COMPARISON OF DIFFERENT DOSAGES OF FENTANYL WHEN ETOMIDATE IS USED AS INDUCTION AGENT

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BRANCH X (ANAESTHESIOLOGY)

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CHENNAI, TAMIL NADU

BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled "**COMPARISON OF DIFFERENT DOSAGES OF FENTANYL WHEN ETOMIDATE IS USED AS INDUCTION AGENT**" submitted by **DR.K.VASANTH** to the FACULTY OF ANAESTHESIOLOGY, THE TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY, CHENNAI, in partial fulfillment of the requirement in the award of the degree of M.D., Branch X (ANAESTHESIOLOGY) for the April 2017 examination is a bonafide research work carried out by him under my direct supervision and guidance.

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DECLARATION

I, **DR.K.VASANTH** declare that the dissertation titled "**COMPARISON OF DIFFERENT DOSAGES OF FENTANYL WHEN ETOMIDATE IS USED AS INDUCTION AGENT**" has been prepared by me. This is submitted to the Tamil Nadu Dr. M.G.R Medical University, Chennai, in partial fulfillment of the requirement for the award of M.D. Degree Branch X (Anaesthesiology) Examination to be held in April 2017. I also declare that this dissertation, in part or full was not submitted by me or any other to any other university or board, either in India or abroad for any award, degree or diploma

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CONTENTS

INTRODUCTION

Etomidate is a carboxylated, imidazole containing compound. Its mechanism of action is through GABA-A receptor which is by enhancing the affinity of GABA for these receptors. It is a rapidly acting induction agent and it has little effect on cardiovascular system and it allows rapid recovery from anaesthesia. But in spite of these good properties, etomidate has some side effects which is partly related to inhibition of adrenal synthesis of cortisone. Most prominent side effects are

a) Pain on injection

b) Myoclonus

c) Post operative nausea and vomiting

The main advantage of etomidate is that it does not cause significant alterations in systolic, diastolic, and mean arterial pressures, heart rate, right atrial pressure, pulmonary and systemic vascular resistance, stroke volume, cardiac- index, systemic blood flow, and shunt flow in pediatric patients undergoing cardiac surgery and in adults.

In spite of the above advantages, etomidate does not have analgesic properties because of which laryngoscopy and tracheal intubation usually results in increase in heart rate and systemic blood pressure.

So, in order to avoid this, pretreatment with narcotic analgesics usually fentanyl can decrease the incidence of pain on injection and myoclonus during induction of anaesthesia with etomidate and also attenuates the stress response to endotracheal intubation.

Fentanyl is a phenyl-piperidine derivative synthetic opioid agonist. It has a more rapid onset and shorter duration of action. It can blunt the circulatory responses to direct laryngoscopy for endotracheal intubation.

Higher doses of fentanyl has the advantage of stable hemodynamics mainly due to

a) Lack of direct myocardial depressant effects

b) Absence of histamine release

c) Suppression of stress response to surgery

The object of this study is to determine whether there is an optimal dose of fentanyl which attenuates the hemodynamic changes and side effects of etomidate during induction and intubation without introducing other problems.

AIM OF THE STUDY

The objective was to find an optimal pre induction dose of fentanyl with etomidate as induction agent which attenuates the haemodynamic changes and side-effects during induction and intubation

ANATOMY AND PHYSIOLOGY OF THE AIRWAY REFLEXES

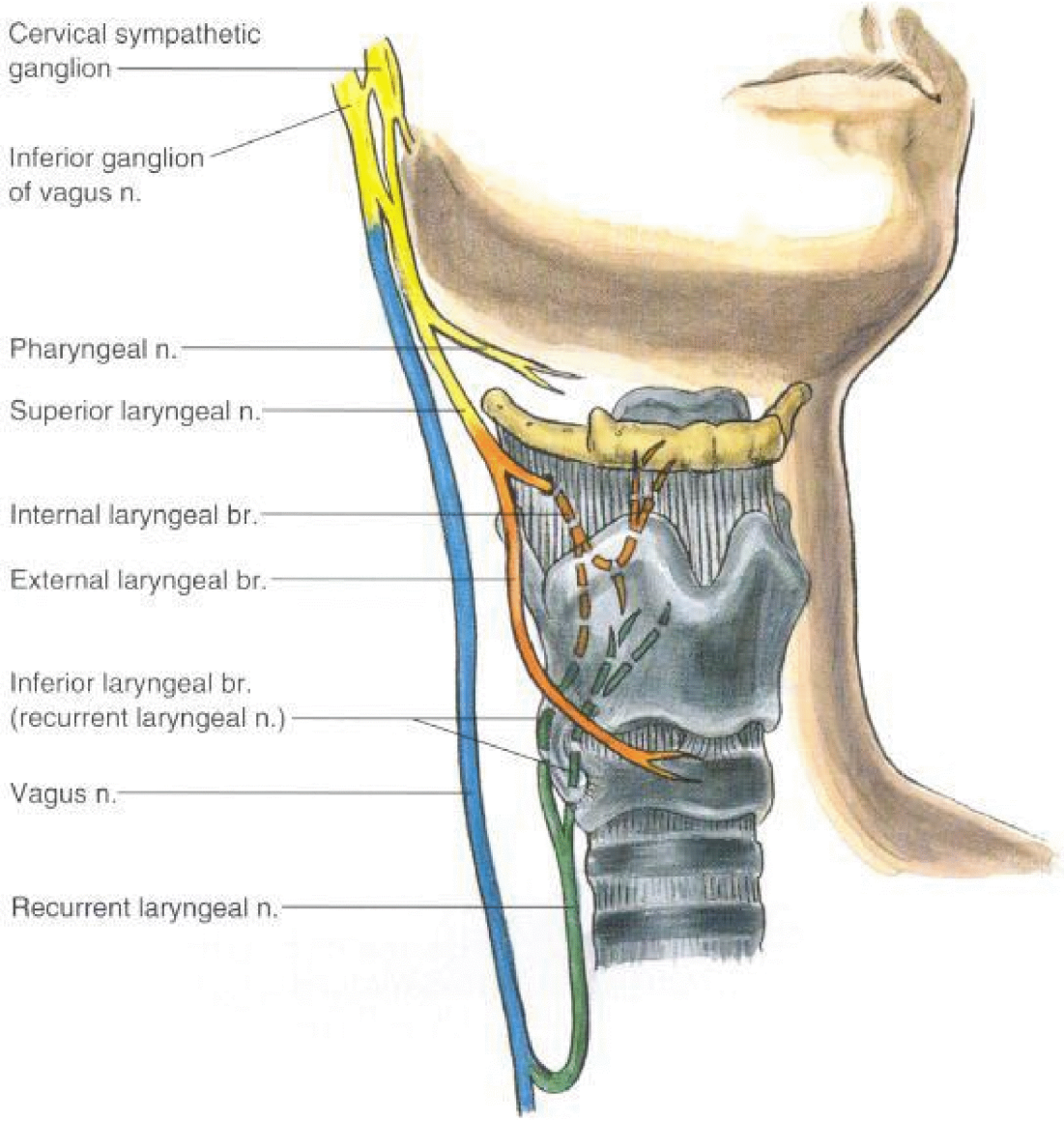
Introduction:

Laryngoscopy, Endotracheal intubation and any airway manipulations like placement of LMA or oropharyngeal airway are stimuli which may induce drastic changes in physiology of cardiovascular system through the airway reflexes. But these changes are of short duration and usually won't cause complications in healthy individuals. But these changes are serious in patients with reactive airways, coronary artery disease, neurosurgery patients.

Anatomy of the airway:

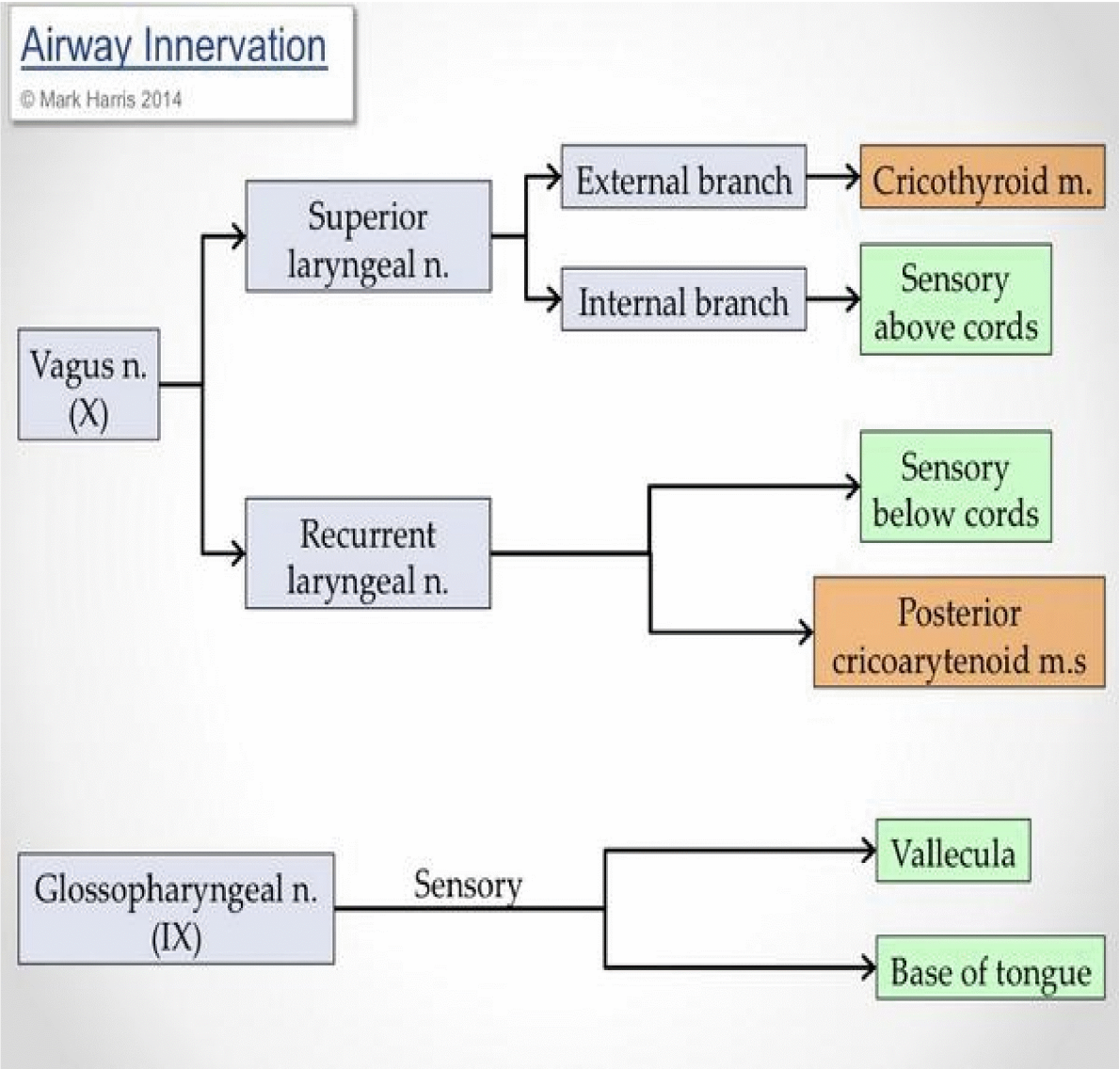
The upper airway lies from nares and mouth to the glottis. Cricoid cartilage is the landmark between the upper and lower respiratory tract.

Nerve supply of the airway:



This figure shows the course of Superior laryngeal nerve and recurrent laryngeal nerve.

Airway innervation:



Oral cavity is innervated by the branches of trigeminal, facial, glossopharyngeal and hypoglossal nerve. Nasal cavity is innervated by anterior and posterior ethmoidal nerves. It is also supplied by anterior-superior alveolar branch and infra orbital branch of maxillary nerve.

Glossopharyngeal Nerve:

Glossopharyngeal nerve supplies base of the tongue, upper part of epiglottis and pharyngeal wall. Superior laryngeal nerve supplies lower part of the epiglottis and supra glottic parts of the pharynx.

The larynx mucous membrane receives its nerve supply from the superior and recurrent laryngeal nerves.

Superior laryngeal nerve:

The superior laryngeal nerve arises from inferior ganglion of vagus but receives a small branch from the superior sympathetic ganglion. At the level of greater horn of hyoid it divides into an internal and external branch.

The internal branch is purely sensory. The upper branch supplies the mucous membrane of the lower part of the pharynx, epiglottis, vallecula and vestibule of the larynx. The lower branch supplies the aryepiglottic fold and mucous membrane of the posterior part of rima glottidis. The lower part of the larynx below the vocal cords is supplied by the recurrent laryngeal nerve. The external branch of superior laryngeal nerve supplies the cricothyroid muscle and all the rest of the muscles of larynx are supplied by recurrent laryngeal nerve.

Physiology of the airway reflexes:

Pharynx lower part, epiglottis and larynx contain numerous sensory receptors which respond to chemical, thermal and mechanical stimuli. The mechanoreceptors are rich in the lower pharynx, epiglottis and vocal cords areas.

Stimulation of these receptors will produce reflex responses like cough, hiccupp, reflex sympathetic stimulation and cardiovascular pressor response.

The sensory unit consists of free nerve endings which lies between the mucosal cells of airway epithelium. Sensory units seems to be particularly more over the arytenoids cartilages and they are also found on the laryngeal side of epiglottis.

The superior laryngeal nerve carries large amount of small diameter myelinated fibres (group III, A-delta, B sensory fibres) which carry afferent impulses.

The recurrent laryngeal nerve carries sensory fibres from rapidly adapting receptors which are activated by light touch. These receptors are more on the inferior surface of vocal cords.

Afferent fibres in the laryngeal nerves lies centrally in the nucleus tractus solitaries, in particularly posterior and caudal parts. The central reflex site lies in medulla. The nucleus tractus solitarius terminate closely with the vasomotor centre.

Sympathetic activity originates in the reticular formation of the lower pons and upper part of medulla which are represented bilaterally. Together these two areas are referred as **vasomotor centre**. The vasomotor centre neurons are under continuous influence of afferent impulses that originates from mechanoreceptors located in the heart, arteries and lungs.

Every efferent sympathetic route is made of a pre-ganglionic neuron. The pre-ganglionic neurons of cell bodies lie within the thoracic, upper lumbar spinal cord. These fibres pass from the spinal cord via anterior routes of each spinal nerve and then via the white ramus to synapse with post ganglionic cell bodies located within the ganglia of the sympathetic chains.

From these ganglia sympathetic post ganglionic fibers pass to effector organs. T8 to T12 pre-ganglionic fibers synapse with adrenal medulla. Stimulation of these receptors can cause release of

catecholamines into the circulation through adrenal medulla leading to pressor response of intubation.

Cardiovascular response to intubation:

In infants, bradycardia and laryngospasm are mainly seen because of the predominant vagal tone in pediatric age group.

In case of adolescents and adults, the predominant response to manipulation of airway is Hypertension and tachycardia which is mediated mainly by the sympathetic chain ganglia and the cardioaccelerator nerves.

Also there is increase in cerebral blood flow and increase in cerebral metabolic rate leading to increase in intracranial pressure

Mediators of cardiovascular response:

a) Secretion of epinephrine from adrenal medulla

b) Release of norepinephrine from adrenergic nerve terminals

c) Activation of Renin-Angiotensin system

Attenuation of Cardiovascular responses:

A) Technical considerations:

- Gentle cricoid pressure
- Laryngoscopy using Macintosh or McCoy blade compared to Miller blade cause less response
- Insertion of LMA compared to ETT cause less hemodynamic disturbance

B) Topical Anaesthesia:

- Topical laryngotracheal spray with lidocaine
- Regional nerve blocks of superior laryngeal nerve, glossopharyngeal nerve and transtracheal blocks

C) Inhalational Anaesthetics:

- Inhalation agents at 1.5 to 1.6 MAC suppress the hemodynamic response to intubation.

D) Intravenous agents:

- Opioids- Fentanyl (2-10µg/kg), alfentanil (150 µg/kg, remifentanil (1 µg/kg)

- Lidocaine (1.5 µg/kg)
- Esmolol (1 mg/kg)
- Nitrolycerine
- Sodium Nitroprusside
- Labetalol
- Clonidine
- Dexmedetomidine
- Hydralazine
- Calcium channel blocker

AIRWAY EFFECTS OF ENDOTRACHEAL INTUBATION

A. Upper Airway Reflexes

It is the upper airway that protects the respiratory gas exchange surface from noxious substances, it is appropriate to say that the nose, mouth, pharynx, larynx, trachea, and carina has lots of sensory nerve endings and reflex motor responses. We, anaesthesiologists are especially familiar with the glottic closure reflex (laryngospasm), which is often encountered. The cough, sneeze and swallow reflexes are also other important upper airway reflexes.

Afferent pathways for laryngospasm and the hemodynamic responses to laryngoscopy and endotracheal intubation are initiated by the glossopharyngeal nerve when the stimulation is superior to the anterior surface of the epiglottis while it is initiated by the vagus nerve when the stimulation occurs from the level of posterior epiglottis down into the lower airway.

As the laryngeal closure reflex is mediated by vagal efferents to the glottis, it is a monosynaptic response, occurring mostly when a patient is not in deeper plane of anaesthesia as vagally innervated sensory endings in the airway are stimulated and conscious respiratory efforts by the patient cannot override the reflex.

B. Dead Space

Patients with already severe lung disease may find it easier to breathe after intubation or a tracheostomy. The most possible explanation is due to reduced dead space.

The normal anatomic dead space in the extrathoracic space, based on measurements from cadaver, is between 70 and 75 ml.

The exact volume (V) of the ETT is calculated as that of a volume of a cylinder using the formula V = r*2*l, where *r* is the radius of the tube and *l* is the length of tube.

For example, an ETT with a 8-mm inner diameter (ID) and a length of 25 cm, has a volume of 12.6 ml. Therefore intubation results in a reduction in dead space of approximately 60 ml.

Tracheostomy tubes which are shorter than oral ETTs have an even smaller dead space. In normal individuals, this reduction in dead space because of insertion of a tracheostomy tube is negligible compared with the normal tidal volume, so there is little benefit.

In a patient with severe restrictive lung disease, tidal volume may be as low as 100 ml and hence intubation confers a major benefit.

Similarly, in patients with emphysema who are changed from manual breathing to tracheostomy tube showed a reduction in minute

volume required and a decrease in total body O2 consumption, most probably due to a decreased work of breathing. The decreased minute volume required compensates for the slight increase in resistance.

C. Airway Resistance

We, anaesthesiologists are well aware that in most of the patients, adequate ventilation can be done with an ETT as small as 6 mm ID in place. While intensivists who look after a patient with respiratory failure in ICU insist that the ETT must have a minimum ID of 8 mm. The size of the ETT are each appropriate for the specific clinical situation.

The high resistance of the 6 mm ETT is of less importance for the low minute ventilation which is required under general anaesthesia, but if high flow rates are required for a patient with respiratory failure, the resistance of a small ETT will be prohibitive.

The ETT is a mechanical burden for a spontaneously breathing patient because of the fixed upper airway resistance which means that it decreases calibre of airway and increases resistance to breathing.

The gas flow across an ETT depends on the pressure difference across the tube and the resistance of the ETT. Gas flows because of the

pressure difference across the ETT, which is caused by atmospheric pressure in case of spontaneous breathing or by the positive pressure created from a mechanical ventilator.

Prevention of Airway reflexes:

The airway reflexes like laryngospasm and bronchospasm can be prevented by

- Technical considerations
- Topical anaesthesia
- Regional nerve blocks
- Intravenous agents
- Inhalation agents
- Choice of neuromuscular blocking drugs

Technical considerations:

Minimising the airway stimulation by using appropriate size blade. Mccoy blades are found to be better when compared to curved Macintosh blades. Insertion of LMA is also considered as a highly stimulant procedure. Appropriate dosage of propofol prior to LMA insertion can suppress the reflex laryngospasm.

Topical Anaesthesia:

It is a good practice to administer antisialogogue 30 to 60 minutes prior to induction. This will dry up the secretions and will help in preventing the laryngospasm.

Using lignocaine spray prior to intubation also helps in preventing the laryngospasm.

Inflating the cuff with 5ml of 1% lignocaine, 1ml of 8.4% sodium bicarbonate and 5ml of sterile water helps in preventing the airway reflexes.

Regional Anaesthesia:

Regional nerve blocks helps in preventing the airway reflexes to intubation. The nerves that are blocked are

- Superior Laryngeal nerve
- Glossopharyngeal nerve
- Transtracheal block

Intravenous agents:

- I.V Lidocaine 1.5mg/kg suppresses airway reflexes to intubation like cough and laryngospasm.
- Propofol in doses of 2.5mg/kg suppresses airway reflexes and facilitates LMA insertion.
- Propofol helps in achieving deeper planes of anaesthesia thereby preventing the airway reflexes

Inhalation agents:

- Inhaled β2-agonists
- Inhaled anticholinergics

  Both can be given 30 to 60 minutes prior to induction helps in bronchodilation and preventing bronchospasm.
- Sevoflurane is the inhalation agent of choice

Choice of neuromuscular blocking drugs:

It is better to use neuromuscular blocking drugs which won't cause release of histamine as it may provocate bronchospasm.

Therefore neuromuscular blocking drugs like atracurium, mivacurium are better avoided.

OPIOIDS

Introduction:

Opioids have become the mainstay of pain management in the perioperative period. Opium poppy or papaver somniferum is the source of 20 different types of alkaloids. The word "opium" is derived from the greek word "opion" (Poppy juice). The drugs derived from the opium are termed as "opiates". Opioids are significant in producing analgesia without loss of consciousness, touch (or) proprioception.

History:

The medicinal use of poppy juice has been mentioned in the religious books as early as 300BC. The first known opiate – Morphine was isolated in 1803. Then codeine was isolated in 1832 and then papaverine in 1848.

Definition:

Opioids are defined as a group of exogenous substances (either natural or synthetic) which binds specifically to any of the opioid receptors and should produce atleast some morphine like effects.

Classification:

1) Semisynthetic opioids

2) Synthetic opioids

Semisynthetic opioids:

These are produced by modification of the morphine molecule. For example

1) Methylmorphine (codeine)

2) Diacetylmorphine(Heroin)

3) Thebaine

Synthetic Opioids:

These are produced by synthesis and not by chemical modification of morphine. These opioids have the phenanthrene nucleus which is present in morphine. For example

1) Morphine derivatives (Levorphanol)
2) Methadone derivatives
3) Benzomorphan derivatives (Pentazocaine)
4) Phenylpiperidine derivatives (Fentanyl)

Endogenous opioids:

The endogenous opioids are

1) Endorphins
2) Dynorphins
3) Enkephalins

Opioid receptors:

1) Mu receptor

2) Kappa receptor

3) Delta receptor

All the opioid receptors are G-protein coupled receptors. The opioid receptors are located in various regions of brain like locus ceruleus, ventral medulla and periqueductal gray matter. They are also located in the interneurons and in the dorsal horn of spinal cord. Apart from the CNS they are also located in sensory neurons and immune cells.

Mechanism of action:

The opioid should be in ionised state for binding to the opioid receptor. The levorotatory forms of the opioids alone exhibit agonistic activity. The main effect of the opioids is decreasing the neurotransmitter release. This occurs mainly by the inhibition of presynaptic release of neurotransmitters like acetylcholine, norepinephrine, substance P, dopamine.

The opioid on binding to opioid receptor (G-protein coupled receptor) causes inhibition of adenylate cyclase, increase in potassium conduction which causes hyperpolarisation, inactivates the calcium channel which causes a decrease in neurotransmitter release. They can also modify the phosphoinositol cascade and also the phospholipase-C.

Effects of the opioid receptors:

1) Mu1 – Euphoria, Analgesia(spinal, supraspinal), miosis, bradycardia, hypothermia, urinary retention
2) Mu2 - Analgesia(spinal), physical dependence, constipation, depression of ventilation
3) Kappa - Analgesia(spinal, supraspinal), miosis, dysphoria, sedation, diuresis
4) Delta - Analgesia(spinal), physical dependence, constipation, depression of ventilation

Classification of opioid agonists and antagonists:

The opioids are classified as follows

Classification of OPIOIDS

- **Strong agonist:**
  - Phenanthrenes: morphine, hydromorphone, oxymorphone, heroin
  - Phenylheptylamines: methadone, levomethadyl
  - Phenylpiperidines: meperidine, fentanyl, sufentanyl, alfentanyl, remifetanyl
  - Morphinans: levorphanol
- **Mild to moderate agonists:**
  - Phenanthrenes: codeine, oxycodone, dihydrocodeine, hydrocodone
  - Phenylheptylamines: propexyphene
  - Phenylpiperidines: diphenoxylate, difenoxine, loperamide
- **Mixed receptor action:**
  - Phenanthrenes: nalbuphine, bupronorphine
  - Morphinans: butorphanol
  - Benzomorphanes: pentazocine, dezocine
- **Miscellaneous:**
  - tramadol
- **Opioids antagonists:**
  - naloxone, naltrexone, nalmefene

Fentanyl

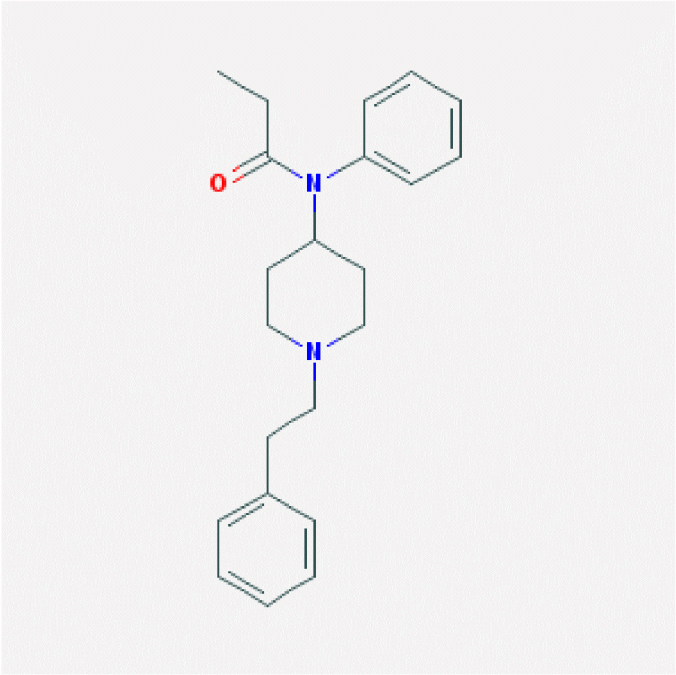
Introduction:

Fentanyl is a synthetic opioid and it is an opioid agonist. It is a phenylpiperidine derivative and it is structurally related to meperidine. Fentanyl was first produced by Janssen pharmaceutica in 1960 when they were doing an assay of the derivatives of meperidine. It was released with the trade name "Sublimaze" as a salt of citrate.

Pharmacokinetics:

Fentanyl has a rapid onset of action and also a shorter duration of action when compared to morphine. Fentanyl is about 75 to 125 times more potent than morphine. The effect site equilibration time between the blood and brain is 6.4 minutes. It has a greater lipid solubility. The 75% of the initial dose of fentanyl undergoes first pass pulmonary uptake. This forms a large inactive storage site of fentanyl.

Chemical Structure:



Metabolism:

Fentanyl is mainly metabolised by N- Demethylation. This produces norfentanyl, hydroxyl-propionyl-fentanyl and hydroxyl-propionyl-norfentanyl. Norfentanyl is the main metabolite and it has structural similarity to normeperidine. This is mainly excreted by the kidneys.

Elimination half time:

Fentanyl rapidly distributes from plasma to highly vascular tissues such as brain, heart and lungs. Also the greater lipid solubility of fentanyl is a factor for its larger Vd. So fentanyl has a longer elimination half life compared to morphine.

Clinical Uses:

- Analgesia (1-2 µg/kg IV)
- Blunting the hemodynamic response to direct laryngoscopy and surgical stimulus (2-20 µg/kg IV)
- Intrathecal fentanyl – rapid and profound analgesia
- Induction agent for cardiac surgeries(50-150 µg/kg IV)
- Transmucosal fentanyl for alleviating preoperative anxiety in children (5-20 µg/kg IV)
- Transdermal fentanyl patches for cancer related chronic pain

Effects on various systems:

Cardiovascular system:

- No direct myocardial depressant effect

- No histamine release
- Causes depression of carotid sinus baroreceptor reflex causing bradycardia

Respiratory system:

- Causes gender specific and dose dependent depression of ventilation because of their action at mu2 receptors and causing direct depressant effect on the ventilation centres in the brain stem
- This depression of ventilation is independent of the level of PaCO2.
- Also it causes provocation of cough reflex because of imbalance between the parasympathetic (vagal) and sympathetic innervation of airways (or) because of the stimulation of juxtacapillary irritant receptors.
- Rapid injection of large dose of fentanyl is associated with generalised skeletal muscle rigidity or chest wall rigidity. This is because of the inhibition of release of GABA from corpus striatum and increased production of dopamine

- Decreases the MAC and the requirement of volatile anaesthetics.

Central Nervous System:

- Causes modest increase in ICP despite the normal level of PaCO2
- Causes miosis due to its excitatory action on the autonomic nervous system component of the Edinger-Westphal nucleus of the oculomotor nerve.
- Seizure like activity following rapid i.v bolus which is not accompanied by EEG changes.
- Causes changes in the Somatosensory evoked potentials.

Gastrointestinal system:

- Causes spasm of the smooth muscles of GIT leading to delayed gastric emptying, constipation
- Also causes spasm of the smooth muscles of biliary tract leading to biliary colic.
- Causes nausea and vomiting because of its direct stimulation in the chemoreceptor trigger zone.

Placental transfer:

- Immediately transported across the placenta and causes neonatal depression.
- But the neonatal depression is very less when compared to morphine.

Hormonal changes:

- Prolonged administration of opioids causes modulation of Hypothalamo-pituitary-gonadal axis and Hypothalamo-pituitary-adrenal axis.
- Causes decreased estrogen,testosterone,FSH,LH and increases prolactin concentration.
- Also it may affect the cortisol concentration in the plasma.

Drug interactions:

- Depression of ventilation is exacerbated by Benzodiazepines, phenothiazines, amphetamines, monoamine-oxidase inhibitors, tricyclic antidepressants
- Potentiates the effect of benzodiazepines

- Decreases the requirement of propofol

Side Effects:

- Depression of ventilation
- Bradycardia
- Seizure like activity or myoclonus
- Chest wall rigidity
- Increase in ICP
- Fentanyl induced Cough
- Biliary colic
- Constipation
- Nausea and vomiting
- Miosis
- Placental transfer and neonatal depression
- Overdose- Triad of Miosis, Hypoventilation, Coma
- Pruritus, urinary retention with neuraxial opioids
- Physical dependence

Etomidate

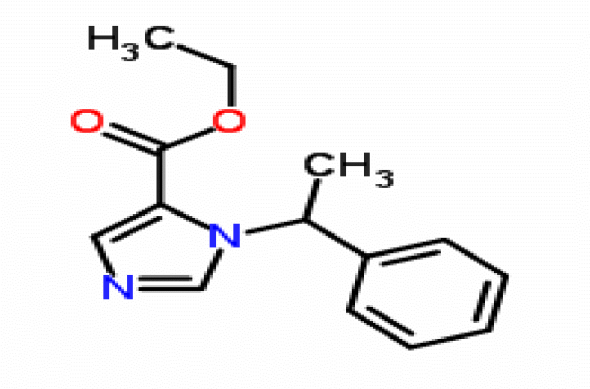
Introduction:

Etomidate is a carboxylated imidazole compound which is chemically different from other drug used for induction. Etomidate imidazole nucleus makes it water soluble at acidic pH and lipid soluble at physiologic pH similar to midazolam.

Etomidate original formulation contains 35% propylene glycol (pH 6.9). It is the reason for higher incidence of pain during IV injection and sometime venous irritation.

Adding fat emulsion to this formulation successfully eliminates pain on injection and irritation of veins, where as the incidence of myoclonus does not change. Etomidate oral formulation through transmucosal route provides dose-dependent sedation. This Oral formulation bypasses hepatic metabolism and results in direct systemic absorption .This makes higher level of blood concentrations to reach more rapidly.

Chemical Structure:



Mechanism of Action:

Etomidate is unique among both the injected and inhaled anaesthetics as it is being administered as a single isomer. The anaesthetic effect of etomidate resides predominantly in the R(+) isomer and it is roughly five times more potent than s(-) isomer.

Etomidate seems to be relatively selective modulator of GABA-A receptors which is contrast to barbiturates. The stereoselectivity of etomidate makes that the site of action of etomidate is mainly GABA-A receptors. Etomidate acts through binding directly to GABA-A receptors at specific site or sites on the protein and through increasing the affinity of GABA inhibitory neurotransmitter for these receptors.

Antagonism of steroid-induced psychosis by etomidate is consistent with enhancement of GABA receptor function by this anaesthetic drug. Other ligand-gated ion channels are not modulated by etomidate at level of therapeutic concentrations.

Pharmacokinetics:

The larger volume of distribution (Vd) of this drug makes more tissue uptake. Its lipid solubility and its weak base property (pH 8.2), makes 99% of the drug unionized at physiologic pH and this makes distribution of etomidate through body water more favourable.

Etomidate reaches peak levels within 1 minute after IV injection because of rapid penetration through brain. Nearly 76% of etomidate is albumin bound and is independant of the plasma concentration of the drug. So dramatic increases in the unbound active fraction of etomidate in the plasma if abrupt decreases in plasma concentrations.

Redistribution of the drug from brain to inactive tissue sites thought to be prompt awakening from single induction dose of etomidate. Rapid metabolism is also likely to contribute to prompt recovery.

Metabolism:

Ethyl ester side chain rapidly hydrolysed to its carboxylic acid ester, resulting in a, pharmacologically inactive water soluble compound. This hydrolysis is done by hepatic microsomal enzymes and plasma esterases.

Hydrolysis is confirmed by evidence of <3% of a total dose of etomidate excreted as unchanged drug in urine. Only 10% to 13% is present as this metabolite in the bile.

Overall, the clearance of etomidate is about five times faster than that for thiopental. This is reflected as a shorter elimination half-time of 2 to 5 hours. Likewise, the context-sensitive half-time of etomidate is less likely to be increased by continuous infusion as compared with thiopental.

Cardiopulmonary Bypass:

Institution of hypothermic cardiopulmonary bypass causes an initial decrease of about 34% in the plasma etomidate concentration. Then it returns to within 11% of the prebypass value. This is followed by a further decrease with rewarming. The return of the plasma concentration toward prebypass levels is attributed to decreased

metabolism, and the subsequent decrease on rewarming is attributed to increased metabolism.

In addition, hepatic blood flow changes during cardiopulmonary bypass may be important, as etomidate is a high hepatic extraction drug.

Clinical Uses:

As Induction agent:

Etomidate may be viewed as an alternative to propofol or barbiturates for the IV induction of anaesthesia, especially in the presence of an unstable cardiovascular system. After a standard intubation dose of 0.2 to 0.4 mg/kg IV, the onset of unconsciousness occurs within one arm-to-brain circulation time.

Involuntary myoclonic movements are common during the induction period as a result of alteration in the balance of inhibitory and excitatory influences on the thalamocortical tract. **Prior opioid administration decreases the frequency of myoclonic like activity.**

Awakening after a single IV dose of etomidate is more rapid than after barbiturates, and there is very little evidence of a hangover or

drug cumulative effect. The Recovery is intermediate between that of methohexital and thiopental.

The duration of action is prolonged by increasing the dose of etomidate or administering the drug as a continuous infusion. But the disadvantage of etomidate is that it does not produce analgesia. **So before induction of anaesthesia with etomidate, opioid administration is necessary to blunt the hemodynamic responses produced by direct laryngoscopy and tracheal intubation.**

In ECT:

Etomidate, 0.15 to 0.3mg/kg intra venous dose, also has minimal effects on the duration of electrically induced seizures and thus it acts as an alternative to drugs that decrease the seizure duration time (propofol, thiopental) in patients posted for electroconvulsive therapy.

Adreno-cortical suppression is one of the important limiting factor for induction with etomidate.

Etomidate intra venous induction is also associated with post operative nausea and vomiting. Nevertheless, comparison of etomidate with propofol did not document an increased incidence of nausea and

vomiting in the first 24 hours after surgery in patients receiving etomidate.

Central Nervous System:

Etomidate decreases the cerebral blood flow and CMRO2 35% to 45% by acting as a potent cerebral vasoconstrictor. Due to this effect, etomidate decreases previously increased intra cranial pressure. These effects of etomidate are equal to those effects produced by comparable doses of thiopental.

Etomidate is relatively contraindicated for long-term treatment of intracranial hypertension due to adrenocortical suppression .

EEG pattern produced by etomidate is similar to thiopental. However, the frequency of excitatory spikes on the EEG is greater with etomidate than with thiopental and methohexital, suggesting caution in administration of etomidate to patients with a history of seizures. Like methohexital, etomidate may produce fast activity on EEG and activate seizure foci. So in the treatment of focal epilepsy, etomidate must be used with high precautions.

Conversely, this characterstic feature of etomidate has been used to facilitate localization of seizure foci in patients undergoing cortical resection of epileptogenic tissue.

Etomidate can be used in status epilepticus because of its anti convulsant property. Etomidate has property to increase the amplitude of somatosensory evoked potentials and this property makes monitoring of these responses better reliable.

Cardiovascular System:

Induction of anaesthesia with 0.3 mg/kg IV of etomidate gives good hemodynamic stability. Only little changes occur in cardiac output, stroke volume, heart rate. But 15% decline in blood pressure occurs due to fall in systemic vascular resistance. The decline in systemic vascular resistance corresponds to changes in systemic blood pressure. So etomidate administration to acutely hypovolemic patients will lead to severe hypotension. Both cardiac output and systemic vascular resistance will fall with 0.45mg/kg dose of induction.

In cases of severe valvular heart disease, continuous infusion of both thiopentone and etomidate produces same cardiovascular effects.

Etomidate can be used in patients with minimal cardiac reserve, because it has minimal effect on myocardial contractility. Etomidate induced negative inotropic effects very difficult to prove in vivo because of concurrent changes in afterload, preload, baroreceptor reflex and sympathetic activity.

In vitro the direct effect on myocardial contractility may be determined. In this regard, etomidate causes dose-dependent decrease in developed tension in isolated cardiac muscle obtained from patients undergoing coronary artery bypass graft operations or cardiac transplantation. This depression was reversible with beta-adrenergic stimulation.

Nevertheless, concentrations required to produce these negative inotropic effects are in excess of those achieved with clinical use. In this regard, etomidate may differ from most other IV anaesthetics in that **depressive effects on myocardial contractility are minimal at concentrations needed for the production of anaesthesia.**

Hepatic and renal effects:

In contrast to other IV anaesthetics, etomidate does not greatly decrease renal blood flow. Hepatic and renal functions tests are not altered by etomidate.

Effect on IOP:

Intraocular pressure is decreased by etomidate to a similar degree as by thiopental. Also etomidate does not result in detrimental effects when accidentally injected into an artery.

Ventilation:

The depressant effects of etomidate on ventilation seem to be less than those of barbiturates, although apnoea may occasionally accompany a rapid IV injection of the drug.

In most of the patients, etomidate induced decreases in tidal volume are offset by compensatory increases in the respiratory rate. These effects on ventilation are transient, only lasts for 3 to 5 minutes.

Etomidate may stimulate ventilation independent of the medullary centers that normally respond to PaCO2. For this reason, etomidate may be useful during spontaneous ventilation but may be exaggerated

when inhaled anaesthetics or opioids is combined with etomidate during continuous infusion techniques.

Side Effects:

Inspite of the advantages of etomidate, it has certain side effects.

Pain on Injection:

Etomidate utilizing lipid emulsion eliminates the injection pain and venous irritation when compared to propylene glycol.

Myoclonus:

Intra venous anaesthetics induced excitatory effects may present as spontaneous movements, such as myoclonus, dystonia, and tremor. Etomidate intra venous induction produces myoclonus in 50 to 80 percent of the patients in the absence of premedication.

In one report, 87% of patients receiving etomidate developed excitatory effects of which 69% were myoclonic. Multiple spikes appeared on the EEG of 22% of these patients. In this same report, the frequency of excitatory effects was 17% after thiopental, 13% after methohexital and 6% after propofol and none of these patients developed myoclonus with spike activity on the EEG.

Using atropine in the preoperative medication suppress spike activity on the EEG associated with the administration of etomidate. **Myoclonus may be reduced by prior administration of an opioid (fentanyl 1 to 5 mcg/kg IV)** or giving a benzodiazepine may decrease the myoclonus incidence after induction of etomidate.

The intensity and incidence of myoclonus following etomidate administration is dose-related and suppressed by pretreatment with small doses of etomidate(0.03 to 0.075 mg/kg IV)before administration of the induction dose.

The mechanism of etomidate-induced myoclonus appears to be disinhibition of subcortical structures that normally suppress extrapyramidal motor activity. In many patients, excitatory movements are seen coincident with the early slow phase of the EEG, which corresponds to the beginning of deep anaesthesia. It is possible that myoclonus could occur on awakening of the cortex that inhibits it.

So the important factor is etomidate-induced myoclonic activity may be associated with seizure activity on the electroenchepalogram suggests caution in the use of this drug for the induction of anaesthesia in patients with a history of focal seizure activity. Conversely, others

have not documented seizure like activity on the EEG in association with etomidate induced myoclonus.

Adrenocortical Suppression:

Etomidate causes a dose-dependent inhibition of the conversion of cholesterol to cortisol which leads to adrenocortical suppression. The specific enzyme inhibited by etomidate appears to be 11-beta-hydroxylase which leads to increased concentration of 11-deoxycorticosterone. This enzyme inhibition lasts for 4 to 8 hours after etomidate induction. So in patients experiencing sepsis or haemorrhage and who might require an intact cortisol response, they would be at a disadvantage if etomidate is administered.

But conversely, suppression of adrenocortical function could be considered desirable from the stand point of "stress-free" anaesthesia. But at the same time, in one report, it was not possible to demonstrate a difference in the plasma concentrations of cortisol, corticosterone, (or) adrenocorticotrophic hormone in patients receiving a single dose of etomidate.

Allergic Reactions:

The incidence of allergic reactions is less common following administration of etomidate. If reactions have occurred, it is very difficult to differentiate the role of etomidate from other concomitantly administered drugs (neuromuscular blocking drugs) that are more likely to evoke histamine release than etomidate.

REVIEW OF LITERATURE

1) A study titled "**Fentanyl Pretreatment Modifies Anaesthetic Induction with Etomidate"** (published in Anaesthesia Intensive care) was conducted to find the effective dosage of fentanyl to minimise the side effects of etomidate and provide better hemodynamic stability with etomidate as induction agent. Patients were randomly assigned to four groups according to the pretreatment dose of fentanyl (Group I = 2 ml normal saline; Group Il = 100 microgram of fentanyl, Group III = 250microgram of fentanyl and Group IV = 500microgram fentanyl) were administered intravenously five minutes prior to induction of anaesthesia with etomidate, 0.3 mg/kg. It was found that there was an increasing incidence of apnoea (53, 87, 87 and 100% in Groups I-IV respectively) but a decreasing incidence of myoclonus (60, 33, 13 and 0% in Groups I-IV respectively) and pain during injection (53, 13, 7 and 0% in Groups I-IV respectively), $P< 0.002$ in chi-square test for linear trends, with increasing dosage of fentanyl. But the incidences of postoperative nausea and vomiting were similar in all the four groups. The collected data demonstrate that increasing the pre-induction doses of fentanyl are more effective at minimising the side-effects and

preventing the increases in systolic blood pressure and heart rate but at the same time also increase the incidence of apnoea during induction. The results suggest that 500microgram of fentanyl is an ideal pretreatment dose in patients who are fit, prior to anaesthetic induction with etomidate.

2) A study titled "**Prevention of etomidate-induced myoclonus: Which is superior: Fentanyl, midazolam, or a combination? A Retrospective comparative study"** (published in Medical Science monitor) was conducted to compare the effectiveness of midazolam, fentanyl and a combination of fentanyl and midazolam to prevent the etomidate-induced myoclonus. Myoclonic movements were evaluated, which were observed and graded according to the clinical severity during the 2 minutes after etomidate injection. The severity of pain due to etomidate injection, heart rate, mean arterial pressure and adverse effects were also evaluated. The results of study showed that myoclonus incidence was decreased in the group which received fentanyl or combination of fentanyl and midazolam. They also concluded that pretreatment with fentanyl or combination of fentanyl and midazolam was effective in preventing etomidate-induced myoclonus.

3) A study titled "**Haemodynamic responses to tracheal intubation following etomidate and fentanyl for anaesthetic induction"** (published in Canadian journal of Anaesthesiology) was conducted to study the effect of fentanyl in attenuating hemodynamic response during endotracheal intubation with etomidate as induction agent. Haemodynamic variables were measured at baseline, after anaesthetic induction, and at one, three, five, and ten minutes after endotracheal intubation. The hemodynamic response was less in the group which recieved fentanyl 5 to 10 microgram/kg. The authors concluded that using fentanyl 5-10 micrograms.kg-1 attenuates the haemodynamic response to laryngoscopy and tracheal intubation following anaesthetic induction with etomidate, 0.3 mg.kg-1.

4) A study titled "**Fentanyl or Remifentanil pretreatment reduces myoclonus after etomidate induction"** (published in Journal of Clinical Anaesthesiology) was conducted to compare the effect of pretreatment with remifentanil or fentanyl on the incidence of myoclonus after anesthetic induction with etomidate. The parameters monitored are grade of sedation (none, mild, moderate, severe), apnoea, nausea, pruritus after injection of both drugs. The incidence of myoclonus was significantly lower in the fentanyl and remifentanil

group (6.7%) than in the placebo group (70%) (P <0.001). No patients experienced nausea or pruritus, sedation and apnoea after injection of both drugs. In the placebo group it was found that male patients were associated with increased incidence of myoclonus after etomidate administration. Hence this study concluded that pretreatment with remifentanil or fentanyl reduces incidence of myoclonus after etomidate induction without side effects such as nausea, or pruritus, apnoea and sedation. Men experienced high incidence of myoclonus than women after etomidate administration.

5) A study titled "**Clinical comparison of either small doses of fentanyl or remifentanil for blunting cardiovascular changes induced by tracheal intubation"** (published in Minerva Anaesthesiology) was done to study the effects on hemodynamic response after tracheal intubation produced by small doses of either remifentanil or fentanyl. Arterial blood pressure and heart rate were recorded before anaesthesia induction (baseline), one minute after induction of anaesthesia, then immediately after tracheal intubation and then every minute for the first five minutes after intubation. The collected data suggested that systolic blood pressure values were significantly higher in the Placebo group than the fentanyl and the

Remifentanil group patients from 2 to 5 min after tracheal intubation ($p < 0.01$), while no differences are observed between the two groups in both diastolic blood pressure and heart rate values. The study concluded that remifentanil has superior effect while both fentanyl and remifentanil are effective in attenuating the cardiovascular changes induced by endotracheal intubation.

6) A study titled "**Comparison of etomidate-fentanyl and propofol-fentanyl sedation in patients scheduled for colonoscopy"** (published in European Journal of Anaesthesiology) was done to compare the haemodynamic responses, recovery and discharge times of etomidate-fentanyl and propofol-fentanyl combinations in the patients undergoing elective colonoscopy. Basal values of heart rate, mean arterial pressure, SpO2, respiratory rate and Ramsay sedation score were recorded. All the values were recorded every 2 minutes for the first 10 minutes and then every 5 minutes thereafter, until the completion of the procedure. Etomidate-fentanyl administration compared to propofol-fentanyl combination for sedation and analgesia during colonoscopy was concluded as having more stable haemodynamic responses.

7) A study titled "**Comparison of the effects of remifentanil or fentanyl on anaesthetic induction characteristics of propofol, thiopental or etomidate"** (published in European Journal of Anaesthesiology) was studied to compare the effects of remifentanil or fentanyl on anaesthetic induction characteristics when propofol, thiopental or etomidate is used as induction agent. Parameters monitored were the amounts of drug necessary for induction, haemodynamic response and the time taken for apnoea, loss of eyelash reflex, and the release of a water-filled syringe which was held in the patient's hand. The results were concluded that when administered with remifentanil, induction times are shorter even with reduced amounts of propofol, thiopental or etomidate while both remifentanil and fentanyl are effective in attenuating the hemodynamic responses to intubation.

8) A study titled "**Induction of anaesthesia in patients with coronary artery disease: a comparison between sevoflurane-remifentanil and fentanyl-etomidate"** (published in Anaesthesia Intensive care) was conducted in which sevoflurane-remifentanil (Group SR) was compared with fentanyl-etomidate (Group FE) for induction of anaesthesia in patients with ischemic heart disease. Hemodynamic stability, heart rate, mean arterial pressure, rescue

medications, rate pressure product and associated myocardial ischemia were measured. Both groups received rocuronium and endotracheal intubation was done two minutes later. Remifentanil administration was associated with severe bradycardia and hemodynamic instability. The results were concluded that fentanyl-etomidate combination was associated with better hemodynamic stability.

9) A study titled "**The effect of fentanyl pretreatment on myoclonus during induction of anaesthesia with etomidate in elderly patients"** (published in Korean Journal of Anaesthesiology) was done to determine whether etomidate-fentanyl based induction can provide better hemodynamic stability and decrease the incidence of myoclonus associated with etomidate. The time interval from etomidate infusion to the loss of eyelash reflex, time taken to decrease the bispectral index (BIS) to 50, time taken to intubation were recorded. Hemodynamic responses, the bispectral index, the incidence, duration and grade of myoclonus were also noted. The data collected showed that in the group which received fentanyl there was better hemodynamic stability with induction with etomidate and decreased incidence of myoclonus. The study was concluded that fentanyl pretreatment with etomidate as induction agent provides better

hemodynamic stability and it also decreases the incidence of myoclonus.

10) A study titled "**Induction of anaesthesia with fentanyl or fentanyl plus etomidate in high-risk patients"** (published in Journal of Cardiothoracic Anaesthesia) was conducted in which anaesthetic doses of fentanyl and oxygen (group I) were compared to a moderate dose of fentanyl + etomidate (0.4 mg/kg) (group II) during the anaesthetic induction-intubation sequence to evaluate hemodynamic responses and also the incidence of side effects in 23 New York Heart Association class III and IV patients. Hemodynamic responses, myoclonus, Chest wall rigidity, pain on injection were monitored in all patients. The collected data suggested that in group II the incidence of side effects like myoclonus is less and there was better hemodynamic stability. The study was concluded that modest dose of fentanyl followed by etomidate induction may be an a suitable alternative to very high doses of fentanyl in patients with limited cardiovascular reserve like ischemic heart disease patients, especially when prolonged postoperative respiratory depression secondary to high doses of an opioid is undesirable

MATERIALS AND METHODS

The institutional ethical committee approval for the study was obtained. The informed written consent was obtained from the patients participating in the study was obtained.

Sample Size:

In order to detect a 15% difference in heart rate and blood pressure, with beta error of 80% (0.8), the sample size was calculated as 30 in each group.

60 ASA I and II patients of age 18 to 60 years undergoing elective surgeries under general anaesthesia were selected.

Patients whose medical history, laboratory data, or physical examination showed evidence of abnormal hepatic or renal function or severe cardiovascular, pulmonary, neurological, psychiatric, or metabolic disease were excluded from the study.

Selected patients were divided randomly into two groups – either to receive 2 µg/kg fentanyl (n=30) or to receive 5 µg/kg fentanyl (n=30).

- **DESIGN OF STUDY:** Prospective Randomised Study
- **PARTICIPANTS : ** Patients posted for elective general surgery procedures expected to last one hour or longer

INCLUSION CRITERIA:

a) Elective surgeries under general anaesthesia

b) Both sexes

c) Age :18-60 years

d) ASA I& II

EXCLUSION CRITERIA:

a) Pregnancy

b) Obese patients (>25% of ideal body weight)

c) Known allergy to etomidate

d) Known allergy to fentanyl

e) Chronic alcoholic

f) Patients on drugs which is likely to cause cardiovascular changes

METHODOLOGY

Patients scheduled for elective surgeries under general anaesthesia were eligible for the study. 60 Patients were randomly assigned to two groups according to the pretreatment dose of fentanyl

1) Group I received 2 microgram kg-1 of fentanyl

2) Group II received 5 microgram kg-1 of fentanyl

After 5 minutes of administration of either one of these all patients were induced with etomidate at a dose of 0.3 mg kg-1

PARAMETERS TO BE MONITORED:

a) Pain on injection

b) Myoclonus

c) Apnoea

d) Heart rate

e) Systemic blood pressure

f) Post operative nausea and vomiting

STATISTICAL TOOLS TO BE APPLIED:

Continuous data like age, heart rate and blood pressure will be presented as mean +/- SD; individual comparisons were done with student t-tests. Frequency counts of gender ratios and side effects among the four groups were analysed with chi square test for linear trends

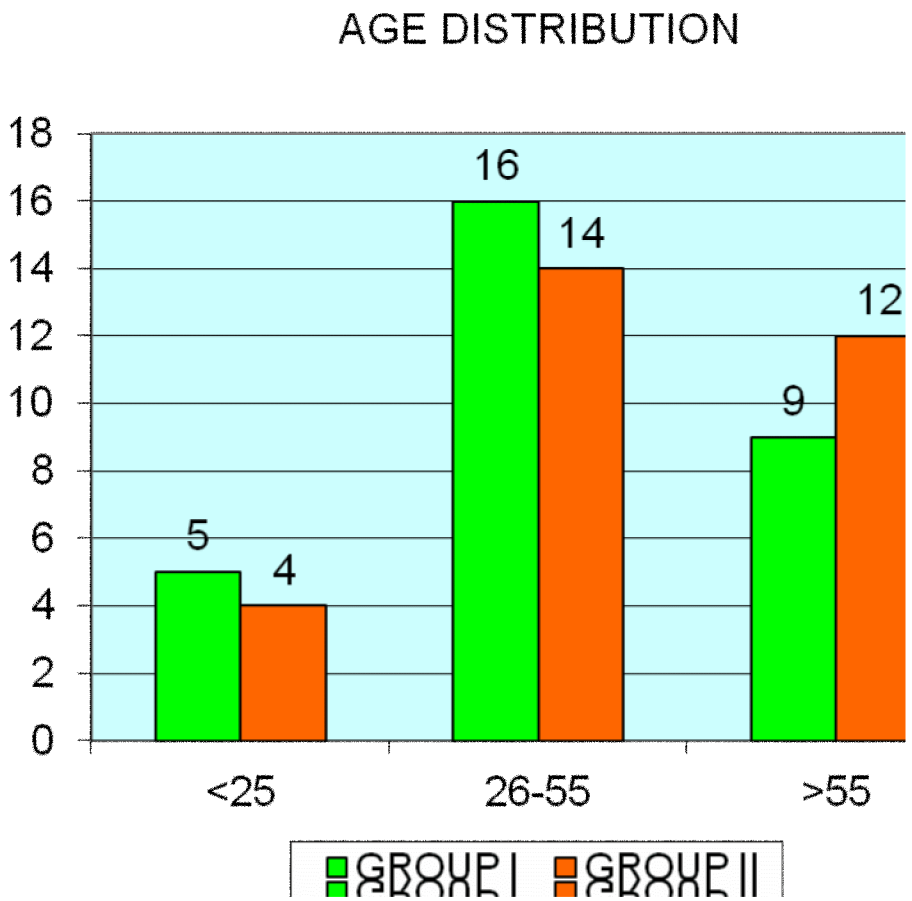
Statistical Analysis

TABLE 1: Age Distribution

Age	**GROUP I**	**GROUP II**
Total	30	30
Mean	45.967	46.533
SD	14.464	14.017
P	0.878	

P value was calculated with Student 'T' test. The mean age of patients in both groups are found to be comparable and statistically insignificant.

Age Distribution



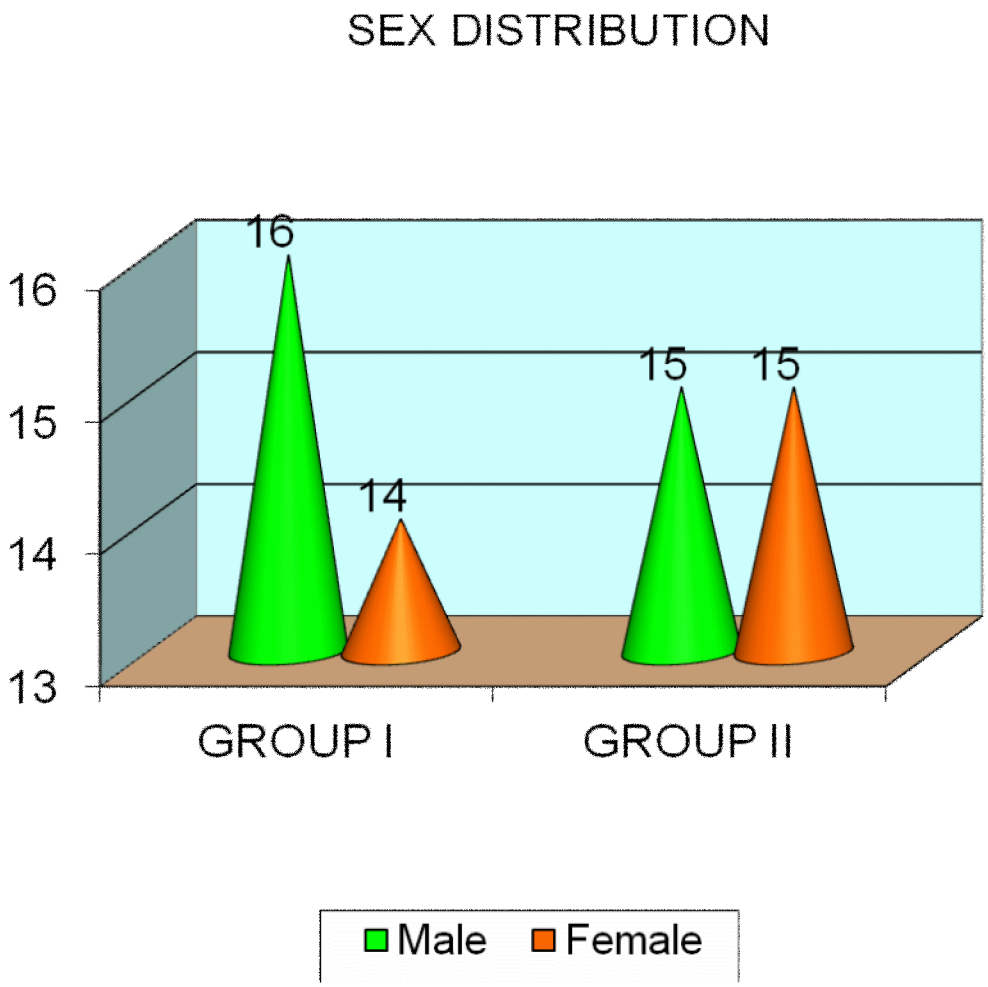
On random allocation, patients of age > 55 years were higher in group II compared to group I. In other age group the distribution was almost similar.

TABLE 2: SEX DISTRIBUTION

Group	Sex			
	Male		Female	
	No	%	No	%
Group I	14	46.6	16	53.4
Group II	15	50	15	50
'p'	0.940			

P value was calculated with Chi Square test. The sex distribution of both the groups are found to be comparable and statistically insignificant

Sex Distribution:

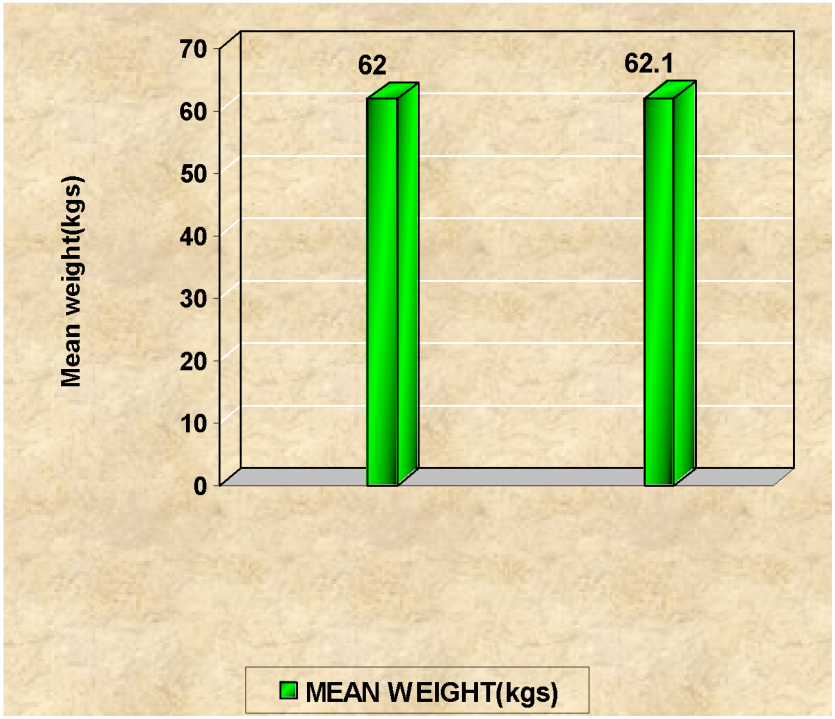


In group II there was equal distribution of males and females but in group I, 16 patients were male while 14 patients were female.

TABLE 3: WEIGHT

Group	Weight (Kg)	
	Mean	SD
Group I	62.0	5.7
Group II	62.1	5.8
'p'	0.9468	

P value was calculated with Student 'T' test. The weight of the patients in both the groups are compared and found to be statistically insignificant.



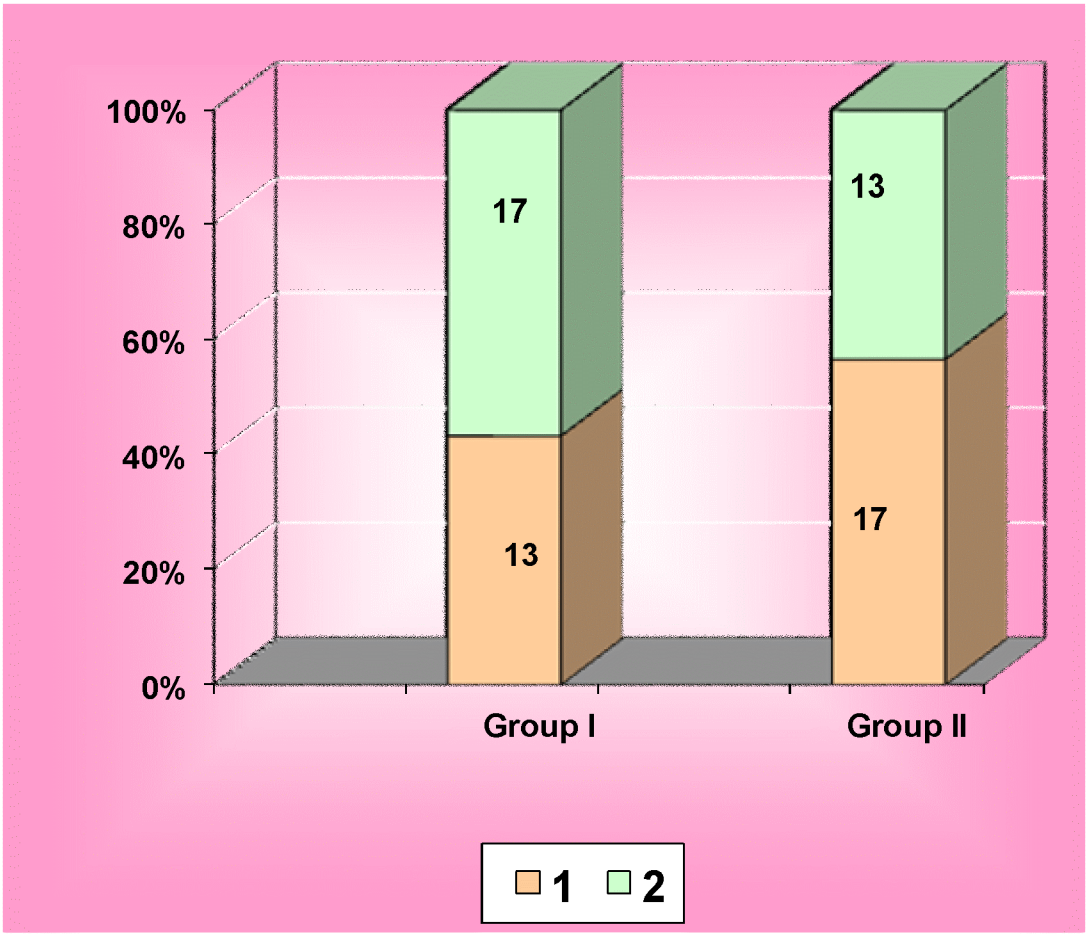
The mean weight in group I is 62kg while in group II the mean weight is 62.1kg. It is comparable and found to be insignificant.

TABLE 4: ASA

Group	ASA			
	1		2	
	No	%	No	%
Group I	13	43.3	17	56.7
Group II	17	56.7	13	43.3
'p'	0.2195			

P value was calculated with Chi square test. The ASA physical status of both the groups are compared and found to be statistically not significant.

ASA GRADE



In group I, 13 patients were ASA I while 17 patients were under ASA II. In group II, 17 patients were ASA I while 13 patients were under ASA II.

TABLE 5: Heart Rate

HEART RATE	GROUP I		GROUP II		P
	MEAN	SD	MEAN	SD	
Base line	84.43	4.082	84.123	5.1	0.523
3 mins After Fentanyl	84.177	5.744	83.12	4.154	0.142
2 mins after Etomidate	83.41	5.661	82.24	5.014	0.214
After giving suxa	84.557	4.972	83.57	5.075	0.273
1 min after intubation	110.237	4.653	96.063	5.051	<0.001

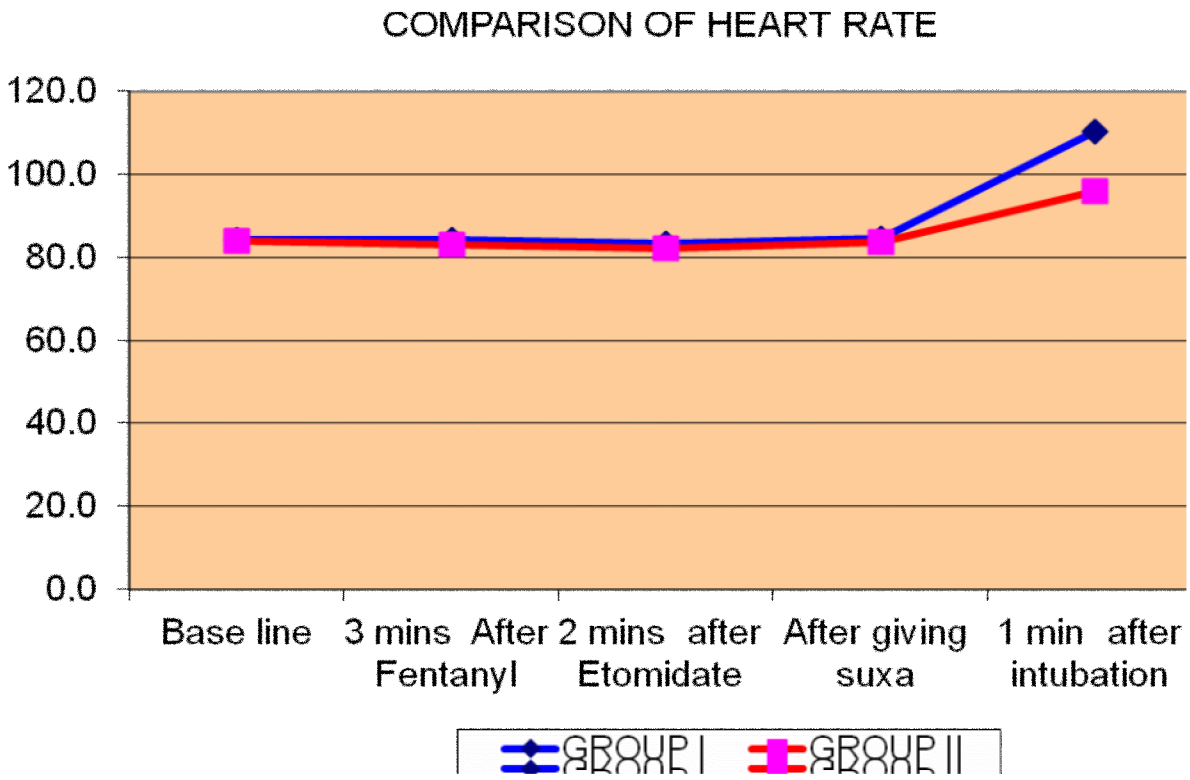
Heart rate at various time intervals are compared between group I and group II. The heart rate one minute after intubation is found to be significant ($p<0.001$).

Heart rate: % increase from base line

HEART RATE	GROUP I		GROUP II		P
	MEAN	SD	MEAN	SD	
Base line	84.43	4.082	84.123	5.1	0.523
3 mins After Fentanyl	84.177	5.744	83.12	4.154	0.142
2 mins after Etomidate	83.41	5.661	82.24	5.014	0.214
After giving suxa	84.557	4.972	83.57	5.075	0.273
1 min after intubation	110.237	4.653	96.063	5.051	<0.001
% increase from baseline	26%		10%		

The percentage increase of Heart rate from baseline is 26% in Group I compared to only 10% in Group II

Comparison of Heart rate:



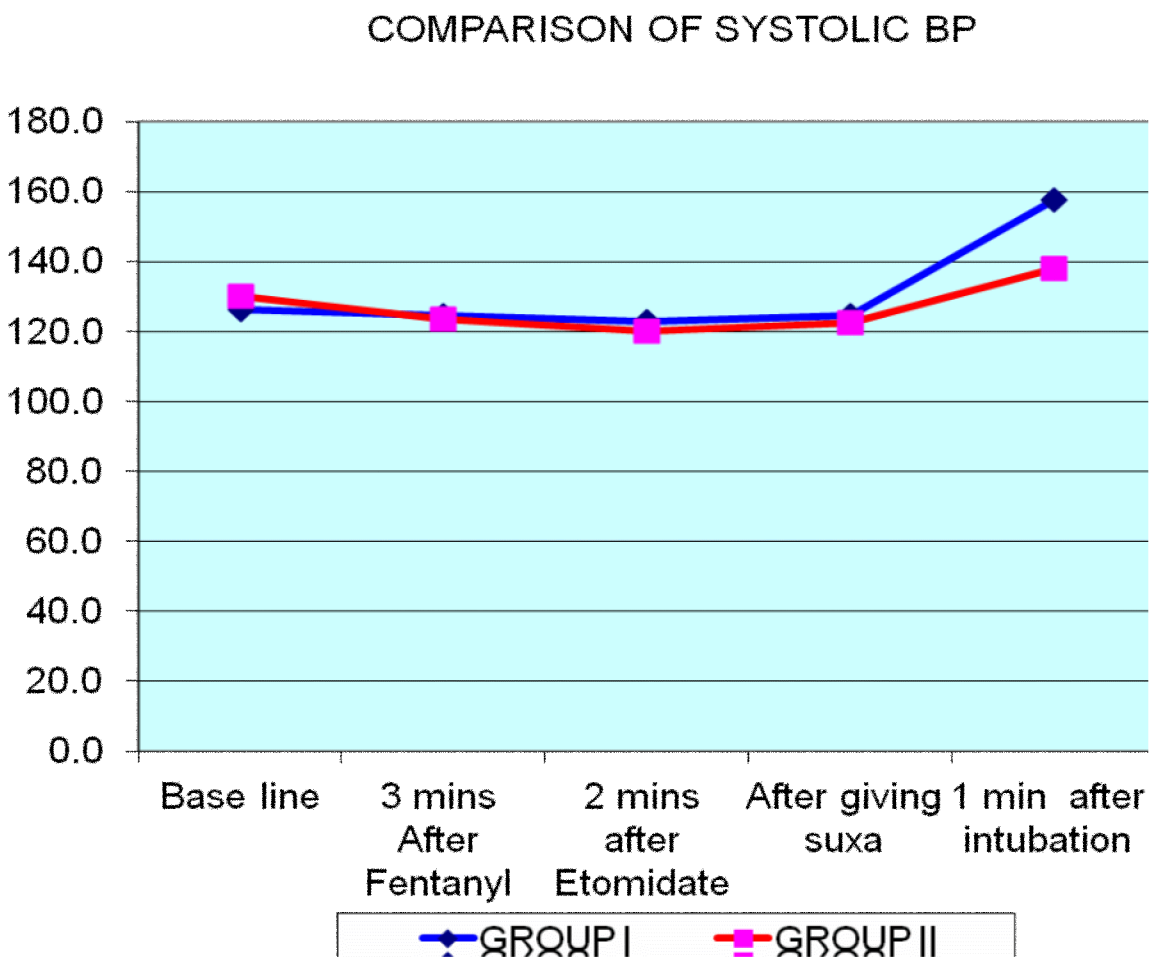
In group I, the increase of heart rate from baseline is 26% while in group II the increase of heart rate is only 10 %

Table 6: Systolic blood pressure

B.P(Systolic BP)		GROUP I		GROUP II		P
		MEAN	SD	MEAN	SD	
Base line		126.3	5.243	126.2	4.174	0.543
3 mins After Fentanyl		124.77	5.198	123.767	4.462	0.424
2 mins after etomidate		122.76	4.814	120.133	5.245	0.368
After giving suxa		124.533	5.083	122.4	4.857	0.148
1 min after intubation		157.767	8.208	138.067	5.145	<0.001

Systolic blood pressure at various time intervals is compared. The systolic blood pressure one minute after intubation is compared and found to be significant. ($p<0.001$)

Comparison of Systolic blood pressure:



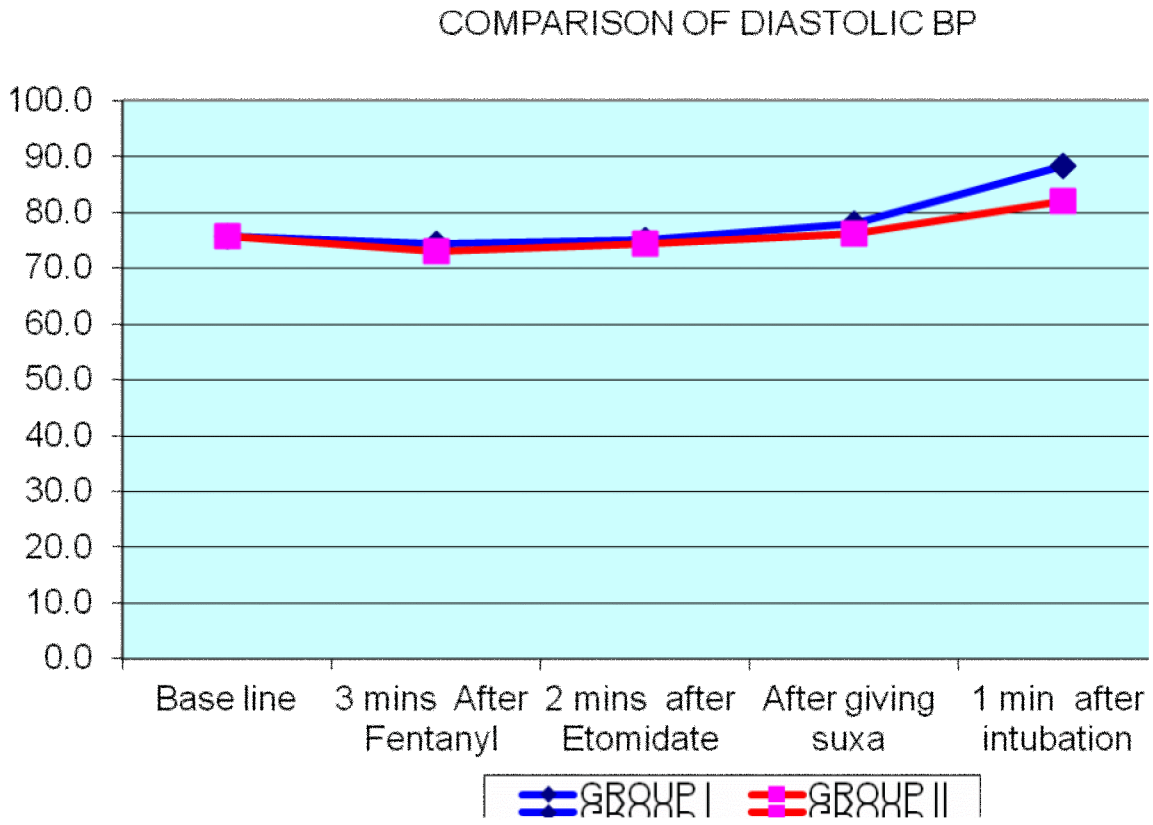
The increase of systolic blood pressure one minute after intubation is higher in group I when compared to group II.

Table 7: Comparison of Diastolic blood pressure

B.P(Diastolic BP)	GROUP I		GROUP II		P
	MEAN	SD	MEAN	SD	
Base line	75.8	3.75	75.7	3.765	0.465
3 mins After Fentanyl	74.5	3.67	73.2	3.35	0.654
2 mins after Etomidate	75.2	3.92	74.4	3.42	0.452
After giving suxa	78	4.12	76.3	3.83	0.376
1 min after intubation	88.4	2.094	82.1	2.187	<0.001

Diastolic blood pressure at various time intervals is compared. The diastolic blood pressure one minute after intubation is compared and found to be significant. ($p<0.001$)

Diastolic blood pressure:



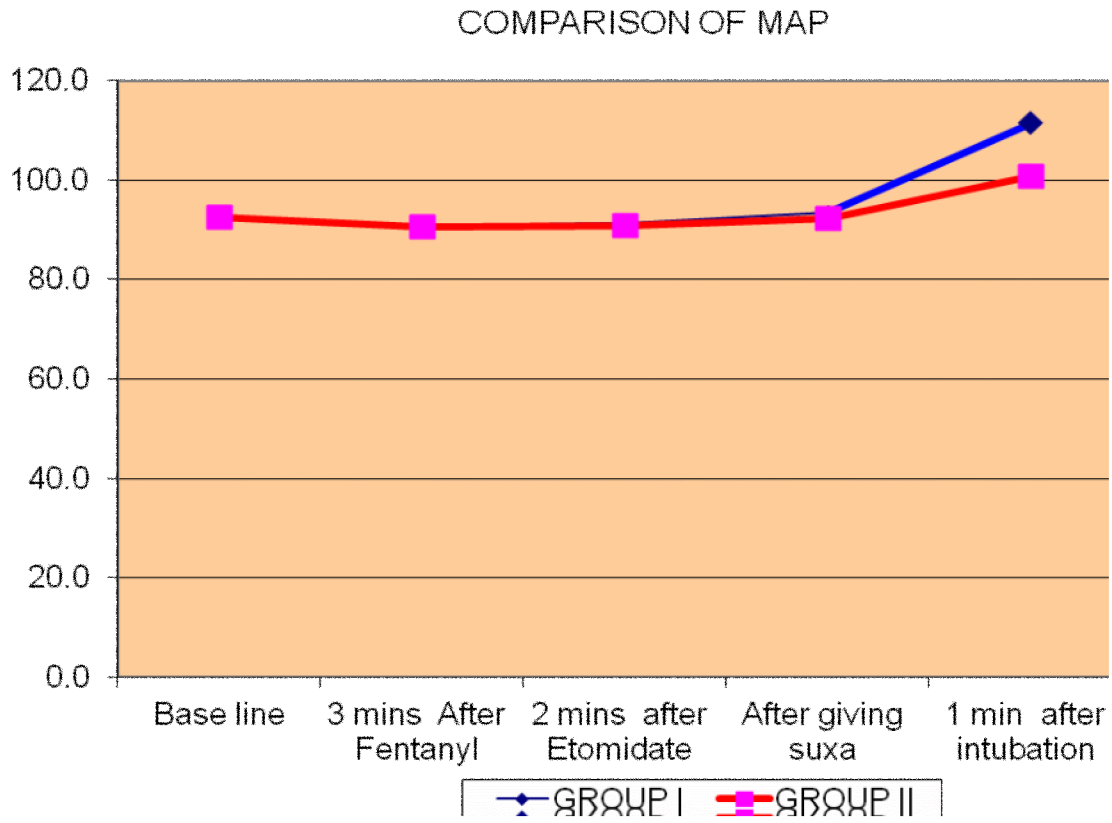
The increase of diastolic blood pressure one minute after intubation is higher in group I when compared to group II.

Table 8: Comparison of Mean arterial pressure

MAP	GROUP I		GROUP II		P
	MEAN	SD	MEAN	SD	
Base line	92.633	3.598	92.53	3.625	0.432
3 mins After Fentanyl	90.944	3.362	90.722	3.428	0.367
2 mins after Etomidate	91.422	4.12	90.92	3.985	0.418
After giving suxa	93.511	4.651	92.25	3.654	0.181
1 min after intubation	111.522	6.533	100.756	4.449	<0.001

Mean arterial pressure at various time intervals is compared. The mean arterial pressure one minute after intubation is compared and found to be significant. ($p<0.001$)

Mean Arterial Pressure:



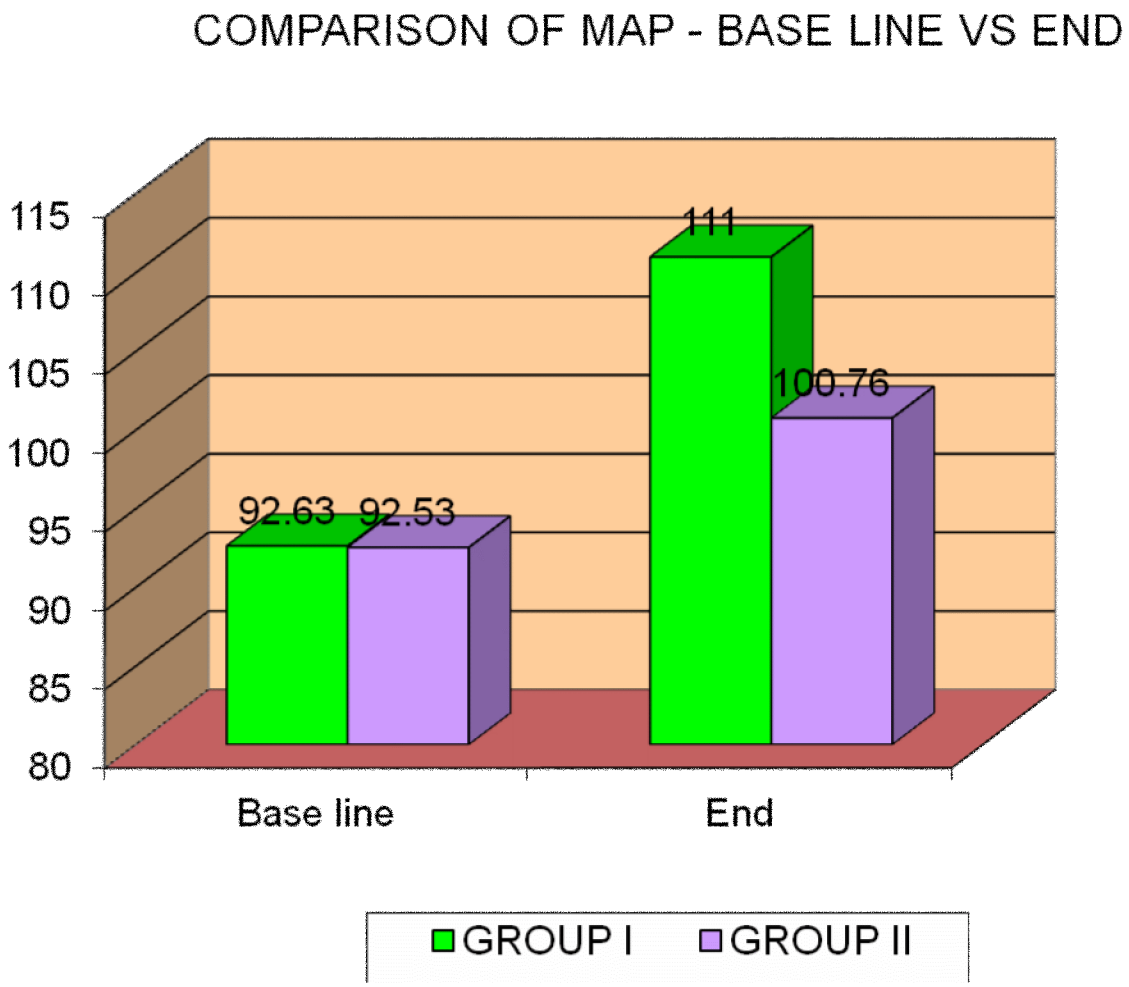
This figure shows the trend of mean arterial pressure at various time intervals in both groups. The increase of mean arterial pressure one minute after intubation is higher in group I when compared to group II.

Table 9: Comparison of MAP

MAP	Base line	End
GROUP I	92.63	111
GROUP II	92.53	100.76

Mean arterial pressure at the baseline is almost similar in Group I and II. However one minute after intubation the increase in mean arterial pressure is much more in Group I compared to Group II.

Comparison of MAP:



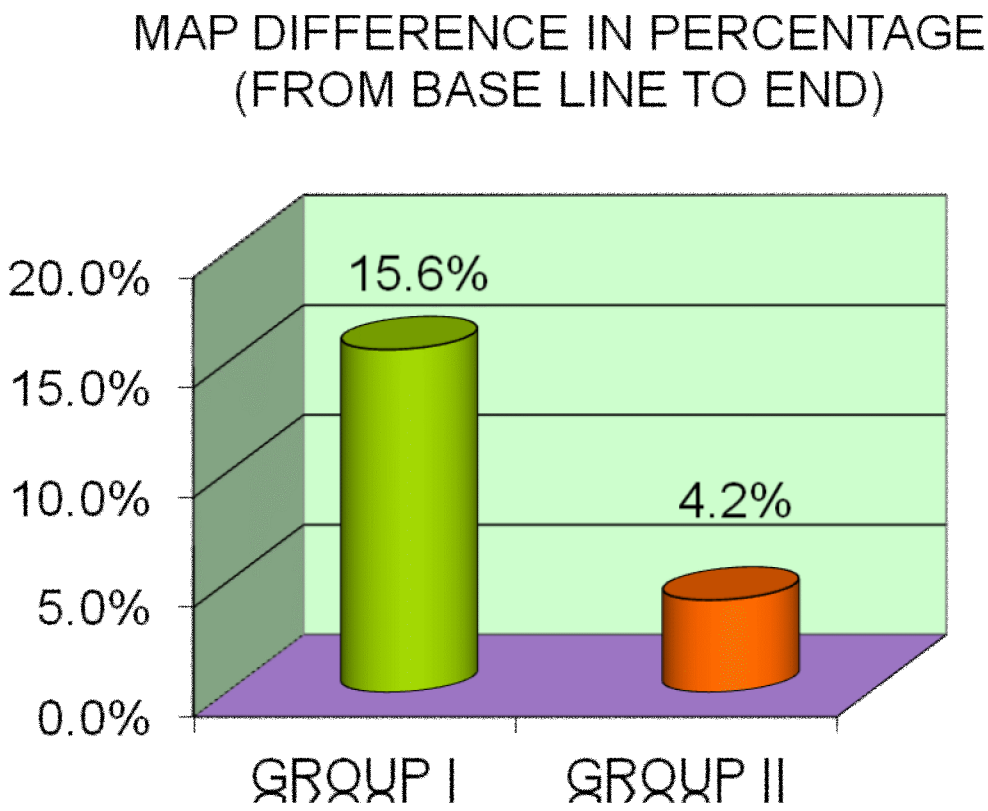
The baseline mean arterial pressure was almost same in both the groups. However one minute after intubation the increase in mean arterial pressure is much more in Group I compared to Group II.

Table 10: % Increase of MAP

MAP	Base Line	End	Difference	%
GROUP I	92.63	111	17.33	15.62
GROUP II	92.53	100.76	4.22	4.17

The increase of mean arterial pressure from baseline is 15.62% in Group I while the increase is only 4.17% in Group II.

MAP: % increase from base line



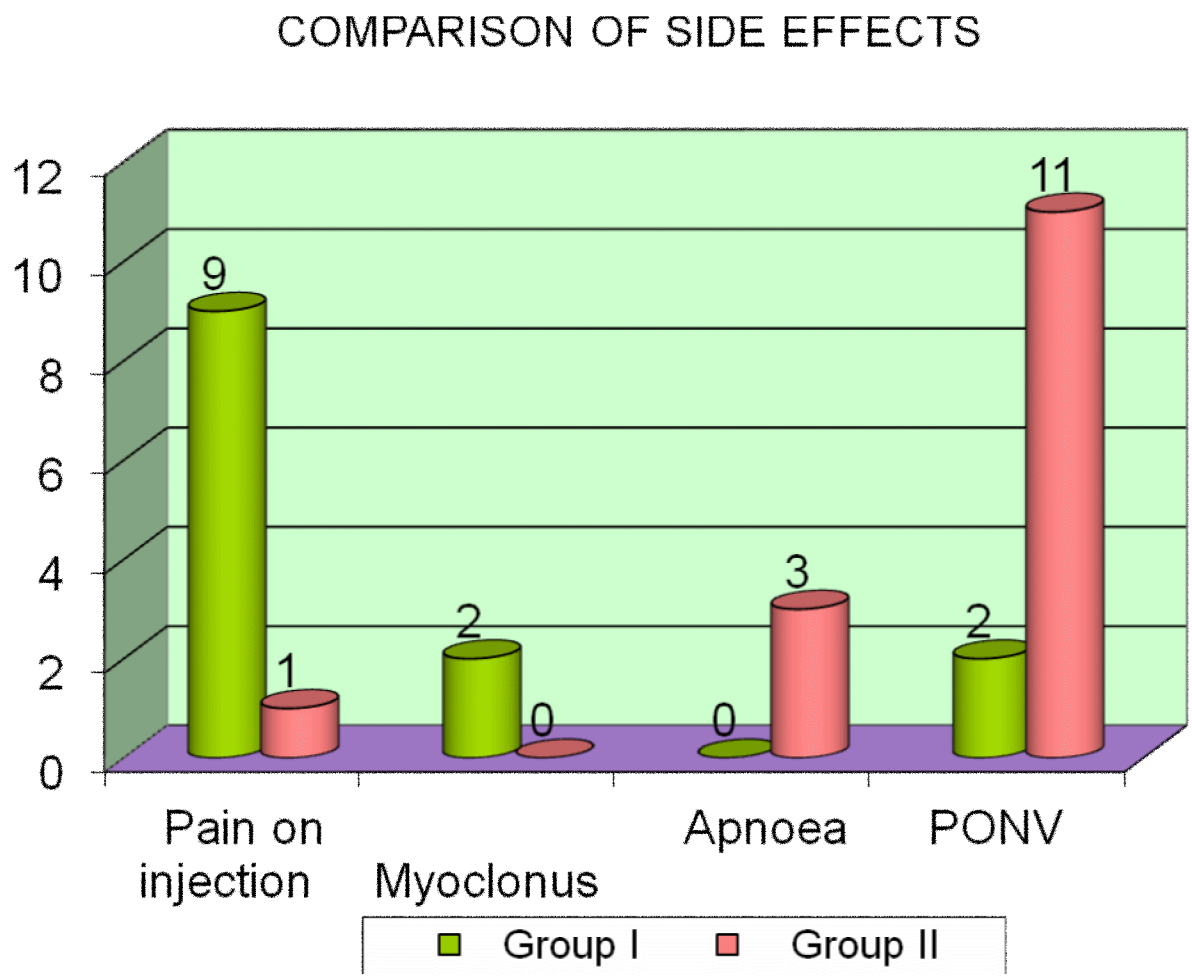
The increase of mean arterial pressure from baseline is 15.6% in Group I while the increase is only 4.2% in Group II.

Table 11: Side effects:

Side Effects	Pain on injection	Myoclonus	Apnoea	PONV
Group I	9	2	0	2
Group II	1	0	3	11
p value	0.044	0.501	0.271	0.049
	Significant	Not Significant	Not Significant	Significant

There is significant decrease of pain on injection in group II while there is significant increase in PONV in group II compared to group I. There is increasing incidence of myoclonus in group I and apnoea in group II

Comparison of side effects:



There is significant decrease of pain on injection in group II while there is significant increase in PONV in group II compared to group I. There is increasing incidence of myoclonus in group I and apnoea in group II

RESULTS

There were no significant differences between the groups with respect to age, weight, preoperative heart rate, blood pressure, respiratory rate and duration of stay in recovery room. Males and females were almost evenly distributed between the two groups.

In Group I, no patient become apnoeic while in group II three patients become apnoeic after administration of fentanyl. But none required naloxone for antagonism of opioid.

Also with increasing dose of fentanyl, there was a decreasing incidence of pain on injection, myoclonus. But at the same time there was increasing incidence of post operative nausea and vomiting in group II.

As mentioned in tables 5 to 10, the increase of heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure after intubation is significantly lower in group II with increasing dose of fentanyl.

DISCUSSION

In several studies it have been demonstrated that pain on injection, myoclonus and increases in arterial blood pressure and heart rate during laryngoscopy and endotracheal intubation can be minimised following pretreatment with fentanyl.

The results of our study demonstrates that increasing the preinduction dose of fentanyl are more effective at minimizing the side-effects of etomidate.

But at the same time, higher pre-treatment doses of fentanyl also cause a high incidence of apnoea and also postopertative nausea and vomiting.

In this study, pretreatment with fentanyl did not cause chest wall rigidity in any patient. While these findings indicate that the incidence of rigidity is low with even 5μg/kg fentanyl, it probably is not absent, as other studies have described rigidity with even low dose of fentanyl.

Similarly, in this study no patient required a narcotic antagonist either immediately after surgery or in the recovery room, also nobody needed mechanical ventilation post operatively. But it doesn't mean that respiratory depression sufficient to require mechanical ventilation

or requirement of a narcotic antagonist for reversal of opioid might not be an occasional occurrence.

In a study conducted by Stockham et al in University of Utah, it has been demonstrated that 250 µg of fentanyl given before administering etomidate, eliminated all increases in heart rate and blood pressure produced by laryngoscopy and intubation (without causing hypotension) in patients with significant cardiovascular disease (NYHA Class III and IV).

In a study conducted by Alberti and Casati, doses of fentanyl of 3µg/kg are effective in blunting the hemodynamic responses to intubation with etomidate as induction agent.

In a study conducted by Zhang and Sun et al, even a low dose of fentanyl (1µg/kg) are effective in blunting the hemodynamic response to intubation with etomidate as induction agent.

In another study conducted by Stockham and Stanley, fentanyl dosage of upto 500µg are used and they concluded that the hemodynamic response to induction-intubation sequence with etomidate as induction agent can be completely eliminated by high dosage of fentanyl of upto 10 µg/kg.

These findings, when combined with the results of our study, suggest that an optimal pre induction dose of fentanyl (5µg/kg) attenuates the increase in heart rate and blood pressure during induction-intubation sequence with etomidate.

Hence with our study it can be suggested that on further increasing the dose of fentanyl, it may be possible to completely eliminate the hemodynamic response to induction intubation sequence with etomidate.

But our study did not deal that whether hemodynamic responses can be completely eliminated with higher doses of the opioid and, if so, at what physiologic and pharmacologic cost.

Another disadvantage in our study is, it did not evaluate the proposed advantages of etomidate, in patients with limited cardiovascular reserve as it is a cardiostable induction agent.

CONCLUSION

Our study indicates that the effectiveness of fentanyl in reducing the side-effects of etomidate and attenuating the haemodynamic responses associated with the induction intubation sequence is dose-dependent. The data analysis suggests that 5µg/kg of fentanyl pretreatment reduces the incidence of myoclonus, pain on injection, and increases in heart rate and blood pressure during the induction-intubation sequence in ASA Class I and II patients but produce a high incidence of post operative nausea and vomiting and may cause apnoea.

The drawbacks of our study are it did not experiment whether hemodynamic responses can be completely eliminated with higher doses of the opioid and, if so, at what physiological and pharmacological cost.

Another disadvantage in our study is, it did not evaluate the proposed advantages of etomidate, in patients with limited cardiovascular reserve as it is a cardiostable induction agent.

SUMMARY

Our study was a prospective randomised study including 60 patients undergoing elective surgeries under general anaesthesia. They were randomly allocated into two groups of 30 each.

Group I received 2 microgram kg-1 of fentanyl and Group II received 5 microgram kg-1 of fentanyl. After 5 minutes of administration of either one of these all patients were induced with etomidate at a dose of 0.3 mg kg-1.

The parameters monitored are Pain on injection, myoclonus, Apnoea, Heart rate, Systemic blood pressure, Post operative nausea and vomiting.

We found that in Group I, no patient become apnoeic while in group II three patients become apnoeic after administration of fentanyl.

Also with increasing dose of fentanyl, there was a decreasing incidence of pain on injection, myoclonus. But at the same time there was increasing incidence of post operative nausea and vomiting in group II.

We also found that the increase of heart rate and blood pressure, during induction-intubation sequence with etomidate is significantly lower in group II with increasing dose of fentanyl.

Therefore we conclude that at a dose of 5µg/kg of fentanyl, there is reduction of side effects of etomidate and also there is attenuation of hemodynamic response to intubation in patients undergoing elective surgeries under general anaesthesia with etomidate as induction agent.

Bibliography

1. Crado A, Maseda J, Navarro E, Escarpa A, Avello F.Induction of anaesthesia with etomidate: Haemodynamic study of 36 patients. Br J Anaesth 1980; 52:803-805.

2. Gooding JM, Weng JT, Smith RA, Benninger G,Kirby R. Cardiovascular and pulmonary responses following etomidate induction of anesthesia in patients with demonstrated cardiac disease, Anesth Analg 1979; 58:40-41.

3. Wagner RL, White PF. Etomidate inhibits adrenocortical function in surgical patients. Anesthesiology 1984; 61:647-651.

4. Shuemans V, Dom J, Pong J, Schujgrond H,Brugmans J. Multinational evaluation of Etomidate for anesthesia induction. Anaesthetist 1978;27:52-59.

5. Giese JL, Stockham RJ, Stanley TH, Pace NL,Nelissen RH. Etomidate versus thiopental for induction of anesthesia. Anesth Analg 1985;64:871-876.

6. Holdcroft A, Morgan M, Whitwam JG, Lumley J.Effect of dose and premedication on induction complications with etomidate. Br J Anaesth 1976;48: 199-205.

7. Stockham RJ, Stan1ey TH, Groen F, Gillmor ST, Pace NL, King K. Fentanyl vs. etomidate plus fentanyl for anesthetic induction in high riskpatients. J Cardiothor Anesth 1987; I: 19-23.

8. BMDP Statistical Software, Department of biomathematics, UCLA. University of California Press, Berkeley, California: 1981.

9. Tornetta FJ, Wilson FS. Innovar-nitrous oxideoxygen: A four year clinical appraisal of neuroleptanalgesia. Anesth Analg 1969; 48:850-857.

10. Foldes FF, Kepes ER, Kronfeld PP, Shiffman HP. A rational approach to neuroleptanesthesia. Anesth Analg 1966; 45:642-654.

11. Brown PM, Moss E. Reduction of pain on injection of etomidate. Anaesthesia 1981; 36:814-816.

12. Ouedraogo N, Roux E, Forestier F et al: Effects of intravenous anesthetics on normal and passively sensitized human isolated airway smooth muscle. Anesthesiology, 1998; 88(2): 317–26

13. Yeung JK, Zed PJ: A review of etomidate for rapid sequence intubation in the emergency department. CJEM, 2002; 4(3): 194–98

14. Baird CR, Hay AW, McKeown DW, Ray DC: Rapid sequence induction in the emergency department: induction drug and outcome of patients admitted to the intensive care unit. Emerg Med J, 2009; 26(8): 576–79

15. Reich DL, Hossain S, Krol M et al: Predictors of hypotension after induction of general anesthesia. Anesth Analg, 2005; 101(3): 622–28 266

16. Guler A, Satilmis T, Akinci SB et al: Magnesium sulfate pretreatment reduces myoclonus after etomidate. Anesth Analg, 2005; 101(3): 705–9

17. Mizrak A, Koruk S, Bilgi M et al: Pretreatment with dexmedetomidine or thiopental decreases myoclonus after etomidate: a randomized, double-blind controlled trial. J Surg Res, 2010; 159(1): e11–16

18. Gultop F, Akkaya T, Bedirli N, Gumus H: Lidocaine pretreatment reduces the frequency and severity of myoclonus induced by etomidate. J Anesth, 2010; 24(2): 300–2

19. Do SH, Han SH, Park SH et al: The effect of injection rate on etomidate-induced myoclonus. Korean J Anesthesiol, 2008; 55(3): 305–7

20. Satılmıs T Guler A, Pamuk AG et al: The comparison of different doses of magnesium sulfate to prevent myclonus after etomidate induction. J Turk Anaesth Int Care, 2010; 38(3): 184–89

PROFORMA

NAME :

I.P.NO :

ASA :

AGE & SEX :

WEIGHT :

DATE&TIME OF ADMISSION:

DATE& TIME OF DISHARGE:

DIAGNOSIS :

PROCEDURE :

RELEVANT HISTORY:

CLINICAL EXAMINATION: PR, BP, SPO2, RS, CVS.

BASIC INVESTIGATIONS:

a) Complete Blood Count,

b) Blood grouping & typing,

c) BT,CT

d) Urine routine

e) Blood urea, RBS, Serum Creatinine, Serum electrolytes

f) CXR-PA view

g) ECG,ECHO

ANAESTHETIC TECHNIQUE:

All patients were given glycopyrrolate 10 µg/kg

1) Group I received 2 microgram kg-1 of fentanyl
2) Group II received 5 microgram kg-1 of fentanyl

After 5 minutes of administration of either one of these all patients were induced with etomidate at a dose of 0.3 mg kg-1. Anaesthesia is maintained with N20:O2, titrated doses of inj.atracurium and inj.fentanyl

SIDE EFFECTS:

GROUP	PAIN ON INJECTION	MYOCLONUS	APNOEA	POST OPERATIVE NAUSEA AND VOMITING
I				
II				

MONITORING OF VITALS:

GROUP	BASE LINE	3 MIN AFTER FEN TANYL	2 MIN AFTER ETOMI DATE	1 MIN AFTER SUXA	1 MIN AFTER INTU BATION	MAX CHANGE DURING INTU BATION
	PR BP	PR BP	PR BP	PR BP	PR BP	PR BP
I						
II						

POST OP PERIOD:

HEART RATE

S. No	Name	Age	Sex	Base line	3 mins After	2 mins after	After giving	1 min after	Base line			3 mins After			2 mins after			After giving			1 min after					pain on injection	M clo
					Fentanyl	Etomidate	suxa	intubation	Systolic	Diastolic	MAP	Systolic	Diastolic	MAP	Systolic	Diastolic	MAP	Systolic	Diastolic	MAP	Systolic	Diastolic	MAP		%		
1	Meena	47	F	84.2	84.3	83.7	84.1	107.2	127	77	93.67	121	78	92.33	118	78	91.33	123	79	93.67	155	86	109.00	15.33	14.07	Yes	
2	Latha	55	F	80.8	80.8	82.8	86.3	112.7	129	79	95.67	120	75	90.00	121	81	94.33	122	81	94.67	158	89	112.00	16.33	14.58		
3	Raman	50	M	81.5	81.2	81.7	88.2	109.5	124	73	90.00	123	74	90.33	123	81	95.00	125	75	91.67	161	91	114.33	24.33	21.28		
4	subramani	57	M	82.2	82.3	82.2	89.3	111.9	127	76	93.00	125	77	93.00	118	83	94.67	127	80	95.67	155	85	108.33	15.33	14.15		Y
5	Selvam	19	M	83.6	83.2	81.9	83.8	110.5	129	78	95.00	125	75	91.67	121	77	91.67	122	77	92.00	158	88	111.33	16.33	14.67	Yes	
6	Prakash	27	F	84.1	80.8	82.4	84.4	108.3	123	75	91.00	119	74	89.00	123	80	94.33	125	76	92.33	156	90	112.00	21.00	18.75		
7	Sunder	60	M	85.5	81.7	81.6	86.4	111.1	126	74	91.33	122	77	92.00	117	82	93.67	127	81	96.33	159	87	111.00	19.67	17.72		
8	Karuppanan	29	M	86.8	82.2	81.5	88.2	110.4	128	77	94.00	121	79	93.00	120	79	92.67	121	75	90.33	161	86	111.00	17.00	15.32	Yes	
9	Poonkothai	56	F	87.3	84.2	82.8	89.1	112.1	125	75	91.67	120	75	90.00	118	78	91.33	124	78	93.33	155	89	111.00	19.33	17.42		
10	Seetha	55	F	88.5	84.5	82.4	87.4	109.8	124	74	90.67	123	73	89.67	121	81	94.33	127	77	93.67	160	91	114.00	23.33	20.47		
11	Prasanna	18	M	89.1	85.4	82.1	85.6	108.7	127	77	93.67	125	76	92.33	123	83	96.33	126	76	92.67	157	89	111.67	18.00	16.12	Yes	
12	Rajan	58	M	81.3	86.8	82.4	83.5	111.2	129	79	95.67	119	78	91.67	117	77	90.33	123	79	93.67	156	91	112.67	17.00	15.09		
13	Kalyani	54	F	82.5	87.6	82.2	84.7	107.9	124	75	91.33	120	75	90.00	123	78	93.00	122	81	94.67	159	85	109.67	18.33	16.72		
14	sivakami	55	F	83.2	87.6	83.1	86.2	112.3	127	78	94.33	123	74	90.33	117	81	93.00	125	77	93.00	158	88	111.33	17.00	15.27	Yes	
15	Murugan	59	M	84.4	84.4	82.2	88.6	109.2	129	75	93.00	125	77	93.00	120	83	95.33	125	76	92.33	156	90	112.00	19.00	16.96		
16	Aanandan	25	M	85.3	82.4	83.7	89.2	111.3	123	74	90.33	119	75	89.67	121	79	93.00	127	81	96.33	159	87	111.00	20.67	18.62		y
17	Ambikavathy	54	F	84.4	84.2	82.4	87.4	108.1	126	77	93.33	125	74	91.00	123	78	93.00	122	75	90.67	161	89	113.00	19.67	17.40		
18	Periyatchi	55	F	85.6	85.3	82.7	85.5	109.4	128	73	91.33	125	75	91.67	118	81	93.33	125	78	93.67	155	91	112.33	21.00	18.69	Yes	
19	Poonkothai	31	F	82.8	86.3	82.4	87.6	110.5	125	76	92.33	119	75	89.67	121	83	95.67	127	77	93.67	160	85	110.00	17.67	16.06		
20	Karupppasamy	58	M	83.9	87.5	82.3	85.2	110.6	124	78	93.33	122	74	90.00	123	77	92.33	121	76	91.00	157	88	111.00	17.67	15.92		
21	Kuppan	22	M	84.2	84.9	82.8	83.3	108.8	127	75	92.33	121	77	91.67	117	78	91.00	124	79	94.00	155	90	111.67	19.33	17.31		
22	Ramayee	58	F	85.3	82.4	82.6	83.7	112.2	129	74	92.33	120	73	88.67	120	82	94.67	127	78	94.33	158	87	110.67	18.33	16.57	Yes	
23	Kandan	60	M	82.8	84.6	82.4	84.8	109.7	127	77	93.67	123	76	91.67	121	79	93.00	124	77	92.67	156	86	109.33	15.67	14.33		
24	Raja	34	M	83.5	82.4	81.2	86.5	107.3	129	75	93.00	125	78	93.67	123	78	93.00	127	76	93.00	159	89	112.33	19.33	17.21		
25	Meena	25	F	84.6	83.8	83.4	88.2	112.3	123	74	90.33	119	75	89.67	117	81	93.00	126	79	94.67	161	91	114.33	24.00	20.99	Yes	
26	Ramalingam	57	M	85.4	84.6	82.2	89.2	109.8	126	75	92.00	120	74	89.33	123	83	96.33	123	81	95.00	155	89	111.00	19.00	17.12		
27	Loganathan	55	M	86.5	85.3	82.9	87.8	109.2	128	78	94.67	123	75	91.00	117	77	90.33	122	77	92.00	161	91	114.33	19.67	17.20		
28	Sunderrajan	54	M	87.6	86.5	82.4	89.6	113.4	125	75	91.67	122	73	89.33	120	78	92.00	125	76	92.33	155	91	112.33	20.67	18.40	Yes	
29	Pandiselvi	38	F	82.3	87.3	83.1	87.5	110.3	124	74	90.67	121	76	91.00	121	81	94.33	125	81	95.67	160	85	110.00	19.33	17.58		
30	Selvipriya	54	F	83.7	80.8	80.8	85.4	111.4	127	77	93.67	120	78	92.00	123	83	96.33	127	81	96.33	157	88	111.00	17.33	15.62		

MASTER CHART

				GROUP II					Base line			3 mins After			2 mins after			After giving			1 min after							
S.No	Name	Age	Sex	Base line	3 mins After	2 mins after	After giving	1 min after	Systalic	Diastalic	MAP	Systalic	Diastalic	MAP	Systalic	Diastalic	MAP	Systalic	Diastalic	MAP	Systalic	Diastalic	MAP			pain on injection	Myoclonus	Apnoea	PONV
					Fentanyl	Etomidate	suxa	intubation																				
1	Kapilan	60	M	90	87.2	90.1	93.1	95.8	128	78	94.67	126	74	91.33	119	76	90.33	125	79	94.33	141	81	101.00	6.33	6.27				Yes
2	Lakshmi	58	F	87	83.5	86.1	90.6	93.7	131	81	97.67	123	77	92.33	118	79	92.00	121	78	92.33	135	80	98.33	0.67	0.68				
3	Mari	60	M	87	84.0	86.4	87.7	93.7	133	83	99.67	122	79	93.33	121	81	94.33	120	81	94.00	138	83	101.33	1.67	1.64				Yes
4	Gopi	18	M	88	84.8	87.5	89.8	94.9	128	77	94.00	125	73	90.33	123	75	91.00	123	81	95.00	141	85	103.67	9.67	9.32			Yes	
5	Rajalakshmi	60	F	89	86.2	88.9	87.6	95.9	131	80	97.00	127	76	93.00	118	80	92.67	125	83	97.00	135	79	97.67	0.67	0.68				
6	Mariappan	57	M	89	83.5	86.7	93.0	94.5	133	82	99.00	127	78	94.33	121	77	91.67	120	79	92.67	138	82	100.67	1.67	1.66				
7	selvan	55	M	91	84.4	87.1	90.1	97.3	127	79	95.00	121	75	90.33	123	76	91.67	123	80	94.33	136	84	101.33	6.33	6.25				Yes
8	Benjamin	54	M	93	84.9	87.6	86.1	98.7	130	78	95.33	124	74	90.67	117	81	93.00	125	82	96.33	139	81	100.33	5.00	4.98	Yes			
9	Vadivu	19	F	93	86.8	89.4	86.4	98.6	132	81	98.00	123	77	92.33	120	75	90.00	119	79	92.33	141	80	100.33	2.33	2.33				Yes
10	chellammal	54	F	94	87.2	89.7	87.5	100	129	79	95.67	122	75	90.67	118	78	91.33	122	78	92.67	135	83	100.33	4.67	4.65				
11	Guru	47	M	95	88.1	88.8	89.1	101	128	78	94.67	125	74	91.00	121	77	91.67	125	81	95.67	140	85	103.33	8.67	8.39				
12	saravanan	50	M	87	89.2	91.7	86.7	93.3	131	81	97.67	127	77	93.67	123	76	91.67	124	83	96.67	137	83	101.00	3.33	3.30				Yes
13	Mookayee	22	F	88	90.1	92.6	87.1	93.8	133	83	99.67	121	79	93.00	117	79	91.67	121	77	91.67	136	85	102.00	2.33	2.29				
14	kandan	58	M	89	90.3	93.3	87.6	94.9	128	79	95.33	122	75	90.67	123	81	95.00	120	78	92.00	139	79	99.00	3.67	3.70			Yes	Yes
15	Chellappan	23	M	90	87.1	89.8	89.4	95.7	131	82	98.33	125	78	93.67	117	77	90.33	123	81	95.00	138	82	100.67	2.33	2.32				
16	Kaviya	28	F	91	84.8	88.6	89.9	96.6	133	79	97.00	127	75	92.33	120	76	90.67	125	83	97.00	136	84	101.33	4.33	4.28				
17	Sagundala	30	F	90	87.0	88.9	88.8	95.3	127	78	94.33	121	74	89.67	121	81	94.33	120	79	92.67	139	81	100.33	6.00	5.98				Yes
18	Kaliammal	57	F	91	87.8	90.2	91.7	96.8	130	81	97.33	127	77	93.67	123	75	91.00	123	78	93.00	141	83	102.33	5.00	4.89				
19	Ponnamma	60	F	88	89.0	91.8	92.6	94.1	132	77	95.33	121	73	89.00	118	78	91.33	120	81	94.00	135	85	101.67	6.33	6.23				
20	Jothi	35	F	89	90.4	93.1	93.3	95.2	129	80	96.33	124	76	92.00	121	77	91.67	123	83	96.33	140	79	99.33	3.00	3.02				Yes
21	Annakili	47	F	90	87.8	90.6	89.8	95.6	128	82	97.33	122	78	92.67	123	76	91.67	125	77	93.00	137	82	100.33	3.00	2.99				
22	Pavithra	60	F	91	85.1	87.7	88.6	96.1	131	79	96.33	125	75	91.67	117	79	91.67	119	78	91.67	138	84	102.00	5.67	5.56			Yes	
23	Mohan	60	M	88	87.2	89.8	88.9	94.7	133	78	96.33	127	74	91.67	120	78	92.00	122	82	95.33	140	81	100.67	4.33	4.30				
24	Malarkannan	36	M	89	85.1	87.6	90.2	94.9	131	81	97.67	123	77	92.33	121	77	91.67	125	79	94.33	136	82	100.00	2.33	2.33				Yes
25	Suganya	48	F	91	86.2	88.7	91.8	96.2	133	79	97.00	121	75	90.33	123	76	91.67	124	78	93.33	139	80	99.67	2.67	2.68				
26	sundari	50	F	91	87.1	89.5	88.7	97.1	127	78	94.33	121	74	89.67	117	79	91.67	120	81	94.00	141	85	103.67	9.33	9.00				
27	Selvaraj	38	M	93	88.3	90.8	89.5	98.5	130	79	96.00	122	75	90.67	123	81	95.00	123	83	96.33	135	83	100.33	4.33	4.32				Yes

28	Ramasamy	39	M	94	89.4	92.4	90.8	100	132	82	98.67	125	78	93.67	117	77	90.33	123	77	92.33	141	79	99.67	1.00	1.00				
29	Ponnaiah	57	M	88	90.0	93.0	92.4	94.1	129	79	95.67	124	75	91.33	120	76	90.67	125	78	93.67	135	85	101.67	6.00	5.90				Yes
30	Balammal	56	F	89	83.5	87.4	88.3	94.8	128	78	94.67	123	74	90.33	121	81	94.33	119	81	93.67	140	78	98.67	4.00	4.05				

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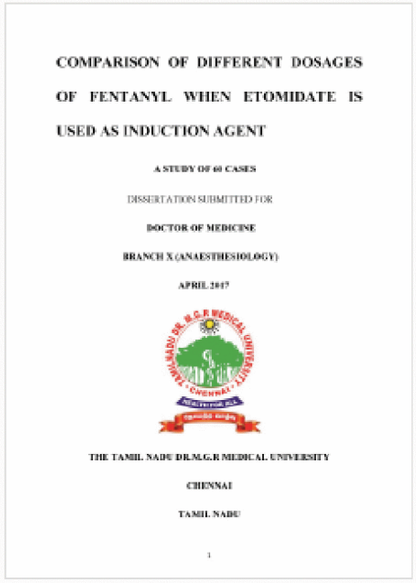

COMPARISON OF DIFFERENT DOSAGES OF FENTANYL WHEN ETOMIDATE IS USED AS INDUCTION AGENT

A STUDY OF 60 CASES

DISSERTATION SUBMITTED FOR

DOCTOR OF MEDICINE

BRANCH X (ANAESTHESIOLOGY)

APRIL 2017

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