

# A Comparison of Fentanyl, Esmolol and their Combination for Attenuation of Hemodynamic Response to Laryngoscopy and Tracheal Intubation

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**Abstract- Background:** Laryngoscopy and endotracheal intubation has become an integral part of anesthetic management and critical care of the patient. It has been practiced since its description by **Rowbotham and Magill** in 1921. Direct laryngoscopy and endotracheal intubation is invariably associated with hemodynamic changes, due to reflex sympathetic discharge caused by epipharyngeal and laryngopharyngeal stimulation.<sup>41</sup> This increase in the sympatho adrenal activity results in hypertension, tachycardia and arrhythmias. Intravenous fentanyl and intravenous esmolol have emerged to be very popular agents used to obtund the hemodynamic stress response to laryngoscopy and endotracheal intubation. The potential benefit and safety of combination therapy of low dose fentanyl and esmolol have been suggested by previous investigations. By modulating both nociceptive input and blunting peripheral adrenergic effects, a combination of intravenous fentanyl and esmolol may prove to be more efficacious than either agent alone

**Methods:** Hundred adults (18–65 yrs), ASA risk I and II, of either sex undergoing elective surgical procedures under general anesthesia were included in this prospective, randomized study. Subjects were divided into four groups of 25 each to receive Normal saline, Fentanyl 4 minutes before induction, Esmolol 2 minutes before induction or Fentanyl and Inj. Esmolol. Pulse rate, Systolic and Diastolic blood pressures were recorded at following stages: Baseline values before premedication, Before induction, On laryngoscopy and intubation, 1 min after intubation, 2 min after intubation, 3 min after intubation, 4 min after intubation, 5 min after intubation. Data analysis was carried out using Statistical Package for Social Science (SPSS, VI 0.5) package. Results were analysed by Anova test.

**Results:** Combination of intravenous fentanyl 2mcg/kg and intravenous esmolol 2 mg/kg is more effective in the attenuation of hemodynamic responses to laryngoscopy and endotracheal intubation than intravenous fentanyl 2mcg/kg or intravenous esmolol 2mg/kg alone.

**Index Terms-** Laryngoscopy, Endotracheal intubation, Esmolol, Fentanyl

## I. INTRODUCTION

Laryngoscopy and endotracheal intubation has become an integral part of anesthetic management and critical care of the patient. Direct laryngoscopy and endotracheal intubation is

invariably associated with hemodynamic changes, due to reflex sympathetic discharge caused by epipharyngeal and laryngopharyngeal stimulation. This increase in the sympatho adrenal activity results in hypertension, tachycardia and arrhythmias.

The rise in the pulse rate and blood pressure is usually transient, variable and unpredictable. Usually, these changes are well tolerated by healthy individuals. However, these transitory changes may be hazardous in patients with hypertension, myocardial insufficiency and cerebrovascular diseases. Left ventricular failure, pulmonary edema, myocardial ischemia, cerebrovascular accidents may occur in such patients.

Various methods have been used in order to blunt this pressor response. Such as - Deepening the plane of anesthesia, Curtailing the duration of laryngoscopy to less than 15 seconds, Lidocaine sprays or gargles prior to intubation, Use of intravenous lidocaine, Use of ACE inhibitors e.g. captopril, enalapril prior to intubation, Vasodilators e.g. hydralazine, nitroglycerine, Calcium channel blockers like nifedipine, Beta blockers like labetalol, esmolol, Opioids like fentanyl, sufentanyl, alfentanyl, Alpha -2 agonists like clonidine, dexmedetomidine, Use of gabapentin and magnesium sulphate. None of the methods have gained universal acceptance.

**ESMOLOL** is an ultra short acting, beta -1 selective adrenergic blocker. It has a rapid onset and short duration of action.

**FENTANYL** is a synthetic opioid agonist ( $\mu$ , receptor), popularly used as an IV analgesic and a component of balanced anesthesia. It is a phenyl piperidine derivative of the 4-aminopiperidine series. It is about one hundred times more potent than morphine as an analgesic.

Intravenous fentanyl and intravenous esmolol have emerged to be very popular agents used to obtund the hemodynamic stress response to laryngoscopy and endotracheal intubation. The potential benefit and safety of combination therapy of low dose fentanyl and esmolol have been suggested by previous investigations.

By modulating both nociceptive input and blunting peripheral adrenergic effects, a combination of intravenous fentanyl and esmolol may prove to be more efficacious than either agent alone.

## II. METHODS

This prospective, randomized and placebo controlled clinical study was designed to include 100 adult patients (18–65 yr) of either sex, ASA risk I and II, undergoing elective surgical procedures under general anesthesia were included in this prospective, randomized study. The patients with baseline heart rate < 60 bpm, history of asthma/ reactive airway disease, history of cardiac disease and hypertension, on treatment with adrenergic augmenting or depleting drugs, PR interval > 0.24 seconds on ECG, 2<sup>nd</sup> and/or 3<sup>rd</sup> degree heart block, history of drug addiction/chronic narcotic use, anticipated difficult airway, requiring more than one attempt at intubation were excluded from the study.

Subjects were divided into four groups of 25 each to receive Normal saline, Fentanyl 4 minutes before induction, Esmolol 2 minutes before induction or Fentanyl and Inj. Esmolol. Pulse rate, Systolic and Diastolic blood pressures were recorded at following stages: Baseline values before premedication, Before induction, On laryngoscopy and intubation, 1 min after intubation, 2 min after intubation, 3 min after intubation, 4 min after intubation, 5 min after intubation.

The study protocol was approved from the institutional ethical committee and written informed consent was obtained from all the patients. All the medications were provided by hospital pharmacy, were identical.

Patients were randomly allocated into 4 groups -

**Group C:** received Inj. Normal saline 10ml IV 4 minutes before induction

**Group F:** received Inj. Fentanyl 2mcg/kg IV 4 minutes before induction.

**Group E:** received Inj. Esmolol 2mg/kg IV 2 minutes before induction.

**Group FE:** received Inj. Fentanyl 2mcg/kg IV 4 minutes and Inj. Esmolol 2mg/kg IV 2 minutes before induction.

All patients were pre oxygenated with 100% oxygen for three minutes, The respective study drug was injected. Patients were then induced with Inj. Sodium Thiopental 5mg - 7mg/kg IV and Inj. Suxamethonium 2mg/kg IV to facilitate laryngoscopy and intubation. Patient was intubated with appropriate size endotracheal tube, one minute after induction and connected to anesthesia machine.

Variables to be monitored were heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure.

Patient characteristic data were analysed with one-way anova for continuous variables Data analysis was carried out using Statistical Package for Social Science (SPSS, VI 0.5) package. Results were analysed by Anova test.  $P < 0.05$  was considered significant.

## III. RESULTS

### (1) PATIENT DEMOGRAPHICS:

**Table 1: Demographic data**

GROUPS	AGE (in years)	GENDER		WEIGHT(in kgs)
		MALE	FEMALE	
GROUP C	31.92 ± 8.87	12	13	60.12 ± 6.41
GROUP F	31.56 ± 7.71	13	12	59.24 ± 8.10
GROUP E	34.16 ± 11.16	12	13	58.16 ± 6.94
GROUP FE	33.08 ± 9.52	13	12	58.68 ± 6.61

There was no statistically significant difference between four groups ( $P = 0.786$ )

### (2) HEART RATE :

The heart rate was measured at baseline, before induction, during laryngoscopy and endotracheal intubation and 1, 2, 3, 4 and 5 minutes after intubation (Table 2)

**Table 2: Changes in Heart Rate**

HEART RATE (bpm)		Baseline Value	Before Induction	On laryngo-scopy and ETI	1 min after ETI	2 min after ETI	3 min after ETI	4 min after ETI	5 min after ETI
GROUP C	MEAN	82.08	92.92	103.08	112.92	110.32	104.28	99.60	92.92
	±SD	10.33	8.34	10.40	11.17	11.33	8.45	7.03	8.18
GROUP F	MEAN	81.44	87.08	95.64	105.24	101.08	96.08	91.88	88.56
	±SD	8.93	8.80	10.06	11.61	11.60	10.39	8.93	8.81
GROUP E	MEAN	83.44	75.40	90.64	102.20	99.64	96.80	96.24	93.04
	±SD	8.99	9.24	10.09	11.06	10.43	9.03	8.53	8.44
GROUP FE	MEAN	83.48	68.92	76.60	85.12	82.68	80.84	78.48	77.52
	±SD	7.63	6.28	6.23	7.66	7.50	7.67	7.14	7.21
P Value		0.813	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Base line Heart Rate of all the groups are comparable to each other and there is no statistical difference between them (p value > 0.05). P value <0.001 (using ANOVA) - highly significant.

**(3) SYSTOLIC BLOOD PRESSURE :**

The systolic blood pressure was measured at baseline, before induction, during laryngoscopy and endotracheal intubation and 1, 2, 3, 4 and 5 minutes after intubation. (Table 3)

**Table 3: Changes in Systolic Blood Pressure**

Systolic blood pressure(mm of Hg)		Baseline Value	Before Induction	On laryngo-scopy and ETI	1 min after ETI	2 min after ETI	3 min after ETI	4 min after ETI	5 min after ETI
GROUP	MEAN	122.92	125.56	143.72	157.84	153.00	141.28	136.08	132.68

C	±SD	8.46	7.01	8.31	7.74	7.85	8.20	7.65	6.93	I
GROUP F	MEAN	125.08	120.08	138.00	147.76	141.44	132.56	123.52	113.28	
	±SD	10.13	10.87	9.00	7.68	7.08	8.26	8.40	7.39	
GROUP E	MEAN	124.24	119.80	137.68	152.00	143.04	136.52	130.20	121.88	
	±SD	4.81	6.38	5.87	5.12	5.37	6.16	5.63	7.04	
GROUP FE	MEAN	127.68	115.92	125.88	136.96	130.28	124.80	118.60	111.08	
	±SD	8.07	7.16	7.66	8.96	8.75	8.06	7.75	7.17	
P Value		0.210	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	

Base line Systolic Blood Pressure of all the groups are comparable to each other and there is no statistical difference between them (p value > 0.05). P value <0.001 (using ANOVA) - highly significant.

**4.) DIASTOLIC BLOOD PRESSURE:**

The diastolic blood pressure was measured at baseline, before induction, during laryngoscopy and endotracheal intubation and 1, 2, 3, 4 and 5 minutes after intubation. (Table 4).

**Table 4: Changes in Diastolic Blood Pressure**

Diastolic blood pressure (mm of Hg)		Baseline Value	Before Induction	On laryngoscopy and ETI	1 min after ETI	2 min after ETI	3 min after ETI	4 min after ETI	5 min after ETI
GROUP C	MEAN	79.36	32.95	91.24	101.20	96.80	92.72	89.60	87.23
	±SD	4.50	4.89	3.61	4.07	4.61	4.35	4.43	4.40
GROUP F	MEAN	75.40	73.36	81.16	88.20	82.36	79.16	74.44	70.44
	±SD	5.87	6.55	5.60	4.67	4.20	4.05	4.46	5.41
GROUP E	MEAN	76.64	82.04	86.16	97.40	90.76	87.00	84.16	79.88
	±SD	4.74	5.23	3.93	3.67	4.42	3.33	3.60	5.03
GROUP FE	MEAN	78.40	69.28	79.16	86.40	81.12	73.52	68.56	64.48
	±SD	6.48	5.96	7.06	6.99	6.53	6.69	5.41	5.16

P Value	0.054	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
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Base line Diastolic Blood Pressure of all the groups are comparable to each other and there is no statistical difference between them (p value > 0.05). P value <0.001 (using ANOVA) - highly significant.

#### IV. DISCUSSION

A hemodynamic response of increased heart rate and blood pressure to laryngoscopy and intubation has been well recognized for over 60 years now. Stimulation of mechanoreceptors in the pharyngeal wall, epiglottis, and vocal cords is thought to be the cause for this hemodynamic response. Various narcotic drugs like morphine, fentanyl, alfentanil, sufentanil and remifentanil have been used. However, **FENTANYL** has been found to be more effective than the other narcotics in preventing the stress response and also seemed to provide a more stable hemodynamic profile prior to laryngoscopy and tracheal intubation. Fentanyl has been used in various doses varying from 2 to 15 meg/kg for blunting the stress response and doses greater than or equal to 5 meg/kg has been reported to be most effective. However, such doses of fentanyl may cause excessive sedation, apnea and chest wall rigidity pre operatively, and nausea, vomiting and prolonged respiratory depression post operatively especially in surgeries with a duration of less than two hours.

**ESMOLOL HYDROCHLORIDE**, an ultra short-acting, cardio selective beta blocker, avoids the above complications, but is found to have variable effectiveness in the recommended doses. In majority of previous studies, esmolol was administered by infusion prior to induction and was found to protect patients from hypertension and tachycardia. But in emergency cases, the preparation and administration of an infusion is time consuming and cumbersome. In such cases, it would be very helpful if esmolol could be administered as a single bolus rather than an infusion prior to intubation.

In various studies conducted before, a bolus dose of 2mg/kg IV Esmolol injected prior to induction has been found to be effective in attenuating cardiovascular response to laryngoscopy and intubation and the optimal time of administration was suggested to be three minutes before laryngoscopy and intubation. Some of the investigators suggested that a modulation of the nociceptive input by fentanyl and blockade of adrenergic receptors by esmolol would enable their combination to provide effective blunting of the response to intubation while minimizing the undesirable effects of larger doses of either agent alone. So, the present study was conducted to compare the efficacy of intravenous fentanyl, intravenous esmolol and their combination in the attenuation of hemodynamic stress responses to laryngoscopy and endotracheal intubation.

A significant attenuation of the heart rate, systolic blood pressure, diastolic blood pressure were observed in groups F, E and FE when compared to the control group C. Group FE however showed the maximum attenuation of heart rate, systolic blood pressure, diastolic blood pressure as compared to the other groups (p<0.001).

The following observations were made:

1. There was a significant increase in the heart rate during laryngoscopy and post endotracheal intubation in all the groups. The increase was highly significant in group C when compared to the other groups. The heart rate returned to pre induction values only in group FE. The combination of fentanyl and esmolol significantly attenuated the rise in heart rate compared to fentanyl and esmolol alone.

2. There was a significant increase in systolic blood pressure during laryngoscopy and post endotracheal intubation in all the groups. The increase was highly significant in group C when compared to the other groups. The systolic blood pressure returned pre induction values within 5 minutes post intubation in groups F, E and FE. The combination of fentanyl and esmolol produced a more significant attenuation of rise in systolic blood pressure compared to fentanyl and esmolol alone.

3. A significant increase in diastolic blood pressure was observed on laryngoscopy and post endotracheal intubation in all the groups. The increase was highly significant in group C when compared to the other groups. The diastolic blood pressure returned to pre induction values within 5 minutes post intubation in groups F and FE. The combination of fentanyl and esmolol produced a more significant attenuation of rise in diastolic blood pressure compared to fentanyl and esmolol alone.

4. A significant increase in the mean arterial blood pressure was observed on laryngoscopy and post endotracheal intubation in all the groups, with mean arterial blood pressure returning to pre induction values within 5 minutes post intubation in groups F and FE. The combination of fentanyl and esmolol significantly attenuated the rise in mean arterial blood pressure compared to fentanyl and esmolol alone.

Therefore, from the present study it is concluded that **the combination of intravenous fentanyl 2mcg/kg and intravenous esmolol 2 mg/kg is more effective in the attenuation of hemodynamic responses to laryngoscopy and endotracheal intubation than intravenous fentanyl 2mcg/kg or intravenous esmolol 2mg/kg alone.**

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