heart rate and MBP in PB group after laryngoscopy and intubation.[20] No significant change in heart rate was seen in previous studies.[17-19]

In our study preoperative level of sedation was significant higher in PB group receiving 150 mg of Pregabalin that was comparable to previous studies.[17,18] In one previous study preoperative Pregabalin administration (75–300 mg per oral) increased perioperative sedation in a dose-related fashion in elective surgical patients.[21] No postoperative respiratory depression, nausea, or vomiting were seen and hemodynamic parameters remained stabilized perioperatively.

Pregabalin is recently used as an adjuvant for acute postoperative pain control. Study demonstrated that single preoperative dose of Pregabalin 300 mg resulted in approximately 50% reduction in 24 hr morphine requirements in patients undergoing hip surgery.[22] In another study, perioperative Pregabalin administration is associated with less pain intensity and better functional outcomes 3 months after lumbar disc surgery.[23] Therefore, its pharmacologic, analgesic and anxiolytic properties make it a useful drug for premedication.[24]

In this study, it was shown that oral premedication with Pregabalin 150 mg one hour before surgery attenuated the hemodynamic response to laryngoscopy and endotracheal intubation. It might be due to adequate sedation and analgesia. 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 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.[25]

Limitation of our study was that we didn't measure perioperative analgesic requirement and level of stress hormones in our study.

CONCLUSION

Pre-treatment with Pregabalin 150 mg one hour before the induction of anaesthesia effectively attenuates pressor response associated with laryngoscopy and intubation but not the tachycardia completely. Pregabalin is a good alternative when used as an adjunct to general anaesthesia as far as haemodynamic effects and perioperative sedation is concerned.

REFERENCES

1. Reid LC, Brace DE. Irritation of the respiratory tract and its reflex effect upon heart. Surg Gynae Obstet. 1940;70:157–62.
2. Hassan HG, EL-Sharkawy TY, Renk H, Mansour G, Fouda A. Hemodynamic and catecholamine stress responses to laryngoscopy with vs without endotracheal intubation. Acta Anesthesiol Scand. 1991;35:442-7.
3. Fox EJ, Sklar GS, Hill CH, Villanoeva R, King BD. Complications related to pressor response to endotracheal intubation. Anesthesiology. 1977; 47: 524-5.
4. Kanchi M, Nair HC, Bankal S, Murthy K, Murugesan C. Hemodynamic response to endotracheal intubation in coronary artery disease. Indian J Anesth. 2011; 55: 260-5.
5. McCoy EP, Muakhur RK, McCloskey BV. A comparison of stress response to laryngoscopy: Macintosh vs McCoy blade. Anesthesia 1995; 50: 943-6.
6. Coleman AJ, Jordan C. Cardiovascular responses to anaesthesia. Influence of beta adrenoceptor blockade with metoprolol. Anaesthesia. 1980;35:972-8.
7. Nishikawa T, Namiki A. Attenuation of pressor response to laryngoscopy and tracheal intubation with intravenous verapamil. Acta Anaesthesiologica Scandinavica. 1989; 33:232-5.
8. Mikawa K, Hasegawa M, Suzuki T, Maekawa N, Kaetsu H, Goto R et al. Attenuation of hypertensive response to tracheal intubation with nitroglycerin. Journal of clinical Anaesthesia. 1992; 4:367-371.
9. Dahlgren N, Messeter K. Treatment of stress response to laryngoscopy and intubation with fentanyl. Anaesthesia. 1981; 36:1022-1026.
10. Bhandari G, Shahi K S. Effect of Gabapentin on pressor response to laryngoscopy and tracheal intubation : a double blind randomized placebo controlled study. PJSR. 2013;6:1-6.
11. Bhandari G, Shahi K S, Parmar N K, Bhakuni R, Kumar H. Efficacy of dexmedetomidine in attenuating sympathoadrenal response to laryngoscopy and tracheal intubation. African Journal of Anaesthesia and Intensive Care. 2012;12:34-9.
12. Ghignone M, Quintin L, Duke PC, Kehler CH, Cavillo O. Effects of clonidine on narcotic requirements and hemodynamic responses during induction of fentanyl

anesthesia and endotracheal intubation. Anesthesiology. 1986;64:36–2.
13. Ghai A, Gupta M, Hooda S, Singla D, Wadhera R.. Arandomized controlled trial to compare pregabalin with gabapentin for postoperative pain in abdominal hysterectomy. Saudi J Anaesth. 2011; 5: 252-7.
14. Durkin B, Page C, Glass P . Pregabalin for the treatment of postsurgical pain. Expert Opin Pharmacother. 2010; 11: 2751-8.
15. Eren G, Kozanhan B, Hergunsel O. Pregabalin Blunts Cardiovascular Responses To Laryngoscopy And Tracheal Intubation. J Anesthesiol Reanim. 2009; 7: 82-7.
16. Sundar AS, Kodali R, Sulaiman S, Ravullapalli H, Karthekeyan R, et al. The effects of preemptive pregabalin on attenuation of stress response to endotracheal intubation and opioid- sparing effect in patients undergoing off-pump coronary artery bypass grafting. Ann Car Anaesth. 2012; 15:18-25.
17. Kumkum gupta, Pranav Bansal,Prashanth K Gupta, YP Singh.Pregabalin premedication, A new treatment option for hemodynamic stability during general anaesthesia. Anesthesia Essays and researches 2011; 5 issue 1:57-62.
18. Rastogi Bhawan , Kumkum Gupta, Prashant Gupta,Salony Agarwal, Manish Jain, et al. Oral pregabalin premedication for attenuation of haemodynamic pressor response of airway instrumentation during general anesthesia. Indian J. Anaesth. 2012; 56 Issue 2: 49-54.
19. Ebru Salman, Cagatay Celik, Selim Candan.Premedication with single dose pregabalin 150mg Attenuates Hemodynamic Response to laryngoscopy and intubation. Research Articl. 2012; 1,05.
20. Eren, Betul Kozanhan, Oya Hergunsel.pregabalin biunts cardiovascular response to laryngoscopy and tracheal intubation. Turkiye Klinikleri Journal of Anesthesiology Reanimation 2009;7, Issue 2.
21. Paul F White, Burcu Tufanogullari, Jimmie Taylor. The Effect of Pregabalin on Preoperative Anxiety and sedation level. anaesthesia and analgesia. 2009;4: 1140-5.
22. Mathiesen O, Jacobsen LS, Holm HE, Randall S, Adamiec – Malmstroem L, et al. Pregabalin and dexamethasone for postoperative pain control: a randomized controlled study in hip arthoplasty. Br J Anaesth. 2008; 101: 535-41.
23. Burke SM, Shorten GD. Perioperative pregabalin administration improves pain and functional outcomes 3 months after lumbar discectomy. Anesth Analg. 2010; 110:1180-5.
24. Gupta K, Sharma D, Gupta PK. Oral premedication with pregabalin or clonidine for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy: A comperative evaluation. Saudi J Anaesth. 2011; 5: 179-84.
25. Kavoussi R.. Pregabalin: From molecule to medicine. Eur Neuropschycopharmacol. 2006; 16: 128-33.

How to cite this article: Bhandari G, Mitra S, Shahi KN, Rani A, Chauhan A. Pre-emptive Use of Oral Pregabalin Attenuates the Pressor Response of Laryngoscopy and Endotracheal Intubation: A Double Blind Randomized Placebo Controlled Study. Ann. Int. Med. Den. Res. 2016;2(3):110-4.

Source of Support: Nil, **Conflict of Interest:** None declared