ATTENUATION OF HEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION-‘A COMPARATIVE STUDY OF FENTANYL AND ESMOLOL.’

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ABSTRACT

Background: Laryngoscopy and endotracheal intubation are integral part of induction of general anesthesia which cause to presser response leading to hemodynamic responses. Several techniques have been studied to attenuate this stress response but none of them are completely satisfactory hence there is a constant search for an ideal drug to attenuate hemodynamic response. Here we studied the hemodynamic response to laryngoscopy and endotracheal intubation and compare the relative efficacy of Esmolol and Fentanyl for attenuation of hemodynamic response during laryngoscopy and endotracheal intubation. Methods: After obtaining approval from the Institutional Ethics Committee and written informed consent form patients, 60 patients were randomly selected & allocated into two groups, Group I: Esmolol group & Group II: Fentanyl group of 30 each. Vital parameters (pulse rate and blood pressure) were measured at various intervals and compared. Multiple pair wise comparisons with Bonferroni’s adjustment done and ANOVA (analysis of variable) test was applied. Results: Significant difference was noted in hemodynamic parameters in both the groups. Conclusion: Intravenous Esmolol was found to be more effective than intravenous Fentanyl in attenuating presser response to laryngoscopy and intubation.
KEY WORDS: Haemodynamic response, laryngoscopy, endotracheal intubation, fentanyl and esmolol.

INTRODUCTION
Laryngoscopy results in stimulation of larynx, pharynx, epipharynx and trachea which are extensively innervated by the autonomic nervous system. Stimulation of these areas leads to sympathetic system activation leading to various cardiovascular changes like increase in heart rate, blood pressure, intracranial pressure, intraocular pressure, dysrrythmias, cardiac asystole and even sudden death[1-5]. These changes may prove to be detrimental especially in patients with ischemic heart disease, cerebrovascular disease, hypertension, old age, and diabetes mellitus. Several techniques have been studied to attenuate this stress response but none of them are completely satisfactory hence there is a constant search for an ideal drug to attenuate hemodynamic response. Various methods and drugs have been used. They are–Deep inhalation anaesthesia[6], Topical Lignocaine 2%, Lignocaine aerosol 10%[7], Intravenous Lignocaine 2%[8].Vasodilators-I.V.SodiumNitroprusside, I.V. Nitroglycerine. Beta blockers-I.V. Metoprolol, I.V. Esmolol[9-11] & I.V.Diltiazem.V.Propranolol. Calcium channel Blockers-Sublingual and I.V.Nifedepine[12], I.V.Verapamil & General anaesthetics: Propofol,[13,15] OpioidsI.V.Fentanyl,[16,17] I.V.Sufentanil,[18,19] I.V.Alfentanil & I.V.Remifentanil.[20,21]

All the above methods need to be studied more to find out the most effective, safe and reliable method for attenuating hemodynamic response due to laryngoscopy. Hence in this view, we studied the effect of intravenous Esmolol 2 mg/kg and intravenous Fentanyl 2 µg/kg for attenuation of stress response given as a bolus 3 minutes prior to laryngoscopy. To find out the most effective safe method of attenuating hemodynamic response.

MATERIALS AND METHODS
After obtaining approval from Institutional Ethics Committee and written informed patient consent, 60 ASA I and II patients in the age group 18-45 years, who were normotensive and undergoing planned elective surgery under general anesthesia were selected in this randomised, prospective study.

Exclusion criteria’s
Patients with anticipated difficult intubation, hypertension, heart disease, old age, cerebrovascular disease, ischaemic heart disease, arrhythmias, shock, chronic obstructive
pulmonary disease, symptomatic lung disease, diabete smellitus, pregnant patient and patients 
requiring duration for laryngoscopy more than 30 seconds and multiple attempts.

These patients were randomly divided into two groups of 30 patients in each group (total 60 patients).

**Group I: Esmolol group**—Consisting 30 of patients who were given bolus inj. Esmolol hydrochloride i.v. 2mg/kg, 3 minutes before laryngoscopy.

**Group II: Fentanyl group**—Consisting 30 of patients who were given Bolus inj. Fentanyl i.v. 2 µg/kg, 3 minutes before laryngoscopy.

All the patients undergoing planned elective surgery were assessed as per the routine preoperative protocol and had been kept nil by mouth for 6 hours before surgery. All patients attached monitors and baseline parameters noted. Intravenous access established and Ringers Lactate was started and all patients were premedicated with Inj. glycopyrrolate 4µg/kg I.V. half an hour prior to induction.

**Anaesthesia protocol**

All patients were preoxygenated with 100% oxygen for 5 minutes. This was followed by induction of general anaesthesia with

- Inj. Propofol 2mg/kg intravenous followed by
- Inj. Succinylcholine 2 mg/kg intravenous to facilitate endotracheal intubation.

Patients were ventilated with 100% oxygen and after full relaxation, laryngoscopy and intubation was carried out. All intubations were smooth and gentle and were done within 30 seconds. Immediately after intubation following parameters were monitored and studied.

- Heart rate (HR), Systolic Blood Pressure (SBP), Rate pressure product (RPP), Diastolic Blood Pressure (DBP), Oxygen saturation (Spo2), Mean arterial pressure (MAP), Electrocardiogram monitoring (lead II) done at the following intervals,— Baseline, Study drug i.v., Induction, Scoline Injection, During laryngoscopy and intubation, 1 minute of intubation, 3 minutes of intubation, 5 minutes of intubation and 10 minutes of intubation. Anaesthesia was maintained on oxygen and nitrous oxide with Bains circuit(40:60%). Halothane was started in 0.5%–1% after 10 minutes of intubation. Muscle relaxation maintained with non depolarising muscle relaxant inj. Vecuronium 0.1 mg/kg I.V. bolus and
intermittent doses. Any airway manipulation such as insertion of Ryle’s tube, throat packing was withheld till 10 minutes after laryngoscopy. Analgesics given after 10 minutes. Group I patients—Inj.Pentazocine 0.6 mg/kg. Group II patients—No analgesics given since it was Fentanyl group. Incision was allowed to be taken after 12 minutes of induction. Further anaesthesia was maintained as per patients requirements.

Mean arterial pressure and rate pressure product calculated by formula –

\[
\text{MAP} = \frac{(\text{SBP} + 2 \times \text{DBP})}{3}
\]

\[
\text{RPP} = \text{SBP} \times \text{HR}
\]

**Statistical Analysis**: Multiple pair wise comparison with Bonferroni’s adjustment done and ANOVA (analysis of variable) test was applied. Mean and standard deviation for all values were calculated and compared within the group with baseline values as well as inter group comparison was done. Efficacy of both the drugs to reduce haemodynamic response was compared. Any adverse effect due to either of drug i.e. inj. Esmolol and Fentanyl was noted.

**Observations and results**

The study was performed with a total of 60 randomly selected patients keeping an eye on the eligibility criteria (excluding those who failed to meet the inclusion criteria and those patients who refused participation) between May 2012 and April 2014. Both the groups were comparable with respect to age, sex and weight.

Inter group (ANOVA test) comparison at different time intervals were done with respect to each parameter. Comparison of Gender, Age and Body Weight of Cases between Esmolol and Fentanyl groups were non-significant so not presented graphically here.

* Implies significant ‘p’ value -(p<0.05) and ** Indicates p<0.01,*# Indicates p<0.001

**Intergroup comparison of heart rate**

Table (1) shows. The baseline heart rates between the two groups were comparable with no statistical significance. Both the groups showed a fall in heart rates till laryngoscopy. Prior to laryngoscopy, Esmolol group had a mean heart rate of 76.3 per minute which was 2.5% below the baseline value. The Fentanyl group had mean heart rate of 85 per minute which was 1% below baseline values. At laryngoscopy Esmolol group had mean heart rate of 80 per
minute which was 2.5% rise above the baseline values. Fentanyl group had the mean heart rate of 100.8 per minute which was 17.6% rise above baseline values.

At 1 minute post–intubation, the heart rates in both the groups were at its peak value. In Esmolol group the mean heart rate was 82.0 per minute (2% above the baseline) which was statistically significant than the findings in the Fentanyl group with the mean heart rate being 95.5 (12% above the baseline)(p=0.001). After this point there was gradual fall in heart rate till 10 minutes post–intubation in both the groups with the pulse rate reverting to the baseline values in Fentanyl group while they remained below baseline in Esmolol group.

Table 1: Comparison of Heart Rate at different Time Interval with its Baseline in Fentanyl and Esmolol groups (inter group comparison).

<table>
<thead>
<tr>
<th>Events</th>
<th>Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Esmolol</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>Baseline</td>
<td>78.1±9.8</td>
<td>85.5±15.5</td>
</tr>
<tr>
<td>Study drug(0 minute)</td>
<td>73.9±9.6</td>
<td>81.6±16.0</td>
</tr>
<tr>
<td>Induction(1 minute)</td>
<td>69.1±9.4</td>
<td>78.1±15.9</td>
</tr>
<tr>
<td>Scoline(2 minute)</td>
<td>76.3±10.0</td>
<td>85±20.6</td>
</tr>
<tr>
<td>Laryngoscopy intubation(3 minute)</td>
<td>80.0±10.0</td>
<td>100.8±18.6</td>
</tr>
<tr>
<td>1 minute of intubation</td>
<td>82.0±10.4</td>
<td>95.5±18.1</td>
</tr>
<tr>
<td>3 minute of intubation</td>
<td>79.8±10.0</td>
<td>82.6±22.6</td>
</tr>
<tr>
<td>5 minute of intubation</td>
<td>75.0±9.6</td>
<td>84.4±16.9</td>
</tr>
<tr>
<td>10 minute of intubation</td>
<td>73.0±9.6</td>
<td>83.4±13.7</td>
</tr>
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</table>

*p indicates p<0.05,**indicates p<0.01,*# indicates p<0.001

Intergroup comparison of Systolic BP: Graph (1) shows, The baseline SBP was comparable between two groups with no statistically significant difference. There was a gradual fall in the mean SBP in both the groups till laryngoscopy.

Prior to laryngoscopy the mean SBP in Esmolol group was 125.9, which was 2.3% lower than the baseline values while the Fentanyl group the mean SBP was 130.7 mmHg, which was only 0.5% lower than the baseline values. The difference being statistically significant (p=0.019). At laryngoscopy the rise is SBP in Esmolol group was upto 129.9 mmHg which was significantly lesser than the rise in the Fentanyl group with the mean SBP of 143.3 mmHg having (p=0.000). At 1 minute post–laryngoscopy Esmolol group showed rise to mean SBP of 132.1 mmHg and Fentanyl group of 137.2 mmHg. The SBP gradually reduced from 1 minute post–laryngoscopy till 5 minutes post–laryngoscopy in both the groups with the value in Esmolol group being significantly lower than those in the Fentanyl group. At 10
minutes post–laryngoscopy the mean SBP in Esmolol group was below baseline values being statistically significant (p=0.093).

**Graph:1**

**Comparison of Systolic Blood Pressure at different Time Interval with its Baseline in Fentanyl and Esmolol Groups (inter group comparison)**

**Intergroup comparison of Diastolic BP**

Graph(2) depicts, the mean DBP at baseline was statistically comparable between two groups, the difference not being significant. Both the groups showed a fall in mean DBP gradually till laryngoscopy. Prior to laryngoscopy, Esmolol group had mean DBP of 80.0 mmHg which was non–significant as compared to in Fentanyl group having a mean of 77.4 mmHg (p=0.372). At laryngoscopy both the groups showed rise in DBP which was non–comparable statistically (p=0.975). At 1 minute post–intubation, the DBP was at its peak in both the groups with the Esmolol group having mean DBP of 84.3 mmHg as compared to the Fentanyl group having mean DBP of 84.4 mmHg the difference being statistically non–significant (p=0.975). After this point, there was a gradual fall in DBP in both the groups till 5 minutes post–laryngoscopy, the fall in Esmolol being greater as compared to Fentanyl group. At 10 minutes post–laryngoscopy, DBP in Esmolol group was 77.2 mmHg as compared to Fentanyl group being 76.2 mmHg which was statistically non–significant (p=0.518).
Graph 2:

Comparison of Diastolic Blood Pressure at different Time Interval with its Baseline in Fentanyl and Esmolol Groups
(inter group comparison)

Intergroup comparison of Mean Arterial Pressure (MAP)

The baseline MAP in Esmolol was 97.3 mmHg statistically comparable with MAP in Fentanyl group of 98.3 mmHg. There is significant fall in MAP prior to laryngoscopy in Esmolol group, the mean being 95.3 mmHg as compared to Fentanyl group having mean MAP of 95.1 mmHg, the difference being statistically significant (p=0.0348). At laryngoscopy the MAP in Esmolol group was 99.3 mmHg as compared to Fentanyl group having a MAP of 106.1 mmHg which is statistically significant (p=0.005). Both the groups show a transient rise in MAP at 1 minute post–intubation with Esmolol group having a MAP of 100.3 mmHg and Fentanyl group having a MAP of 102.0 mmHg which is statistically non–significant (p=0.403).

At 5 minutes post–intubation, the mean MAP is 95.2 mmHg which is lower than the baseline values in the Esmolol group. In Fentanyl group, MAP is near the baseline value is 91.7 mmHg. At 10 minutes post–intubation, the MAP in Esmolol group is 92.5 mmHg which is below baseline values, whereas MAP is Fentanyl group is 91.9 mmHg which is also below baseline value.
Table 2: Comparison of Mean Arterial Pressure (MAP at different Time Interval with its Baseline in Fentanyl and Esmolol groups (inter group comparison)).

<table>
<thead>
<tr>
<th>Events</th>
<th>Group</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Esmolol</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>Baseline</td>
<td>97.3±4.0</td>
<td>93.3±9.7</td>
</tr>
<tr>
<td>Study drug (0 minute)</td>
<td>94.2±4.3</td>
<td>93.5±10.9</td>
</tr>
<tr>
<td>Induction (1 minute)</td>
<td>88.3±4.4</td>
<td>86.2±11.2</td>
</tr>
<tr>
<td>Scoline (2 minute)</td>
<td>95.3±4.2</td>
<td>95.1±14.8</td>
</tr>
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<td>Laryngoscopy intubation (3 minute)</td>
<td>99.3±4.1</td>
<td>106.1±12.0</td>
</tr>
<tr>
<td>1 minute of intubation</td>
<td>100.3±4.9</td>
<td>102.0±10.2</td>
</tr>
<tr>
<td>3 minute of intubation</td>
<td>98.4±4.2</td>
<td>91.7±7.8</td>
</tr>
<tr>
<td>5 minute of intubation</td>
<td>95.2±4.2</td>
<td>91.7±7.8</td>
</tr>
<tr>
<td>10 minute of intubation</td>
<td>92.5±4.7</td>
<td>91.9±7.1</td>
</tr>
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</table>

*indicates p<0.05,**indicates p<0.01,*# indicates p<0.001

Inter group comparison of Rate pressure product (RPP)

The baseline RPP in Esmolol group was 9998.7 which was comparable statistically with the RPP Mean in Fentanyl group which was 11185.3. The RPP gradually reduced till laryngoscopy in both the groups. Prior to laryngoscopy there was fall in RPP in both the groups with Esmolol group showing a greater fall in RPP with a mean value of 9613.7 as compared to that in Fentanyl.

At laryngoscopy RPP in Esmolol group was 10392.3 which was statistically significant as compared to that in Fentanyl group which was 14555.1 higher with 30%. The RPP in Esmolol group at 1 min. post–laryngoscopy was at its peak with a value of 10827.8 which was 8.2% above baseline values. The RPP in the Fentanyl group at 1 minute post–laryngoscopy was 12156.6, which was 9% above being statistically significant than values in Esmolol group with p value of 0.001. The RPP showed a gradual decline in both groups from 1 minute post–laryngoscopy till 5 minutes post–laryngoscopy. At 5 minutes post–laryngoscopy, the RPP had reached near baseline values in Fentanyl group with mean of 10390.5. In Esmolol group the mean RPP at 5 minutes post–laryngoscopy was 9401.6 showing statistically significant difference between the two groups (p value 0.057). At 10 minutes post–laryngoscopy, RPP in Esmolol group was 8983.0 which was much lower as compared to baseline values. In Fentanyl group, RPP at 10 minutes post–laryngoscopy was 10293.5 being only slightly below baseline readings.
Table 3: Comparison of Rate pressure product (RPP) at different Time Interval with its Baseline in Fentanyl and Esmolol groups (inter group comparison).

<table>
<thead>
<tr>
<th>Events</th>
<th>Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Esmolol</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>Baseline</td>
<td>9999.0±1342.1</td>
<td>11185.3±2140.2</td>
</tr>
<tr>
<td>Study drug(0 minute)</td>
<td>9222.7±1330.4</td>
<td>10282.6±2193.4</td>
</tr>
<tr>
<td>Induction(1 minute)</td>
<td>7962.6±1230.4</td>
<td>8956.6±2208.8</td>
</tr>
<tr>
<td>Scoline(2 minute)</td>
<td>9613.7±1395.3</td>
<td>12192.6±4163.4</td>
</tr>
<tr>
<td>Laryngoscopy intubation(3 minute)</td>
<td>10392.3±1399.1</td>
<td>14555.1±3771.0</td>
</tr>
<tr>
<td>1 minute of intubation</td>
<td>10827.8±1450.0</td>
<td>12156.6±3290.8</td>
</tr>
<tr>
<td>3 minute of intubation</td>
<td>10295.9±1383.7</td>
<td>10371.9±2547.7</td>
</tr>
<tr>
<td>5 minute of intubation</td>
<td>9401.6±1287.6</td>
<td>10390.5±2455.0</td>
</tr>
<tr>
<td>10 minute of intubation</td>
<td>8983.0±1342.8</td>
<td>10293.5±2175.4</td>
</tr>
</tbody>
</table>

*indicates p<0.05,**indicates p<0.01,*# indicates p<0.001

DISCUSSION

Laryngoscopy and tracheal intubation are usually accompanied by increase in arterial blood pressure and heart rate. This transient response can be easily tolerated by a young and normotensive ASA I patient but it can be hazardous in the patient of chronic hypertension, ischemic heart disease, and cerebrovascular disease. The essence of this study lies in knowing the efficacy of drugs such as Fentanyl and Esmolol in attenuating this response and thereby preventing catastrophies in known high risk patients.

Significance of attenuating this response: This can be only understood when one knows the effects produced by an exaggerated response to laryngoscopy and intubation. In hypertensive patients especially the long standing hypertensives or uncontrolled hypertensive’s, an exaggerated response to laryngoscopy can cause intracerebral haemorrhage, ventricular tachycardia, fibrillation or myocardial infarction\[2-5]\.

In patients with ischemic heart disease an increased rate pressure product can lead to increased myocardial oxygen demand and infarction followed by cardiac failure.\[^3,4^\] In patients of Pregnancy induced hypertension the exaggerated response can precipitate convulsions, intracerebral bleed or pulmonary oedema. In neurosurgical patients with raised intracranial pressure or aneurysm, an excessive raise in SBP causes it to reach above levels of normal auto regulation leading to further rise in intracranial pressures and midline shift or tonsillar herniation or brain stem hemorrhages leading to adverse neurological outcomes. Rupture of aneurysm can lead to sudden catastrophes. In patients with raised intraocular pressure such
glaucoma can experience sudden loss of eyesight due to retinal hemorrhages, retinal detachments, vitreous hemorrhages. Hence, it is of utmost important to attenuate this presser response to laryngoscopy and intubation by feasible means to avoid such adverse outcomes in critically ill patients and high risk patients.

In both group following readings were obtained at baseline, after study drug was given, prior to laryngoscopy (after Scoline), at laryngoscopy and intubation, 1 minute, 3 minutes, 5 minutes, 10 minutes after laryngoscopy. The readings were compared within the group as well as in between the two groups. Both groups were comparable as regards to age, sex, weight. The hemodynamic variables assessed throughout the study were: baseline heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and rate pressure product. Similar, parameters were recorded after study drug was given, prior to laryngoscopy (after Scoline), at laryngoscopy and intubation, 1 minute, 3 minutes, 5 minutes, 10 minutes after laryngoscopy.

Heart rate comparison shows that heart rate remains suppressed for a longer time after inj. Esmolol than inj. Fentanyl. These findings are comparable with study of Hussain AM, Sultan ST et al. They studied efficacy of Fentanyl and Esmolol in prevention of haemodynamic response to laryngoscopy and endotracheal intubation in elective cases. Esmolol2 mg/kg provided consistent and reliable protection against the increase of heart rate.

Suppression of systolic blood pressure with Esmolol group is maximum prior to laryngoscopy and it remains suppressed till 5 minutes after laryngoscopy. The percentage fall in systolic blood pressure in Esmolol group prior to laryngoscopy was 2.3% as compared to percentage fall in Fentanyl group being 0.5% and this is comparable in study by K Sam Chung, Raymond et al, who compared Fentanyl and Esmolol for attenuation of haemodynamic response Esmolol was found more effective in dose of 2 mg/kg. The baseline diastolic blood pressure in the two groups were comparable. The difference not being significant from statistical point of view.

Esmolol maintains the rate pressure product values as near to the baseline values as far a possible not allowing it to rise above 12000 which was well below the angina threshold. The result obtained with this study was comparable with the study conducted by M Saif Ghaus et al demonstrated that the use of Esmolol infusion controls rise in rate pressure product by blunting cardiovascular stress response associated with laryngoscopy and intubation.
our study, 2 patients out of 60 patients showed an exaggerated response to laryngoscopy and intubation which was treated promptly.

In Esmolol group, 9 patients out of 30 patients had systolic blood pressure below 90 mmHg during induction which was treated by rapid i.v. fluids. 3 out of 30 patients in the Esmolol group developed Bradycardia heart rate less than 50 beats per minutes during induction. None of the patients developed muscle rigidity, thus advantages of Esmolol compared to Fentanyl was –

1. Esmolol can be used with patients with ischemic heart disease it reduces the heart rate by negative chronotrophic effect so reduces the work load on the heart and myocardial oxygen consumption.

2. Esmolol can be used in hypertensive patients and tachyarrhythmic patients.

3. Esmolol is short acting drug for around 10 minutes.

**CONCLUSION**

Esmolol 2 mg/kg intravenous and Fentanyl 2 µg/kg intravenous both produces attenuation of hemodynamic response to laryngoscopy and intubation when given 3 minutes prior to laryngoscopy and it is safe and effective method for attenuating presser response to laryngoscopy and intubation and it was found to be more effective than intravenous Fentanyl in attenuating presser response to laryngoscopy and intubation.

**REFERENCES**


