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Comparative Study on the Effect of Oral Clonidine and Gabapentin Premedication in Hemodynamic Response to Laryngoscopy and Tracheal Intubation

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Abstract

The aim of the study is designed as double blinded randomized controlled trial to compare the effect of preoperative oral clonidine 0.3mg and oral gabapentin 600mg on the changes in the systolic, diastolic, mean blood pressure and heart rate measured following laryngoscopy and tracheal intubation. Sample of 99 patients was required assuming effect size as 30%, level of significance 5%, power of study 75% using independent t-test. Patients were randomly divided into 2 equal groups of 33 each according to a computerized random table. Tracheal intubation was performed using clonidine and gabapentin premedication after induction of anaesthesia. Systolic (SBP), diastolic (DBP), mean arterial blood pressure (MAP), heart rate (HR) were recorded before induction, 3 minutes after induction before laryngoscopy, 1 minute, 3 minute, 5 minute & 10 minute after laryngoscopy and intubation. Clonidine is superior to gabapentin in attenuating the stress response induced by laryngoscopy and intubation. Dose of gabapentin in the study was not sufficient to blunt the hemodynamic stress response significantly. We conclude that clonidine was better than gabapentin for attenuating haemodynamic response to laryngoscopy and intubation.

Keywords: Clonidine, gabapentin, anesthesia, laryngoscopy, intubation

INTRODUCTION

Laryngoscopy and tracheal intubation is gold standard for patients undergoing operation under general Anaesthesia. It has been well documented that laryngoscopy and tracheal intubation maneuvers invariably release catecholamines and induce sympathetic responses resulting in certain cardiovascular changes such as tachycardia, rise in blood pressure and wide variety of cardiac dysrhythmia's. [1, 2] The major cause of sympathoadrenal responses is believed to arise from stimulation of supraglottic region laryngoscope blade with tracheal tube placement and cuff inflation contributing to additional stimulation. [3] If no specific measures are taken to prevent hemodynamic response, reflex changes in the cardiovascular system after laryngoscopy and intubation lead to an average increase in blood pressure by 40-50% and 20% increase in heart rate. These hemodynamic changes are usually transient and without any sequelae in majority of patients. However these changes can facilitate and accelerate the development of myocardial ischemia, infarction, arrhythmias and cerebral hemorrhage in patients with coronary artery disease, hypertension or cerebrovascular disease. [4] So, this rise in heart rate & blood pressure may be fatal in patients with hypertension and Coronary artery disease. Several techniques have been proposed to prevent or attenuate the hemodynamic responses following laryngoscopy and tracheal intubation such as deepening of plane of anaesthesia [3], using alternative methods of intubation. The method or drug of choice depends on many factors, including the urgency and length of surgery, choice of anaesthetic technique, route of administration, medical condition of the patient, and individual preference.

Clonidine is an imidazole compound which is an elective agonist for alpha 2 adrenoceptor (alpha 2: alpha 1 ratio of 200:1). It was introduced into clinical practice in 1970s. The clinical applications of clonidine may decrease oxygen consumption and episodes of shivering during recovery from anaesthesia. This feature may provide justification for its use in coronary artery disease patients. Other

gases incorporate the use of clonidine in reflex sympathetic dystrophy & management of cancer pain. It may also be used to control loose motions due to diabetic neuropathy probably by acting on alpha2 receptor and mediating enhancement of salt absorption in the gut mucosa. Gabapentin is a second generation anticonvulsant it was first introduced in 1993 as an adjuvant to anticonvulsant drug for the treatment of refractory partial seizures subsequently it was shown to be effective in the treatment of variety of chronic neuropathic pain. Gabapentin, l-(aminomethyl) cyclohexane acetic acid, is a structural analogue of the Neurotransmitter γ-aminobutyric acid (GABA). A variety of drugs have been used to control this hemodynamic response. Recently gabapentin has been effectively used to attenuate hemodynamic response to laryngoscopy and tracheal intubation [6, 7, 8, 9].The present study is designed as double blinded randomized controlled trial to compare the effect of preoperative oral clonidine 0.3mg and oral gabapentin 600mg on the changes in the systolic, diastolic, mean blood pressure and heart rate measured following laryngoscopy and tracheal intubation.

MATERIALS AND METHODS

Date source

After institutional board approval this randomized double blind study was conducted in dept of anaesthesia, Karpagam Faculty of Medical Sciences, Coimbatore. 99 **ASA**-1 Adult patients (18-45 years) of either sex, scheduled for elective orthopaedic and general surgical procedures were enrolled in this study. Sample of 99 patients was required assuming effect size as 30%, level of significance 5%, power of study 75% using independent t-test on software **G**-power-3.1

Randomization and drugs

Patients were randomly divided into 2 equal groups of 33 each according to a computerized random table. All patients received premedication drugs 120 minutes before admission to the operating room.

Group - 1 Patients received 0.25mg alprazolam HS night before surgery & 0.3mg clonidine tablets 2 hours before surgery.

Group - 2 Patients received 0.25mg alprazolam HS night before surgery & 600 mg gabapentin tablets 2 hours before surgery.

Technique of anaesthesia

All patients underwent pre-medication with tablet alprazolam 0.25 mg and ranitidine 150mg night before the surgery. Designated drug was given in the morning 2 hours prior to the planned surgery to the person not actively involved in the study. Standard monitoring for ECG, NIBP, SPO2, three baseline readings for heart rate and blood pressure were taken at interval of 1 minute, the mean of three readings was taken as baseline parameter. Following this 2 mcg/kg fentanyl and 0.03mg/kg midazolam was given intravenously 5 minutes before induction of anaesthesia. All patients were preoxygenated and anaesthesia was induced with 5mg/kg thiopental sodium. The patient was intubated with appropriate size ETT &Macintosh blade 3 minutes after neuromuscular blockade with 0.l mg/kg vecuronium bromide. Anaesthesia was maintained with 50% N20 in oxygen with 0.8% isoflurane. Heart rate, systolic, diastolic and mean arterial blood pressure was recorded before induction of anaesthesia, before laryngoscopy and at 1, 3 , 5 & 10 minutes after intubation.

Statistical analysis

Statistical significance of different hemodynamic parameter (HR, SBP, DBP, MAP and RPP) was carried out by one way analysis of variance across the four groups whereas between the two groups the significance was carried out by 2 sample student t test. Non-parametric variables like age, sex and weight were compared using chi-square test. Statistical significance of various parameters over the period of time was carried out by paired test under each group separately. $p<.05$ was taken as a level of statistical significance. The data was analyzed by using statistical software version 12.0.

RESULTS

Randomization and drugs

The premeditation drugs such as clonidine and gabapentin given according to mean age (yrs) [Table 1], sex distribution (M/F) [Table 2] and weight (Kg) [Table 3] was comparable between the groups. Statistically the difference was not significant (P>0.05) [Figure 1].

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Table 1: Age distribution

Group	Clonidine	Gabapentin	Control	
	Mean ±SD	Mean ±SD	Mean ±SD	Significance
Age(Year)	35.45 ± 9.118	33.18 ± 9.986	34.18 ± 10.318	0.643

Table 2: Sex distribution

Sex	Clonidine	Gabapentin	Control	Total
Male	16	16	19	51
Female	17	17	14	48
Total	33	33	33	99

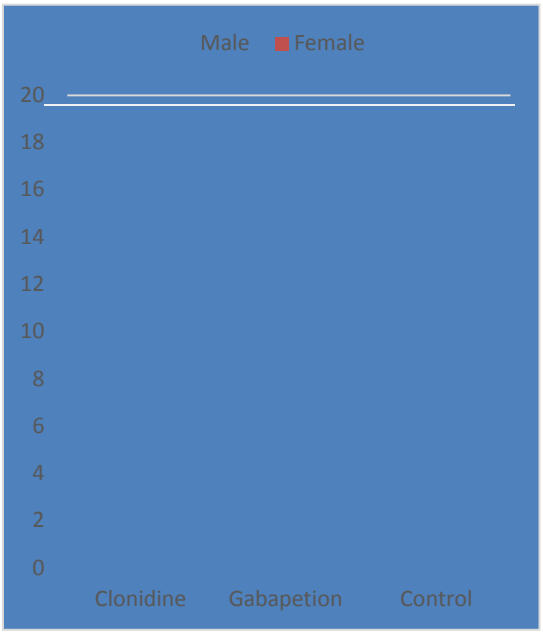

Figure 1: Sex distribution

Table 3: Weight distribution

Group	Clonidine	Gabapentin	Control	
	Mean ±SD	Mean ±SD	Mean ±SD	Significance
Weight (kg)	55.58 ± 9.401	52.39± 10.642	56.94 ± 10.727	0.188

Technique of anaesthesia

The mean duration of laryngoscopy and baseline parameter were comparable before giving the study drug in all the groups (P>0.05) was comparable between the groups. Statistically the difference was insignificant [Table 4 and Table 5].

Table 4: Duration of laryngoscopy and tracheal intubation

Group	Clonidine	Gabapentin	Control	
	Mean ±SD	Mean ±SD	Mean ±SD	Significance
BMI	17.36±2.289	17.52±2.884	17.79±2.484	0.793

Table 5: Baseline values before giving study drug

	Clonidine	Gabapentin	Control
MBP-1	95.33	94.68	97.41
SBP-2	128.34	124.33	131.67
DBP-1	78.26	75.43	81.31
Heart rate-1	92.31	94.36	90.27

HR before induction of anaesthesia in the clonidine group was 86.18 bpm (mean) comparison to 91.82 in gabapentin and 92.18 control group respectively. The fall in HR in control and gabapentin group was not significant (P value -0.91 S). HR taken three minutes after the induction of anaesthesia and just before laryngoscopy was 82 bpm (mean) in clonidine group, 80.52 bpm in gabapentin group and 82.15 bpm in control group. There was more falls in HR in clonidine group in comparison to patients in control group which was statistically not significant. However, the fall in SBP in other groups were comparable. The HR taken one minute after laryngoscopy and intubation in patients who received clonidine was 89.73bpm (mean), as comparison to 96.42 bpm in gabapentin group and 98.67 bpm in control group. Patients in control group had more increased in HR as comparison to clonidine and gabapentin group. This increase in HR was more significant while comparing control and clonidine group. The p value was 0.009 for control and clonidine group, which is statistically significant. The p value for clonidine and gabapentin group was 0,047 and for control and gabapentin group was 0.53.

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HR taken three minute after laryngoscopy and intubation in patients who received clonidine group was 88.76 bpm (mean), as comparison to 95.88 bpm in gabapentin group and 98.39 bpm in control group. Patients in control group had more increased in HR as comparison to clonidine and gabapentin group. Similarly, the HR taken five minutes after laryngoscopy in clonidine group was 85.64 bpm (mean), as comparison to 91.91 bpm in gabapentin group and 93.45 bpm in control group. The fall in HR (mean) was more in clonidine group as compared to control and gabapentin group. The p value was 0.007 for control and clonidine group, and 0.029 for clonidine and gabapentin group, both of which are statistically significant. However, the p value for control and gabapentin group was 0.586, which is statistically not significant. Hence, the patients in clonidine group had more fall in HR even after five minutes of laryngoscopy as compared to both the groups [Table 6] are represented in the [Figure 2].

Table 6: Heart rate before, at and after tracheal intubation in various groups

Heart rate	Clonidine	Gabapentin	Control
	Mean	Mean	Mean
HR 0	86.18	91.82	32.18
HR 1	82	80.52	82.15
HR 2	89.73	96.42	98.67
HR 3	88.76	95.88	98.39
HR 4	85.64	91.91	93.45
HR 5	79.33	87.97	89.94

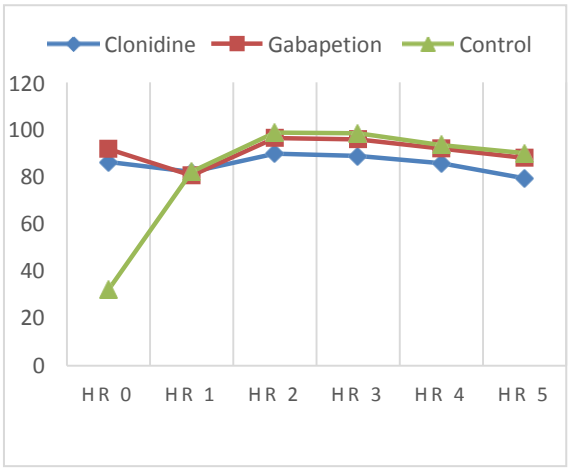

Figure 2: Heart rate before, at and after tracheal intubation in various groups

(HR 0 - Baseline heart rate before induction, HR 1 – heart rate 3 minutes after induction and just before laryngoscopy, HR 2 – Heart rate 1 minutes after intubation, HR 3 – Heart rate 3 minutes after intubation, HR 4 – Heart rate 5 minutes after intubation, HR 5 – Heart rate 10 minutes after intubation).

Systolic Blood Pressure before, at and after tracheal intubation in various groups.

SBP before induction of anaesthesia in the clonidine group was 119.12 mm Hg (mean), as comparison to 126.36 mmHg and 126.15mmHg in gabapentin and control group respectively. Patients in clonidine group had more fall in SBP before induction as compared to patients incontrol group and gabapentin group. This fall in MBP was statistically significant. P value was (0.045) for the clonidine and control group, and 0.038 for the clonidine and gabapentin group. The fall in MBP in control and gabapentin group was not significant (Pvalue - 0.997).

The SBPtaken three minutes after the induction of anaesthesia and just before laryngoscopy was 104.21rnmHg (mean) in clonidine group, 105 mmHg in gabapentin group and 112 . 36 mmHg in control group. There was more falls in SBP in clonidine group in comparison to patients in control group (p value -0.036) which is statistically significant. However, the fall in SBP in other groups were comparable [Table 7] and represented in the Figure 3.

Table 7: Systolic Blood Pressure before, at and after tracheal intubation in various groups

Systolic blood pressure	Clonidine	Gabapentin	Control
	Mean	Mean	Mean
SBP 0	119.12	126.36	126.15
SBP 1	104.21	105	112.36
SBP 2	115.15	126.06	139.06
SBP 3	110.18	124.06	131.42
SBP 4	104.12	116.91	117.45
SBP 5	101.06	105.91	114.79

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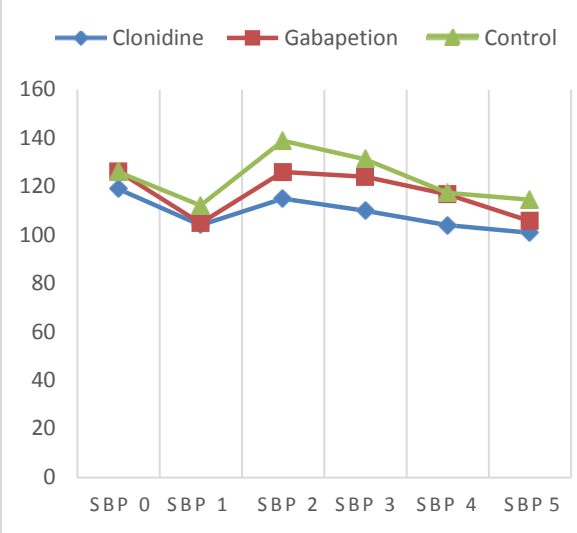

Figure 3: Systolic Blood Pressure before, at and after tracheal intubation in various groups

(SBP 0- Baseline systolic blood pressure before induction, SBP 1– systolic blood pressure 3 minutes after induction and just before laryngoscopy, SBP 2– systolic blood pressure 1 minutes after intubation, SBP 3– systolic blood pressure 3 minutes after intubation, SBP 4– systolic blood pressure 5 minutes after intubation, SBP 5– systolic blood pressure 10 minutes after intubation).

DBP before induction of anesthesia in the clonidine group was 75.64 mmHg (mean), as comparison to 78.76 mmHg and 79.85 mmHg in gabapentin and control group respectively. Patients in clonidine group had more fall in DBP before induction as compared to patients in control group and gabapentin group. The DBP taken three minutes after the induction of anesthesia and just before laryngoscopy was 68.33 mmHg (mean) in clonidine group, 69.79 mmHg in gabapentin group and 65.15 mmHg in control group.

DBP taken one minute after laryngoscopy and intubation in patients who received clonidine was 74.85 mmHg as comparison to 86.67 mmHg in gabapentin group and 90.45 mmHg in control group. The DBP taken three minutes after laryngoscopy and intubation in clonidine group was 69.73 mmHg as comparison to 81.24 mmHg in gabapentin group and 85.75 mmHg in control group. Similarly, the DBP taken five minutes after laryngoscopy in clonidine group was 66.21 mmHg, as comparsion to 71.48 mmHg in gabapentin group and 75.33 mm Hg in control group. The DBP taken after laryngoscopy in clonidine group was 62.15 mmHg as comparison to 66.52 mmHg in gabapentin grup and 75.33 mmHg in control group. Hence, the clonidine group patient had more fall in DBP as compared to both the groups [Table 8 and Figure 4].

Table 8: Diastolic blood pressure before, at and after tracheal intubation in various groups

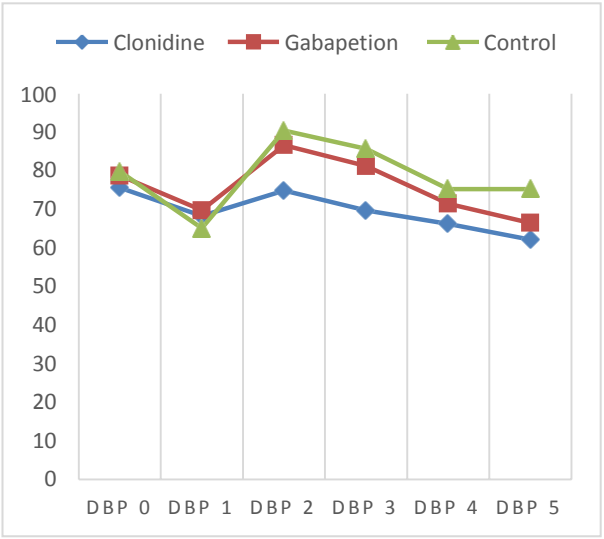

Figure 4: Diastolic blood pressure before, at and after tracheal intubation in various groups

(DBP 0- Baseline Diastolic blood pressure before induction, DBP 1– Diastolic blood pressure 3 minutes after induction and just before laryngoscopy, DBP 2– Diastolic blood pressure 1 minutes after intubation, DBP 3– Diastolic blood pressure 3 minutes after intubation, DBP 4– Diastolic blood pressure 5 minutes after intubation, DBP 5– Diastolic blood pressure 10 minutes after intubation).

MBP before induction of anaesthesia in the clonidine group was 88.88 mmHg (mean), as comparison to 94.64 mmHg and 95.06 mmHg in gabapentin and control group respectively. Patients in clonidine group had more fall in MBP before induction as compared to patients in control group and gabapentin group. This fall in MBP was statistically significant, p value was (0.010) for the clonidine and control group, and 0.017 for the clonidine and gabapentin group.

The fall in MBP in control and gabapentin group was not significant, (p value - 0.977).

The MBP taken three minutes after the induction of anaesthesia and just before laryngoscopy was 80.48 mmHg (mean) in clonidine group, 81.36mmHg in gabapentin group and 81.18 mmHg in control group. MRB taken one minute after laryngoscopy and intubation in patients who received clonidine was 89.30 mmHg (mean), as comparison to 96.76mmHg in gabapentin group and mmHg in control group. Patients in control group had more increased in MBP was comparison to clonidine and gabapentin group. This increase in MBP was more significant comparing control and clonidine group. The p value was 0.002 for control and clonidine group, which is statistically significant. The p value for control and gabapentin was 0.151 and for clonidine and gabapentin group was 0.218, both of which are not significant. Hence, the clonidine group patient had less increased in MBP as compared to the groups.

MBP taken three minute after laryngoscopy and intubation in patients who received clonidine group was 89.30 mmHg (mean), as comparison to 96.76 mmHg in gabapentin and 105.09 mmHg in control group. Patients in control group had more increased in as compared to clonidine and gabapentin group. This increase in MBP was more significant while comparing control and clonidine group. The p value was 0.002 for control clonidine group, which is statistically significant. The p value for control and gabapentin 3 was 0.151 and for clonidine and gabapentin group was 0.218, both of which are non-significant. Hence, the clonidine group patient had less increased in MBP as compared to the groups.

MBP taken three minutes after laryngoscopy and intubation in clonidine group 83.45 mmHg (mean) as comparison to 96.15mmHg in gabapentin group and 100.09 mmHg in control group. Patients in clonidine group had less increased in MBP in comparison control and gabapentin group. This small increase in MBP in clonidine group was significant when compared with patients in control and gabapentin group.

Similarly, the MBP taken five minutes after laryngoscopy in clonidine group was mmHg (mean), as comparison to 87.09 mmHg in gabapentin group and 89.36 mmHg control groups. The fall in MBP (mean) was more in clonidine group as compared to and gabapentin group. The p value was 0.000 for control and clonidine group, and for clonidine and gabapentin group, both of which are statistically significant. Never the p value for control and gabapentin group was 0.669, which is statistically non-signifiicant. Hence, the patients in clonidine group had more fall in MBP even after five minutes of laryngoscopy as compared to both the groups [Table 9].

The MBP (mean) taken ten minutes after laryngoscopy in clonidine group was 75.82 g (mean), as comparison to 80.24 mmHg in gabapentin group and 88.61 mmHg in control group. The fall in MBP (mean) was more in clonidine group as compared to control gabapentin group. The p value was 0.000 for control and clonidine group, which is statistically significant. However, the p value for clonidine and gabapentin group was 0.174, h is comparable. There was more fallen in MBP in gabapentin group in comparison to control group. The p value was 0.003 for control and gabapentin group, which is statistically significant. Hence, the patients in both clonidine and gabapentin group had more fall in MBP patients in control group, after ten minutes of laryngoscopy and the graphical representation is shown in[Figure 5].

Table 9: Mean arterial pressure before, at and after tracheal intubation in various groups

Mean arterial pressure	Clonidine	Gabapentin	Control
	Mean	Mean	Mean
MBP 0	88.88	94.64	95.06
MBP 1	80.48	81.36	81.18
MBP 2	89.3	86.15	105.09
MBP 3	83.45	96.15	100.09
MBP 4	77.55	87.09	89.36
MBP 5	75.82	80.24	88.61

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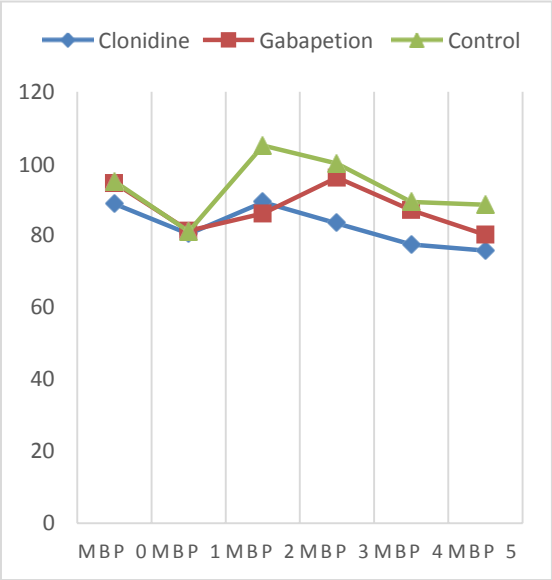

Figure 5: Mean arterial pressure before, at and after tracheal intubation in various group

(MBP 0- Baseline Mean blood pressure before induction, MBP 1– Mean blood pressure 3 minutes after induction and just before laryngoscopy, MBP 2– Mean blood pressure 1 minutes after intubation, MBP 3– Mean blood pressure 3 minutes after intubation, MBP 4– Mean blood pressure 5 minutes after intubation, MBP 5– Mean blood pressure 10 minutes after intubation).

DISCUSSION

In the study, a total of 99 patients in clonidine, gabapentin and control group were randomly included. But, there is no literature available till date to compare gabapentin and clonidine. So, we had a double blind randomised control study in our hospital to evaluate the effect of oral 3 and gabapentine in attenuating stress response to intubation. The cardiovascular changes to laryngoscopy and tracheal intubation are well known extensively studied. [1, 5, 6, 7] These are associated with increase in the arterial pressures that increase in serum catecholamine levels. This stress response caused by copy and endotracheal intubation may be harmful for the coronary of high-risk patients. Thus these hemodynamic variations need to be controlled, techniques have been proposed to prevent or attenuate the hemodynamic responses laryngoscopy and tracheal intubation such as deepening of plane of anaesthesia,[5] alternative methods of intubation (McCoy laryngoscopy blade, intubating IMA), duration of laryngoscopy for <15 seconds, several drugs such as vasodilators , beta blockers (esmolol) [8,9,10], calcium channel blockers (nicardipin, verapamil,[11,12,13] clomdme, opiods, (fentanyl, sufenteml, alfentanil) [9,14, 15] lignocame [3,5], magnesium [16,7] and recently gabapentin etc.

Memis *et al.* [17] compared intubation response of two doses of gabapentin and 800mg in ninetyASA-1 patients undergoing elective surgeries. However in this study medication was done, unlike our study where the patients were premedicated with alprazolam and fentanyl. Also they induced anaesthesia with propofol unlike our patients received thiopentone for induction of anaesthesia. In our study the hemodynamic responses in gabapentin group less than the control group but these were statistically not significant and gabapentin offered no specific advantage over the control group which might be due to the quote dose of gabapentin. [6] Clonidine, an imidazole compound, is a selective agonist for alpba2adrenoceptors. It is almost completely absorbed after oral administration and reaches peak plasma within 60-90 minutes by this route. The elimination half life of clonidine is in 9 and 12 hours. It causes sedation and anxiolysis. It potentiates the anaesthetic action of other agents and reduces anaesthetic requirements during surgery. It also decreases highly requirements for induction and intubation by 45%. Doses of thiopentone required for induction are reported to be reduced by pre-anaesthetic medication with clonidine. It also acts on the receptors of medulla and presynaptically on peripheral nerve also to reduce activity of the sympathetic nervous system.

Batra *et al.* [20] conducted a study on 40 (ASA 1-2) patients of both sexes aged between 20 to 45 years undergoing routine surgical procedures were divided into 2 groups of 20 each. One group received clonidine 5ug/kg 90 minutes before induction of anaesthesia and other group acted as controls without any pre-treatment. They concluded that control group showed a significant rise in heart rate and blood pressure compared to clonidine receiving group. They observed that heart rate increased in control patients to 94.9 bpm and in clonidine treated patients to 87.7 bpm immediately following intubation compared to initial value of 73.8 bpm and 73.1 bpm respectively. In our study heart rate increased to 89.7 bpm from 82 bom in clonidine group and 98.6 bpm from 82.15 bpm in the control group. Also clonidine treated patients showed significant fewer rises in blood pressure following intubation. Changes in heart rate and blood pressure in our study are in concordance with the above mentioned study although they are at a lesser extent which might be due to difference in anaesthetic technique (choice of premedication, muscle relaxant and inhalation agents). [21] Another interesting study was done by Pouttu *et al.* [22] assessed the effects premedication on stress response. They compared clonidine with diazepam and concluded that clonidine acted the sympathoadrenal response to

intubation were lower throughout and 3 hours after surgery in clonidine group. Adrenaline levels lower in this group 2 minutes after intubation. In our study also clonidine has resulted in decrease in the mean blood pressure and late even before induction of anaesthesia as shown in previous studies. Also stress caused by laryngoscopy and tracheal intubation was more blunted in clonidine patients as compared to other two groups. As, there is no single study conducted previously which compare the attenuation of dynamic response to laryngoscopy by clonidine and gabapentin premedication We attempted to do that in our study and concluded that clonidine affords better attenuation depressor response when compared to gabapentin. This could be because of the fact that the dose we have chosen is probably not tough to attenuate the depressor response.

CONCLUSION

A total of 99 patients, 33 in clonidine group (Group I), 33 in gabapentin group (Group 1 33 in control group (Group 111) were selected. Among that clonidine is superior to gabapentin in attenuating the stress response induced by laryngoscopy and intubation. Dose of gabapentin in the study was not sufficient to blunt the hemodynamic stress response significantly. We further recommend studies to be done in future with higher doses of gabapentin. Estimation of serum catecholamines could be added in future studies to get better results. Further studies on study drugs if conducted should include other monitoring parameters (Sedation score, PONV score, postoperative VAS/VRS scoring, postoperative delirium) intra-operatively and post-operatively to know benefits and side-effects associated with them.

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