A COMPARISION OF MIDAZOLAM COINDUCTION WITH PROPOFOL PREDOSING FOR INDUCTION OF ANAESTHESIA

Dissertation submitted to
THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the regulations
For the award of the degree of

M.D., BRANCH – X
ANAESTHESIOLOGY
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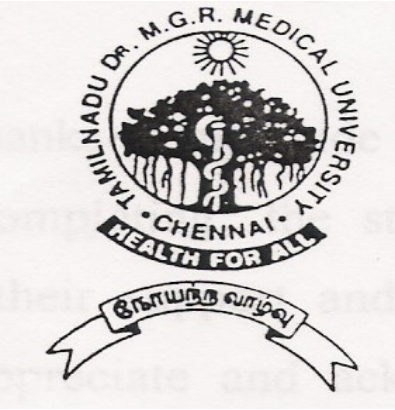

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CERTIFICATE

This is to certify that the dissertation **"A COMPARISION OF MIDAZOLAM COINDUCTION WITH PROPOFOL PREDOSING FOR INDUCTION OF ANAESTHESIA"** submitted herein is a bonafide work originally done by Dr V.SENTHILKUMAR under my guidance and supervision in government general hospital, Madras Medical College, Chennai, during the academic year 2003-2006.

Date
Chennai - 3

DR. KALAVATHYPONNIRAIVAN M.D.,
Dean, Madras Medical College, Chennai.

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CONTENTS

INTRODUCTION

The term co-induction has been used to describe the practice of administering a small dose of sedative or another anaesthetic agent[10] to reduce the dose of induction agent required. The term co-induction of anaesthesia has been applied to the use of two or more drugs to induce anaesthesia.[11].The term was introduced in 1986 to describe the unplanned induction of anaesthesia by non-anaesthetically trained personnel practicing sedation, unplanned anaesthesia in unsuitable environment leading to several fatalities. Currently, planned co-induction of anaesthesia is practiced by anaesthesiologists exploiting drug interaction particularly synergism.[3].The arguments for co-induction are two fold. First, to improve the balance of desired versus adverse effects and secondly to reduce cost. When used this way midazolam has been shown to reduce the dose of propofol required to induce anaesthesia by up to 50% without affecting recovery profile [33]

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The technique of administering two or more hypnotic drugs to facilitate induction and maintenance of general anaesthesia has gained considerable popularity. One rationale for combining drugs in anaesthesia is to achieve more “specific target responses, while minimizing side effects and facilitating rapid and predictable recovery”.

As yet, no single intravenous anaesthetic drug can effectively and safely provide hypnosis, analgesia and amnesia. Thus intelligent combinations of hypnotics and opioids are necessary, especially for total intravenous anaesthesia (TIVA). Inescapable interactions occur, most of which are synergistic and should be evaluated for the optimal care of the patient. This synergism varies considerably according to the different drugs, the different endpoints of anaesthesia and the differently combined dosage of both agents.

M. A. Khan, et al observed co-induction of anaesthesia with midazolam 0.02 mg.kg-1 and thiopentone 3 mg.kg-1 was associated with a smooth and significantly faster induction, better airway control, greater haemodynamic stability and lesser incidence of untoward effects compared to midazolam 0.02 mg.kg-1 and thiopentone 2 mg.kg-1 or thiopentone 4 mg.kg-1 alone.

The most common disadvantages with propofol are its greater cost as compared to thiopentone is high incidence of pain on injection (50 - 100%) and relatively more hypotension as compared to thiopentone.

Short TG. et al, in 1991,studied the dose of propofol required to produce anaesthesia was reduced by 52% in the presence of midazolam .The cause of synergism was not clear but may have been interaction at CNS GABA(A) receptors.

Amrein R, et al .in 1995 investigated midazolam and propofol as potential partners. The relationship between desired effects and adverse effects could be improved by skillful use of the synergism between midazolam and propofol. Co-induction of anaesthesia and co-administration in long-term sedation can offer improvements in therapeutic situations compared with monotherapy.

Whitlam JG.etal in 1995 studied the use of midazolam and propofol with or without either fentanyl or alfentanil is probably the principal technique for the induction of day-case anaesthesia A major advantage is that by reducing the dose of propofol there is less chance of the severe bradycardia that is sometimes associated with the combined use of propofol and opioids, although this can be prevented by vagolytic agents. However, the use of opioids increases the incidence of post-operative nausea and vomiting.

Howard-Griffin, R. et al **in 1997** compared the co-induction with midazolam-alfentanil-thiopentone and midazolam-alfentanil-propofol. Following pre-induction doses of midazolam 0.04 mg.kg-1 and alfentanil 10 microgm/.kg, Patients received equipotent doses of either thiopentone or propofol. It was concluded that using these doses propofol is superior to thiopentone for laryngeal mask airway insertion when using a co-induction technique.

AIM OF STUDY

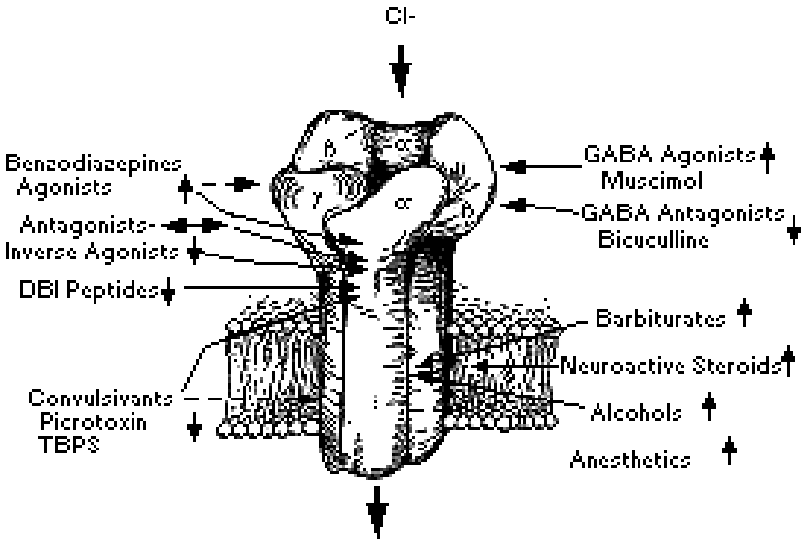
This study compares the midazolam co-induction and propofol predosing with regard to

1. Dose of propofol required for induction.
2. Blood pressure variability during induction
3. Heart rate variability during induction

For adult patients undergoing elective surgeries

ANATOMY AND PHARMACOLOGY OF GABA RECEPTORS

STRUCTURE AND FUNCTION



The receptor is a multimeric transmembrane receptor that consists of five subunits arranged around a central pore. The receptor sits in the membrane of its neuron at a synapse. The ligand GABA is the endogenous compound that causes this receptor to open; once bound to GABA, the protein receptor changes conformation within the membrane, opening the pore in order to allow chloride ions (Cl-) to pass down their electrochemical gradient. Because the chloride ion concentration is high outside of the cell, opening of the channel pore results in an influx of chloride into the cell, thus making it more negative (hyperpolarizing it). The GABAA channel opens quickly and thus contributes to the early part of the inhibitory postsynaptic potential (IPSP).

GABA is the chief inhibitory neurotransmitter in the mammalian brain. Along with glycine--that primarily has effects in the spine, brainstem and retina--it is responsible for the vast majority of all inhibitory neurotransmission in the central nervous system (CNS). Between 20-50% of all central synapses use GABA as their transmitter. The enzyme responsible for the formation of GABA from the amino acid glutamate is glutamic acid decarboxylase

There were once thought to be three types of receptors for GABA in the mammalian CNS, designated A, B, and C. The GABA A and GABA C receptors are GABA-gated chloride ion-conducting channels while the GABA B receptor is a member of the seven transmembrane helix-containing, guanine nucleotide-binding receptor G-protein-coupled receptors. The GABA A and GABA C receptors were initially distinguished by their sensitivity to the ligand bicuculline with the former being antagonized by it while the latter were insensitive. While varieties of the GABA A receptor are found all over the CNS, the GABA C receptors are primarily found in the retina.

It has become increasingly clear since the mid-1990s that the GABA A and GABA C receptors are simply variants of the same GABA-gated chloride channel that should be simply denoted by the “GABA A” receptor design

The GABA A receptor is a member of the Cys-loop ligand-gated ion channel super family which also includes the glycine, 5-hydroxytryptamine (5-HT, serotonin), and nicotinic acetylcholine receptors. Receptors of this super family consist of pentamers of homologous subunits arranged around a central ion-conducting channel. There are 19 different subunit genes—not including alternatively-spliced variants such as the short (S) and long (L) forms of the 1-6, γ1-3,αγ2 subunit—divided into eight subunit classes: β1-3, θ, ρ1-2, δ, π, ε (listed according to sequence relatedness). It is presumed that these subunits all arose as a result of gene duplications of an original sequence. Within a class of subunits there is approximately 70% sequence identity, and between subunit classes there is approximately 30% sequence identity .The majority of GABA A receptor subtypes in the mammalian brain contain at least one α, β, and γ subunit .Most GABA A receptors consist of assemblies of these three subunit classes.

The most abundantly expressed isoform of the GABA A receptor in the mammalian brain is composed of α1, β2, and γ2. The likely stoichiometry is two α, two β and one γ subunit arranged around the ion channel anti-clockwise γ-β-α-β-α as seen from the synaptic cleft

Ligand binding to the GABA A receptor

GABA binding (to the "GABA site") activates the GABA A receptor, allowing chloride ions to flow through the central pore and hyperpolarize the neuron, decreasing the probability that it will propagate an action potential. In this activity, the GABA A receptor does not differ from any other ligand-gated ion channels. However, among neurotransmitter receptors, GABA A receptors are unique in the number of ligands that allosterically modulate receptor function GABA A receptors can exist in at least three different conformations: open, closed, and desensitized .Up to 14 different ligand binding sites have been proposed to account for the modulation of GABA .

Binding to the receptor can alter the conformation in such a way as to enhance or diminish the chloride flux in response to GABA binding. Some anesthetics (etomidate, pentobarbitone) both enhance chloride flow in response to GABA binding as well as activating it directly in the absence of GABA. Other ligands, cage convulsants of the picrotoxin type, bind within the central pore, occluding the channel and preventing chloride flow no matter what other ligand subsequently binds. Some of these compounds have seen commercial use as pesticides.

Subunits There are numerous subunit isoforms for the $GABA_A$ receptor, which determine the receptor's agonist affinity, chance of opening, conductance, and other properties .There are six types of α subunits, three β's, three γ's, as well as a δ, an ε, a π, a θ, and three ρs .Five subunits can combine in different ways to form $GABA_A$ channels, but the most common type in the brain has two α's, two β's, and a γ .The receptor binds two GABA molecules, somewhere between an α and a β subunit

Agonists and antagonists

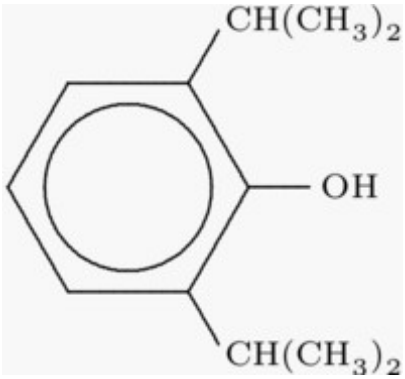
Other ligands (besides GABA) interact with the $GABA_A$ receptor to activate it (agonists), to inhibit its activation (antagonists) or to increase or decrease its response to an agonist (positive and negative allosteric modulators). Such other ligands include benzodiazepines (increase pore opening frequency; often the ingredient of sleep pills and anxiety medications), barbiturates (increase pore opening duration; used as sedatives), and certain steroids, called neuroactive steroids.

Among antagonists are picrotoxin (which blocks the channel pore) and bicuculline (which occupies the GABA site and prevents GABA from activating the receptor). The antagonist flumazenil is used medically to reverse the effects of the benzodiazepines.

A useful property of the many agonists and some antagonists is that they often have a greater interaction with $GABA_A$ receptors which contain specific subunits.

This allows one to determine which $GABA_A$ receptor subunit combinations are prevalent in particular brain areas and provides a clue as to which subunit combintations may be responsible for behavioral effects of drugs acting at $GABA_A$ receptors. Among the behavioral effects of such drugs are relief of anxiety (anxiolysis), muscle relaxation, sedation, anticonvulsion, and anesthesia

PHARMACOLOGY OF PROPOFOL



2,6-bis(1-methylethyl)-phenol

Physicochemical characteristics:

Molecular weight—178.28

pH Propofol emulsion: 7 to 8.5.

PHARMACODYNAMICS

Hemodynamic effects:

Propofol's hemodynamic effects are generally more pronounced than those of other intravenous anesthetic agents Arterial hypotension[28], with readings decreased by as much as 30% or more has been reported, possibly due to inhibition of sympathetic vasoconstrictor nerve activity [44] Hypotensive effects are generally proportional to dose and rate of administration of propofol(8), and may be potentiated by opioid analgesics[4] Endotracheal intubation and surgical stimulation may increases in heart rate and/or blood pressure[10] to greater than baseline values, which occur frequently with other agents, are not as significant with propofol, possibly due to central sympatholytic and/or vagotonic effects[4]. Propofol may also decrease systemic vascular resistance [10] myocardial blood flow, and oxygen consumption[4]. The mechanism of these effects may involve direct vasodilation [9]and negative inotropy [10] Effects such as decreased stroke volume and cardiac output have been demonstrated in some studies[32]

Respiratory effects:

Propofol is a respiratory depressant, frequently producing apnea that may persist for longer than 60 seconds[15], depending on factors such as premedication[8], rate of administration [10] , dose administered, and presence of hyperventilation or hyperoxia. In addition, propofol may produce significant decreases in respiratory rate , minute volume, tidal volume [6], mean inspiratory flow rate, and functional residual capacity[14]. These respiratory depressant effects may be the result of depression of the central inspiratory drive as opposed to a change in central timing [14].The ventilatory depressant effects of propofol may be counteracted by painful surgical stimulation [06].

Cerebral effects:

Propofol decreases cerebral blood flow[15], cerebral metabolic oxygen consumption and intracranial pressure and increases cerebrovascular resistance. It does not appear to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension [15]

Other effects:

Preliminary findings suggest that in patients with normal intraocular pressure, propofol decreases intraocular pressure[18] by as much as 30 to 50%. This decrease may be associated with a concomitant decrease in systemic vascular resistance [7]

Clinical studies have shown that propofol does not cause significant signs of histamine release [22]or significant increases in plasma immunoglobulin or complement C_3 levels[22]. Respiratory resistance after tracheal intubation is lower when propofol is used for induction of anesthesia than when thiopental or high-dose etomidate is used for induction of anesthesia [14]

Although propofol has the potential for affecting adrenal steroidogenesis (18)it does not appear to block cortisol and aldosterone secretion in response to surgical stress or adrenocorticotropic hormone (ACTH) [8] in clinical practice Although transient decreases in plasma cortisol concentrations have occurred, these reductions have not been sustained [8]

Propofol appears to have no analgesic activity . In addition, animal studies have demonstrated no significant effect on coagulation profiles

Propofol has antiemetic properties [19] Anesthesia with propofol results in less nausea and vomiting than anesthesia with desflurane, enflurane, isoflurane, methohexital, nitrous oxide, or thiopental.

Pharmacokinetics

Distribution:

Propofol is rapidly [4]and extensively[27]distributed in the body. It crosses the blood-brain barrier quickly [4], and its short duration of action is due to rapid redistribution from the CNS to other tissues [27], high metabolic clearance [4] and high lipophilicity

Volumes of distribution 4

Initial apparent (Vol_D): 13 to 76 liters (L)

Steady-state (Vol_{DSS}): 171 to 349 L

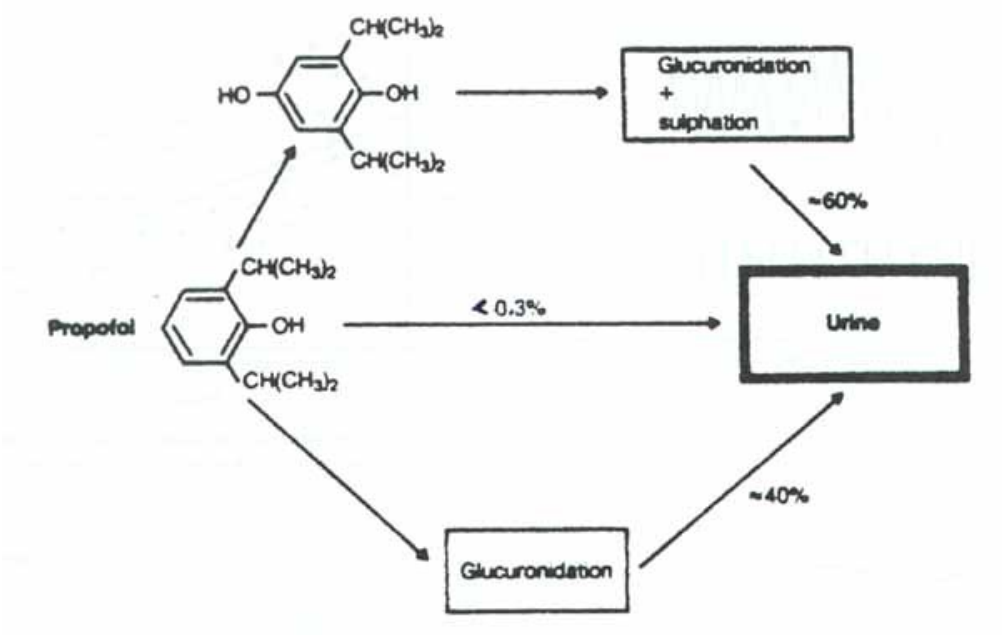
Elimination (Vol_D): 209 to 1008 L

Steady-state (Vol_{DSS}) in pediatric patients: 9.5 ± 3.71 liters per kg of body weight (L/kg)

Protein binding:

Very high (95 to 99%) {04}

Metabolism(27)



Liver glucuronate & sulfate conjugation -> excreted in urine (70% in 24 hours, 90% in 5 days).

Metabolites probably inactive.

Cl exceeds hepatic blood flow. Extrahepatic metabolism has been shown during liver transplantation.

Half-life:

Distribution:

Two distribution phases(27)—

Rapid—2 to 4 minutes

Slower—30 to 64 minutes

Blood-brain equilibration half-life: 2.9 minutes (4)

Terminal elimination half-life is 3 to 12 hours

Prolonged administration of propofol may result in a longer duration (28)

Note: The long terminal elimination half-life of propofol does not reflect elimination, as more than 70% is eliminated during the first 2 phases (28) Some investigators believe that the second exponential phase half-life (30 to 64 minutes) best explains the properties of propofol in clinical practice (27)

Onset of action:

Loss of consciousness occurs rapidly and smoothly, usually within 40 seconds (one arm-brain circulation time) from the start of intravenous injection of propofol {10}. Loss of consciousness is dependent on the dose administered, the rate of administration, and the extent of premedication (16)

Plasma concentrations

Propofol concentrations of 1.5 to 6 mcg per mL (8.42 to 33.66 micromoles per liter [micromoles/L]) will maintain hypnosis, although needs vary with type of surgery and use of other anesthetic agents {04} .

Duration of action:

Mean duration following a single bolus dose of 2 to 2.5 mg per kg of body weight is 3 to 5 minutes (18)

Time to recovery (40)

Recovery from anesthesia with propofol is rapid , with minimal psychomotor impairment (15) . Emergence following induction (with 2 to 2.5 mg of propofol per kg) and maintenance (with 0.1 to 0.2 mg of propofol per kg per minute) for up to 2 hours occurs in most patients within 8 minutes {01} {04} {11} . If an opioid has been used, recovery may take up to 19 minutes (55)

Recovery occurs faster than recovery following the use of etomidate, methohexital, midazolam , or thiopental (25). When anesthesia has included use of an opioid with propofol, recovery has occurred more quickly than with similar use of etomidate (6) , midazolam (39), or thiopental (25).

Elimination:

Renal (35) approximately 70% of a dose is excreted in the urine within 24 hours after administration, and 90% is excreted within 5 days. Clearance of propofol ranges from 1.6 to 3.4 liters per minute in healthy 70 kg patients. As the age of the patient increases, total body clearance of propofol may decrease. Clearance rates ranging from 1.4 to 2.2 liters per minute in patients 18 to 35 years of age have been reported, in contrast to clearance rates of 1 to 1.8 liters per minute in patients 65 to 80 years of age (48)

Note: Pharmacokinetic parameters of propofol appear to be unaffected by gender, obesity, chronic hepatic cirrhosis (46) and chronic renal failure (35)

Propofol is indicated for the induction of general anesthesia in adults and in pediatric patients greater than 3 years of age. [(31)] It is also indicated for maintenance of anesthesia utilizing balanced techniques with other appropriate agents such as opioids and inhalation anesthetics (41) in adults and pediatric patients greater than 2 months of age. (31)

INDICATIONS AND USES

Propofol is indicated for the induction of general anesthesia in adults and in pediatric patients greater than 3 years of age. (31).It is also indicated for maintenance of anesthesia utilizing balanced techniques with other appropriate agents such as opioids and inhalation anesthetics in adults and pediatric patients greater than 2 months of age (21).

Sedation—Propofol is indicated for sedation in critically ill patients confined to intensive care units [(8)]—Propofol is indicated to produce sedation or amnesia as a supplement to local or regional anesthetics (8), and in diagnostic procedures, such as endoscopy (53).

Anti emetic -in dose of 10 to 20mgs

Anti pruritic- in dose of 20 to 30 mgs

Side/Adverse Effects

Incidence more frequent

Apnea [29]

bradycardia [32]

hypotension [23]

Incidence less frequent or rare

Hypertension [7]

perioperative myoclonia, rarely including opisthotonus [8]

pancreatitis [30]abdominal pain)—symptoms may not occur until after discharge from medical care following use of propofol

Involuntary muscle movements, temporary [28]

nausea and/or vomiting

pain, burning, or stinging at injection site

Note: Excitatory movements reportedly occur more often than with thiopental but less often than with etomidate or methohexital. Pain is usually mild and short-lived , and may be decreased by using the larger veins of the forearm or the antecubital fossa [16]or a dedicated intravenous catheter . Pain may be decreased by prior intravenous injection of 10 to 20 mg of lidocaine . Post-injection thrombosis or phlebitis is rare .

Incidence less frequent or rare

Abdominal cramping

Cough, dizziness, fever, flushing, headache

Hiccups, tingling, numbness, or coldness at injection site

Clinical effects of overdose

Acute

Cardiovascular depression

Respiratory depression

Treatment of overdose

Specific treatment: Discontinuation of propofol [01].

For respiratory depression: artificial ventilation with oxygen [01].

For cardiovascular depression: elevation of legs, increasing flow rate of intravenous fluids, and administration of pressor agents and/or anticholinergic agents [01]

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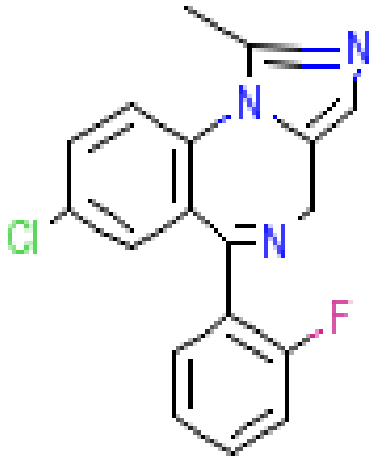
PHARMACOLOGY OF MIDAZOLAM HYDROCHLORIDE



$C_{18}H_{13}ClFN_3$ 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-Imidazo (1,5-a) (1,4)benzodiazepine

Midazolam, a water-soluble imidazo benzodiazepine, has anxiolytic, sedative and anticonvulsive characteristics. These are based on its bond with receptors in the central nervous system; these receptors cause an increased inhibitory effect of g-aminobutyric acid (GABA). Midazolam is lipid-soluble in physiological pH and it reaches the central nervous system quickly.

It was first synthesized in 1976 by Fryer and Walser.

Midazolam is water soluble as the imidazole ring is open at low pH. When it is in a solution with a pH greater than 4, the imidazole ring closes and it becomes much more lipid soluble, facilitating its rapid uptake into nerve tissue. This partly accounts for its rapid onset of action and its high protein binding in the blood (up to 97%).

Molecular Weight	325.767 g/mol
Melting Point	159°C
H2O Solubility	40.0 mg/ml
State	Solid (White Crystalline Powder)
LogP/Hphobicity	3.868
Half Life	2.2-6.8 hours

Absorption	Rapidly absorbed after oral administration (absolute bioavailability of the midazolom is about 36% and intramuscular injection is greater than 90%)
Protein Binding (%)	97%
Bio transformation	Midazolam is primarily metabolized in the liver and gut by human cytochrome cyp34a to its pharmacologically active metabolite alpha hydroxymidazolam and 4-hydroxymidazolam

CLINICAL PHARMACOLOGY

Pharmacodynamics[26]

Pharmacodynamic properties of midazolam and its metabolites, which are similar to those of other benzodiazepines, include sedative, anxiolytic, amnesic and **hypnotic** activities. Benzodiazepine pharmacologic effects appear to result from **reversible** interactions with the (gamma)-amino butyric **acid** (GABA) **benzodiazepine receptor** in the CNS, the major inhibitory **neurotransmitter** in the **central nervous** system. The **action** of midazolam is readily reversed by the **benzodiazepine receptor** antagonist, flumazenil.

The effects of midazolam on the CNS are dependent on the dose administered, the route of administration, and the presence or absence of other medications. Following premedication with midazolam, time to recovery has been assessed using various measures, such as time to eye opening, time to extubation, time in the recovery room, and time to discharge from the hospital. Most placebo-controlled trials (8 total) have shown little effect of midazolam on recovery time from general anesthesia[48] however, a number of other placebo-controlled studies (5 total) have demonstrated some prolongation in recovery time following premedication with oral midazolam. Prolonged recovery may be

related to duration of the surgical procedure and/or use of other medications with central nervous system depressant properties. [40]

Partial or complete impairment of recall following midazolam has been demonstrated in several studies. Amnesia for the surgical experience was greater after midazolam when used as a premedicant than after placebo and was generally considered a benefit. In one study, 69% of midazolam patients did not remember mask application versus 6% of placebo patients.

Episodes of oxygen desaturation, respiratory depression, apnea, and airway obstruction have been reported following premedication (; the potential for such adverse events are markedly increased when midazolam is combined with other central nervous system depressing agents and in patients with abnormal airway anatomy, patients with cyanotic congenital heart disease, or patients with sepsis or severe pulmonary disease (Concomitant use of barbiturates or other central nervous system depressants may increase the risk of hypoventilation, airway obstruction, desaturation or apnea, and may contribute to profound and/or prolonged drug effect.

Pharmacokinetics(26)

Absorption: Midazolam is rapidly absorbed after oral administration and is subject to substantial intestinal and hepatic first-pass metabolism. The pharmacokinetics of midazolam and its major metabolite, (alpha)-hydroxymidazolam

Distribution: The extent of plasma protein binding of midazolam is moderately high and concentration independent. In adults and pediatric patients older than 1 year, midazolam is approximately 97% bound to plasma protein, principally albumin. In healthy volunteers, (alpha)-hydroxymidazolam is bound to the extent of 89%., the mean steady-state volume of distribution ranged from 1.24 to 2.02 L/kg.

Metabolism: Midazolam is primarily metabolized in the liver and gut by human cytochrome P450 IIIA4 (CYP3A4) to its pharmacologic active metabolite, (alpha)-hydroxymidazolam, followed by glucuronidation of the (alpha)-hydroxyl metabolite which is present in unconjugated and conjugated forms in human plasma. The (alpha)-hydroxymidazolam glucuronide is then excreted in urine.

In a study in which adult volunteers were administered intravenous midazolam (0.1 mg/kg) and (alpha)-hydroxymidazolam (0.15 mg/kg), the pharmacodynamic parameter values of the maximum effect (E_{max}) and concentration eliciting half-maximal effect (EC_{50}) were similar for both compounds. Midazolam is also metabolized to two other minor metabolites: 4-hydroxy metabolite (about 3% of the dose) and 1,4-dihydroxy metabolite (about 1% of the dose) are excreted in small amounts in the urine as conjugates.

Elimination: The mean elimination half-life of midazolam ranged from 2.2 to 6.8 hours following single ,oral doses of 0.25, 0.5, and 1.0 mg/kg of midazolam Similar results (ranged from 2.9 to 4.5 hours) for the mean elimination half-life were observed following IV administration of 0.15 mg/kg of midazolam (6 months to <16 years old). the mean total clearance ranged from 9.3 to 11.0 mL/min/kg.

Renal Impairment: Although the pharmacokinetics of intravenous midazolam in adult patients with chronic renal failure differed from those of subjects with normal renal function, there were no alterations in the distribution, elimination, or clearance of unbound drug in the renal failure patients.

Hepatic Dysfunction: Chronic hepatic disease alters the pharmacokinetics of midazolam. Following oral administration of 15 mg of midazolam, C_{max} and bioavailability values were 43% and 100% higher, respectively, in adult patients with hepatic cirrhosis than adult subjects with normal liver function. In the same patients with hepatic cirrhosis, following IV administration of 7.5 mg of midazolam, the clearance of midazolam was reduced by about 40% and the elimination half-life was increased by about 90% compared with subjects with normal liver function. Midazolam should be titrated for the desired effect in patients with chronic hepatic disease.

Congestive Heart Failure: Following oral administration of 7.5 mg of midazolam, elimination half-life values were 43% higher in adult patients with congestive heart failure than in control subjects

Neonates: has not been studied in pediatric patients less than 6 months of age.

SIDE EFFECTS: Dizziness, headache and pain or redness at the injection site fainting, confusion, mental/mood changes, trouble breathing, muscle twitching, uncontrolled movements, however unlikely. Symptoms include: throat discomfort, difficulty breathing, skin rash, hives, itching.

Depending on its dose, midazolam can cause any stage of a cardiovascular and respiratory depression. High i.v. doses have caused cardiac and respiratory arrest with lethal consequences. Usual doses normally cause a minor decrease of the blood pressure and oxygen saturation. The amnesia desired, e.g. for endoscopies, can last much longer than the intervention, sometimes for hours (semi consciousness). Occasionally daydreams with sexual content occur. In addition to a multitude of central nervous symptoms (vertigo, dizziness, headaches, rarely hallucinations, etc.), midazolam can also cause visual disturbances and nausea. Repeated administration (e.g. as a sleeping aid) leads to tolerance and dependence within weeks; withdrawal syndrome often occurs if the drug is discontinued abruptly.

Midazolam: Interactions A dangerous central nervous sedation can develop if midazolam is combined with alcohol or other centrally sedative drugs (e.g. opioids). Cimetidine and ranitidine cause higher midazolam levels.

Midazolam: Risk Groups

Pregnant women:

Even though a correlation between benzodiazepines and malformations is not safely established, midazolam should be avoided if possible.

Nursing mothers:

Midazolam is eliminated through breast milk: better avoided

Children:

Usual parenteral single dose: 0.08 to 0.15 mg/kg (maximum of 0.20 mg/kg). 0.35 to 0.45 mg/kg can be given rectally.

Elderly people:

Greatest care is indicated in the elderly (and when general condition is impaired): initially no more than 50% of the usual dose!

Renal failure:

Dose reduction may be indicated (individual adjustment).

Liver insufficiency:

Dose reduction may be indicated (individual adjustment).

INDICATIONS AND USES

1. Intramuscularlyorintravenouslyforpreoperative sedation/anxiolysis/amnesia;

2.Intravenously as an agent for sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography, cardiac catheterization, oncology procedures, radiologic procedures, suture of lacerations and other procedures either alone or in combination with other CNS depressants;

3.Intravenously for induction of general anesthesia, before administration of other anesthetic agents. With the use of narcotic premedication, induction of anesthesia can be attained within a relatively narrow dose range and in a short period of time. Intravenous midazolm can also be used as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia)

4. Continuous intravenous infusion for sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in critical care settings

REVIEW OF LITERATURE

Short TG. et al in 1991 studied interactions between IV propofol and midazolam for induction of anaesthesia in 200 unpremedicated female patients undergoing elective gynaecological surgery using end points of hypnosis (loss of response to verbal command) and anaesthesia (loss of response to 5-s transcutaneous tetanic stimulus) and found that synergestic interaction was found. The combination having 1.44 times the potency of the individual agents. The dose of propofol required to produce anaesthesia was reduced by 52% in the presence of midazolam. The cause of synergism was not clear but may have been due to interaction at CNS GABA(A) receptors.

McClune S. et al in 1992 compared synergestic interaction between propofol and midazolam in 140 ASA 1 and 2 female patients (18-60 years). Clinical end points included loss of response to command, loss of eye lash reflex and failure to respond to application of anaesthetic face mask. Administration of 25% of ED 50 of midazolam followed by 50% of ED 50 of propofol resulted in loss of response to command in 50% of patients while 50% of ED 50 of midazolam followed by 25% of ED 50 of propofol had the same effect.

Caba F. et al in 1993 studied the synergism of midazolam and propofol in the induction of anaesthesia. A double blind study of 90 ASA 1 and 2 women undergoing elective surgery revealed the ED 50 in propofol group was 1.56 mg/kg and that of midazolam group was 0.24 mg/kg. In the midazolam propofol group the ED 50 of midazolam was reduced approximately quarter and reduced dose was 0.068 mg/kg.

Teh J, **Short TG**, et al .in 1994 tested the hypothesis that the "synergistic interaction which occurs when midazolam and propofol are combined for i.v. sedation is caused by an increase in the free plasma concentration of one of the drugs." Six patients undergoing general anaesthesia received an infusion of propofol with the addition of an infusion of midazolam commenced 30 min later. Another six patients received an infusion of midazolam with the addition of an infusion of propofol 30 min later It was concluded that the observed synergism with this combination could not be explained solely by alteration in free plasma concentration of either of these drugs when they were administered together.

Vinik HR, et al .in 1994 tested the hypnotic effects of propofol, midazolam, alfentanil. Their binary and triple combinations were studied in 130 unpremedicated patients in a randomized, double-blind fashion. The ability to open eyes on verbal command was used as an end-point. Dose-response curves for the three drugs given separately and in combination were determined with a probit procedure and the ED50 values were compared with an isobolographic analysis. The ratios of a single-drug fractional dose to a combined fractional dose indicating the degree of superadditivity (synergism) were:1.4 for propofol-alfentanil, 1.8 for midazolam-propofol, 2.8 for midazolam-alfentanil, and 2.6 for propofol-midazolam-alfentanil. The results indicate that the propofol-midazolam-alfentanil interaction produces a profound hypnotic synergism which is not significantly different from that of the binary midazolam-alfentanil combination.

Amrein R, et al .in 1995 investigated midazolam and propofol as potential partners. The mechanism of action, pharmacokinetic properties, pharmacological effect, the way in which they interact at the receptor site, the differences in pharmaceutical formulations, the side-effect profiles and economic considerations were compared.

Animal experiments and clinical pharmacology studies have shown that midazolam and propofol have synergy with other centrally active drugs. It could be expected that the relationship between desired effects and adverse effects could be improved by skilful use of the synergism between midazolam and propofol.

Co-induction of anaesthesia and co-administration in long-term sedation can offer improvements in therapeutic situations compared with monotherapy. These improvements are in terms of a more suitable effect profile, a more favorable ratio of desirable effects to side-effects, optimization of the time-course of effects and reduced costs.

Elwood T, et al . in 1995 tested the hypothesis that, "in the presence of alfentanil, the combination of midazolam with propofol for a very brief operative procedure would not affect the recovery phase". 64 outpatients scheduled for dilatation and curettage received placebo, or low-dose midazolam (0.03 mg.kg-1), or high-dose midazolam (0.06 mg.kg-1) iv, in a randomized double-blind manner. They then received alfentanil 10 micrograms.kg-1 iv, followed by titrated doses of propofol iv for induction and maintenance of anaesthesia.

Outcome measures were: propofol dose (induction and maintenance), time until eye-opening to command, and time to discharge-readiness. Propofol induction dose was decreased by increasing doses of midazolam. Midazolam delayed the time to eye-opening but not time to discharge-readiness. It was concluded that midazolam propofol co-induction in the presence of alfentanil delays eye-opening, but does not delay discharge after anaesthesia.

Martlew RA, et al .in 1996 determined the dose-response curves and effective doses of propofol for insertion of the laryngeal mask airway (LMA) in 50 unpremedicated children and in 60 children premedicated with midazolam, aged 3-12 yr. One of several doses of propofol was administered i.v. over 15 s to groups of 10 children, and conditions for LMA insertion were assessed at 60 s. The doses required for satisfactory LMA insertion in 50% and 90% of unpremedicated patients (ED50, ED90) were 3.8 mg kg-1 and 5.4 mg kg-1, respectively; those for premedicated patients were 2.6 mg kg-1 and 3.6 mg kg-1, respectively.

Reinhart DJ, et al . in 1997 Compared the hemodynamics, efficacy, safety and postoperative recovery of patients following the use of either midazolam plus propofol or placebo plus propofol for induction and maintenance of general anesthesia for outpatient surgical procedures of less than two hours' duration. The study included 203 ASA I, II, and III patients undergoing various outpatient surgical procedures. Concluded that concomitantly administered midazolam and reduction-concentration propofol did not exacerbate the well-described hypotensive effects of full-strength propofol during induction of anesthesia. The time to intubation was same with the combination of midazolam/propofol as compared with propofol alone. Recovery from the two regimens was not significantly different. However, reduced recall of perioperative events was observed more often in the midazolam/propofol regimen compared with propofol alone.

Tighe, K. et al ***in 1997*** studied the influence of co-induction with midazolam in conjunction with propofol/alfentanil anaesthesia on postoperative psychomotor recovery. The study was placebo controlled and double blind with patients receiving either 0.03 mg.kg-1 of midazolam or saline 2 min before induction of anaesthesia..

Patients who underwent co-induction with midazolam had significantly impaired concentration and rapidity of response but improved accuracy and vigilance when compared with those who received saline. The study confirmed that co-induction with a subanaesthetic dose of midazolam reduced the induction dose of propofol by up to 50%. It was concluded that co-induction with midazolam reduces psychomotor recovery in the immediate postoperative phase following propofol infusion anaesthesia.

McAdam LC, et al in 1998 evaluated the interactions between propofol and midazolam in modulating GABA(A) receptor activity in embryonic hippocampal neurons. The effects of midazolam and propofol on peak current evoked by submaximal concentrations of GABA were studied using the patch clamp method. Isobolographic analysis was undertaken by constructing concentration-response curves for midazolam and propofol alone and then evaluating the potency of combinations of midazolam and propofol. In other experiments, the concentration of GABA was increased and flurazepam was substituted for midazolam. Isobolographic analysis confirmed that midazolam and propofol interact synergistically to enhance currents evoked by low concentrations of GABA (1 microM).

However, when the concentration of GABA was increased to 3 microM, the interaction was additive. The interaction between flurazepam and propofol was also additive for enhancement of currents evoked by 3 microM GABA. It was concluded that the interaction between midazolam and propofol was critically dependent on the concentration of GABA: Synergism was evident at low concentrations of GABA, but an additive interaction was apparent when the concentration of GABA was increased. Changes in GABA(A) receptor function may underlie the synergistic interaction between propofol and midazolam for clinical effects such as hypnosis. The clinical implication of the results is that the benefits of synergism observed at one concentration ratio of these drugs may not be apparent at another

D. H. Conway, et al in 2000 Investigated the influence of co-induction with remifentanil and midazolam on effect site propofol requirements at induction of anaesthesia using target-controlled infusions .in Sixty-six consenting adult patient's propofol dose and effect site concentration at loss of verbal response were recorded. It resolved that the effect site concentration of propofol alone was 2.19 μg mL^{-1} .This was reduced to 1.55 μg mL^{1} during co-induction with remifentanil and further reduced to 0.64 μg mL^{-1} with midazolam premedication.

It was concluded that co-induction with remifentanil alone or with midazolam can be used to reduce propofol doses at induction of anaesthesia using target-controlled infusions.

Yukihiro Yoshida [1], et al study in 2001 to determine whether propofol reduces extracellular concentrations of dopamine in the rat nucleus accumbens and if so, whether this effect is potentiated by midazolam.. The study demonstrated that propofol dose-dependently reduced dopamine release in rat nucleus accumbens, and that the effect was facilitated by midazolam; a similar interaction is also seen clinically, on preoperative anxiety and on anaesthesia

Cressey DM, etal 2001 in a double-blind, randomised trial, compared the effects of pretreatment with midazolam at two different doses (0.025 and 0.05 mg / kg with placebo, on the induction dose requirements of propofol in two different age groups. 60 younger patients (aged 18-35 years) and 60 older patients (aged over 60 years). All patients received 0.75 microg / kg of fentanyl, plus a blinded pretreatment with either saline or one of two doses of midazolam. Induction continued with a fixed rate infusion of propofol.

Propofol dose requirement was recorded, as were cardiovascular parameters and the occurrence of significant apnoea (> 60 s). Midazolam pretreatment was associated with a significant reduction in propofol dose requirement in both younger and older patients. The reduction in older patients was significantly greater than the equivalent response in younger groups. There was no demonstrable benefit in terms of improved cardiovascular stability or reduction in the incidence of apnoea. One should be cautious in the use of midazolam as an agent for co-induction with propofol in the elderly.

Stegmann, G.F. et al (2001). in a clinical trial, induced anaesthesia with propofol (4 mg/kg) after intravenous premedication with or without midazolam (0.1 mg/kg), in a group of 8 dogs scheduled for ovariohysterectomy.

Midazolam administration induced acute behavioral changes, and increased reflex suppression after propofol induction. Compared to the control group, the dose required to obtain loss of the pedal reflex was significantly reduced by 37%, and the end-tidal isoflurane concentration during maintenance, reduced by 23%.

MATERIALS AND METHODS

The study was done at Government General Hospital, Madras Medical College, Chennai after getting permission from the ethical committee. All patients gave informed consent. Both the patient and observer were unaware of the group allocations.

INCLUSION CRITERIA

ASA 1 and 2 patients

Age 16 to 50 years

Elective surgeries

EXCLUSION CRITERIA

ASA 3 and 4patients

Age <15years >50 years

Any co morbid illnesses

Patients on benzodiazepines

Ninety ASA1 patients age 16-50 years scheduled for elective surgery were studied. All patients were pre operatively investigated for baseline investigations like blood sugar, urea, serum creatinine ,ECG in 12 leads,

chest x-ray PA view and other specific investigations relevant to the disease. All patients were assessed for their physicl status.

The subjects were not pre medicated and were randomly allocated to one of the three groups.

Group1 received midazolam 2 mg 2min prior to induction

Group 2 received propofol 30 mg 2min prior to induction

Group 3 received 3ml of 0.9%saline 2min prior to induction of anaesthesia. This was given as a bolus over a few seconds. Patients were counseled about the method of study.

Baseline measurement of Blood pressure, heart rate and oxygen saturation were made prior to insertion of a 18 gauge venflon and these were repeated at 60 seconds intervals for the reminder of the study. Anaesthesia was induced by infusing 1% propofol. Patients were encouraged to flex their arms to the command of the observer .and the blood pressure and heart rate were recorded simultaneously if there was no response to verbal command. The propofol infusion was stopped at this point and face mask applied firmly. Any response to placement of the mask was noted. The study was deemed complete at this

point and taken as the end point of induction. Induction dose of propofol was noted at this point.. And further management was not influenced by the study.

OBSERVATIONS AND RESULTS

90 patients were taken up for the study.

Group 1 30 patients Group 2 30 patients and Group 3 30 patients.

Group1 received midazolam 2 mg 2min prior to induction

Group 2 received propofol 30 mg 2min prior to induction

Group 3 received 3ml of 0.9%saline 2min prior to induction of anaesthesia.

STATISTICAL ANALYSIS

Chi-square test

Paired t-test

ANOVA F-test

Multiple comparison by Bonferroni t- test

Qualitative data (sex,weight age) were were given in frequencies with their percentages

Quantitative data (systolic blood pressure, pulse rate, dosage)were given in mean and standard deviation.

Differences between the three groups on systolic bloodpressure, pulse rate were analysed using one way analysis of variance(ANOVA) and multiple comparison was done by using BONFERRONI TEST

Comparison between each group pre and post induction values were analysed using PAIRED T TEST

Demographic data (age ,sex.weight) between the groups were analysed using PEARSON CHI SQUARE TEST

Table 1: Demographic Profile

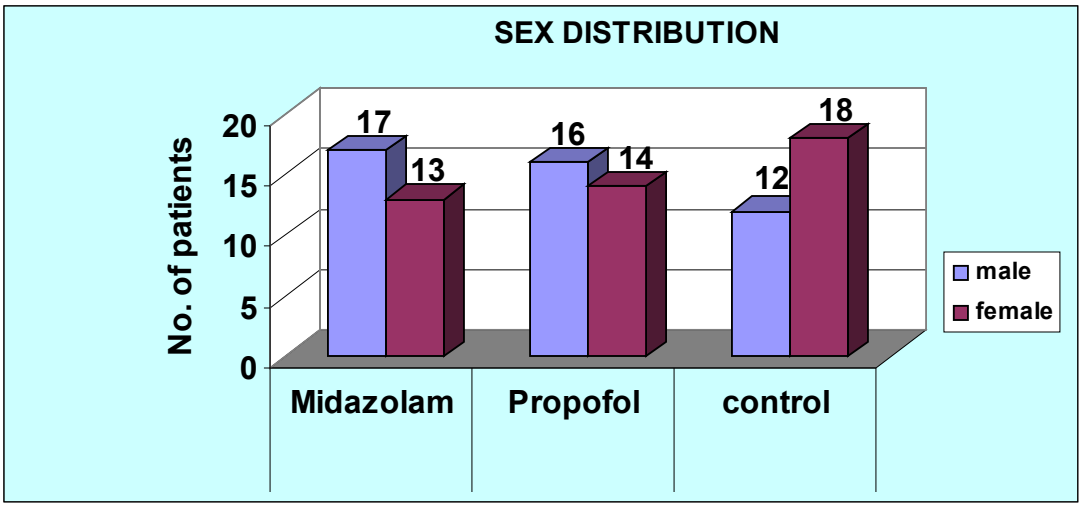
	Group 1		**Group 2**		**Group 3**	
	Midazolam		**Propofol**		**Control**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age	**29.37**	**6.18**	**30.93**	**6.43**	**33.03**	**7.35**
Wt	**46.17**	**6.06**	**42.03**	**7.78**	**48.33**	**7.82**
ASA	**1.00**	**.00**	**1.00**	**.00**	**1.00**	**.00**
SBP(baseline)	**128.27**	**5.51**	**127.30**	**4.91**	**128.90**	**4.47**
DBP	**80.60**	**2.67**	**83.43**	**4.70**	**82.53**	**3.93**
PR	**88.20**	**6.33**	**86.23**	**6.58**	**89.03**	**4.64**
SBP(pre-induction)	**127.20**	**3.88**	**126.70**	**5.00**	**128.37**	**4.60**
DBP	**80.37**	**3.89**	**83.23**	**5.50**	**81.67**	**4.16**
PR	**86.70**	**5.09**	**83.53**	**6.77**	**87.63**	**4.54**
SBP(post-induction)	**118.43**	**3.46**	**114.27**	**4.56**	**115.00**	**4.85**
DBP	**75.93**	**3.23**	**73.13**	**3.67**	**72.33**	**3.86**
PR	**78.73**	**4.43**	**74.67**	**5.77**	**74.63**	**4.12**
Dosage	**74.83**	**7.82**	**68.83**	**6.65**	**103.50**	**14.09**

Sex

		Male		Female	
		n	%	n	%
group	Midazolam	17	37.8	13	28.9
	Propofol	16	35.6	14	31.1
	control	12	26.7	18	40.0

χ2=1.86 P=0.39 not significant

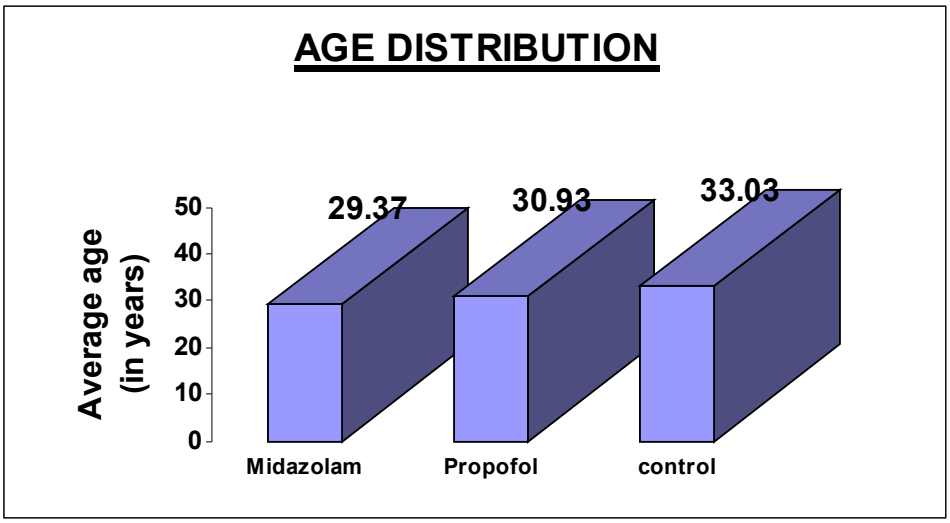
Sex wise there is no significant differences between three groups. Male and female ratio is equal in all three groups(x2=1.86 p=0.39)



Age

	N	Mean	Std. Deviation	ANOVA F-test
Midazolam	**30**	**29.37**	**6.184**	
Propofol	**30**	**30.93**	**6.432**	**F=2.28 P=0.11**
control	**30**	**33.03**	**7.351**	

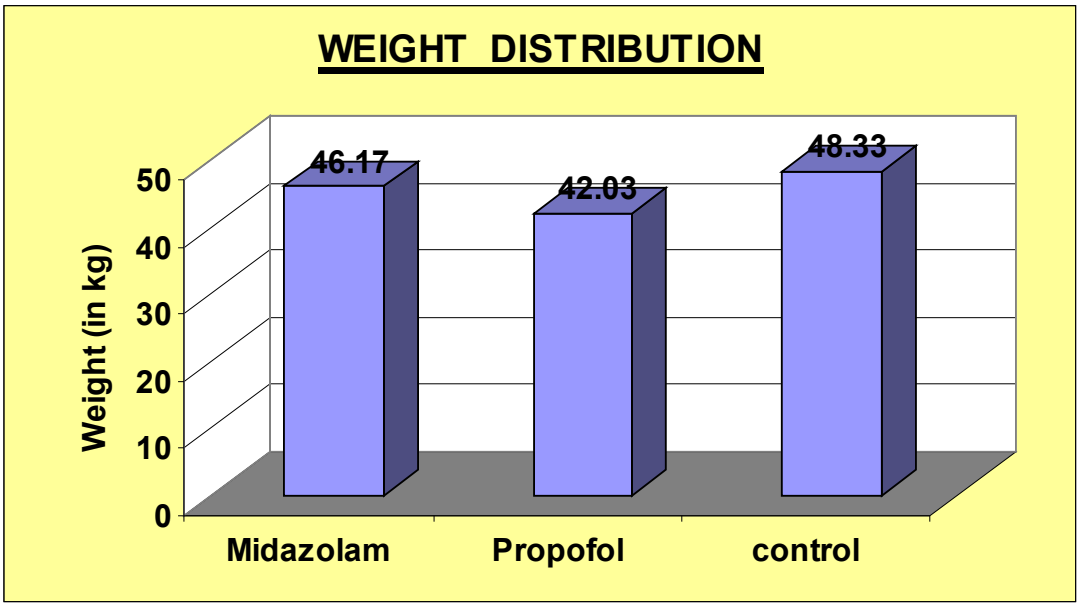
Age wise there is no significant differences between the three groups (p=0.11)



Weight

	N	Mean	Std. Deviation	ANOVA F-test
Midazolam	**30**	**46.17**	**6.058**	
Propofol	**30**	**42.03**	**7.784**	**F=5.82 P=0.01**
control	**30**	**48.33**	**7.818**	

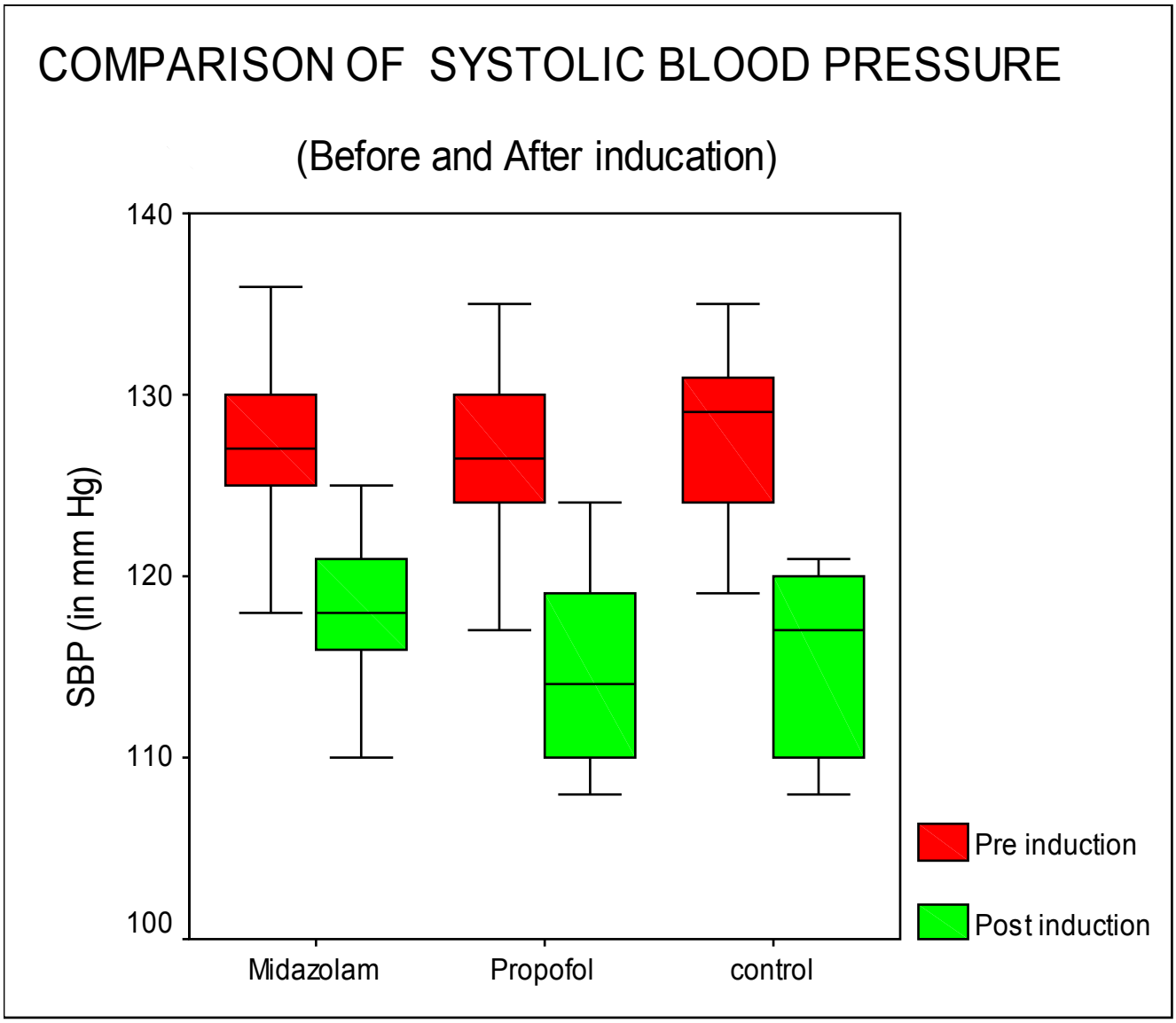
In weight distribution there was significant difference between group1 and group2as well as group2 and group3 (p=0.01)



Descriptives

SYSTOLIC BLOOD PRESSURE-DIFFERENCE

	N	Mean	Std. Deviation	ANOVA F-test	Minimum	Maximum



Multiple Comparisons

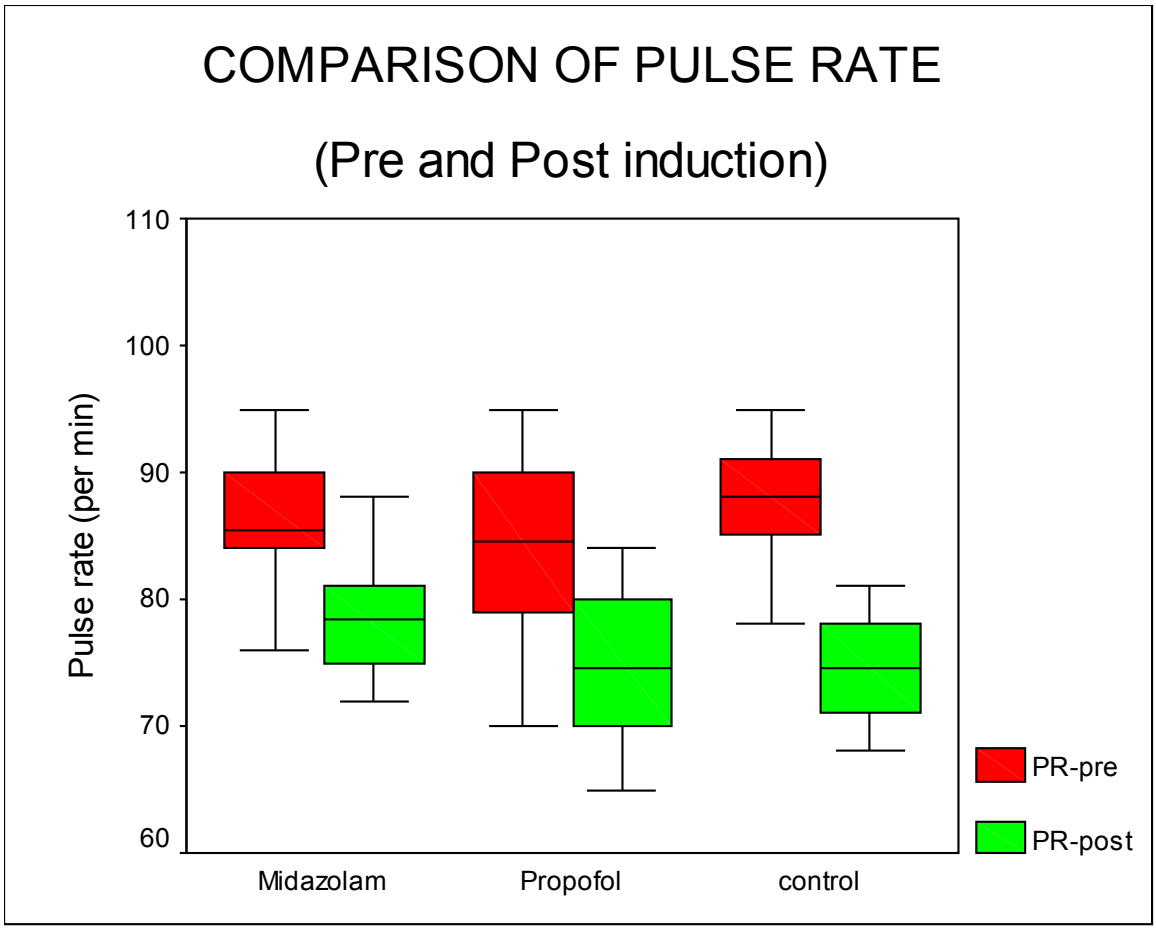
Dependent Variable: SBP_DIFF
Bonferroni t-test

(I) group	(J) group	Mean Difference (I-J)
Midazolam	**Propofol**	**-3.6667(*)**
	control	**-4.6000(*)**
Propofol	**Midazolam**	**3.6667(*)**

	control	**-.9333**
control	**Midazolam**	**4.6000(*)**
	Propofol	**.9333**

- The mean difference is significant at the .05 level.
-

There was significant difference in systolic blood pressure before and after induction between group 1 and group 2as well as group 2 and group3 (p=0.001)



Pulse rate

group		Mean	N	Std. Deviation	Paired t-test
Midazolam	PR-pre	86.70	30	5.093	t=12.86
	PR-post	78.73	30	4.425	P=0.001
Propofol	PR-pre	83.53	30	6.766	t=11.94
	PR-post	74.67	30	5.774	P=0.001
control	PR-pre	87.63	30	4.537	
	PR-post				t=23.51
		74.63	30	4.123	P=0.001

PULSE RATE DIFFERENCE

Midazolam	30	7.9667	2.44221	F=20.47	4.00	14.00
					1.00	17.00
Propofol	30	8.8667	4.06612	P=0.001	6.00	19.00
control	30	13.0000	3.02860			

There was significant reduction in pulse rate between the control group and the other two groups(f=20.47,p=0.001)

Multiple Comparisons
Dependent Variable: PR_DIFF Bonferroni t-test

(I) group	(J) group	Mean Difference (I-J)
Midazolam	Propofol	-.9000
	control	-5.0333(*)
Propofol	Midazolam	.9000
	control	-4.1333(*)
control	Midazolam	5.0333(*)
	Propofol	4.1333(*)

* The mean difference is significant at the .05 level.

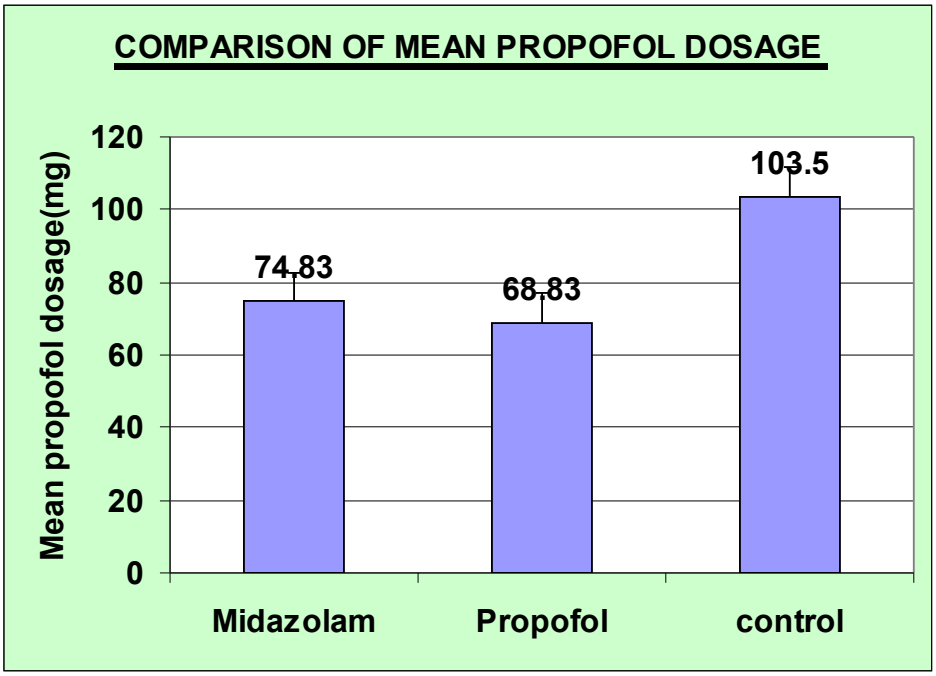
Descriptives

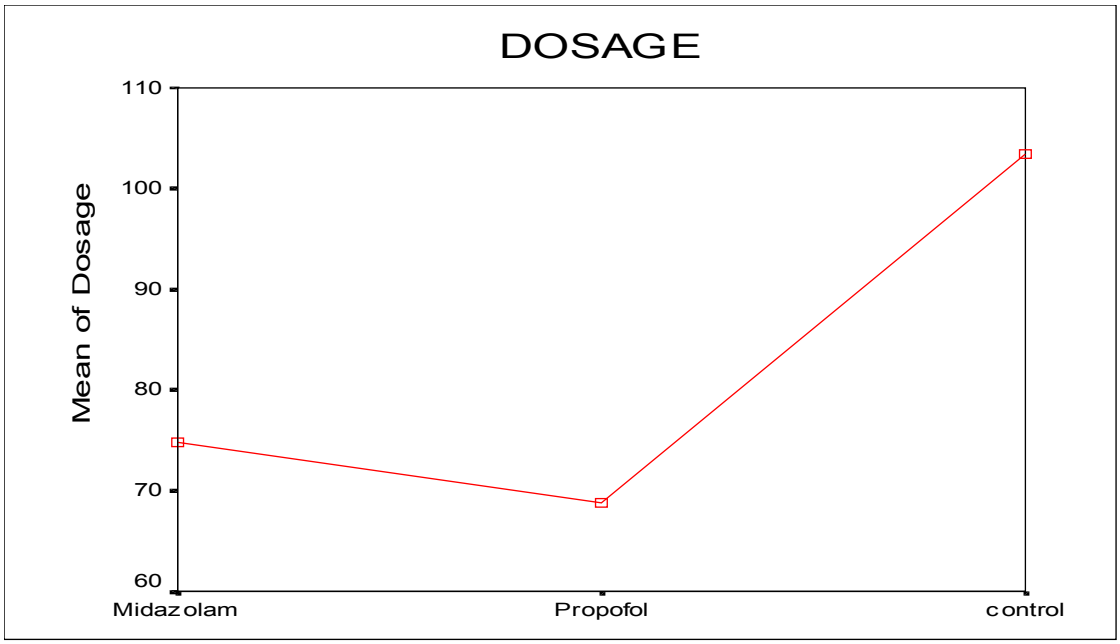
DOSAGE

	N	Mean	Std. Deviation	ANOVA F-test	Minimum	Maximum
Midazolam	30	74.83	7.822	F=101.63 P=0.001	65	100
Propofol	30	68.83	6.654		55	80
control	30	103.50	14.090		80	130

DOSAGE

	N	Mean	SD	ANOVA F-test
Midazolam	30	74.83	7.822	F=101.6 P=0.001
Propofol	30	68.83	6.654	
control	30	103.50	14.090	





Multiple Comparisons

Dependent Variable: DOSAGE
Bonferroni

(I) group	(J) group	Mean Difference (I-J)	Sig.
Midazolam	Propofol	6.00	.070
	control	-28.67(*)	.000
Propofol	Midazolam	-6.00	.070
	control	-34.67(*)	.000
control	Midazolam	28.67(*)	.000
	Propofol	34.67(*)	.000

*

The mean difference is significant at the .05 level. The dosage requirement in midazolam group(1) was (mean=74.83 mgs),propofol predosing group(2) was (mean=68.83 mgs) and control group3 was (mean=103.50 mgs) which was significant(p=0.001).

Discussion

The dose of propofol required to induce anaesthesia depends on several variables – the end point used[34], the age of the patient [6], the rate of injection [6], and the use of pre medication [8]. Pre dosing with midazolam[16] has been shown to be reliable and effective method of reducing propofol requirement [9]. We have shown that predosing with 30 mg of propofol is as effective in reducing the induction dose of propofol as co induction with 2 mg of midazolam when loss of verbal contact is taken as end point. In our study the induction dosage were reduced by 36% in group 1(midazolam group) and 32% in group2 (propofol predosing group).The combination having 1.35 times the potency of individual agents.

Short TG. et al in 1991 studied interactions between IV propofol and midazolam for induction of anaesthesia in 200 unpremedicated female patients undergoing elective gynaecological surgery using end points of hypnosis (loss of response to verbal command) and anaesthesia (loss of response to 5-s transcutaneous tetanic stimulus) and found that synergestic interaction was found.

The combination having 1.44 times the potency of the individual agents. The dose of propofol required to produce anaesthesia was reduced by 52% in the presence of midazolam In our study the induction dosage were reduced by 36% in group 1(midazolam group) and 32% in group2 (propofol predosing group).The combination having 1.35 times the potency of individual agents

Caba F. et al in 1993 studied the synergism of midazolam and propofol in the induction of anaesthesia. A double blind study of 90 ASA 1 and 2 women undergoing elective surgery revealed the ED 50 in propofol group was 1.56 mg/kg and that of midazolam group was 0.24 mg/kg. In the midazolam propofol group the ED 50 of midazolam was reduced approximately quarter 0.068 mg/kg..In our study the induction dosage were reduced by 36% in group 1(midazolam group) and 32% in group2 (propofol predosing group).The combination having 1.35 times the potency of individual agents In our study the induction dosage were reduced by 36% in group 1(midazolam group) and 32% in group2 (propofol predosing group).The combination having 1.35 times the potency of individual agents

AndersonLetalin 1999 in a double-blind, placebo-controlled study of 90 ASA 1 and 2 patients scheduled for elective surgery compared the effect of pre-administering midazolam 2 mg or propofol 30 mg on the dose of propofol subsequently required to induce anaesthesia.

Using loss of response to verbal command and tolerance to placement of a facemask as end-points, the dose of propofol required to induce anaesthesia was significantly smaller in the patients given propofol (1.87 mg.kg-1) or midazolam (1.71 mg.kg-1) when compared to the control group (2.38 mg.kg-1).In our study the dosage requirement in midazolam group(1)(n=30) was (mean=74.83 mgs),propofol predosing group(2)(n=30) was (mean=68.83 mgs) and control group3 (n=30)was (mean=103.50 mgs) which was significant (p=0.001).

Cressey DM. etal 2001 compared the effects of pretreatment with midazolam at two different doses (0.025 and 0.05 mg /kg) with placebo, on the induction dose requirements of propofol in two different age groups.: 60 younger patients (aged 18-35 years) and 60 older patients (aged over 60 years)

It was concluded that Midazolam pretreatment was associated with a significant reduction in propofol dose requirement in both younger and older patients. The reduction in older patients was significantly greater than the equivalent response in younger groups..Hence one should be Cautious is in the use of midazolam as an agent for co-induction with propofol in the elderly. Hence in our study the age group selected for the study were between 16 to 50 years.

Reinhart DJ, etal. in 1997 compared the hemodynamics, efficacy, safety, and postoperative recovery of patients following the use of either midazolam plus propofol or placebo plus propofol for induction and maintenance of general anesthesia for outpatient surgical procedures of less than two hours' duration: The study. included 203 ASA I, II, and III patients undergoing various outpatient surgical procedures. It was concluded that concomitantly administered midazolam and reduction-concentration propofol did not exacerbate the well-described hypotensive effects of full-strength propofol during induction of anesthesia

In our study. there was significant reduction in systolicblood pressure between group1 and group2 as well as group1 and group3.(p=0.001) There was significant reduction in pulse rate between the control group and the other two groups(f=20.47,p=0.001).

Although midazolam may work synergistically with propofol[51], a major clinical benefit is the rapid attainment of anxiolysis. We did not attempt to quantify or compare the anxiolysis achieved by the administration of either midazolam or propofol but the patients appeared to be more relaxed and settled and the associated reduction in sympathetic drive may have allowed induction of anaesthesia with lower doses of propofol. Pre dosing and co induction both reduce the dose of induction agent required to achieve hypnosis and any form of pre medication is likely to have similar effect [47].

Both midazolam and propofol groups(Group1&2) are therefore cost effective, in that the propofol requirements in our study where limited to a single ampoule for each patient. Pre dosing with propofol is as effective as midazolam in reducing the dose of propofol to induce anaesthesia

We used two end points – loss of response to verbal command and response to placement of face mask. Of these we found loss of response to verbal command the more reproducible. However if we had used a different end points such as laryngeal mask insertion [34] the results may have been different. Our study was blinded, the assessor being unaware of the pre dosing agent, and we consider this essential for any objective assessment.

SUMMARY

In this study pre dosing of 2 mg of midazolam as co-induction agent (group 1) where propofol is used as an induction agent had Lesser blood pressure variability and Lesser heart rate variability during and after induction. Midazolam co-induction is more cost effective than control (group 3) ,since it requires only a single vial of propofol for induction.

Pre dosing of 30 mg of propofol(Group 2) before propofol induction had Reduced dosage requirement, lesser blood pressure variability, lesser heart rate variability than group 3(control group).It is more cost effective than the control group and midazolm co-induction.

control group (Group 3) is less cost effective than the other two groups, since it requires more than one vial of propofol for induction. It produces more hemodynamic variability which is statically significant. when compared with the other two groups.

CONCLUSION

Predosing of midazolam for propofol induction had less hemodynamic variability (fall in blood pressure and heart rate during and after induction) and more cost effective since it requires only single vial of propofol for induction, whereas control group had significant hemodynamic variability ,significant fall in blood pressure and heart rate .and requires more than a single vial of propofol for induction, hence it is not cost effective..

Predosing of propofol for induction with propofol had less hemodynamic variability(fall in blood pressure and heart rate) than the control group. It is more cost effective when compared to control group and midazolam co-induction group.

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PROFORMA

A comparison of midazolam co induction with propofol predosing for induction of anaesthesia

Aim:

Comparing the effect of preadministering midzolm 2mg with propofol 30 mg on the dose of propofol required subsequently to induce anaesthesia

Inclusion criteria:

ASA1&2 patients

Age 16 to 50 years

Elective surgeries

Exclusion criteria:

ASA 3& 4 patients

Any co morbid illnesses

Patients on oral benzodiazepines

NAME :

AGE :

SEX :

WEIGHT :

ASA status :

MONITORS :

Systolic blood pressure before and after induction

Heart rate before and after induction

Propofol induction dosage (mg/kg)

GROUP 1 :MIDAZOLM GROUP (n=30)

GROUP 2 :PROPOFOL PREDOSING GROUP(n=30)

GROUP 3 :CONTROL GROUP (n=30)

METHOD :

Administering either midazolam 2mgs or propofol 30 mgs or 3 ml of 0.9%norml saline two minutes before induction

End point of induction:

1. Loss of response to verbal command
2. Tolerance to placement of face mask

Group 1

Name	IP No.	Age	Sex	Wt	ASA	Pre Op		Pre Induction		Post Induction		Propofol Dose	Co
						BP	PR	BP	PR	BP	PR		
darmajirao	772853	28	M	65	1	150/80	109	136/84	100	123/78	92	100	
aswinidevi	768182	19	F	45	1	130/78	98	130/76	94	120/70	88	75	
alamelu	765234	25	F	48	1	128/80	92	128/80	90	122/72	82	80	
balasundaram	753261	32	M	50	1	132/80	95	130/80	94	118/78	80	85	
selvi	743422	26	F	42	1	126/82	89	126/88	86	118/76	78	75	
maragatham	754821	36	F	46	1	134/82	89	134/88	88	125/78	80	80	
jayanthi	762431	21	F	38	1	120/78	82	120/76	83	116/72	75	70	
paramasivam	754411	30	M	55	1	130/84	90	130/82	89	122/78	81	85	
saraswathy	754889	35	F	45	1	128/79	86	128/78	89	120/75	80	75	
gomathy	745621	28	F	42	1	130/79	81	130/78	80	121/78	74	80	
vinoth	758412	18	M	35	1	120/76	82	120/75	83	112/70	72	65	
nagaraj	742541	24	M	50	1	126/84	85	126/84	82	118/76	78	85	
chandrakala	752663	30	F	49	1	125/84	86	126/86	84	120/78	80	85	
shanthi	749632	27	F	38	1	130/76	93	130/75	95	121/80	85	65	
shankar	758261	30	M	52	1	125/79	89	124/78	86	118/75	81	80	
anand	735219	19	M	46	1	126/78	75	126/74	76	118/70	72	75	
lakshmipathy	743165	28	M	39	1	130/78	86	130/78	84	121/70	79	70	
rani	752698	33	F	45	1	129/84	84	129/84	81	118/78	76	70	
amudha	744412	29	F	46	1	125/80	90	125/82	86	119/76	78	75	
boopathy	74326	30	M	53	1	132/84	86	130/82	84	118/80	76	75	

	9												
jeyapradapan	739569	42	M	48	1	129/84	84	129/84	85	120/78	75	70	
kumar	744123	26	M	38	1	130/79	84	130/78	84	119/76	78	65	
kaliamoorthy	739562	41	M	48	1	128/79	92	126/76	90	118/72	81	70	
anand	741142	29	M	46	1	131/82	89	130/82	85	124/76	75	70	
thirunavukkarasu	758412	25	M	50	1	126/82	94	125/81	92	116/78	80	75	
rathidevi	741398	29	F	48	1	130/85	92	125/84	90	113/79	81	70	
sushanthkumar	739984	36	M	46	1	125/79	86	125/78	85	116/79	75	70	
farooq	746982	40	M	38	1	118/79	80	118/78	81	110/74	74	65	
sathya	758391	35	F	35	1	132/81	95	132/80	92	124/74	78	65	
suresh	733331	29	M	46	1	126/78	85	125/75	84	110/70	70	70	

Group 2

Name	**IP No.**	**Age**	**Sex**	**Wt**	**ASA**	**Pre Op**		**Pre Induction**		**Post Induction**		**Propofol Dose**	**Commen**
						BP	**PR**	**BP**	**PR**	**BP**	**PR**		
Kumar	741256	35	M	45	1	125/86	89	125/87	85	110/74	74	70	
aravinth	732589	28	M	43	1	130/92	96	130/96	95	114/80	80	70	
aswin	749856	27	M	35	1	129/78	85	128/76	87	116/71	70	65	
mallika	725869	30	F	38	1	125/86	89	125/86	88	115/74	80	65	
manohar	741090	45	M	56	1	130/89	86	130/88	85	120/76	78	80	
kalpana	731111	29	F	30	1	129/76	95	129/78	92	119/71	84	60	
rajesh	7461032	27	M	45	1	135/84	92	134/86	91	120/79	80	70	
ramya	736185	24	F	38	1	129/85	91	129/86	90	110/78	82	65	
settu	744658	35	M	48	1	125/90	86	126/89	79	112/74	78	70	
loganathan	748547	41	M	56	1	131/86	82	130/87	80	120/74	71	80	

indira	741767	29	F	30	1	126/87	81	126/89	79	110/70	70	60	
uma	746980	35	F	39	1	124/74	80	124/75	76	108/70	69	65	
ganesh	736770	31	M	47	1	126/84	79	126/86	80	113/76	71	70	
williams	739500	46	M	51	1	135/82	78	135/80	81	120/79	70	80	
sakunthala	725021	29	F	35	1	126/84	91	125/85	89	116/70	81	65	
selvi	741399	25	F	40	1	124/80	94	123/79	85	114/72	80	65	
ranjith	726262	31	M	48	1	130/78	89	128/76	90	115/70	78	75	
premkumar	736560	26	M	40	1	126/89	76	127/90	80	109/79	65	70	
ravi	751020	31	M	46	1	132/90	93	130/90	90	119/80	84	75	
easwari	741335	21	F	30	1	118/78	85	118/76	81	109/69	79	60	
banu	736699	28	F	35	1	119/80	75	118/79	72	110/71	69	65	
vijay	728846	36	M	50	1	129/90	81	128/86	76	112/69	70	80	
sangeetha	719890	20	F	27	1	119/80	94	117/79	89	108/70	75	55	
kishore	736251	24	M	42	1	124/85	86	123/86	81	113/70	71	65	
jamuna	749821	30	F	40	1	125/84	84	124/83	79	114/69	70	65	
vijaya	746094	36	F	45	1	135/85	96	134/82	90	121/71	81	70	
nithya	739104	25	F	48	1	119/78	78	117/76	70	109/70	67	70	
palani	721560	40	M	53	1	136/84	76	135/86	70	118/74	65	80	

Group 3

Name	**IP No.**	**Age**	**Sex**	**Wt**	**ASA**	**Pre Op**		**Pre Induction**		**Post Induction**		**Propofol Dose**	**Comment**
						BP	**PR**	**BP**	**PR**	**BP**	**PR**		
Murugan	746566	35	M	45	1	125/78	96	124/75	94	109/70	78	100	
Thangam	739652	30	F	38	1	130/80	89	129/85	88	121/74	74	90	
Easwari	741444	25	F	40	1	124/80	85	124/79	83	108/73	70	95	
Jamuna	738652	24	F	43	1	125/84	84	121/80	80	108/69	71	100	
Reeta	744651	25	F	39	1	126/85	85	125/84	86	110/71	72	90	
Raju	73392	40	M	56	1	130/87	90	132/88	88	120/79	79	100	

	1											
Grace	738952	35	F	48	1	131/79	86	130/80	85	119/69	71	100
Mani	736524	40	M	60	1	136/84	87	135/82	85	120/74	79	130
Nithya	738745	29	F	35	1	124/78	79	124/76	78	109/78	68	80
Kavitha	738721	27	F	46	1	126/80	87	125/79	85	112/70	74	90
Manjula	738779	30	F	48	1	130/79	85	130/78	83	117/69	75	100
Jeya	738659	40	F	50	1	135/78	86	134/76	85	120/79	74	110
Arumugam	738547	48	M	57	1	136/89	95	135/87	93	121/78	79	120
Suguna	738498	35	F	47	1	124/79	84	124/78	83	108/67	70	100
Ramya	741020	26	F	39	1	121/80	86	120/79	85	108/69	68	90
Selvam	740056	35	M	60	1	130/91	93	130/90	91	112/78	80	130
Hari	741158	25	M	52	1	135/86	92	135/85	90	120/79	78	110
Banu	746985	28	F	47	1	129/84	90	128/83	89	117/70	70	100
Gomathy	738014	30	F	48	1	131/82	89	130/81	88	118/69	71	100
Deepa	740031	27	F	46	1	129/86	93	128/85	92	117/72	78	100
Mohan	745012	30	M	50	1	132/85	92	131/84	91	120/70	76	110
Sundaram	739050	45	M	58	1	129/87	94	129/86	90	117/71	78	120
Jareena	739128	26	F	39	1	119/78	81	119/78	80	108/69	70	80
Francis	738947	35	M	50	1	130/84	92	130/82	90	119/74	75	110
Hamsaveni	736458	29	F	45	1	128/79	96	128/78	95	113/69	80	100
David	740017	50	M	62	1	135/90	94	135/90	93	120/78	81	130
Lavanya	740258	26	F	40	1	128/80	96	128/79	95	117/69	78	90
Moorthy	739105	35	M	59	1	135/85	92	135/85	91	114/74	80	120
Andal	74009	36	F	42	1	130/81	89	130/81	88	118/70	72	90

	5												
Kuppan	740158	45	M	61	1	124/78	84	124/77	85	110/69	70	120	