A COMPARATIVE STUDY OF EFFICACY OF ESMOLOL AND FENTANYL FOR ATTENUATION OF INTUBATION RESPONSE DURING LARYNGOSCOPY

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ABSTRACT: AIM: To compare the attenuation of haemodynamic changes to laryngoscopy and intubation with IV bolus Esmolol 2mg/kg and IV Fentanyl 2µg/kg. METHODS: 90 adult patients of both sex between age 18 and 55 years with ASA grade I and II normotensive with normal rhythm in ECG are divided randomly into three groups. Group-C was control group. In these patients no drug was given. Group-E was Esmolol group. In this group patients were given Inj. Esmolol-2mg/kg IV 3 min. before intubation over 30 seconds Group-F was Fentanyl group. In this group patients were given Inj. Fentanyl-2µg/kg IV 3 min. before intubation over 30 seconds. Heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were recorded as baseline and after administration of study drug. **RESULTS:** Heart rate, systolic, diastolic blood pressures and mean arterial blood pressures were compared at pre op, 1 minute after induction and 1, 3, 5 and 10 minute intervals from the onset of laryngoscopy and intubation. Esmolol showed better attenuation of sympathetic response which is statistically highly significant. It remains significant till the end of 5 minutes. CONCLUSION: Esmolol is more effective than Fentanyl in attenuation of sympathetic response to laryngoscopy and intubation. IV. bolus dose of Esmolol 2mg/kg administered 3 minutes before laryngoscopy and intubation can be recommended to attenuate the sympathetic response to laryngoscopy and intubation without any side effects of the drug.

KEYWORDS: Esmolol, fentanyl, laryngoscopy, endotracheal intubation, pressure response.

INTRODUCTION: Direct laryngoscopy and endotracheal intubation is almost always associated with haemodynamic changes due to reflex sympathetic discharge caused by epipharyngeal and laryngopharyngeal stimulation. This increased sympathoadrenal activity results in hypertension, tachycardia and arrhythmias which are potentially dangerous. These changes are maximum at 1 minute after intubation and last for 5-10 min. This increase in blood pressure and heart rate are usually transitory, variable and unpredictable. Hypertensive patients are more prone to have significant rise in BP. Transient hypertension and tachycardia may be hazardous to those with hypertension, myocardial diseases and cerebrovascular diseases. Various pharmacological agents e.g β -blockers, calcium channel blockers, nitroglycerine, opioids, α_2 adrenergic agonists, inhalational anaesthetics, pregabalin, loroxicam, lidocaine, etc, have been used to suppress this response.¹⁻⁸

Esmolol hydrochloride,^{9,10} is a cardioselective, intravenous β adrenoceptor antagonist. It has a rapid onset of action, exerts peak haemodynamic effect within minutes, and possesses a short elimination half-life of 9 minutes. Consequently it is proved ideal for control of short lived haemodynamic sequelae, associated with laryngoscopy and intubation.

Fentanyl,¹¹ is an opioid analgesic which is extensively used for anaesthesia and analgesia in operation theatres and intensive care unit (I.C.U). It produces effective analgesia and attenuates the cardiovascular, hormonal and metabolic responses to stress. It has a shorter duration of action.

Fentanyl suppresses the nociceptive stimulation and centrally decreases the sympathetic tone. Hence it is used in practice in attenuating the intubatory responses. The present study is undertaken to determine the efficacy of Esmolol 2mg/kg IV bolus and Fentanyl 2 μ g/kg IV bolus in attenuating the sympathetic responses to laryngoscopy and tracheal intubation.

AIMS AND OBJECTIVES OF THE STUDY: To compare the attenuation of haemodynamic changes to laryngoscopy and intubation with IV bolus Esmolol 2mg/kg and IV Fentanyl $2\mu g/kg$.

MATERIAL AND METHODS: After obtaining the ethics committee approval and written consent from patients, a prospective randomized comparative study on adult patients who were scheduled for elective surgeries under general anaesthesia and required endotracheal intubation were included in this study at King George hospital, Visakhapatnam.

This study was conducted on 90 adult patients of both sex between age 18 and 55 years with ASA grade I and II normotensive with normal rhythm in ECG are divided randomly into three groups. Group - C was control group. In these patients no drug was given. Group - E was Esmolol group. In this group patients were given Inj. Esmolol- 2mg/kg IV 3 min. before intubation over 30 seconds Group - F was Fentanyl group. In this group patients were given Inj. Fentanyl-2µg/kg IV 3min before intubation over 30 seconds.

Patients having hypertension, bronchospastic disease, cardiac problem, anticipated difficult airway and patients on beta blockers were excluded from the study.

All patients were premedicated with Tab. diazepam 10mg at bed time the previous day. In the operation theatre, an 18G IV cannula was secured. Monitoring of SpO₂, ECG, Non-invasive BP was started. After establishing intravenous access, Ringer Lactate was started and all patients were premedicated with Inj. Glycopyrrolate 0.2mg I.V. half an hour prior to induction.

The study drug was administered intravenously over 30 sec 3min before laryngoscopy and endotracheal intubation. Patients were preoxygenated with 100% oxygen for three minutes before induction. Induction of anaesthesia with inj. Thiopentone 5 mg/kg IV. After checking for adequate ventilation, inj. Succinylcholine 2mg/kg was given. Direct laryngoscopy and tracheal intubation was performed 90 seconds after the administration of Succinylcholine. In all the groups intubation was done with in a period of 30 seconds. Anaesthesia was maintained with Oxygen: nitrous oxide (33%:66%). Neuromuscular blockade was achieved with Vecuronium -0.08mg/kg (loading dose) and 0.02mg/kg (Incremental dose). The HR, SBP, DBP and MAP were recorded 1 min after induction, 1 min after intubation and there after 3, 5 and 10 minutes after intubation. Group C and E patients provided either with intravenous Fentanyl (1µg/kg body weight) or Inj. Pentazocine 0.5mg/kg before skin incision. In Group F patients no analgesics given since it was Fentanyl group. Further anaesthesia was maintained as per patient's requirements.

Complications like pain on injection, bradycardia, hypotension, abnormal ECG, nausea and vomiting are recorded during the study.

Parametric data including heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were compared using unpaired student's t test. Multiple group comparison were made by one way ANOVA and pair wise comparison by unpaired 't' test. If the p value <0.05 it was considered statistically significant.

RESULTS:

Ago (Vrc)	Groups						
Age (Trs)	Control (C)	Esmolol (E)	Fentanyl (F)				
RANGE	18-55 years	18-55 years	18-55 years				
Mean±SD	34.3±8.77	36.5±9.58	37.7±9.55				
Table 1: Age Distribution							

There was no significant difference between three groups (p = 0.361).

	Mean±SD			Difference between groups**		
Time	Control	Esmolol	Fentanyl	C-E	C-F	E-F
				p value	P value	P value
Pre Op (basal value)	82.7±7.83	79.21±10.66	80.86±6.83	0.0993	0.4663	0.3261
1 min after induction	90.4±10.66	79.9±5.37	82.8±6.76	< 0.0001	0.0017	0.0709
1 min after	117.17±10.98	92.38±5.74	101.76±7.28	0.0001	<0.0001	<0.0001
intubation						
3 min after	116.7±13.88	89.41±4.57	97.59±9.10	<0.0001	<0.0001	<0.0001
intubation						
5 min after	106.23±13.61	84.55±5.47	91.59±7.28	<0.0001	<0.0001	<0.0001
intubation						
after10 min	84.63±6.26	78.62±5.96	81.17±8.35	0.0004	< 0.0001	0.1786
Table 2: Comparison of Changes in Heart Rate						



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Changes in heart rate assessed at pre op and 1 min after induction and at different time intervals from the onset of laryngoscopy and intubation in control and study groups and their comparative statistics are presented.

The difference in heart rate between control and Esmolol groups is not significant pre operatively but remains highly significant at all times of assessment (p<0.0001). Attenuation of heart rate by Fentanyl when compared with control group is highly significant (p<0.001). Maximum increase in heart rate is 42.6% in control group and 16.4% in Esmolol group. It is statistically highly significant (p<0.001) It reaches to a level which is clinically less significant by the end of 10 minutes in control group and 5 minutes in Fentanyl group.

The difference in heart rate between control and Esmolol group remains statistically significant at all times of assessment (p<0.001) The maximum increase in heart rate is 42.6% in control group and 26.2% in Fentanyl group. There appeared no significant difference in heart rate at pre op and post induction levels between Esmolol and Fentanyl groups The heart rate response between Esmolol and Fentanyl group is clinically and statistically highly significant at 1, 3 and 5 minutes (p<0.001).

		Difference between groups**				
Time	Control	Esmolol	Fentanyl	C-E	C-F	E-F
				P value	P value	P value
Pre Op (basal value)	130.7±9.44	129±11.31	131.6±11.4	0.5298	0.7403	0.3786
1 min after induction	127.33±9.22	128.2±11.2	129.8±10.97	0.7437	0.3490	0.5783
1 min after intubation	155.5±9.46	137.2±10.08	148.2±11.08	< 0.0001	0.0081	0.0002
3 min after intubation	153.9±10.7	134.9±9.81	145.7±11.8	< 0.0001	0.0066	0.0003
5 min after intubation	143.5±10.2	129.6±10.3	137.9±10.4	< 0.0001	0.0396	0.0029
10 min after intubation	131.3±9.03	125±9.6	128.6±11.09	0.0259	0.3054	0.3001
Table 3: Comparision of Changes in Systolic Blood Pressure						

S= Significant, NS= Not significant.

The changes in systolic blood pressure assessed pre op and 1 minute after induction of anaesthesia and at various time intervals from the onset of laryngoscopy and intubation in control and study groups and their statistical comparison is presented in the table.

No significant variation is found in all the groups with pre op and post induction values. A statistically significant difference is observed among all the groups at 1, 3 and 5 minutes after intubation (p<0.05). Attenuation of rise in systolic blood pressure is significant in Fentanyl group when compared to control group. A rise of 12.9% (19mmHg) is seen in Fentanyl group when compared to control group which is about 19.2% (28mmHg) (p<0.01).

A similar attenuation is highly significant with Esmolol group. A rise of only 9mmHg is observed in Esmolol group (p<0.001). It returned nearer to basal values earlier in both Fentanyl and Esmolol groups (5 minutes). Attenuation of systolic blood pressure is highly significant with Esmolol when compared with Fentanyl. A rise of only 6.2% (9mmHg) is observed in Esmolol when compared to Fentanyl which was 12.9% (19mmHg) (p<0.01).

	Mean±SD			Difference between groups**			
Time	Control	Esmolol	Fentanyl	C-E	C-F	E-F	
				P value	P value	P value	
Pre Op (basal value)	77.6±6.12	76.06±5.26	77.7±5.56	0.3002	0.9474	0.2453	
1 min after induction	73.9±6.19	75.2±4.73	75.9±5.45	0.3645	0.1893	0.5972	
1 min after intubation	90±4.87	80.1±4.85	86.5±4.48	< 0.0001	0.0053	< 0.0001	
3 min after intubation	89.4±4.88	79.3±4.46	85.1±3.45	< 0.0001	0.0002	< 0.0001	
5 min after intubation	85.3±5.96	76.4±3.98	81.1±3.28	< 0.0001	0.0013	< 0.0001	
10 min after intubation	78.2±5.36	75.06±4.75	75.8±4.5	0.0196	0.0654	0.5380	
Table 4: Comparision Of Diastolic Blood Pressure							

A significant difference is observed in all the three groups at 1, 3 and 5 minutes after intubation. But it returned to near basal level in Esmolol group at 5 minutes. Suppression of maximum rise in diastolic blood pressure by Fentanyl is statistically significant (p<0.001). Maximum rise is 11.6% (9mmHg) in Fentanyl group and 16.8% (13mmHg) in control group. Esmolol is also efficient in attenuating the rise in diastolic blood pressure. The maximum rise was only 5.2% (4mmHg). Statistically it is highly significant (p<0.001). When compared with Fentanyl, Esmolol shows highly significant suppression of diastolic blood pressure. The maximum rise was 5.2% (4mmHg) and 11.6% (9mmHg) in Esmolol and Fentanyl groups respectively (p<0.001).

	Mean±SD			Difference between groups**			
Time	Control	Esmolol	Fentanyl	C-E	C-F	E-F	
				P value	P value	P value	
Pre Op (basal value)	95.1±6.47	93.68±5.7	95.65±6.22	0.3484	0.7702	0.2063	
1 min after induction	91.57±6.39	93.1±5.3	93.1±7.63	0.3172	0.3852	0.9686	
1 min after intubation	111.7±5.42	98.8±4.71	106.9±5.7	< 0.0001	0.0015	< 0.0001	
3 min after	111.01±5.94	97.66±4.96	105.2±4.71	< 0.0001	< 0.0001	< 0.0001	
5 min after	104.63±6.6	94.4±4.69	100.07±4.09	< 0.0001	0.0021	< 0.0001	
after10 min	95.58±5.67	91.60±5.25	93.4±5.53	0.0065	0.1371	0.2012	
Table 5: Comparision of Changes in Mean Arterial Pressure							

The changes in mean arterial pressure assessed at pre op and 1 minute after induction and at various time intervals from the onset of laryngoscopy and intubation in control and study groups and their comparative statistics are shown in this table.

A significant difference is seen in all the groups at 1, 3 and 5 minutes interval. (p<0.001).

Among the two study groups Esmolol is highly significantly in attenuating pressure response. Fentanyl shows 11.5% (11mmHg) increase in mean arterial pressure. But Esmolol shows only 5.3% (5mmHg) increase (p<0.001). No cases were excluded from study. Bradycardia is recorded in 2 cases of Group E, nausea and vomiting are noted in 3 cases in Group F which is insignificant.

DISCUSSION: Intubation is associated with a cardiovascular response of elevated blood pressure, heart rate and occasional dysrrhythmias, it also causes increased intracranial pressure, and increased intraocular pressure. If no specific measures are taken to prevent this haemodynamic response, the HR can increase from 26%-66% depending on the method of induction, and SBP can increase from

36%-45%. In patients with atherosclerotic heart disease, intracranial lesions and potential penetrating eye injuries these responses to intubation are of greater risk. About half the patients with coronary artery disease experience episodes of myocardial ischemia during intubation when no specific precaution is undertaken.

More attention is given to the use of selective β -adrenergic antagonists to prevent the reflex sympathoadrenal discharge-mediated tachycardia and hypertension during procedures of laryngoscopy and endotracheal intubation.

β-blockers with negative chronotropic, anti-hypertensive, anti-arrhythmic and anti-ischemic properties have been advocated.

Fentanyl was found to be more effective than other narcotics at preventing increases in cerebral blood flow velocity during intubation and also seemed to provide a more stable haemodynamic profile prior to laryngoscopy and tracheal intubation. Fentanyl has various advantages like no histamine release or bronchospasm, cardiostability, rapid onset and short duration of action. So this study is designed to find out its efficacy for attenuation of pressor response.

Baclofen M,¹² stated the criteria for selection of appropriate drug to prevent sympathetic response are as follows. The drug must be applicable, regardless of patient collaboration, prevent impairment of cerebral blood flow, and avoid arousal of the patient. It should neither be time consuming nor affect the modality of the ensuing anaesthesia. Intravenous Esmolol and Fentanyl appear to fulfill the above criteria.

In our study Esmolol was administered 3 min before laryngoscopy and endotracheal intubation. It correlates with the study of Feng et al¹³ who concluded that Esmolol controls the rise in mean systolic blood pressure when administered 3 min before intubation. Fentanyl was also administered 3 min before larvngoscopy and endotracheal intubation.

With regard to age, sex and weight there was no statistical difference between the three group.

In our study heart rate increased by 42.6% when compared with preop or basal value in control group (p<0.001). Similar increase with Esmolol was 16.4% and Fentanyl was 26.2%. Both Esmolol and Fentanyl attenuated the heart rate highly significantly (P<0.001). This was similar to the study of Ugur et al¹⁴ who compared the efficacy of Esmolol 1.5mg/kg, Fentanyl 1µg/kg, Lignocaine 1. 5 mg/kg and control which showed decrease in heart rate in Esmolol group when compared to control group after induction and 1 min after intubation (p<0.0083).

Singh H et al,¹⁵ also showed similar attenuation in Esmolol group, . They compared the efficacy of Esmolol, Lignocaine, Nitroglycerine and control for attenuation of haemodynamic response.

In control group, systolic blood pressure increased maximally 1 minute after the onset of laryngoscopy and intubation. The rise in SBP in control group was 19.2%. With administration of Fentanyl maximum increase was 12.9% above baseline and with Esmolol it was only 6.2%.

Similar results were shown by Hussain A M et al,¹⁶ who compared the efficacy of control, Esmolol 2 mg/kg and Fentanyl 2µg/kg. The study showed increase in blood pressure in all groups but least in Esmolol group.

Maximum increase in diastolic blood pressure was 16.8% when compared with pre op value in control group (p<0.05). It was 11.6%, 5.2% in Fentanyl and Esmolol groups respectively. The p value with Fentanyl and Esmolol groups was < 0.05.^{16,17}

Similarly mean arterial pressure increased by 16.8% from the pre op value in control group at 1 minute (p<0.05) and gradually reached basal level over a period of time. Fentanyl limited the maximum rise to 11.5% (p<0.05) while Esmolol to only 5.3% (p<0.05).¹⁵

Esmolol has been used in various forms either as bolus or in an infusion form. Esmolol, 2 mg/kg, as a single bolus dose successfully attenuated the pressor response. There was minimal increase in heart rate than the other group but the blood pressure showed a rise although, it was less than other groups after laryngoscopy and endotracheal intubation.

Ebert et al,¹⁸ did a comparative study of attenuation by Esmolol (500µg/kg/min X 6 minutes, followed by 300µg/kg/min X 9 minutes), or Fentanyl (0.8µg/kg/min X 10 minutes). Fentanyl decreased the SBP, MAP and DBP significantly below the baseline, while these pressures were either retained at or elevated slightly above control in the Esmolol group. In these doses, the HR response to laryngoscopy was more effectively blocked by Fentanyl, while Esmolol better retained perfusion pressure. There were no complications or ischemic electrocardiographic changes in any patient.

Shobana gupta and purvi tank et al,¹⁹ also showed a rise of mean arterial pressure in all the groups but less in Esmolol group (p<0.05).

The efficacy of Esmolol over Fentanyl has been verified in many other studies. Both Esmolol and Fentanyl together are also recommended to suppress the pressor response.²⁰

CONCLUSION: In patients with no drugs to attenuate the sympathetic response to laryngoscopy and intubation the maximum rise of heart rate, systolic, diastolic and mean arterial blood pressures are 41.1%, 20.0%, 17.2% and 18.1% respectively when compared with pre op values. Esmolol is more effective than Fentanyl in attenuation of sympathetic response to laryngoscopy and intubation.

IV. bolus dose of Esmolol 2mg/kg administered 3 minutes before laryngoscopy and intubation can be recommended to attenuate the sympathetic response to laryngoscopy and intubation without any side effects of the drug.

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