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A Comparative Study between Oral Premedication with Pregabalin and Clonidine during Laryngoscopy for Hemodynamic Stability

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ABSTRACT

Introduction: To compare the efficacy of oral pregabalin and oral clonidine in the attenuation of the hemodynamic pressor response to laryngoscopy and endotracheal intubation.

Method: 60 normotensive patients with ASA physical status I and II of either gender posted for elective surgery under general anaesthesia were divided into two groups of 30 each randomly i.e. group C, oral clonidine (100µg) and group P, oral pregabalin (150 mg) respectively. Drug was given 1 hour prior to induction. Hemodynamic parameters were recorded starting from baseline, before and after administering drug, after intubation and at intervals of 1, 3,5,10, 15 minutes. Any side effect occurring was noted.

Results: Incidence of increase in heart rate was seen at all stages of airway manipulation in both groups but lower in group P as compared to group C at every stage. Systolic blood pressure in both groups rose after administering drug till intubation. However, values were higher in group C as compared to group P. There was a dip seen in diastolic blood pressure in both groups after 15 minutes of intubation, but more in group C as compared to group P. Group P showed significant lower mean arterial pressure than group C, thus proving to be a better choice. All other parameters i.e. electrocardiogram, SpO_2 and $EtCO_2$ didn't show significant differences.

Conclusion: It can be concluded that pregabalin is a better drug than clonidine in attenuating pressor response caused by direct laryngoscopy and endotracheal intubation.

Keywords: oral pregabalin, oral clonidine, direct laryngoscopy, intubation, pressor response.

INTRODUCTION

Airway manipulation like laryngoscopy and endotracheal intubation generally leads to cardiovascular stress responses which are characterised by tachycardia, rise in blood pressure and dysrhythmias due to sympathetic reflex stimulation, although it is transient, variable and unpredictable.

Increase in heart rate and blood pressure are two dynamic predictors of perioperative cardiac morbidity, so avoidance of these pressor responses to laryngoscopy and intubation remains an essential clinical goal particularly for the patients with cardiac or cerebral disease [(1)]. Other adverse effects can be cardiac arrhythmias, left ventricular dysfunction, myocardial ischaemia and cerebral haemorrhage.

The haemodynamic pressor responses during laryngoscopy and airway instrumentation should be suppressed especially in patients with cardiovascular or neurosurgical diseases to balance the myocardial oxygen supply and demand. It leads to safe conduct of anaesthesia [(2)].

Over the years, many research studies have been conducted to find out ways to decrease the pressor response caused by laryngoscopy and tracheal intubation using various inhalational and pharmacological agents [(3)].

Various pharmacological drugs are used to attenuate the pressor responses and maintain hemodynamic stability. The commonly used drugs are vasodilators, narcotics, β-blockers, calcium channel blockers, lignocaine, Clonidine and other sympatholytics.

Clonidine is in clinical use since 1996 as a popular antihypertensive drug and is an imidazoline derivative, central sympatholytic drug. It is a partial agonist with high affinity and high intrinsic activity at alpha2 receptors to decrease sympathetic outflow.

Pregabalin is a gabapentinoid compound which was made in 1990 as an anticonvulsant. It is structurally but not functionally related to gamma aminuteo butyric acid (GABA), an inhibitory neurotransmitter. It decreases the synthesis of the neurotransmitter glutamate system. It acts as good analgesic, anticonvulsant and anxiolytic drug[4].

In this study, we aimed to compare at efficacy of oral clonidine versus oral pregabalin for attenuation of hemodynamic response to laryngoscopy and intubation.

MATERIAL AND METHOD

After obtaining Institutional Ethics Committee clearance, study was conducted on 60 patients in American Society of Anaesthesiologists (ASA) grade I and II, of both sex and 30-70 years age group, undergoing elective surgery under general anaesthesia. All participants were subjected to pre-anaesthetic evaluation and relevant laboratory investigations. Informed written consent was obtained from all the patients.

No. Of cases: 60 normotensive patients were randomly divided into two groups:

- Group C(n=30):Clonidine
- Group P(n=30): Pregabalin

Sample size calculation: By keeping the significance level of 5%, power of the study at 80% the sample size was calculated using Winpepi statistical package. The minimum sample size obtained is 10 per group but, considering dropout rate and for effective study, we chose a sample size of 30 participants per group, making total sample size as 60.

Method of randomization: 60 patients were randomly divided into two groups by a computer generated random number table. The random allocation sequence generation and group allocation was done by an anaesthesiologist who was not aware of the study protocol and participating in the study. Participants were enrolled for the study by the investigator. The patient and investigator were not aware of the drugs given. The drug packet were prepared and labelled as “C” and “P” respectively. These were administered by the theatre anaesthesiologist, who is not part of data collection and analysis.

60 patients will be divided into two equal groups: Group C and Group P.

- Group C(n=30):premedication with tablet clonidine 100 µg
- Group P(n=30): premedication with tablet pregabalin 150 mg

Exclusion criteria used during selection of patients was as follows patient's with cardiac, respiratory and renal disease, difficult intubation, on prolong antihypertensive drugs, sedatives and hypnotic drugs, presence of known allergy to any anaesthetic medication and obese patient.

Procedure: On arrival in pre-operative room monitors were attached and baseline heart rate and systolic, diatolic and mean arterial blood pressure were recorded. Clonidine and pregabalin was given 1 hour prior to induction respectively. On OT table, patient was started with crystalloid infusion of 6-8ml/kg and pre-medicated with injection glycopyrolate (0.004mg/kg), injection midazolam(0.02mg/kg),injection ondansetron(0.1mg/kg), injection fentanyl(2mcg/kg). Patient was pre-oxygenated for 3 minutes with 100% oxygen and induced with injection propofol(2mg/kg).

Volume 4, Issue 2; March-April 2021; Page No 757-764

The direct laryngocopy and intubation was facilitated with injection succinylcholine(2mg/kg). Anesthesia was maintained on isoflurane,nitrous oxide(67%) and oxygen (33%) with intermittent muscle relaxant injection vecoronium bromide. Parameters like heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, electrocardiogram, pulse oximeter(SpO2), and ETCO2 were continuously monitored. These were recorded before administering drug and after intubation and 1,3,5,and 10 minutes, thereafter at every 15 minutes interval till end of surgery. Patients were observed for complications of hypotension, bradycardia, hypertension, arrhythmias, hypoxia, bronchospasm and treated accordingly. After completion of surgery, neuromuscular block was reversed with appropriate doses of injection neostigmine(0.05mg/kg) and injection glycopyrolate(0.008mg/kg) , patient was extubated after meeting extubation criteria..Patients were observed post-operatively for 1 hour for any complications like need of post operative analgesia opioid medication,incidence of nausea and vomiting.

All cases were completed in stipulated time. Data was collected, compiled and tabulated. The statistical analysis was done using parametric test and the final interpretation was based on Z-test [standard normal variate] with 95% level of significance. Confidence interval is taken as 95%, so p value less than 0.05 is considered statistically significant. Results were statistically analysed.

Quantitative data was analysed by student “t” test.

Qualitative data was analysed by chi square test.

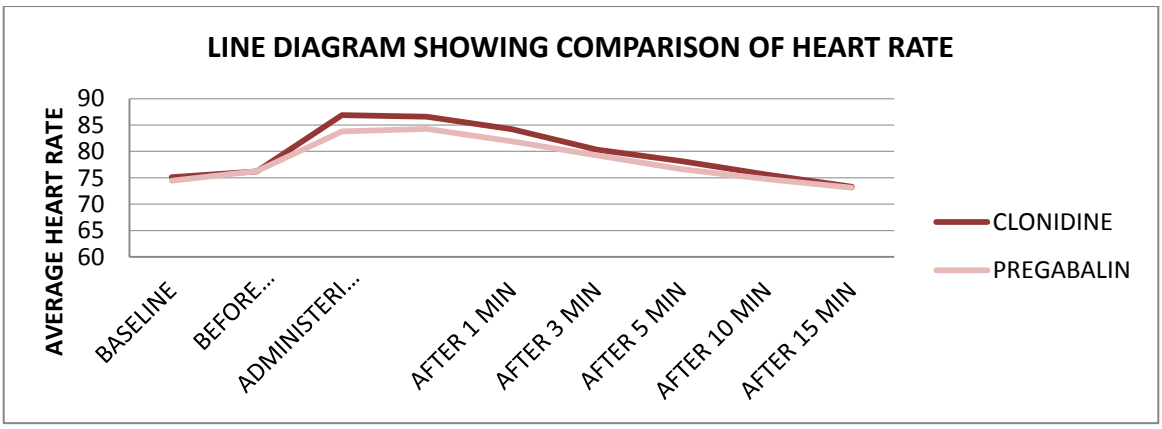
Winpepi software was used to analyse statistical data.

OBSERVATION AND RESULTS

DEMOGRAPHIC VALUES			
CATEGORY	CLONIDINE	PREGABALIN	P VALUE
	MEAN±SD		
AGE	42.7±8.83	43.6±11.66	0.7373
WEIGHT	57.60±7.295	54.27±5.477	0.062
GENDER(MALE/FEMALE)	14/16	13/17	0.79
ASA (I/II)	12/18	10/20	0.59

The above data does not show any statistically significant differences in their age, gender and weight distribution and in terms of ASA grading. (P> 0.05).

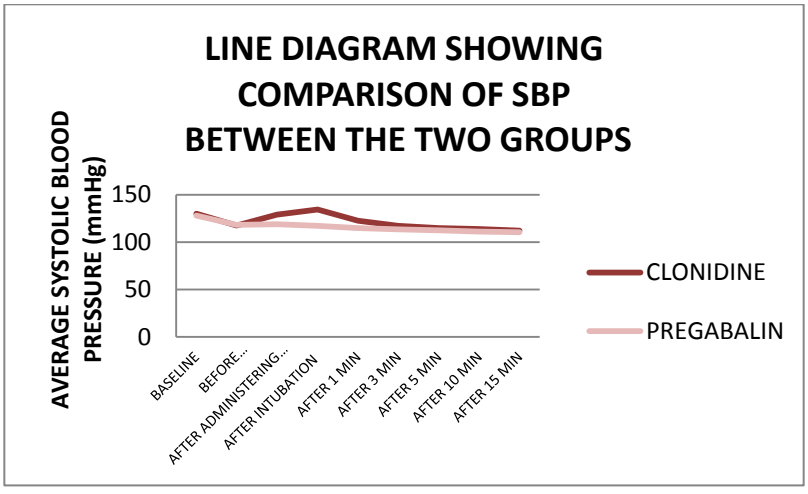
COMPARISON OF HEART RATE IN STUDY GROUPS



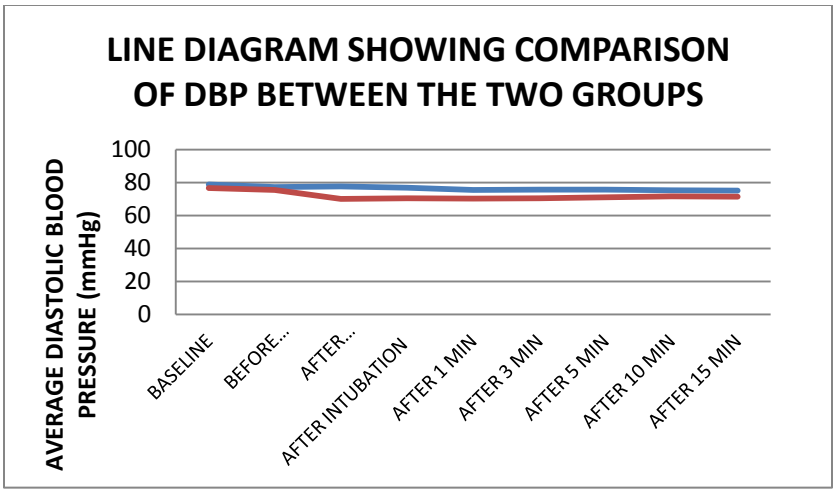
Volume 4, Issue 2; March-April 2021; Page No 757-764

COMPARISION OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE

INTERVALS	SBP			DBP		
	C	P		C	P	
	MEAN±SD	MEAN±SD	P VALUE	MEAN±SD	MEAN±SD	P VALUE
BASELINE	130.03±8.41	128.03±8.08	0.3515	78.86±5.52	76.8±6.97	0.2095
BEFORE ADMINISTERING DRUG	117.6±7.52	118.3±6.39	0.6991	77.4±4.58	75.63±6.16	0.2117
AFTER ADMINISTERING DRUG	128.93±7.2	118.76±7.07	0.0001	77.8±5.77	70.16±5.54	0.0001
AFTER INTUBATION	134.33±7.32	117.3±7	0.0001	77.03±4.95	70.63±4.55	0.0001
AFTER 1 MIN	122.46±6.08	114.8±6.75	0.0001	75.56±4.46	70.46±4.76	0.0001
AFTER 3 MIN	117.2±6.29	113.6±6.24	0.3	75.86±4.49	70.6±5.02	0.0001
AFTER 5 MIN	114.83±6.58	112.53±5.92	0.1600	75.73±3.94	71.2±4.51	0.0001
AFTER 10 MIN	113.66±6.34	111.06±5.63	0.0984	75.43±4.09	71.63±4.36	0.01
AFTER 15 MIN	111.96±6.53	110.4±5.96	0.3378	75.2±4.82	71.46±4.4	0.0027



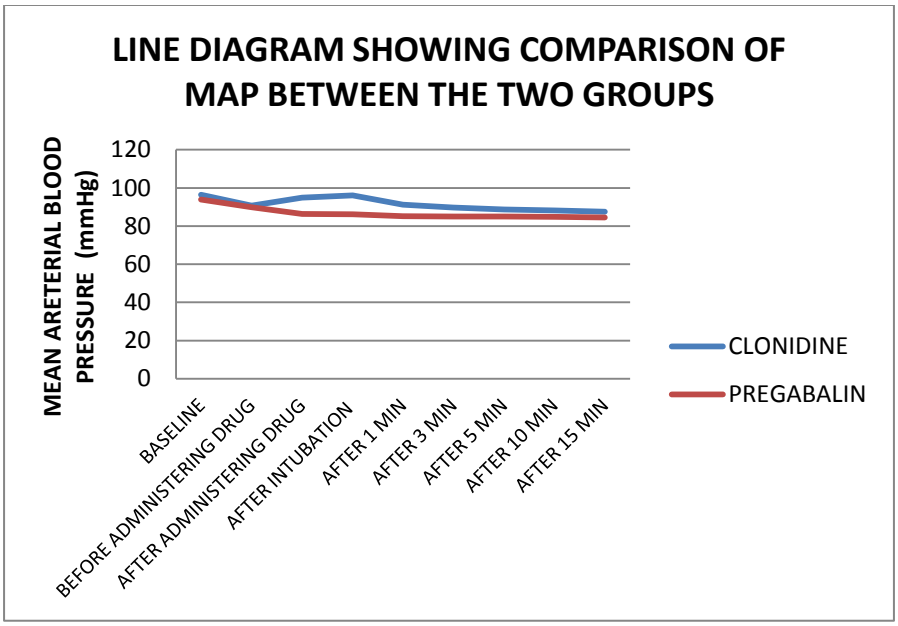
Volume 4, Issue 2; March-April 2021; Page No 757-764



COMPARISON OF MEAN ARTERIAL BLOOD PRESSURE IN STUDY GROUPS

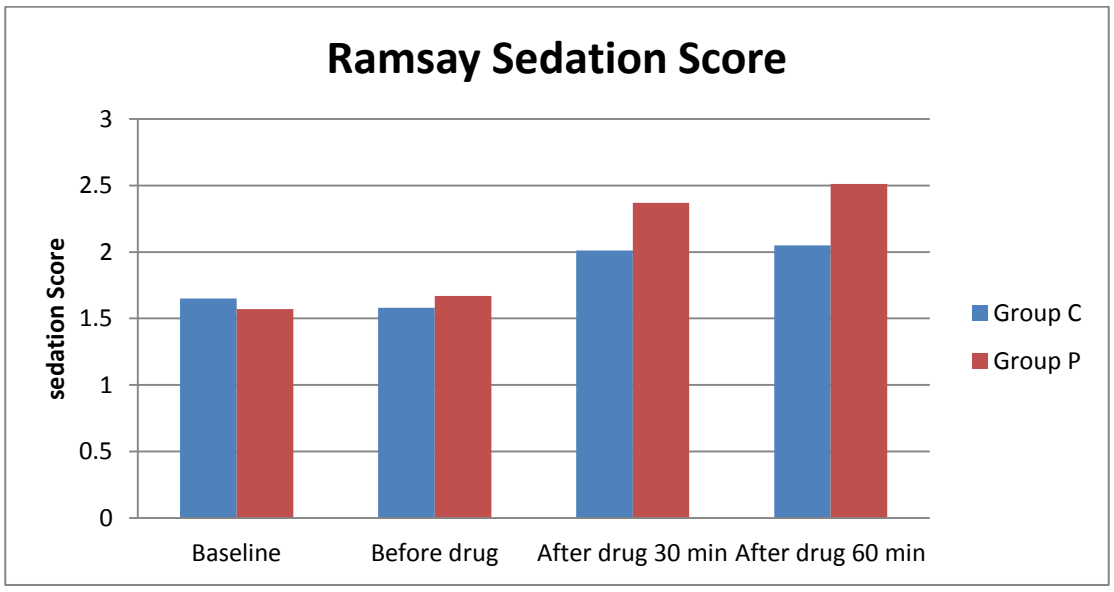
INTERVALS	C MEAN ±SD	P MEAN ±SD	P VALUE
BASELINE	96.46±5.77	93.88±6.35	0.105
BEFORE ADMINISTERING DRUG	90.8±3.92	89.87±4.61	0.4034
AFTER ADMINISTERING DRUG	94.84±4.63	86.37±4.8	0.0001
AFTER INTUBATION	96.13±4.31	86.21±4.19	0.0001
AFTER 1 MIN	91.2±3.9	85.24±4.26	0.0001
AFTER 3 MIN	89.64±4.25	84.94±4.32	0.0001
AFTER 5 MIN	88.77±3.57	84.98±3.95	0.0003
AFTER 10 MIN	88.18±3.46	84.78±3.73	0.0005
AFTER 15 MIN	87.46±3.31	84.44±3.54	0.0012

Volume 4, Issue 2; March-April 2021; Page No 757-764



ECG and SpO_2 were monitored continuously in all cases for both the groups. ECG and SpO_2 were within normal limits throughout the procedures in all the patients.

COMPARISION OF RAMSAY SEDATION SCORE



Graph showing Ramsay Sedation Score

We recorded sedation score at various time intervals as shown in table.Sedation score was highly significantly in group P in comparison to group C after administration of drug.

Post-operative side effects: awakening and recovery time were similar in both the groups. We did not observe any significant side effects in the form of bradycardia, hypotension, nausea or vomiting.

DISCUSSION

Demographic profile:

The patients in both the groups did not show any statistically significant differences in their age, gender and weight distribution and in terms of ASA grading. (P> 0.05)

Volume 4, Issue 2; March-April 2021; Page No 757-764

Hemodynamic parameters:

Baseline: baseline values (before administering any drug) of HR, SBP, DBP, MAP and SPO_2 were comparable in both the groups C and P, i.e. p value was not significant (p >0.05).

Heart rate: it was analysed quantitatively within groups for each stage from baseline to 15 minutes after intubation. There was a clinically and statistically no significant difference in heart rate values during any stage (p<0.05). The heart rate was more or less near the normal range at baseline. The heart rate in both the groups is mildly raised after administering the drug and till intubation was done. However, the heart rate was comparatively always noted to be on lower side in group P in comparison with group C at every stage.

Systolic blood pressure: There was no statistically significant difference in systolic blood pressure values between the two groups, at baseline and before administration of study drugs (p=0.6991).After administering the drug, the systolic blood pressure had rise in the groups C and P immediately after tracheal intubation, however, the values were more in the clonidine group in comparison to pregabalin group and this was significant statistically (i.e. p <0.05). The maximum rise in systolic blood pressure values in the C group was seen immediately after intubation , while systolic blood pressure was always on lower side in the P group throughout the study period.

Diastolic blood pressure:

In the clonidine group, a marginal decrease in mean DBP was observed at 1 minute after intubation when compared with baseline DBP and was statistically significant. Thereafter it remains more or less same. In the pregabalin group, the decrease in mean DBP observed is significant when compared with basal DBP 1 hour after administering the drug, but thereafter it remains more or less stable after tracheal intubation and after 1 minute and 3 minute of intubation to slightly increase after 5minute and remain more or less stable thereon. Statistical evaluation between both the groups showed that the decrease in mean DBP in the pregabalin group was statistically significant in comparison to decrease in mean DBP in the clonidine group.

Mean arterial pressure:

The mean arterial pressure was lower than baseline after administering the drug in both the cases. It increased after 1 hour of administering the drug and till intubation in the clonidine group and then started to decrease after 1 minute of endotracheal intubation and further trend of decrease continued to 3 minute, 5 minute, 10 minute and 15 minute after intubation. Whereas in the pregabalin group, after 1 hour of administering the drug, the mean arterial pressure continued declining after intubation at 1 minute, 3 minute , 5 minute, 10 minute and 15 minute after intubation and this decline was statistically significant (i.e. p <0.05).

Ramsay sedation score: It was recorded at various time intervals from baseline to postoperatively 1 hour. Sedation score was significantly higher in group P as compared to group C after administration of drugs at 30 minutes and 60 minutes. Patients in Group P are calm and less anxious.

ECG and oxygen saturation were continuously monitored and were within normal limits.

Post operatively, awakening and recovery times were similar in both the groups. We didn't observe any significant side effects in the form of bradycardia, hypotension, nausea or vomiting.

In 1988, Indu B, Batra YK, Puri GD[5] attempted to attenuate the pressor response due to laryngoscopy and intubation by giving oral clonidine as premedicant drug. Group A (placebo) and group B, which received oral clonidine in dose of 5µg/kg 90 minutes prior to induction found that increase in heart rate was significantly lesser in group B as compared to group A (p<0.001).

Archana K [6] in 2015, did a comparative study between oral pregabalin and clonidine for blunting the intubation stress response with 150mg and 200µg doses respectively in two groups of 30 patients in each group. It was noted that heart rate increased after 1minute and 3 minutes of intubation in pregabalin group more than clonidine. Also, at 5 and 10 minutes, there was no significant difference among both the groups. In case of blood pressure, pregabalin proved to better drug in controlling the rise as compared to clonidine. Thus, it was stated that both the drugs were effective in decreasing the hemodynamic reflex to intubation but pregabalin was better in attenuating the pressor response than

Volume 4, Issue 2; March-April 2021; Page No 757-764

clonidine. While clonidine was more effective in blunting the tachycardia.

In 2016, Shirin Parveen Negi et al [(7)] did a comparative study between oral pregabalin versus oral clonidine as premedicants to circumvent stress responses to airway manipulation in patients undergoing laproscopic cholecystectomy. They performed study on 80 healthy patients of ASA grades I and II. These patients were randomly allocated into two groups i.e. group A receiving clonidine as 0.3mg and group B receiving pregabalin as 150mg, 60 minutes prior to induction. In this study it was noted that after administration of drugs, there was significant statistical difference in systolic pressures between two groups($p<0.05$). Lowering of blood pressure as compared to baseline was more in clonidine group than pregabalin group. Also, it was observed that systolic blood pressure remain more or less same in clonidine group i.e. better controlled than pregabalin group. In case of diastolic blood pressure, readings were found similar at baseline i.e pre-operatively and were statistically insignificant. In group A, DBP were observed lower than group B always after administration of drug and after laryngoscopy and airway instrumentation. This difference was statistically significant ($p<0.05$).

Raichurkar [(6)]and Waiker [(8)] observed similar sedation score with clonidine and pregabalin ,but we observed patients in Group P are more calm and sedation score is more as compared to Clonidine, which may be because of clonidine dose we used is less than above researchers.

CONCLUSION

Pregbalin(150mg) was found to be more effective in attenuating the hemodynamic responses following laryngoscopy and intubation as compared to clonidine(100µg). It however does not attenuate heart rate, which may be due to reflex tachycardia in response to vasodilatation. Yet, it can be a better choice amongst the two.

Limitations of the study:

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Volume 4, Issue 2; March-April 2021; Page No 757-764