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Research Article

Comparison of Oral Clonidine with Oral Pregabalin Premedication for the Attenuation of Pressor Response to Direct Laryngoscopy and Tracheal Intubation in Elective Surgery: A Prospective Randomized Study

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ABSTRACT

Background: Laryngoscopy and intubation has adverse effects like tachycardia, hypertension, myocardial ischemia and cerebral hemorrhage. There are many studies on various pharmacological agents to attenuate pressor response. Aim of the study was to compare efficacy and safety of oral clonidine versus oral pregabalin premedication to attenuate stress response in patients undergoing elective surgery.

Methods: 106 patients of American Society of Anesthesiologist (ASA) class I, aged between 18-60 years of either sex scheduled for elective surgery were randomized into two groups. Group A received oral clonidine 0.2mg and group B received oral pregabalin 150mg, 90 minutes before surgery. Primary objectives of the study heart rate(HR), systolic blood pressure(SBP) diastolic blood pressure(DBP) and mean blood pressure(MBP) were noted baseline, before induction, immediately after intubation (0) and at 1, 3, 5, 10 and 15 minutes after intubation. sedation, postoperative pain scores and any adverse effects were also noted.

Results: The demographic data were comparable in group A and group B. There was no significant difference at baseline for mean (SD) HR, SBP, DBP, and MBP in both groups ($p>0.05$). The mean (SD) HR was significantly lower in group A as compared to group B, before induction and at 1, 3, 5, 10 and 15 minutes ($p <0.05$). The mean (SD) SBP, MBP was significantly lower in group A as compared to group B, before induction immediately after intubation and at 1, 3, and 5 minutes ($p <0.05$). The mean (SD) DBP was significantly lower in group A as compared to group B, before induction (p 0.012). but post-operative analgesia was better in pregabalin group. Bradycardia was more in clonidine group and sedation was more with the use of pregabalin.

Conclusion: We concluded that oral premedication with either clonidine or pregabalin attenuates hemodynamic response to laryngoscopy and tracheal intubation, but Clonidine is superior to pregabalin.

Laryngoscopy is a noxious and most invasive stimulus during endotracheal intubation [1]. Endotracheal intubation is associated with hemodynamic and cardiovascular responses leading to increased circulating catecholamine's resulting in increased heart rate, blood pressure, myocardial oxygen demand and arrhythmias [2].

These responses are more marked in hypertensive patients. In patients with coronary artery disease, leaking abdominal aneurysm, intracranial aneurysm, and recent

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myocardial infarction these transient changes can result in potentially deleterious effects such as myocardial ischemia, left ventricular failure and cerebral hemorrhage [3].

A study has reported that 10%– 18% of the patients develop ischemic ST segment changes during the procedure [4]. Though these undesirable changes are transitory in nature and well tolerated in healthy individuals, it may result in potentially deleterious effects in patients with co-morbid conditions like hypertension, raised intracranial pressure or coronary artery disease. An array of anesthetic techniques and drugs are available to control the hemodynamic responses to laryngoscopy and intubation, like administration of topical anesthesia, reducing the duration of laryngoscopy and intubation to less than 15 seconds, increasing the depth of anesthesia and administration of drugs like topical and intravenous lidocaine [5], opioids [6-7], beta blockers [5,8] calcium channel blockers [9], N_2O [10], melatonin [11] and α2 adrenergic agonists. In recent times a few drugs when used as premedicants have been found to be useful in achieving all the above goals. These include α2 adrenoreceptor agonist (clonidine and dexmedetomidine [12]) and gabapentinoids. (gabapentin and pregabalin)

Pregabalin acts by decreasing the synthesis of the neurotransmitter glutamate to act on the central nervous system, and possesses analgesic, anticonvulsant and anxiolytic activity [13] by reduction of neurotransmitter glutamate, nor-adrenaline, serotonin, dopamine and substance P [14].

Pregabalin is currently in use for treatment of neuropathic pain, fibromyalgia etc [15]. It is being evaluated as a premedicant to help in attenuating the hemodynamic response to laryngoscopy and intubation [16-17].

Clonidine activates the α2-adrenergic receptors in the brain and spinal cord to decrease sympathetic outflow, causing sedation, analgesia, hypotension and bradycardia without significant respiratory depression [18]. It has also been shown to have beneficial effects of blunting hemodynamic responses to laryngoscopy and tracheal intubation [1,19] It is well absorbed after oral administration with peak plasma concentration within 75-90 min. The preoperative use decreases the intraoperative stress response by reducing nociceptive transmission and decrease norepinephrine concentration in serum, provided hemodynamic stability [3].

Based on these information, we hypothesize that oral clonidine is better than oral pregabalin as premedication for the attenuation of pressor response to direct laryngoscopy and tracheal intubation. Aim of the study was to compare oral clonidine with oral pregabalin as premedication for the attenuation of pressor response to direct laryngoscopy and tracheal intubation during elective surgery.

Methods

This comparative randomized study was conducted after approval from institutional ethical committee (IEC/PGIMER/RMLH-1856/17) between 1st November 2018 to 31stMarch 2020.Inclusion criteria were patients of either sex, age between 18 to 60 years belonging to ASA class I, posted for elective surgery. Patients with anticipated difficult airway, allergic to any of drugs used in the study, pregnant patients were excluded.

Sample size was calculated based on a previous study [20] in which it was observed that there was significant difference in heart rate(HR) and mean blood pressure(MBP) between pregabalin 150 mg and clonidine 200 μg at 5 min and 3 min respectively with mean values of heart rate and Mean Arterial Pressure at 5 min and 3 min in pregabalin 150 mg was 80.48±4.68 and 94.45±2.01 respectively and in clonidine 200 μg was 78.32±3.02 and 96.12±3.10 respectively. Taking these values as reference, the minimum required sample size with 80% power of study and 5% level of significance is 53 patients in each study group. So total sample size taken is 106 (53 patients per group). Formula for calculating sample size was: comparing mean of two groups

N>=2(standard deviation)2 *(Zα + Zβ)2/ (Mean difference)2

Where Zα is value of Z at two-sided alpha error of 5% and Zβ is value of Z at power of 80% and mean difference is difference in mean values of two groups.

For HR at 5 min pooled standard deviation=square root (4.68*4.68+3.02*3.02)/2) =3.94

n>= (2*3.94*3.94*(1.96+.84)2)/ (80.48-78.32)2 = 52.17 = 53(approx.)

For MAP at 3 min pooled standard deviation=square root (2.01*2.01+3.10*3.10)/2) =2.61

n>= (2*2.61*2.61*(1.96+.84)2)/ (96.12-94.45)2 = 38.30 = 39(approx.)

Written informed consent was taken from all the patients. After careful pre-anesthetic examination and investigation, patients meeting the inclusion criteria were taken for the study. The Visual Analog Scale (VAS) of pain was explained to the patient a day before surgery. 106 patients were randomly divided into two group of 53 patients each by computer generated random number. Patient received Clonidine and pregabalin as per group allotted.

Group A - received oral clonidine 0.2 mg 90 minutes prior to surgery.

Group B – received oral pregabalin 150 mg 90 minutes prior to surgery.

Baseline vital parameters of patients were recorded before administering the drug. Drug selected for the study was given with sips of water. Patients were shifted to operation theatre. All the patients were given inj. Fentanyl 1.5 μg/kg and pre oxygenated with 100% oxygen for 3 min. General anesthesia was induced with inj. Propofol (2mg/kg). Vecuronium bromide (0.1mg/kg) was used to facilitate laryngoscopy and tracheal intubation. Laryngoscopy and intubation was done after

3 minutes of Vecuronium bromide administration by using cuffed endotracheal tube. All intubations were performed by an experienced anesthesiologist. General anesthesia was maintained with 50:50 oxygen and nitrous oxide and Vecuronium bromide and volatile 1% Sevoflurane throughout the surgery. No surgical intervention was allowed till observation was complete. At the end of surgery residual neuromuscular blockade was reversed with Neostigmine 0.05 mg/kg of body weight and Glycopyrrolate 0.01 mg/kg of body weight. Patient was extubated after adequate reversal.

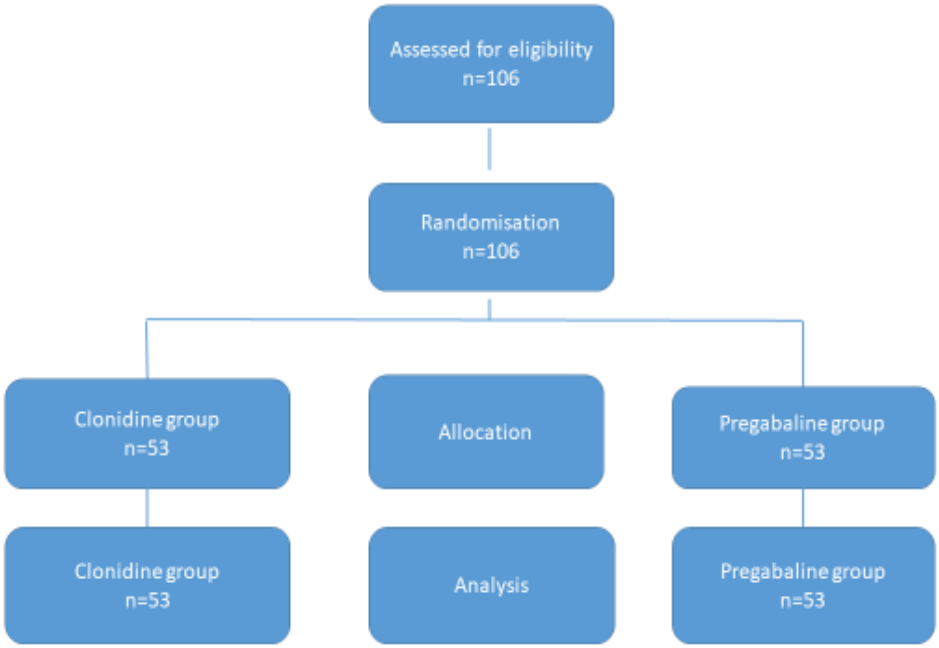
Primary objectives of the study were hemodynamic changes like HR, SBP, DBP and MBP and these parameters were recorded at baseline, before induction, immediately after intubation (0) and at 1, 3, 5, 10 and 15 minutes after intubation. Secondary objectives of the study were requirement of intraoperative narcotic analgesic, level of sedation in the immediate post-operative period, duration of postoperative analgesia.

The Statistical Package for Social Sciences (SPSS) version 21.0 was for the analysis. Categorical variables for number and percentage (%) and continuous variables were presented as mean ± SD and median. was Kolmogorov-Smirnov test was used for Normality of data. Independent t test was used for quantitative variables. Mann-Whitney Test was used for comparison between two groups. Qualitative variables were compared during Chi-Square test/Fisher's Exact test. A p value of <0.05 was considered statistically significant.

Results

Total 106 patients included and completed the study. Total assessed, recruited, and randomized patients are shown in consort diagram (Figure 1).

Figure 1- Consort Diagram



The mean age of patients in Group A was 39.85 ± 10.38 years and in Group B was 39.38 ± 10.9. The data was comparable in both the groups and there was no significant difference found in demographic profile in the two groups i.e. patient's age, weight, height, duration of laryngoscopy and surgery between the groups (Table 1).

Table 1- Demographic details

		Group A (n=53)	Group B (n=53)	P value
Age in years		39.85 ± 10.38	39.38 ± 10.9	0.812
Age in years	<=20	1	1	0.812
	21-30	13	13	
	31-40	15	15	
	41-50	13	15	
	51-60	11	9	

Gender	Male	30(56.6%)	28(52.8%)	
	Female	23(43.4%)	25(47.2%)	
Height(cm) (Mean ± SD)		161.04 ± 7.34	159.57 ± 6.43	0.279
Weight(kg) (Mean ± SD		67.28 ± 6.88	67.74 ± 7.59	0.750
Duration of surgery (minutes) (Mean ± SD)		106.53 ± 11.88	108.23 ± 13.03	0.488
Duration of Laryngoscopy (seconds) (Mean ± SD)		19.57 ± 5.02	19.17 ± 4.33	0.667

Data is represented as Mean ± SD (Range) or n (%). SD: Standard Deviation

There was no significant difference at baseline for mean and SD HR between group A and group B (96.38 ± 10.11 vs 95.83 ± 13.01, p=0.811), The mean and SD HR was significantly lower in group A as compared to group B, before induction [HR (74.7 ± 10.27 vs 79.83 ± 12.46, p=0.023), 1 min after intubation [HR (78.98 ± 7.87 vs 86.08 ± 11.94, p<0.001), 3 min after intubation [HR (76.6 ± 9.44 vs 83.23 ± 12.27, p=0.002), 5 min after intubation [HR (72.28 ± 9.67 vs 79.91 ± 9.96, p<0.001), 10 min after intubation [HR (71.38 ± 9.91 vs 78.06 ± 9.29, p<0.001) and 15 min after intubation [HR (70.38 ± 9.91 vs 76.91 ± 9.35, p=0.001) (Table 2).

Table 2- Comparison of Heart Rate between study groups

	Baseline	Before Induction	0 Min	1 min	3 min	5 min	10 min	15 min
Group A (Mean ± SD)	96.38 ± 10.11	74.7 ± 10.27	72.32 ± 10.24	78.98 ± 7.87	76.6 ± 9.44	72.28 ± 9.67	71.38 ± 9.91	70.38 ± 9.91
Group B (Mean ± SD)	95.83 ± 13.01	79.83 ± 12.46	73.89 ± 10.22	86.08 ± 11.94	83.23 ± 12.27	79.91 ± 9.96	78.06 ± 9.29	76.91 ± 9.35
P value	0.811	0.023	0.436	<0.001	0.002	<0.001	<0.001	0.001

There was no significant difference at baseline for mean and SD SBP between group A and group B (126.79 ± 10.29 vs 129.17 ± 14.41, p=0.335), The mean and SD SBP was significantly lower in group A as compared to group B, before induction [SBP (110.91 ± 12.88 vs 118.91 ± 13.52, p=0.002), immediately after intubation [SBP (104.85 ± 12.36 vs 110.57 ± 13.42, p=0.025), 1 min after intubation [SBP (98.91 ± 12.36 vs 103.87 ± 12.7, p=0.0046), 3 min after intubation [SBP (112.34 ± 13.75 vs 120.62 ± 15.6, p=0.004), 5 min after intubation [SBP (108.19 ± 13.91 vs 116.98 ± 10.58, p=0.005) (Table 3).

There was no significant difference at baseline for mean and SD DBP between group A and group B (96.36 ± 9.96 vs 95.38 ± 7.35, p=0.568), The mean and SD DBP was significantly lower in group A as compared to group B, before induction [DBP (75.23 ± 9.05 vs 80.09 ± 10.44, p=0.012) (Table 4).

There was no significant difference at baseline for mean and SD MBP between group A and group B (106.5 ± 8.45 vs 106.64 ± 6.83, p=0.927), The mean and SD MBP was significantly lower in group A as compared to group B, before induction [MBP (87.12 ± 8.79 vs 93.03 ± 10.29, p=0.002), immediately after intubation [MBP (86.4 ± 9.56 vs 90.91 ± 9.65, p=0.018), 1 min after intubation [MBP (76.05 ± 9.26 vs 83.37 ± 11.01, p<0.001), 3 min after intubation [MBP (77.8 ± 9.78 vs 83.77 ± 10.33, p=0.003), 5 min after intubation [MBP (82.59 ± 11.65 vs 88.38 ± 9.46, p=0.006) (Table 5).

Table 3- Comparison of Systolic blood pressure between study groups

	Baseline	Before Induction	0 Min	1 min	3 min	5 min	10 min	15 min
Group A (Mean ± SD)	126.79 ± 10.29	110.91 ± 12.88	104.85 ± 12.36	98.91 ± 12.36	112.34 ± 13.75	108.19 ± 13.91	104.55 ± 12.56	105.09 ± 12.5
Group B (Mean ± SD)	129.17 ± 14.41	118.91 ± 13.52	110.57 ± 13.42	103.87 ± 12.7	120.62 ± 15.6	116.98 ± 10.58	105.3 ± 9.5	105.8 ± 8.5
P value	0.335	0.002	0.025	0.046	0.004	0.005	0.730	0.461

The mean(SD) fentanyl requirement in group A was 111.32 ± 10.19 mcg whereas in group B was 107.26 ± 11.18 mcg. This difference was not statistically significant (P=0.056).

The mean(SD) sedation score in group A was 1.32 ± 0.47 while group B had a higher mean sedation score of 1.51 ± 0.6. this was not statistically significant (p=0.071).

The mean(SD) duration of postoperative analgesia in group A was 53.96 ± 16.47 minutes while in group B was 76.86 ± 24.72 and this difference was statistically significant (p<0.01).

Table 4- Comparison of Diastolic blood pressure between study groups

	Baseline	Before Induction	0 Min	1 Min	3 Min	5 Min	10 Min	15 Min
Group A (Mean ± SD)	96.36 ± 9.96	75.23 ± 9.05	77.17 ± 10.36	64.62 ± 8.58	60.53 ± 9.75	69.79 ± 12.37	69.15 ± 10.83	67.15 ± 10.83
Group B (Mean ± SD)	95.38 ± 7.35	80.09 ± 10.44	81.08 ± 11.26	68.62 ± 12.95	60.85 ± 10.4	69.58 ± 11.3	66.94 ± 10.94	68.94 ± 10.94
P value	0.568	0.012	0.068	0.066	0.871	0.928	0.303	0.403

Table 5- Comparison of Mean blood pressure between study groups

	Baseline	Before Induction	0 Min	1 Min	3 Min	5 Min	10 Min	15 Min
Group A (Mean ± SD)	106.5 ± 8.45	87.12 ± 8.79	86.4 ± 9.56	76.05 ± 9.26	77.8 ± 9.78	82.59 ± 11.65	80.95 ± 10.71	79.8 ± 8.31
Group B (Mean ± SD)	106.64 ± 6.83	93.03 ± 10.29	90.91 ± 9.65	83.37 ± 11.01	83.77 ± 10.33	88.38 ± 9.46	82.73 ± 9.49	81.53 ± 7.68
P value	0.927	0.002	0.018	<0.001	0.003	0.006	0.371	0.273

None of the patients in both the study group complained of nausea or vomiting. 4 patients in group B complained of dizziness, while 3 patients in group A developed bradycardia.

Discussion

Laryngoscopy is a noxious and most invasive stimulus during endotracheal intubation, Hemodynamic stress response associated with many serious complications, special in patients with comorbidities such as hypertension and cardiovascular diseases.

In our study baseline HR is comparable between the study groups but decrease was more in group A as compared to group B and the difference was statistically significant before induction and at 1, 3, 5, 10 and 15 minutes. Gupta et al, [17] and Waikar et al, [20] reported similar findings in their study. They reported heart rate being significantly lower in clonidine group. Praveen S et al, also reported that heart rate of clonidine group was found to be lower than that of pregabalin group, however this difference was statistically significant only at time of intubation ($p<0.001$) and at rest observation periods this difference was not found to be statistically significant [21]. However, Bahgat et al, reported that HR comparison between pregabalin versus clonidine was statistically not significant [22].

Baseline SBP is comparable between the study groups, but decrease was more in group A as compared to group B and the difference was statistically significant before induction and at 0,1,3 and 5 minutes. Praveen S et al, also reported that after premedication SBP was better controlled in Clonidine Group in comparison to Pregabalin Group throughout the study period which was statistically significant at 1 and 3 minute [21].

Baseline DBP was comparable between the study groups. Our findings are like those of Praveen S et al, who reported DBP of patients receiving clonidine was lower than that of patients who received pregabalin. This difference was found to be statistically significant at all the above periods of observation ($p<0.05$) except at baseline, 10 minute and 15 minutes [21]. Raval DL et al, observed reductions in SBP and DBP following premedication with oral clonidine 0.2 mg by 7.63%. These findings may be favorably compared with the findings of our study [23].

Baseline MBP is comparable between the study groups, but decrease was more in group A as compared to group B and the difference was statistically significant before induction and at 0,1, 3 and 5 minutes. These findings are in accordance with those of Praveen S et al, [21] and Gupta et al, [17]. Bhandari et al, found that MBP in both groups decreased at 0 min, 1 min, 3 min but was statistically significant only at 3 minutes [24]. Waikar et al, reported that the MBP was significantly less among the patient group receiving pregabalin following laryngoscopy and tracheal intubation than other groups during 1 min and 3 min [20].

The mean fentanyl requirement in group A was 111.32 ± 10.19 mcg whereas in group B was 107.26 ± 11.18 mcg. This difference was not statistically significant with a p value of 0.056. Bahgat et al, [22] and Aghamohammadi et al, [25] also reported findings similar to our study.

The mean sedation score in group A was 1.32 ± 0.47 while group B had a higher mean sedation score of 1.51 ± 0.6. Bahgat et al, [22] and Raichurkar A et al, [26] were reported a higher post- operative sedation score in pregabalin group as compared to clonidine group.

The mean duration of post op analgesia in group A was 53.96 ± 16.47 minutes while in group B was 76.86 ± 24.72 and this difference was statistically significant (p value <0.01). Praveen S et, al also reported that VAS scores of clonidine group was higher than pregabalin group with difference in mean VAS score was statistically significant up to a time period of 2-4 hours. [21]

None of the patients in both the study group complained of nausea or vomiting. 4 patients in group B complained of dizziness, while 3 patients in group A developed bradycardia. Similar findings were reported by Gupta et al, Praveen S et al, and Bahgat et al, [17,21-22].

Our study has certain limitations, firstly, the study was conducted in a single center. A multi-centered larger study may be more informative. Secondly, there was no measurement of stress mediators, i.e., endogenous plasma catecholamines or cortisol values perioperatively. The present study did not include younger people(age<18), elderly(age>60) and ASA grade 2,3 and 4 in study group.

Conclusion

In conclusion, oral premedication with either clonidine 200 mcg or pregabalin 150 mg attenuates hemodynamic response to laryngoscopy and tracheal intubation, but Clonidine is superior to pregabalin.

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