"A RANDOMISED CLINICAL STUDY TO COMPARE THE HAEMODYNAMIC EFFECTS OF ETOMIDATE WITH THIOPENTONE SODIUM AND PROPOFOL DURING INDUCTION OF GENERAL ANAESTHESIA".

DISSERTATION

BY

DR. R. Ravi Naik

SUBMITTED TO

KLE UNIVERSITY, BELGAUM

KARNATAKA

IN PARTIAL FULFILLMENT

OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER DEGREE

IN

ANAESTHESIOLOGY

Under the Guidance of

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BELGAUM – 10, KARNATAKA,

MAY 2010

KLE UNIVERSITY, BELGAUM, KARNATAKA

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"A RANDOMISED CLINICAL STUDY TO COMPARE THE HAEMODYNAMIC EFFECTS OF ETOMIDATE WITH THIOPENTONE SODIUM AND PROPOFOL DURING INDUCTION OF GENERAL ANAESTHESIA"** *is a bonafide and genuine research work carried out by me under the guidance of* ***Dr.*** **VANDANA GOGATE** **M.D.** *Associate Professor, Department of Anaesthesiology, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum-590010.*

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Place: Belgaum

Dr. R. Ravi Naik

LIST OF ABBREVATIONS

ASA – American Society of Anesthesiologists

ED- Emergency Department

Group T – Thiopentone sodium group

Group P – Propofol group

Group E – Etomidate group

HR – Heart rate

IV – Intra venous

Kg – Kilogram

mg – Milligram

Sec- Seconds

Min - Minutes

µg – Microgram

bpm – beats per minute

NS – Non significant

S - Significant

SD – Standard Deviation

ponv – Post operative nausea and vomiting

ABSTRACT

Background: Thiopentone sodium and propofol which are used extensively in general anesthesia for induction are known to produce cardiovascular side effects like hypotension and bradycardia or tachycardia. This is disadvantageous especially in patients with borderline cardiac function. Etomidate an inducing agent is believed to produce minimal side effects on cardiovascular system. Hence this study was conducted to compare the hemodynamic effects of Etomidate with thiopentone sodium and propofol.

Objective: To compare the hemodynamic effects of Etomidate with that of Thiopentone and Propofol during induction in general anaesthesia.

Study design: Randomized clinical trial.

Methods: 75 patients of either sex, between age group of 18-50 years who were scheduled to undergo surgery under general anaesthesia after meeting inclusion and exclusion criteria were enrolled for the study. The patients were randomly allocated into three groups (Group T =25 patients), (Group P =25 patients) and (Group E =25 patients). In group T, patients received Thiopentone 5mg/kg, in group P - Propofol 2mg/kg and in group E - Etomidate 0.3mg/kg for induction.

Heart rate and blood pressure were measured before induction, and every minute for 3 minute after induction.

Results: When compared to etomidate group there was a significant fall in blood pressure in both thiopentone and propofol group. There was no significant change in hearts rate in all three groups.

Conclusion: When etomidate is used as an induction agent during general anaesthesia there is a better hemodynamic stability in comparison to thiopentone and propofol.

Key words: Thiopentone sodium, Propofol, Etomidate

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INTRODUCTION

Traditionally anaesthesia meant making patient unconscious by inhaling gases. This allowed patient to undergo surgery and other procedures. The technical difficulties associated with administration of these gases lead to many deaths during anaesthesia. These lead to development of many new apparatus for delivering these gases. These apparatus are more complicated and these inhaled gases did not produce balanced anaesthesia.[1, 2, 3, 4]

Discovery of barbituric acid derivatives lead to the advent of modern intravenous anaesthesia. The ideal intravenous anesthetic drug should provide hypnosis, amnesia, analgesia and muscle relaxation without any side effects.[5]

Thiopentone sodium was synthesized in 1932 and introduced into clinical practice in 1934 by LUNDY. It is considered gold standard inducing agent, because of its rapid onset of action and short duration of action without excitatory effects which is seen during inhalation anesthesia.[6, 7, 8] Use of thiopentone as a sole anaesthetic agent lead to many deaths at Pearl Harbor on 9th December 1941.It was found that these deaths occurred due cardio respiratory depression.[9] Later studies showed that thiopentone causes peripheral vasodilatation, decrease in blood pressure, increase in heart rate and direct negative inotropic effect.[10]

In 1970 a new inducing agent 2, 6-di-isopropofol was discovered and introduced in clinical practice in 1977.[11] It was considered superior to thiopentone because propofol provided faster onset of action, rapid recovery, potent attenuation of pharyngeal,

laryngeal reflexes, adequate depth of anesthesia during intubation and antiemesis.[12, 13, 14] The major disadvantage of propofol is rapid fall in blood pressure due to vasodilatation.[15, 16, 17, 18] The earlier preparation of propofol was insoluble in water and therefore was initially prepared with cremophor EL. Because of anaphylactoid reactions associated with cremophor EL, the drug was reformulated using soya been oil emulsion and reintroduced in 1986.

Etomidate an inducing agent was synthesized in 1964 and introduced in clinical practice in 1972. It provided faster onset of action and rapid recovery with hemodynamic stability and minimal respiratory depression. These beneficial properties lead to wide spread use of etomidate.[21, 22, 23, 24, 25] Use of etomidate declined due to reports of adrenocortical suppression and other minor side effects (pain on injection, myoclonus, and ponv).[29] Rediscovery of beneficial effect of etomidate and lack of new reports of adrenocortical suppression lead to renewed interest for etomidate.[30] The drug was reformulated using lipid emulsion and reintroduced in 2007 in India.

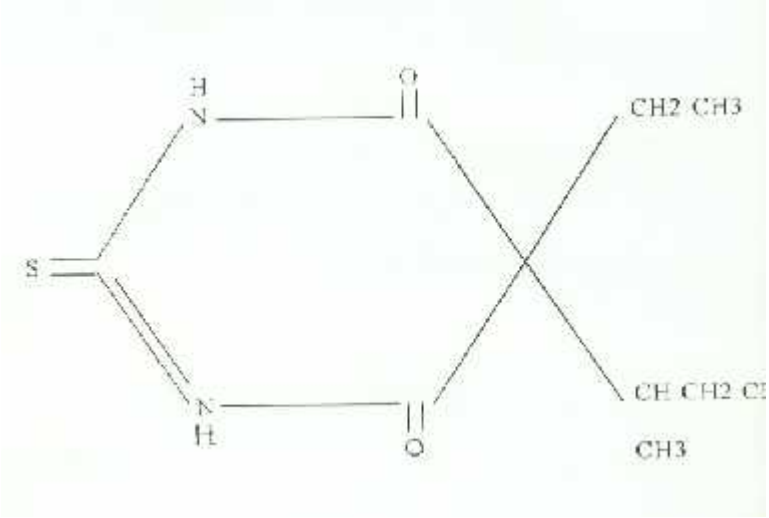
Due to lack of study comparing the hemodynamic stability of thiopentone, propofol and etomidate, under general anaesthesia, we made an attempt to evaluate the hemodynamic stability of etomidate in comparison with thiopentone and propofol during induction in general anesthesia.

OBJECTIVES

To compare etomidate with propofol and thiopentone sodium as an anesthetic induction agent in general anesthesia in standardized premedicated patient with respect to changes to heart rate, systolic blood pressure, diastolic blood pressure and mean blood pressure.

THIOPENTONE[6]

Structure



Chemical name:

5-ethyl 5-(methyl, butyl) 2-thiobarbiturate

History:

The thiobarbiturates were first described in 1903. However, because of fatal experiments in dogs, their use was not further explored until the 1930.

In 1935, Tabern and Volwiler synthesized a series of sulfur containing barbiturates, of which thiopental became the most widely used.

Thiopental was introduced clinically by Ralph Water and John Lundy and became preferred clinically because of the rapid onset of action and short duration, without the excitatory effects of hexobarbital. Even though many other barbiturate derivatives have been synthesized throughout the past several decades, none has enjoyed the clinical success and popularity of thiopental. Thiopental has survived the test of time as an intravenous anaesthetic agent.

Chemistry and Physical Properties:

Thiopentone is an ultra short acting barbiturate. It is a derivative of barbituric acid and is a sulphur analogue of pentobarbitone, which accounts for its rapid induction and recovery.

It is a pale yellow powder, hygroscopic with bitter taste and sulphur smell, resembling that of hydrogen sulphide. It is soluble in water and alcohol, but not very stable and may remain so for 24-48 hours. Commercial preparations contain sodium carbonate 6% which acts as a buffer and prevents precipitation of free acid by atmospheric carbon dioxide and resulting in an alkaline solution (pH 10.5-11). It is largely in unionized form at body pH, a fact which facilitates its diffusion through membranes. The oil/gas solubility ratio is 4.7%, molecular weight 264.3 and pKa 7.6.

Dosage and Administration:

Thiopentone is supplied in vials of 0.5 gm and 1gm which are made up into a 2.5%, solution. The usual induction dose is 4-7 mg kg^{-1} body weight.

Pharmacokinetics:

Thiopentone is highly lipid soluble. Following a bolus iv injection, 60-80 % of the drug becomes bound to plasma proteins. Its high lipid solubility makes it to diffuse rapidly into the brain. EEG changes with loss of consciousness occur in 10-20 sec (one arm brain circulation time). Rapid redistribution into muscles is responsible for rapid recovery from small doses. Thiopentone is metabolized by the liver and virtually none is excreted unchanged. Three pathways of hepatic extraction and metabolism are.

1. Oxidation of C_5 side chain

2. Oxidative replacement of sulphur at C_5 to form pentobarbitone.

3. Cleavage of barbiturate to form urea and three carbon fragments.

$t_{½}\ \alpha_1$ → 2 to 6 min → corresponds to diffusion into tissues of high blood flow

$t_{½}\ \alpha_2$ → 30 to 60 min → diffusion into adipose tissue

$t_{½}\ \beta$ → 3 to 23 hr → elimination phase (due to hepatic metabolism and excretion)

Factors affecting pharmacokinetics:

Pregnancy has little effect on the pharmacokinetics of thiopentone, although the clearance is greater in pregnant patients. The elimination half life is longer. The drug diffuses freely across the placental barrier. Renal failure reduces the dose requirement of

thiopentone. Liver failure may also lead to hypoproteinemia and reduces the dose requirement.

Increasing age is associated with a lower induction dose of thiopentone probably on the basis of lower cardiac out put and failure to compensate for the effects of the drug in the circulation.

Pharmacodynamics:

1) Central Nervous system:

Thiopentone rapidly diffuses across the blood brain barrier, causing cortical depression, the cerebral metabolic requirement of oxygen ($CMRO_2$) falls by about 50% with an infusion of thiopentone. Thiopentone is not an analgesic and small doses may increase sensitivity to pain (antanalgesia)

- It is an anticonvulsant.
- Sympathetic system is depressed more than the parasympathetic system.
- Intra cranial tension is reduced.

2) Cardiovascular system:

Thiopentone when given as a bolus dose causes a reduction in arterial blood pressure with marked peripheral vasodilatation. There is some degree of tachycardia (10-20 %), which contributes to the maintenance of blood pressure and C.O. (cardiac output).

Ability for haemodynamic stability is impaired in hypovolaemic patients and induction is hazardous in patients with compensated shock.

Thiopentone has been shown to increase myocardial oxygen consumption in healthy patients but reduces it by 39 % in those with ischaemic heart disease. The latter effect is due to reduced oxygen requirements and even in patients with ischaemic heart disease there is no evidence that it cause adverse effect.

3) Respiratory system:

It depresses spontaneous respiratory rate and tidal volume, decreases the sensitivity of respiratory centre to CO_2. Laryngeal reflexes are not depressed until deep levels of anesthesia are reached. Minor stimuli frequently cause laryngospasm during light anesthesia. Bronchospasm is common in asthmatics.

4) Action on kidney & liver:

Kidney:

Decreases renal blood flow, increases secretion of antidiuretic hormone, urine out put is decreased.

Liver:

It causes enzyme induction leading to increased drug metabolism and also liver dysfunction in hypoxia and reduced hepatic blood flow conditions.

5) Eye:

Loss of eyelash, conjunctival and corneal reflexes, sensitivity to light reflex is lost in deeper anaesthetic levels but preserved till the patient reaches the surgical plane. It reduces intraocular tension.

6) Pregnant uterus:

It readily crosses placental barrier and maximum concentration in fetus is seen soon after injection. There is no effect on the tone of the uterine musculature.

7) Miscellaneous effects:

Acid base and electrolyte disturbances can occur secondary to hyperventilation, skin rashes and urticarial responses are also reported. Hypersensitivity and anaphylactic responses occasionally occur.

Complications:

Local:

1. Perivenous injection: pain, redness, swelling etc.
2. Intra–arterial injection: Arterial spasm, white hand, and cyanosis, skin discoloration, edema and gangrene.
3. Thrombophlebitis
4. Nerve injury

General:

1. Respiratory depression , apnea, laryngospasm, bronchospasm
2. Circulatory collapse and dysrrythmia
3. Hiccoughs and coughing
4. Euphoria and disorientation
5. Severe anaphylactic reaction

Contra indications:

1. Anaphylaxis to thiopentone
2. Porphyria
3. Fixed low cardiac out put syndrome

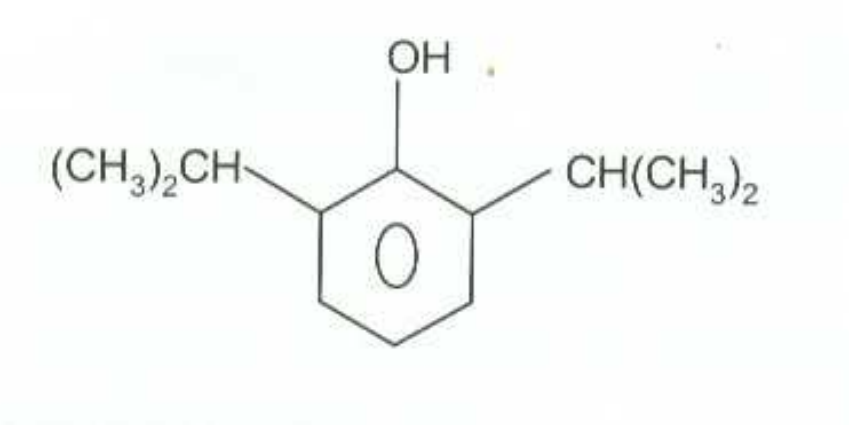
4. Hypovolemic shock
5. It is also not indicated in patients with gross dyspnoea due to respiratory obstruction, asthma and acute inflammation of mouth, jaw and neck.

Indications:

1. For induction of general anaesthesia
2. As sole induction agent for short surgical procedures
3. Supplementation of regional anaesthesia
4. For electro convulsive therapy
5. As an anticonvulsant following local anaesthetic toxicity, eclampsia, epilepsy, tetanus etc.
6. Used in cerebral protection.

PROPOFOL[11]

Structure



Chemical name:

2-6, di-isopropyl phenol

History:

Propofol was first introduced clinically by Ray and Rolly in 1977A lot of work in the early 1970's on substituted derivatives of phenol with hypnotic properties, resulted in the development of 2-6, di-isopropyl phenol.

Propofol is insoluble in water and therefore was initially prepared in with cremophor EL. Because of anaphylactoid reactions associated with cremophor EL, the drug was reformulated using soya been oil emulsion.

Propofol was first marketed in UK in 1986 and since then, has been accepted world wide as a general anaesthetic agent both in developed and developing countries.

Physiochemical Properties:

Chemical formula:	$C_{12}H_{18}0$.	Milky white liquid
Molecular weight:	178.27,	Oil at room temperature
Melting point:	19^0C	highly lipid soluble
Boiling point:	242^0 C	
pH range:	7-8.5	

Formulations:

Each ml. of propofol 1 % (w/v) formulation contains

Propofol : 10 mg (Active ingredient)

Soya bean oil : 10 % Lipid base.

Egg lecithin : 1.2 % Emulsifier

Glycerol : 2.25 % to maintain iso-tonicity.

Distilled water for injection: q.s.

Sodium hydroxide to maintain pH

In USA: Metabisulfite or disodium EDTA added as an anti microbial agent

In Europe: 2% propofol available is compatible with 5% dextrose if dilution is required.

Mechanism of action:

Propofol is primarily a hypnotic. The exact mechanism of action is not known. However evidence suggests that hypnotic actions are mediated by potentiating the Gama-amino butyric acid (GABA) induced chloride current through binding to β-submit of $GABA_A$ receptor sites on β_1, β_2 and β_3 sub-units of trans membrane domains have been shown to be critical for the hypnotic action of propofol.

The α_2 - adrenoceptor system plays an indirect role in the sedative effects of propofol. Propofol also causes widespread inhibition of N-methyl D-aspartate (NMDA) subtype of glutamate receptor through modulation of sodium channel gating, an action which may also contribute to the CNS effects of the drug.

Studies have demonstrated that propofol also has a direct depressant effect on neurons of the spinal cord.

The pharmacokinetics of propofol has been evaluated by numerous investigations and it has been described by both two and three compartment models.

After a single injection whole blood propofol levels decrease rapidly as a result of both redistribution and elimination. In studies using two compartments the initial distribution half life of propofol is 2-8 mins and elimination half life varies from 1.0 to 3 hrs.

An open three compartment model, describes distribution of propofol as:-

1. Rapid initial distribution from the blood to highly perfused tissues (Viz., brain, heart, lung, liver) $t_{½}\ \alpha$ - 1.8 –4.1mins

2. Redistribution and metabolic clearance, $t_{½}\ \beta$ - 21 – 69 mins.

3. Slow return from poorly perfused tissues to blood $t_{½}$ 184 - 834 mins.

The context sensitive half life of propofol is less than 40 mins. More than 98 % of propofol is plasma protein bound and so it has a large central distribution of 20 - 40L. Clearance of propofol is extremely high 1.5 to 2.2 L min^{-1}The time of peak effect is 90-100 sec. The pharmacokinetics of propofol may be altered by a variety of factors viz. gender, weight, pre-existing diseases, age and concomitant medications.

Propofol is rapidly metabolized in the liver by conjugation with glucuronide sulphate to produce soluble compounds, which are excreted by kidneys.

Less than 1 % of propofol is excreted unchanged in urine and only 2 % is excreted in faeces. The metabolites of propofol are not thought to be active.

Since clearance of propofol (1.5 to 2.2 l/min) exceeds hepatic blood flow, extra hepatic metabolism or extra renal elimination has been suggested. This explains the faster and clear headed recovery of its use.

Propofol itself results in concentration dependent inhibition of cytochrome P_{450} enzyme system complex and thus may alter the metabolism of other drugs.

Pharmacodynamics:

Central Nervous system:

Propofol is primarily a hypnotic. The onset of hypnosis after doses of 2.5 mg kg^{-1} is rapid (one arm brain circulation), with a peak effect seen at 90-100 sec. The median effective dose (ED50) of propofol for loss of consciousness is 1-1.5 mg kg-1 after a bolus. The duration of hypnosis being dose dependant, propofol provides sedation and amnesia. It alters the mood to a lesser extent than thiopentone after short surgical

procedures. Propofol also tends to produce a general state of well being. Hallucinations, sexual fantasies and opisthotonus have been reported after propofol administration.

Effects of propofol on EEG are dose dependant. Infusion of propofol demonstrates an initial increase in alpha rhythm, followed by a shift to gamma and theta frequency. High infusion rates produce burst suppression.

Propofol causes a concentration dependant decrease in the bispectral index with 50 % and 90 % patients unable to respond to verbal commands at BIS values of 63 and 51 respectively

Effect of propofol on epileptogenic EEG activity is controversial. Some report dose dependant anticonvulsant effect of propofol. But propofol is also associated with grandmal seizures and has been used for cortical mapping of epileptogenic foci.

Cardiovascular system:

The most prominent effect of propofol is a decrease in arterial blood pressure during induction of anesthesia independent of the presence of cardiovascular disease. An induction dose of 2 to 2.5 mg kg^{-1} produces a 25-40 % reduction in systolic blood pressure similar changes are seen in mean and diastolic blood pressure.

This is associated with a decrease in Cardiac Index (15 %), systemic vascular resistance (15-25 %), left ventricular stroke work index (30 %), mean PAP and PAOP.

The effect is maximal at 2 mins after induction due to -

i. Direct myocardial depression and

ii. Decreased peripheral resistance and preload.

The hypotensive effect of propofol is potentiated by -

1. Hypovolaemia or cardiovascular decompensation.
2. Advanced age
3. Large doses of propofol
4. Pre medication with opioids
5. Pre- existing cardiovascular disease

An infusion of propofol result in significant reduction in both myocardial blood flow and myocardial 0_2 consumption, a finding that suggest preservation of the global myocardial oxygen supply demand ratio

Respiratory system:

Propofol acts as a moderate respiratory depressant and can cause apnea in upto 25-30 % population after an induction dose.

The incidence and duration of apnea is dependent on dose, speed of injection and concomitant pre-medication. The onset of apnea is usually preceded by marked tidal volume reduction and tachypnea.

Propofol is mild bronchodilator and causes bronchodilatation in patients with chronic obstructive pulmonary disease.In animal models propofol significantly reduced free radical mediated and cyclo- oxygenase catalyzed lipid peroxidation so it is proposed that propofol may have an impact on adult respiratory distress syndrome (ARDS)

Effect on liver and kidney function:

Post-operative hepatic function tests are not altered following propofol anesthesia.

No evidence of any altered renal function has been reported.

Effect on uterus:

Propofol has little or no effect on pregnant uterus propofol readily crosses the placenta but usual induction does not appear to depress neonates, propofol has no adverse effects on the uterine contraction or intra-operative blood loss.

Effect on adrenocortical function:

Propofol is not an analgesic but, does not cause ant-analgesia. Propofol causes minimal inhibition of cortisol production unlike other anaesthetic agents. It tends to decrease cortisol levels during infusion period shows no impairment of adrenal-steroidogenesis

Other miscellaneous effects

a) Anti-Emetic effect:

At low (sub – hypnotic) doses, propofol possesses a significant anti – emetic effect. The exact cause is not known. Studies suggest that it may occur as a result of direct depression of chemoreceptor trigger zone (CTZ), may also be due to anti – serotonergic ($5HT3_)$ properties of propofol.

b) Anti-pruritic effect:

At sub – hypnotic doses, propofol has been reported to relieve cholestatic pruritis and is found to be as effective as naloxone in treating pruritis induced by spinal opioids.

c) Anti-oxidant activity:

Propofol has been found to possess anti oxidant effects and thus acts as free

radical scavenger. This suggests that propofol can be useful in conditions such as multi – organ failure and acute respiratory distress syndrome.

d) Anxiolysis:

Sub – hypnotic doses of propofol possess anxiolytic properties strengthening the cause for its use during sedation and as an adjuvant to local or regional anaesthesia.

e) Other effects:

1 Does not interfere with coagulation

2 Does not trigger malignant hyperthermia

3 Can be used in patients with porphyrias

4 Decrease polymorphonuclear leukocyte chemotaxis, but not adherence, phagocytosis and killing.

5 Also inhibits the ability of cancer cells to invade by modulating Rho-A

Side effects:

- Pain on injection
- Pro-convulsant activity viz., myoclonus
- Thrombophlebitis
- Hypotension and apnea
- Supports growth of E-Coli, hence unused infusions should be discarded within 12 hours
- Propofol infusion syndrome
- Rarely anaphylactic reaction.

Presentation:

Propofol is available as 1% i.e. 10 mg/ml emulsion in 10ml and 20 ml vials for induction

and 50ml, 100 ml vials for infusion. In Europe, 2 % formulation is also available, as well as a formulation in which emulsion contains medium and long chain triglycerides.

Dosage:

Induction of anesthesia: Child: 2.5- 3.5 mg/kg

Adult: 1.0 –2.5 mg/kg

Sedation: 25 to 75 $\mu g\ kg^{-1}$ min

Maintenance of anesthesia: 50 to 150 $\mu g\ kg^{-1}\ min^{-1}$

Uses:

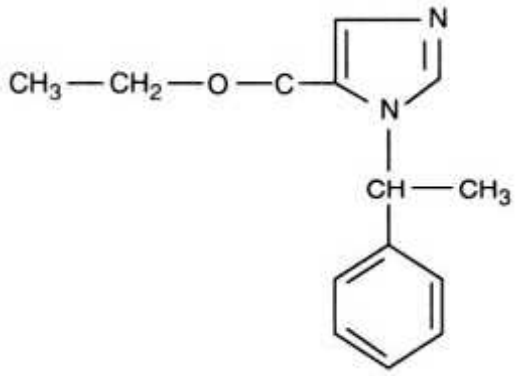
1. For induction and maintenance of general anaesthesia
2. In ICU for IV sedation and total intra-venous anaesthesia (TIVA)
3. For day care surgery as it has rapid recovery
4. In patients with bronchial asthma, porphyria and in those patients where thiopentone is contraindicated
5. In patients with malignant hyperthermia
6. As an anticonvulsant
7. As an antiemetic

Contraindication:

- Patient hypersensitive to propofol formulation
- Hypovolemia
- Epilepsy and dyslipidemia.

ETOMIDATE[21]

Structure



Chemical name:

R-(+)-pentylethyl-1H-imidazole-5 carboxylate sulfate

History:

Etomidate (Amidate, Hypnomidate) was synthesized in 1964 and introduced into clinical practice in 1972. Its properties include hemodynamic stability, minimal respiratory depression, cerebral protection, and pharmacokinetics enabling rapid recovery following either a single dose or a continuous infusion. These beneficial properties led to widespread use of etomidate for induction, for maintenance of anesthesia, and for prolonged sedation in the critically ill. Anesthesiologists' enthusiasm for etomidate, however, was tempered by reports that the drug can cause temporary inhibition of steroid synthesis after both single doses and infusions. This effect, combined with other minor disadvantages (e.g., pain on injection, superficial thrombophlebitis, myoclonus, and a relatively high incidence of nausea and vomiting) led to several editorials questioning the role of etomidate in modern anesthetic practice. Use of the drug waned significantly

following those editorials, but has been expanding over the past several years owing to rediscovery of etomidate beneficial physiologic profile combined with a lack of any new reports describing clinically significant adrenocortical suppression

Physiochemical Properties:

Chemical formula:	C12H180.	Milky white liquid
Molecular weight:	342.36 kd.	Unstable in a neutral solution
PH range:	6.9	water insoluble

Formulations:

Each ml. of Etomidate (w/v) formulation contains

Etomidate : 2 mg /ml (Active ingredient)

Propylene glycol : 35 %

Osmolality : 4640 mOsm/L.

Mechanism of action:

Etomidate is primarily a hypnotic. The exact mechanism of action is not known. However evidence suggests that hypnotic actions are mediated by potentiating the Gama-amino butyric acid (GABA) induced chloride current through binding to β-submit of GABAA receptor sites on β2 and β3 sub-units of trans membrane domains have been shown to be critical for the hypnotic action of etomidate.

Pharmacokinetics:

The pharmacokinetics of etomidate has been calculated following single bolus doses and following continuous infusion.

An open three compartment model, describes distribution of etomidate as:-

- Rapid initial distribution from the blood to highly perfused tissues (Viz., brain, heart, lung, liver) t ½ α - 2.7 mins
- Redistribution and metabolic clearance, t ½ β - 29 mins.
- Slow return from poorly perfused tissues to blood t ½ 2.9 – 5.3 hrs.

The context sensitive half life of etomidate is less than 10 mins. 75 % of etomidate is plasma protein bound Clearance of etomidate by liver is extremely high 18 to 25 ml/kg min-1. The volume of distribution at steady state is 2.5 to 4.5 L/kg. Drugs affecting hepatic blood flow will alter its elimination half-life. Since redistribution is the mechanism whereby the effect of a bolus of etomidate is dissipated, hepatic dysfunction should not appreciably alter recovery from its hypnotic effect .Pathologic conditions altering serum proteins (e.g., hepatic or renal disease) vary the amount of the free (unbound) fraction and may cause a given dose to have an exaggerated pharmacodynamic effect.

In patients with cirrhosis, the volume of distribution is doubled while clearance is normal, the result being an elimination half-life that is twice normal. It is likely that the initial distribution half-life and clinical effect are unaffected. Increasing age is associated with a smaller initial volume of distribution and a decreased clearance of etomidate.

Etomidate is metabolized in the liver primarily by ester hydrolysis to the corresponding carboxylic acid of etomidate (major metabolite) or by N-dealkylation. The main metabolite is inactive. Only 2 percent of the drug is excreted unchanged; the rest being excreted as metabolites by the kidney (85 percent) and bile (13 percent).

Pharmacodynamics:

1) **Central Nervous system:**

Etomidate is primarily a hypnotic. The onset of hypnosis after doses of 0.3 mg kg-1 is rapid (one arm brain circulation).Etomidate has no analgesic activity.

Plasma levels required during the maintenance of anesthesia are approximately 300 to 500 ng/ml, those for sedation 150 to 300 ng/ml, and those for awakening 150 to 250 ng/ml. At a dose of 0.2 to 0.3 mg/kg, etomidate reduces CBF (by 34 percent) and CMRO2 (by 45 percent) without altering mean arterial pressure. Thus, cerebral perfusion pressure is maintained or increased, and there is a beneficial net increase in the cerebral oxygen supply/demand ratio.

Etomidate given in doses sufficient to produce EEG burst suppression acutely lowers ICP by up to 50 percent in patients with already raised ICP, returning raised ICP to almost normal values. The decrease in ICP is maintained in the period immediately following intubation To maintain the effects of etomidate on ICP, high infusion rates (60 mg/kg/min) are necessary. In contrast to the situation with other neuroprotective agents such as thiopental, reduction of ICP and maintenance of burst suppression are not associated with a drop in mean arterial blood pressure. Since cerebral vascular reactivity is still maintained following etomidate administration, hyperventilation theoretically may further reduce ICP when used in conjunction with etomidate

A dose of 0.3 mg/kg rapidly reduces intraocular pressure by 30 to 60 percent. The decrease in intraocular pressure following a single dose lasts 5 minutes, but the reduction may be maintained by an infusion of 20 mg/kg/min.

Etomidate produces changes in the EEG similar to those produced by the barbiturates. There is an initial increase in a amplitude with sharp b bursts followed by mixed d-u waves, with d-wave activity predominating prior to the onset of periodic burst

suppression. The absence of b waves in the initial phase of induction with etomidate is the major difference in EEG changes as compared with thiopental. Etomidate has been associated with grand mal seizures and has been shown to produce increased EEG activity in epileptogenic foci. This has proved useful for intraoperative mapping of seizure foci prior to surgical ablation.

Etomidate is also associated with a high incidence of myoclonic movement, but the myoclonus is not associated with seizure-like EEG activity. The myoclonic movement is believed to result from activity either in the brain stem or in deep cerebral structures.The effect of etomidate on auditory evoked potentials is similar to that produced by the inhaled anesthetics

2) **Cardiovascular system:**

An induction dose of 0.3 mg/kg of etomidate given to cardiac patients for noncardiac surgery results in almost no change in heart rate, mean arterial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, central venous pressure, stroke volume, cardiac index, and pulmonary and systemic vascular resistant.

A relatively large dose of etomidate, 0.45 mg/kg (which is 50 percent larger than a normal induction dose), also produces minimal changes in cardiovascular parameters. In patients with ischemic heart disease or valvular pathology, etomidate (0.3 mg/kg) produces similar minimal alterations in cardiovascular parameters. In patients with mitral or aortic valve pathology, etomidate may produce greater changes in mean arterial pressure (an approximate 20 percent decrease) than in patients without cardiac valvular disease.

Following induction (18 mg) and infusion (2.4 mg/min), etomidate produces a 50

percent decrease in myocardial blood flow and oxygen consumption and a 20 to 30 percent increase in coronary sinus blood oxygen saturation. Myocardial oxygen/supply demand ratio is thus well maintained.

The hemodynamic stability seen with etomidate may be due in part to its unique lack of effect both on the sympathetic nervous system and on baroreceptor function. However, etomidate, because of its lack of analgesic efficacy, may not totally ablate the sympathetic response to laryngoscopy and intubation. Thus, for the smoothest hemodynamic induction/intubation sequence, a low dose (1.5 to 5.0 mg/kg) of fentanyl is often combined with etomidate.

3) **Respiratory system:**

Etomidate has minimal effect on ventilation. It does not induce histamine release either in normal patients or in patients with reactive airways disease. Ventilatory response to carbon dioxide is depressed by etomidate, but the ventilatory drive at any given carbon dioxide tension is greater than that following an equipotent dose of methohexital..

Induction with etomidate produces a brief period of hyperventilation, sometimes followed by a similarly brief period of apnea, which results in a slight (±15 percent) increase in PaCO2 but no change in PaO2.Hiccups or coughing may accompany etomidate induction, with an incidence similar to that following methohexital induction

4) **Effect on adrenocortical function:**

The specific endocrine effects manifested by etomidate are a dose-dependent reversible inhibition of the enzyme 11b-hydroxylase, which converts 11-deoxycortisol to cortisol, and a relatively minor effect on 17-a-hydroxylase. This results in an increase in the cortisol precursor’s 11-deoxycortisol and 17-hydroxyprogesterone as well as an

increase in adrenocorticotropic hormone (ACTH). The blockade of 11-b-hydroxylase (and to a lesser extent 17-a-hydroxylase) appears to be related to the free imidazole radical of etomidate-binding cytochrome P450. This results in inhibition of ascorbic acid resynthesis, which is required for steroid production in humans. The blockade of the cytochrome P450-dependent enzyme 11-b-hydroxylase also results in decreased mineralocorticoid production and an increase in intermediaries (11-deoxycorticosterone). Vitamin C supplementation restores cortisol levels to normal following use of etomidate.

However, the universal lack of demonstrable negative effect from temporary adrenocortical suppression associated with induction doses of etomidate in any study, as well as the finding that mean cortisol levels usually remain in the low normal range after etomidate induction, suggests that the issue of temporary adrenocortical suppression following induction doses may not be clinically significant.

Other miscellaneous effects:

1. Nausea and vomiting, pain on injection, myoclonic movement and hic-cups. Superficial thrombophlebitis of the vein used may occur 48 to 72 hours after etomidate injection.

2. Etomidate reduces the ED50 of pancuronium and therefore appears to enhance the neuromuscular blockade of nondepolarizing neuromuscular blockers.

3. Hepatic function is unaltered by etomidate.

4. In vitro, etomidate inhibits aminolivulinic acid synthetase, but it has been administered to patients with porphyria without inducing an acute attack of porphyria.

Presentation:

Etomidate is available as 2 mg/ml emulsion in 10ml .In Europe, new formulation

in lipid emulsion also available, in which emulsion contains medium and long chain triglycerides.

Dosage:

Induction of anesthesia: 0.2 – 0.6 mg/kg IV

Sedation: 5 to 10 µg kg–1 min

Maintenance of anesthesia: 10 µg kg–1 min–1 IV with N2O and an opiate.

Uses:

1. For induction and maintenance of general anaesthesia for patients with cardiovascular disease, reactive airways disease, intracranial hypertension, or any combination of pathologies indicating the need for an induction agent with limited or beneficial physiologic side effects
2. For cardioversion, in hemodynamically unstable patients,
3. For day care surgery as it has rapid recovery
4. In patients with porphyria and in those patients where thiopentone is contraindicated
5. Short-term sedation for those requiring sedation following an acute myocardial infarction or with unstable angina for a minor operative procedure or for intubation both in the emergency room and the ICU.
6. Electroconvulsive therapy.

REVIEW OF LITERATURE

The technique of anesthesia before 1930's was administration of one or two volatile agents to produce unconsciousness, muscle relaxation and deafferentation.[1]

In 1846 on 16th October W.T.G.Morton demonstrated ether anaesthesia at Massachusetts general hospital[1].

John snow investigated into new anesthetics agents and methods of their administration and devised several pieces of apparatus for delivering to patients known % concentration of anesthetic vapors in an attempt to increase safety.[1]

The technical difficulties associated with administration of these gases lead to many deaths during anesthesia. These lead to development of many new apparatus for delivering these gases. These apparatus are more complicated and these inhaled gases did not produce balanced anesthesia.[2,3,4]

The technique of intravenous anesthesia started gaining popularity because of its ease of administration.[5]

In 1872, French surgeon, Pierre Cyprien experimented with intravenous injection of chloral hydrate but undesirable side effects of prolonged unconsciousness did not give popularity to this drug.[5]

In 1903 Fisher and Von Mering synthesized the first barbiturate - barbital, Phenobarbital and all other successors had very protracted action and found little use in intravenous anesthesia.[8]

In 1932 first short acting oxybarbiturate hexobarbital was used clinically and was enthusiastically used clinically for its short induction time.[8]

In 1932 Thiopentone was synthesized by Volwiler and Tabern but it was on 8th march 1934 Sir Water and on 18th June 1934 Lundy of Mayo clinic introduced Thiopentone in clinical practice. [6, 8]

Thiopentone gained popularity because of its fast onset of action and smooth induction and considered gold standard inducing drug[7]. In 1941, when it was given as a sole agent to war causalities at Pearl Harbour, it had disastrous consequences.[9]

In 1969 Dr.Edward and Dr. Dwyer observed the effect of thiopentone anesthesia on left ventricular function in humans. It was shown that induction with thiopentone is associated with increase in heart rate by 5 beats per minute, and decrease in both cardiac output by 25% and stroke volume by 21%.[10]

In 1977 the first clinical trials with IC 35868 were carried out by Dr.Ronald Shark. Propofol was introduced clinically by Dr.Brain Kay and Dr.Gorges Rolly.[11,12]

When compared with thiopentone, induction with propofol was smoother, more rapid and had rapid awakening, orientation times.[13]

Mackenzie N, Grant IS in the year 1985 compared propofol with methohexitone and thiopentone for induction of anaesthesia in day care patients. The conclusion of the study was that propofol was a suitable agent for day case with smooth and rapid induction and recovery. During the study, it was found that, propofol caused more marked decreases in systolic arterial blood pressure in the first 2 minutes after induction,

with more than half of the patients experiencing a decrease of more than 20%. The mean decrease in the systolic blood pressure in the propofol group was 30 mmHg, compared to18mmHg in the other groups[14].

In 1985, Grounds and colleagues compared hemodynamic effects of thiopentone and propofol and noted greater hypotensive effect with propofol than thiopentone[15]. A similar conclusion was also drawn by Rolly and Versichelen when they compared propofol and thiopentone for induction in unpremedicated patients.[16]

In 1991 Fairfield and colleagues observed the hemodynamic effects of propofol induction and noted that at 2 min. after induction there was a fall in heart rate, cardiac output, and mean arterial pressure.[17]

Lindgren and Randell in the year 1993 compared hemodynamic and catecholamine responses to induction of anesthesia and tracheal intubation between propofol and thiopentone in 24 ASA I patients. With thiopentone, heart rate was greater than propofol before intubation. During induction, systolic and diastolic arterial pressure decreased more with propofol than with thiopentone. In both groups, HR, SAP, and DAP were increased in response to intubation. The SAP responses to intubation were significantly greater with thiopentone than with propofol. In both groups, concentrations of noradrenalin in mixed venous plasma increased after intubation .Concentrations of adrenaline increased after intubation only in the thiopentone group[18].

In 1999 Williams and Thomas conducted a study on 30 children with congenital heart disease undergoing elective cardiac catheterization to know the hemodynamic effects of propofol. Sixteen patients were without cardiac shunt, six had left-to-right

cardiac shunt, and eight had right-to-left cardiac shunt. After sedation and cardiac catheter insertion, hemodynamic data and oxygen consumption were measured before and after the administration of propofol. After the propofol administration, systemic mean arterial pressure and systemic vascular resistance decreased significantly and systemic blood flow increased significantly in all patient groups. Heart rate, pulmonary mean arterial pressure, and pulmonary vascular resistance were unchanged. Propofol can result in clinically important changes in cardiac shunt direction and flow[19].

In 2008 Jack and colleagues conducted a study on 10 patients to know cardiovascular changes after achieving constant effect site concentration of propofol, it was observed that there was a fall in heart rate by 21%, cardiac index by 14% mean arterial pressure by 28% due to vasodilatation.[20]

Etomidate (Amidate, Hypnomidate) was synthesized in 1964 and introduced into clinical practice in 1972. Its properties include hemodynamic stability, minimal respiratory depression, cerebral protection, and pharmacokinetics enabling rapid recovery following either a single dose or a continuous infusion. These beneficial properties led to widespread use of etomidate for induction, for maintenance of anesthesia, and for prolonged sedation in the critically ill.[21] Anesthesiologists' enthusiasm for etomidate, however, was tempered by reports that the drug can cause temporary inhibition of steroid synthesis after both single doses and infusions. This effect, combined with other minor disadvantages (e.g., pain on injection, superficial thrombophlebitis, myoclonus, and a relatively high incidence of nausea and vomiting) led to several editorials questioning the role of etomidate in modern anesthetic practice. Use of the drug waned significantly following those editorials. Rediscovery of the beneficial physiologic profile of etomidate

combined with a lack of any new reports describing clinically significant adrenocortical suppression[21] lead to renewed interest for the drug since 2000.

In 1986 Dundee and colleagues conducted a study comparing the induction characteristics of 4 intravenous anesthetic agents, showed that induction was successful with thiopentone 5mg/kg, etomidate 0.3mg/kg, propofol 2mg/kg, and methohexitone 1.5 mg/kg. Propofol produced more hypotension than thiopentone. In propofol group mean blood pressure decreased by 15%, in thiopentone group decreased by 10% ,in etomidate group decreased by 5 %.[22]

In 1992 Ebert and colleagues conducted a study to know the Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. It showed that Etomidate maintains hemodynamic stability through preservation of both sympathetic outflow and autonomic reflexes where as propofol induced hypotension by an inhibition of the sympathetic nervous system and impairment of baroreflex regulatory mechanisms. Both cardiac and sympathetic baroslopes were maintained with etomidate but were significantly reduced with propofol, especially in response to hypotension.[23]

In another study conducted by Sprung and colleagues in the year 2000 showed the effects of etomidate on contractility of human cardiac muscle. In human myocardium, etomidate exerts a dose-dependent negative inotropic effect, which is reversible with β-adrenergic stimulation. Concentrations required to produce these negative inotropic effects are, in excess of those reached during clinical use. Therefore, etomidate-induced negative inotropy is unlikely to be a problem clinically, even in patients with cardiac dysfunction[24].

In 2005 Molly, Peter and colleagues conducted a study on twelve children undergoing cardiac catheterization for procedures such as device closure of secundum atrial septal defects and radiofrequency catheter ablation procedures for supraventricular tachycardia Using IV sedation, they studied the hemodynamic effects of etomidate. For the entire group, no significant changes in right atrial, aortic, or pulmonary artery pressure, oxygen saturations, calculated Qp:Qs ratio or systemic or pulmonary vascular resistance were detected after the bolus dose of etomidate. The lack of clinically significant hemodynamic changes after etomidate administration supports the clinical impression that etomidate is safe in children.[25]

Bendel, Ruokonen and colleagues in the year 2005 conducted a randomized double-blind study comparing the hemodynamic effects of propofol and etomidate in patients with severe aortic stenosis. Sixty-six patients with severe aortic stenosis scheduled for elective aortic valve replacement were induced with propofol or etomidate. MAP decreased in all patients MAP decreased to a greater extent in patients receiving propofol than in those receiving etomidate .Patients receiving propofol needed phenyl ephedrine more often than those receiving etomidate (20/30 vs. 8/30,).CI and PCWP decreased in both groups with no difference between the groups. Patients receiving etomidate had a lower serum cortisol concentration immediately after the operation than those receiving propofol, but no differences between the groups were observed on the first post-operative morning.[26]

In an Observational Cohort Study, the Intubating Conditions and Hemodynamic Effects of Etomidate for Rapid Sequence Intubation in the Emergency Department showed that etomidate provided appropriate Intubating conditions and hemodynamic

stability in a heterogeneous group of patients. Hemodynamic stability appears to be present following administration of this agent, even in patients with low pre- Rapid Sequence Intubation blood pressure.[27]

Toklu and colleagues in the year 2009, compared the hemodynamic and sedation quality of etomidate-remifentanil and propofol-remifentanil sedation in patients scheduled for colonoscopy. Mean arterial pressure was lower in the propofol group. Mean respiratory rate in the propofol group was also lower. The incidence of apnea and hypotension was significantly lower in the etomidate group. Arrival time into the postoperative care unit and recovery time were shorter in the etomidate group. Etomidate-remifentanil administration for sedation and analgesia during colonoscopy resulted in more stable hemodynamic responses and shorter recovery and discharge times.[31]

Most of the above studies were conducted on western population. Very few studies are available which compare the hemodynamic effects of etomidate as an inducing agent recently reintroduced, with thiopentone and propofol in the Indian population.

Hence this study was conducted comparing the hemodynamic effects of etomidate with thiopentone and propofol during induction in general anesthesia.

METHODOLOGY

The study was conducted after approval from institutional ethics committee. The study was conducted in seventy five adult patients belonging to ASA grade I and II, undergoing elective surgery under general anesthesia. The study was conducted in the age group of 18 to 50 years of both sexes. Informed written consent was obtained from the patient.

A sample size of 75 was calculated. It was calculated by taking a difference of 25mm of Hg in blood pressure as significant, with p- value 0.05 ($Z\alpha = 2.58$) and the power of study as 90% ($Z\beta = 1.64$). The study population was divided into three groups of 25 each – group T, group P and group E.

INCLUSION CRITERIA:

i) ASA grades I and II.

ii) Age between 18-50 years

iii) Patients undergoing General anesthesia.

EXCLUSION CRITERIA:

i) ASA grade>II

ii) Age less than 18years and age more than 50 years.

iii) Patients with Diabetes mellitus, hypertension.

iv) Patients taken for emergency surgery

PRE-ANAESTHETIC EVALUATION:

A thorough pre-anesthetic evaluation was performed by taking history and clinical examination. In all patients pulse rate, blood pressure, respiratory rate and relevant clinical signs if any were recorded.

INVESTIGATIONS:

Hb %:

Urine routine: (Sugar, Albumin, Micro.)

If required other necessary investigations done. Eg.ECG if age > 40 years.

RANDOMIZATION:

Patients were allocated randomly by computer generated random number table into three groups. Group T, group P and group E of 25 each.

DATA COLLECTION PROCEDURE:

On the day of surgery, pre-operative baseline values of heart rate and blood pressure were recorded. I.V line secured with 18g branula for males, 20g branula for females in a peripheral vein. Patients were premedicated with injection midazolam 0.05mg/kg body weight intravenously, injection fentanyl 1 microgram/kg body weight intravenously. One minute after premedication, heart rate and blood pressure were recorded. Patients preoxygenated with 100% oxygen for 3 min.

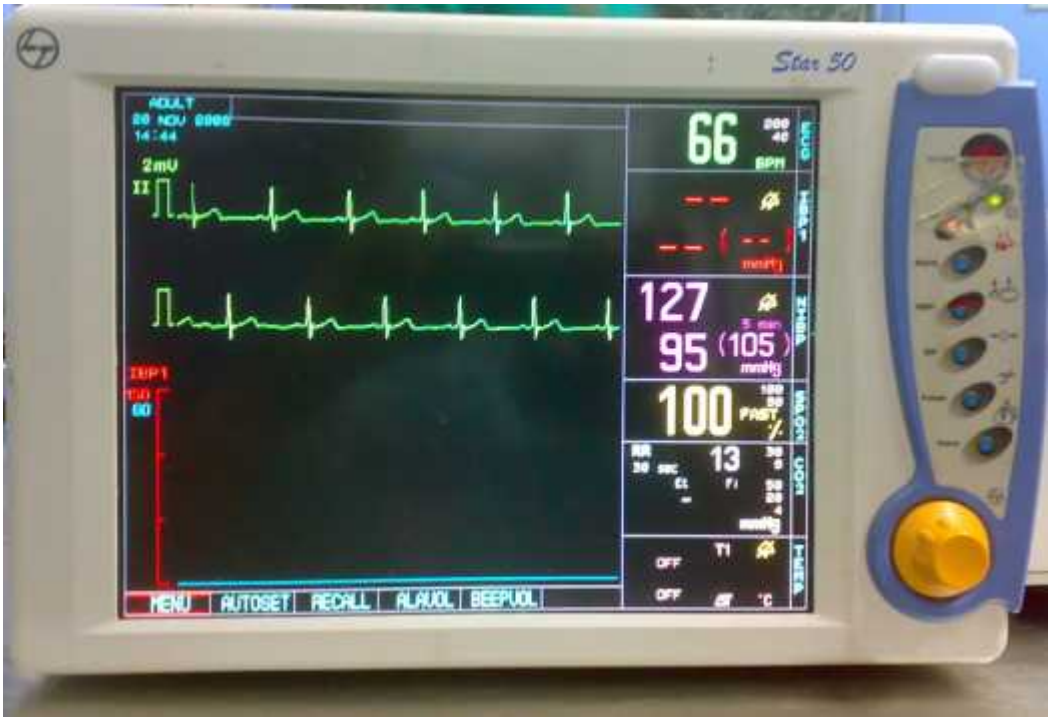
In group T patients were induced with injection thiopentone sodium 5mg/kg body weight intravenously, in group P patients were induced with injection propofol 2mg/kg body weight intravenously and in group E patients were induced with injection etomidate 0.3 mg/kg body weight intravenously. Heart rate and blood pressure were recorded during induction and every minute for three minutes after induction. Induction of anesthesia is defined as the disappearance of eyelash reflex.100% oxygen administration was continued. Ventilation was assisted if patients developed apnea. Apnea is defined as no respiration for more than 10 seconds.

MONITORING:

All patients had continuous pulse oximeter; ECG monitoring and blood pressure monitoring. Baseline Heart rate, systolic, diastolic and mean arterial pressures were noted just before securing the intravenous cannula. The same parameters were noted one minute after pre-medication, during induction, and every minute up to three minute after induction. Systolic, diastolic and mean arterial pressures were recorded and monitored using an automated blood pressure machine.

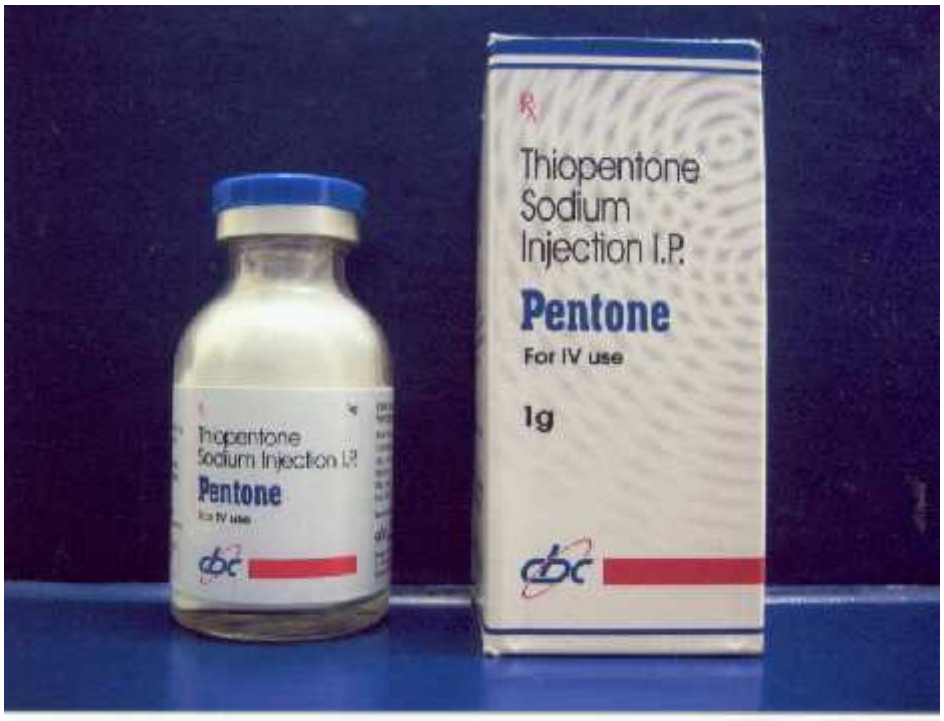
STATISTICAL ANALYSIS:

Data are presented as mean and standard deviation. Statistical analysis of the demographic data was done by using chi-square test. The paired Student t-test was used for quantitative data and $p<0.05$ will be considered significant. The statistical analysis was performed using Microsoft office (2007).



Larsen and Toubro Monitor (Star 50)

Etomidate ampoule (10ml)



Thiopentone vial (1 gm)

Propofol 1% Vial (10 ml)

RESULTS

The present study was undertaken in 75 ASA class 1& 2 patients of either sex between 18 – 50 years, scheduled for elective surgeries under general anesthesia. The patients were divided into three groups, as group T, group P and group E.

The objective of the study was to compare the hemodynamic effects of etomidate with that of thiopentone and propofol during induction in general anesthesia.

The hemodynamic parameters were compared just before induction, during induction, one minute after induction, two minute after induction, and three minute after induction.

TABLE 1: COMPARISON OF DEMOGRAPHIC DATA BETWEEN THREE GROUPS.

	GROUP T (Mean ± SD)	**GROUP P (Mean ± SD)**	**GROUP E (Mean ± SD)**	**'p - VALUE**
AGE	36.8 ± 9.46	33.1 ± 10.28	36.9 ± 10.05	0.302
SEX (M/F)	11/14	11/14	15/10	0.426

The demographic data were comparable for age and gender in all three groups as shown in table 1.

TABLE 2: CHANGES IN MEAN HEART RATE IN THREE GROUPS.

(GRAPH 1):

TIME	GROUP - T	'p - value	GROUP - P	'p - value	GROUP - E	'p - value
BASE LINE	90.8 ± 14.58	-	88.8 ± 16.64	-	83.2 ± 11.04	-
PRE –MEDICATION	83.6 ± 15.28	-	83.9 ± 16.94	-	79.2 ± 11.28	-
INDUCTION	86.1 ± 14.57	-	83.2 ± 13.36	-	77.5 ± 10.34	-
1' AFTER INDUCTION	88.8 ± 14.3	0.511	81.3 ± 12.14	0.599	77.3 ± 9.75	0.944
2' AFTER INDUCTION	88.6 ± 12.33	0.519	80.9 ± 12.57	0.532	77.7 ± 9.62	0.943
3' AFTER INDUCTION	90.1 ± 11.07	0.284	82.6 ± 12.46	0.869	77.5 ± 10.19	1.000

In all three groups there is no significant change in heart rate, 1^{st}, 2^{nd} and 3^{rd} minute after induction when compared with induction value, as shown in table 2.

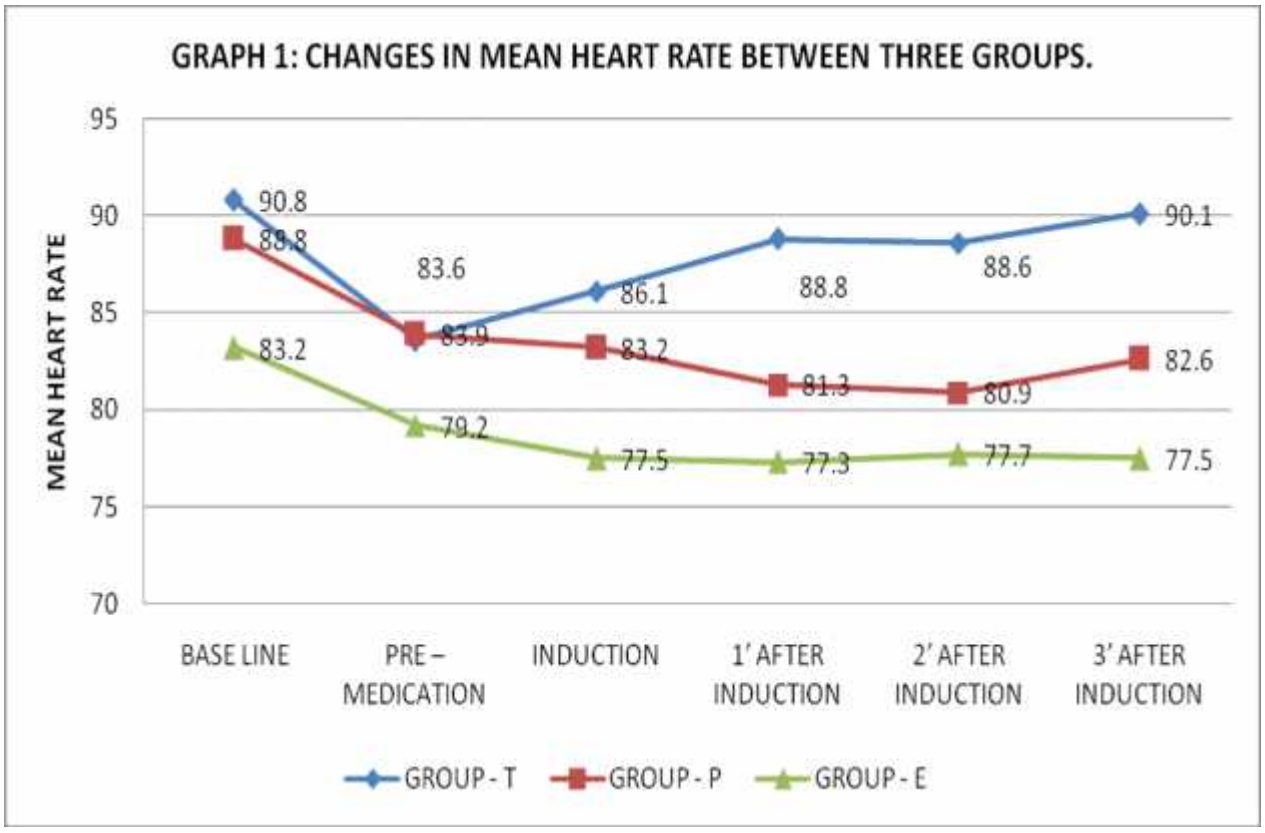

GRAPH 1: CHANGES IN MEAN HEART RATE BETWEEN THREE GROUPS.
MEAN HEART RATE
95
90
85
80
75
70
90.8
88.8
83.6
86.1
88.8
88.6
90.1
83.2
83.9
83.2
81.3
80.9
82.6
79.2
77.5
77.3
77.7
77.5
BASE LINE
PRE – MEDICATION
INDUCTION
1' AFTER INDUCTION
2' AFTER INDUCTION
3' AFTER INDUCTION
GROUP - T
GROUP - P
GROUP - E

TABLE 3: CHANGES IN MEAN SYSTOLIC BLOOD PRESSURE IN THREE GROUPS. (GRAPH 2)

TIME	GROUP - T	'p - value	GROUP - P	'p - value	GROUP - E	'p - value
BASE LINE	138.4 ± 15.31	-	131.5 ± 10.21	-	128.5 ± 11.23	-
PRE –MEDICATION	131.1 ± 14.98	-	124.9 ± 10.42	-	122.4 ± 9.95	-
INDUCTION	122.1 ± 14.21	-	118.2 ± 7.15	-	115.1 ± 12.14	-
1' AFTER INDUCTION	113.9 ± 14.18	0.046	106.8 ± 9.53	0.000	114.5 ± 12.55	0.864
2' AFTER INDUCTION	113.3 ± 11.96	0.023	104.8 ± 10.46	0.000	115.1 ± 13.21	1.000
3' AFTER INDUCTION	113.5 ± 12.54	0.026	107.5 ± 11.77	0.000	114.4 ± 13.26	0.845

In group T there is significant fall in mean systolic blood pressure at 1st, 2nd and 3rd minute after induction when compared with induction value, the maximum fall is during 2nd minute, as shown in table 3.

In group P there is significant fall in mean systolic blood pressure at 1st, 2nd and 3rd minute after induction when compared with induction value, the maximum fall is during 2nd minute, as shown in table 3.

In group E there is no significant change in mean systolic blood pressure at 1st, 2nd and 3rd minute after induction when compared with induction value, as shown in table 3.

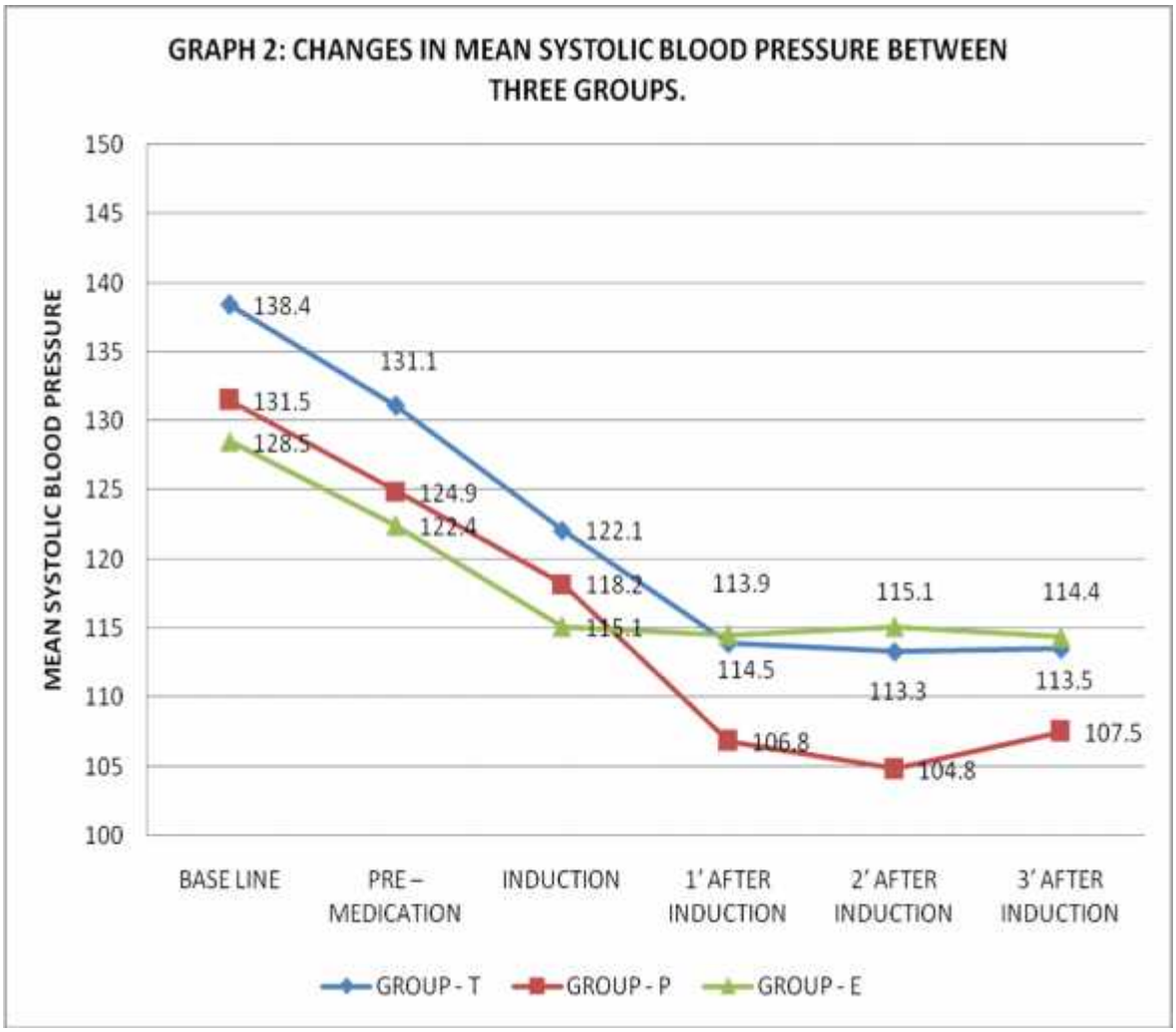

GRAPH 2: CHANGES IN MEAN SYSTOLIC BLOOD PRESSURE BETWEEN THREE GROUPS.
MEAN SYSTOLIC BLOOD PRESSURE
150
145
140
135
130
125
120
115
110
105
100
138.4
131.1
122.1
113.9
115.1
114.4
131.5
124.9
118.2
115.1
114.5
113.3
113.5
128.5
122.4
106.8
104.8
107.5
BASE LINE
PRE – MEDICATION
INDUCTION
1' AFTER INDUCTION
2' AFTER INDUCTION
3' AFTER INDUCTION
GROUP - T
GROUP - P
GROUP - E

TABLE 4: CHANGES IN MEAN DIASTOLIC BLOOD PRESSURE IN THREE GROUPS. (GRAPH 3)

TIME	GROUP - T	'p - value	GROUP - P	'p - value	GROUP - E	'p - value
BASE LINE	84.1 ± 11.81	-	84.6 ± 10.03	-	81.6 ± 9.17	-
PRE –MEDICATION	82.6 ± 9.93	-	79.2 ± 12.84	-	77.2 ± 10.37	-
INDUCTION	78.2 ± 11.18	-	74.4 ± 10.15	-	72.4 ± 11.23	-
1' AFTER INDUCTION	74.8 ± 11.98	0.303	66.6 ± 11.49	0.013	71.4 ± 12.01	0.761
2' AFTER INDUCTION	74 ± 10.69	0.180	64.9 ± 10.71	0.002	71.9 ± 11.87	0.878
3' AFTER INDUCTION	74.4 ± 11.19	0.235	69 ± 11.82	0.089	71.4 ± 12.26	0.764

In group T there is no significant fall in mean diastolic blood pressure at 1st, 2nd and 3rd minute after induction when compared with induction value, as shown in table 4.

In group P there is significant fall in mean diastolic blood pressure at 1st and 2nd minute after induction when compared with induction value, as shown in table 4.

In group E there is no significant fall in mean diastolic blood pressure at 1st, 2nd and 3rd minute after induction when compared with induction value, as shown in table 4.

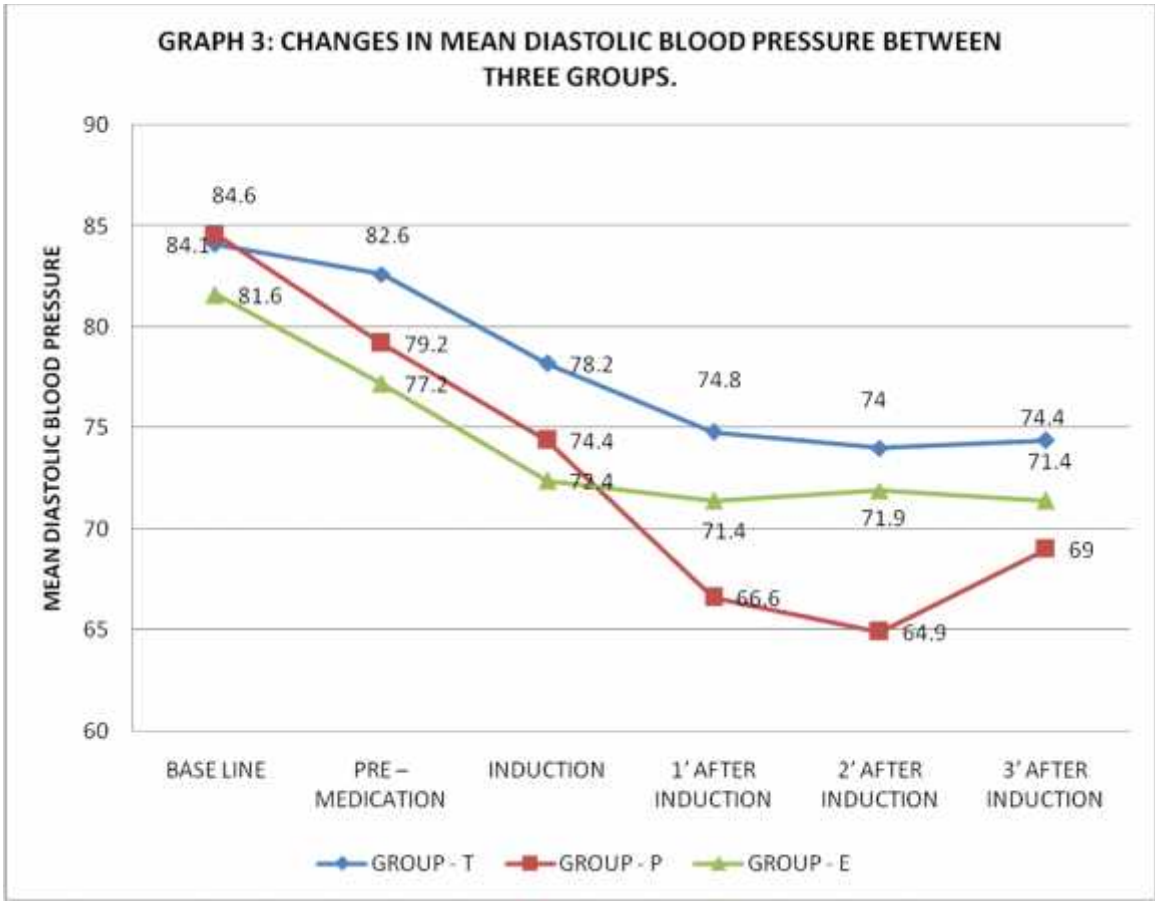

GRAPH 3: CHANGES IN MEAN DIASTOLIC BLOOD PRESSURE BETWEEN THREE GROUPS.
MEAN DIASTOLIC BLOOD PRESSURE
90
85
80
75
70
65
60
84.6
84.1
82.6
81.6
79.2
77.2
78.2
74.4
72.4
74.8
71.4
74
71.9
74.4
71.4
69
66.6
64.9
BASE LINE
PRE – MEDICATION
INDUCTION
1' AFTER INDUCTION
2' AFTER INDUCTION
3' AFTER INDUCTION
GROUP - T
GROUP - P
GROUP - E

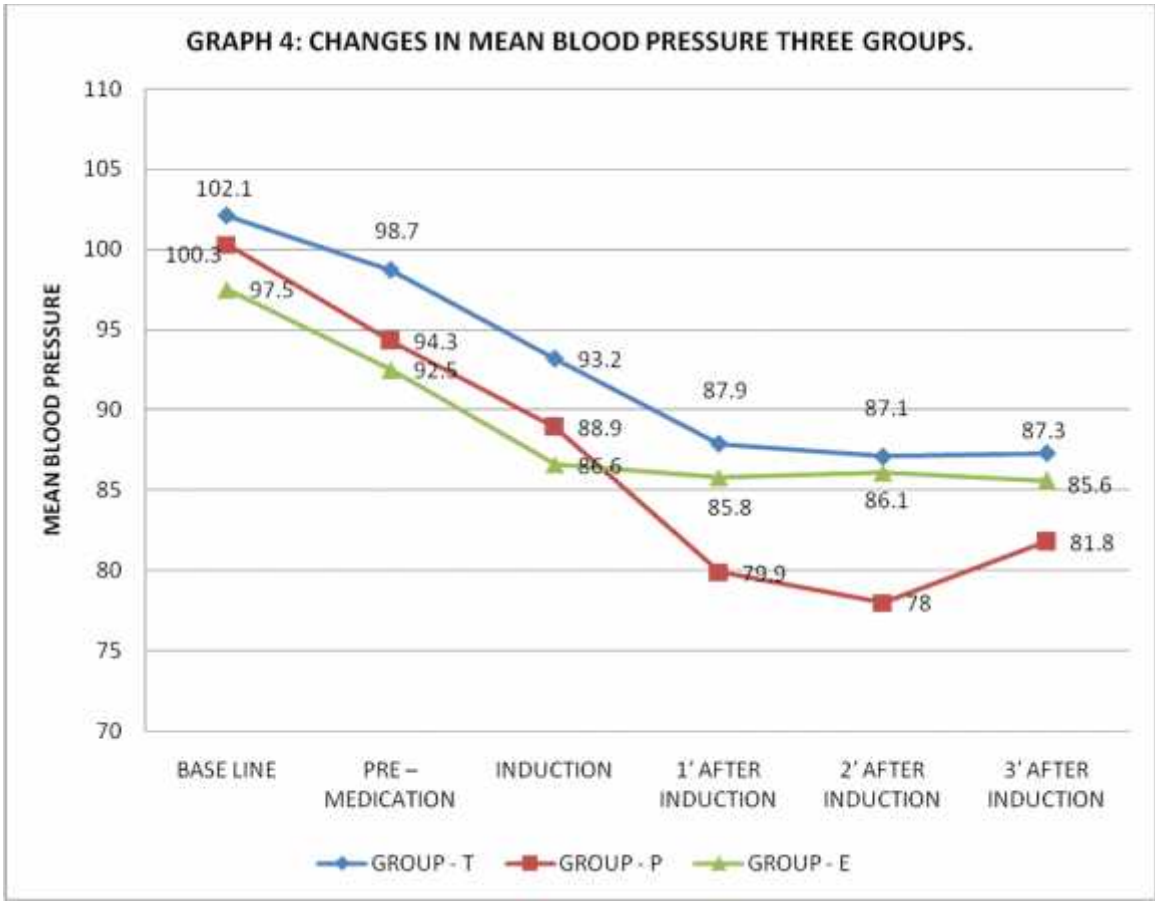
TABLE 5: CHANGES IN MEAN BLOOD PRESSURE IN THREE GROUPS: (GRAPH 4)

TIME	GROUP - T	'p - value	GROUP - P	'p - value	GROUP - E	'p - value
BASE LINE	102.1 ± 11.60	-	100.3± 9.35	-	97.5 ± 9.50	-
PRE –MEDICATION	98.7 ± 10.55	-	94.3 ± 11.16	-	92.5 ± 9.74	-
INDUCTION	93.2 ± 11.73	-	88.9 ± 8.63	-	86.6 ± 11.08	-
1' AFTER INDUCTION	87.9 ± 12.04	0.121	79.9 ± 9.98	0.001	85.8 ± 11.72	0.804
2' AFTER INDUCTION	87.1 ± 10.58	0.058	78 ± 9.62	0.000	86.1 ± 11.79	0.877
3' AFTER INDUCTION	87.3 ± 11.18	0.074	81.8 ± 10.90	0.013	85.6 ± 12.13	0.761

In group T there is no significant fall in mean blood pressure at 1st, 2nd and 3rd minute after induction when compared with induction value, as shown in table 5.

In group P there is significant fall in mean blood pressure at 1st, 2nd and 3rd minute after induction when compared with induction value, as shown in table 5.

In group E there is no significant fall in mean blood pressure at 1st, 2nd and 3rd minute after induction when compared with induction value, as shown in table 5.


GRAPH 4: CHANGES IN MEAN BLOOD PRESSURE THREE GROUPS.
MEAN BLOOD PRESSURE
110
105
100
95
90
85
80
75
70
102.1
98.7
100.3
97.5
94.3
92.5
93.2
88.9
86.6
87.9
85.8
87.1
86.1
87.3
85.6
79.9
78
81.8
BASE LINE
PRE – MEDICATION
INDUCTION
1' AFTER INDUCTION
2' AFTER INDUCTION
3' AFTER INDUCTION
GROUP - T
GROUP - P
GROUP - E

DISCUSSION

Induction of anaesthesia is one important event in the conduct of general anaesthesia. Initially it was achieved with inhalation of gases, but due to increase in concern over anaesthetic gas vaporizer malfunction, explosions, and technical difficulties in giving exact concentration of gases to patients, [1,2,3,4] there was an increased interest in intravenous anesthesia. Intravenous anesthesia became popular with discovery of barbituric acid derivatives.

Thiopentone sodium was discovered by Volwiler and introduced into clinical practice by Sir Ralph Water in 1934. Thiopentone sodium is considered as "gold standard" inducing agent because of its rapid onset of action, smooth induction and considerable safety.[6,7,8] Its major disadvantages are delayed recovery, decrease in systemic blood pressure, and increase in heart rate and absence of suppression of upper airway reflexes. [9, 10] However thiopentone does not possess all the properties of an ideal intravenous inducing agent. This lead to development of other inducing agents such as propofol and etomidate.

Propofol was discovered by Ronald and introduced into clinical practice by Brain and Rolly in the year 1977. Propofol provides faster onset of action, antiemesis, rapid recovery, potent attenuation of upper airway reflexes and adequate depth of anaesthesia during intubation.[11, 12] Major disadvantage of induction with propofol is decrease in systemic blood pressure and pain during injection.[17]

Another inducing agent etomidate was introduced into clinical practice in 1972. It provides more cardiac stability with faster onset of action and rapid recovery.[21,22] Major

disadvantage was adrenal suppression and use of this drug was declined.[28,29] A search through the literature revealed that lack of evidence for adrenal suppression after single dose etomidate.[30] This rekindled interest in the drug and was once again used since 2000. Due to absence of any studies using the drug in the Indian setting, we conducted a study to evaluate the hemodynamic stability of etomidate in comparison with thiopentone and propofol during induction in general anesthesia.

In our study the demographic data were comparable for age and sex in all three groups (Table 1).

The mean heart rate was increased in group T, at one minute, two minute, and three minute after induction. (Table 2, Graph 1). In our study the maximum increase in heart rate was 4 beats per minute was similar to increase in heart rate observed in studies conducted in the past.[10] This has been attributed to decreased sensitivity of the baroreflex following administration of thiopentone. The increase however was not found to be statistically significant.

In group P there was decrease in mean heart rate, but the decrease was not significant, this observation was similar to studies conducted in the past. They attributed it to the resetting of the baroreflex mechanism that enables a reduced heart rate to be sustained, despite decreased arterial pressure due to propofol.[15, 16]

In our study we found that the heart rate was more stable in group E as compared to group T and group P. Etomidate, maintains hemodynamic stability through preservation of both sympathetic outflow and autonomic reflexes.[22, 23]

The mean systolic blood pressure was significantly lower in group T and group P at one minute, two minute and three minute after induction when compared to mean systolic blood pressure at induction. (Table 3, Graph 2) The maximum fall in mean systolic blood pressure in group T was 8.8 mm of Hg and in group P was 13.4 mm of Hg. But the maximum decrease in mean systolic blood pressure in group E was 0.7 mm of Hg. (Table 3)

Similar results were observed in another study done by Mackenzie and Grant in 1985, where mean systolic blood pressure was reduced by 20% after induction with propofol, and by 15% after induction with thiopentone.[14] They observed that the fall in blood pressure during induction with propofol and thiopentone is due to decrease in systemic vascular resistance and decrease in cardiac output, and alteration in baroreceptor sensitivity. Etomidate, maintains hemodynamic stability through preservation of both sympathetic outflow and autonomic reflexes were as propofol-induces hypotension by an inhibition of the sympathetic nervous system and impairment of baroreflex regulatory mechanisms. Both cardiac and sympathetic baroslopes were maintained with etomidate but were significantly reduced with propofol, especially in response to hypotension.[23]

The mean diastolic blood pressure was significantly lower in group P at one minute, two minute and three minute, after induction when compared to mean diastolic blood pressure at induction. (Table 4, Graph 3)

There was a maximum fall in mean diastolic blood pressure by 4.2 mm of Hg in group T and by 9.5 mm of Hg in group P. But in group E the fall in mean diastolic blood pressure is 1.0 mm of Hg. (Table 4)

The mean blood pressure was significantly lower in group P at one minute, two minute, and three minute after induction when compared to mean blood pressure at induction. (Table5, Graph 4)

There was a fall in mean blood pressure by 6.1 mm of Hg in group T and by 10.9 mm of Hg in group P. But in group E the fall in mean blood pressure is 1 mm of Hg. (Table 5)

Similar results were observed in another study done by, where mean blood pressure was reduced by 15% after induction with propofol, by 10% after induction with thiopentone, and by 5% after induction with etomidate.[22]

Thus our study showed that induction of anesthesia with etomidate there was insignificant fall in blood pressure. However our study group belonged to ASA class I and II and did not include patients with low cardiac reserve or patients with hemodynamic instability eg.Patients with shock etc. From the drug profile available etomidate should show similar hemodynamic stability even in these patients. Hence it would be interesting to determine the hemodynamic effects of etomidate in such patients who have low cardiac reserve or who are hemodynamically unstable.

SUMMARY

It is now a standard practice to induce general anesthesia by using intravenous anaesthetic agent. Until now thiopentone and propofol were commonly used for induction. The hemodynamic stability during induction is poorly maintained with thiopentone and propofol. Hemodynamic instability during induction can be prevented by using etomidate which maintains hemodynamic stability during induction. Hence in this study we compared etomidate with thiopentone and propofol as induction agents. Seventy five patients undergoing general anaesthesia were randomly divided into three groups to receive the induction agent etomidate, thiopentone or propofol. The hemodynamic parameters namely heart rate, systolic, diastolic, and mean blood pressure were monitored before induction and after induction every minute for three minutes. There was fall in systolic, diastolic and mean blood pressure after thiopentone and propofol induction. But the fall in blood pressure in propofol group was significant. With thiopentone induction there is increase in heart rate and with propofol induction there is decrease in heart rate. But the change in heart rate was insignificant in both groups. With etomidate induction there is no significant change in heart rate, systolic, diastolic, and mean blood pressure. Etomidate offers the superior hemodynamic stability during induction. In conclusion etomidate is found to be a better induction agent for general anaesthesia with respect to haemodynamic stability compared to thiopentone and propofol. Etomidate can be an induction agent of choice in patients with co morbid cardiovascular illness.

CONCLUSION

From our study we conclude that, when etomidate is used as an induction agent during general anaesthesia there is a better hemodynamic stability in comparison to thiopentone and propofol.

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INFORMED CONSENT FORM

A study, "A RANDOMISED CLINICAL STUDY TO COMPARE THE HAEMODYNAMIC EFFECTS OF ETOMIDATE WITH THIOPENTONE SODIUM AND PROPOFOL DURING INDUCTION OF GENERAL ANAESTHESIA".A one year randomized controlled trial conducted by Dr. RAVI NAIK.R Postgraduate Student, Department of Anesthesiology, JNMC, and Belgaum.

Respected Sir/ Madam, We request you to participate in our study as you are eligible to be included. During the study you will be asked questions regarding your present and past medical history and you are supposed to answer to the best of your knowledge.

Your participation in this study is voluntary. Your decision whether or, not, to participate in the study will not affect your relationship with J.N.M.C. If you decide to participate you are free to withdraw at any point of time. The purpose of the study is to compare the hemodynamic changes during and till 3 mins after induction with thiopentone or propofol or etomidate.

Procedure involved:

If you agree to enroll yourself in my study, you will be interviewed regarding your present, past and family history, you will be clinically examined in detail and investigated accordingly. You will be randomly allocated either into group T or group P, or group E. In group T induction will be achieved with injection thiopentone sodium 5mg/kg body weight intravenously, in group P, induction will be achieved with injection propofol 2mg/kg body weight intravenously and in group E,

induction will be achieved with injection etomidate 0.3mg/kg body weight intravenously. Heart rate and blood pressure will be recorded before premedication, after premedication, during induction, and every minute for 3 minute after induction.

Benefits and Risks:

No serious side effects.

Alternatives:

Even if you decline the participation in the study, you will get the routine line of management.

Confidentiality:

All information collected by me during the course of the study will be kept confidential to the extent permitted by law. The code numbers will identify you in this study records and the information from this study may be published but your identity will be confidential in any publication.

Compensation:

In the event of injury, related to the study, treatment will be made available at KLES Hospital & MRC, Belgaum. No reimbursement, compensation or free medical care will be given, by law. If you are injured, you can contact Dr. RAVI NAIK.R. Postgraduate student, in Anesthesiology, JNMC, Belgaum. Ph. No.: 9449980144

Queries:

If you have any queries, in future or in case of study related injury or illness, you may contact. Dr. RAVI NAIK.R.Postgraduate student in Anesthesiology, JNMC, Belgaum.Ph. No.: 9449980144

If you have any queries about your rights as a study subject, you may call Dr. V.D. Patil. Principal and Chairman. J.N. Medical College Institutional Ethical Committee for Human Subjects Research, Ph. 0831-2473777 at J.N. Medical College, Belgaum.

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

I, Mr./ Mrs. _____

voluntarily agree to take part in this study. By signing this consent form I am not giving up my legal rights. I may withdraw at any time. I am signing after having read, or been read to me in the vernacular language all risks and the benefits and having all queries cleared.

Signature of the study patient

_____

Name of Study patient Date

_____ _____

Signature of the legally authorized representative Date

_____ _____

Relationship with the patient

_____

Name and Signature of Witness Date

_____ _____

Signature of investigator/ designee obtaining Date

_____ _____

PROFORMA

Title "A RANDOMISED CLINICAL STUDY TO COMPARE THE HAEMODYNAMIC EFFECTS OF ETOMIDATE WITH THIOPENTONE SODIUM AND PROPOFOL DURING INDUCTION OF GENERAL ANAESTHESIA".

Patients Name : I.P. No. :

Age : Wt: Sex :

Occupation : Date of operation:

Address :

Anesthesiologist:

PRE-ANAESTHETIC EVALUATION:

Chief Complaints:

Past History:

a) HTN/D.M/Asthma/Epilepsy/Drug allergy.

b) Drug therapy.

c) Previous exposure to anesthesia.

Family History:

General Physical Examination

Pallor / Icterus / Clubbing / Lymphadenopathy / Odema

P.R: B.P:

R.R:

Musculoskeletal System Examination:

Jaw movements: Teeth:

Airway assessment: Spine:

Systemic Examination:

a. R.S b. CNS

c. C.V.S d. GIT

Investigations:

Hb%

Urine routine

Any others

Pre operative physical status: ASA grade I II

Inclusion criteria:

1. ASA grades I and II.

2. Age between 18-50 years

3. Patients undergoing General anesthesia.

Exclusion criteria:

1. ASA grade>II

2. Age less than 18years and age more than 50 years.

3. Patients with DM, HT.

4. Patients taken for emergency surgery.

Diagnosis:

Proposed surgery:

Patients will be allocated by computer generated randomization into group T, group P and group E.

On the day of surgery, I.V line secured with 18g branula for males, 20g branula for females in a peripheral vein.

Preoperative baseline:

Heart rate:

Blood pressure:

Monitors attached:

Pulse oximeter: Non invasive blood pressure:

ECG: Etco2:

Study subjects will be premedicated with Midazolam 0.05mg/kg body weight, fentanyl 1 microgram/kg body weight. One minute after premedication heart rate and blood pressure recorded. Patients preoxygenated with 100% oxygen for 3 minutes.

In each group patients are induced with respective drugs. Heart rate and blood pressure are recorded during induction and every minute for three minutes after induction. Induction of anesthesia is defined as the disappearance of eyelash reflex.100% oxygen administration is continued. If necessary ventilation is assisted when patient develops apnea. Apnea is defined as no respiration for more than 10 seconds.

Time interval in min.	**Heart rate**	**Blood pressure**		
		systolic	**diastolic**	**mean**
Base line				
1 min after premed.				
During induction				
1 min after induction				
2 min after induction				
3 min after induction.				

Side effects :

Signature of the Staff in charge:

MASTER CHART - GROUP T

				Base line				After Pre Med				During induction				1'min				2'min				3'min			
S.NO.	IP NO.	AGE	SEX	HR	SBP	DBP	M	HR	SBP	DBP	M	HR	SBP	DBP	M	HR	SBP	DBP	M	HR	SBP	DBP	M	HR	SBP	DBP	M
1	297387	42	M	84	164	71	102	80	155	78	104	87	135	66	89	96	127	62	84	98	125	62	83	96	120	58	79
2	298679	35	F	92	132	77	95	57	122	84	97	65	112	72	85	77	109	74	86	75	101	66	78	72	106	69	81
3	297282	50	M	80	131	72	92	75	121	62	81	78	102	61	75	80	105	65	78	82	101	69	79	82	104	66	79
4	298389	42	F	99	161	89	113	100	162	92	115	104	150	103	119	109	145	98	114	105	140	96	111	103	150	98	115
5	298462	40	F	99	128	92	104	100	127	90	102	106	117	89	98	109	108	74	85	108	113	77	89	107	113	77	89
6	300463	38	F	102	162	97	119	96	152	97	115	98	148	96	113	98	146	97	113	97	139	96	110	96	130	94	106
7	300090	24	F	96	128	83	98	90	120	76	91	86	111	72	85	88	107	68	81	94	114	75	88	96	115	69	84
8	300208	35	M	61	116	81	93	65	113	79	90	85	110	76	87	78	106	74	85	87	109	75	86	86	105	73	84
9	294856	50	M	76	121	71	88	80	115	70	85	80	109	74	86	82	89	66	74	85	99	70	80	88	100	65	77
10	295002	50	M	97	167	101	123	79	151	84	106	80	130	80	97	81	117	75	89	78	115	72	86	87	111	68	82
11	298040	27	F	90	144	75	98	75	124	68	87	86	105	64	78	90	98	61	73	92	104	60	75	91	105	62	76
12	298965	30	M	93	129	80	96	70	122	88	99	67	108	68	81	79	105	67	80	75	104	67	79	84	103	66	78
13	301510	25	F	70	164	109	127	72	154	102	119	72	150	100	117	78	139	109	119	80	137	100	112	88	147	107	120
14	307424	50	F	87	140	90	107	83	135	85	102	83	135	85	102	87	111	75	87	89	110	74	86	90	111	76	88
15	301515	35	F	84	153	89	110	70	149	90	110	56	128	81	97	56	128	81	97	58	125	79	94	59	120	80	93
16	1021736	24	F	112	144	105	118	98	136	98	111	99	122	87	99	101	115	79	91	99	110	72	85	98	108	71	83
17	308749	49	M	109	143	91	108	100	143	92	109	96	139	87	104	94	129	86	100	89	123	85	98	92	119	81	94
18	309514	25	F	135	123	59	80	134	116	82	93	129	122	61	81	133	114	63	80	121	117	68	84	119	115	72	86
19	303738	44	M	86	130	90	103	82	124	86	99	86	120	80	103	92	110	76	87	90	108	74	85	92	112	78	89
20	304646	28	F	82	122	70	87	76	110	68	82	80	112	70	84	84	100	76	84	88	98	62	74	86	104	70	81
21	305127	22	F	82	124	76	92	80	120	74	89	86	110	76	87	84	108	64	79	88	106	62	77	90	103	70	81
22	304946	45	M	90	130	80	97	86	124	82	96	88	120	76	91	84	106	64	78	82	110	70	83	88	108	68	81
23	305219	36	F	96	136	84	101	80	128	80	96	81	120	78	92	86	110	68	82	88	108	66	80	86	106	68	81
24	305062	32	M	84	130	80	97	80	124	76	92	86	110	72	85	88	107	76	86	86	110	80	90	88	112	78	89
25	305690	43	M	86	138	90	106	82	130	82	98	88	128	80	96	86	110	72	85	82	108	74	85	88	110	76	87

MASTER CHART - GROUP P

				Base Line				After Pre Med				During induction				1'min				2'min				3'min			
S.NO.	IP NO.	AGE	SEX	HR	SBP	DBP	M	HR	SBP	DBP	M	HR	SBP	DBP	M	HR	SBP	DBP	M	HR	SBP	DBP	M	HR	SBP	DBP	M
1	300018	31	F	120	150	100	117	116	141	92	106	98	134	90	105	94	124	78	93	90	123	76	91	88	120	73	89
2	300902	39	M	80	129	82	98	78	120	80	93	78	112	78	89	84	100	70	80	88	98	65	76	86	104	71	82
3	299124	29	F	100	148	103	118	95	144	99	114	86	125	82	96	80	105	69	81	78	107	68	81	73	101	65	77
4	299739	22	F	76	130	93	105	72	124	91	102	67	118	72	87	58	103	67	79	59	93	58	70	60	98	63	75
5	300639	40	F	91	139	96	110	87	130	90	103	83	125	88	100	83	87	53	64	85	90	60	70	87	95	65	75
6	301011	42	F	87	129	80	96	85	120	75	90	80	112	72	85	81	105	63	77	79	99	57	71	80	113	75	88
7	301509	22	F	80	133	92	106	76	122	86	98	81	120	84	96	84	114	82	93	86	115	81	92	89	113	77	89
8	306521	22	F	108	125	74	91	104	120	72	88	94	120	70	87	91	117	74	88	90	115	73	87	90	121	84	96
9	307440	24	M	89	138	67	91	84	130	65	87	82	124	60	81	77	113	43	66	81	114	41	65	78	117	41	66
10	307295	42	M	54	130	87	101	56	128	85	99	70	120	87	98	83	117	89	98	83	118	89	97	87	118	83	95
11	304733	42	M	112	155	99	118	109	147	101	116	111	127	82	97	102	106	68	81	99	109	71	84	101	122	87	99
12	308059	41	F	75	115	70	85	71	108	49	69	68	105	56	72	70	89	48	62	66	90	47	61	68	100	79	86
13	308281	20	F	112	128	82	97	110	122	78	93	100	118	74	89	100	100	60	73	103	92	55	67	94	90	56	67
14	308210	25	F	108	125	84	98	98	123	84	97	93	124	84	97	75	109	78	88	74	106	72	83	83	116	78	91
15	307573	37	M	58	144	82	103	52	138	82	101	51	124	71	89	53	123	69	87	53	121	67	85	54	119	67	84
16	308654	49	F	94	132	74	93	90	126	82	97	89	120	80	93	70	105	57	73	74	104	64	77	76	102	55	71
17	308832	28	M	80	126	80	95	72	117	77	90	90	110	74	86	96	105	62	76	99	97	61	73	114	82	54	63
18	308689	35	M	84	124	86	99	76	112	76	88	76	110	70	83	78	104	72	83	74	100	68	79	76	102	74	83
19	309331	49	F	80	130	86	101	62	130	80	97	72	120	80	93	72	110	70	83	70	112	68	83	76	110	66	81
20	309141	21	F	86	120	90	100	80	120	90	100	76	110	70	83	71	106	68	81	73	104	70	81	75	108	70	83
21	310431	20	M	75	126	81	96	71	110	66	81	79	109	57	74	86	107	52	70	78	100	54	69	79	101	58	72
22	305091	21	F	82	112	64	80	80	110	62	78	78	108	60	76	78	96	56	69	76	98	58	71	80	100	60	73
23	307404	31	M	82	138	92	107	81	135	88	104	76	125	86	99	81	124	87	99	76	123	78	93	86	128	86	100
24	310660	50	M	94	134	90	105	82	118	53	75	102	116	59	78	86	103	69	80	86	100	67	78	92	118	82	94
25	312782	32	M	112	128	82	97	110	128	78	93	100	118	74	89	100	100	60	73	103	92	55	67	94	90	56	67

MASTER CHART - GROUP E

				Base Line				After Pre Med				During induction				1'min				2'min				3'min			
S.NO.	IP NO.	AGE	SEX	HR	SBP	DBP	M	HR	SBP	DBP	M	HR	SBP	DBP	M	HR	SBP	DBP	M	HR	SBP	DBP	M	HR	SBP	DBP	M
1	291176	37	M	71	132	78	99	67	126	76	98	65	109	66	79	65	108	64	79	64	105	61	75	61	105	59	72
2	294858	45	M	62	149	92	111	57	138	86	103	62	118	73	88	64	120	72	88	68	125	74	91	70	128	76	93
3	307549	22	F	97	120	80	93	96	110	70	83	95	100	54	69	94	100	52	68	94	100	54	69	95	102	56	71
4	307594	30	F	83	150	100	117	75	140	97	111	76	142	98	113	75	140	97	111	74	143	98	113	75	140	97	111
5	307789	49	M	80	126	91	103	78	118	80	93	82	102	75	84	85	108	75	86	85	106	70	82	86	103	76	85
6	308375	40	M	76	130	90	103	72	128	90	103	74	118	80	93	75	116	76	89	74	115	60	78	74	108	60	76
7	308160	18	F	112	126	70	89	108	118	54	75	98	106	48	67	96	103	47	66	98	107	51	70	96	101	48	66
8	307476	35	M	67	122	80	94	60	110	80	90	60	98	62	74	62	98	64	75	62	102	76	85	58	104	72	83
9	308948	28	M	76	116	71	86	75	119	71	87	74	117	64	82	74	113	62	79	75	110	64	79	75	108	55	73
10	309884	45	M	86	140	86	104	80	130	70	90	81	110	80	90	81	109	76	87	82	110	78	89	81	110	70	83
11	310541	45	F	96	130	78	95	93	123	85	98	88	100	63	75	88	98	63	75	87	97	62	74	88	92	62	72
12	310529	49	F	83	123	81	95	76	117	72	87	56	100	70	80	56	98	53	68	58	96	54	68	56	100	56	71
13	304869	47	F	86	128	78	95	84	120	76	91	80	110	72	85	78	108	76	87	76	106	74	85	78	110	78	89
14	314241	49	M	84	132	94	107	80	128	90	103	81	125	89	101	80	124	86	99	79	125	88	100	81	124	88	100
15	314106	20	F	78	112	74	87	76	110	70	83	74	110	70	83	76	108	68	81	78	109	68	82	76	108	69	82
16	314039	48	F	94	136	92	107	86	124	86	99	82	120	80	93	80	118	76	90	79	120	78	87	80	122	80	94
17	313552	28	M	90	126	76	93	82	120	70	87	80	122	72	89	82	120	76	91	80	118	78	91	81	120	78	92
18	314129	28	M	82	110	70	83	76	108	68	81	76	108	70	83	74	106	68	81	75	108	68	81	76	106	70	82
19	314112	50	M	76	140	90	107	74	136	88	104	74	134	86	102	75	136	90	105	76	138	90	106	76	135	88	104
20	311676	45	M	92	144	90	108	90	140	90	107	90	136	88	104	88	138	88	105	89	140	90	107	90	142	90	107
21	311616	45	F	86	120	70	87	84	118	66	83	82	116	66	83	80	116	66	83	81	118	68	85	80	116	66	83
22	312828	49	F	90	140	90	107	88	132	86	101	86	130	80	97	86	132	84	100	88	130	80	97	86	130	82	98
23	312066	19	M	86	110	70	83	82	106	66	79	80	104	62	76	78	104	66	79	80	105	68	80	78	106	66	79
24	311610	50	M	64	120	70	87	62	116	66	83	64	118	68	85	64	118	66	83	65	120	70	87	64	116	70	85
25	320324	21	M	82	130	80	97	80	126	76	93	78	124	74	91	78	124	74	91	76	126	76	93	78	124	74	91