# Attenuation of Cadiovascular Responses to Laryngoscopy and intubation: A Comparative Study between IV Esmolol Hydrochloride and Fentanyl Citrate

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Abstract: <u>Objectives</u>: To study the effects of Esmolol (2mg/kg IV) bolus and Fentanyl(2mcg/kg IV) bolus given 3 minute before laryngoscopy and intubation in attenuating the sympathetic stress response. <u>Study design</u>: Hundred adults (18–60 yrs), ASA grade I and II, of either sex undergoing elective surgical procedures under general anesthesia were included in this comparative study. Subjects were divided into two groups of 50 each. Group 'E' receive Esmolol 2mg/kg IV bolus and Group 'F' receive Fentanyl 2mcg/kg IV bolus 3 minute prior to laryngoscopy and intubation. Pulse rate, Systolic and Diastolic blood pressures, mean arterial pressure were recorded at following stages: Baseline values 3 minute prior to laryngoscopy and intubation, 3min after intubation, 4min after intubation, 5min after intubation and finally at 10minute after intubation. <u>Results</u>: Pulse rate, Systolic BP, Rate pressure product was significantly attenuated by esmolol. Esmolol has very liitel effect on mean arterial pressure and has no effect on diastolic pressure. <u>Conclusion</u>: Intravenous esmolol 2 mg/kg is more effective in the attenuation of hemodynamic responses to laryngoscopy and endotracheal intubation than intravenous fentanyl 2mcg/kg.

Keywords: Attenuation, Esmolol, Fentanyl, Hemodynamic response, Intubation, Laryngoscopy

# 1. Introduction

Laryngoscopy and Endotracheal intubation are gold standard for securing the airway and giving positive pressure ventilation. Intubation has become necessary for most patients undergoing operation under general anesthesia. Direct laryngoscopy has been used since many years as a conventional and routine to facilitate this procedure. Various types of laryngoscope with different sizes and shape have been invented so far, aiming to overcome difficulties with visualization and facilitate uneventful endotracheal intubation. Drugs like esmolol hydrochloride1,2,3,4 used frequently to attenuate pressor response to laryngoscopy and intubation, which are associated with transient but marked cardiovascular changes because sensory afferents from epipharynx and laryngopharynx are mainly carried by glossopharyngeal nerve to vasomotor center, which are responsible for both rise in PR and BP causing tachycardia, hypertension and dysrhythmias. Drugs like Fentanyl citrate<sup>5,6</sup> is also effective and frequently used for attenuation of hemodynamic stress responses upon laryngoscopy and intubation like hypertension, tachycardia, myocardial ischemia and increased circulating catecholamine . In higher doses fentanyl may cause respiratory depression.

Many strategies have been applied to attenuate

hemodynamic stress responses and objected at different levels of the reflex arc. e.g.:

- Blocking of the peripheral sensory receptors and afferent input by topical application and infiltration of superior laryngeal nerve.
- Blocking of the central mechanisms of integration of sensory input by drugs like Fentanyl,<sup>7</sup> Morphine, Droperidol, etc.
- Blocking of the efferent pathway and effector sites by drugs like Intravenous lignocaine<sup>7,8</sup>, Beta-Blockers, Calcium Channel Blockers, Hydralazine, nitroglycerine<sup>8</sup>etc.

Increase in arterial pressure begins after about 15 seconds and peaks within 30-45 seconds after laryngoscopy. It is associated with significant rise in heart rate as well. However, it returns to baseline within 5 to 10 minutes after intubation. Although rise in heart rate and blood pressure and disturbances in the cardiac rhythm are short lived, they may have detrimental effects in patients with cardiovascular diseases, increased intracranial pressure or anomalies of cerebral vessels. During and immediately following intubation, there is a reduction in the left ventricular ejection fraction due to reduced ventricular filling because of tachycardia and increased peripheral vascular resistance. This is particularly seen in patients with coronary artery disease and may predispose to myocardial ischemia<sup>9</sup>. This pressor response can be well tolerated in healthy adults but the same response can lead to significant morbidity in compromised patient such as those with underlying cardiovascular disease.

Single drug or technique is not satisfactory. Different methods of attenuation of response to laryngoscopy and intubation are still to be studied with new drugs tried every once a while.

the recommended procedures Intravenous Among Lignocaine, Fentanyl and Esmolol<sup>10</sup> are commonly used drugs. Out of these Esmolol<sup>11</sup> is an attractive option because of its Beta 1 cardio selectivity and ultra short duration of action (9 to10 minutes). Fentanyl<sup>11</sup> causes relaxation of pharyngeal, laryngeal and jaw musculature, suppresses cough reflex and provides sedation and analgesia but has associated respiratory depression at higher doses. King BD and Harris L.C. et al in 1951<sup>12</sup> described the circulatory response to laryngeal and tracheal stimulation following and tracheal laryngoscopy intubation as reflex sympathoadrenal stimulation. Sympathetic reflex is provoked by the stimulation of epipharynx and larynx.

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Research Question:- What is the effect of Esmolol(2mg/kg) IV bolus V/S Fentanyl(2mcg/kg) IV bolus on attenuation of sympathetic cardiovascular stress responses to laryngoscopy and intubation?

The present study is being done to determine the efficacy of intravenous bolus doses of Esmolol 2mg/kg and injection Fentanyl citrate 2  $\mu$ g/kg in attenuating the sympathetic stress response to laryngoscopy and tracheal intubation

#### 1.1 Aim and Objectives of Study

This comparative study of Esmlol Hydrochloride and Fentanyl citrate aims for attenuation of hemodynamic responses to laryngoscopy and intubation with respect to:-

- To study the effects of Esmolol (2mg/kg IV) bolus and Fentanyl(2mcg/kg IV) bolus given 3 minute before laryngoscopy and intubation in attenuating the sympathetic stress response.
- To compare and ascertain the efficacy of these two drugs in attenuating the stress response in terms of changes in Pulse rate, Systolic blood pressure, Diastolic blood pressure and Mean arterial blood pressure.
- To predict the cardio-protection given by these drugs against the stress response in the form of changes in rate pressure product.
- To study the adverse effects if any, of IV Esmolol (2mg/kg) and IV Fentanyl(2mcg/kg).

#### 1.2 Anatomy



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# 1.3 Anatomy of Larynx

Larynx is an organ of phonation.

# Situation

Larynx lies opposite  $4^{th}$ ,  $5^{th}$ ,  $6^{th}$  cervical vertebrae in adults and in children it may be higher.

# **Constituents of Larynx**

- a) Laryngeal cartilages
- b) Laryngeal ligaments
- c) Cavity of larynx
- d) Laryngeal muscle

# Laryngeal Cartilages

It consist of two sets of 3 paired and 3 unpaired cartilages. Paired cartilages:- Arytenoid, corniculate, cuneiform. Unpaired cartilages: Thyroid, Cricoid, Epiglottis.

- a) Thyroid cartilage: It is a shield like structure and consist of two laminae which meet in the midline
- b) Cricoid cartilage: It is in the shape of a signet ring, the signet lies posteriorly as a quadrilateral laminae joined in front by a thin arch. The laminae bears two articular facets, one for the inferior horn of the thyroid cartilage and other near its upper extremity for arytenoid cartilage.
- c) Epiglottic cartilage: It is attached at its lower tapering end to the back of the thyroid cartilage by means of the thyro-epiglottic ligament. Its superior extremity projects upward and backward behind the hyoid and base of tongue and over hangs the inlet of the larynx.
- d) Arytenoid Cartilages: The arytenoid cartilages are the three sided pyramids and sits one on either side of the supero-lateral aspect of the laminae of the cricoid.
- e) Corniculate Cartilage: The Corniculate cartilage is a small nodule lying at the apex of the aryepiglottic fold.

# Laryngeal Ligaments

# **Extrinsic Ligaments**

- a) **Thyrohyoid membrane:** Stretches between the upper border of the thyroid cartilage and the hyoid .
- b) **Cricothyroid membrane:** Lies between the thyroid cartilage and the cricoid .
- c) **Hyoepiglottic Ligament:** Connects the epiglottis to the back of the body of the hyoid

# **Intrinsic Ligaments:**

These are formed by a submucous broad sheet of fibroelastic tissue known as fibroelastic membrane of larynx. The intrinsic ligaments comprise of the capsule of the tiny synovial joints between the arytenoids and cricoid and between thyroid and cricoid cartilages.

# **Cavity of Larynx**

It is comprised of the two folds, the upper vestibular and the lower vocal folds (the false and true vocal cords), between which is a slit like recess termed the sinus of the larynx.

# Muscles of the Larynx

Muscles of the larynx can be divided into extrinsic group, which attaches the larynx to its neighboringstructure and intrinsic group which are responsible for movement of the cartilages of the larynx one against the other.

#### **Extrinsic Muscles**

- a) Sternohyoid depress larynx
- b) Inferior constrictor of the pharynx constrict pharynx
- c) Few fibers of stylopharyngeus
- d) Few fibers of palatopharyngeus

Other muscle which help to elevate and depress the larynx.

#### The indirect elevator

- Mylohyoid
- Stylohyoid
- Geniohyoid

# The Indirect depressors

- Sternohyoid
- Omohyoid

#### Intrinsic muscles

- a) Posterior cricoarytenoid muscle it abducts the cord by external rotation of the arytenoids and thus opens the glottis.
- b) Laryngeal cricoarytenoid muscle It adducts the cord by internal rotation of arytenoid cartilages and hence closes the glottis.
- c) Interarytenoids muscle It helps to close glottis , particularly the posterior part of its orifice. It acts as feeble sphincter at the inlet of the larynx.
- d) Thyroarytenoids muscle it causes relaxation of the cords, also assist in the sphincter mechanism of laryngeal inlet.
- e) Cricothyroid The contraction of this muscle puts the vocal cords on stretch. This muscle is the only tensor of the cords.

# Intrisic Muscles has three functions:-

- To open the cords during inspiration .
- To close the cords and laryngeal inlet during deglutition.
- To alter the tension of the cords during speech.

# **Constituents of Larynx**

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Figure 1: Anatomy of larynx (anterior view)



Figure 2: Anatomy of larynx (posterior view)

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#### Arterial Supply and Venous Drainage of Larynx

#### A) Above the vocal cords:

Arterial: Superior laryngeal artery, a branch of superior thyroid artery.

**Venous:** Superior laryngeal vein drains in superior thyroid vein.

#### B) Below the vocal cords:

Arterial: Inferior laryngeal artery, a branch of inferior thyroid artery.

**Venous:** Inferior laryngeal vein drains into inferior thyroid vein.

#### Lympahtic Drainage

- A) **Above the vocal cords:** Lymphatics drain along the superior thyroid vessels to the anteroposterior group of deep cervical nodes.
- B) **Below the vocal cords:** Lymphatics drain into the posteroinferior group of deep cervical nodes. Few drain through prelaryngeal nodes.

#### Nerve Supply<sup>13</sup>

Larynx receive nerve supply from the vagus nerve, through its superior and recurrent laryngeal branches .

a) Superior laryngeal nerve arises from the inferior

ganglion of vagus but receive a small branch from the cervical sympathetic ganglion. It passes deep to both internal and external carotid arteries and divides into :

External branch - supplies the cricothyroid muscle .

**Internal branch** – gives sensory supply apart from few motor fibers to the interarytenoid muscle. It pierce the thyrohyoid membrane and divides into upper and lower branch. Upper branch supplies the mucous membrane of lower part of the pharynx, epiglottis, vallecula and vestibule of larynx. Lower branch passes medial to the pyriform fossa beneath the mucous membrane and supplies aryepiglottic fold and posterior part of rima glottidis.

- **b)** The recurrent laryngeal nerve accompanies laryngeal branches of inferior thyroid artery and travels upward, deep to lower border of inferior constrictor of the pharynx. Its sensory fibers supply the mucous membrane of the larynx below the level of the vocal cords. It innervates all the muscle of the larynx except the cricothyroid.
- c) The glossopharyngeal nervesupplies superior aspect of epiglottis, posterior one third of the tongue and lower pharynx. The sensory impulse from the larynx ascend via internal and recurrent laryngeal nerve to the nucleus of the tractus solitaries in the medulla.



Nerve supply of the Larynx

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Nerve Supply of Airwa

# 2. Physiology of Pressure Response During Laryngoscopy Andtracheal Intubation

The occurrence of pressure response to tracheal intubation is caused by following :

- (1) Reflex sympathoadrenal stimulation. There is consistent increase in norepinephrine.
- (2) Stimulation of cardio accelerator nerves increases heart rate.
- (3) The sensory afferents from epipharynx and laryngopharynx are mainly carried by glossopharyngeal nerve to vasomotor center, which are responsible for both rise in Pulse rate and Blood Pressure. The sensory afferent from tracheobronchial tree are carried by vagus nerve which is responsible for bradycardia.
- (4) Contributory pathways: Anxiety, atropine premedication, reflex baroreceptor effect following fall of BP after the induction of anesthesia with Propofol, vagolytic action of certain muscle relaxants.

The laryngoscope blade pressing on base of tongue initiates the pressure response during and following laryngoscopy. The pressure response is most pronounced during stimulation of epipharynx and tracheobronchial tree. Subsequent to the insertion of the endotracheal tube and withdrawal of the laryngoscope, there is gradual subsidence in the tachycardia and hypertension, usually peak increase is observed for approximately 1-2 minutes and it gradually returns to baseline within next 5-10 minutes. Many investigators have demonstrated that tracheal intubation causes tachycardia, hypertension,arrhythmias, myocardial ischemia<sup>9</sup> and myocardial infarction.

Reid L.C and Brace<sup>14</sup>described the hemodynamic response to laryngoscopy and intubation, probably due to intense sympathetic discharge caused by stimulation of epipharynx and laryngopharynx. Hassan et al<sup>15</sup> reported high incidence of increase in heart rate, increase in systolic blood pressure and plasma catecholamine after laryngoscopy and intubation. These lead to cardiac arrhythmias, myocardial ischemia, acute left ventricular failure and cerebrovascular accident following intubation in hypertensive patients.

Afferent stimuli trigger cardiac, airways, cerebral, adrenal responses. neuromuscular and Although bradycardia can develop in up to 10% of patients undergoing endotracheal intubation, the typical result, even under general anesthesia, hypertension and tachycardia causes increase in myocardial oxygen consumption. Furthermore many of the medications used for endotracheal intubation had direct and indirect cardiovascular effects. It has been shown that up to 15% of patients undergoing endotracheal intubation under general anesthesia will have ventricular arrhythmias, with majority of events occurring at time of tube insertion, as opposed to the time of  $laryngoscopy^{12}$ .

In addition the pressor response is harmful to patients with decreased intracranial compliance, cerebral and aortic aneurysms and to those undergoing open eye surgeries. Hence, attenuation of the hemodynamic response to tracheal intubation will be helpful in achieving a favorable outcome of surgery in all groups of patients, especially in the above mentioned groups.

# **Rate Pressure Product**

Also known as Cardiovascular Product or Double Product it is used in cardiology and exercise physiology to determine the cardiovascular risk of subjects.

Rate Pressure Product (RPP) = Heart Rate (HR) x Systolic Blood Pressure (SBP)

Rate pressure product is a measure of the stress put on the cardiac muscle. It is a direct indication of the energy demand

of the heart and thus a good measure of the energy consumption of the heart. Increase in Rate pressure product increases risk of myocardial ischemia<sup>9</sup> leading to myocardial infarction, acute cardiac failure, pulmonary edema and arrhythmias. Therefore, perioperative measurement of rate pressure product is of vital importance.

Values higher than 20000 are associated with increased myocardial risk of ischemia. Range of rate pressure product are as follows:-Low : 10000 to 14999 Low intermediate: 15000 to 19999 Intermediate : 20000 to 24999 High intermediate : 25000 to 29999 High : more than 30000

Gobel FL et al <sup>9</sup>shows that pulse rate and Pulse rate multiplied by systolic blood pressure both easily measured hemodynamic variables, are good predictor of myocardial oxygen consumption (MVO<sub>2</sub>) during exercise in normotensive patients with ischemic heart disease.

#### Pharmacology

In our studyEsmolol hydrochloride<sup>16</sup> and Fentanyl citrate<sup>17</sup> is used for attenuation of hemodynamic stress response to Laryngoscopy and intubation .

#### Esmolol Hydrochloride:



#### • History

Esmolol is an ultra short  $\operatorname{acting}^{18} \beta 1$  cardioselective adrenergic receptor blocking agent which attenuates hemodynamic stress response to laryngoscopy and intubation. It was introduced in United States in 1987 by Erhardt. Esmolol also prevent neuroendocrine response to electroconvulsive therapy<sup>19</sup>.

#### • Chemical structure:



It is a phenoxypropanolamine derivative with an ester group at para position of its aromatic ring. Such para substitution confers cardioselectivity of Esmolol, with ester group accounting for high metabolic liability and therefore short duration of action.

• **Pharmacokinetics**<sup>20</sup>:

#### Absorption:

It is rapidly absorbed and steady state blood levels for dosage from 50-300 mg/kg/min are attained in 5 minutes. Steady state blood levels are maintained during infusion but decrease rapidly after termination of infusion.

#### Metabolism:

It is metabolized extensively by esterase present in the red blood cells.Metabolism is not influenced by renal or hepatic dysfunction. Acid metabolite of Esmolol is an extremely weak beta blocker. Less than 2% of the drug is excreted unchanged in urine.

#### **Distribution:**

The distribution half life is 1 to 2.03 min.Peak effect is achieved on heart rate within 1 min, on BP within 3 min and peak hemodynamic effect within 3-4 min.Onset of action to 90% of steady state blockage within 5 min.

#### **Elimination**:

Elimination half life is 9.19 minute.Partial recovery is within 2 min of completion of dose and complete recovery is within 18 min post infusion.

#### • Mechanism of action:

Esmolol blocks the agonistic effect of the sympathetic neurotransmitters by competing for receptor binding sites. It predominantly blocks the Beta receptors in cardiac tissuebut begins to block Beta2 receptors as the dose increases. Antiarrhythmic activity is due to blockage of adrenergic stimulation of cardiac pacemaker potentials.

# • Pharmacodynamics<sup>21</sup>:

#### Cardiovascular effects<sup>22</sup>:

It is a Beta-1-cardioselective antagonist. It has partial agonist activity and membrane stabilizing activity. It decreases resting heart rate (10%), systolic BP (6%), rate pressure product (20%), left and right ventricular ejection fraction (12-18%) and cardiac index (17%). It decreases AV nodal conduction. It significantly increases the sinus node

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recovery time, relative refractory period, functional recovery period and wenckebach cycle length.

#### Effects on respiratory system<sup>23</sup>:

It mildly increases specific airway resistance by increasing bronchomotor tone by acting on Beta2 receptors of smooth muscle in bronchi etc.

#### Effects during anesthesia and surgery<sup>24</sup>:

Esmolol helps in attenuating the adrenergic response that occurs during stressful perioperative stimuli.

#### Indications and usages:

- (1) Supraventricular tachycardia:For rapid control of ventricular rates in the patients with atrial fibrillation
- (2) Myocardial ischemia:Esmolol causes rapid and reversible reduction in heart rate, BP and improves indices of cardiovascular work load<sup>24</sup>.
- (3) Uses in anesthesia:
  - <u>Before anesthesia:</u> During laryngoscopy and endotracheal intubation reflex mediated increase in sympathetic activity can be attenuated by Esmolol<sup>25</sup>.
  - **During anesthesia**: Skin incision, cystoscopy, sternotomy and surgery on periosteum and/or skeletal joints cause sympathetic overactivity. So Esmolol can be used to attenuate all the responses.
  - <u>After anesthesia:</u> During emergence and extubation sympathetic blunting will prevent postoperative hypertension, bleeding, myocardial ischemia, infarction and cerebral hemorrhage.

(4) Other perioperative and intraoperative applications:

- In intraoperative catecholamine mediated spasm of infundibulum in pediatric patients.
- In hypertension after coronary artery bypass grafting.
- Preoperative to prepare the patients with acute thyrotoxic crisis for thyroid resection.
- To deliberately induce hypotension before resection of intracranial arteriovenous malformation.
- During resection of pheochromocytoma.
- (5) To minimize tachycardia and hypertension during electroconvulsive therapy19.

Contraindications:

- Sinus bradycardia
- Second and third degree heart block.
- Cardiogenic shock
- Congestive cardiac failure
- Hypotension
- Bronchial asthma.

# Adverse effects:

- <u>Cardiovascular system:</u>Hypotension, peripheral ischemia, bradycardia, pallor, flushing, chest pain, atrioventricular block, syncope.
- <u>Respiratory system</u>: Bronchospasm, dyspneoa.
- <u>Central nervous system</u>: Dizziness, somnolence, confusion, agitation, headache, fatigue, seizure.
- <u>Gastrointestinal system</u>: Nausea, vomiting, dyspepsia, constipation,
- <u>Skin</u>: thrombophlebitis.
- <u>Others</u>: Urinary retention, speech disorders, abnormal vision, rigors and fever.

Dosage and administration in various medical conditions:

- For heart rate and BP control during surgery: 80 mg bolus over 15-30 sec followed by 150-300 microgram/kg/min.
- For supraventricular tachycardia and acute myocardial ischemia: 500 microgram/kg/min bolus over 1 min followed by 50-300 microgram/kg/min.
- For laryngoscopy and intubation<sup>26</sup>:Dose ranges from 0.5 mg to 2 mg/kg as bolus and infusion.

#### Fentanyl Citrate



#### • History

Fentanyl is a synthetic opioid agonist with rapid onset and short duration of action. It was first synthesized in 1960 by Paul Jenssen and was introduced in anesthesia in 1970.

- Chemical Structure
- Fentanyl is N(1 PHENYLETHYL-4PIPERIDINE) propionilide derivative



# **MOLECULAR WEIGHT : 528-561**

#### **EMPERICAL FORMULA :** C<sub>22</sub>H<sub>28</sub>N<sub>2</sub>C<sub>6</sub>H<sub>8</sub>O<sub>2</sub> • Mechanism of Action<sup>27</sup>

Fentanyl citrate is a p - opiate receptor agonist. Analgesia is produced by action on supraspinal sites. It binds to a much lesser degree to the k - receptors, causing sedation and miosis. They act by increasing K+ conductance into cells & inhibit calcium channel, thus decreasing the neurotransmitter release.

# Pharmacokinetics<sup>28</sup>

<u>Absorption</u>:- A single intravenous dose has rapid onset of action within 1 to 2 min & peak effect at 5 min. As it is highly lipid soluble it rapidly crosses all the membranes and is distributed to other organs like muscles, fat, liver & brain.

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**Distribution:** Fentanyl citrate is highly lipid soluble. Initially it is distributed rapidly to highly vascular organs such as heart, brain & muscles (Rapid distribution  $T1/2\pi$  phase1.5 – 2.0 min.) and then slowly redistributed to fat (slow distribution phase Tl/2 $\alpha$ 5.2 - 19 min.). Plasma protein binding is 84%.

<u>Metabolism</u>: It is metabolized in liver by N-demethylation to nor-Fentanyl. All metabolites are pharmacologically inactive or minimally active.

**Elimination**: Fentanyl citrate is excreted mainly by kidney in urine as metabolites; only 8% unchanged drug is excreted. Terminal elimination half-life is 3.1 to 6.6 hrs due to large volume of distribution (3-6 Lit / kg).

# Pharmacodynamics<sup>29</sup>

#### **CNS Effects**

Fentanyl citrate inhibits release of neurotransmitter (acetylcholine, nor - adrenaline, dopamine & substance - p). It produces sedation & analgesia with lower dose and unconsciousness& anaesthesia with higher dose. With higher dose it also blunts neuroendocrine response to surgery. It decreases cerebral metabolic rate & blood flow.

#### **CVS Effects**

Fentanyl citrate decreases heart rate by vagomimetic action. Bradycardia is variable, but severe bradycardia is possible with high doses. It produces minor reduction in blood pressure, orthostatic hypotension, postural syncope and occasionally severe hypotension primarily due to reduction in systemic vascular resistance. Carotid sinus baroreceptor reflex is markedly reduced with Fentanyl citrate.

#### **Respiratory System Effects**

It leads to dose related depression of respiratory center in brainstem and decreases respiratory rate, tidal volume and minute ventilation. It blunts the ventilatory response to hypercapnia and hypoxia. It leads to irregular breathing or apneic spells with high plasma levels.

#### **GIT Effects**

It slows the gastric emptying by reducing peristalsis and produces biliary spasm due to contraction of sphincter of oddi. It leads to nausea and vomiting due to stimulation of chemoreceptor trigger zone.

#### **Skeletal Muscle Effects**

Rigidity of abdominal and thoracic muscles.

#### **Adverse Reactions**

- (1) Respiratory Depression -Occurs with high & repeated dose, in elderly, and with other CNS depressant drug.
- (2) Abdominal and thoracic muscle rigidity -May lead to decreased pulmonary compliance, laryngospasm and apnea. It may be difficult to ventilate the patient.It is treated with naloxone and muscle relaxants.
- (3) Bradycardia and Hypotension
- (4) Nausea and vomiting
- (5) Pruritus
- (6) Urinary Retention

#### Dosage

- (1) Premedication -1-3 mcg/kg 30 to 45 minute prior to induction intramuscularly.
- (2) Attenuation of laryngoscopy reflex<sup>30</sup> 1-3  $\mu$ g/kg IV, 3 min. before induction.
- (3) Adjuvant to general anaesthesia —>
  - a) Minor procedure 2 5  $\mu$ g / kg IV.
  - b) Major Procedure 2 20  $\mu$ g / kg IV.
- (4) Induction of Anesthesia 50-100  $\mu$ g / kg IV.
- (5) Post-op Analgesia 1-2  $\mu$ g / kg IV bolus and 0.5 -1.5  $\mu$ g/kg / hr IV infusion.
- (6) Intrathecal 25-50  $\mu$ g with local anaesthetic agents.
- (7) Epidural 50-75  $\mu$ g in 20 ml volume with 0.125-0.25% bupivacaine.
- (8) Patient Controlled Analgesia (PCA):-

It is used with both intravenous & epidural PCA., as background infusion of 20-50  $\mu$ g / hr plus bolus demand dose of 10 - 25  $\mu$ g, with lockout period of 5 minutes.

# 3. Review of Literature

Endotracheal intubation is the placement of a tube into the trachea to maintain a patent airway in those who are unconscious or unable to maintain their airway for other reason. Airway management is a fundamental aspect of the anesthetic practice and of emergency and critical care medicine. Endotracheal intubation following laryngoscopy is a rapid, simple, safe and non surgical technique that achieves all goals of airway management namely maintain airway patency, protect the lungs from aspiration and permits leak free ventilation during mechanical ventilation, and remains gold standard procedure for airway management. There have been continuous and extensive studies for cardiovascular responses to laryngoscopy and endotracheal intubation and various drug regimes for attenuating these responses. Reid L.C and Brace et al  $(1940)^{14}$  studied the reflex effect upon the heart during irritation of respiratory tract. Changes seen in cardiovascular system included sinus bradycardia, sinus tachycardia, atrial and ventricular extrasystoles, delayed conduction time and slowing of heart with escape beats. King B.D, Harris L.C., Greifenstein FE et al (1951)<sup>12</sup> postulated that deepening of anesthesia with potent inhalation agents attenuates reflex circulatory responses in normotensive but, in IHD and hypertensive patients this may cause myocardial depression. A.M. Forbes et al (1970)<sup>31</sup> reported that laryngoscopy and endotracheal intubation was immediately followed by an average increase in MAP of 25 mm of Hg. Dahlgren N et al (1981)<sup>5</sup> compared varying doses of Fentanyl and found that Fentanyl 5 mcg/kg given 3 minutes before intubation causes a significant reduction of the blood pressure and pulse rate response to laryngoscopy and intubation. Seong-HoonKo et al (198I)<sup>32</sup> had studied the dose of Fentanyl and the optimal time of injection to attenuate the circulatory response to laryngoscopy. They had used 2 mcg/kg of Fentanyl at 1,3,5& 10 min prior to intubation. They found that optimal time for injection is 3 min before intubation. Kautto UMet al (1982)<sup>33</sup> studied effect of Fentanyl on arterial pressure & heart rate during laryngoscopy and intubation in 45 normotensive ASA grade I patients. They demonstrated increase in baseline value of blood pressure with 2µg/kg dose but with 6µg/kg blood pressure does not increase after intubation. Heart rate remains near to baseline

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with  $6\mu g/kg$ . No respiratory depression was found in both groups. **Philip L. Liu et al** (**1986**)<sup>34</sup> studied Esmolol for attenuation of sympathetic response during tracheal intubation after Thiopentone and Succinylcholine and suggested that Esmolol has a predominant effect on chronotropy with little alteration in the mean arterial blood pressure.

In 1989 Gold M.I. et al<sup>35</sup> studied the clinical effectiveness of esmolol, an ultra-short-acting, cardioselective betaadrenergic receptor blocker, in controlling sinus tachycardia and increased systolic blood pressure occurring perioperatively in 30 ASA grade II or III patients having elective non-cardiac surgery. Esmolol 80 mg I.V. bolus (N = 15) or placebo (N = 15) followed by 12 mg/min or placebo were infused in 30 isoflurane-anesthetized patients using a randomized double-blind study design. The bolus plus infusions were given when surgical stimuli caused heart rate to exceed 95 bpm or systolic blood pressure 140 mm Hg. Esmolol significantly decreased heart rate (107 +/- 4, mean +/- SEM to 99 +/-4, mean +/- SEM bpm) within 45 sec after starting the bolus plus infusion; the placebo had no effect, heart rate being 105 +/- 4 before and 106 +/- 3 bpm after the bolus plus infusion. Patients given esmolol continued to have heart rates significantly lower than patients given placebo injections throughout a six min infusion (Ex., at 5 min 81 +/- 3 v/s 91 +/- 4 bpm). The study demonstrated no apparent effect of esmolol on blood pressure but that esmolol is effective in treating perioperative sinus tachycardia.

Matthew B. and Weinger et al (1991)<sup>19</sup> studied Electroconvulsive therapy (ECT) under anesthesia and was associated with hypertension and tachycardia. The cardiovascular effects of ECT were studied after pretreatment of 10 patients with esmolol (1.0 mg/kg), fentanyl (1.5 mcg/kg), labetalol (0.3 mg/kg), lidocaine (1.0 mg/kg), and saline solution (control), using a double blind randomized block-design. Each patient received all five pretreatment regimens over the course of five ECT sessions. During control studies, arterial blood pressure and heart rate increased significantly in all patients after ECT (P < 0.05and P < 0.01, respectively). The rate-pressure product increased by an average of 336% +/- 14% (P < 0.01). There were appreciable individual differences in the cardiovascular response to ECT, independent of pretreatment (P < 0.01). Pretreatment with esmolol and labetalol significantly reduced the hemodynamic response to ECT as compared with fentanyl, lidocaine, or saline solution (P < 0.05). Esmolol attenuated arterial blood pressure to a larger extent than did labetalol (P < 0.05). Compared with saline solution (control), pretreatment with labetalol, fentanyl, or lidocaine significantly reduced seizure duration (P < 0.05) and increased the frequency with which a second electrical stimulus was required. In contrast, esmolol pretreatment did not significantly affect seizure duration. Esmolol (1 mg/kg) administered 1 min before induction of anesthesia produced significant amelioration of the cardiovascular response to ECT with minimal effect on seizure duration.

**Steven M. and Helfman et al** (1991)<sup>10</sup> divided Eighty patients, ASA grade II-IV, scheduled for noncardiac surgery, were randomly assigned in a double blind placebo-

controlled manner to receive a preintubation dose of either placebo, 200 mg lidocaine, 200 pg fentanyl, or 150 mg esmolol. Induction of anesthesia was accomplished with 4-6 mg/kg thiopental IV followed immediately by the study drug. Succinylcholine 1-1.5 mg/kg was given at 1 minute. Laryngoscopy and intubation were performed at minute 2 with anesthesia thereafter maintained with 1 MAC (+/-10%) isoflurane in 60% nitrous oxide in oxygen at a 5 L/min flow for 10 min. Heart rate was recorded every 15sec and blood pressure every minute from induction until 10 min after intubation. Maximum percent increases in heart rate (mean +/- SE) during and after intubation were similar in the placebo (44% +/- 6%), lidocaine (51% +/- 10%), and fentanyl (37% +/- 5%) groups, but lower in the esmolol (18% +/- 5%) group (P<0.05). Maximum systolic blood pressure percent increases were lower in the lidocaine (20% +/- 6%), fentanyl (12% +/- 3%), and esmolol (19% +/- 4%) groups than in the placebo (36% + - 5%) group (P<0.05), but not different from each other (P>0.05). Only esmolol provided consistent and reliable protection against increases in both heart rate and systolic blood pressure accompanying laryngoscopy and intubation.

Lindgren L., Yli-Hankala A., Rnandell T. et al (1993)<sup>36</sup> had studied increases in hemodynamic variables and catecholamine levels after rapid increase in isoflurane concentration. Twenty-two healthy patients in whom the trachea was intubated were given 15 min of stable isoflurane-O2-air anesthesia [end-tidal concentration of isoflurane (ETIso) of 1.3%] (baseline). Patients were then randomly allocated to one of two groups. For 13 "IsoHigh" patients, the inspired concentration of isoflurane was increased abruptly. In those patients, the ETIso was kept at 2.6% for 10 min, i.e., until the end of the study, after which the depth of anesthesia was reduced. For nine "IsoLow" control patients, the ETIso level of 1.3% was continued until the end of the study. Heart rate, arterial pressures, catecholamine levels, and end-tidal concentration of CO2 were recorded at baseline and at 1, 1.5, 2, 4, 6, and 10 min after increase in isoflurane. They founded IsoHigh patients showed significant increases in heart rate (40% from 84.6 to 118.1 beats/min), systolic arterial pressure (SAP, 23%, from 96.4 to 118.3 mmHg), and diastolic arterial pressure (DAP, 30%, from 53.9 to 70.0 mmHg); all three variables peaked at 2 min. Significant increases occurred also in norepinephrine levels (80%, from 0.342 to 0.615 ng/ml) and in end-tidal concentration of CO2 (from 4.22% to 4.43%), both of which peaked at 4 min. Epinephrine levels did not increase significantly, although significant differences were seen between IsoHigh and IsoLow patients during the trial. IsoLow patients had no changes in these variables.

**Feng CK and Chan KH et al** (**1996**)<sup>7</sup> studiedcomparison of lidocaine, fentanyl, and esmolol for attenuation of cardiovascular response to laryngoscopy and tracheal intubation. In this study Eighty ASA grade grade I or II patients undergoing elective non-cardiac procedures were included in a randomized, single-blinded study consisting of 4 groups with each group receiving a designated drug: group A received normal saline as control, while group B, group C and group D received lidocaine 2 mg/kg, fentanyl 3 micrograms/kg and esmolol 2 mg/kg, respectively. Monitoring included ECG, pulse oximetry, capnometry and

arterial pressure. All patients were premedicated with diazepam 0.1 mg/kg 30 min before induction of general anesthesia. Each designated drug was given upon induction of anesthesia (time zero). Anesthesia was induced with thiopental 5 mg/kg and succinylcholine 1.5 mg/kg, and maintained with N2O, 1% isoflurane in 50% O2 and vecuronium. Intubation was carried out 3 min after the designated drug was given. Heart rate (HR) and systolic arterial blood pressure (SBP) were obtained every min for 10 min after induction. Either chi-square test or analysis of variances (ANOVA) was used for statistical comparison. A p value less than 0.05 was considered statistically significant. They found that there was no difference in the demographic data among the four groups. After intubation, the incidence of tachycardia (HR > 100/min) was found in 3 of 20 (15%) patients in esmolol group, significantly lower than 17 of 20 (85%) patients in the control group, 15 of 20 (75%) patients in lidocaine group, and 11 of 20 (55%) patients in fentanyl group, respectively (p < 0.05). The incidence of hypertension (SBP > 180 mmHg) was found in 4 of 20 (20%) patients in esmolol group, significantly lower than 16 of 20 (80%) patients in control group and 14 of 20 (70%) patients in lidocaine group, respectively (p < 0.05), but not in 8 of 20 (40%) patients in fentanyl group. Besides, the incidence of hypertension in fentanyl group (40%) was significantly lower than control group (80%; p < 0.05), but not in lidocaine group (70%). Results of this study showed that only esmolol could reliably offer protection against the increase in both HR and SBP. Low dose of fentanyl (3 micrograms/kg) prevented hypertension but not tachycardia, and 2 mg/kg lidocaine had no effect to blunt adverse hemodynamic responses during laryngoscopy and tracheal intubation.

F L Gobel et al (2001)<sup>9</sup> studied the rate-pressure product(RPP) as an index of myocardial oxygen consumption during exercising patients with angina pectoris. RPP best correlates with myocardial oxygen consumption  $(MV0_2)$  and is therefore critical in defining the response of coronary circulation to myocardial metabolic demands. In order to evaluate hemodynamic predictors of myocardial oxygen consumption (MVO<sub>2</sub>) 27 normotensive men with angina pectoris were studied at rest and during a steady state at sympton-tolerated maximal exercise (STME). Myocardial blood flow (MBF) was measured by the nitrous oxide method using gas chromatography. MBF increased by 71% from a resting value of 57.4 +/- 10.2 to 98.3 +/- 15.6 ml/100 g LV/min (P less than 0.001) during STME while MVO<sub>2</sub> increased by 81% from a resting value of 6.7 +/- 1.3 to 12.1 +/- 2.8 ml O2/100 g LV/min (P less than 0.001). MVO<sub>2</sub> correlated well with heart rate (HR) (r = 0.79), with HR x blood pressure (BP) (r = 0.83), and adding end-diastolic pressure and peak LV dp/dt as independent variables, slightly improved this correlation (r = .86). Including the ejection period (tension-time index) did not improve the correlation (r = 0.80). Thus, HR and HR x BP, both easily measured hemodynamic variables are good predictors of MVO<sub>2</sub> during exercise in normotensive patients with ischemic heart disease. Including variables reflecting the contractile state of the heart and ventricular volume may further improve the predictability.

Arti Rathore, H.K. Gupta et al (2002)<sup>37</sup> studied attenuation of the pressure responses to laryngoscopy and endotracheal intubation with different doses of esmolol.Study was conducted to determine an effective bolus dose of esmolol hydrochloride which would attenuate the pressor response of laryngoscopy and endotracheal intubation. A randomized controlled study was carried out on 100 healthy adult patients (ASA I and II) undergoing elective surgery under general anesthesia. The patients were randomly allocated into 4 groups of 25 each i.e. A (control), B, C and D receiving, 50mgs, 100mgs, 150 mgs of esmolol hydrochloride intravenously 2 minutes before intubation. The pulse rate, systolic blood pressure, ECG were recorded continuously after giving preanesthetic medication till seven minutes after intubation. The study showed that all the doses were effective in blunting the pulse rate response but only the 150 mgs proved effective significantly in blunting the blood pressure response. The rate pressure product, a measure of cardiac oxygenconsumption was also found to be significantly lower in groups, C and D. So we conclude that to blunt both the pulse rate and systolic blood pressure response of laryngoscopy and intubation higher doses of esmolol are effective. They found that 150 mg proved to be good in reducing the systolic BP.

Hussain AM et al (2005)<sup>11</sup> studied the effectiveness of single bolus dose of esmolol or fentanyl in attenuating the hemodynamic responses during laryngoscopy and endotracheal intubation. Sixty adult ASA-I and ASA-II patients undergoing elective surgery were included in the study. The patients were randomly divided into three groups i.e., A, B and C. Heart rate, systolic, diastolic and mean blood pressures were recorded with 0= as baseline and after administration of study drug, laryngoscopy and endotracheal intubation and 10 minutes thereafter. Study agent was injected 30 seconds before the induction of anesthesia. Group 'A' (control) received 10 ml saline, group 'B' and group 'C' received fentanyl 2 mg/kg and esmolol 2 mg/kg respectively diluted to make a total volume of 10 ml in normal saline. Readings of heart rate, systolic, diastolic and mean arterial pressures were compared with baseline and among each group. The rise in heart rate was minimal in esmolol group and was statistically significant. Following intubation, blood pressure was increased in all groups but was least in group C. Bolus injection of fentanyl 2 mg/kg given 2 minutes prior to laryngoscopy and intubation failed to protect against elevation of both the heart rate and systolic blood pressure whereas, esmolol at 2 mg/kg provided consistent and reliable protection against the increase of heart rate but not arterial blood pressure.

Akgul A, Ugur B et al (2007)<sup>38</sup>studied usage of remifentanyl and fentanyl in intravenous patient-controlled sedo-analgesia. Aim was to investigate the effects of patient-controlled sedo/analgesia with fentanyl or remifentanyl during cataract surgery with phacoemulsification method under topical anesthesia. The ethical committee had approved the prospective, randomized, double blind study. ASA I-III, 120 patients undergoing cataract surgery were randomly allocated to 3 groups. Fentanyl was administered in 0.7 mcg/kg loading, 10 mcg bolus dose with 5 minutes lockout time, remifentanyl was administered 0.3 mcg/kg loading, 20 mcg bolus dose with 3 minutes lockout time by

patient controlled analgesia (PCA) equipment. In the control group, saline solution was given without any analgesic drug. Cardiorespiratory system findings, verbal pain scale and sedation scores were recorded preoperatively and intraoperatively at the 5th, 10th, 15th, 20th and 30th minutes. Discomfort during surgery, pressing the PCA button and complications were recorded. The verbal pain scale scores was significantly lower in the drug groups than those in control group at the 15th minute. The sedation scores was significantly higher in the remifentanyl group at the 5th minute (p=0.019) and in the fentanyl group at the 10th minute (p=0.007) than those in the control group. The number of patients pressing the PCA button was much higher in the control group than the drug groups (p < 0.05). Patient comfort and surgeon satisfaction were higher in the drug groups (p<0.05). Intravenous-PCA sedo/analgesia addition to topical anesthesia provides an advantage in sedo/analgesia, patient comfort, and surgeon satisfaction. PCA is a convenient and safe method, especially at the beginning of the operation when anxiety is intense, and during lens implantation.

Shobhana Gupta and Purvi Tank et al (2011)<sup>39</sup> studied the effectiveness of single bolus dose of Esmolol or Fentanyl. In their study ninety adult ASA I and ASA II patients were included in the study who underwent elective surgical procedures. Patients were divided into three groups. Group C (control) receiving 10 ml normal saline, group E (esmolol) receiving bolus dose of esmolol 2 mg/kg and group F (fentanyl) receiving bolus dose of fentanyl 2  $\mu$ g/kg intravenously slowly. Study drug was injected 3 min before induction of anesthesia. Heart rate, systemic arterial pressure and ECG were recorded as baseline and after administration of study drug at intubation and 15 min thereafter. Reading of heart rate, blood pressure and rate pressure product were compared with baseline and among each group. The rise in heart rate was minimal in esmolol group and was highly significant. Also the rate pressure product at the time of intubation was minimal and was statistically significant 15 min thereafter in group E. Esmolol 2 mg/kg as a bolus dose proved to be effective in attenuating rise in heart rate following laryngoscopy and intubation while, the rise in blood pressure was suppressed but not abolished by bolus dose of esmolol.

S. Singh, E.F. Laing, W.K.B.A. Owiredu and A. Singh et al  $(2012)^{40}$ studied the attenuation of cardiovascular response by ß-blocker esmolol during laryngoscopy and intubation. Cardiovascular responses to laryngoscopy and intubation have long been recognized and various efforts have been made to attenuate this response. The aim of this study was to evaluate the efficacy and safety of ß-blocker esmolol in attenuating cardiovascular response to laryngoscopy and tracheal intubation in the Ghanaian population. After obtaining institutional ethical committee approval, 80 patients aged 18 to 65 years from either sex and classified as American Society of Anesthesiologists (ASA) grade I (normal healthy patients) or II (Patients with mild systemic disease) undergoing elective surgery under general anesthesia were selected for the study. Participants were randomly allocated into two groups comprising 40 subjects each. Group I received esmolol 2 mg kg -1 I.V. bolus and group II (control) received a placebo 2 minutes prior to

laryngoscopy. Changes in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and rate pressure product (RPP) were measured before induction as baseline, and at minute 1<sup>st</sup>, 3<sup>rd</sup> and 5<sup>th</sup> minute respectively after tracheal intubation while they were also observed for any complications. There was a significant attenuation in HR, SBP, DBP, MAP and RPP in the experimental group as compared to the control group (P < 0.05) at 1 minute with onward decreases at 3 and minutes respectively after intubation. 5 However. attenuation to baseline values at 5 minutes after intubation in the experimental group was significantly higher than that in the control group. Percentage changes in hemodynamic variables in experimental group versus control group at 5 minutes are as follows: HR = -2.90% v/s 10.22%; SBP = 0.96% v/s 6.21%; DBP = -3.54% v/s 4.06%; MAP = -1.56% v/s 4.94%; RPP = -1.86% v/s 17.25%. Prophylactic therapy with esmolol was found to be safe and effective in attenuating cardiovascular responses to laryngoscopy and tracheal intubation among the Ghanaian population.

Habib Bostan, Ahmet Eroglu et al (2012)<sup>2</sup> studied the efficacy of intravenous fentanyl, esmolol and lidocaine in preventing hemodynamic response to laryngoscopy, endotracheal intubation and extubation in abdominal surgeries. A hundred and twenty patients (aging from 18 to 65, ASA grade I or II, Mallampati grade I) were randomly divided into 4 groups. Fentanyl 1µg kg<sup>-1</sup> (n = 30), Esmolol 1 mg kg<sup>-1</sup> (n = 30), Lidocaine 1 mg kg<sup>-1</sup> (n = 30) and NaCl 0.9% 10 mL (Control group, n = 30) were administered before induction and extubation. Heart rate, systolic arterial pressure and diastolic arterial pressure were recorded before anesthesia induction and at laryngoscopy, at 1st, 3rd ,5th and 10th minutes of intubation, and then at the end of surgery before extubation, and at 1<sup>st</sup>, 3<sup>rd</sup>, 5<sup>th</sup>, and 10<sup>th</sup> minutes following extubation. Amounts of the administered drugs and side effects were recorded . The heart rates and the arterial blood pressures values of the study groups after intubation and extubation were lower than those in the control group (P < 0.01). The heart rates, the systolic and diastolic arterial blood pressure values after intubation and extubation at 1<sup>st</sup>, 3th, and 5<sup>th</sup> minutes were significantly lower in esmolol group when compared to fentanyl and lidocaine groups (P < 0.05). In all other measurement times, there was no difference of hemodynamic values among the three groups. When administered before induction and after emergence from an esthesia 1 mg  $kg^{\text{-1}}$  of esmolol and lidocaine, and 1µg  $kg^{\text{-1}}$  of fentanyl are effective in suppressing the hemodynamic response to laryngoscopy, intubation and extubation. Esmolol may be more effective to prevent those responses comparing fentanyl and lidocaine. Furthermore studies regarding the dose of those drugs should be required.

Sanjeev Singh, Edwin Ferguson Laing et al (2013)<sup>41</sup> studied comparison of esmolol and lidocaine for attenuation of cardiovascular stress response to laryngoscopy and endotracheal intubation. Direct laryngoscopy and endotracheal intubation always trigger powerful cardiovascular responses. Various attempts have been made to attenuate these responses. The aim of this study was to compare the efficacy and safety of esmolol and

lidocaine for suppressing cardiovascular response to laryngoscopy and tracheal intubation in a normotensive African population. A randomized controlled trial was conducted in 120 adult patients of American Society of Anesthesiologists (ASA) grade I or II undergoing various elective surgeries. The patients were randomly divided into three groups of 40 patients each group - C, L, and E. Group - "C" received no drug (control) as placebo, group -"L" received 1.5 [1] mg/ kg preservative free lidocaine and group -"E" received 2mg/kg esmolol IV 2 min before intubation. Mean arterial pressure (MAP) and rate-pressure product (RPP) were measured before induction as baseline and after tracheal intubation at minute 1<sup>st</sup>, 3<sup>rd</sup>, and 5<sup>th</sup>. The patients were randomly allocated to receive saline (Group C), lidocaine 1.5 mg/kg (Group L), or esmolol 2 mg/kg (Group E) (n = 40, each group). After induction of general anesthesia with thiopental 6 mg/kg and vecuronium 0.12 mg/kg, the test solution was infused 2 min before tracheal intubation. Changes in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), and rate-pressure product (RPP) were measured before induction of general anesthesia at (baseline),  $1^{st}$ ,  $3^{rd}$ , and  $5^{th}$  min after tracheal intubation. Patients were also observed for any complications. They found that there was a significant increase in HR, SBP, DBP, MAP, and RPP from the base line in control group "C" at 1 min with onward decreases at 3 and 5 min respectively after intubation. Percentage change in hemodynamic variables in groups C, L, and E at 1 min are as follows: HR = 30.45, 26.00, and 1.50%; MAP = 20.80, 15.89, and 10.20%; RPP = 61.44, 40.86, and 11.68%, respectively. Only patients receiving placebo had increased HR, MAP, and RPP values after intubation compared with baseline values (P < 0.05). [F] Prophylactic therapy with 2 mg/ kg esmolol is more effective and safe for attenuating cardiovascular responses to laryngoscopy and tracheal intubation in a black population.

Parth Shah, Hitesh Patel, Rashmi d'souza et al (2014)<sup>42</sup> comparison of Fentanyl, Esmolol and their studied combination for attenuation of hemodynamic response to laryngoscopy and tracheal Intubation. 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. This increase in the sympathoadrenal 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. Hundred adults (18-65 yrs), ASA grade 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 and Fentanyl and Inj. Esmolol 2minute before induction. Pulse rate, Systolic and Diastolic blood pressures were recorded at following stages: Baseline values before premedication, before induction, on laryngoscopy and intubation,  $1^{st}$ ,  $2^{nd}$ ,  $3^{rd}$ ,  $4^{th}$ ,  $5^{th}$  minute after intubation were recorded. Data analysis was carried out using Statistical Package for Social Science (SPSS, VI 0.5) package. Results were analyzed by Anova test. They concluded that 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.

Sathappan Karuppiah, Nongthombam Ratan Singh et al  $(2015)^{\overline{43}}$  studied attenuation of hemodynamic response to laryngoscopy and intubation using intravenous fentanyl and esmolol. Study was designed to compare the effect of intravenous fentanyl and esmolol for the attenuation of hemodynamic responses to laryngoscopy and intubation. Ninety patients undergoing elective surgical procedures were allocated into three groups viz., Group I (control): Identical volume of normal saline intravenously (IV) 3 min before induction; Group II (fentanyl): Injection fentanyl 2 mcg/kg IV 3 min before induction; Group III (esmolol): Injection esmolol 0.2 mg/kg i.v 3 min before induction. The heart rate and arterial blood pressure changes were monitored at the following time intervals: Before intubation, at intubation, and after intubation at different time intervals. The results were tabulated and statistically analyzed and  $P \le P$ 0.05 was considered significant. They founded thatmaximum rise in systolic blood pressure was observed at the post-intubation first minute, i.e., 22% (163.60  $\pm$  16.25); 15% (144.13  $\pm$  24.72); and 15% (153.80  $\pm$  24.75) in the Group I, II, and III from the baseline, respectively. Changes in the systolic blood pressure (SBP) was found to be minimum with fentanyl and esmolol groups when compared to the control group (P < 0.001). The diastolic blood pressure and mean arterial pressure changes was significant between fentanyl and esmolol groups with the control but not between esmolol and fentanyl. Group II showed better control of heart rate during laryngoscopy and intubation at the first min after intubation compared to other groups (P <0.05). Fentanyl 2 µg/kg bolus or esmolol 0.2 mg/kg bolus 3 before induction significantly attenuates the min hemodynamic response to laryngoscopy and intubation better than control group.

# 4. Materials And Methods

This Comparative study was carried out on randomly selected 100 patients of ASA Grade I and II, with age group of 18 to 60 years, scheduled for elective surgery requiring general anesthesia with endotracheal intubation.

On the day before surgery, all the patients were examined thoroughly and investigated accordingly. After proper preanesthetic counseling a written and informed consent was taken.

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#### (A) Patients inclusion and exclusion criteria:-

# Inclusion Criteria :

- Patients scheduled for elective surgeries.
- Age between 18 to 60 years of both the sexes.
- Patients with ASA Grade I or II.
- Mallampati airway assessment of Grade I.

# **Exclusion Criteria :**

- Patients with history of known allergies to study drugs.
- Unwilling Patient
- Emergency Surgeries
- Anticipated difficult intubation
- Patients with ASA Grade III or IV.
- Patients with cardiovascular diseases and severe respiratory diseases, endocrinal disorders like Diabetes Mellitus ,Hyperthyroidism etc and Renal failure patients
- Patients on beta blockers or Calcium Channel blockers or sympatholytic drugs.
- Patients in whom laryngoscopy and intubation proved to be prolonged >30seconds.

#### (B) Preanaesthetic evaluation

Preanaesthetic evaluation of all the patients consisted of detailed history, physical examination , routine investigations.

#### (C) Anaesthetic protocol

#### (l) Preoperative Preparation:

All patients were kept nil per orally for 6 hours. Written and informed consent was taken. Tablet Alprazolam 0.25 mg was given the night before the surgery to allay anxiety.

# (2) Premedication:

On the day of surgery pulse rate, SBP, DBP were recorded just prior to induction and were considered as baseline values.

In the operation theatre IV line secured with 18 G IV Cannula . Pulse Oximeter, non- invasive BP, ECG monitor were applied. Heart rate, SBP, DBP and MAP were recorded & RPP was calculated. and injection Midazolam 0.05 mg/kg and Injection Glycopyrrolate 0.004 mg/kg were given intravenously and infusion of ringer lactate was started.

# (3) Pre-Oxygenation:

After premedication all the patients were preoxygenated with 100% oxygen by mask for 3 minutes before induction.

# (4) Study Groups:

Patients were divided into two groups and each group consisted of 50 patients.

Group E: Esmolol group 2 mg / kg IV bolus 3 minutes prior to induction while preoxygenating .

Group F: Fentanyl citrate group.  $2 \mu g / kg$  IV bolus 3 minutes prior to induction while preoxygenating.

# (5) Induction and Intubation:

Induction was achieved with injection Propofol 2 mg/kg intravenously till loss of eyelash reflex and injection succinylcholine 2mg/kg was given Intravenously.

After 30 seconds laryngoscopy was done using standard Macintosh blade. Oral Intubation was done with appropriate sized, disposable, high volume low pressure, portex cuffed endotracheal tube within 30 seconds. Heart rate , SBP, DBP, MAP were recorded and RPP was calculated.

# (6) Maintenance

All the patients were ventilated with Bain's Circuit and anesthesia was maintained with  $O_2$  (35%),  $N_20$  (65%), Isoflurane (0.5-1.0%) and injection vecuronium bromide.

# (7) Monitoring

Intraoperative vitals were monitored using ECG, Pulse Oxymeter, NIBP and Capnography. HR, SBP, DBP and MAP were recorded & RPP was calculated in all patients inside the operation theater just before induction(baseline), after giving study drug, after larygoscopy and intubation, after laryngoscopy and intubation every minute upto 5 minutes after intubation during which no stimulus was given to patient and finally at 10 minutes after laryngoscopy and intubation. After 10 minute of observation Injection Butorphanol in dose of 0.04mg/kg was given for analgesia.

# (8) Complications

An observation was made related to adverse effects of drugs and anaesthesia related problems . Such problems if any were attended to appropriately.

# (9) Reversal

At the end of surgery anaesthesia was reversed with injection Neostigmine 0.05 mg/kg and injection Glycopyrollate 0.004 mg/kg Intravenously. Patients were shifted to recovery room after adequate reversal and monitored for vital parameters postoperatively.

# (10) Statistical analysis

Statistical analysis was done by using descriptive and inferential statistics using Chisquare test, students paired and unpaired t test and software used in the analysis were SPSS17.0, EPI 6.0 and Graph Pad Prism 5.0 version and p<0.05 is considered as level of significance.

# 5. Observations and Results

A total Hundred ASA Grade I and II patients of either sex between 18 - 60 years of age were selected for study scheduled for elective surgery under general anesthesia.

The patients were divided in to 2 groups of 50 patients each:

- I. Esmolol Hydrochloride Group ( Group E )
- II. Fentanyl Citrate Group ( Group F )

| patients in the two groups |            |             |                   |  |  |  |  |  |
|----------------------------|------------|-------------|-------------------|--|--|--|--|--|
| Age Group(yrs)             | value*     |             |                   |  |  |  |  |  |
| Upto 18 yrs                | 4(8%)      | 2(4%)       |                   |  |  |  |  |  |
| 21-30 yrs                  | 22(44%)    | 22(44%)     |                   |  |  |  |  |  |
| 31-40 yrs                  | 17(34%)    | 13(26%)     | 2 20              |  |  |  |  |  |
| 41-50 yrs                  | 6(12%)     | 12(24%)     | 5.20<br>D=0.52 NS |  |  |  |  |  |
| 51-60 yrs                  | 1(2%)      | 1(2%)       | r=0.32,1NS        |  |  |  |  |  |
| Total                      | 50(100%)   | 50(100%)    | ]                 |  |  |  |  |  |
| Mean+SD                    | 30.90+9.57 | 33.46+10.39 |                   |  |  |  |  |  |

 Table 1: Comparison of Mean Age Group distribution of

Table 1 Displays :- In present study all the patient in Group E and Group F are between the age of 18 to 60 years as shown in table no 1. The mean age for group E around  $30.90 \quad 57$  years and for group F around  $33.46 \quad 10.39$  years of age in which there was no statistically significant difference in terms of age . Maximum number of patient with age 21 to 40 years in both the groups . It was observed that both groups were comparable (p=0.52, non significant) with respect to mean age of patient.



Graph 1: Age wise distribution of patients in percentage in two groups

| 4 | 2: Gender wise distribution of patients in two |          |          |                   |  |  |  |  |  |
|---|--|----------|----------|-------------------|--|--|--|--|--|
|   | Gender   | Group E  | Group F  | ₹2-value          |  |  |  |  |  |
|   | Male   | 32(64%)  | 28(56%)  | 0.66              |  |  |  |  |  |
|   | Female   | 18(36%)  | 22(44%)  | 0.00<br>P=0.81 NS |  |  |  |  |  |
|   | Total  | 50(100%) | 50(100%) | 1 -0.01,105       |  |  |  |  |  |
|   |  |          |          |                   |  |  |  |  |  |





Graph 2: Gender wise distribution of patients in percentage in two groups

Table 2: It was observed that out of the total patient in group E 64 % were males and 36 % were female ,in group F 56 % were males and 44 % were females . Statistically , both the groups were similar with respect to the gender (p=0.81,non significant)

#### Table 3: Distribution of patients according to ASA grading

| ASA     | Group E  | Group F  | 2-value           |
|---------|----------|----------|-------------------|
| Grading | -        | -        |                   |
| Grade 1 | 25(50%)  | 27(54%)  | 1.07              |
| Grade 2 | 25(50%)  | 23(46%)  | 1.07<br>D=0.20 NS |
| Total   | 50(100%) | 50(100%) | r=0.30,INS        |

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Table 3 Displays:- In present study it was observed that out of the total patient in group E 50 % were ASA grade 1 and 50 % were ASA grade 2, in group F 54 % were ASA grade 1 and 46 % were ASA grade 2. Statistically there was no significant difference (p=0.30) in the two groups in terms of ASA grading.



Graph 3: Distribution of patients according to ASA grading in percentage in two groups

| 2 | re 4. Distribution of patients according to type of surge |          |          |           |  |  |  |  |
|---|---|----------|----------|-----------|--|--|--|--|
|   | Type of surgery   | Group E  | Group F  | value&    |  |  |  |  |
|   | Oral Surgery  | 20(40%)  | 20(40%)  |           |  |  |  |  |
|   | ENT   | 20(40%)  | 20(40%)  | 0.00      |  |  |  |  |
|   | General Surgery   | 10(20%)  | 10(20%)  | P=1.00,NS |  |  |  |  |
|   | Total   | 50(100%) | 50(100%) |           |  |  |  |  |

| <b>Fable</b> | 4: | Distribution | of | patients | according | to | type | of sur | gery |
|--------------|----|--------------|----|----------|-----------|----|------|--------|------|
|--------------|----|--------------|----|----------|-----------|----|------|--------|------|



Graph 4: Distribution of patients according to type of surgery in percentage in two groups

Tabel 4 Displays:- In the present study it was observed that out of the total patient in group E 40 % patient are from oral surgery , 40 % from ENT and 20 % from General surgery and in group F 40 % patient are from oral surgery , 40 % from ENT and 20 % from General surgery. Statistically there was no significant difference in the two groups in terms of types of surgery.

| Table 5: Comparision of mean | Weight wise distribution of |
|------------------------------|-----------------------------|
| patients in ty               | wo groups                   |

| putterne in the groups |              |              |  |  |  |  |  |  |  |
|------------------------|--------------|--------------|--|--|--|--|--|--|--|
| weight (kgs)           | Group E n(%) | Group F n(%) |  |  |  |  |  |  |  |
| <40                    | 3(6%)        | 3(6%)        |  |  |  |  |  |  |  |
| 41-50                  | 20(40%)      | 15(30%)      |  |  |  |  |  |  |  |
| 51-60                  | 27(54%)      | 32(64%)      |  |  |  |  |  |  |  |
| 61-70                  | 0(0%)        | 0(0%)        |  |  |  |  |  |  |  |
| Total                  | 50(100%)     | 50(100%)     |  |  |  |  |  |  |  |
| mean weight ± SD       | 52.04±5.83   | 50.90±5.54   |  |  |  |  |  |  |  |



Graph 5: Weight wise distribution of patients in percentage in both group

**Table 5 Displays:** It was observed that both the two groups were comparable (p value > 0.05) with respect to the mean weight of the patients. The weight of majority patients i.e 94% in group 'E' and 94% in group 'F' respectively was recorded between 41 – 60 kg.

#### **Hemodynamic Variables**

#### Hemodynamic parameters were recorded at:

BV (Baseline Value): Baseline readings taken just before intravenous Esmolol Hydrochloride 2mg/kg and Fentanyl Citrate  $2\mu g/kg$  was given i.e 3 min before laryngoscopy and intubation.

AS (After study Drug): Readings taken just after the study drugs were given.

ALI: Readings taken at Laryngoscopy and intubation.

ETI 1: Readings taken after intubation at 1 minute.

ETI 2: Readings taken after intubation at 2 minute

ETI 3: Readings taken after intubation at 3 minute

ETI 4 Readings taken after intubation at 4 minute

ETI 5 Readings taken after intubation at 5 minute

ETI 10 Readings taken after intubation at 10 minute

(P<0.05 significant(S), p=0.05, significant(S), p>0.05- Non-significant(NS)

Table 6: Comparison of changes in Mean pulse rate(bpm) at different interval in two groups

| Interval | Group E |       | Group F  |        |      | t voluo  | n-value |         |
|----------|---------|-------|----------|--------|------|----------|---------|---------|
| mtervar  | Mean    | SD    | % change | Mean   | SD   | % change | t-value | p-value |
| BV       | 82.30   | 12.27 | -        | 79.84  | 4.28 | -        | 1.33    | 0.184   |
| AS       | 80.60   | 11.14 | -2.07%   | 82.16  | 3.91 | 2.91%    | 0.93    | 0.353   |
| ALI      | 85.82   | 10.38 | 4.28%    | 86.02  | 5.03 | 7.74%    | 0.12    | 0.903   |
| ETI1     | 91.74   | 11.01 | 11.47%   | 102.72 | 7.23 | 28.66%   | 5.88    | 0.0001  |
| ETI2     | 90.26   | 10.96 | 9.67%    | 99.30  | 5.83 | 24.37%   | 5.14    | 0.0001  |
| ETI3     | 87.30   | 10.94 | 6.08%    | 95.58  | 5.68 | 19.71%   | 4.74    | 0.0001  |
| ETI4     | 86.18   | 10.45 | 4.71%    | 93.14  | 5.31 | 16.66%   | 4.19    | 0.0001  |
| ETI5     | 83.54   | 10.53 | 1.51%    | 90.16  | 4.94 | 12.93%   | 4.02    | 0.0001  |
| ETI10    | 80.90   | 11.17 | -1.70%   | 82.84  | 5.30 | 3.76%    | 1.10    | 0.270   |



Graph 6: Comparison of changes in Mean pulse rate(beats/mins) at different interval in two groups.

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**Table 6:** Displays the changes in the mean pulse rate(PR) at different interval:- Mean Pulse rate at baseline in Esmolol group was 82.30 12.27 beats per minute(bpm) and in Fentanyl group was 79.84 4.28 beats per minute (p value >0.05 non significant). After giving study drug comparison of pulse rate in Esmolol group was 80.60 11.14 and in Fentanyl group was 82.16 3.91 (p value >0.05, non significant). At laryngoscopy and intubation comparison of Pulse rate in Esmolol group was 85.82 10 38 and in Fentanyl group was 86.02 5.03 (p value >0.05, non significant).

After laryngoscopy and intubation at  $1^{st}$ ,  $2^{nd}$ ,  $3^{rd}$ ,  $4^{th}$  and  $5^{th}$  minutes comparison of pulse rate in Esmolol group was

91.74 11.01, 90.26 10.96, 87.30 10.94, 86.18 10.45 and 83.54 10.53 respectively and in Fentanyl group at  $1^{st},2^{nd},3^{rd},4^{th}$  and  $5^{th}$  minutes was 102.72 7.23, 99.30 5.83, 95.58 5.68, 93.14 5.31 and 90.16 4.94 respectively (p value <0.05) which was statistically significant.At 10<sup>th</sup> minute after laryngoscopy and intubation comparison of pulse rate in Esmolol group was 80.90 11.17 and in Fentanyl group was 82.84 5.30 (p value > 0.05 non significant). None of the patient in any of the study group developed bradycardia by the end of 10<sup>th</sup> minutes of intubation and pulse rate was not less than 60 beats per minute in any of the readings.



Graph 7: Comparison of Mean % Change in Pulse rate in two groups at different time interval

**Graph 7:** Displays there was fall in mean pulse rate 2.07% after study drug given in Esmolol group.

In group 'E' Mean Pulse rate following laryngoscopy and intubation increased by 11.47%, 9.67%, 6.08%, 4.71% and 1.51% respectively in first 5 minutes and then at  $10^{\text{th}}$  minute decreased by 1.70 %.

In group 'F' Mean pulse rate following laryngoscopy and intubation increased by 28.66%, 24.37%, 19.71%, 16.66%

and 12.93% respectively in first 5 minutes. At  $10^{\text{th}}$  minute pulse rate comes near normal.

Thus, attenuation of pressor response (rise in mean pulse rate) is better in esmolol group than in Fentanyl group. The mean pulse rate comes near to baseline in Esmolol group at 5 minute, while it is higher in Fentanyl group at all intervals. Esmolol at dose of 2mg/kg provided a reliable and consistent attenuation against the increase of heart rate.

| Table7: Com | parison of | changes in | n Mean | SBP(mml     | Hg) at | different | time | interval | in two | grou | ps |
|-------------|------------|------------|--------|-------------|--------|-----------|------|----------|--------|------|----|
|             | 1          | 0          |        | <pre></pre> | 0/     |           |      |          |        | 0    |    |

| Interval | Group E |       |          | Group F |       |          | t-value | n-value |
|----------|---------|-------|----------|---------|-------|----------|---------|---------|
| Interval | Mean    | SD    | % change | Mean    | SD    | % change | t-value | p-value |
| BV       | 120.36  | 12.27 |          | 121.36  | 8.55  |          | 0.473   | 0.638   |
| AS       | 122.48  | 13.15 | 1.76%    | 123.36  | 8.96  | 1.65%    | 0.391   | 0.697   |
| ALI      | 129.04  | 13.57 | 7.21%    | 131.68  | 9.99  | 8.50%    | 1.107   | 0.271   |
| ETI1     | 128.08  | 15.68 | 6.41%    | 139.68  | 10.08 | 15.10%   | 4.400   | 0.0001  |
| ETI2     | 127.40  | 16.05 | 5.85%    | 130.80  | 10.03 | 7.78%    | 1.270   | 0.207   |
| ETI3     | 123.64  | 13.82 | 2.73%    | 126.24  | 9.53  | 4.02%    | 1.095   | 0.276   |
| ETI4     | 122.08  | 14.68 | 1.43%    | 123.16  | 9.85  | 1.48%    | 0.432   | 0.667   |
| ETI5     | 117.60  | 12.80 | -2.29%   | 117.08  | 9.52  | -3.53%   | 0.230   | 0.818   |
| ETI10    | 111.64  | 11.76 | -7.24%   | 115.08  | 8.46  | -5.17%   | 1.678   | 0.097   |

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Graph 8: Comparison of changes in Mean SBP (mmHg) at different time interval in two groups

**Table 7 :-** Displays the changes in mean SBP at different time interval compared to the baseline in the two groups .It was seen that the baseline mean SBP in Esmolol group was 120.36 12.27 and Fentanyl group was 121.36 8.55 ( p value >0.05 non significant) . Values for mean SBP after giving study drug at laryngoscopy and intubation in Esmolol group were 122.48 13.15 and 129.04 13.57 respectively. In Fentanyl group values after giving study drug at laryngoscopy and intubation 131.68 9.99 repectively( p value >0.05 non significant). After intubation at 1 minute comparison of mean SBP in Esmolol group was 128.08 15.68 and in Fentanyl group was 139.68 10.08 ( p value < 0.05 ) which was statistically significant only at 1minute after intubation . After intubation

at  $2^{nd}$ ,  $3^{th}$ ,  $4^{th}$ ,  $5^{th}$  and  $10^{th}$  minute comparison of mean SBP in Esmolol group was 127.40 16.05, 123.64 13.82 , 1468, 117.60 1280 and 111.64 122.08 11.76 respectively . After intubation at  $2^{nd}\ , 3^{rd}\ , 4^{th}\ , 5^{th}$ and 10<sup>th</sup> minute comparison of mean SBP in Fentanyl group was 130.80 10.03 , 126.24 9.53 , 123.16 9.85 , 117.08 9.52 and 115.08 8.46( p value >0.05 non significant). Maximum attenuation in mean SBP achieved by Esmolol group(2mg/kg IV bolus) as compared to Fentanyl group(2mcg/kg IV bolus) was at first minute only. Esmolol gives consistent and reliable fall in mean SBP than Fentanyl groups at all intervals.



Graph 9: Comparision of Mean % change in SBP at different time interval in two groups

**Graph 9:** Displays in group 'E' following intubation mean SBP in first 3 minutes increased by 6.41%,5.82%,2.73% respectively and comes to normal at 3rd to 5th minute .

In group 'F' following intubation mean SBP at  $1^{st}$ ,  $2^{nd}$ ,  $3^{rd}$  minute was increased by 15.10%, 7.78%, 4.02% respectively and comes near to baseline at  $4^{th}$  minute.

The difference was significant in favour of group 'E' at the end of  $1^{st}$  minute only (p Value <0.05). It shows that attenuation of hemodynamic response in mean SBP is better with Esmolol than Fentanyl. But was not significant in subsequent  $2^{nd}$ ,  $3^{rd}$ ,  $4^{th}$ ,  $5^{th}$  and  $10^{th}$  minute (p>0.05, non significant).

| Interval | Group E |      |          | Group F |       |          | t-value | n-value |
|----------|---------|------|----------|---------|-------|----------|---------|---------|
| Interval | Mean    | SD   | % change | Mean    | SD    | % change | t-value | p-value |
| BV       | 76.64   | 6.43 |          | 75.32   | 4.89  |          | 1.155   | 0.251   |
| AS       | 80.12   | 6.31 | 4.54%    | 78.16   | 6.51  | 3.77%    | 1.527   | 0.130   |
| ALI      | 87.76   | 7.59 | 14.51%   | 87.08   | 7.37  | 15.61%   | 0.454   | 0.651   |
| ETI1     | 90.72   | 8.05 | 18.37%   | 90.36   | 7.44  | 19.97%   | 0.232   | 0.817   |
| ETI2     | 88.00   | 7.02 | 14.82%   | 86.36   | 7.26  | 14.66%   | 1.147   | 0.254   |
| ETI3     | 84.92   | 6.93 | 10.80%   | 81.96   | 5.733 | 8.82%    | 2.327   | 0.022   |
| ETI4     | 83.48   | 7.44 | 8.92%    | 80.16   | 5.14  | 6.43%    | 2.594   | 0.011   |
| ETI5     | 81.12   | 7.45 | 5.85%    | 75.56   | 4.78  | 0.32%    | 4.439   | 0.0001  |
| ETI10    | 77.56   | 7.58 | 1.20%    | 72.68   | 3.60  | -3.51%   | 4.143   | 0.0001  |

Table 8: Comparison of changes in Mean DBP (mmHg) at different time interval in two groups



Graph 10: Comparison of changes in mean DBP (mmHg) at different time interval in two groups

**Table 8:-** Displays the changes in mean DBP at different time interval compared to the baseline in the two groups .It was seen that the baseline mean DBP in Esmolol group was 76.64 6.43 and Fentanyl group was 75.32 4.89 ( p value >0.05 non significant). After giving study drug , at laryngoscopy and intubation, comparison of DBP in Esmolol group was 80.12 6.31 and 87.76 7.59 respectively. In Fentanyl group after giving study drug , at laryngoscopy and intuabtion comparison of DBP was 78.16 6.51 and 87.08 7.37 repectively( p value > 0.05 non significant). After intubation at 1 minute and 2 minute comparison of DBP in Esmolol group was 90.72 8.05 and 88.00 7.02 respectively. In Fentanyl group comparison of

DBP was 90.36 7.44 and 86.36 7.26 (  $p\ value > 0.05\ non\ significant)$ 

After intuabtion at 3<sup>th</sup>,4<sup>th</sup>,5<sup>th</sup> and 10<sup>th</sup> minute values of mean DBP in Esmolol group was 84.92 6.93, 83.48 7.44, 81.12 7.45 and 77.56 7.58 respectively. After intubation at 3<sup>th</sup>,4<sup>th</sup>,5<sup>th</sup> and 10<sup>th</sup> minute values of mean DBP in Fentanyl group was 81.96 5.73, 80.16 5.14, 75.56 4.78 and 72.68 3.60 ( p value < 0.05) which was statistically significant. The difference in the two groups was not statistically significant after laryngoscopy and intubation upto first two minutes.(p > 0.05)



Graph 11: Comparision of Mean % change in DBP at different time interval in two groups

**Graph 11:** Displays that during laryngoscopy and intuabtion mean DBP increases by 14.51% in group 'E' and 15.61% in group F was observed.

In group 'E' following intubation mean DBP increased by 18.37%, 14.82%, 10.80%, 8.92% and 5.85% respectively in first 5 minutes and comes to near normal at 10 minutes. In group 'F' following intuabtion mean DBP increased by 19.97%, 14.46%, 8.82% and 6.43% respectively during first 4 minutes and comes near to baseline at 5 minutes. The difference in the two groups was not statistically significant after laryngoscopy and intubation upto first two minutes. (p > 0.05)

In table 8 values From the  $3^{rd}$ ,  $4^{th}$ , $5^{th}$  and  $10^{th}$  minute after laryngoscopy and intubation are statistically significant. The reason behind this outcome is that the peak action of esmolol comes at 2 minutes and peak action of Fentanyl comes at 5 minutes .Action of the Esmolol starts wearing off at 5 minutes and ends at 9 minutes and action of Fentanyl starts wearing off at 20 minute and ends at 2 hours . In simple words by the time the action of esmolol is wearing off,Fentanyl is having its peak action(p<0.05)which was found to be statistically significant. So esmolol 2mg/kg does not provide consistent and reliable protection against rise in mean diastolic blood pressure as compared to fentanyl.

| Interval | Group E |      | Group F  |        |      | t voluo  | n-value |         |
|----------|---------|------|----------|--------|------|----------|---------|---------|
| mtervar  | Mean    | SD   | % change | Mean   | SD   | % change | t-value | p-value |
| BV       | 91.10   | 5.88 | -        | 90.64  | 5.32 | -        | 0.410   | 0.683   |
| AS       | 94.44   | 5.62 | 3.67%    | 93.14  | 6.67 | 2.76%    | 1.052   | 0.295   |
| ALI      | 101.58  | 6.34 | 11.50%   | 102.02 | 7.50 | 12.56%   | 0.316   | 0.752   |
| ETI1     | 102.34  | 8.78 | 12.34%   | 106.80 | 7.51 | 17.83%   | 2.727   | 0.008   |
| ETI2     | 101.38  | 7.95 | 11.28%   | 101.20 | 7.51 | 11.65%   | 0.116   | 0.908   |
| ETI3     | 97.72   | 7.28 | 7.27%    | 96.66  | 6.49 | 6.64%    | 0.768   | 0.444   |
| ETI4     | 95.62   | 8.11 | 4.96%    | 94.42  | 5.93 | 4.17%    | 0.844   | 0.401   |
| ETI5     | 93.58   | 7.03 | 2.72%    | 89.34  | 5.71 | -1.43%   | 3.307   | 0.001   |
| ETI10    | 88.96   | 6.61 | -2.35%   | 86.88  | 4.86 | -4.15%   | 1.790   | 0.077   |

Table 9: Comparison of changes in Mean MAP(mmHg) at different time interval in two groups

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Graph 12: Comparison of changes in Mean MAP(mmHg) at different time interval in two groups.

**Table 9**: Displays that the changes in MAP at different time interval compared to the baseline in the two groups .It was seen that the baseline mean MAP in Esmolol group was 91.10 5.88 and Fentanyl group was 90.64 5.32 (p value >0.05 non significant). After giving study, at laryngoscopy and intubation comparison of MAP in Esmolol group was 94.44 5.62 and 101.58 6.34 respectively. In Fentanyl group after giving study drug, at laryngoscopy and intubation comparison of MAP was 93.14 6.67 and 102.02 7.50 repectively(p value > 0.05 non significant).

After intubation at 1 minute comparison of MAP in Esmolol group was 102.34 8.78 and in Fentanyl group comparison of MAP was 106.80 7.51 respectively,( p value < 0.05) which was statistically significant.

After intubation at  $2^{nd}$ ,  $3^{rd}$  and  $4^{th}$  minutes comparison of MAP in Esmolol group was 101.38 7.95, 97.72 7.28 and 95.62 8.11 respectively. After intuabtion at  $2^{nd}$ ,  $3^{rd}$  and  $4^{th}$  minutes comparison of MAP in Fentanyl group was 101.20 7.51, 96.66 6.49 and 94.42 5.93 respectively (p value > 0.05, non significant).

After intubation at 5<sup>th</sup> minute comparison of MAP in Esmolol group was 93.58 7.03 and in Fentanyl group

comparison of MAP was 89.34  $\,$  5.71 respectively . ( p value <0.05 ) which was statistically significant .

After intubation at  $10^{th}$  minute comparison of MAP in Esmolol group was 88.96 6.61 and in Fentanyl group comparison of MAP was 86.88 4.86 respectively. (p value > 0.05, non significant).

At 1 minute after intubation the mean of mean arterial pressure in two groups shows significance (p <0.05) this is because onset of esmolol occurs in 1 minute and onset fentanyl occurs 1.5 to 2minutes so difference is statistically significant and was in favour of Esmolol group .

Again at 5<sup>th</sup> minute after intubation the mean of mean arterial pressure in the two groups shows significance (p<0.05) this is because peak action of Esmolol is at 2-4 minutes and peak action of Fentanyl is at 5 -20 minutes ,so difference is statistically significant and was in favour of Fentanyl group. Esmolol 2mg/kg attenuate mean arterial pressure maximum at first minute only, when used for prophylaxis against sympathetic responses to laryngoscopy and intubation.



Graph 13: Comparison of Mean % changes in MAP (mmHg) at different time interval in two groups.

**Graph 13:** Displays that in present study, preoperative baseline MAP in group 'E' was 91 mmHg and in Fentanyl group was 90 mmHg.During laryngoscopy and endotracheal intubation mean MAP increased by 10 mmHg in group 'E' and increased by 12 mmHg in group 'F'.

In group 'E' following intubation mean MAP during first 5 minutes increased by 12.34%, 11.28%, 7.27%, 4.96% and 2.72% and come to near normal at 5-10 minutes. In group 'F' following intubation mean MAP during first 5 minutes

increased by 17.83% , 11.65% , 6.64% , 4.17% and 1.43% comes to near normal at 5-10 minutes.

Attenuation of the hemodynamic response was better in Esmolol group at 1 minute after laryngoscopy and intubation than Fentanyl group (p = 0.008) which was statistically significant as the onset of action of Esmolol is at 1-2 minutes. Esmolol 2mg/kg has little effect on mean arterial pressure when used for prophylaxis against sympathetic responses to laryngoscopy and intubation in subsequent minutes.

| Intornal | Group E  |         |          | Group F  |         |          | t voluo | n voluo |  |
|----------|----------|---------|----------|----------|---------|----------|---------|---------|--|
| Interval | Mean     | SD      | % change | Mean     | SD      | % change | t-value | p-value |  |
| BV       | 9846.92  | 1386.51 |          | 9681.36  | 770.00  |          | 0.738   | 0.462   |  |
| AS       | 9812.48  | 1308.90 | 0.35%    | 10142.40 | 968.17  | 4.76%    | 1.433   | 0.155   |  |
| ALI      | 11032.40 | 1429.84 | 12.04%   | 11343.60 | 1270.84 | 17.17%   | 1.150   | 0.253   |  |
| ETI1     | 11725.68 | 1863.88 | 19.08%   | 14361.28 | 1581.57 | 48.34%   | 7.624   | 0.0001  |  |
| ETI2     | 11468.36 | 1809.46 | 16.47%   | 12999.36 | 1381.54 | 34.27%   | 4.755   | 0.0001  |  |
| ETI3     | 10764.24 | 1626.55 | 9.32%    | 12085.56 | 1365.93 | 24.83%   | 4.399   | 0.0001  |  |
| ETI4     | 10442.72 | 1564.79 | 6.05%    | 11490.88 | 1335.94 | 18.69%   | 3.602   | 0.0001  |  |
| ETI5     | 9806.92  | 1499.35 | -0.41%   | 10570.60 | 1184.86 | 9.19%    | 2.826   | 0.006   |  |
| ETI10    | 9006.40  | 1392.40 | -8.54%   | 9539.40  | 995.87  | -1.47%   | 2.202   | 0.030   |  |

**Table 10:** Comparison of changes in Mean RPP in two groups at different time interval



Graph 14: Comparison of changes in Mean RPP in two groups at different time interval

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Table 10 : Displays that the changes in the mean Rate pressure product (RPP) at different time interval compared to the baseline RPP in Esmolol group was 9846.92 1386.51 and in Fentanyl group was 9681.36 770.00 (p value >0.05 non significant ). After giving study drug comparison of RPP in Esmolol group was 9812.48 1308.90 and in Fentanyl group was 10142.40 968.17 (p value >0.05 , non significant ). At laryngoscopy and intubation comparison of RPP in Esmolol group was 11032.40 1429 84 and in Fentanyl group was 11343.60 1270.84 (p value >0.05, non significant).

After intubation at 1<sup>st</sup> ,2<sup>nd</sup> ,3<sup>rd</sup> ,4<sup>th</sup> ,5<sup>th</sup> and 10<sup>th</sup>minutes comparison of pulse pressure product in Esmolol group was 11725.68 1863.88, 11468.36 1809.46, 10764.24 1626.55, 10442.72 1564.79, 9806.92 1499.35 and 9006.40 1392.40 respectively and in Fentanyl group at ,4<sup>th</sup> ,3<sup>th</sup> ,5<sup>th</sup>  $1^{\text{st}}$ ,  $2^{\text{nd}}$ and 10<sup>th</sup> minutes was 14361.28 1581.57, 12999.36 1381.54, 12085.56 1365.93, 11490.88 1335.94, 10570.60 1184 86 and 9539.40 995.87 respectively (p value <0.05) which was statistically significant.



Graph 15: Comparison of Mean % changes in RPP at different time interval in two groups

**Graph 15:** Displays that mean increase in RPP is maximum at 1 minute after intubation in both the groups. In group 'E', it increases by 19.08%, 16.47%, 9.32 and 6.05% respectively at 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup> and 4<sup>th</sup> minutes after intubation. In group 'F', it increases at the same intervals was 48.34 %, 34.27 %, 24.83% and 18.69% respectively.

Thus, after intubation rise in RPP in group 'F' was almost double from the rise in group 'E' & remained higher throughout the study period. The difference in the two groups was highly significant at 1minute after intubation ( p Value = 0.0001) and remained significant till 10 minutes.

Attenuation of hemodyamic response (mean Rate pressure product) is better in Esmolol group than in Fentanyl group. So Esmolol provides better cardioprotection than Fentanyl.

# 6. Discussion

The sequence of induction , laryngoscopy and intubation are associated with marked hemodynamic changes and autonomic reflex activity which may be a cause of concern in many high risk pateint <sup>44</sup>.

Normal hemodynamic response to intubation is seen in all pateints but well tolerated by healthy subjects . However, in certain patients this response proves to be deterimental to the health or to the successful outcome of the patient . Hemodynamic response to the stress of laryngoscopy and intubation does not present a problem for most patients .

However, patients with cardiovascular or cerebral disease may be at increased risk of morbidity and mortality from the tachycardia and hypertension<sup>45</sup> resulting from the stress reflex caused by irritation of the respiratory tract. **Reid LC**, **Brace et al**<sup>26</sup> concluded that laryngoscopy and endotracheal intubation is associated with rise in blood pressure , heart rate and cardiac dysrythmias.

Increase in blood pressure and heart rate at the time of intubation increases the cardiac workload and oxygen demand of myocardium in normal subjects, this increased rquirement is achieved by coronary vasodialatation and increased coronary blood flow. But the patient with the history of Ischemic heart disease are at greater risk of developing a fresh episode of myocardial ischemia<sup>46</sup> and infarction<sup>47</sup> due to fixed coronary blood flow along with fall in cardiac index and ejection fraction.

Many factors like drugs , age , type of procedure , depth of anaesthesia<sup>33</sup> , hypoxia , hypercarbia, status of myocardium and baseline catechloaminelevel etc can influence the haemodynamic response associated with laryngoscopy and intubation. These haemodynamic responses need to be attenuated so as to decrease associated risk of myocardial ischemia , myocardial infarction, cerebral haemorrhage and raised intraoccular tension which may lead to optic disc ischemia and even blindness in high risk patients.

A number of techniques and drugs have been tried to ameliorate the response to intubation, these include:

- a) Intubation in deeper plane of anaesthesia.<sup>33</sup>
- b) Avoiding or reducing the duration of the laryngoscopy before intubation<sup>34</sup>.
- c) Use of LMA instead of endotracheal intubation.
- d) Use of topical airway anesthesia with lignocaine.
- e) Use of intracuff lignocaine .
- f) Use of intravenous lignocaine <sup>10</sup>.
- g) Pretreatment with intravenous beta Blockers<sup>20,21</sup>,.calcium channel blockers.
- h) Pretreatment with narcotic like Fentanyl <sup>43</sup> and remifentayl<sup>38</sup>.
- i) Use of vasodialators like nitrates ,magnesium sulphate , nitroglycerine<sup>8</sup>.

Unfortunaltely, only a limited number of these have been found to be really useful as many techniques have their own complications .This is because, these responses are mutifactorial including pain of wound , change in body temprature and irritation caused by endotracheal tube to laryngotracheal mucosa.

An ideal agent for attenuation of pressor responses should posses following properties:

- a) Rapid onset of action .
- b) Brief duration of action, ideally matching the duration of pressor response to intubation.
- c) Selectively acting towards cardiovascular system.
- d) No side effect
- e) Convenient to use ( ideally single bolus )
- f) Cost effectivity.

We have used Esmolol hydrochloride  $(2\text{mg/kg})\text{IV}^{39}$  and Fentanyl Citrate<sup>42,43</sup> ( $2\mu$  g/kg)IV for attenuating hemodynamic resposes to laryngoscopy endotracheal intubation. There are many studies previously documented for attenuation of pressor response to laryngoscopy and intubation.

This comparative study was conducted in the Department of Anesthesiology, Acharya Vinoba Bhave Rural Hospital, Jawaharlal Nehru Medical College, Sawangi (Meghe) Wardha. 100 patient undergoing surgery exclusively under general anesthesia were included (50 patient in each group). We compared safety and efficacy of intravenous Esmolol(2mg/kg) and Fentanyl( $2\mu$ g/kg) in attenuating the hemodynamic responses that occur with the laryngoscopy and endotracheal intubation.

We selected the optimal age between 18 to 60 years excluding the patients taking antihypertensive drugs as these may interfere with the pressure response . Also the sympathetic responses may be exaggerated in hypertensive patient especially in those having systolic hypertension with increased pulse pressure .

Different drugs used in anesthesia influence the sympathetic responses to laryngoscopy and intubation such as inj Gylcopyrrrolate given i.v. can cause tachycardia in some patients. Midazolam in dose of 0.05mg/kg intravenous, decreases the blood pressure and increase in the heart rate. So in our study we gave these two drugs 10 minutes before the study drug to minimize interference. We used Succinylcholine<sup>24</sup> in intubating dose of 2mg/kg to fascilitate

endotracheal intubation as it has rapid and short duration of action.

Propofol was selected for induction. In normovolumeic patient, propofol 2mg/kg i.v. can transiently decrease blood pressure by 10 - 20 mmHg and increase the heart rate by 15 - 20 beats/minute . There is increase in catehcholamine levels, both noradrenaline and adrenaline . Decreased in blood pressure is usually offset by increase in heart rate.

The most important laryngoscopic factor influencing the cardiovascular response is found to be duration of laryngoscopy . A linear increase in heart rate and mean arterial pressure during first 45 seconds has been observed. Further prolongation has little effect. As duration of laryngoscopy and intubation is normally less than 30 seconds the result of studies in which it takes longer than this have less clinical relevance. In our study the duration of laryngoscopy and intubation was limited to =< 30 seconds<sup>34</sup>

Criteria for selection of appropriate drug to prevent sympathetic response are the followings:

- 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 prolong the duration of anesthesia .
- Intravenous Esmolol and Fentanyl appear best to fulfill the above criteria.

Esmolol is advocated for attenuation of sympathetic responses to laryngoscopy and intubation. It is cardioselective and blunting of sympathetic responses is dose dependent. In high dose esmolol may cause bradycardia and hypotension<sup>16</sup>.

Esmolol has been used in various bolus doses or in an infusion form. Esmolol 2mg/kg as single bolus sucessfully attenuated the pressure response. There was minimal increase in heart rate from other group but blood pressure showed rise although it was less than other group after laryngoscopy and intubation<sup>18</sup>. Among the Beta Blockers the ultra short acting like Esmolol owing to its unique pharmacokinetic behaviour is well suited for controlling cardiovascular responses to tracheal intubation.

**Singhal et al**<sup>48</sup>studied about the timing of Esmolol injection for attenuating the hemodynamic responses to laryngoscopy and intubation and they concluded that esmolol 1.5 mg/kg single intravenous bolus given 3 minute prior to induction was very effective when compared to 90sec and 6min before. In our present study we gave the study drug 3 minute prior to laryngoscopy and intubation.

**H** Boston and Ahmet  $\text{Eroglu}^2$  showed that when administered before induction of anaesthesia 1mg/kg of Esmolol and lidocaine 1mg/kg, and 1 $\mu$ g/kg of Fentanyl are effective in supperssing the hemodynamic response to laryngoscopy, intubation and extubation. Esmolol may be more effective to prevent those responses compared to the

other two . However, they recommended more studies regarding the ideal dose of these drugs.

Fentanyl is also recommended for bunting laryngoscopy response. Blunting of sympathetic responses is dose dependent. At high dose Fentanyl being lipophilic produces tissue accumulation and thus longer lasting plasma and brain concentration of the drug which may lead to respiratory depression and chest rigidity. These patient may require mechanical ventilatory support. It is believed that Fentanyl suppresses the hemodynamic response by increasing the depth of anesthesia and decreasing sympathetic discharge. A low dose of Fentanyl (2mcg/kg) was considered in our study because large doses of Fentanyl often leads to muscular rigidity<sup>49</sup>, bradycardia, respiratory depression ,nausea and vomiting .

In our study we gave fentanyl<sup>50</sup> 3 minutes prior to laryngoscopy and intubation in a dose of  $2\mu$  g/kg (IV) to avoid postoperative respiratory depression.Heart rate and blood pressure is measured every minute till 5 minutes and then at 10 minute. Mean blood pressure and Rate pressure product were also computed and compared between the two groups. **Seonghoon ko et al**<sup>32</sup> studied the effective timing and dose of fentanyl by analyzing responses when given 1 to 10 minutes before laryngoscopy. He has recommended 3 minute before laryngoscopy to be the ideal time.

# Comparison Of Changes in Mean Pulse Rate at different time interval [ Table 6 ]

The mean Pulse rate before giving study drug was considered as baseline in current study and later values were comapred with it. The preoperative mean Pulse rate of the patient in both the groups were comparable (p>0.05) which were 82.30 12.27 and 79.84 4.28 in Esmolol and Fentanyl group respectively, which was statistically nonsignificant. Mean Pulse rate at time of laryngoscopy and intubation in both groups were comparable (p>0.05) which were 85.82 10.38 and 86.02 5.03 in Esmolol and Fentanyl group respectively which was statistically nonsignificant.After laryngoscopy and intubation at 1 minute the mean Pulse rate increased by a maximum of 91.74 11.01 and 102.72 7.23 in Esmolol group and Fentanyl group respectively (p<0.05) which was statistically significant. The mean pulse rate declined to reach a level below baseline by 5 minutes in Esmolol group, whereas all values subsequent to laryngoscopy and intubation remained much higher than the baseline in Fentanyl group.Maximum attenuation of rise in mean pulse rate over 1-5 minute after laryngoscopy and intubation in Esmolol<sup>51</sup> group is evidently significant and statistcally highly significant than Fentanyl group (p = 0.0001). Shobhana Gupta et al<sup>39</sup> found that the increase in heart rate was seen in all the three groups compared to the baseline value . But the rise was minimal in Fentanyl  $(2\mu g/kg)$  group and Esmolol (2mg/kg) group as compared to control(0.9% saline ) group , which was statistically significant (p<0.05). Also, only in Esmolol group there was no significant rise at any time interval (p<0.001). These changes were significant upto 15 min postintubation. Our study corelates with this study during first five minutes. Attenuation with Esmolol group is highly significant than Fentanyl group (p=0.0001). Steven M. Helfman et al<sup>10</sup>studied attenuation of hemodynamic response with placebo-control group, 200mg lignocaine, 200microgram/kg Fentanyl, Esmolol 150 mg. They have given study drugs 2 minutes prior to intubationand found maximum percent increase in mean pulse rate during and after laryngoscopy and intubation and were similar in placebo(44%+/- 6%),lidocaine (51% +/- 10%) and Fentanyl(37% +/- 5%) groups, but lower in Esmolol(18% +/-5%) group . In our study we have given study drugs 3 minutes before induction and increase in mean pulse rate at laryngoscopy and intubation was similar. But the rise in mean pulse rate was significantly (p<0.05) higher in Fentanyl group as compared to Esmolol group. Thus, Esmolol provides consistent and reliable protection again increase in mean pulse rate. Hussain AM et al<sup>11</sup> study shows that bolus injection of fentanyl  $2\mu g/kg$  2 minute prior to laryngoscopy and intubation failed to protect against elevation of both heart rate and systolic blood pressure, whereas Esmolol at 2mg/kg provided consistent and reliable protection against the increase of the heart rate but not the arterial blood pressure. In our study bolus injection of Fentanyl  $2 \mu$  g/kg 3 minute prior to laryngoscopy and intubation failed to protect against elevation of mean pulse rate, whereas Esmolol at 2mg/kg provided consistent and reliable protection against the increase of the mean pulse rate. Feng CK et al<sup>7</sup> compared lidocaine 2mg/kg , Fentanyl  $3\mu$  g/kg and Esmolol 2mg/kg, his study also showed that only Esmolol could reliably offer protection against the increase in both HR and SBP while Fentanvl  $(3 \mu g/kg)$ prevented hypertension but not tachycardia. In our study we found that Esmolol provides better attenuation in rise in mean pulse rate responses to laryngoscopy and endotracheal intubation. Esmolol appears to be drug of choice in maintaining hemodynamic stability during laryngoscopy and intubation . The mean pulse rate was more in patients of Fentanyl group as compared to Esmolol group. In our study Esmolol (2mg/kg) I.V and Fentanyl (2µg/kg) I.V does not show any events of bradycardia, hypotension in Esmolol group and allergic urticaria & respiratory depression in Fentanyl group. Esmolol<sup>52</sup> provides more reliable protection against increase in mean pulse rate than Fentanyl group.

# Comparison of changes in Mean SBP at different interval[Table 7]

In Esmolol group the mean SBP increased from 120.36 12.27mmHg at baseline to 122.48 13.15mmHg after giving study drug, whereas an increase from 121.36 8.55mmHg at baseline to 123.36 8.96mmHg after after giving study drug was seen in Fentanyl group(p>0.05, non significant). The maximal rise in mean SBP in both the groups occurred at 1 minute after laryngoscopy and intubation . At 1 min it increased above the baseline from 120 36 12.27 mmHg to 128.04 15.68 mmHg in Esmolol group as compared to Fentanyl group in which it increased above the baseline from 121.36 8.55 mmHg to 10.08 mmHg(p=0.0001). This was highly 139.68 significant only at 1 minute after intubation. After intubation at 2<sup>nd</sup> ,3<sup>rd</sup> and 4<sup>th</sup> minute comparison of mean SBP in Esmolol group was 127.40 16.05, 123.64 13.82 and 122.08 14 68 respectively, which remained increased from baseline . After intubation at 2<sup>nd</sup> ,3<sup>rd</sup> and 4<sup>th</sup> minute comparison of mean SBP in Fentanyl group was

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130.80 10.03, 126.24 9.53 and 123.16 9.85 respectivley, which remained increased from baseline (p value >0.05 non significant). After intubation at 5<sup>th</sup> and 10<sup>th</sup> minute comparison of mean SBP in Esmolol group was 117.60 12 80 and 111.64 11.76 respectively, which came below the baseline . After intubation at  $5^{th}\;$  and  $10^{th}\;minutes$ comparison of mean SBP in Fentanyl group was 117.08 9.52 and 115.08 8.46 respectively, which came below the baseline ( p value >0.05 non significant). Thus, in our study Mean SBP is better attenuated by Esmolol than Fentanyl Group at 1 min after Laryngoscopy and intubation. Esmolol gives consistent and reliable fall in mean SBP than Fentanyl groups at all intervals. After the initial rise both drugs showed similar rise of mean SBP with no significant difference (P >0.05). Mean Systolic blood pressure returned to baseline values after 4minutes in both the groups. H Boston and Ahmet Eroglu et al.<sup>2</sup> showed that when administered before induction of anaesthesia 1mg/kg of Esmolol, lidocaine 1mg/kg and 1  $\mu$  g/kg of Fentanyl are effective in supperssing the hemodynamic response to laryngoscopy, intubation and extubation. Esmolol was more effective to prevent rise in mean SBP as compared to the other two. The findings of this study correlates with our study as rise in mean SBP after laryngoscopy and intubation<sup>53</sup> was seen lower at all interval in Esmolol group than Fentanyl group. So Esmolol<sup>54</sup> attenutes SBP better than Fentanyl. Difference in the mean SBP in the two group was significant only at 1 minute after larygoscopy and intubation but in the subsequent minutes from  $2^{nd}$ ,  $3^{rd}$ ,  $4^{th}$ ,  $5^{th}$  and finally at  $10^{th}$  minute was non significant(p>0.05). Hussain AM et al<sup>11</sup> studied the effectiveness of single IV bolus dose of esmolol (2mg/kg) and fentanyl  $(2 \mu g/kg)$  in attenuating the hemodynamic responses during laryngoscopy and endotracheal intubation. He concluded fentanyl  $2\mu$  g/kg given 2 minute prior to laryngoscopy and intubation failed to protect against elevation of both the heart rate and systolic blood pressure, whereas esmolol at 2 mg/kg provided consistent and reliable protection against the increase of heart rate but not arterial blood pressure. In our study Esmolol protect against the rise in mean SBP at all intervals, which correlates with this study. Feng CK et al<sup>7</sup> compared lidocaine 2mg/kg, Fentanyl  $3\mu$  g/kg and Esmolol 2mg/kg, his study also showed that only Esmolol could reliably offer protection against the increase in both HR and SBP while Fentanyl  $(3 \mu g/kg)$ prevented hypertension but not tachycardia. In our study we concluded that Esmolol provides better attenuation in rise of mean SBP responses to laryngoscopy and endotracheal intubation than Fentanyl. In our study Esmolol (2mg/kg) I.V and Fentanyl  $(2\mu g/kg)$  I.V did not show any events of side effects like hypotension in Esmolol group and respiratory depression in Fentanyl group. Esmolol provides more reliable protection against increase in mean SBP55 than Fentanyl group.

# Comparison of changes in Mean DBP at different time interval [ Table 8]

In Esmolol group the mean DBP increased from 76.64 6.43 mmHg at baseline to 80.12 6.31 mmHg after giving study drug, whereas an increase from 75.32 4.89 mmHg at baseline to 78.16 6.51 mmHg after after giving study drug was seen in Fentanyl group(p > 0.05, nonsignificant). The

maximal rise in mean DBP in both the groups occurred at 1 minute after laryngoscopy and intubation. At 1 min DBP increased above the baseline from 76.64 6.43 mmHg to 90.72 8.05 mmHg in Esmolol group as compared to Fentanyl group in which it increases above the baseline from 75.32 4.89 mmHg to 90.36 7.44 mmHg(p>0.05)which was not significant. Similarly there was no significant change in mean DBP at 2 minute after laryngoscopy and intubation. Both Esmolol and Fentanyl attenuate the(rise in diastolic pressure) in first two minute but was not statistically significant(p>0.05). There was significant difference between two groups at 3<sup>rd</sup>,4<sup>th</sup>,5<sup>th</sup> and 10<sup>th</sup> minutes, the mean change in DBP of Esmolol group was 84.92 6.93 , 83.48 7.44 , 81.12 7.45 and 77.56 758 respectively , and in fentanyl group was 81.96 5733, 80.16 5.14. 75.56 4.78 and 72.68 3.60 respectively (p < 0.05) which was statistically significant. Thus, Esmolol was not able to attenuate DBP as compared to Fentanyl. Peak action of fentanyl starts from 5 to 20 minutes and esmolol is from 2- 4 minutes, so finding is significant and is in favour of Fentanyl. The diastolic blood pressure returned to pre induction values within 5 minutes post intubation in Fentanyl(2mcg/kg) group and comes near to baseline value at 10<sup>th</sup> minute in Esmolol group(2mg/kg).**Parth shah et al**<sup>42</sup> found that there was a significant increase in diastolic blood pressure during laryngoscopy and post endotracheal intubation in all the four groups as control group (0.9%)saline), fentanyl group(2mcg/kg), esmolol group (2mg/kg), combination of fentanyl(2mcg/kg) and esmolol(2mg/kg). The increase was highly significant in control group when compared to the other groups. The diastolic blood pressure returned to pre induction values within 5 minutes of post intubation in Fentanyl(2mcg/kg) group, Esmolol group(2mg/kg) and group with both drugs(FE). The combination of fentanyl and esmolol produced a more significant attenuation of rise in diastolic blood pressure compared to fentanyl and esmolol alone. The findings of this study in Esmolol and Fentanyl group correlate with our study, that is in Esmolol group mean DBP is raised at all interval than in Fentanyl group. In Fentanyl( $2\mu$ g/kg) group mean DBP returned to pre induction values within 5 minutes post intubation . In our study Fentanyl attenuates mean DBP more significantly than Esmolol from 3<sup>rd</sup> minute onwards following laryngoscopy and intubation till 10<sup>th</sup> minute.

# Comparison of changes in Mean MAP at different time interval [Table 9]

The changes in MAP at different time interval were compared to the baseline in the two groups .It was seen that the baseline mean MAP in Esmolol group was 91.10 5.88 and Fentanyl group was 90.64 5.32 (p value >0.05 non siginificant). After giving study drug and at laryngoscopy and intubation comparison of MAP in Esmolol group was 94.44 5.62 and 101.58 6.34 respectively. In Fentanyl group after giving study drug and at laryngoscopy and intubation comparison of MAP was 93.14 6.67 and 102.02 7.50 repectively( p value > 0.05 non significant). After intubation at 1 minute comparison of MAP in Esmolol group was 102.34 8.78 and in Fentanyl group was 106.80 7.51 respectively ( p value < 0.05 ) which was statistically significant . After intubation at  $2^{nd}$   $3^{rd}$  and  $4^{th}$ minute values of MAP in Esmolol group was 101.38 7.95,

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97.72 7.28 and 95.62 8.11 respectively. After intubation at  $2^{nd}$ ,  $3^{rd}$  and  $4^{th}$  minute values of MAP in Fentanyl group was 101.20 7.51 , 96.66 6.49 and 94.42 5.93 respectively ( p value > 0.05 ,non significant) . After intubation at 5 minute comparison of MAP in Esmolol group was 93.58 7.03 and in Fentanyl group was 89.34 5.71 respectively , ( p value < 0.05 ) which was statistically significant. After intubation at 10<sup>th</sup> minute comparison of MAP in Esmolol group was 88.96 6.61 and in Fentanyl group comparison of MAP was 86.88 4.86 respectively. ( p value > 0.05, non significant). At 1 minute after intubation the mean arterial pressure in two groups shows significance (p < 0.05), this is because onset of esmolol occurs in 1 minute and onset of fentanyl occurs 1.5 to 2minutes , so difference is statistically significant and was in favour of Esmolol group. Again at 5 minutes after intubation the mean arterial pressure in the two groups shows significance (p<0.05), this is because peak action of Esmolol is from 2-4 minutes and peak action of Fentanyl is from 5 -20 minutes, so difference is statistically significant and was in favour of Fentanyl group. Shobhana Gupta and Purvi tank et al<sup>39</sup> did a comparative study of efficacy of Esmolol and Fentanyl for pressure attenuation during laryngoscopy and endotracheal intubation with dose of Esmolol 2mg/kg IV bolus and Fentanyl  $2\mu$  g/kg IV bolus. The changes in mean MAP were significant upto 15 minutes postintubation after which it declined gradually and reached to baseline level after 15 minute of laryngoscopy and intubation in all groups. In our study maximum attenuation of mean MAP occured in Esmolol group at first minute after laryngoscopy and intubation than in Fentanyl group(p=0.0001, significant). But after subsequent  $2^{nd}$ ,  $3^{rd}$ ,  $4^{th}$ ,  $5^{th}$  and finally at 10<sup>th</sup> minute after larygoscopy and intubation Esmolol does not attenuate mean MAP . Fentanyl attenuates mean MAP significantly on 5<sup>th</sup> minute after laryngoscopy and intubation. Overall Esmolol<sup>56</sup> attenuates mean MAP at 1 minute after laryngoscopy and intubation siginificantly(p=0.008), but not so in subsequent minutes. In subsequent minutes fentanyl attenuates mean MAP more than esmolol this finding of our study was similar to Sathappan karuppiah et al<sup>43</sup>. Thus, our study shows mixed response to mean MAP.

# Comparison of Change in Rate Pressure Product at different time interval[ Table 10]

Rate pressure product<sup>11</sup> is a product of SBP and HR and is a measure of cardiac workload. Increase in RPP increases the risk of myocardial ischemia, myocardial infarction, acute cardiac failure,pulmonary<sup>7</sup> edema and arrythmias <sup>16</sup>.The mean RPP before giving study drug was considered as baseline in current study and rest of the values were compared with it. At the same time interval(baseline) mean RPP in two groups were comparable(p>0.05) with values as 9846.92 1386.51 and 9681.36 770.00 in Esmolol and group respectively and were statistically Fentanyl nonsignificant. After intubation maximum increase in mean RPP in Esmolol group was 11725.68 1863.88 and in Fentanyl group was 14361.28 1581.57 respectively at first minute (p value <0.05) which was statistically significant, which indicates low hemodynamic response of Rate pressure product thus workloadput on cardiac heart muscle is least in Esmolol<sup>57</sup> group. In our study there is significant decrease in mean RPP post intubation. The increase was 50 % less in Esmolol treated patient compared to Fentanyl treated patient suggesting that, Esmolol has a predominant effect on chronotropy with appericiable effect on mean systolic blood pressure when used for prophylaxis against sympathetic responses to laryngoscopy. The values are below 20000 so there are less chances of myocardial ischemia. So Esmolol<sup>58</sup> provide more reliable cardio-protection than Fentanyl. Again our study correlates with the study of Philip L. Liu et al<sup>34</sup> who used esmolol infusion to control hemodynamic responses associated with intubation. They found significant decrease in RPP prior to induction and post intubation the increase was 50 % less in Esmolol treated patient compared to placebo treated patient. Shobhana Gupta et al<sup>39</sup> in their study also found significant decrease in RPP. Post intubation the increase was 50 % less in Esmolol treated patient compared to Fentanyl treated patient suggesting that, Esmolol<sup>59</sup> has a predominant effect on chronotropy with little effect on mean arterial pressure when used for prophylaxis against sympathetic responses to laryngoscopy. F L Gobel et al<sup>9</sup> studied normotensive cases with IHD during exercise. He found that heart rate multiplied by SBP is a good haemodynamic predictor of myocardial oxygen consumption(MVO<sub>2</sub>). In our study the result showed that rate pressure product is less than 50 % in Esmolol group than in Fentanyl group. Thus, Esmolol gives better cardioprotection than Fentanyl.

# 7. Summary

The laryngeal and tracheal stimulation causes reflex sympathoadrenal response with marked increase in heart rate and blood pressure, which is very common during laryngoscopy and intubation<sup>60</sup>. Arrhythmias can be precipitated. Various techniques and drugs have been advocated to decrease the hemodynamic responses but none of them is totally acceptable.

The present clinical comparative study was done in 100 normotensive, ASA grade I and II patients scheduled for various elective surgical procedure under general anesthesia, randomly divided into 2 groups of 50 patient each. Group E receiving Esmolol (2mg/kg) IV bolus and Group F receiving Fentanyl (2mcg/kg)IV bolus. The objective of the study was to study and ascertain the effectiveness of Esmolol Hydrochloride 2mg/kg IV bolus and Fentanyl citrate  $2\mu$  g/kg IV bolus in attenuating this cardiovascular responses when given 3 minutes prior to laryngoscopy and intubation.

PR, SBP,DBP, MAP were recorded and RPP was computed and the data was compared between the two groups at baseline value 3 minute prior to laryngoscopy and intubation, after giving study drug, at laryngoscopy and intubation , than at every minute up to 5 minutes and finally at 10 minute.

Various hemodynamic parameters stated above like pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure were recorded and rate pressure product was calculated at various specified time interval and end at 10 minute after laryngoscopy and intubation. The mean and standard deviations were calculated for all observations and

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the two groups were compared using student 't' test and chi square test where applicable. Probability value (p value) of < 0.05 was considered statistically significant.

In our study, we found that:

- Both the groups were well matched with respect with age, sex and weight. The mean age in Esmolol group was 30.90±9.57 years, compared to a mean age of 33.46±10.39 years, in the Fentanyl group(P=0.52, non significant). Majority of the subject in this study were male (60 out 100) compared to 40 female and they were proportionately distributed(P=0.81, non significant).
- The mean weight in the Esmolol group was 52.04±5.83 kg, as compared to 50.90±5.54kg in Fentanyl group.(p >0.05 non significant).
- Esmolol in dose of 2mg/kg IV bolus was significantly more effective in suppressing the rise in pulse rate as compared to Fentanyl(2mcg/kg) at all time interval following laryngoscopy and intubation.
- There was no statistically significant difference between the two groups with respect to mean pulse rate at baseline, after giving the study drug and at laryngoscopy and intubation.(p>0.05) However, following laryngoscopy and intubation from 1 minute to 5 minute the mean pulse rate in Esmolol group remained significantly lower than the mean pulse rate in the Fentanyl group(p=0.0001). Again at  $10^{th}$  minute following laryngoscopy and intubation there was no statistically significant difference between the two groups (p > 0.05). Esmolol (2mg/kg IV bolus) provides more reliable and consistent protection against increase in mean pulse rate than Fentanyl (2mcg/kg IV bolus) group.
- There was no statistically significant difference between the two groups with respect to mean SBP at baseline value, after giving the study drug, and at laryngoscopy and intubation (p > 0.05). However following laryngoscopy and intubation at 1 minute only the mean SBP was lower in Esmolol group than in Fentanyl group (p < 0.05), which was statistically significant. Later the mean SBP values following laryngoscopy and intubation from 2<sup>nd</sup> minute to 5<sup>th</sup> minute and finally at 10<sup>th</sup> minute were lower in esmolol group than fentanyl group, but was not statistically significant(p > 0.05).
- There was no statistically significant difference between the two groups with respect to mean DBP at baseline value, after giving the study drug, and at laryngoscopy and intubation, following intubation at 1<sup>st</sup> and 2<sup>nd</sup> minute (p > 0.05, non significant). Later the mean DBP following laryngoscopy and intubation from 3<sup>rd</sup> minute to 5<sup>th</sup> minute and finally at 10<sup>th</sup> minute was statistically significant lower in Fentanyl group as compared to Esmolol group(p < 0.05).
- There was no statistically significant difference between the two groups with respect to mean MAP at baseline value, after giving the study drug, and at laryngoscopy and intubation (p>0.05). The mean MAP following laryngoscopy and intubation at 1 minute statistically significant difference in two groups was seen and was lower in Esmolol group as compared to Fentanyl group(p <0.05). The mean MAP from 2<sup>nd</sup> minute to 4<sup>th</sup> minute in both the groups was not statistically significant (p > 0.05, non significant). The mean MAP following laryngoscopy and intubation at 5<sup>th</sup> minute had statistically significant difference in two groups and was lower in Fentanyl group

as compared to Esmolol group(p <0.05). The mean MAP at  $10^{\text{th}}$  minute in both the groups was not statistically significant (p > 0.05, non significant).

There was no statistically significant difference between the two groups with respect to mean RPP at baseline value, after giving the study drug, and at laryngoscopy and intubation (p>0.05). Later measurement following laryngoscopy and intubation from 1 minute to 5 minute and finally at 10<sup>th</sup> minute was statistically significant in the two groups (p < 0.05) and was lower in Esmolol group as compared to Fentanyl group.

# 8. Conclusion

# We conclude the following:

- 1) Esmolol (2mg/kg IV bolus) provides more reliable and consistent protection against increase in mean pulse rate than Fentanyl (2mcg/kg IV bolus).
- 2) Maximum attenuation in mean SBP achieved by Esmolol group(2mg/kg IV bolus) as compared to Fentanyl group(2mcg/kg IV bolus) was at first minute only.
- 3) There was consistent and reliable fall in mean SBP in Esmolol group than Fentanyl group at all intervals.
- 4) Esmolol does not attenuate mean DBP to the extent that was observed with Fentanyl group at all intervals.Fentanyl attenuates mean DBP more significantly than Esmolol in subsequent minutes.
- 5) Maximum attenuation of mean MAP occur in Esmolol group at first minute after laryngoscopy and intubation than in Fentanyl group.
- 6) Esmolol has proved to be better in achieving a low RPP, which is a good predictor of myocardial oxygen consumption(MVO2).
- 7) Esmolol provides better cardio-protection in patients against hyperadrenergic responses to laryngoscopy and endotracheal intubation as evidenced by lower values in Rate Pressure Product. Esmolol appears to be drug of choice in maintaining hemodynamic stability during laryngoscopy and intubation.
- 8) The doses of esmolol and fentanyl used in our study did not show any adverse effects such as bradycardia, hypotension in esmolol group and allergic urticaria, muscular rigidity, nausea, vomiting & respiratory depression in Fentanyl group.

Thus, from our study we conclude that in patients with ASA grade I and II, intravenous bolus dose of Esmolol (2mg/kg) and Fentanyl(2mcg/kg) given 3 minute prior to laryngoscopy and intubation is safe and effective prophylactic method for attenuating hemodynamic response to laryngoscopy and intubation. Esmolol provides reliable and consistent protection against rise in pulse rate, systolic blood pressure and rate pressure product. Maximum attenuation in mean arterial pressure by esmolol is at 1 minute only by esmolol. Esmolol does not attenuates diastolic blood pressure as compared to fentanyl at all interval. Hence, esmolol is a useful adjunct to our therapeutic armamentarium.

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# 9. Recommendation

From our study we found that in patients with ASA grade I and II, intravenous bolus dose of Esmolol (2mg/kg) IV and Fentanyl(2mcg/kg) IV given 3 minute prior to laryngoscopy and intubation is safe and effective prophylactic method for attenuating hemodynamic response to laryngoscopy and intubation. But Esmolol provides reliable and consistent protection against rise in pulse rate, systolic blood pressure and rate pressure product. We are recommending this study because:-

- Esmolol causes significant reduction in tachycardia and hypertension post intubation.
- No respiratory depression.
- Elimination half life was only 9 minutes.
- Esmolol does not cause amnesia and sedation.
- Esmolol did not potentiate the action of non-depolarizing muscle relaxant.
- Minimal drug interaction.
- Fentanyl has abuse potential and should be used with caution in chronic users for risk of tolerance and withdrawal.

As Esmolol is cardio-selective drug, the side effect like bronchospasm , bradycardia and hypotension are observed only with very large dose. Which are not used in our study.

# 10. Limitation

- Varying degree of resting sympathetic tone of patients can cause interference with the readings.
- ASA gradeIII and IV patients especially with IHD,MI, HTN were not included in study.
- As our sample size is only of 100 patients, so this study cannot be generalized to all ASA I and II patients and further studies with larger sample size is needed.
- Infusion of study drugs after bolus might have yielded better results than single bolus dose of study drugs. Which require more studies in future.
- Influence of premedication with glycopyrrolate, which cause tachycardia and midazolam cause decrease in mean arterial pressure. Which may interferes with the readings.
- Succinylcholine used in our study as muscle relaxant can cause bradycardia occasionally in some patients which can interfere with the readings.
- Other variables reflecting the contractile state of the heart and ventricular volume may further improve the predictability of myocardial oxygen consumption.

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ANNEXURE – I Institutional Ethics Committee Letter



# Datta Meghe Institute Of Medical Sciences

(Deemed University)

(Established under Siction 3 of The UGC Act 1956 vide Notification No F-9-48/2004 - U 3 Govt of India)

NAAC Accredited Grade 'A'

# INSTITUTIONAL ETHICS COMMITTEE

Regd. Office : Atrey Layout, Pratap Nagar, NAGPUR -4420 22, Maharashtra (India) Ph-0712-325652/3253764 Fax-07152-2245318-E-mail-info@dmims.org website-dmims.org Comp Office : Sawangi (Meghe), Wardha - 442 064, Maharashtra (India), Ph-07152-287701,287702,287703, Fax- 07152-287714, E-mail-info@dmims.org

Ref.No. DMIMS(DU)/IEC/2014-15/786

Date: 22/09/2014

The Institutional Ethics Committee in its meeting held on 20.09.2014 has approved the following research work proposed to be carried out at Jawaharlal Nehru Medical College & A.V.B.R.Hospital, Sawangi (Meghe), Wardha.

This approval has been granted on the assumption that the proposed work will be carried out in accordance with the ethical guidelines prescribed by Central Ethics Committee on Human Research (C.E.C.H.R.)

The details of the proposed research work approved by the committee are as under:-

| Sr.<br>No. | Research worker<br>(Guide/Supervision)  | Category               | Topic of the proposed research   |
|------------|---|------------------------|--|
| 1.         | Dr. Devavrat Vaishnav<br>(Dr. A.R. Chaudhari)<br>Dept. of Anaesthesiology<br>JNMC | Postgraduate<br>Thesis | Attenuation of cardiovascular responses to<br>Laryngoscopy and Intubation: A comparative<br>study between LV. Esmolol Hydrochloride<br>and Fentanyl Citrate. |

2 m

(Dr.A.J.Anjankar) Secretary Institutional Ethics Committee D.M.I.M.S. (D.U.)

Copy to :-

- 1. Dr. Devavrat Vaishnav, Dept. of Anaesthesiology
- 2. HOD, Anaesthesiology, JNMC

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#### ANNEXURE – II PROFORMA

- ➢ Bio data:
  - IPD No.: Diagnosis: Age & Sex: Weight:

Surgery: ASA Grading:

Date of operation:Preoperative assessment:

# History:

Chief complaints.

| ≻ | Past H/o | Major disease |
|---|----------|---------------|
|   |          | Operation     |
|   |          | Anaesthesia   |
|   |          | Drug allergy  |

- Family History

#### General examination:

- Level of consciousness.
- Built/nourishment
- Pallor/clubbing/cyanosis/jaundice/oedema
- Teeth, mouth opening, spine

#### Vital data:

- ➢ Temperature
- Pulse rate, rhythm, volume
- Blood pressure
- Respiratory rate and pattern

# Airway assessment:

Mouth opening Neck movement, Teeth. Airway gradation (according to Malampatti classification)

# Systemic examination:

- Respiratory system
- Cardiovascular system
- Central nervous system
- Alimentary system

#### **Routine investigation:**

| $\triangleright$ | Haemogram   | ECG RBS       |
|------------------|-------------|---------------|
|                  | Blood urea, | S. creatinine |

S. electrolytes X ray chest (PA) view

#### ANNEXURE III

#### **Observation sheet:**

| Recording                      | PR (Beats / min) | SBP(mmHg) | DBP(mmHg) | MAP(mm Hg) | RPP |
|--------------------------------|------------------|-----------|-----------|------------|-----|
| Baseline value                 |                  |           |           |            |     |
| After study drug               |                  |           |           |            |     |
| At laryngoscopy and intubation |                  |           |           |            |     |
| 1 min after intubation         |                  |           |           |            |     |
| 2 min after intubation         |                  |           |           |            |     |
| 3 min after intubation         |                  |           |           |            |     |
| 4 min after intubation         |                  |           |           |            |     |
| 5 min after intubation         |                  |           |           |            |     |
| 10 min after intubation        |                  |           |           |            |     |

#### (A) Basal value

On the day of surgery inside operation theater before study drug and induction of anesthesia on operation theater table. **Complications:** 

#### <u>Remarks:</u>

# ANNEXURE – IV

# JAWAHARLAL NEHRU MEDICAL COLLEGE DEPARTMENT OF ANAESTHESIOLOGY

#### CONSENT FORM

I Mr/ Mrs. \_\_\_\_\_\_, age \_\_\_\_\_ years residing at \_\_\_\_\_\_ hereby give my informed consent to participate in the "Attenuation of cadiovascular responses to laryngoscopy and intubation: A comparative study between IV Esmolol Hydrochloride and Fentanyl Citrate"

1. There is no compulsion on me to participate in this project and I am giving my consent for it.

2. I am ready and willing to undergo all tests in the present study.

3. I have read and I have been explained the general information and purpose of the present study.

4. I have been informed the probable complications while participating in the present study.

5. I know that I can withdraw from the present study at any time.

6. Any data or analysis of this project will be purely used for scientific purpose and my name will be kept confidential except when required for any legal purpose.

7. I have been explained all the procedures in the language I best understood.

# भूलतंत्रविभागसंमतीपत्र

मीश्री / श्रीमती \_\_\_\_\_\_, वय \_\_\_\_\_\_वर्षे, रा. \_\_\_\_\_\_ याद्वारे "Attenuation of cadiovascular responses to laryngoscopy and intubation: A comparative study between IV Esmolol Hydrochloride and Fentanyl Citrate"यासंशोधनातसहभागीहोण्यासाठीमाझीमाहितीपूर्णसंमतीदेतआहे.

- याप्रकल्पातसहभागीमलासक्तीनाहीआहेआणिमीसंमतीदेतआहे.
- मीयासंशोधनाकरिताआवश्यकअसलेल्यासर्वचाचण्याकरण्यासंतयारआहे
- यासंशोधनाबद्दलमीवाचलेलीआहेतसेचमलासर्वमाहितीवउद्देशसमजावूनसांगण्यातआलीआहे
- यासंशोधनातहोऊशकणार्यासंभावितधोक्याबद्दलमलासांगण्यातआलेलेआहे.
- मीकोणत्याहीवेळीयासंशोधनातूनबाहेरपडुशकतेयाचीमलामाहितीदेण्यातआलीआहे
- हाप्रकल्पकोणत्याहीडेटार्किवाविंश्लेषणनिव्वळवैज्ञानिककारणासाठीवापरलेजाईलआणिमाझेनावकोणत्याहीकायदेशीरप्रयोजनार्थ आवश्यकतेव्हावगळतागोपनीयठेवलीजाईल.
- संशोधनाचीसर्वप्रक्रीयामलासमजणाऱ्याभाषेतमलासमजावूनसांगितलीआहे.

सहभागीचीस्वाक्षरी: Signature of Participant: संशोधकाचीस्वाक्षरी Signature of Investigat

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# Abbreviations

| %                     | Percentage                                 |
|-----------------------|--|
| &                     | And  |
| mcg or <i>µg</i>      | Microgram                                  |
| ASA                   | American society of Anesthesiologist       |
| BP                    | Blood pressure                             |
| SBP                   | Systolic blood pressure                    |
| DBP                   | Diastolic blood pressure                   |
| MAP                   | Mean arterial pressure                     |
| PR                    | Pulse rate                                 |
| RPP                   | Rate Pressure Product                      |
| BV                    | Baseline Value                             |
| AS                    | After study drug                           |
| ALI                   | At laryngoscopy and intubation             |
| ET1                   | After intubation at 1 minute               |
| ET2                   | After intubation at 2 minute               |
| ET3                   | After intubation at 3 minute               |
| ET4                   | After intubation at 4 minute               |
| ET5                   | After intubation at 5 minute               |
| ET10                  | After intubation at 10 minute              |
| HR                    | Heart rate                                 |
| ECG                   | Electrocardiogram                          |
| IV                    | Intravenous                                |
| IHD                   | Ischemic heart disease                     |
| INJ                   | Injection                                  |
| IPPV                  | Intermittent positive pressure ventilation |
| Kg                    | Kilograms                                  |
| Lap                   | Laproscopy                                 |
| Lit                   | liters                                     |
| Mg                    | Milligrams                                 |
| MĬ                    | Myocardial infarction                      |
| Min                   | Minute                                     |
| $N_2 O$               | Nitrous oxide                              |
| <b>O</b> <sub>2</sub> | Oxygen                                     |
| RS                    | Respiratory system                         |
| CVS                   | Cardiovascualr system                      |
| CNS                   | Central Nervous system                     |
| P/A                   | Per Abdomen                                |
| RBS                   | Random Blood sugar                         |
| RR                    | Respiratory rate                           |
| S.Creat               | Serum creatnine                            |
| S.Elec                | Serum Electrolyte                          |
| Sec                   | Seconds                                    |
| SpO <sub>2</sub>      | Hemoglobin saturation pulse oximetery      |
|                       |  |