Journal of Anesthesia & Clinical Research

Meena, et al., J Anesth Clin Res 2016, 7:2
http://dx.doi.org/10.4172/2155-6148.1000607

Research Article Open Access

Study of Attenuation of Cardiovascular Response during Laryngoscopy and Intubation Using Two Different Doses of Pregabalin as Premedication in Controlled Hypertensive Patients-A RCT

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Received date: Jan 11, 2016; **Accepted date:** Feb 17, 2016; **Published date:** Feb 27, 2016

Abstract

Introduction: Laryngoscopy and tracheal intubation are powerful noxious stimuli that should be attenuated. Effect more severe in hypertensive patients. The present study evaluated the safe and clinically effective dose of oral pregabalin as premedication for attenuation of pressor response of airway instrumentation in controlled hypertensive patients.

Methods: After ethical committee clearance total of 90 controlled hypertensive adult consented patients aged 30-60 years (M/F), ASA grade II were included, and randomized into three groups of 30 patients each by computer generated random number tables. Group I received oral placebo, Group II oral pregabalin 75 mg HS+150 mg 1 h before surgery and Group III oral pregabalin 75 mg HS+300 mg 1 h prior to induction. Duration of study 2012-2013. Data was analysed using Chi-square, Anova and T test and statistical analysis was performed using SPSS, windows version 19.0. The power of the study from primary object is 80%. Anaesthetic technique was standardized and all groups were assessed for preoperative sedation, haemodynamic changes after the premedication, before and after induction, after laryngoscopy and intubation.

Results: Pre-operative sedation levels were higher with pregabalin premedication. 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.

Conclusion: Oral pregabalin as premedication adequately sedated the patients, attenuated haemodynamic pressor response in a doserelated fashion.

Keywords: Controlled hypertension; Haemodynamic pressor response; Intubation; Laryngoscopy; Pregabalin; Sedation

Introduction

Endotracheal intubation is an integral part of anaesthesiologist's contribution to patient care. Laryngoscopy and tracheal intubation are noxious stimuli that evoke a transient but marked sympathetic response manifesting as increase in heart rate, blood pressure and arrhythmias. Usually these changes are well tolerated in healthy individuals but in hypertensive patients, the pressor response to intubation is more marked. Deepening of anaesthesia [1], lidocaine spray [2], sodium nitroprusside [3], opoids [4], alpha blockers [5], I.V lignocaine [6], nitroglycerine ointment [7] and oral clonidine [8] have traditionally been used as preoperative medication to eliminate or to suppress the stress response to laryngoscopy and intubation. Pregabalin has anxiolytic, sedative, antiallodynic, antihyperalgesic, antinociceptive and antisecretory properties [9-11]. Pregabalin has been used for attenuation of pressor response in normotensive patients [12-15] but no randomized controlled study has been carried out to evaluate hemodynamic pressor response of airway instrumentation in controlled hypertensive patients.

Pregabalin is structural analogue of gamma-aminobutyric acid (GABA). Pregabalin reduces or modulates the release of several excitatory neurotransmitters, including glutamate, norepinephrine, substance P, and calcitoningenerelated peptide, producing inhibitory modulation of "overexcited" neurons and returning them to a "normal" state. It increases neuronal GABA levels by producing dose- dependent increase in glutamic acid decarboxylase. It does not bind to GABAa, GABAb or benzodiazepine receptors. It also has no effect on opoid, serotonin and DOPA receptors or cyclooxygenase inhibiting activity [3]. It is well absorbed and tolerated after oral administration, with peak plasma concentrations occurring within 1 h.

The present study was designed as a prospective, blind, randomized controlled study to evaluate and compare the efficacy and safety of two doses of oral pregabalin as premedication for attenuation of haemodynamic pressor response of airway instrumentation with preoperative sedation and perioperative haemodynamic stability.

Methods

The study, approved by the Institutional Ethical Committee, was carried out from January 2013-2014. This prospective, blind, randomized controlled study consisted of 90 controlled hypertensive

adult consented patients aged 30-60 years of both genders, scheduled for elective surgery under general anaesthesia with ASA physical status II. Patients with anticipated difficult intubation, history of cardiac, pulmonary or renal disease, obesity, sensitivity to any drug, and taking antipsychotics, oral hypoglycemics were excluded from study.

After thorough preanaesthetic evaluation, patients were randomly allocated to three groups of 30 patients each by a computergenerated random number table. Group I (CD10) received tab diazepam 10 mg HS+tab diazepam 5 mg 1 hour before surgery. Group II (PG150) received capsule pregabalin 75 mg HS+150 mg 1 hour before surgery and Group III received capsule pregabalin 75 mg HS+300 mg 1 hour before surgery. Group allocations were performed by an anaesthetist who was unaware of the study protocol and was not involved in the study.

On arrival in the operating room, monitors were attached and baseline heart rate and systolic, diastolic and mean arterial blood pressure were recorded. The preoperative level of sedation was assessed by the Ramsay sedation scale: 1, anxious, agitated or restless; 2, cooperative, oriented and tranquil; 3, responds to command; 4, asleep with brisk response to stimulus; 5, asleep with sluggish response to stimulus; 6, asleep with no response. Inj Fentanyl citrate (1 microgram/kg) was administered to all patients and anaesthesia was induced with Inj. Thiopentone sodium (3-5 mg/kg) till abolition of eyelash reflex. After careful check ventilation, Inj. Rocuronium bromide (1 mg/kg) was given to facilitate tracheal intubation. Patients were ventilated with 50:50 N_2O and Oxygen using Bains circuit. Laryngoscopy and intubation was done after 90 seconds of Inj. Rocuronium administration by an experienced anaesthesiologist. No Surgical intervention was allowed for first 15 minutes till observation of haemodynamic response to laryngoscopy and intubation.

Maintenance of anaesthesia was done by 66% N_2O+33% O_2 gas mixture with Sevoflurane 1% at a fresh gas flow rate of 6 Lt/minute. Inj Rouronium (0.2 mg/kg) was repeated as per requirement. Additional dose of Fentanyl was administered in the dose of (0.5 microgram/kg) if there were signs of inadequate analgesia i.e. increase in Pulse rate & Blood Pressure (>20% of Base line), lacrimation & sweating in presence of normal end tidal carbon dioxide. Any acute or severe changes in haemodynamics (MAP <60 or >110) was treated by decreasing or increasing the concentration of Sevoflurane. Intraoperatively, the heart rate, 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, 10 and 15 min after intubation. Patients were observed for complications like hypotension, hypertension, arrhythmias, hypoxemia and bronchospasm, and treated as required. Tachycardia was defined as heart rate greater than 100 beats/min and hypertension when systolic blood pressure was more than 180 mmHg. Hypotension was defined as fall in mean arterial pressure by more than 20% from baseline, and was treated by increasing the intravenous infusion and, additionally, with vasoactive drugs. Bradycardia was defined as reduction in heart rate less than 60 beats/min, and was treated with intravenous Anaesthetic and surgical techniques were standardized for all patients. All groups were assessed for preoperative sedation and changes in heart rate and mean arterial blood pressure after induction and airway instrumentation intraoperatively. The patients were monitored for at least 6 h, or until there were no signs of any drug induced effects such as nausea, vomiting, any respiratory inadequacy or haemodynamic instability in form of hypotension/hypertension or tachycardia/bradycardia. If any sideeffects were noted, they were treated accordingly.

The sample size was decided in consultation with the statistician, and was based on initial pilot observations, indicating that approximately 20-23 patients should be included in each group in order to ensure a power of 0.80 for detecting clinically meaningful reduction by 10-20%in heart rate and mean arterial blood pressure. Assuming a 5% dropout rate, the final sample size was set at 90 patients, which would permit a type I error of alfa=0.05, with a type II error of beta=0.5 and power of 0.8.

Statistical analysis

The results obtained in the study are presented in a tabulated manner and analyzed using Microsoft Excel and SPSS software. The haemodynamic variables were represented by mean value ± SD. The statistical significance in mean difference was performed using analysis of variance (ANOVA) and Chi square test as appropriate. A P value of <0.05 was considered significant and <0.001 as highly significant. The failure rate of drug was defined as >30% increase in haemodynamic parameters from the baseline values.

Results

From total 90 patients, 30 patients in each group were evaluated and compared. All the three groups were comparable with respect to the demographic and operational factors. No significant differences were found among them with respect to age, sex, weight, time between oral premedication of pregabalin administration to anaesthetic induction, duration of laryngoscopy and intubation (Table 1).

Variables	Group I	Group II	Group III	p-Value
Age (Yrs)	43.96 ± 9.67	43.90 ± 8.66	44.47 ± 9.43	0.966
Weight (Kgs)	54.43 ± 2.15	54.43 ± 2.11	54.43 ± 3.36	1.00
Sex (M/F)	16/14	15/15	12/18	0.723
Duration Of Laryngoscopy(Sec)	10.39 ± 0.96	10.33 ± 0.96	10.43 ± 0.77	0.911
Duration Of Surgery(Min)	75.00 ± 20.28	75.00 ± 22.63	75.00 ± 21.85	1

Table1: Patients characteristics, duration of laryngoscopy and duration of surgery

The degree of sedation before pregabalin premedication was comparable between the groups. Sedation was significantly higher in the pregabalin 300 mg group III at the preinduction stage as compared with groups I and II (Table 2).

	Group I	Group II	Group III	P-Value		
				I/II	I/III	II/III
Mean ± Sd	4.00 ± 0.00	3.37 ± 0.490	2.27 ± 0.728	0.0116	0.000	0.001

Table 2: Preoperative sedation score after premedication

There was no significant difference in the heart rate before and after premedication. Immediately after laryngoscopy and intubation, the heart rate increased significantly in all groups, but the increase was least in group III(PG300) (Table 3).

Time Interval	Group I	Group II	Group III	p-Value		
				I/II	I/III	II/III
Before Premedication	86.6 8 ± 7.42	86.47 ± 6.36	86.40 ± 5.89	0.454	0.437	0.483
Before I/V Induction	92.0 7 ± 8.53(0.004)	91.43 ± 10.06(0.009)	90.53 ± 10.87(0.022)	0.398	0.277	0.370
0 Min	117.61 ± 17.62(0.000)	104.87 ± 19.76(0.000)	102.87 ± 16.10(0.000)	0.006	0.001	0.334
1 Min	115.7 4 ± 16.39(0.000)	102.97 ± 13.02(0.000)	100.73 ± 10.27(0.000)	0.001	0.000	0.232
3 Min	114.75 ± 18.36(0.000)	100.03 ± 15.19(0.000)	98.23 ± 12.76(0.000)	0.001	0.000	0.311
5 Min	112.86 ± 15.19(0.000)	99.87 ± 8.70(0.000)	97.60 ± 9.34(0.000)	0.000	0.000	0.167
10 Min	110.71 ± 109.25(0.000)	97.40 ± 16.42(0.002)	95.47 ± 14.76(0.005)	0.001	0.000	0.317
15 Min	109.25 ± 12.56(o.ooo)	91.13 ± 18.22 ± (0.067)	90 ± 13.13(0.060)	0.000	0.000	0.392

Table 3: Changes in heart rate (beats/minute) at different time interval following laryngoscopy and intubation

Rise in heart rate was maximum at 0 min after laryngoscopy and intubation in the entire three groups. But it was of shorter duration in pregabalin group. The difference in increase in heart rate following laryngoscopy and intubation between control group and pregabalin group II (PG150) and group III (PG300) was highly significant till 15 minute post intubation $p<0.05$ this shows that response to laryngoscopy and intubation was very much exaggerated in group I. When group II (PG150) was compared with group III (PG300) increase in heart rate was more in group II (PG150). This shows that attenuation of heart rate was more in pregablin group III (PG300) than group II (PG150). Though heart rate was not completely attenuated by pregabalin but it definitely had a blunting effect on heart rate after laryngoscopy and intubation.

Baseline MAP was comparable in all the three groups there was a significant rise in the MAP in all the three groups at 0 minutes after laryngoscopy and intubation. Increase in MAP was maximum in diazepam group (as compared to pregabalin group. Whereas in pregabalin group, when group II (PG150) was compared to group III (PG300), the increase was more in group II (PG150) than in group III, but this difference was insignificant. In group III (PG300) MAP touched the base line at 10 minutes and in group II (PG150) at 15 minutes after intubation. Intergroup comparison between group II(PG150) and group III(PG300) showed that both the doses of pregabalin were effective in attenuating the rise in MAP but attenuation was more in group III(PG300) than group II(PG150) and this difference was not significant $p>0.05$. In diazepam group MAP remained significantly increased even at 15 minutes post intubation (Table 4).

Time Interval	Group I	Group II	Group III	p-Value		
				I/II	I/III	II/III
Before Remedication	91.14 ± 4.16	91.22 ± 6.90	90.91 ± 7.74	0.479	0.444	0.435
Before I/V Induction	93.54 ± 3.68(0.30)	92.81 ± 8.33(0.21)	92.04 ± 8.23(0.13)	0.234	0.095	0.316
After Laryngoscopy	109.10 ± 6.21(0.000)	100.59 ± 6.94(0.000)	98.10 ± 8.58(0.000)	0.000	0.000	0.111
1 Min	106.44 ± 6.24(0.000)	98.43 ± 7.78(0.000)	96.69 ± 7.76(0.000)	0.001	0.000	0.195

3 Min	103.93 ± 7.53(0.000)	97.27 ± 8.01(0.000)	95.11 ± 6.94(0.000)	0.000	0.000	0.135
5 Min	102.93 ± 7.06(0.000)	95.38 ± 7.68(0.003)	93.47 ± 7.19(0.000)	0.001	0.000	0.162
10 Min	100.94 ± 5.57(0.00)	93.41 ± 7.40(0.030)	91.42 ± 7.86(0.115)	0.001	0.000	0.159
15 Min	99.45 ± 6.44(0.000)	91.89 ± 7.21(0.287)	90.60 ± 8.24(0.363)	0.001	0.000	0.260

Table 4: Changes in mean arterial blood pressure (mm of Hg) at different time interval following laryngoscopy and intubation

In this study fentanyl 1 μ/kg was given universally to all patients on OT table for intra operative narcosis. Additional dose of fentanyl was avoided and administered only if there were signs of inadequate analgesia i.e., increase in pulse rate, blood pressure and lacrimation. Amount of thiopentone needed for loss of eye reflex was recorded. Sevoflurane concentration was recorded in percentage during intra-operative period.

Analgesia was measured according to VAS score in immediate postoperative period and follow up was done till 6 hours. Immediate postoperative VAS score in group I was 6.43 ± 1.03, group II 3.80 ± 1.21 and 1.80 ± 1.06 in group III. In group I immediate postoperative VAS score was high compared to group II and III. This difference was statically significant p<0.00 tables 5 and 6.

Post-Op Vas	**Mean ± Sd**				**P Value**		
		Group I	**Group II**	**Group III**	**I/II**	**I/III**	**II/III**
		6.43 ± 1.03	**3.80 ± 1.21**	**1.80 ± 1.06**	**0.000**	**0.000**	**0.000**
Table no showing immediate post operative VAS score in group I is 6.43 ± 1.03, in group II it is 3.80 ± 1.21 and in group III 1.80 ± 1.06. Post operative VAS score is more in dizepam group compared to pregabalin group. This difference is statically significant when all three groups were compared with each other p value is highly significant p<0.000.							

Table 5: Post operative visual analogue score.

Range	**Group I**	**Group II**	**Group III**	**P-Value**		
	No. Of Patients	**No. Of Patients**	**No Of Patients**	**I/II**	**I/III**	**II/III**
0-2 Hrs	24	5	2	0.000	0.000	0.000
2-4 Hrs	6	13	2			
4-6 Hrs		7	7			
Maximum no of patients required post operative rescue analgesia within 0-2 hrs of surgery in group I. In group II out of 30 patients, 5 patients required analgesia within 0-2 hrs, 13 patients within 2-4 hrs and 7 within 4-6 hrs. In group III, analgesia was given within hrs in 2 patients, 2-4hrs in 2 patient and within 4-6 hrs in 7 patients. 19 patients required analgesia after 6 hrs. This was statically as well clinically highly significant p<0.00. This shows that patients remained pain free for longer period in pregabalin (PG300>PG150) as compared to diazepam premedication.						

Table 6: Requirement of rescue analgesia in immediate postoperative in various groups.

Side effect in the form of dizziness, light headness, confusion and ataxia are described with pregabalin in literature. However in our study only 1 patients in PG 150 mg and 2 patients in PG 300 mg group suffered dizziness which was statically insignificant.

Discussion

The present study compares the efficacy of two different doses of Pregabalin as premedication for the attenuation of cardiovascular response to laryngoscopy and intubation in controlled hypertensive patients. Cardiovascular response to laryngoscopy and intubation are well known and linked with increases in catecholamine blood levels. In 1987 Shribman et al. [16] found that laryngoscopy alone or followed by intubation increases arterial pressure and catecholamine levels while intubation significantly increases heart rate. These effects are more detrimental in hypertensive patients Hassan et al reported high incidence of cardiac arrhythmias, myocardial ischemia, acute left ventricular failure, and cerebrovascular accidents following intubation in hypertensive patients. Hypertension may affect perioperative morbidity through the extent of end organ damage [17].

Significant attenuation of pressor response was observed by oral pregabalin premedication in dose related manner. Our results are in accordance with Sundar et al. [14] who evaluated and compared single preoperative dose of pregabalin 150 mg to a placebo for attenuation of hemodynamic response to laryngoscopy and endotracheal intubation in patients undergoing off-pump coronary artery bypass grafting. In the control group, the patients were given placebo capsules, and in the

pregabalin group, the patients were given pregabalin 150 mg capsule orally 1 h before surgery. The patients were compared for hemodynamic changes before the start of the surgery, after induction, 1, 3 and 5 minute after intubation. They observed that the increase in heart rate 1 minute after intubation was significantly higher in the control group in comparison with the pregabalin group.

Rastogi et al. [15] studied the effect of different doses of pregabalin premedication for attenuation of hemodynamic pressor response of airway instrumentation during general anaesthesia. They reported that that the heart rate increased significantly immediately after laryngoscopy and intubation in all the groups. But it was least with 150 mg of pregabalin.

A similar observation was also noted by Eren et al. [12] who studied the effect of pregabalin 150 mg to a placebo on cardiovascular response to tracheal intubation in the patients' underdergoing lumbar discal hernia repair. Heart rate was significantly lower in the pregabalin group during and after intubation.

The mechanism by which pregabalin attenuates the hemodynamic response to laryngoscopy and intubation remains unknown. It inhibits membrane voltage dependent calcium channels. It is possible that it may act in a manner similar to calcium channel blockers in controlling the hemodynamic response.

Memis et al. [18] 2006 reported that the inhibition of calcium efflux from muscle cells with a consequent inhibition of smooth muscle relaxation might explain the effectiveness of gabapentenoids in relaxation of laryngoscopy.

Sedation includes the whole spectrum of anxiety, amnesia and hypnosis. There is very narrow margin between anxiety and sedation. In the present study anxiety was not measured and sedation was measured. Patients were less apprehensive and well sedated in pregabalin group compared to diazepam group. Patients were more comfortable and asleep in pregabalin groups (PG>300 PG>150) as compared to diazepam group in which more no of patients were awake and agitated. In present study patients who received pregabalin were very comfortable.

The result of our study are not in concordance with the White et al. [19] who studied the effect of pregabalin on preoperative anxiety and sedation levels. According to them preoperative pregabalin administration (75, 150, 300) increased peri-operative sedation in dose related fashion, but failed to reduce pre operative anxiety, post operative pain, or to improve the recovery process after minor elective surgical procedures. The reason for this discrepancy may be many. First, they used only a single dose of pregabalin and we used double dosing which included night dose of 75 mg. Second, their patients have low base line level of anxiety due to minor procedures and they studied acute anxiolytic effect. Third, they used 11 point VRS (verbal rating scale) and we used 5 point sedation score for our patients. Finally, the variety of superficial surgical procedure with relatively low levels of pain in post operative period may have limited their ability to detect a significant effect on post operative pain and need for opioid analgesic medication as compare to our study.

Our results are in comparison with studies conducted by Pande et al. [20] and Christopher et al. [21] who studied the effect of oral pregablin on social anxiety disorder and on patients undergoing minor orthopaedic surgery. Both of them concluded that pregbalin reduces anxiety in an effective and well tolerated manner.

Analgesia was measured according to VAS score in immediate postoperative period and follow up was done till 6 hour. This study has similar findings with that of Jokela et al. (2008) [22], Sarawat et al. [23], Peng et al. [24], Patricia et al. [25], Burke et al. [26], Kim et al. [27], Mathiesen et al. [28]. All these have reported the analgesic property of pregabalin.

Findings of our study suggests that oral pregabalin as premedication reduces intra-operative and post operative opoids consumption because of its anxiolytic and antinociceptive effect. This effect of pregabalin is mainly because of central neuronal sensitisation. Pregabalin's anti-hyperalgesic effect result from its action on α2-δ1 subunit of voltage gated calcium channels which are up regulated in dorsal root ganglia and spinal cord after peripheral injury. pregabalin causes modulation of both visceral sensitization and effective component.

Conclusion

Oral pregabalin is a better premedication than diazepam, pregabalin 300 mg is more efficacious in comparison to 150 mg as it not only provides anxiolysis/sedation but also blunts the arterial pressor response to laryngoscopy and intubation, reduces intra-operative anaesthetic drug requirement and maintains haemodynamic stability. Patients were also more comfortable and asleep during pre and post-operative period with longer duration of post-operative analgesia.

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