Original Research Article

Comparison of Intravenous Esmolol and Oral Clonidine for Attenuation of Stress Response to Laryngoscopy and Intubation in Patients Undergoing Surgery under General Anesthesia: A Randomized Clinical Study

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Abstract

Introduction: Direct laryngoscopy and endotracheal intubation are the most noxious stimuli during induction of anaesthesia. Airway instrumentation frequently induces a cardiovascular stress response characterized by hypertension and tachycardia due to reflex sympathoadrenal discharge caused by epipharyngeal and parapharyngeal stimulation. Various pharmacological approaches have been used to attenuate the pressure responses to laryngoscopy and tracheal intubation e.g. volatile inhalational agents, lignocaine, opioids, sodium nitroprusside, nitroglycerine, calcium channel blockers, and adrenergic blockers (alpha -2 agonists and beta blockers).**Objectives:** The purpose of this study is to compare the efficacy and safety of i.v esmolol and oral clonidine in attenuating the changes of blood pressure and heart rate by tracheal intubation.**Materials and Methods:** 40 patients posted for various surgeries under general anesthesia were randomly divided into two groups. Group C subjects received Clonidine 150 mcg PO, 90 minutes prior to induction of anaesthesia where as Group E subjects received I.V Esmolol 0.5mg/kg 90 seconds prior to intubation. To maintain blinding, Group C patients received I.V 0.9% Normal saline 90 seconds prior to intubation where as Group E patients received placebo tablet containing multi vitamins 90 minutes prior to induction .HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), Mean arterial pressure (MAP) , rate pressure product (RPP), Spo2, ECG will be recorded prior to induction (Base line), at the time of intubation and 1, 3, 5, and 10 min after intubation . **Type of study**: A randomized clinical study.**Results:** Pulse rate, SBP, DBP, MAP and RPP were comparable at baseline, at time of induction, during laryngoscopy and intubation and throughout whole study period it was not statistically significant in both groups ($p>0.05$). However in Intergroup comparison, SBP was comparable at base line and after 5 min of laryngoscopy and intubation in both groups, but SBP was significantly higher after 1 and 3 min of laryngoscopy and intubation in Group E than Group C. Also, there was statistically significant increase in MAP following laryngoscopy and intubation at one min in Group E than Group C ($P<0.05$). RPP was significantly higher after 1 and 3 min of laryngoscopy and intubation in Group E than Group C. Postoperative complications like dryness of mouth, excessive sedation, PONV, hypotension, Bradycardia, bronchospasm were not observed in any case in both groups. **Conclusion:** This study concluded that clonidine and esmolol provide hemodynamic stability but clonidine provides more stability with postoperative sedation.

Keywords: Clonidine, Esmolol, Intubation, Laryngoscopy, General anesthesia.

Introduction

Laryngoscopy and tracheal intubation are noxious stimuli that produce marked sympathetic response manifesting as hypertension and tachycardia, increase in serum concentration of catecholamine and various arrhythmias ranging from ventricular ectopic, ventricular tachycardia, heart blocketc.[1,2] Some patients unquestionably require careful hemodynamic control during induction of anaesthesia and intubation of the trachea. Even a transient hyperdynamic response may cause serious complications in patients with symptomatic aortic aneurysm, recent myocardial infarction, cerebral aneurysm, or intracranial hypertension. Knowledge and studies of cardiovascular stress response has led to development of techniques, used to modify cardiovascular stressresponse.[3,4]

Various agents have been used to attenuate cardiovascular stress response during laryngoscopy and endotracheal intubation including oral clonidine (α-agonist), topical lignocaine, intravenous vasodilator like nitro glycerine, sodium nitropruside, β - adrenergic blockers - like esmolol, narcotics like fentanyl, sufentanyl, alfentanyl, inhalation anesthetics like isoflurane, desflurnae. Along with their usefulness, they have some drawbacks which limit their application. A narcotic produces respiratory depression and fentanyl causes truncal rigidity, vasodilators produces reflex tachycardia and rebound hypertension. Lignocaine does not reliably obtund heart rate response. Non selective β - blockers may produce bronchospasm.

An ideal attenuating drug should have some of the following properties like easy route of administration, sedative, anti-sialogouge effect, analgesic antiemetic facilitates induction, reduces doses of anesthetic agents, post operative delirium. Clonidine and Esmolol possesses some of theseproperties. Various studies have shown that Clonidine and Esmolol are effective in attenuation of cardiovascular stress response as well as in reducing the requirement of anesthetic drug and thus enhances the recovery and making anesthesia safer and cost effective, however only few comparative studies are reported till date .[5-9] So, this study was conducted with an objective to compare the efficacy of oral Clonidine and intravenous Esmolol for attenuation of cardiovascular stress response following laryngoscopy andintubation.

Materials and Methods

This randomized controlled study was carried out at among 40 patients scheduled for various surgeries.

Inclusion criteria: All patients undergoing middle ear surgery and requiring endotracheal intubation with ASA physical status -1, II only, i.e. patients had no other major illness were included instudy.

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Exclusion criteria: Patients with bradycardia (Heart rate < 60 beats/min), hypotension (Systolic blood pressure < 100 mmhg diastolic blood pressure < 50mmhg), H/o congestive cardiac failure, chronic obstructive pulmonary disease, bronchial asthma, peripheral vascular disease, H/o myocardial infarction in last 3 months, Impaired hepatic and renal function, Pregnant women, Patient receiving beta-blocker, alpha- agonist, AVblock were excluded from thestudy. All patients underwent a pre-study evaluation which consisted of a medical history, physical examination and routine investigations including complete haemogram, urine examination and appropriate blood chemistry like blood urea, serum creatinine, random blood sugar, Serum electrolytes, X- ray chest PA view and Electrocardiogram. All patients were advised to remain nil orally from 10 pm and Tab. Diazepam (0.2mg/kg) was given orally on previous night of operation. A written informed consent was obtained from the patients. All patients were randomly divided in two groups. Group – C: Tab. Clonidine - 150µgorally, 90 minutes before induction. Group – E: Inj. Esmolol HC1 -0.5 mg/kg, 90 seconds before tracheal intubation.

Premedication was given 45 minutes before induction in each group in the form of Inj. Glycopyrolate(10 µg/kg)intramuscular. After 45 minutes of premedication (PM), all patients were shifted to operation theatre from pre operative room. In operation theatre patients were monitored for pulse rate, SBP, DBP, MAP, RPP, ECG and oxygen saturation, with multiparameter monitor. All patients were cannulated with 20 gauze intravenous cannula and Inj. Dextrose 5% was started at5ml/kg/hr.

Induction:Pre oxygenation was done with 100% oxygen with Bain's circuit for 5 minutes. Induction was done with Inj.Propofol1.5-2.5 mg/kg intravenously till loss of eyelid reflex followed by Inj. Succinylcholine 1.5mg/kg intravenously. Lungs were ventilated with bag and mask with oxygen for 90 seconds. Laryngoscopy was performed and trachea was intubated with appropriate size disposable cuffed portex endotracheal tube. Bain's circuit was connected and after confirming position of endotracheal tube, it was fixed properly. All patients were observed for pulse, SBP, DBP, MAP, RPP and $Sp0_2$ at 1, 3, 5, 7, 10 and 15 min during studyperiod.

Maintenance: Anesthesia was maintained with 0_2 + N_20 (50:50) + Inj. Vecuronium bromide 0.lmg/kg as muscle relaxant in bothgroups.In Group E during intra operative period patients were given Inj. Tramadol lmg/kg intravenously as analgesic and isoflurane inhalation and considering sedative, analgesic properties of clonidine patients were given only inhalation of isoflurane intraoperatively in Group C. Patients were monitored for vital sign till the end of surgery.

Reversal: After completion of surgery, residual neuromuscular blockade was antagonized with Inj. Neostigmine and Inj. Glycopyrolate intravenously. Thorough oropharangeal toilet wasdone; trachea was extubated when clinical criteria for extubation were fulfilled.Post- operative monitoring of various parameters like pulse, SBP, DBP, MAP, RPP, oxygen saturation, color of lips, tongue was observed. All patients were shifted to ward. Patients were observed for any complications.

Statistical Analysis

The statistically significant level was $P < 0.05$. Statistical analysis was performed using the SPSS package (version 19, SPSS, Chicago, IL). Normality of the distribution of data was tested by the Kolmogorov-Simirnov test. Hemodynamic variables between the two groups and within each group were analyzed using the repeated measure test. Demographic data were analyzed by an independent t test or Chi-square when appropriate.

Results

Age in both the groups varied from 15 - 55 years. The mean age in both the groups was comparable. The sex, height and weight in both the groups were comparable. ASA physical status of patients was comparable between the groups. (Table 1)

Table 1: Age, Gender and ASA Status Wise Distribution of Patients among the groups

Variables	Group C (n=20)	Group E (n=20)	p-value
Age	49.82± 7.2	52.24±7.5	>0.05
Male/Female	12/8	14/6	>0.05
Height	155±3.2	152±8.4	>0.05
Weight	61±4.8	63±5.2	>0.05
ASA status I/II	11/9	12/8	>0.05

Pulse rate was comparable at baseline, at time of induction, during laryngoscopy and intubation and throughout whole study period it was not statistically significant between the groups. (Table 2)

Table 2: Comparison of Pulse rate at Various Intervals among the groups

Stages	Pulse rate (beats/min)		
	Group C	Group E	P Value
BL	88.9±18.26	91.48±13.42	0.456(NS)
PM	82.68±6.62	92.52±16.30	0.003 (S)
I	83.32±10.42	83.72±12.16	0.564 (NS)
L&I	84.42±14.60	88.28 ±14.14	0.723(NS)
T_1	88.08±12.8	90.32±13.90	0.652 (NS)
T_3	88.8±11.90	90.68±14.68	0.543(NS)
T_5	85.26±9.60	88.12±10.32	0.254 (NS)
T_7	85.16 ±7.62	88.18 ±10.84	0.287(NS)
T10	88.12±11.24	88.28±10.52	0.458 (NS)
T15	88.68±11.22	88.86±11.32	0.345 (NS)

Values are expressed as Mean ± SD; S-Significant; NS- Non significant

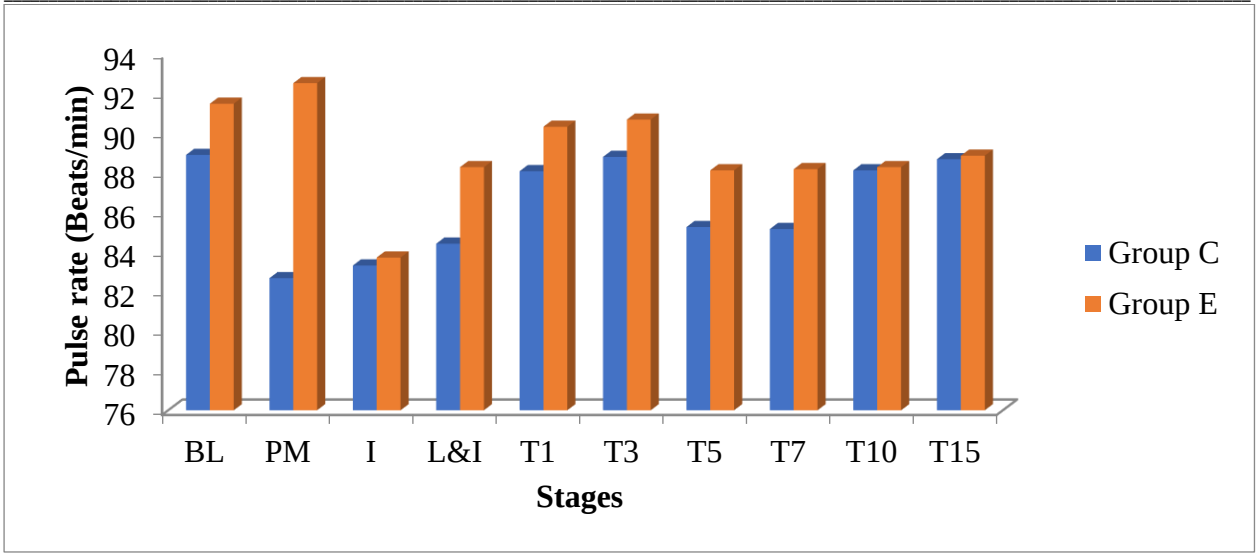

Fig 1: Pulse rate

In Intergroup comparison, SBP (Table 3) was comparable at base line and after 5 min of laryngoscopy and intubation in both groups, but SBP was significantly higher after 1 and 3 min of laryngoscopy and intubation in Group E than Group C. Moreover, DBP(Table 4) was significantly lower following premedication with clonidine, at time of induction in Group C. After that DBP was comparable in both groups.

Table 3: Comparison of Systolic B Pat Various Intervals between the groups

Stages	Systolic BP(mmHg)		
	Group C	Group E	P Value
BL	124.04 ±23.5	120 +17.16	0.245(NS)
PM	110.88±10.46	118 +21.4	0.345(NS)
I	110.56±20.14	104 ±14.56	0.124(NS)
L&I	118.28 +15.6	108±21.26	0.006 (S)
T_1	114.4 +22.50	134±30.80	0.000 (S)
T_3	104 ±22.62	128±20.58	0.001 (S)
T_5	108.12±17.16	118±17.6	0.004(S)
T_7	108.16±18.60	110±16.84	0.765(NS)
T10	108.04±19.66	111±19.2	0.345(NS)
T15	108.6 ±17	112 +18.42	0.237(NS)

Values are expressed as Mean±SD. In all tables • BL - base line, • PM - 45 min after premedication, • I - at beginning of intubation, • Tn- time after laryngoscopy and intubation where n = 1,3,5,...15.S-Significant; NS- Non significant

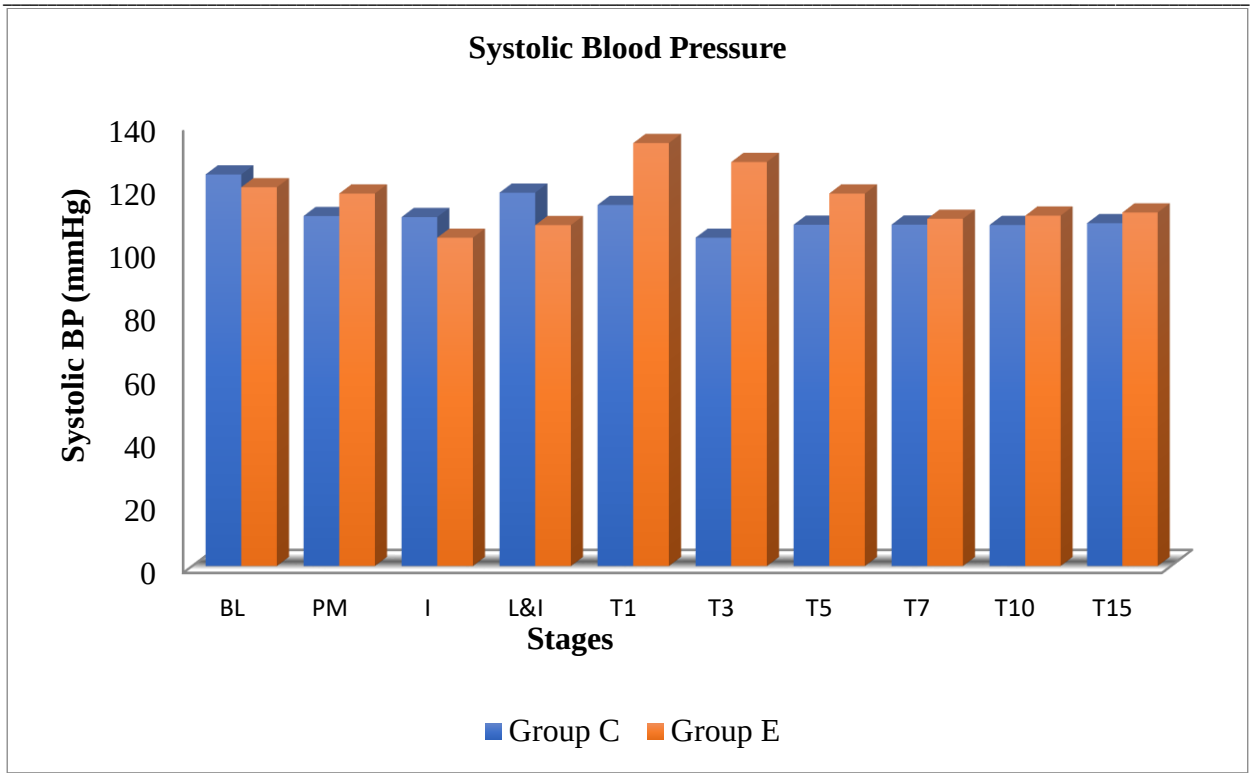

Fig 2: Systolic Blood Pressure

Table 4: Comparison of Diastolic BP at Various Intervals among the groups

Stages	Diastolic BP (mmHg)		
	Group C	Group E	P Value
BL	78.22±11.4	80.9 ±11.4	0.125(NS)
PM	75.96±11.43	79.6 ±10.2	0.004(S)
I	70.04±13.57	79.8 ±11.4	0.245(NS)
L&I	76.44±15.51	80.8±11.4	0.124(NS)
T_1	76.44±15.51	83.4 ±16.7	0.345(NS)
T_3	77.64 ±9.77	79.2 ±11.6	0.762(NS)
T_5	78.64 ±9.77	77 ±10.2	0.542(NS)
T_7	79.56 ±9.96	76.8 ±13.2	0.264(NS)
T10	78.28±12.48	76 ±10.5	0.187(NS)
	76.04 ±10.2	79.3 ±7.63	0.282(NS)

Values are expressed as Mean ± SD; S-Significant; NS- Non significant

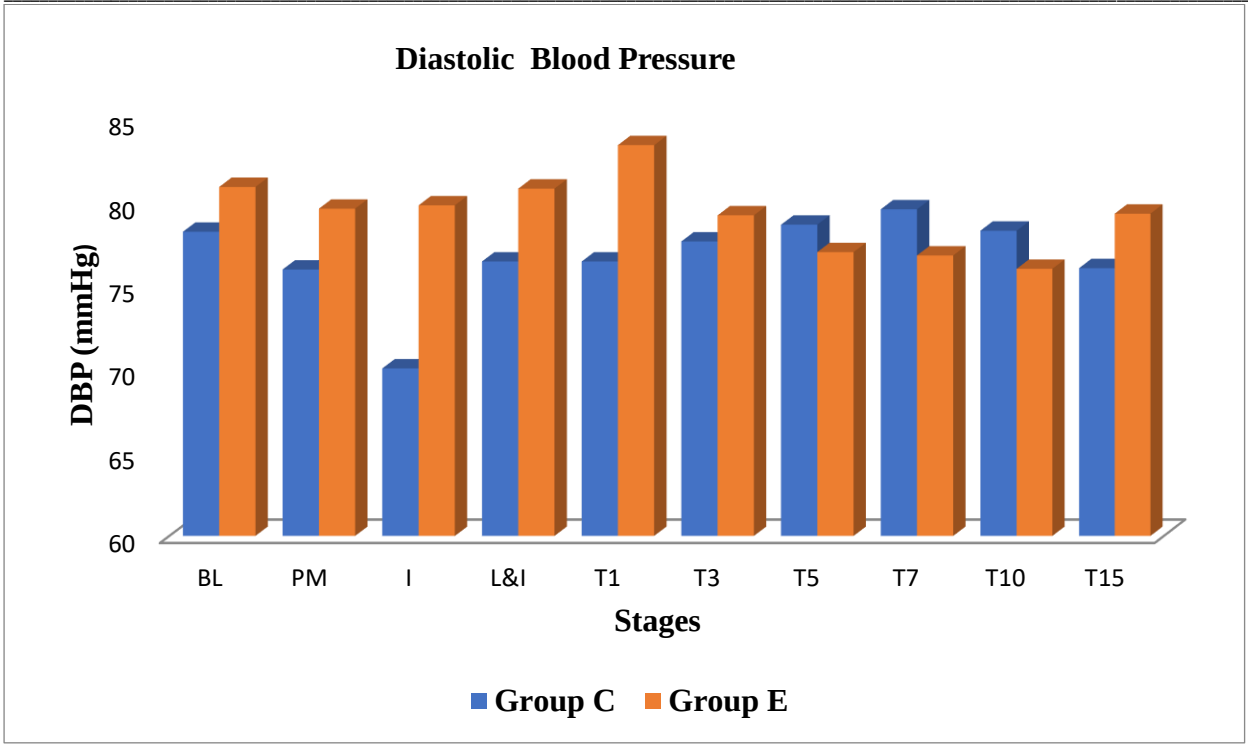

Fig 3: Diastolic Blood pressure

At baseline, MAP (Table 5) were comparable between the groups, but there was statistically significant increase in MAP in Group E following laryngoscopy and intubation at one min in Group E than Group C, after that MAP remained comparable to each other through out whole study period in both groups. RPP was comparable at base line and after 5 min of laryngoscopy and intubation in both groups, but RPP was significantly higher after 1 and 3 min of laryngoscopy and intubation in Group E than Group C. (Table 6). We have not observed any complication in any patients in any group during perioperative period. All patients in both groups were observed until they attained pre operative vitalparameter.

Table 5: Comparison of Mean Arterial Pressure at Various Intervals

Stages	MAP (mmHg)		
	Group C	Group E	P Value
BL	94.63 ±13.20	92.51 ±9.35	0.125 (NS)
PM	84.27 ±8.87	92.07 ±9.17	0.387 (NS)
I	83.31 ±14.02	88.35 ±8.56	0.562 (NS)
L&I	88.05 ±12.73	88.77 ±9.41	0.765 (NS)
T_1	88.43 ±13.03	100.21±15.86	0.001 (S)
T_3	86.09 ±11.60	96.24 ±10.62	0.452 (NS)
T_5	86.80 ±9.18	90.73 ±9.84	0.872 (NS)
T_7	88.09 ±9.64	88.44 ±11.04	0.126 (NS)
T10	88.71 ±12.85	88.59 ±9.82	0.187 (NS)
T15	88.56 ±8.85	89.05 ±7.39	0.389 (NS)

Values are expressed as Mean ± SD; S - Significant; NS- Non significant

In alltables • BL - baseline, • PM - 45 min after premedication, • I - at beginning of intubation, • T_n- time after laryngoscopy and intubation where n = 1, 3, 5,...15.

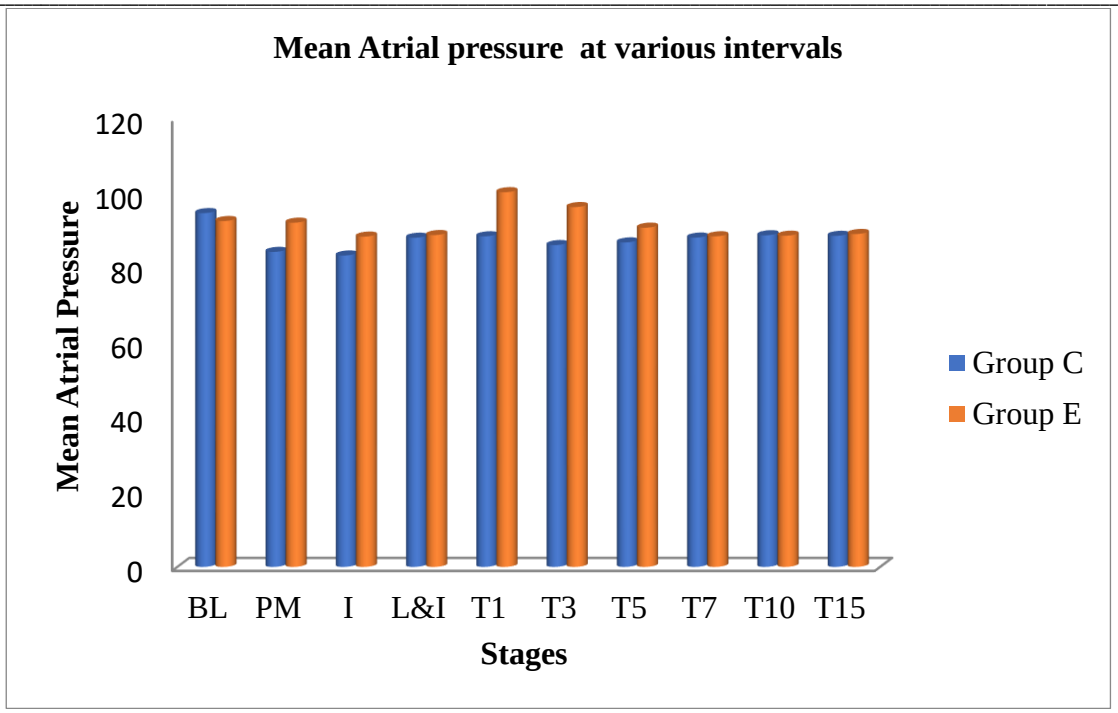

Fig 4: Mean ARTERIAL Pressure

Table 6: Comparison of Rate Pressure Product at Various Intervals among the groups

Stages	RPP (Mean ± SD)		
	Group C	Group E	P Value
BL	10681.12±3574.67	10654±2308.54	0.134(NS)
PM	8886.12±1244.254	12227±2430.99	0.001 (S)
I	8961.2±2389.396	8442.12±1478.839	0.256(NS)
L&I	10016.8±2592.26	9558.56±2602.87	0.654(NS)
T_1	9891.68±2585.73	12485.3±3539.77	0.001 (S)
T_3	8982.4±2516.74	11581.52±3096.42	0.002(S)
T_5	8986.64±1303.51	10481.76±1824.037	0.005 (S)
T_7	9423.44±1646.106	9843.20±1716.746	0.329(NS)
T10	9649.6±2494.96	9730.72±2252.931	0.763(NS)
T15	9685.36±1478.45	9808.12±2003.48	0.465 (NS)

Values are expressed as Mean ± SD; S - Significant; NS - Non significant

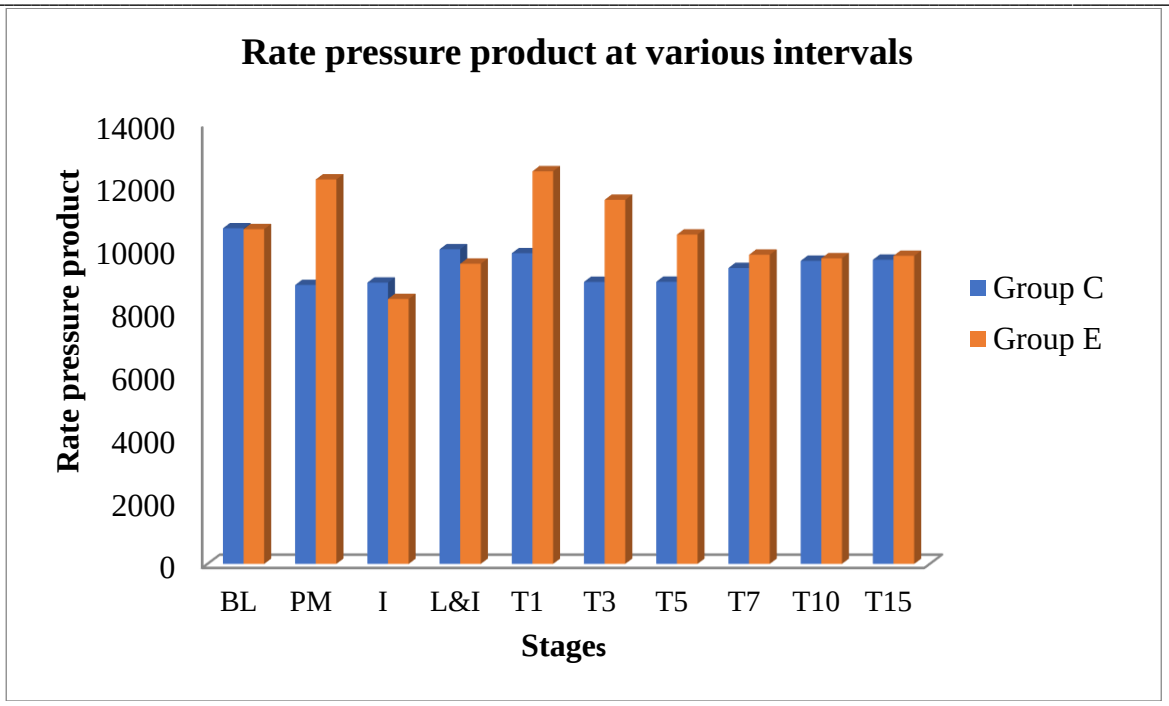

Fig 5: Rate pressure product at various Intervals

Degree of sedation according to Ramsay sedation score was assessed in patients 15 min after reaching post anesthesia care unit (PACU). The mean score in group C was significantly higher than the mean score in group E (Table 7).

Table 7: Comparison of Ramsay sedation score among the groups

Groups	Ramsay sedation score		P value
	Range	Mean ± SD	
Group C	1–4	2.76 ± 0.76	0.03 (S)
Group E	0–2	1.24 ± 0.34	

Values are expressed as Mean ± SD; S - Significant; NS - Non significant

Discussion

Laryngoscopy and intubation are powerful noxious stimuli. Stimulation of supraglottic region by tissue tension induced by laryngoscopy and that of subglottic region by endotracheal intubation leads to reflex sympathoadrenal response. The circulatory response of this is hypertension and tachycardia.[1-4] Hypertension and tachycardia are transient changes but have deleterious effects in patient with cerebral and cardiovascular disease.2 Persistence of these changes may be harmful in surgeries were hypotensive anesthesia is required or in surgeries where there is maximum chances of sympathoadrenal stimulation like head and neck surgeries, earsurgeries.

Numerous pharmacological methods have been recommended to obtund pressure response to laryngoscopy and intubation. They may be classified as non specific means achieved by deepening the plane of anesthesia or by specific means involving various pharmacological preparations. Various drugs used are either partially effective or may have deleterious side effects. Clonidine and Esmolol have already proved their efficacy as an attenuating agent in various studies done previously.Comparing both the groups in our study HR was comparable at baseline, at time of induction, during laryngoscopy and intubation and throughout whole study period. It was not statistically significant. Similar findings have been observed by Miller et al, Wang et al and Zsigmond etal.[9-11]. SBP was comparable at base line and after 5 min of laryngoscopy and intubation. But SBP was significantly higher after 1 and 3 min of laryngoscopy and intubation. This suggests esmololdoes not obtund the hypertensive response to laryngoscopy and intubation. Our findings were similar to studies of Donald Oxorn et al, Suman Sharma et al, Fuji Y et al.[4,5,12]

Moreover, DBP was significantly lower following premedication with clonidine, at time of induction & during laryngoscopy and intubation. DBP was comparable to esmolol after thatduring whole study period. Our finding was similar to Donald Oxorn etal.[5]On comparing both group we found statistically significant increase in MAP in esmolol group following laryngoscopy and intubation. Our findings were similar to Philip et al Carabin UA et al.6,7 However, RPP was comparable at base line and after 7 min of laryngoscopy and intubation, but it was significantly higher after 1, 3 and 5 min of laryngoscopy and intubation. This suggests esmolol does not obtund the hypertensive response to laryngoscopy and intubation. Our findings were similar to study of Philip L. Liu.6We have monitored for ECG changes but did not observe any arrhythmia during whole study period. We have not observed any complication in any group. Contrary to this, Suman sharma et al observed ventricular bigeminy in patients receiving esmolol 200 mg intravenously.[4] Marchal et al and Pilli G et al observed Bradycardia in patients receiving clonidine but did not require anytreatment.[13,14]

Conclusion

Oral clonidine (150µg/kg) attenuates stress response whereas Inj. Esmolol (0.5mg/kg) prevents rise in heart rate only. Oral clonidine and intravenous esmolol both controls rise in pulse rate following laryngoscopy and endotracheal intubation. Intravenous esmolol is not effective in obtunding hypertensive response following laryngoscopy and intubation and associated with significant rise in SBP, MAP and

RPP. No significant change in DBP was observed following laryngoscopy and intubation in any group. No adverse effects like dryness of mouth, excessive sedation, bradycardia, hypotension, post operative nausea vomiting, bronchospasm, ventricular arrhythmia observed in any patients. So, oral clonidine (150µg/kg) is more effective in attenuating stress response than intravenous esmolol (0.5mg/kg).

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