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A Randomised Comparative Study Between Clonidine and Esmolol as an Adjuvant to Fentanyl in Attenuating Hemodynamic Response During Laryngoscopy and Orotracheal Intubation

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ABSTRACT

Objectives: To compare the effectiveness of single bolus dose of esmolol or clonidine as an adjuvant to fentanyl in attenuating the hemodynamic responses during laryngoscopy and endotracheal intubation.
Material and Methods: 90 adult ASA I and ASA II patients were included in the study who underwent elective surgical procedures. Patients were divided into three groups. Group I (control) receiving 10ml normal saline, group II (esmolol) receiving bolus dose of 1.5 mg/kg and group III (clonidine) receiving bolus dose of 1.5 mcg/kg. All the patients received 2 mcg/kg of fentanyl before the induction of anaesthesia. Heart rate, systolic and diastolic blood pressure and ECG were recorded as baseline and after administration of study drugs at intubation and at 1, 3, 5 and 10 minutes thereafter.
Results: Demographic data and the baseline hemodynamic parameters were comparable among each group. The rise in heart rate was controlled better in esmolol group and was statistically significant. After 3 minutes of intubation there was statistically significant decrease in blood pressure in clonidine group when compared to the other groups.
Conclusion: Esmolol 1.5 mg/kg as a bolus dose prevented rise in heart rate following laryngoscopy and intubation. Rise in blood pressure was better controlled by clonidine 1.5 mcg/kg and also hemodynamic parameters were better maintained throughout the procedure.

KEYWORDS Esmolol, fentanyl, clonidine, laryngoscopy, endotracheal intubation, stress response

Introduction:
Cardiovascular stress response characterized by hypertension and tachycardia due to reflex sympathetic stimulation is the common presentation of direct laryngoscopy and endotracheal intubation. Healthy people may tolerate it well, but may be hazardous in patients with hypertension, coronary artery disease, cerebrovascular disease, myocardial infarction and thyrotoxicosis[1]. Numerous agents like opioids, calcium channel blockers, beta Blockers, magnesium sulphate, alpha-2 agonists and local anaesthetics etc. have been used to blunt the stress response.[2, 3, 4]

Esmolol is an attractive beta blocker because of its cardio selectivity and ultra short duration of action (9 minutes)[5].

Premedication with clonidine, an alpha-2 adrenergic agonist was shown to blunt the stress response to the surgical stimuli and the anaesthetic requirements.(16). Clonidine also increases the cardiac baroreceptor reflex sensitivity to an increase in the systolic blood pressure and thus stabilizes the blood pressure.(17,18). Comparison between esmolol and clonidine on stress response is limited by the number of studies.

Hence we undertook this study to compare the effectiveness of intravenous esmolol and clonidine in attenuating stress response to laryngoscopy and intubation.

Materials and Methods:
After approval from hospital ethics committee a written informed consent from the patients was obtained. We studied 90 patients posted for elective surgery who were divided into three groups.

Group I - received 10 ml normal saline (CONTROL group)
Group II - received bolus dose of esmolol 1.5 *m*g /kg (ESMOLOL group)
Group III - received intravenous dose of clonidine 1.5 µg/kg (CLONIDINE group)

All the patients received inj.fentanyl 2 μg/kg 4 minutes before the induction of anaesthesia.

The patients were subjected to detailed pre anaesthetic evaluation and routine investigations to exclude any associated systemic disorder.

The study was conducted in ASRAM Medical College and Hospital, Eluru during the period November 2015 to October 2016 for a period of one year.

Selection criteria:

A) Inclusion Criteria:
- Age 18 to 60 years.
- Either sex.
- ASA Grade I or II.

B) Exclusion Criteria:
- Anticipated or encountered difficult airway.
- Emergency surgeries.
- Patients with ASA Grade III or higher.
- Patients with cardiovascular, renal, hepatic, neurological and endocrine disorders
- Patients on psychotropic drugs or history of drug allergies.
- Patients with H/O asthma and reactive airway disease.

Pre-operative procedure:
All the patients were subjected to pre anaesthetic evaluation one day before surgery. Patients were kept nil per oral for 8 hours before the surgery.

Patients were allocated randomly, using a computer-generated randomization scheme into three groups of 30 each.

Pre medication:
All patients received Tab Alprazolam 0.5 mg (>40 kg) or 0.25 mg (<40 Kg) in the night before surgery and at 6 AM on the

day of surgery. Inj. Ondansetron 4mg IV was given 10 minutes before induction.

The patients were wheeled in to the operation theatre and the standard ASA monitoring equipment like ECG, Pulse oximeter and non invasive blood pressure monitor were connected. The patients were monitored for heart rate, ECG, SpO2, EtCO2, temperature and Urine output and baseline readings recorded.

An appropriate sized intravenous cannula was placed and intravenous fluid infusion was started at the rate of 2ml/kg/hr. Patients belonging to group I received 10 ml normal saline. Patients belonging to group II received Inj. Esmolol 1.5 mg/kg intravenously. Patients belonging to group III received Inj. Clonidine 1.5 mcg/kg intravenously. All the patients received Inj. Fentanyl 2 μg/kg 4 minutes before induction of anaesthesia.

Patients were induced with Inj. Propofol 2mg/kg intravenously over 30 seconds up to the loss of eye lash reflex. Ability to ventilate was checked and they were paralyzed with Inj. Vecuronium bromide 0.1 mg/kg intravenously. After 3 minutes of ventilation gentle laryngoscopy was done and trachea intubated. Anaesthesia was maintained with intermittent positive pressure ventilation using semi closed circuit with CO_2 absorber with O_2: N_2O (50:50). Muscle relaxation was maintained with vecuronium bromide by repeating with 1/5th of the intubating dose when curare notch appeared on capnography. After induction, propofol infusion was started at a maintenance dose of 150 µg/kg/min till the end of surgery. Ringer's lactate as i.v. fluid was administered at the rate of 15 ml/kg in the 1st hour followed by 7.5 ml/kg/hr till the end of surgery to all patients.

Base line haemodynamic parameters, heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were noted and monitored during the procedure.

Statistical analysis was done using the independent student's t-test to test the difference between the control and study groups. A p-value of <0.05 was considered significant. The means of parameters at different time points for control and study groups individually were tested using repeated measures of ANOVA (one way analysis).

Observation and Results

This study evaluated 90 patients of either sex, aged between 18 to 60 years, belonging to ASA physical status I and II. These patients were randomly divided into three groups-

Group A Control group
Group B Esmolol + Fentanyl group
Group C Clonidine + Fentanyl group

From the study conducted the observations were made at following intervals

Baseline value before induction.
1 minute after intubation.
3 minutes after intubation.
5 minutes after intubation.
10 minutes after intubation.

All the results are presented as mean ± SD.

Demographic data like age, sex and ASA physical status are presented as mean ± SD where appropriate. There were thirty patients in each study group, and the groups were demographically similar.

TABLE 1: COMPARISON OF MEAN AGE, WEIGHT AND SEX

	Age (Years)	Weight (Kg)	Male / Female
Control group (n=30)	39.80 ± 8.84	54.37 ± 2.1	14/16
Esmolol + Fentanyl group (n=30)	35.83 ± 1.8	59.06 ± 1.7	17/13
Clonidine + Fentanyl group (n=30)	37.46 ± 1.5	58.26 ± 2.2	18/12

Table 1 shows the age, weight and sex distribution of the patients in all three groups. The age ranged from 18 to 60years in three groups. The range for weight was 46 to 67 kg, 43 to 72 kg and 46 to 74 kg in control, Esmolol and Clonidine groups respectively.The demographic data was comparable in all three groups.

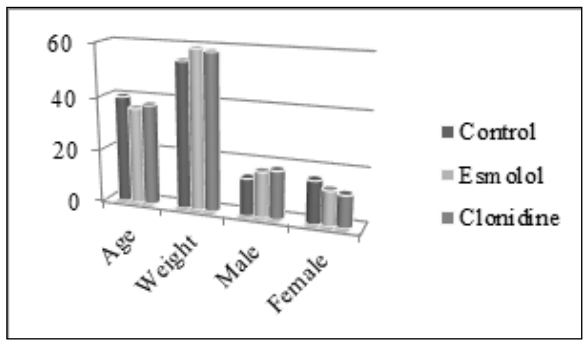

Figure 1. Multiple bar diagram showing age, weight and sex distribution among three groups.

TABLE–II: BASELINE HAEMODYNAMIC PARAMETERS

Parameters	CONTROL group	ESMOLOL group	CLONIDINE group	p value
HR	80.03 ± 9.47	83.2 ± 8.78	82.5 ± 8.6	0.19 [a]
SBP	122.6 ± 8.43	123.46 ± 11.50	120 ± 9.5	0.74 [a]
DBP	78.4 ± 6.95	79.13 ± 5.57	78.90**±6.95**	0.65 [a]
MAP	93.13 ± 4.95	93.91 ± 6.09	93.69±4.762	0.59 [a]

[a]: Not significant, *: Highly significant

• Values are means with standard deviation in brackets (**±**). Tests of significance were carried out by student's t-test. The above table shows the hemodynamic parameters in control and study groups recorded during the Baseline time. There was no significant difference in these readings (p > 0.05).

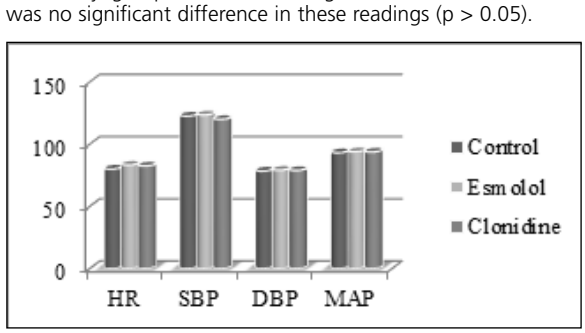

Figure 2: Multiple bar diagram showing comparison of baseline parameters (HR, SBP, DBP, MAP) among three groups

TABLE –III: COMPARISON OF MEAN HEART RATE (beats\ min) IN STUDY AND CONTROL GROUPS

Heart Rate	Control Group	Esmolol Group	Clonidine group	p-value
Baseline	80.03± 9.47	83.20± 8.78	81.63±8.92	0.6022[a]
At 1 min	111.33± 11.30	85.53± 8.006	92.83±9.02	<0.0001*

At 3 min	98.60± 5.580	78.33± 8.3225	87.76±4.65	<0.0001*
At 5 min	89.33± 9.546	76.46± 8.54	86.33±4.67	<0.0001*
At 10 min	86.10± 9.33	76.33± 7.7162	84.10±5.25	<0.0001*

[a]: Not significant, *: Significant

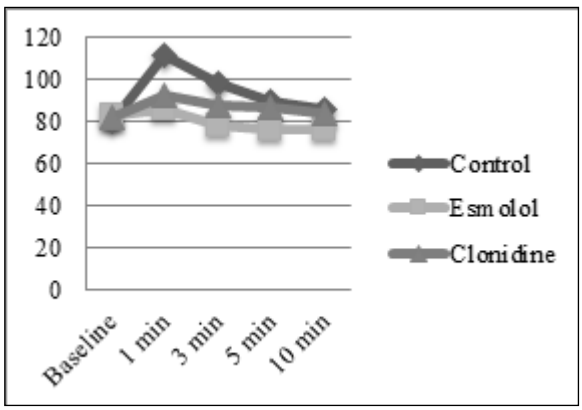

Figure 3 shows that the heart rate in control group reached maximum (111.33/min) at 1 min after laryngoscopy and stayed above baseline till 10 min after laryngoscopy & intubation. Heart rate in study groups reached maximum 92.83/min at 1 min for Clonidine and 85.53/ min for Esmolol. The lowest heart rate recorded in esmolol group was 76.33/ min and in clonidine group was 84.10/min at 10 min after laryngoscopy. Heart rate differed with regard to groups (p<0.0001) also with regard to time between groups (p<0.0001).

TABLE–IV COMPARISON OF MEAN SBP (mm Hg) IN STUDY AND CONTROL GROUPS

SBP	Control Group	Esmolol group	Clonidine group	p-Value
Baseline	122.60±8.43	123.47±11.50	123.26±8.19	0.91[a]
At 1 min	151.33±8.47	122.33±5.77	118.26±3.99	<0.0001*
At 3 min	129.60±8.21	123.60±6.23	114.86±4.22	<0.0001*
At 5 min	126.53±8.21	120.13±5.72	112.33±4.75	<0.0001*
At 10 min	124.53±7.42	116.33±7.06	109.36±5.89	<0.0001*

[a]: Not significant, *: Significant

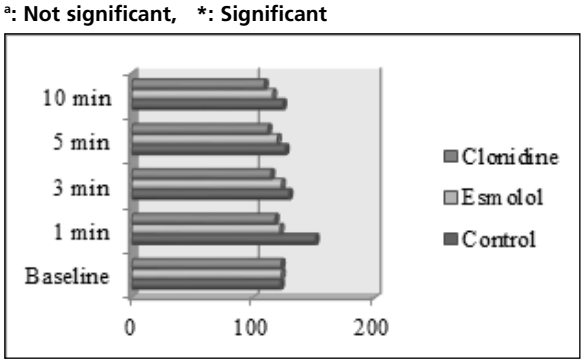

FIGURE 4: The highest mean SBP 151.33 **±8.47 (mmHg) was seen in control group in 1 min after laryngoscopy. The lowest mean SBP** 109.36 **± 5.89 (mmHg) was seen in clonidine group at 10 min after laryngoscopy. The SBP** differed with regard to group (p<0.0001) also with regard to time between groups (p<0.0001).

TABLE V COMPARISON OF MEAN DBP (mm Hg) IN STUDY AND CONTROL GROUPS

DBP	Control Group	Esmolol group	Clonidine group	p-value
Baseline	78.40±6.95	79.66±5.20	78.90±6.95	0.6782[a]
At 1 min	100.33±6.70	78.93±6.34	74.93±7.04	<.0001*
At 3 min	84.53±9.43	76.53±6.96	73.43±5.14	<.0001*
At 5 min	82.66±7.09	73.33±5.73	72.53±5.11	<.0001*
At 10 min	80.26±6.38	73.46±5.40	72.06±5.40	<.0001*

a: Not significant, *: Significant

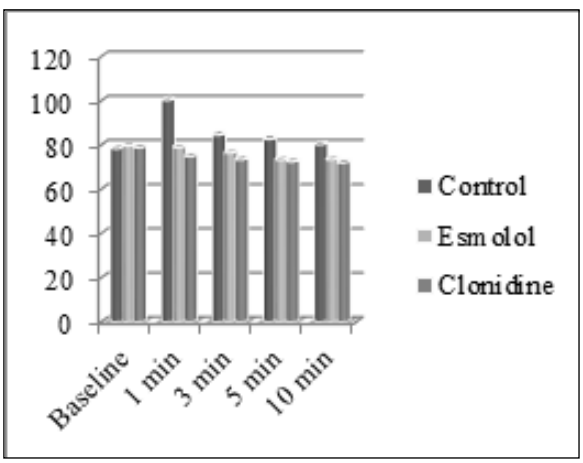

FIGURE 5: The highest mean DBP 100.33 **± 6.70** (mmHg) was seen in control group in 1 min after laryngoscopy. The lowest mean DBP72.06 **± 5.40(mmHg) was seen in Clonidine group at 10 min after laryngoscopy. The DBP** differed with regard to group (p<0.0001) also with regard to time between groups (p<0.0001).

TABLE VI— COMPARISON OF MEAN OF MAP IN STUDY AND CONTROL GROUPS

MAP	Control Group	Esmolol Group	Clonidine Group	p-value
Baseline	93.13±4.95	94.91±6.09	93.69±4.762	0.664926[a]
1 min	117.11±5.04	92.91±4.86	89.66±4.84	<.0001*
3 min	99.53±7.26	91.37±5.48	87.24±3.96	<.0001*
5 min	97.28±7.26	88.02±5.14	85.80±3.96	<.0001*
10 min	94.84±6.31	87.75 ±5.37	84.50± 3.92	<.0001*

a: Not significant, *: Significant

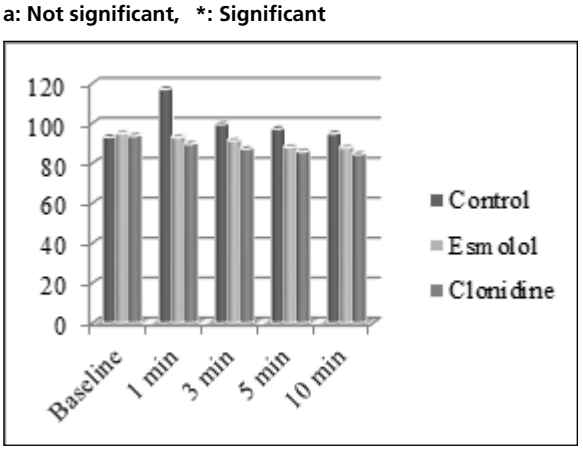

FIGURE 6: The highest mean MAP 117.11 **± 5.04 (mmHg) was seen in control group in 1 min after laryngoscopy. The lowest mean MAP** 84.50 **± 3.92(mmHg) was seen in Clonidine group at 10 min after laryngoscopy. The MAP** differed with regard to group (p<0.0001) also with regard to time between groups (p<0.0001).

Discussion:

Direct laryngoscopy and endotracheal intubation lead to increasing blood pressure and heart rate. Laryngoscopic stimulation of oropharyngeal structures is an important factor in hemodynamic stress response associated with tracheal intubation.[6] Mechanism of cardiovascular response to intubation is considered to be a reflex sympathetic response to the mechanical stimulation of larynx and trachea. Instrumentation of the pharynx and tracheal intubation may result in tachycardia, hypertension and increased catecholamine concentration that may evoke life threatening condition among susceptible individuals especially those with cardiovascular disease.7 If no specific measures are taken to prevent the hemodynamic response, the HR can increase from 26% to 66% depending on the method of induction, and SBP can increase from 36% to 45%.[8]

A number of studies have indicated the oral premedication of clonidine to achieve the attenuating effect of clonidine before laryngoscopy intubation. [9,10] However, as the bioavailability after oral intake varies between 70% and 90%, we chose the IV route of administration to relate pharmacodynamic effects more precisely to a certain dose. Carabine ***et al***.11 demonstrated that 0.625 and 1.25 µg/kg clonidine IV 15 min prior to induction of anesthesia attenuates the pressor response to laryngoscopy and intubation. In contrast, Wright ***et al***. [12] observed in noncardiac ASA physical status I patients that under almost identical conditions 1.25 µg/kg clonidine IV was not effective. In the present study, we achieved a reasonable attenuation effect of clonidine using a dose of 1.5 µg/kg.

Esmolol possesses several properties which makes it a valuable agent to obtund the cardiovascular response. Firstly it is a cardio selective agent. Secondly, it has ultra short duration of action (9 minutes) and finally, significant drug interactions with commonly used anesthetics have not been reported[13]. In our study we found that heart rate increase in patients receiving esmolol was statistically attenuated as compared to other 2 groups. This is not consistent with studies by Korpinen et al[14] and Shroff et al[15] who found that there was statistically significant increase in heart rate in all the three groups after 3 minutes of intubation.

Esmolol in a dose of 1.5 mg/kg given 3 minutes before induction controls increase in heart rate when compared to the other groups. After 3 minutes of intubation control of heart rate as well as systolic and diastolic blood pressure was better in clonidine group when compared to esmolol group.

Conclusion:

We studied the haemodynamic variations to laryngoscopy and intubation and the effectiveness of intravenous esmolol and intravenous clonidine when added to intravenous fentanyl in attenuating the stress responses. We conclude from our study that Esmolol 1.5 mg/kg I.V. 3 minutes before laryngoscopy and intubation is a better drug to control increase in heart rate. Clonidine 1.5 µg/kg I.V. 15 minutes prior to laryngoscopy and intubation is a preferred drug of choice to attenuate hypertensive responses.

Bibliography:

1. Fox EJ,SklarGS, Hill CH,et al. Complications related to pressor response to endotracheal intubation. Anaesthesiology 1977;47:524-25
2. Helfmann SM, Gold MI, Delisser EA. Which drug prevents tachycardia and hypertension associated with tracheal intubation lignocaine, fentanyl or esmolol? Anaesth Analg 1991; 72: 482-86.
3. Sharma J, Sharma V, Ranbushan , Gupta S. Comparative study of magnesium sulphate and Esmolol in Attenuating the pressor response to Endotracheal intubation in controlled hypertensive patients . J Anaesth Clin Pharmacol 2006; 22(3):255–59.
4. Mikawa K, Nishina K, Maekawa N, et al .Compariso of nicardipine, diltiazen and verapamil for controlling the cardiovascular responses to tracheal intubation. Br J Anaesth 1996; 76: 221–26.
5. Anthony LS,James H, Edward LC. Pharmacokinetics and pharmacodynamics of esmolol Administered as an intravenous bolus. Clin Pharmacol Ther 1987; 41:112 – 17.
6. S. Kihara, J. Brimacombe, Y. Yuguchi, S. Watanabe, N. Taguchi, T. Kumatsuzaki Haemodynamic responses among three tracheal intubation devices in normotensive and hypertensive patients Anaesth Analg, 96 (2003), pp. 890–895
7. Kim, Woon-Young, Lee, Yoon-Sook, Ok, Se Jim, Kim, Jac-Hwan, Park, Young-Cheol, Lim, Hye-Ja. Lidocaine does not prevent bispectral index increases in response to endotracheal intubation. Anaesth Analg 2006; 102: 156–9 [International Anaesthesia Research Society].
8. Wylie, Churchill Davidson Stress management A practice of anesthesia (7th ed.), 0340731303, Arnold, London (2003), p. 1326
9. Batra YK, Indu B, Puri GD. Attenuation of pulse rate and blood pressure response to laryngoscopy and tracheal intubation by clonidine. Int J Clin Pharmacol Ther Toxicol 1988; 26:360-3.
10. Talebi H, Nourozi A, Fateh S, Mohammadzadeh A, Eghtesadi-Araghi P, Jabbari S, ***et al.*** Effects of oral clonidine premedication on haemodynamic response to laryngoscopy and tracheal intubation: A clinical trial. Pak J Biol Sci 2010; 13:1146-50.
11. Carabine UA, Allen RW, Moore J. Partial attenuation of the pressor response to endotracheal intubation. A comparison of the effects of intravenous clonidine and fentanyl. Eur J Anaesthesiol 1992; 9:325-9.
12. Wright PM, Carabine ZA, Kearney E, Howe JP. Intravenous clonidine: Effect on the cardiovascular response to intubation. Anesth Analg 1991; 72:5327.
13. Vucevic M, Purdy M ,Ellis FR. Esmolol hydrochloride for management of cardiovascular stress response to laryngoscopy and tracheal intubation . B J Anaesth1992; 68: 529-30.
14. . Korpinen R, Saarnivaara L, Siren K, et al. Modification of the haemodynamic responses to induction of anaesthesia and tracheal intubation with alfentanil, esmolol and their combinations. Can J Anaesth 1985; 55; 652-56.
15. Shroff PP, Mohite SN, Panchal ID. Bolus administration of esmolol in controlling the haemodynamic response to tracheal intubation. J Anaesth Clin Pharmacol 2004; 20 (1):69-72.
16. Singh S, Arora K. Effect of oral clonidine premedication on perioperative haemodynamic response and post-operative analgesic requirement for patients undergoing laparoscopic cholecystectomy. Indian J Anaesth. 2011 Jan-Feb; 55(1):26–30.
17. Kalra NK, Verma A, Agarwal A, Pandey HD. Comparative study of intravenously administered clonidine and magnesium sulfate on hemodynamic responses during laparoscopic cholecystectomy. J Anaesthesiol Clin Pharmacol. 2011 Jul-Sep; 27(3):344–48.
18. Yu HP, Hseu SS, Yien HW, Teng YH, Chan KH. Oral clonidine premedication preserves heart rate variability for patients undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Scand. 2003;47:185–90