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EFFECT OF ORAL PREGABALIN AND ORAL CLONIDINE FOR ATTENUATION OF HEMODYNAMIC RESPONSES TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION: PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Laryngoscopy and endotracheal intubation are an integral part of an anaesthesiologist's contribution to patient care and are regarded as one of the core skills of anesthesiologist. A number of pharmacological measures have been used to attenuate the hemodynamic stress response associated with larngoscopy and intubation. **Aim**: To evaluate the effect of oral Clonidine 300 mcg vs oral Pregabalin 75 mg premedication in attenuating the hemodynamic response following laryngoscopy. **Methods:** The study was designed as a hospital-based prospective observational trial involving 120 patients of ASA physical status I ofeither sex scheduled to undergo elective general surgical procedures under general anaesthesia. The patients were randomly allocated to three equal groups of 40 each bymeans of a computer-generated table of random numbers. The Heart Rate, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP),Mean Arterial Pressure values, and arrhythmias (if any) were recorded. Statistical testing was conducted with the statistical package for the social science system (SPSS) version 17.0. Continuous variables were presented as mean±SD ormedian (IQR) for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. **Results:** The heart rate increased by 27.7% 1 min after direct laryngoscopy and endotracheal intubation compared to baseline value in the placebo group ($p<0.01$). Asimilar increase in pregabalin group was 29.9% and

in clonidine group was 12.7%. The mean arterial pressure increased by 28.5% in placebo group while it increased by 26.6% in pregabalin group and only by 11.17% in clonidine group compared to baseline values during laryngoscopy and intubation. Attenuation of mean arterial pressure is significant in clonidine group as compared to both pregabalin and placebo groups ($p<0.01$). With regard to arrhythmia, which was our secondary objective, it was observed that none of the patients who participated in our study developed arrhythmias, either at induction or anytime later during the surgeries. **Conclusion:** Oral clonidine (300µg) given 120 min before induction was effective in attenuating hemodynamic stress response to laryngoscopy and endotracheal intubation. There was no statistically significant difference between placebo and pregabalin groups.

Key words: laryngoscopy, Intubation, Hemodynamic stress, Oral clonidine, Oral pregabalin

Introduction:

Laryngoscopy and endotracheal intubation are an integral part of an anaesthesiologist's contribution to patient care and are regarded as one of the core skills of anesthesiologist. They are the fundamental components of airway management. Laryngoscopy itself is a noxious and highly invasive stimulus during endotracheal intubation.[1,2] Manipulation of the respiratory tract during laryngoscopy and endotracheal intubation are associated with hemodynamic and cardiovascular responses arising from increased circulating catecholamines leadingto increase in heart rate, blood pressure, myocardial oxygen demand, and dysrhythmias.[2,3-6]

The changes in heart rate and blood pressure are usually transient occurring 30 seconds after intubation and lasting for less than 10 minutes, and are usually well tolerated by 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 ischemia, left ventricular failure as a result of increased myocardial oxygen demand and cerebral haemorrhage.[1,7]

Clonidine and other α2-adrenergic agonists like Dexmedetomidine are under intense investigation as an adjunct to anaesthesia.[8] These drugs reduce anaesthetic requirements, attenuate adrenergic, hormonal, and hemodynamic stressresponses to surgery, reduce anxiety, and lead to sedation.[9] A dose of 300µg clonidine orally reduces sympathetic activity. It has been proved in many studies thatclonidine is beneficial in blunting reflex tachycardia and hypertensive responses.[10-13] The risk of undesirable side effects is extremely important in evaluating the overall safety of pre-anesthetic medication. The potentially beneficial effect of α2 adrenoceptor agonists may be negated by bradycardia and hypotension.

Gabapentin was introduced as an antiepileptic drug in 1993. But recent studies aiming attenuating hemodynamic response to laryngoscopy and intubation focussed on this effect of gabapentin.[14]

Pregabalin, like gabapentin is a novel drug that has analgesic, anticonvulsant and anxiolytic actions.[15-17] It is mainly used for the treatment of neuropathic pain, postherpetic neuralgia and as adjunctive therapy in patients with partial onset seizures. The efficacy of oral pregabalin on postoperative analgesia and reduction of parenteral analgesics has been demonstrated in several studies.

Methods:

Study area and duration:

The study was carried out in the Department of Anaesthesia and Critical Care at Government Medical College, Srinagar. After obtaining approval from Hospital Ethics Committee, a written informed consent was taken from the patients for participation in this study, who were recruited from the out-patient department at the time of pre-anesthetic check-up after meeting inclusion criteria.

The study was carried out from June 2021 to Feb 2022 over a period of 10 months.

Study population:

Inclusion Criteria: The study included patients who were:

1. ASA grade I.
2. 20-50 years of age.
3. Who gave informed written consent.
4. Patients scheduled to undergo elective surgical procedures under general anesthesia.

Exclusion Criteria: The study excluded patients with:

1. ASA physical status II or greater.
2. Age more than 50 years, less than 20 years.
3. Pregnant, lactating and menstruating females.
4. History of Drug/alcohol abuse.
5. Patients with chronic pain, psychiatric disease, peripheral vascular disease.
6. Anticipated difficult intubation.
7. Patients allergic to study medications.

Study design:

The study was designed as a hospital-based prospective observational trial involving 120 patients of ASA physical status I of either sex scheduled to undergo elective general surgical procedures under general anaesthesia.

Methodology:

Patients selected for surgery were admitted 24 hours prior to surgery. Pre- anaesthetic evaluation was done at this stage. Age, gender, weight, type of surgery, ASA physical status was noted down in all patients. A thorough history including history of any co-morbid disease, previous anaesthetic exposure, smoking, medications, allergy to any drugs and personal habits was elicited. Any history of palpitations and previous heart conditions was

duly noted.

General physical examination as well as systemic examination of cardiovascular system, respiratory system and central nervous system was performed. Airway assessment was also done to predict any difficult intubation. All routine investigations like haemoglobin, platelet count, BT/CT, blood urea and serum Creatinine, blood glucose, chest X-ray (P/A view), ECG were checked. The patients were advised to remain fasting overnight. Double blinding was done by means of sealed envelope technique using 120 similar looking thick opaque envelopes and the code name 1, 2, or 3 was mentioned on top of the envelope. The assistant separated the tablets of Clonidine (300 micrograms), capsules of pregabalin (75mg), and tablets of placebo into 3 equal groups of 40 each. The tablets were taken out of their sachets and loaded separately into the envelopes and sealed in such a way that an envelope was containing either,

Tablets of Clonidine (300 µg)
OR
Capsules of Pregabalin (75mg)OR
Placebo tablet (1 tablet)

Thus, three groups of 40 envelopes were prepared containing either tablets of Clonidine, capsules of pregabalin or tablet of Placebo with the same code (1 or 2 or 3)mentioned on them. Only the assistant was aware of the code identity which was revealed at the end of the study.

The patients were randomly allocated to three equal groups of 40 each bymeans of a computer-generated table of random numbers so that:

Group 1: Patient received tablets from the envelope labelled code "1".Group 2: Patient received tablets from the envelope labelled code "2'.Group 3: Patient received tablets from the envelope labelled code "3"

Anesthesia protocol:

Intravenous line was established with an 18 G cannula and infusion of Ringer Lactate ml/kg started. Multichannel monitor with all the standard monitoring including heart rate, non-invasive blood pressure, SpO_2 and ECG was attached to the patient.

Intravenous fentanyl 1 mcg/kg was given. Pre-oxygenation with 100% O_2 was done for 3 minutes. Anesthetic induction was done with Inj. Propofol 2mg/kg and subsequent relaxation accomplished with Inj. Succinylcholine 1.5 mg/kg.

Direct laryngoscopy and endotracheal intubation were performed by an experienced anesthesiologist. Duration of laryngoscopy was recorded in all the patients. Any patient with more than one attempt required for intubation was dropped out from the study. Similarly, patients requiring more than 30 seconds for intubation were dropped out from the study. No surgical stimulus was applied for the first 10 minutes. Anesthesia was maintained with Oxygen (33%), Nitrous oxide (66%) and Isoflurane (1%) used as inhalational agent. Inj. Atracurium 0.5 mg/kg was used as a muscle relaxant intra-operatively. At the end of the surgical procedure, residual neuromuscular block was antagonized with Inj. Neostigmine 50µg/kg IV and Inj. Glycopyrrolate 10µg/kg IV. After extubation the patients were shifted to post- anesthesia recovery room and discharged from recovery once adequate level of

consciousness with adequate muscle power was achieved.

Outcome measures:

The following parameters were observed and recorded:

The Heart Rate, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure values, and arrhythmias (if any) were recorded at following intervals:

- Baseline,
- Before induction,
- Immediately before intubation,
- One minute after intubation,
- Three minutes after intubation,
- Five minutes after intubation,
- Ten minutes after intubation.

Any side effects like hypotension, bradycardia, dry mouth, vomiting, or others were recorded. Hypotension, defined as 20% fall of blood pressure below baseline, was treated with increasing infusion rate of crystalloids and aliquots of Inj. Mephentermine 6mg. Bradycardia, defined as a heart rate slower than 60 beats per minute, was treated with Inj. Atropine 0.5 mg/kg.

STATISTICAL ANALYSIS

Statistical testing was conducted with the statistical package for the social science system (SPSS) version 17.0. Continuous variables were presented as mean±SD or median (IQR) for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The comparison of normally distributed continuous variables between the groups was performed using ANOVA (Analysis of Variance). If the F value was significant, Tukey or Tamhane's T2 multiple comparison test was used to assess the differences between the individual groups. Nominal categorical data between the groups was compared using Chi-squared test or Fisher's exact test as appropriate. Non-normal distribution continuous variables were compared using Kruskal Wallis test and further paired comparisons were done using Mann Whitney U test. For all statistical tests, a p value less than 0.05 was taken to indicate a significantdifference.

Conflict of Interest: nil

Funding: Nil

Results:

120 patients undergoing elective surgery under General Anesthesia with endotracheal intubation divided randomly into 3 groups with 40 patients each. All the patients in three study groups were comparable regarding the demographic profile [table 1].

Table 1: Demographic Profile of the Patients

Variable	Group1	Group 2 (n=40)	Group 3 (n=40)	P-value

	(n=40)			
Age(years)	**37.8±6.70**	**39.7±8.41**	**36.6±8.30**	**0.208**
Weight(kg)	**58.2±6.21**	**57.5±6.16**	**58.7±6.92**	**0.686**
Height(cm)	**160.3±6.49**	**169.2±6.07**	**166.4±5.44**	**0.562**
Gender(M/F)	**22/18**	**18/22**	**18/22**	**0.586**
ASA status I/II	**32/8**	**30/10**	**31/9**	**0.761**

Values in the table are mean ± SD or absolute numbers (percentage). SD = Standard deviation, ASA = American Society of Anesthesiologists.

The heart rate increased by 27.7% 1 min after direct laryngoscopy and endotracheal intubation compared to baseline value in the placebo group ($p<0.01$). A similar increase in pregabalin group was 29.9% and in clonidine group was 12.7% [table 2].

Systolic blood pressure in the placebo group 1 min after direct laryngoscopy and endotracheal intubation was 27% from baseline, with pregabalin group the maximum rise in systolic blood pressure was 25% and with clonidine it was only 9% from baseline values. Among the two drugs studied, only clonidine attenuated the rise in SBP following laryngoscopy ($p<0.01$) [Fig 1].

The rise in DBP 1 minute after direct laryngoscopy and endotracheal intubation in the placebo group was 29.6% when compared to baseline values ($p<0.01$). In pregabalin group the increase was 27.8% and in clonidine group it was 12.9%. Among the two study drugs, clonidine showed attenuation of DBP following laryngoscopy and intubation while pregabalin was not successful in attenuating DBPfollowing laryngoscopy and intubation [Fig 2].

The mean arterial pressure increased by 28.5% in placebo group while it increased by 26.6% in pregabalin group and only by 11.17% in clonidine group compared to baseline values during laryngoscopy and intubation. Attenuation of mean arterial pressure is significant in clonidine group as compared to both pregabalin and placebo groups ($p<0.01$) [Fig 3].

Table 2: Changes in mean heart rate in three groups (beats per min):

Heart Rate	Group 1 (Mean±SD)	Group 2 (Mean±SD)	Group 3 (Mean±SD)	P-value (ANOVA)
Base line	**78.7±10.13**	**80.6±7.10**	**81.2±10.56**	**0.464 (SNSD)**
Before Induction	**65.7±12.54**	**85.6±9.48**	**86.5±10.36**	**<0.001 (SSD)**
Immediate before Intubation	**75.8±9.29**	**88.7±12.64**	**87.6±10.23**	**<0.001 (SSD)**

1 min after intubation	88.7±10.90	104.7±9.45	103.5±11.0	<0.001 (SSD)
3 min after intubation	85.3±11.27	98.8±9.60	100.5±8.41	<0.001 (SSD)
5 min after intubation	84.2±9.92	91.5±11.27	93.3±8.40	<0.001 (SSD)
10 min after intubation	67.4±10.78	86±11.02	87.5±7.66	<0.001 (SSD)

Group 1 = Clonidine; Group 2 = Pregabalin; Group 3 = Placebo

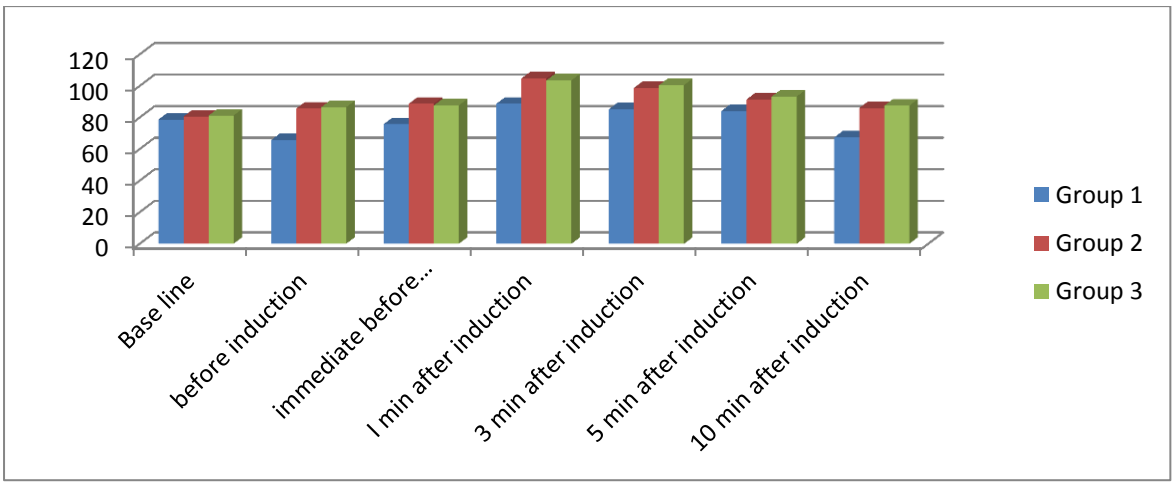

Fig 1: Changes in mean systolic Blood Pressure in three groups(in mm of Hg)

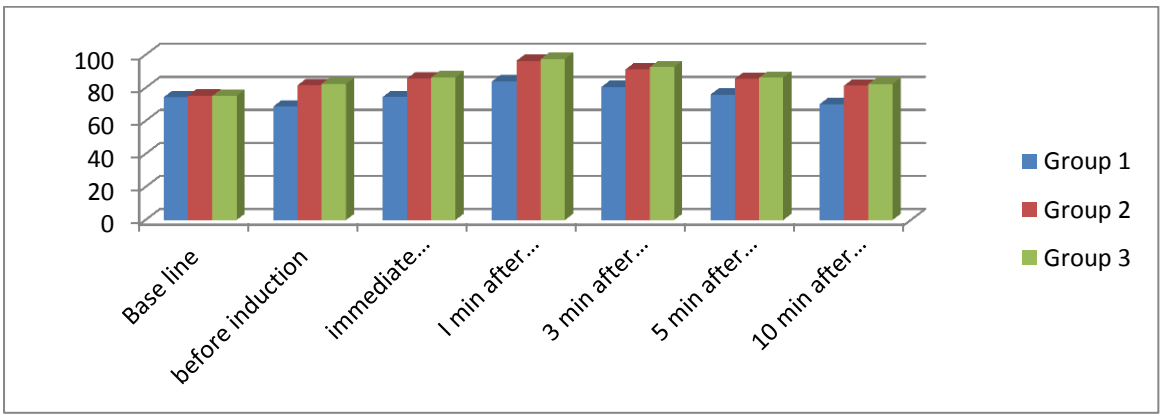

Fig 2 :Changes in mean diastolic BP in three groups (in mm of Hg)

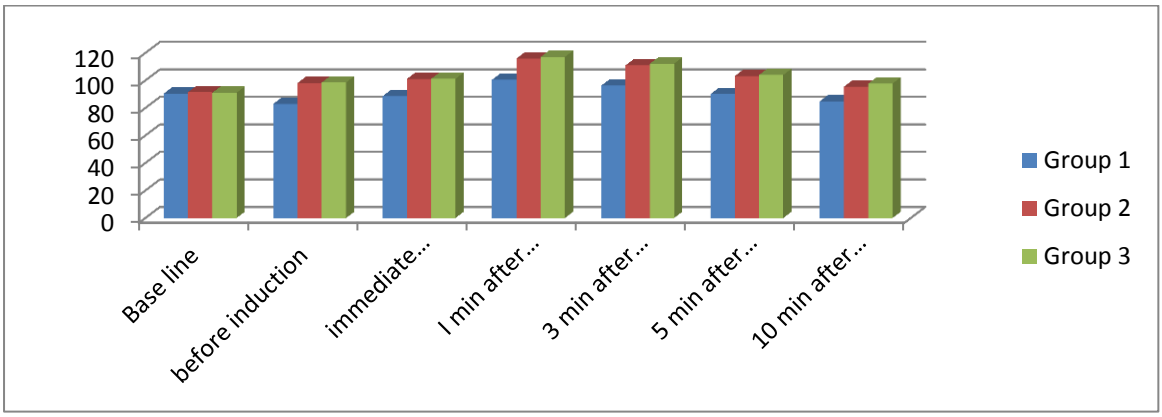
120
100
80
60
40
20
0
Base line
before induction
immediate...
I min after...
3 min after...
5 min after...
10 min after...
Group 1
Group 2
Group 3

Fig 3: Changes in Mean MAP in three groups
(in mm of Hg)

Discussion:

Laryngoscopy and endotracheal intubation are the fundamental componentsof airway management. Manipulation of the respiratory tract such as during laryngoscopy and endotracheal intubation are associated with hemodynamic and cardiovascular responses consisting of increased circulating catecholamines, heartrate, blood pressure, myocardial oxygen demand, and cardiac dysrhythmias.[18]

The cardiovascular responses to noxious airway manipulation are initiated by proprioceptors responding to tissue irritation in the supra-glottic region and trachea. Located in close proximity to the airway mucosa, these proprioceptors consist of mechano-receptors with small diameter myelinated fibers. The glossopharyngeal and vagal afferent nerves transmit these impulses to the brain stem, which, in turn, causes widespread autonomic activation through both the sympathetic and parasympathetic nervous systems.

Mean duration of laryngoscopy in all the three groups was l8 seconds. A linear increase in heart rate and mean arterial pressure during the first 45 seconds has been observed.[19] Robert K Stoelting[19] noted that the best way to prevent laryngoscopic reactions was to minimize the duration of laryngoscopy and intubation. He noted that if laryngoscopy and intubation were performed within 15 seconds, the hemodynamic changes seemed to be minimal. Hence, in our study the duration of laryngoscopy was restricted as much as possible and all the laryngoscopy and intubations were performed by an expert anesthesiologist.

Clonidine and pregabalin have been administered orally in various doses for blunting the cardiovascular response to laryngoscopy and intubation. Oral Clonidine is used in the range of 100µg-300µg[10-13] and Oral Pregabalin is used in the range of 75mg-300mg. In our study we used ‘300µg’ clonidine and ‘75mg’ Pregabalin.

In the present study, the groups were comparable with respect to their demographic variables and their baseline values of Heart Rate, Systolic Blood Pressure and Diastolic Blood Pressure and Mean Arterial Pressure. There was a significant increase in SBP, DBP, MAP and Heart Rate compared to baseline in all the groups during laryngoscopy and endotracheal intubation. But there was lesser rise inclonidine group when compared to other two groups.

The heart rate increased by 27.7% 1 min after direct laryngoscopy and endotracheal intubation compared to baseline value in the placebo group ($p<0.01$). A similar increase in pregabalin group was 29.9% and in clonidine group was 12.7%. Attenuation of rise in the heart rate by clonidine is evident and statistically significant when compared with pregabalin & placebo ($p<0.001$).

Subsequently heart rate started to settle down and approached to baseline in clonidine group at the end of 5 min but was still high in pregabalin and placebo groups even after 10 min. Though there were decreased heart rate values in pregabalin group there was no statistically significant difference when compared to placebo indicating that pregabalin was not successful in attenuating the increase inHR following laryngoscopy and endotracheal intubation.

Systolic blood pressure increased maximally in the placebo group 1 min afterdirect laryngoscopy and endotracheal intubation (27% from baseline). It gradually decreased to near baseline values over 10 minutes. With pregabalin group the maximum rise in systolic blood pressure was 25% and with clonidine it was only 9% from baseline values. Among the two drugs studied, only clonidine attenuated the rise in SBP following laryngoscopy ($p<0.01$). At the end of 5 minutes, SBP returned tobaseline value in clonidine group but not in other two groups. There was no statistically significant difference between pregabalin and placebo in attenuation of SBP.

The rise in DBP 1 minute after direct laryngoscopy and endotracheal intubation in the placebo group was 29.6% when compared to baseline values($p<0.01$). In pregabalin group the increase was 27.8% and in clonidine group it was 12.9%. Among the two study drugs, clonidine showed attenuation of DBP following laryngoscopy and intubation while pregabalin was not successful in attenuating DBP following laryngoscopy and intubation.

Similarly mean arterial pressure increased by 28.5% in placebo group while it increased by 26.6% in pregabalin group and only by 11.17% in clonidine group compared to baseline values during laryngoscopy and intubation. Attenuation of mean arterial pressure is significant in clonidine group as compared to both pregabalin and placebo groups ($p<0.01$).

There was significant reduction in HR, BP in clonidine group during the pre- induction period (120 min after oral administration) which was not observed with other two groups. In the other two groups, instead of fall, a rise in HR & BP was observed during the pre-induction

period.

The efficiency of clonidine in attenuation of cardiovascular responses similarto our study has been verified by many other studies.

Batra YK, Indu B, Puri GD[20] have studied the attenuation of pulse rate and blood pressure response to laryngoscopy and tracheal intubation by clonidine in forty healthy patients. Heart rate and blood pressure were significantly lower in the clonidine treated group immediately after intubation ($p<0.001$).

Laurito et al [21] found that clonidine blunted the hemodynamic response (HR, SBP and DBP) to 15 sec laryngoscopy but not to 45 sec laryngoscopy when compared with the corresponding control group.

Ghignone M [22] et al studied the effects of oral clonidine on depths of Fentanyl anaesthesia and on cardiovascular response to laryngoscopy & intubation in 24 patients undergoing aorto-coronary bypass surgery and concluded that oral clonidine reduced the fentanyl requirement and prevented the hemodynamic response to intubation.

All the above authors have used 5µg/kg clonidine which will be 300µg in an average 60kg adult. In our study we have used single dose of 300µg clonidine 120 min before induction. Our study fully confirms the findings of the above authors i.e. clonidine 300µg decreases the stress response (HR, SBP and DBP) to laryngoscopy and endotracheal intubation.

Gupta K, et.al [23] in their placebo controlled randomized comparative study evaluated the clinical efficacy of oral premedication with Pregabalin (150mg) or Clonidine (0.2mg) for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy given 75 to 90 minutes before surgery. Clonidine was superior to pregabalin for attenuation of the hemodynamic responses to laryngoscopy and laparoscopy, but it increased the incidence of intra-and postoperative bradycardia. No significant differences in the parameters of recovery were observed between the groups. Results of our study are in accordance though the doses of clonidine and pregabalin we used were 0.3mg and 75mg respectively.

Bhawna Rastogi et al[24] evaluated the safe and clinically effective dose of oral pregabalin premedication for attenuation of hemodynamic pressor response of airway instrumentation. The hemodynamic pressor response of airway instrumentation was attenuated in a dose-related fashion. The premedicated patients were hemodynamically stable perioperatively without prolongation of recovery time and side-effects. Our study confirms these findings i.e.,

pregabalin 75mg (used in lower doses) doesn't attenuate hemodynamic pressor response of airway instrumentation.

Ayya Syama Sundar et al[25] evaluated and compared single preoperative dose of pregabalin to a placebo regarding hemodynamic responses to laryngoscopy and endotracheal intubation, to assess perioperative fentanyl requirement and any side- effects. The present study shows that a single oral dose of 150 mg pregabalin given 1 h before surgery attenuated the pressor response to tracheal intubation in adults, but the drug did not show any effect on perioperative opioid consumption and was devoid of side-effects in the given dose. In our study we didn't find any significant attenuation of hemodynamic response to laryngoscopy and intubation with 75mg ofpregabalin.

Ebru Salman et al[26] investigated the effect of pregabalin premedication on the hemodynamic responses to laryngoscopy and intubation. They concluded, oral pregabalin premedication at a dose of 150 mg one hour prior to surgery attenuates early hemodynamic changes associated with laryngoscopy and endotracheal intubation. In our study dose of pregabalin used was 75mg and we didn't corroborate these findings.

Our study partly confirms the findings of above authors. Even we found no significant attenuation of HR with laryngoscopy and endotracheal intubation with single dose of pregabalin 75mg.

It is pertinent to mention that no arrhythmias were observed in the patients who participated in our study, neither at induction nor any time later during the surgeries. But, as previously mentioned, the patients in all the study groups belonged to ASA-1 physical status, so the chances of getting arrhythmias were meagre. But, since the study supports clonidine with regard to better hemodynamic parameters, it can be concluded that the patients belonging to this group are least likely to be prone to arrhythmias, as the latter develop with persistent or precipitous alteration ofhemodynamics.

In our study no significant attenuation of pressor response was observed in pregabalin group during laryngoscopy and endotracheal intubation. Our study design & patient selection with respect to age, sex and ASA status was similar to the abovestudies. The negative result that pregabalin does not attenuate stress response could be due to the lower single dose of pregabalin (75mg) which we used. Our negative result may be explained by the findings of Bhawna Rastogi and Kumkum Gupta [24] who in their study found that the hemodynamic pressor response of airway instrumentation by pregabalin was attenuated in a

dose-related fashion. This is further corroborated by Preetha Elizabeth et al[25] who found 150 mg pregabalin as effective premedication for attenuation of pressor response to laryngoscopy and intubation.

Conclusion:

Oral clonidine (300µg) given 120 min before induction was effective in attenuating hemodynamic stress response to laryngoscopy and endotracheal intubation. There was no statistically significant difference between placebo and pregabalin groups.

From the present study it can be concluded that:

- Oral clonidine (300µg), given 120 min before induction is effective in attenuating both HR & BP rise associated with laryngoscopy and endotrachealintubation.
- Oral pregabalin (75mg), given 120 min before induction is not effective in attenuating stress response to laryngoscopy and endotracheal intubation.

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