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AN OBSERVATIONAL STUDY OF EFFECT OF ESMOLOL ON ATTENUATION OF PRESSOR RESPONSE TO LARYNGOSCOPY AND INTUBATION

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ABSTRACT

Introduction: Endotracheal intubation and laryngoscopy provides an intense noxious stimulus via vagal and glossopharyngeal afferents that result in a reflex autonomic activation, which is usually manifested as hypertension and tachycardia. This reflex is termed as pressor response. Esmolol possesses several properties to attenuate this response. Primary objective- to study the effect of 0.4mg/kg esmolol on attenuation of pressor response Secondary objective- assess hemodynamic changes during laryngoscopy and intubation. **Methods:** After institutional review, board approval and written informed consent, 62 patients with ASA physical status I-II aged 18-50 years to undergo elective surgery under general anaesthesia were studied. Patients with known allergies, hypertension ,diabetes, heart blocks, ischemic heart disease, brain disease and baseline HR<60 and SBP<100 were excluded. Patients were randomly divided into two groups, group E received injection Esmolol 0.4mg/kg and group C received normal saline 3min before intubation. All hemodynamic changes were monitored at baseline, before induction, before intubation and after intubation. **Observation and results:** The differences in parameters was statistically significant. The rise in heart rate 30sec after intubation was more in group C than group E. The blood pressure, mean arterial pressure and rate pressure product were more in group C than group E after intubation. No significant ECG changes were seen in both groups. **Conclusions:** This study confirmed that there is significant increase in hemodynamic variables on laryngoscopy and intubation and concludes that esmolol in low dose attenuates pressor response to some extent.

INTRODUCTION

Reid and Brace first described hemodynamic response to laryngoscopy and intubation. Endotracheal intubation as well as laryngoscopy provides an intense noxious stimulus via vagal and glossopharyngeal afferents that results in a reflex autonomic activation, which is usually manifested as hypertension and tachycardia in adults and adolescents; in infants and small children, autonomic activation may result in bradycardia.[1] This reflex has been termed 'pressor response' and has been attributed to the sudden release of catecholamines during direct laryngoscopy and intubation.[2] These pressor responses following laryngoscopy and intubation are transient occurring within 30 seconds of intubation and lasting for less than 10 minutes.[3]

Though these sympathoadrenal responses are probably of little consequence in healthy individuals, however it is major clinical significance in patients with hypertension, coronary heart disease, intra cranial pathology, eclampsia, aneurysmal vascular disease, head injury and hyper reactive airways in whom these changes may culminate in perioperative myocardial ischaemia or infarction, cardiac failure, dysrhythmias, cerebrovascular accidents or secondary brain injury.[4] In such cases, reflex circulatory responses such as increase in heart rate, systematic arterial blood pressure and disturbances in cardiac rhythm needs to be suppressed.

Many drugs belonging to different pharmacological groups are studied for preventing morbidity associated with the hemodynamic response to tracheal intubation. Drugs have been used to attenuate pressor response are local anaesthetic agents like Lignocaine, Beta Blockers like Esmolol, Peripheral Vasodialators like Sodium Nitroprusside, Alpha Agonists- Dexmedetomidine, Opioids like Fentanyl, Calcium Channel Blockers like Diltiazem and Inhaled anaesthetics by using deeper planes of anaesthesia.

ESMOLOL

possesses several properties which make it a valuable agent to attenuate the cardiovascular response. It is cardio selective (beta 1) beta adrenoreceptor antagonist and has ultrashort duration of action (9min).[5] Finally, significant drug interaction with commonly used anesthetics has not been reported.[6] These characteristics make Esmolol a useful drug to blunt the increase in heart rate and blood pressure that occurs during laryngoscopy and intubation. Esmolol should be used with caution in

patients with bronchospastic disease. The use of Esmolol may result in hypotension in some patients. Also Esmolol may exacerbate symptoms of cardiac failure in congestive heart failure.[7]

AIM: To study effect of 0.4 mg/kg Esmolol on attenuation of pressor response to Laryngoscopy and intubation.

OBJECTIVES

Assess haemodynamic changes by following parameters during Laryngoscopy and intubation
Heart rate
Systolic Blood Pressure
Diastolic Blood Pressure
Mean Arterial Pressure
Rate Pressure Product
Percentage change in haemodynamics
Electrocardiogram (ECG) changes

MATERIALS AND METHODS

Patients of either sex belonging to ASA I – II of the age group 18-50 years were studied after approval from institutional ethical committee and informed written consent.

Pre-anesthetic evaluation was done before surgery with the special consideration to elicit history of hypertension, dyspnea, chest pain, cough, wheezing, convulsions, diabetes mellitus, previous anesthetic history, drug sensitivity. A routine pre anesthetic examination was conducted assessing general condition of the patient, airway assessment, nutritional status & body weight of the patient and systemic examination. Basic investigations were done. After patient identification immediate pre-anesthestic checkup was done. Study objective and procedure was explained to the participants and a written informed consent was taken from each participant. Pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure noted 1 hour prior to surgery. After securing intravenous access, for all patients intravenous fluid was started. All the patients were pre medicated with injection Glycopyrrolate 0.2 mg intramuscular 30 minutes before induction and injection ondansetron 4 mg iv. and monitors were applied which included ECG, Manual and Noninvasive Blood Pressure, Pulse oximetry and Capnography. Injection Midazolam 0.02mg/kg and injection Pentazocine 0.3mg/kg were administered intravenously over 30 sec as premedication. Induction of anesthesia in each case was done in supine position with the head on the standard pillow (7-10 cm). Senior Anesthesiologist gave injection Esmolol 0.4mg/kg (group E) or normal saline (group C) 3 minutes before intubation. After preoxygenation, each patient received induction dose of Thiopentone (5mg/kg) over 30-40 seconds with end point of induction being loss of eyelash reflex. Injection succinylcholine 2mg/kg was given after confirmation of effective mask ventilation. Face mask ventilation was done with 100 % O2. Laryngoscopy was performed with Macintosh laryngoscope blade and trachea was intubated with appropriate size cuffed endotracheal tube by senior anesthesiologist. After confirmation of correct placement of endotracheal tube, anesthesia was then maintained with oxygen and nitrous oxide, sevoflurane and Injection Atracurium 0.5mg/kg. No manipulation like painting, draping the area of operation was allowed till 10 min after the study drug administration. After surgery reversal was done with injection Neostigmine (0.05mg/kg) and injection Glyocopyrrolate (4mcg/kg) .All haemodynamic changes were monitored at baseline, before induction, before tracheal intubation, at the intubation, after the intubation at 30sec, 1 minute, 90 sec, 2 minute,3, 4, 5, 10 and 15 minute . These changes were compared in group C and group E.

Parameters Observed for pressor response

Heart Rate
Systolic Blood Pressure
Diastolic Blood Pressure
Mean Arterial Pressure
Rate Pressure Product
ECG for Arrhythmia, Ischemia
SPO2 for hypoxia

STATISTICAL ANALYSIS

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square test or was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. Independent t test was used as test of significance to identify the mean difference between two quantitative variables. **P value** (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

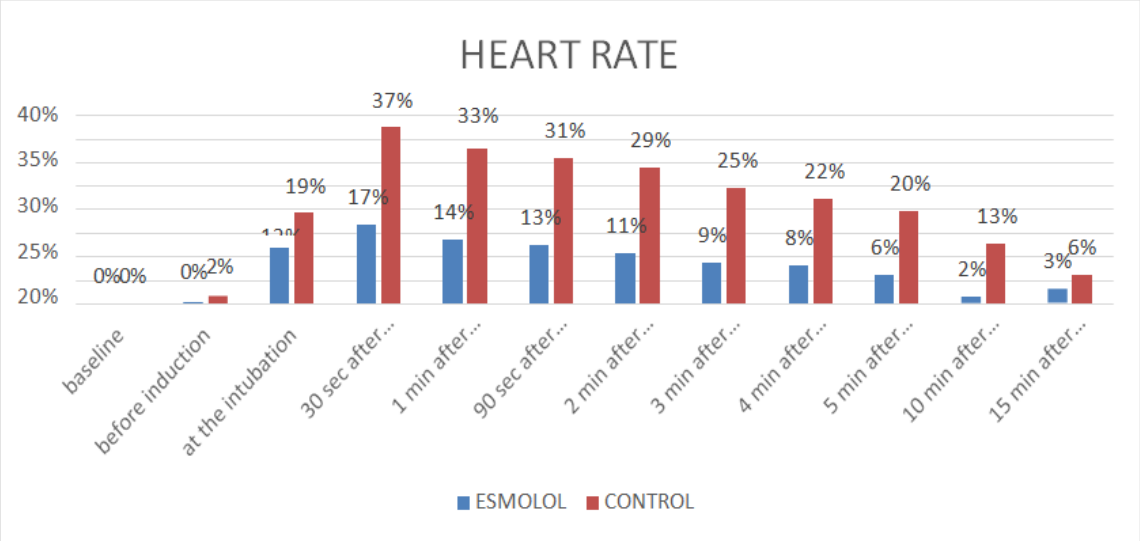
RESULTS

1. Heart rate between two groups

Compared with the baseline readings, the mean heart rate(HR) was increased after laryngoscopy and tracheal intubation in the two groups. This was more in the group C where 30 sec after intubation caused a rise in the heart rate from a mean baseline value of 84.625 ± 8.705 to 116.34 ± 13.899, an increase of 37% which was statistically highly significant (P=0.000), whereas in the group E, mean heart rate increased from 80.36 ± 7.39 to 93.96 ± 8.37, increase of 17% occured. This differed significantly from the control group. Increase in HR was observed as 37% of baseline values at 30 seconds to 20% at 5 minutes in group C. It fails close to baseline in group E at 10 minutes and near to baseline in group C at 15 minutes.

Table.no.1-heart rate comparison between two groups at different time intervals						
	GROUP	**N**	**Mean**	**Std. Deviation**	**p-value**	**Unpaired t test**
Baseline	Esmolol	30	80.367	7.3975	.042	Not significant
	control	32	84.625	8.7058		
30 sec after intubation	Esmolol	30	93.967	8.3768	.000	Significant
	control	32	116.344	13.8997		
5 min after intubation	Esmolol	30	85.233	8.1354	.000	Significant
	control	32	101.250	10.4881		
10 min after intubation	Esmolol	30	81.633	7.6044	.000	Significant
	control	32	95.375	9.8103		
15 min after intubation	Esmolol	30	83.067	7.7368	.003	Significant
	control	32	89.844	9.2217		

Bar diagram showing percentage change from baseline in Heart Rate comparison between two groups at different time intervals

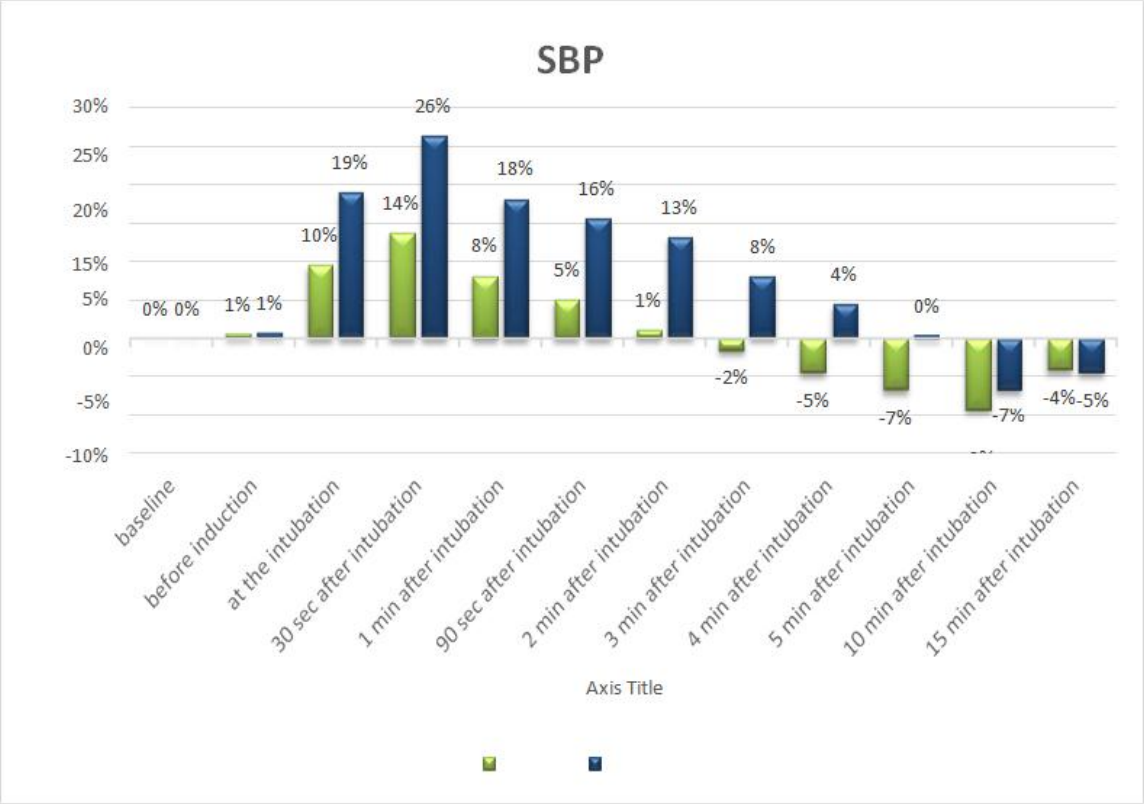


2. Mean systolic blood pressure

Compared to the baseline values, the systolic blood pressure (SBP) increased in these two groups following laryngoscopy and intubation. The increase was highest in the control group where it rose significantly from a mean baseline value of 122.56 ± 7.67 to 154.96 ± 9.74 (26%) 30 sec after intubation which was highly statistically significant (P=0.000), and in the Esmolol group, which increased from 119.7 ± 6.742 to 136.2 ± 7.04(14%). It fails close to baseline in group C at 5 minutes and in group E at 2 minutes.

Table.no.2-SBP comparison between two groups at different time intervals						
	GROUP	**N**	**Mean**	**Std.Deviation**	**p-value**	**unpaired t test**
Baseline	Esmolol	30	119.700	6.7423	.125	not significant
	control	32	122.563	7.6788		
30 sec after Intubation	Esmolol	30	136.200	7.0486	.000	Significant
	control	32	154.969	9.7467		
2 min after Intubation	Esmolol	30	121.000	6.9382	.000	Significant
	control	32	138.688	8.7490		
5 min after Intubation	Esmolol	30	111.500	5.6918	.000	Significant
	control	32	123.031	7.6136		

Bar diagram showing percentage change from baseline in SBP comparison between two groups at different time intervals



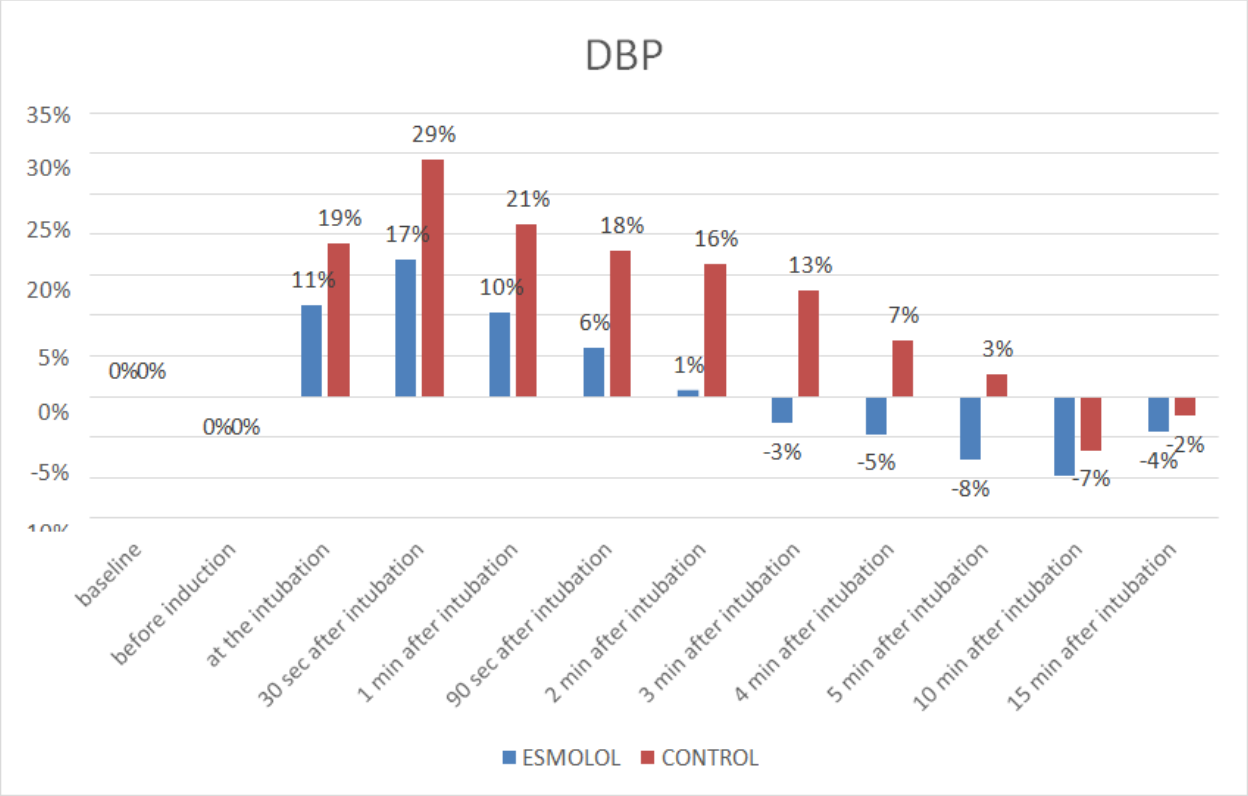
3. Mean diastolic blood pressure

The control group (C) and study group (E) a rise in the mean diastolic blood pressure(DBP) immediately after laryngoscopy and intubation noted. The mean DBP in the control group rose from 75.15 ± 5.69 mmHg to 97.12 ± 7.1 mmHg (29.1%)(P 0.000)(table 6) 30 seconds after intubation, whereas in Esmolol groups, the values rose from 76.1 ± 4.76 mmHg to 88.9 ± 5.52 mmHg (17%). It decreased to baseline values at 2 minutes in group E and between 5-10 minutes in group C.

Table.no.3-DBP comparison between two groups at different time intervals

	Group	N	Mean	Std.Deviation	p-value	Unpaired t test
Baseline	Esmolol	30	76.100	4.7659	.481	Not Significant
	Control	32	75.156	5.6973		
30 Sec After Intubation	Esmolol	30	88.900	5.5233	.000	Significant
	Control	32	97.125	7.1018		
2 Min After Intubation	Esmolol	30	76.733	5.0850	.000	Significant
	Control	32	87.375	6.3538		
5 Min After Intubation	Esmolol	30	70.167	4.5035	.000	Significant
	Control	32	77.188	5.7890		
10 Min After Intubation	Esmolol	30	68.667	4.2535	.207	Not Significant
	Control	32	70.188	5.1144		

Bar diagram showing percentage change from baseline in DBP comparison between two groups at different time intervals



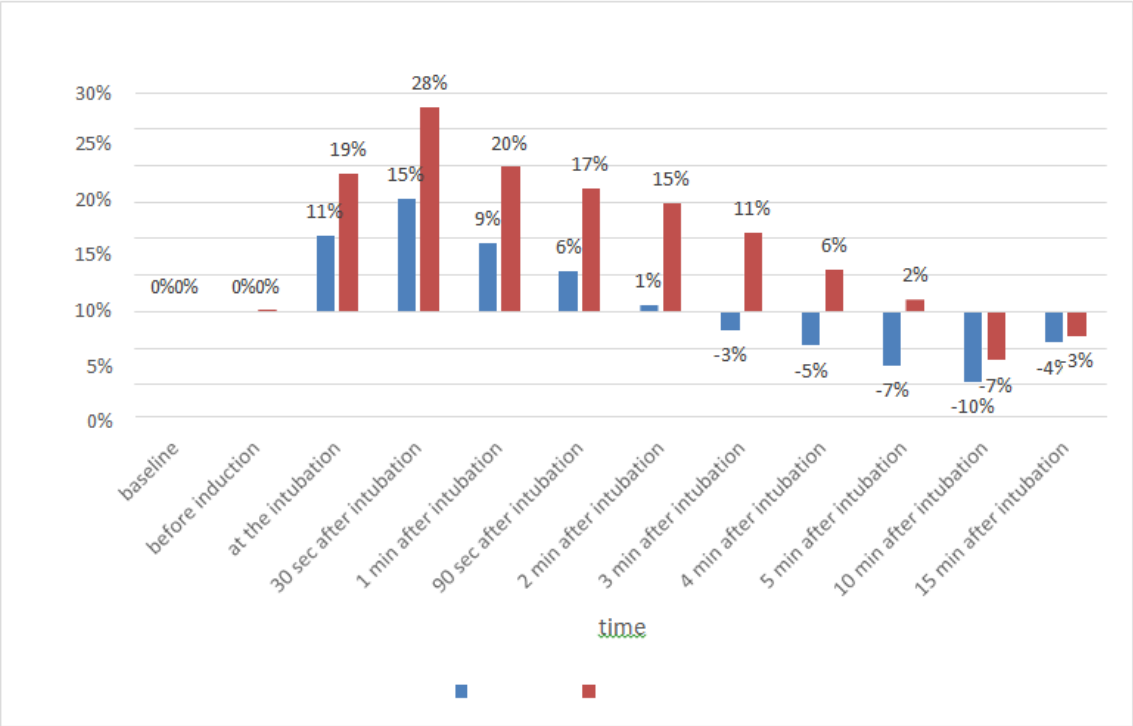
4. Mean arterial pressure

Mean arterial pressure (MAP) increased in all groups following laryngoscopy and intubation. 30 seconds after intubation, in the control group, there was a significant 28% increase from mean baseline value of 90.95 ± 5.98 to 116.4 ± 7.54 which was statistically highly significant (P=0.001). The increase was to some extent in the Esmolol group where it rose from 90.63 ± 5.29 to 104.66 ± 5.9 (15%). It reaches close to baseline in group E at 2 min after intubation and between 5-10 minutes in group C.

Table.no.4-MAP comparison between two groups at different time intervals

	group	n	Mean	std. deviation	p-value	Unpaired t test
Baseline	Esmolol	30	90.63	5.29	.82	not significant
	control	32	90.95	5.98		
30 sec after intubation	Esmolol	30	104.66	5.90	.00	Significant
	control	32	116.40	7.54		
2 min after intubation	Esmolol	30	91.48	5.53	.00	Significant
	control	32	104.47	6.60		
5 min after	Esmolol	30	83.94	4.67	.00	Significant
intubation	control	32	92.46	5.94		
10 min after intubation	Esmolol	30	81.95	4.60	.02	not significant
	control	32	84.88	5.23		
15 min after intubation	Esmolol	30	86.75	5.14	.36	not significant
	control	32	87.94	5.12		

Bar diagram showing percentage change from baseline in MAP comparison between two groups at different time intervals



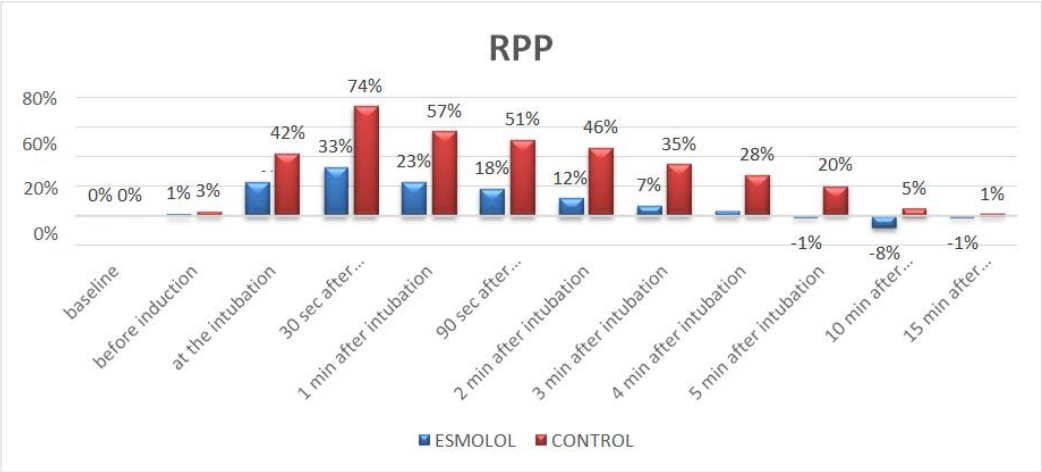
5. The mean rate pressure product

The mean rate pressure product(RPP) values in the control group showed a significant increase at 30 sec after intubation from 10342.75 ± 990.9 to 17997.34 ± 2226.64 (74%). The values in the Esmolol group also showed an increase from 9603.73 ± 847.84 to 12781.06 ± 1104.86 (33%) (P=0.000) (statistically highly significant). It fails close to baseline values in group E at 5 minutes and in group C at 15 minutes after intubation.

Table.no.5-RPP comparison between two groups at different time intervals

	GROUP	N	Mean	Std. Deviation	p-value	Unpaired t test
Baseline	Esmolol	30	9603.73	847.84	.002	Significant
	Control	32	10342.75	990.90		
30 sec after intubation	Esmolol	30	12781.06	1104.86	.000	Significant
	Control	32	17997.34	2226.64		
5 min after intubation	Esmolol	30	9490.03	870.81	.000	Significant
	Control	32	12426.96	1243.84		
15 min after intubation	Esmolol	30	9513.43	839.31	.000	Significant
	control	32	10486.96	998.96		

Bar diagram showing percentage change from baseline in RPP comparison between two groups at different time intervals



6. Spo2

In the study there was no significant difference in mean SpO2 between two groups at all the intervals of follow up.

DISCUSSION

Laryngoscopy and intubation are associated with a cardiovascular response of elevated blood pressure and pulse rate as well as occasional dysrhythmias.[1] These pressor responses following laryngoscopy and intubation are transient occurring within 30 seconds of intubation and lasting for less than 10 minutes.[3] In this study administration of intravenous Esmolol used to attenuate pressor response to laryngoscopy and intubation. It is cardio selective (beta 1) beta adrenoreceptor antagonist and has ultrashort duration of action (9min).[5] It prevents increase in pulse rate and blood pressure. It is suitable for said purpose to attenuate cardiovascular response to intubation and is also short lived and lasts less than 10 minutes.

The rationale for the administration of Esmolol as a bolus rather than as an infusion in this study as the desire for a rapid onset and short duration of action in order to promptly treat a transient haemodynamic event as well as the convenience of bolus administration compared with the preparation and administration of an infusion.

The studies reviewed used a wide range of Esmolol. Doses of 0.4 to 4 mg/kg were used. A dose of 0.4 mg/kg administered prior to laryngoscopy and intubation was chosen for this study based on trial evaluating the use of Esmolol for attenuation of the pressor response by Bensky et al.[8] Drug is administered 3 minutes before laryngoscopy and intubation.[9]

This was an observational study to study effect of attenuation of pressor response to laryngoscopy and intubation and assessed the haemodynamic changes- heart rate, systolic blood pressures, diastolic blood pressures, mean arterial pressures, rate pressure product, percentage change in hemodynamics and ECG changes associated with laryngoscopy and endotracheal intubation in patients who received Esmolol 0.4 mg/kg (group E) and in patients not received Esmolol (group C).

After taking approval from hospital ethics committee and a written consent from each patient, consecutive sampling method was followed. Patients were randomly allocated into two groups, group C and group E.

The haemodynamic values at predefined time intervals were compared with the 'Baseline' reading. Because the baseline reading represents the stable pre-intervention reading, having no effect of any anaesthetic medication. In most of the referred articles too 'Baseline readings' were considered for reference. A clinically significant variation was taken as 20% increase or decrease of the value as compared to 'baseline value'. MAP was chosen as the representative value of blood pressure readings as it indicates the organ perfusion pressure.

After analysing the demographic data, by using unpaired t -test P-value > 0.05, both groups were comparable in confounding factors like age, gender and weight so that other clinical criteria under study could be evaluated.

Heart rate response

Unpaired t –test was used to compare the mean heart rates at respective time intervals for intergroup comparison of group C and E . By using this test, the 'baseline' values in both groups are statistically comparable (p=0.04) and there is a statistically significant (p<0.05) difference between mean heart rate in both groups at 'at the intubation and onwards. This was more in the control group where 30 sec after intubation caused a rise in the heart rate from a mean baseline value of 84.62 to 116.34, an increase of 37% which was statistically highly significant (p=0.000). In the Esmolol group, mean heart rate increased from 80.36 to 93.96, an increase of 17%. After laryngoscopy and

endotracheal intubation, there was a decrease in heart rate in all groups and the changes were statistically significant (P=0.00) and at 10 minutes post-intubation, this parameter closely approached baseline values in the Esmolol group.

Blood pressure response

According to unpaired t-test, the systolic arterial pressures (SBP) in both the groups C and E are statistically comparable at baseline values (p = 0.125). There is statistically no significant difference in SBPs before induction (p =0.51). The increase was more in the control group where it rose significantly from a mean baseline value of 122.56 to 154.96 (26%) 30 sec after intubation (p=0.000), and in the Esmolol group, which increased from 119.7 to 136.2 (14%) (p=0.00). It fails close to baseline in group E at 2 minutes and in group C at 5 minutes. There is statistically no significant difference in DBPs before induction (p =0.43). The mean diastolic pressure in the control group rose from 75.10mmHg to 97.10mmHg (29.1%) 30 seconds after intubation, whereas in Esmolol groups, the values rose from 76.15 mmHg to 88.9 mmHg (17%).It decreased to baseline at 2 minutes and between 5-10 minutes in group E and C respectively . There is statistically no significant difference in MAP before induction (p =0.75). From 30 seconds after intubation upto 5th minute after intubation, the MAP in group E is statistically significantly lower than in group C (p<0.05). It reaches close to baseline at 2 minutes in group E and between 5-10 minutes in group C.

Thus it is observed that decrease in SBP, DBP and MAP is more in group C than in group E.

Rate pressure product (rpp)

According to unpaired t-test the rate pressure product (RPP) is in both the groups C and E are statistically comparable at baseline values (p = 0.003). 30 seconds after intubation in group C showed increase in 74% and group E 33% of baseline values. At 5 minutes post intubation, a decrease in mean rate pressure product to baseline was observed in group E . Whereas it comes to baseline at 15 minutes in group C. Esmolol showed significantly greater effects in attenuating the post-intubation rise in RPP.

Sanjeev Singh et al found that percentange change in HR and RPP 1 minute after intubation from baseline was 1.5% and 11.68% respectively.[10] Differences with our study could be due to larger doses of Esmolol (2mg/kg) used by them.

Esmolol in 1.5 mg/kg used by Gupta C et al obtained percentange change in HR and MAP 1 minute after intubation from baseline was 2.20% and 8.8% respectively. This difference may be due to use of propofol as induction agent by them.[11]

Whereas low doses such as 0.2mg/kg Esmolol used by Karuppiah et al observed rise in HR, SBP and DBP upto 15% from baseline 1 minute after intubation. MAP fell below baseline after 5 minutes. surprisingly they used too low dose of Esmolol, only partially attenuates pressor response.[12]

The rate-pressure product (a product of the systolic blood pressure and heart rate) is a good index of myocardial oxygen consumption and a threshold of RPP has been correlated with the onset of angina in patients with known coronary artery diseases or those who have risk factors for coronary artery disease.[13] Increased blood pressure and heart rate lead to elevated myocardial oxygen demand and the haemodynamic changes at intubation may precipitate myocardial ischaemia and infarction. Tachycardia increases myocardial oxygen demand, decreases diastolic filling time, and hence coronary blood flow. A moderate increase in heart rate (15%) has been shown to be accompanied by a 17% decrease in coronary perfusion pressure.[14] Raised blood pressure, on the other hand, increases both oxygen demand and supply and thus has a less predictable effect on myocardial oxygen balance. Furthermore, the increase in blood pressure accompanying laryngoscopy and intubation has been attributed to an increase in cardiac output rather than increased systemic resistance.[15] Hence, by its predominant attenuation of increases in heart rate, Esmolol is more likely to optimize the myocardial oxygen supply/demand relationship. It is said that Rate Pressure Product of more than 22000 often signifies the risk of myocardial ischemia and angina.[16] The patient's preoperative level should however serve as a guide. Rao et al recommended that in the anaesthetic management of patients with cardiac morbidity presenting for non-cardiac surgery, the heart rate and systolic blood pressure and thus the RPP should not fluctuate beyond 20% of the baseline value.[17] Although RPP does not predict regional myocardial supply-demand relationships, examination of the individual components (heart rate and systolic blood pressure) is a useful guide in the management of ischaemic heart disease. In our study Esmolol significantly attenuated the heart rate, blood pressure and rate-pressure product changes. However, the 33% rise in RPP recorded in the Esmolol group still exceeds Rao's 20% recommendation. This is however significantly superior to the control group.

In present study in group E, 30 seconds and 2 minutes after intubation HR rose to 17% and 11% respectively and MAP fell near to baseline at 2 minutes after initial increase of 17% at 30 seconds. This results are comparable to results obtained by Bensky et al[8] (dose-Esmolol 0.4 mg/kg.). The side effects like Bradycardia, Tachycardia, Hypotension, Hypertension and ECG changes were looked for. A decrease in MAP greater than 20% is often chosen to define clinically significant hypotension. There were no side effects noted in study. This absence of side effects may be due to smaller dose

of Esmolol administered in present study. No abnormal ECG changes were noted in both study groups.

CONCLUSION

This study has confirmed that significant increases in haemodynamic variables accompany laryngoscopy and endotracheal intubation following the widely utilized technique of induction of anaesthesia. These changes are maximal immediately after intubation, but return to baseline values by 5 -10 minutes.

Esmolol in low dose 0.4mg/kg administered in present study attenuates pressor response to some extent. Further studies are needed to determine appropriate dose of Esmolol to attenuate the pressor response adequately. There were no adverse outcomes and abnormal ECG changes noted in the present study.

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