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Attenuation of Pressor Response to Direct Laryngoscopy and Tracheal Intubation: Oral Clonidine Versus Oral Pregabalin as Pre - Medication

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Abstract: ***Introduction: Direct laryngoscopy and tracheal intubation are noxious stimuli that can provoke undesirable responses in the cardiovascular, respiratory and other physiologic systems. This effect is more exaggerated when the patient has already preexisting diseases mainly coronary artery diseases, myocardial infarction, and intracranial aneurysm. Hence, to decrease this adverse effect of laryngoscopy and intubation, a number of drugs are used such as beta - blockers, lignocaine, and opioids. Material and method: This was prospective, double blind study conducted on 80 patients posted for elective surgeries under general anaesthesia. The patients were randomised into two groups to receive 200 microgram of clonidine in Group I and 150 mg of pregabalin in group II about 90 mins before induction of anaesthesia. Patients were observed for heart rate, systolic - diastolic - mean Blood Pressure response during endotracheal intubation and 1, 3, 5 and 10 minutes after intubation. Results: There were no significant difference in Heart rate at 1 minute post intubation in both the groups. Mean heart rate in the group receiving clonidine was lesser than the group receiving pregabalin. There was a significant lower systolic and mean BLOOD PRESSURE after intubation in pregabalin group. Hemodynamic stability is better with pregabalin group than clonidine group. Clonidine is better for attenuation of tachycardia response. Pregabalin group produced more sedation and relieved anxiety after premedication and post operatively compare to clonidine group. Conclusion: Pregabalin is better for hypertensive response control and more effective in attenuating anxiety and stress response to endotracheal intubation compared to Clonidine but tachycardia response is better attenuated by clonidine***

Keywords: Blood pressure, clonidine, direct laryngoscopy, heart rate, pregabalin, Tracheal intubation

1. Introduction

Endotracheal intubation is gold standard for providing balanced general anaesthesia. Direct laryngoscopy and tracheal intubation are noxious stimuli that can provoke undesirable responses in the cardiovascular, respiratory and other physiologic systems. Significant tachycardia and hypertension can arise due to these manipulations. [1] The magnitude of the response is greater with increasing force and time of laryngoscopy. The pressure response of laryngoscopy or endotracheal intubation does not present a problem for most patients. However, in patients with cardio - vascular and cerebral diseases these transient responses can result in morbidity and mortality from tachycardia and hypertension. [2] An array of anaesthetic techniques and drugs are available to control the hemodynamic responses to laryngoscopy and intubation like administration of topical anaesthesia, reducing the duration of laryngoscopy and intubation to less than 15 seconds, increasing the depth of anaesthesia, vasodilators [3], adrenal receptor blockers [4], calcium channel blockers [5, 6], topical and intravenous lidocaine [7] α2 adrenergic agonists and opioids [8, 9]. Yet no single agent has been established for this purpose.

The basic purpose of Pre - anaesthetic medication is to reduce fear & anxiety before anaesthesia & operation, to antagonise autonomic nervous system reflexes. eg. changes from laryngoscopy, surgical manipulation etc., to decrease the requirement of anaesthetic agents and thereby minimise undesirable side effects of anaesthetic agents, to produce amnesia and to relieve pre - operative & post - operative pain. These aims can be achieved by various drug combinations g. Hypnotic, opiates, anticholinergics & antihistaminic. Recent work in animals & men suggests that a2 - adrenergic agonist drugs have properties which are considered advantageous as premedication in both normotensive as well as hypertensive patients.

Clonidine, a centrally acting antihypertensive agent acting through Alpha - 2 - adrenergic agonist action, decreases circulatory catecholamines, plasma renin activity and aldosterone. [10] Pregabalin, a gabapentinoid compound is structurally related to inhibitory neurotransmitter gamma - aminobutyric acid (GABA). Pregabalin acts by decreasing the synthesis of glutamate, possessing analgesic, anticonvulsant, and anxiolytic activities. [11]

2. Objective of study

This study was designed to compare the efficacy and safety of oral clonidine 200 mcg and oral pregabalin 150mg given as premedication in patients undergoing elective surgery from the following point of view: Attenuation of cardiovascular response to laryngoscopy and intubation, Relieve anxiety and as sedative, Alleviate post operative side effects.

3. Material &Methods

After approval of institutional ethical committee, Total 80 patients of ASA grade I and II, aged between 18 - 60 years of both sexes scheduled for elective surgery were included in the study. A thorough pre - anaesthetic check up, including detailed history, general and systemic examination, and review of routine investigation was conducted a day before surgery. All the patients were assured & explained about the drug and Its effects during the pre - operative visit and consent was taken. All the patients were starved 8 hours prior to surgery.80 Patients will allocated randomly using double blinding into two groups; 40 patients in each, Group A: 40 patients received clonidine 200 µg and Group B: 40 patients received pregabalin 150mg.

On the day of surgery, patient received study drug 90 min before surgery with sips of water. Baseline pulse, blood pressure, saturation and anxiety state were recorded before premedication. Sedation and anxiety score were noted after oral administration of the drug at 90 minute. Sedation was assessed by Ramsay sedation score, Anxiety was assessed by anxiety score and Patients will be monitored for any side effects pertaining to drugs (nausea, vomiting, drowsiness, PONV). After shifting the patients to the operation theatre, baseline standard monitoring including NIBP, saturation, and ECG were applied and baseline vitals such as Heart rate, blood pressure, respiratory rate and saturation were recorded. Intravenous line was secured with18G intracath. Similar anaesthetic technique is used in all the patients. All patients premedicated with inj. ondansetron (0.1mg/kg), inj. glycopyrrolate (0.004mg/kg) were given 10 minutes prior to induction. After premedication heart rate and blood pressure were recorded. Pre - oxygenation was done for 3 minutes. All patients were induced with sodium pentothal 5 - 7 mg/kg intravenously followed by succinylcholine 1 - 2 mg/Kg intravenously to facilitate endotracheal intubation. Laryngoscopy was done and airway was secured with portex cuff endotracheal tube. Laryngoscopy time was noted. After intubation heart rate and blood pressure were recorded as 1 minute, 3 minute, 5 minute and 10 minute after endotracheal intubation. Anaesthesia was maintained with nitrous oxide 67%, oxygen 33%, atracurium 0.1mg/kg and inhalation agent - sevoflurane. Throughout the surgery heart rate, blood pressure, oxygen saturation and ETCO2 (end - tidal co2) were monitored. After completion of operation all the patients were reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.008mg/kg intravenously and extubation was done. The patients were transferred to post anaesthesia care unit and Sedation score and anxiety scores were noted.

Study design:

Study - prospective, randomised, controlled study.

Sample size calculation: Preliminary sample size was decided in consultation with statistician and was based on initial pilot observations, indicated that approximately 20–23 patients should be included in each group in order to ensure power 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 80 patients.

Eligibility criteria:
Patients between the age of 18 - 60 years, ASA - I and ASA - II

Exclusion criteria:
Patients with anticipated difficult intubation, Pregnant patients, Obese patients, Patients with anatomical abnormality of upper airway, Patients with facial fractures, Patients with cervical spine instability, hypertensive patient, allergic to drug, ASA - III and ASA - IV

Source - hospitalised patients posted for planned surgery.

Statistical Data Analysis:
All the parameters recorded were entered in excel sheet. Microsoft word and Excel have been used to generate graphs and tables. The statistical software, namely Statistical package for social sciences for windows (SPSS) version 21.0 was used for the analysis of the data. Hemodynamic variables were represented by mean ± SD. Statistical significance in mean difference was done by using analysis of variance (ANOVA), Student's t - test, and chi square test as appropriate. A *P* - value of <0.05 was considered significant and <0.001 as highly significant

4. Results

This was prospective, randomised controlled study demographic data were as shown in table - I and figure - I, there were no significant differences among the groups regarding age, weight, gender. Mean age of the patients were 43 years, while weight was 59 kg in both the groups.

Table I: Demographic Data

Demographic Data	Group- A (N=40) (Mean ±SD)	Group- B (N=40) (Mean ±SD)	*P* – value
Age (Years)	42.95 ±4.041	43.85 ±3.358	0.28 (NS)
Gender (M/F)	24/16	22/18	0.65 (NS)
Weight (KG)	58.75 ±4.289	60.4 ±3.583	0.06 (NS)

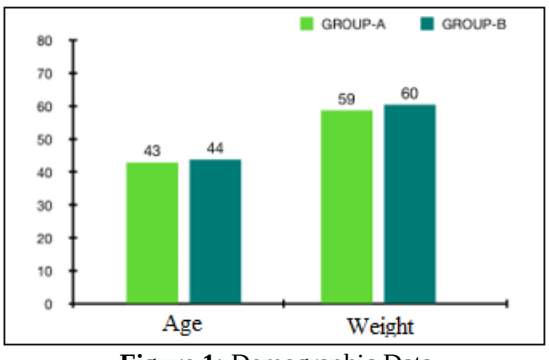

Figure 1: Demographic Data

Table - II shows various type of surgery conducted in two groups. Most of the surgical procedure were of urology. There were no significant differences between two groups.

Table II: Type of Surgery

Sr no	Procedure	Group- A (N=40)	Group – B (N=40)	*P* - Value
1	PCNL (percutanous nephrolithotomy)	25 (62%)	17 (42.5%)	0.08 (NS)
2	Nephrectomy	12 (30%)	10 (25%)	0.62 (NS)
3	RIRS (Retrograde intrarenal surgery)	1 (2.5%)	2 (5%)	0.56 (NS)
4	Radical Nephrectomy	1 (2.5%)	1 (2.5%)	1.00 (NS)
5	Robotic Prostatectomy	1 (2.5%)	1 (2.5%)	1.00 (NS)
6	TLH (Total Laparoscopic hysterectomy)	-	3 (7.5%)	0.08 (NS)
7	Laparoscopic cholecystectomy	-	2 (5%)	0.15 (NS)
8	Operative laparoscopy	-	1 (2.5%)	0.32 (NS)
9	Umbilical hernia repair	-	1 (2.5%)	0.32 (NS)
10	Laparoscopic ULT	-	1 (2.5%)	0.32 (NS)
11	Laparoscopic pyeloplasty	-	1 (2.5%)	0.32 (NS)

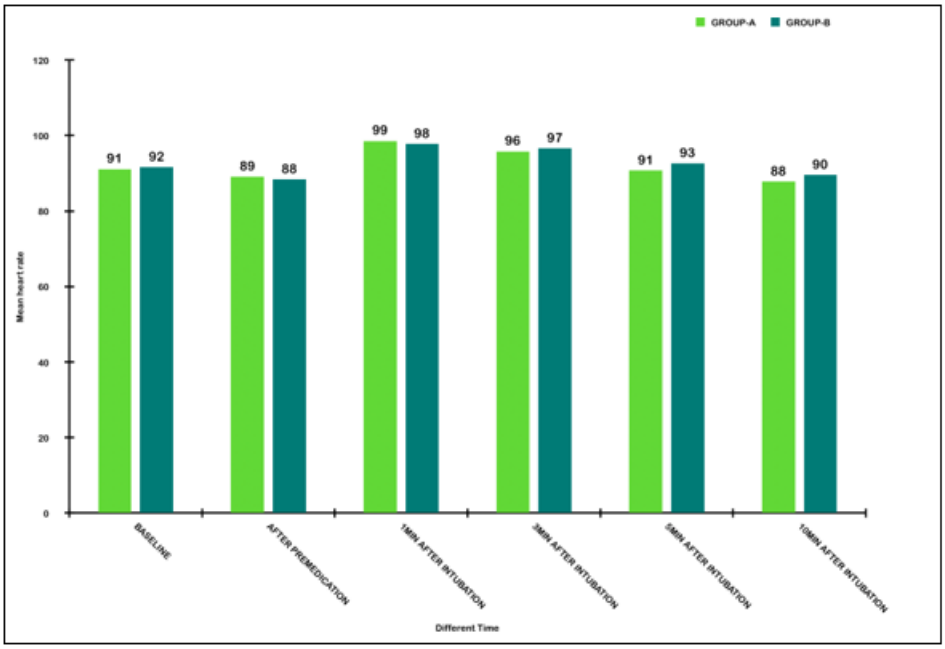

Figure 2: Mean heart rate changes at different Time interval

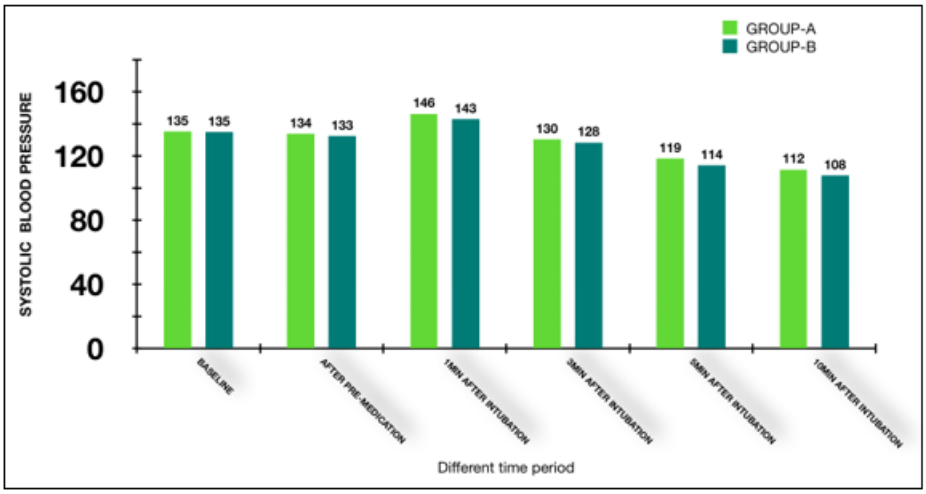

Figure 3: Systolic Blood pressure changes at different Time interval

Table III: Mean Heart Rate Changes

Heart Rate	Group- A (N=40) (Mean ±SD)	Group - B (N=40) (Mean ±SD)	*P* - Value
Baseline	91.075 ±3.117	91.625 ±2.539	0.39 (NS)
After pre - medication	89.075 ±2.944	88.425 ±2.952	0.32 (NS)
1min after intubation	98.575 ±3.076	97.825 ±6.142	0.49 (NS)
3min after intubation	95.775 ±2.867	96.65 ±3.553	0.23 (NS)
5min after intubation	90.7 ±2.672	92.675 ±3.58	.006*
10min after intubation	87.825 ±2.33	89.55 ±3.463	0.01*

Table IV: Systolic Blood Pressure Changes

Systolic Blood Pressure	Group- A (N=40) (Mean ±SD)	Group - B (N=40) (Mean ±SD)	*P* - Value
Baseline	135.35 ±3.031	134.9 ±3.732	0.56 (NS)
After pre - medication	133.85 ±3.304	132.55 ±3.306	0.08 (NS)
1min after intubation	146.3 ±3.441	143 ±3.238	.0001*
3min after intubation	130.3 ±3.505	128.35 ±3.375	0.01*
5min after intubation	118.475 ±3.98	114.3 ±2.791	.0001*
10min after intubation	111.575 ±3.176	107.85 ±2.312	.0001*

Table V: Mean Blood Pressure Changes

Mean Blood Pressure	Group- A (N=40) (Mean ±SD)	Group - B (N=40) (Mean ±SD)	*P* - Value
Baseline	99.225 ±2.053	99.525 ±2.111	0.52 (NS)
After pre - medication	98.675 ±2.144	98.475 ±1.772	0.65 (NS)
1min after intubation	105.375 ±1.96	103.95 ±1.877	.001*
3min after intubation	99.5 ±2.243	98.375 ±2.259	0.03*
5min after intubation	91.2 ±2.906	90.4 ±1.855	0.15 (NS)
10min after intubation	86.9 ±2.316	86.1 ±1.895	0.09 (NS)

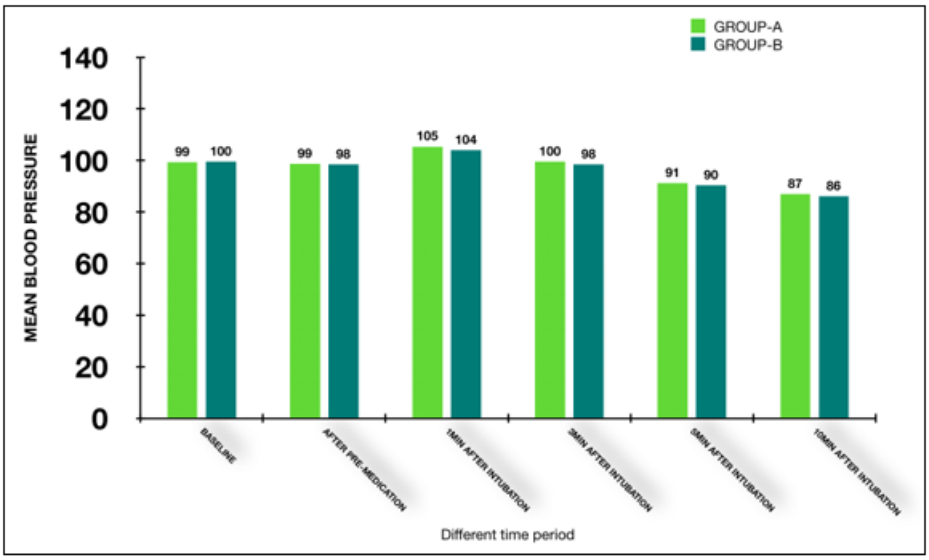

Figure IV: Mean blood Pressure changes at different Time interval

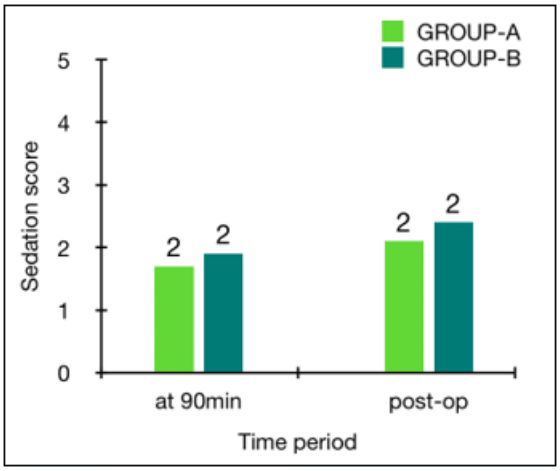

Figure V: Sedation Score at different Time interval

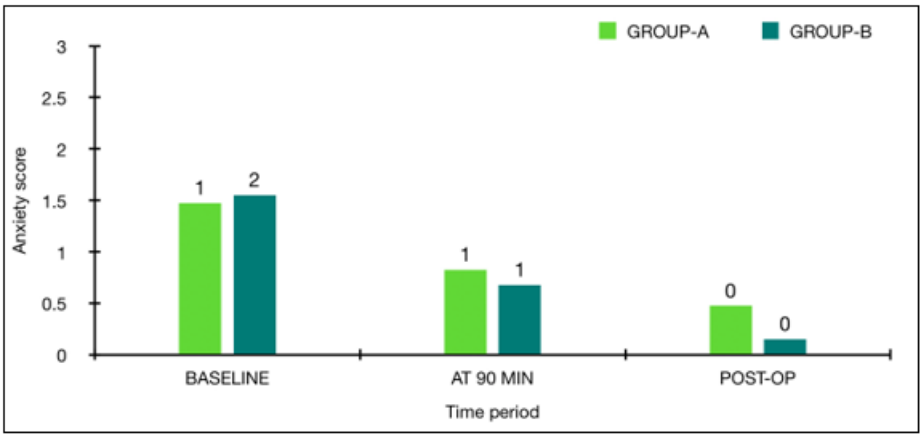

Figure VI: (Anxiety Score at different Time interval)

Table VI: Sedation Score

Sedation Score	Group- A (N=40) (Mean ±SD)	Group- B (N=40) (Mean ±SD)	*P* - value
At 90 Minute	1.7 ± 0.144	1.9 ±0.093	.0001*
Post - OP	2.1 ± 0.169	2.425 ±0.153	.0001*

Table VII: Anxiety Score

Anxiety Score	Group- A (N=40) (Mean ±SD)	Group- B (N=40) (Mean ±SD)	*P* - value
Baseline	1.475 ±0.23	1.55 ±0.24	0.15 (NS)
At 90 Minute	0.825 ±0.182	0.675 ±0.175	.0003*
Post - OP	0.475 ±0.155	0.15 ±0.111	.001*

Table: VIII Post Operative Side Effects

Adverse Effects	Group - A (N=40)	Group - B (N=40)	*P* - Value
PONV	3 (7.5%)	5 (12.5%)	0.46 (NS)
Drowsiness	1 (2.5%)	2 (5%)	0.56 (NS)
Headache	1 (2.5%)	3 (7.5%)	0.31 (NS)
Bradycardia	2 (5%)	0 (0%)	0.37 (NS)
Hypotension	0 (0%)	0 (0%)	NS
Respiratory Depression	0 (0%)	0 (0%)	NS
Dizziness	0 (0%)	0 (0%)	NS
Visual Disturbance	0 (0%)	0 (0%)	NS

5. Discussion

Endotracheal intubation is one of the most invasive stimuli in anesthesia which can lead to detrimental effects. **Reid and Brace** described, hemodynamic responses to laryngoscopy and intubation probably due to intense sympathetic discharge caused by stimulation of epipharynx and laryngopharynx. This may lead to high incidences of cardiac arrhythmias, myocardial ischemia, acute left ventricular failure, and cerebrovascular accidents following intubation in hypertensive patients. If no specific measures are taken to prevent hemodynamic responses, HR can increase from 26% to 66% and SBP can increase from 36% to 45%. Carbon dioxide pneumoperitoneum for laparoscopic surgery also increases the arterial pressure, HR, and systemic vascular resistance and decreases the cardiac output. These vasopressor responses are mainly due to release of catecholamines, vasopressin, or both; the reverse trendelenburg position further decreases the cardiac output. **Hassan *et al*.** reported high incidences of cardiac arrhythmias, myocardial ischemia, acute left ventricular failure, and cerebrovascular accidents following intubation in hypertensive patients. [12 - 14]

The advantages of using pregabalin or clonidine premedication for laryngoscopy is attenuation of cardiovascular responses to the laryngoscopy are easy drugs administration and availability with low price. Both the drugs have nociceptive effects that way be beneficial for controlling post - op pain.

In the present study, pregabalin 150 mg was chosen fearing that smaller doses may not achieve a effective decrease in postoperative pain and analgesic consumption and higher doses might cause post - op side effect and sedation. **Rastogi *et al*** studied different doses of oral pregabalin (75 and 150 mg) premedication for attenuation of haemodynamic pressor response of airway instrumentation. They showed, pregabalin 150 mg was able to achieve hemodynamic stability with no postoperative side effects with no difference in recovery and awakening times. [16]

We preferred a clonidine 200ug (dose of 4 µg/kg) in the present study because previous studies showed that administration of 4 µg/kg clonidine blunted catecholamine release during intubation and surgery and that larger clonidine doses were not more effective can cause peripheral α stimulation which could result in an increase in blood pressure. Smaller doses, nevertheless, were not adequate to blunt the reaction to laryngoscopy. In most human researches, 4 µg/kg clonidine was used without signs of peripheral α stimulation. [17]

Haemodynamics

Our study showed that,

Table - III and figure - II showed that there is no significant difference in heart rate at baseline, after premedications, 1 min and 3 min after intubation in both the groups. But there was significant decrease in heart rate at 5 min and 10 min after intubation in group - A. Thus, mean heart rate changes in the groups receiving clonidine was lesser than the group receiving pregabalin and was statistically significant ($P < 0.05$) at 5 min and 10 min.

Table - IV and figure - III showed, there was no significant difference in baseline SBP in both group. Premedication had no significant difference on SBP in two groups at 90 minute. There is significant low systolic blood pressure in Pregabalin

group after intubation at 1, 3, 5 and 10min compare to clonidine group, which is statistically significant (*P* - value <0.05) at 1 and 3min after intubation.

Table - V and figure - IV showed, there was no significant difference in mean blood pressure at baseline, after premedications, 5 min and 10 min after intubation in both the groups. There was a significant decrease in mean blood pressure in group - B compare to group - A at 1 min and 3 min after intubation.

It might be due to clonidine acts on nucleus tractus solitarius and locus ceruleus of the brainstem, activation of postsynaptic a, - adrenoceptors reduces sympathetic drive. It also activates non - adrenergic imidazoline - preferring binding sites in the lateral reticular nucleus, thereby producing hypotension and an anti - arrhythmogenic action. In the periphery, its action on presynaptic alpha - adrenoceptors at sympathetic terminals reduces the release of norepinephrine causing vasorelaxation and reduced chronotropic drive. [18]

Pregabalin attenuates pressure responses by inhibition of membrane voltage gated calcium channel, which signifies that it causes lesser calcium load on myocardium compared to clonidine. It modulates the release of excitatory neurotransmitters, reducing glutamate, noradrenaline and substance - p in hyper - excited neurons, restoring them to normal physiologic state, by reducing calcium influx at nerve terminals. Its analgesic and anticonvulsant activity makes it useful oral premedicant. [19]

Other study done by **Archana *et al***, **Chandrakant waikar et al, Devanand j et al, Asmita et al** also compared the effect of clonidine 200 µg and pregabalin 150 mg in attenuation of the hemodynamic response to laryngoscopy and intubation. They demonstrated that mean heart rate following laryngoscopy and intubation was attenuated by clonidine group significantly and Mean arterial pressure was well attenuated by pregabalin than other groups, which was observed in our study too. [20 - 23]

From all these studies and results of our study, we could say that heart rate changes are more in clonidine group and Pregabalin premedication causes significant attenuation of hemodynamic pressure response of direct instrumentation of direct laryngoscopy and intubation in dose related manner with minimum effect on heart rate.

Contrary to our findings, **Parveen et al, Gupta et al, Bahgat et al**, evaluated the clinical efficacy of oral premedication with pregabalin and clonidine for hemodynamic stability during laryngoscopy in elective surgery. They observed that Clonidine was superior to pregabalin for attenuation of the hemodynamic responses to laryngoscopy and laparoscopy. [24 - 26]

Sedation and Anxiety

Table - VI and figure - V showed, Sedation score was statistically significant in Pregabalin group at 90 minute and in post - op period. Table - VII and figure - VI showed, Anxiety score was statistically significant in Pregabalin group at 90 minute and in post - op period.

Sedative effects of Pregabalin related to binding to the α2d subunit of 'hyperexcited' voltage - gated calcium channels, which changes their conformation, reducing calcium influx at nerve terminals in the sleep related area of the brain. Pregabalin only modulates the release of excitatory neurotransmitters in 'hyperexcited neurons. [19] The sedative and anxiolytic effect of Clonidine is thought to result from an inhibitory effect as spontaneous and evoked activity of central mono - aminergic systems involved in modulation of sleep and cortical arousal. [10]

White *et al* studied different doses of pregabalin and compared it with placebo. Anxiety levels remained unchanged in their study during the preoperative evaluation period with lower dose (75mg), while they showed that dose of 300 mg of Pregabalin produced increased level of sedation after surgery, so we used 150mg of pregabalin in our study. [27] Same as our study, **Bhawna et al** compared 150mg Pregabalin and 200ug of clonidine. They achieved a better preoperative sedation with 150mg of pregabalin. [16] Another studies, where low dose of 100ug of oral clonidine caused lesser sedation preoperatively compared to 150mg pregabalin. [18]

Adverse Effects

Table - VIII and figure - VII showed, in post operative period both the groups had comparable side effects, 2 (5%) patient's developed bradycardia in clonidine group; drowsiness in 1 (2.5%) patient in clonidine and 2 (5%) patient in Pregabalin group; headache in 1 (2.5%) patient in clonidine and 3 (7.5%) patient in Pregabalin group. There was no respiratory depression, dizziness and visual disturbance in any of patient's during the first four hours after recovery from anaesthesia.

In our study, 3 (7.5%) patients had PONV in clonidine group and 5 (12.5%) patient's had PONV in pregabalin group which is not statistically significant. The incidence of nausea and vomiting after general anaesthesia has been reported to be as high as 24%. The incidence of post - operative emetic sequel was not significantly affected by premedication with Clonidine and Pregabalin groups. While **Marimony et al (2007)** found "a decreased incidence of nausea and vomiting in patients receiving Clonidine. Clonidine increases gastrointestinal motility by decreasing sympathetic outflow and increasing parasympathetic outflow from the central nervous system". [28, 29]

In our study we didn't came across hypotensive episode in either group contrary to this findings in the previous study, **Montazeri et al,** there was hypotension in 30% of the patient's premeditated with 300ug clonidine, but no patients in 150ug clonidine group. [30] We used lesser dose of 200ug clonidine as a premedicant which avoided hypotensive episode.

While **Gupta et al** didn't found any significant side effects related to pregabalin. [25] A Study conducted by **Bhawana Rastogi** found that oral Pregabalin in dosage of 75 and 150 mg was given as premedicant caused perioperative hemodynamic stability with no postoperative side effects and respiratory inadequacy. [16]

6. Conclusion

We conclude that Pregabalin is better for hypertensive response control and more effective in attenuating anxiety and stress response to endotracheal intubation compared to Clonidine but tachycardia response is better attenuated by clonidine.

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Conflicts Of Interest: - None

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