A COMPARISON BETWEEN PROPOFOL AND THIOPENTONE AS INDUCTION AGENTS IN OBSTETRIC ANAESTHESIA

By

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A dissertation submitted in partial fulfilment of the requirements for the degree of Masters of Medicine (Anaesthesiology) of the University of Dar es Salaam.

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CERTIFICATION

The undersigned certify that he has read and hereby recommend for acceptance by the University of Dar es salaam a dissertation entitled *; A comparison between propofol and thiopentone as induction agents in obstetric anaesthesia*, in partial fulfillment of the requirements for the degree of Masters of Medicine (Anaesthesiology).

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DEDICATION.

To my husband Mr. Hassan Ross and my children Abdullah, Said and Raya.

ABSTRACT

Propofol 2.5mg/kg was compared with thiopentone 5mg/kg as an induction agent for elective caesarean section. 206 healthy patients were included in an open randomized study, among whom 104 patients received thiopentone and 102 received propofol. These patients were unpremedicated, after induction dose the maintenance was similar for both groups. Both propofol and thiopentone group produced a rapid and smooth induction of anaesthesia with a low incidence of side effects. Diastolic blood pressure was lower in propofol group during the induction to delivery interval. Other haemodynamic changes were similar for both groups. Respiratory upsets occurred less frequently with propofol (7.8%) than with thiopentone (22.5%), but propofol caused more pain (28.8%) on injection compared to thiopentone. Recovery time was shorter after propofol as evaluated by time to open eyes on commands. There was no significant neonatal depression as assessed by Apgar score. Propofol appears to be a suitable alternative to thiopentone as induction agent for obstetric anaesthesia.

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LIST OF ABBREVIATIONS

ACTH ; Adrenal Corticotrophic Hormone

ASA II/III ; American Society of Anaesthesiologist Physical Status II/III

BIS ; Bispectral Index

$CMRO_2$; Cerebral Metabolic Rate for Oxygen

CNS ; Central Nervous System

CO_2 ; Carbon dioxide

Cp_{50} ; Concentration in the plasma

DBP ; Diastolic Blood pressure

ECG ; Elecrocardiogram, -graphic, -graphy

EEG ; Elecroencephalogram, -graphic, -graphy

ED_{95} , Effective Dose 95

GABA ; Gamma aminobutyric acid

HR ; Heart rate

ICU ; Intensive Care Unit

MAC ; Minimum Alveolar Concentration

MAP ; Mean Arterial Pressure

NACS ; Neurological Adaptive Capacity Score

PSA ; Patient Control Sedation

SBP ; Systolic blood Pressure

STP ; Sodium thiopentone

PART ONE

INTRODUCTION

The concept of intravenous anaesthesia was known to Sir Christopher Wren since 1665, but it first became established in 1920's with the use of intravenous alcohol, tribromoethanol and the barbiturate, pernoston. It was later popularized by a German obstetrician Bumm, the name pernoston being adopted in 1935 for the 10% aqueous solution of this barbiturate.[1, 2.]

However the first drug capable of producing loss of consciousness in one arm brain circulation time was hexobarbitone produced in the laboratories of Helmut Weese in 1932. Despite that it causes muscle movements, hexobarbitone enjoyed popularity in the 1930's and 40's, an estimated number of about ten million patients were anaesthetized using it in the first decade post its introduction.[2.]

The hypnotic effect of thio-barbiturates has been appreciated and had advantages for use as intravenous anaesthetic agent. Clinical trials of thiopentone were started in 1934 at Mayo clinic in Minnesota. It gradually displaced hexobarbitone because it provided smoother induction of anaesthesia and was shorter acting. Since then thiopental has remained the most popular intravenous anaesthetic agent.[2]

Other agents like thiamylal, (sulphurated barbiturate) and methohexitone (oxybarbiturate) had many similarities with thiopental were also in clinical use.

In search of ideal agent, non barbiturates were also investigated. Gamma aminobutyric acid introduced in anaesthesia in 1960 became unpopular due to its slow onset of action and associated extrapyramidal motor activities.[2]

Ketamine entered in clinical use since 1970, holds a unique position among intravenous anaesthetic agent due to its amnesic, analgesic and cardiovascular system effects in addition to its hypnotic effects, which makes it popular for use in high-risk patients.[2]

Etomidate, a carboxylated imidazole derivative was found to be more potent than thiopentone and methohexitone but causes pain on induction (propylene glycol vehicle), and it was associated with higher incidences of tremor, hypertonia, muscle movements, hiccups, nausea, and vomiting. These side effects have limited its usefulness. [1, 2.]

Other anaesthetic agents like propanidid and Althesin a mixture of two water insoluble steroids alphadolone and alphaxalone solubilized in cremophor EL, have been withdrawn from the market because of adverse anaphylactic reaction and depression of the adrenal cortical function.

Work in the early 1970s on substituted derivatives of phenol with hypnotic properties resulted in the development of 2, 6 diisopropofol.[3] The first clinical trial by Kay and Rolly reported in 1977 confirmed the potential of propofol as an anaesthetic induction agent.[4] Initially propofol was prepared with Cremophor EL. Because of anaphylactoid reactions associated with cremophor EL in this early formulation of propofol the drug was reformulated in fat emulsion in 1983. This emulsion form is still in use providing the greater challenge to thiopental with regards to rapid and smooth induction of anaesthesia, non cumulative effects and rapid recovery.[5]

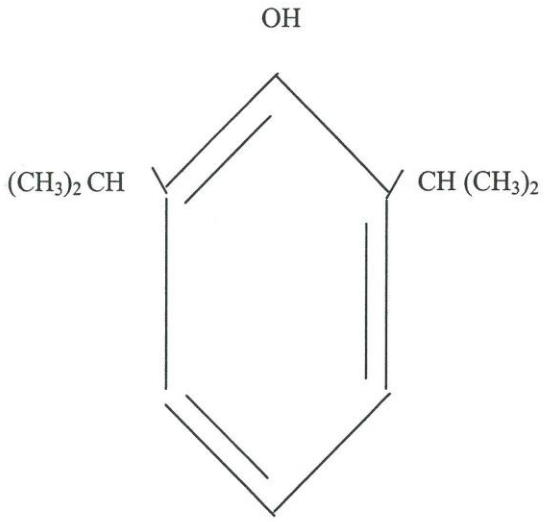
Several studies have been performed to evaluate the value and safety of propofol as an induction agent for general anaesthesia in comparison with thiopentone in parturient undergoing elective caesarean section and found that induction characteristics of propofol to be similar to thiopental.[6-13]

LITERATURE REVIEW

PHARMACOLOGY OF PROPOFOL

Chemical structure of propofol:

Propofol is the most recent intravenous anaesthetic agent to be introduced into clinical practice. It is one of a group of alkylphenols that have hypnotic properties in animals.[14] Chemically it is known as 2, 6, DIISOPROPYLPHENOL and has a molecular weight of 178.27. The structural and empirical formula are



$C_{12}\ H_{18}\ 0$

2, 6, Diisopropyl phenol.

Physical and chemical properties

Propofol appears as a slightly viscous milky white, sterile non pyrogenic emulsion, suitable for intravenous administration. It is available as 1% solution in 20ml clear glass ampoules and 50ml vials. The alkylphenols are oil at room

temperature and are insoluble in aqueous solution but are highly lipid – soluble. The present formulation in an oil in water emulsion containing: Soybean oil – 10%, Glycerol – 2.25%, Purified egg phosphatide 1.2%.[15, 16.]

A newer solvent is medium and long-chain triglyceride emulsion.[17] Propofol injection emulsion is isotonic and has a pH of 7-8.5. It is stable at room temperature, can be stored between 2°C and 25°C. It should not be frozen. It is not light sensitive. If a dilute solution of propofol is required, it is compatible with 5% dextrose in water. The pKa is 11. The octanol/water partition coefficient for propofol is 6761:1 at physiological pH. [18.]

Mechanism of action

Little is known of its neurochemical mechanisms of action. Hales and Lambert documented that propofol reversibly and in a dose dependent manner potentiated the amplitude of membrane currents elicited by local applied GABA in an experiment using bovine adrenomedullary chromaffin cells.[19]. Subsequently, Collins confirmed that propofol enhance GABA – evoked neuronal inhibition in rat olfactory cortex slices.[20] However the ability to potentiate the GABA – induced response both in central neurons and in bovine chromaffin cells is believed to be a general feature of many anaesthetic drugs, such as barbiturates and benzodiazepines.[21,22]

GABA is the principal inhibitory neurotransmitter in the mammalian CNS.

Like the barbiturate and benzodiazepines, propofol may enhance GABA – activated chloride ion channel function. However, it appears to do so through a separate recognition site on the GABA receptor complex [23]or by a different mechanism described for the barbiturates and benzodiazepines.[24]

Pharmacokinetics and pharmacodynamics

Following an intravenous bolus dose, whole blood propofol level decrease very rapidly as a result of both redistribution and elimination. The pharmacokinetics of propofol is well described by a three compartment linear model with compartments representing the plasma, rapidly equilibrating tissues and slowly equilibrating tissues. Using this model, studies have given initial and slow distribution half-lives of 1 to 8 minutes and 30 to 70 minutes and an elimination of 4 to 23.5 hours.[25] This longer elimination half life is indicative of a deep compartment with limited perfusion, which results in a slow return of propofol back to the central compartment. Owing to the very rapid clearance of the drug from the central compartment, the slow return from this deep compartment contributes little to the initial rapid decrease in propofol concentrations. The context-sensitive half time of propofol for infusion of up to 8 hours is less than 40 minutes. As the required decrease in concentration for awakening following anaesthesia or sedation with propofol is generally less than 50%, recovery from anaesthesia will remain rapid even following prolonged propofol infusions.[26]

The blood level of propofol alone for loss of consciousness are 2.5 to 4.5micrograms/ml, and the blood concentrations (when combined with nitrous oxide) required for surgery are 2.5 to 2.8micrograms/ml. Similar concentrations are necessary when propofol is combined with an opioid for total intravenous technique. The blood concentration of propofol were fairly steady even during cardiopulmonary bypass and hypothermia when propofol was infused during cardiac surgery under alfentanil anaesthesia.

The propofol Cp_{50} for loss of response to verbal command is 3.5micrograms/ml. To prevent movement on skin incision the Cp_{50} (arterial whole blood concentration) is 16micrograms/ml. When benzodiazepines premedication

combined with 66% nitrous oxide the propofol Cp_{50} for skin incision is 2.5micrograms/ml (venous). This is markedly reduced when morphine is used for premedication. Awakening usually occurs below concentration of 1.6micrograms/ml and orientation below 1.2micrograms/ml.[27]

Propofol is highly lipophylic compound and is extensively bound to plasma protein (97 – 99%). [28 29]

The volume of distribution of the central compartment has been calculated as 20 to 40L and the volume of distribution at steady state as 150 to 700L. The clearance of propofol is extremely high 1.5 to 2.2 L/min.[25,30] This exceeds hepatic blood flow and extrahepatic metabolism has been demonstrated.

Propofol is rapidly metabolized in the liver by conjugation to glucuronide and sulphate to produce water soluble compounds, which are excreted by the kidneys.[31] Less than 1 percent propofol is excreted unchanged in urine, and only 2 percent is excreted in faeces. The metabolites of propofol are thought not to be active. Extrahepatic metabolism has been confirmed during the anhepatic phase of patients receiving a transplanted liver. [32, 33]

Pharmacokinetics in special clinical situations.

Elderly patients:

Elderly patients require significantly lower induction doses of propofol.[28,34] This does not appear to be an age related changes of pharmacodynamics or brain sensitivity. With increasing age pharmacokinetic changes are such that for a given intravenous bolus dose, higher peak plasma concentrations occur, which can explain the decreased dose requirement. The higher plasma levels reflects an age related decrease in volume of distribution and reduced intercompartmental clearance. Kirkpatric et al in 1988 pointed out that the clearance of propofol is significantly lower in elderly than in younger

patients, and the volume of the central compartment in the elderly patients was significantly smaller.[28]

A dose of 1mg/kg (with premedication) to 1.75 mg/kg (without premedication) is recommended in patients over 60 years of age. [35]

Paediatrics:

The induction dose is higher in younger patients (2.9 mg/kg for ages < 2 years) than in older patients (2.2mg/kg for patients 6 to 12 years).[36]

A greater dose requirement in infants 1-6 months of age than 10-16 years of age is explained by their differences in pharmacokinetic or pharmacodynamic characteristics.[37]

Pharmacokinetic differences seem likely because infants have greater cardiac output in relation to body weight. Also, the vessel-rich compartment is comparatively greater in infants than in older children. Moreover, changes in body composition, like a decrease in body water from 75% to about 60% and a reduction of extra cellular body water may increase dose requirements for infants.

The incidence of pain on injection limits its usefulness in paediatric anaesthesia.

Hepatic disease

Hepatic disease appear to result in a larger steady state and central compartment volumes, clearance is unchanged but the elimination half-life is slightly prolonged.[38] Despite the rapid clearance by metabolism there is no evidence of impaired elimination in patient with cirrhosis.

Renal dysfunction

Renal dysfunction does not influence the clearance of propofol. Morcos et al in 1985 cites that the pharmacokinetics of propofol do not appear to be different in patients with chronic renal impairment.[39]

Toxicity:

Animal toxicological studies were carried out to determine toxicity associated with the use of propofol. The scope of these studies include carcinogenesis, mutagenesis and impairment of fertility. Animal carcinogenicity studies have not been performed with propofol. In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Studies in female rats at IV dose up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to 7 days of gestation did not show impaired fertility. Male fertility was neither affected in a dominant lethal study at IV doses up to 15mg/kg/day for 5 days.[18]

Effects of propofol on organ systems:

A number of studies have been carried out to assess the suitability and safety of propofol as induction agent of anaesthesia for surgery of different systems and its effects on various body systems evaluated. Most of these results showed comparable results to those obtained with other induction agents.

Cardiovascular system:

The cardiovascular effects of propofol have been evaluated following its use both for induction and maintenance of anaesthesia.

An induction dose of 2 to 2.5mg/kg produces a 25 to 40% reduction in systolic blood pressure without significant changes in heart rate.[40, 41]

The decrease in arterial pressure is often associated with decrease in cardiac output, stroke volume and systemic vascular resistance.

Coates et al pointed out that decrease in systolic arterial pressure (28%) was associated with decreased cardiac output (12%) and decrease in systemic vascular resistance (15%).[41]

Claeys et al in 1988 found the haemodynamic effect of propofol was decrease in systolic and diastolic arterial pressure and were related to decrease in systemic vascular resistance (20-30%) while cardiac output and stroke volume were not affected. This decrease in afterload may be influenced by hypercarbia in spontaneously breathing patients.[42]

In patients with valvular heart disease, pulmonary artery and pulmonary capillary wedge pressure are also reduced, which implies that the resultant decrease in pressure is due to a decrease in both preload and afterload. [43]

After receiving propofol, 2.5mg/kg, for coronary artery by pass grafting, patients who had no myocardial infarct for at least 3 months and ejection fraction over 30% had a significant decrease in mean arterial pressure, systemic vascular resistance and left ventricular stroke work index, their heart rate increased. The changes were transient and without sequelae in these patients, but they probably represent both vasodilation and direct myocardial depression. [44]

The vasodilatory effect of propofol appears to be due to both, to a reduction in sympathetic activity [45] and to a direct effect on intracellular smooth muscle Ca^{2+} mobilization. [46]

Rolly et al gave 2mg/kg of propofol over 5, 20, and 60 seconds to adult and found no correlation between the speed of injection and the decrease in blood pressure.[47]

Despite decrease in blood pressure, heart rate often remains unchanged in contrast to the modest increases that typically accompany the rapid intravenous

injection of thiopental. Cullen PM et al in 1987 suggested that propofol either resets or inhibits the baroreflex, thus reducing the response to hypotension.[48] This has been also speculated to reflect vagotonic effect of propofol.[49]

When assessed by transesophageal echocardiography, the negative inotropic effect of propofol is less pronounced and of shorter duration than that caused by thiopental.[50]

Asystole and atrioventricular block may develop very rarely, so premedication with an anticholinergic drug may be desirable especially in beta-blocked and Ca^{2+} channel blocked patients.[17]

At anaesthetic concentrations, cardiac output rises slightly, with a reduction of cardiac work and myocardial oxygen consumption. However no evidence of myocardial regional oxygenation imbalance was reported.[51]

The effect of propofol on coronary circulation were addressed in one study, an induction dose of 2mg/kg was followed by a 200mg/kg/min continuous infusion. Myocardial blood flow decreased 26%, myocardial oxygen consumption decreased 31%, and coronary vascular resistance increased 19% without change in arterial – coronary sinus oxygen content difference. A few patients had some myocardial lactate production, suggesting possible imbalance of regional myocardial oxygen demand and supply associated with propofol.[52]

Propofol can have effects on atrioventricular node conduction. Kannan et al reported a case where administration of propofol was associated with termination of supraventricular tachycardia.[53] Similar phenomenon has been reported in children.

Haemodynamic effects of propofol were compared with other induction agents. Propofol (2 to 2.5mg/kg) compared with equipotent dose of thiopentone (5mg/kg) and methohexitone 1.5mg/kg. It has been found that propofol resulted in greater decrease in blood pressure than other agents.[15,40,54..]

The haemodynamic responses to laryngoscopy and tracheal intubation during general anaesthesia can be deleterious with serious cardiovascular and cerebral effects. Propofol attenuate laryngoscopy and the pressor response to tracheal intubation more effective than thiopentone.[55 56] Peak values of arterial pressures[57] and heart rate did not exceed those recorded in awake state. [37.]

Study on haemodynamic and catecholamine response to tracheal intubation when propofol compared with thiopentone shows that systolic arterial pressure and QT interval responses to intubation were significantly greater with thiopentone than with propofol ($P<0.05$). After intubation, concentrations of noradrenaline in mixed venous plasma were found to be increased in both groups but concentration of adrenaline increased only in thiopentone group. [58]

Respiratory effects:

Propofol produces a profound respiratory depression. When propofol is given alone, the respiratory rate increases for the first 30 seconds, then rapidly decreases to apnea in most patients. An induction dose of propofol results in a 25 to 30% incidence of apnea.[59, 60]

The incidence of prolonged apnea (longer than 30 seconds) is further increased by addition of an opiate, and is greater with propofol than with other commonly used intravenous induction agents. [54, 61] Compared to thiopentone propofol causes respiratory depression in a similar degree by using ventilatory inductance plethysmography. However, although the function residual capacity was reduced in patient receiving propofol, it increased slightly after induction with thiopentone.[62]

Propofol was found to cause decrease in respiratory rate for 2 minutes and minute volume is significantly decreased for up to 4 minutes after injection of

2.5mg/kg, which indicates a more prolonged effect of propofol on tidal volume than on respiratory rate. [59]

The ventilatory response to CO_2 is also decreased during maintenance infusion of propofol. [63]

Propofol (50 to 120 micrograms/kg/min) also depresses the ventilatory response to hypoxia. [64]

In patients with chronic obstructive pulmonary disease, propofol induces bronchodilation but not as effective bronchodilating properties as halothane. [65, 66]

Central nervous system (CNS):

Propofol is primarily a hypnotic. Onset of hypnosis following doses of 2.5mg/kg is rapid (one arm – brain circulation).[47]

The duration of hypnosis is dose-dependent, being 5 to 10 minutes following 2 to 2.5mg/kg.[67]

At subhypnotic doses propofol will provide sedation and amnesia. [68]

Propofol causes a general state of well being and has been documented to alter mood to a lesser extent than thiopental. [69]

Hallucinations, sexual fantasies, and opisthotonus have been reported following propofol administration. [70, 71.]

Other drugs that cause CNS depression (hypnotics, sedatives, inhalation anaesthetics, opiods) can increase the CNS depression induced by propofol. [18]

Effects on cerebral blood flow and intracranial pressure

In brain-injured patients, propofol of 2mg/kg IV, followed by 150micrograms/kg/min result in decreased cerebral perfusion pressure, cerebral blood flow and intracranial pressure. [72]

In patients with normal intracranial pressure, the decreased intracranial pressure (`~30%) is associated with a small decrease in cerebral perfusion pressure (~10%). [73]

The decrease of intracranial pressure (30 to 50%) in patients with elevated intracranial pressure, is associated with significant decreases in cerebral perfusion pressure and therefore may not be beneficial. [74,75]

Normal cerebral reactivity to CO_2 and autoregulation are maintained during propofol infusion showing its beneficial effects on cerebral haemodynamic. [76]

Propofol reduces $CMRO_2$ by 36%. With a background of 0.5% enflurane, propofol still reduces $CMRO_2$ by 18%.[52,77]

Propofol will also provide cerebral protective effect following an acute ischemic insult to the same degree as either halothane or thiopental. [78]

Effects on intraocular pressure

Propofol acutely reduces intraocular pressure by 30 to 40%. As compared with thiopental propofol produces a greater decrease in intraocular pressure, and has been shown that following a small second dose it is more effective in preventing a rise in intraocular pressure secondary to succinylcholine and endotracheal intubation. [79]

Possible mechanisms for this decrease in intraocular pressure are an increase in the outflow of aqueous humor, relaxation of extra ocular muscles, and peripheral vasodilatation.[80]

Effects on EEG

The effect of propofol on EEG as assessed after 2.5mg/kg followed by an infusion demonstrates an initial increase of in alpha –rhythm followed by shift to

delta and theta frequency. High infusion rates produce burst suppression. [81]

Bispectral index (BIS) has been shown to be a reasonably objective method of determining the depth of sedation and general anaesthesia. [82] It is a complex EEG variable that combines several descriptors of the EEG into a single value.

Bruhn et al reported a case of two patients in which the EEG effect of propofol was quantified very similarly by BIS and approximate entropy [83] (a novel EEG measure that quantifies the regularity of a data time series such as EEG).However, at the beginning of burst suppression of the EEG, BIS did not indicate an increased anaesthetic drug effect, while approximate entropy did.

Propofol and seizures

The effect on epileptogenic EEG activity is controversial. Initial studies in mice indicate that propofol neither induce convulsions nor provide anticonvulsant activity. [84] Several recent reports have shown in a variety of models a direct anticonvulsant effect which is dose dependent. [85, 86] Propofol has been used to treat epileptic seizures. [87, 88]

As compared with methohexitone, propofol results in a shorter duration of motor and EEG seizure activity following electroconvulsive therapy.[89] The incidence of convulsion following propofol is rare (approximately 1 in 50,000 administrations).[90]

Effect on adrenal steroidogenesis

Anti-adrenal steroidogenic effects have been studied for anaesthetic agents propofol, thiopentone and etomidate using an in vitro approach based upon isolated guinea pig adrenal cells. It has demonstrated that propofol and thiopentone are relatively weak inhibitors of adrenal steroidogenesis in vitro.

Etomidate has been furthermore confirmed as potent inhibitor of adrenal function.[91]

In humans, following single dose for intravenous infusion of propofol or continuous infusion for long as 24 hours to provide sedation for intensive care patients, neither block of cortisol secretion were found nor alteration on the normal ACTH stimulation. [92]

Effects on hepatic and renal function

Propofol does not adversely affect hepatic or renal function as reflected by measurement of liver transaminase enzymes or creatinine concentrations.[93] Prolonged intravenous infusion of propofol may result in excretion of green urine, reflecting the presence of phenols in the urine. This discoloration does not alter renal function.

Effects on coagulation

Propofol in the emulsion formulation does not alter hematologic or fibrinolytic function.[93] However, lipid emulsion per se reduces in vitro platelet aggregation. [94]

Maintenance of anaesthesia with propofol target–controlled infusion at 2-5 microgram/ml does not cause detectable coagulation changes on thrombelastography nor increase surgical blood loss when compared to inhaled isoflurane in patients undergone head and neck surgery.[95]

The inhibitory effect of propofol on platelet aggregation has been found to be related to a reduction in the intracellular Ca^{2+} concentration. Propofol was found to inhibit the influx and the discharge of calcium ions, thus supporting the inhibitory effect of propofol on platelets. However, as there was not change in

the bleeding time, it suggests that this inhibitory effect did not clinically impair haemostasis.[96]

Effect on phagocytic capacity

Propofol has been reported to produce a dose dependent inhibition of phagocytosis and superoxide anion production during the respiratory burst (RB) of polymorph nuclear cell (PMNs) in vitro. In contrast to published in vitro results, no reduction of phagocytic capacity were found in humans.[97]

In randomized, blinded study, RB and phagocytosis were compared during propofol or isoflurane anaesthesia in patients had undergone elective interventional embolization of cerebral arterio-venous malformations. After 4h of propofol infusion (at 6-8mg/kg/hour) or isoflurane anaesthesia, (0.8 – 1.0% end tidal) the mean (SD) phagocytosis of Escherichia coli was 93.2% (7.0%) and 94.3% (9.2%) respectively, of that before anaesthesia. The percentage of PMN with RB activity following Tumour Necrosis factor alpha/N-formyl – methiomyl – lency/phenyl-alanine (TNF-alpha/FMLP) stimulation was significantly reduced after 2h (80.9% (24.2%); PL 0.05) and 4 h (53.7% (27.3%, PL 0.5) of anaesthesia with propofol compared with the values before induction. 4 hour of anaesthesia did not reduce the phagocytic capacity of human PMN more than isoflurane anaesthesia.[97]

Effect on enzymatic inhibition

In vitro studies on human hepatocytes, propofol, inhibited in a dose – dependent manner the enzymatic degradation of both sufentanil and alfentanil.[98] In other study the functional activities of phase II enzymes, including uridine diphosphote glucuronosly transferase (UDPGT) and glutathione s-transferase(GST) were potentially interfered as a result of inhibition of

propofol. Therefore, it should be considered when using propofol with other drugs for anaesthesia.[99]

Allergic reaction

Anaphylactoid reactions has been attributed to agents which had been dissolved in cremophor EL. [100]

The emulsion formulation of propofol appear to be devoid of allergic potential. Changes in plasma histamine concentration do not follow the intravenous administration of propofol. [101]

In patients with multiple drug allergies, propofol should be used with caution [102] as high percentage of patients developing the anaphylactoid reaction to an emulsion formulation of propofol had a previous history of allergic response.

Clinical uses

Clinical uses of propofol include:

- Induction and maintenance of anaesthesia
- Sedative in ICU
- Supplementation of Regional Blockade
- As antiemetic and antipruritis

Induction and maintenance of anaesthesia

Propofol is suitable for both the induction and maintenance of anaesthesia in adult and in children 3 years of age or older. Because of its rapid onset, short duration of action, and rapid recovery with a low incidence of side effects, it offered challenge to thiopentone. It is compatible with a range of premedicants, neuromuscular blocking drugs and other anaesthetic agent. Propofol is a useful

induction agent especially for outpatient surgery or otherwise brief procedures (cardioversion, electroconvulsive therapy) requiring a short period of unconsciousness.

The induction dose varies from 1 to 2.5mg/kg. The dosage varies depending on age, premedication and state of health. ED95 in healthy unpremedicated adult patient is 2.25 to 2.5mg/kg for loss of eyelash reflex. [15,103]

With the increasing of age the dose of propofol required to induce anaesthesia should be reduced. A dose of 1mg/kg (with premedication) to 1.75mg/kg (without premedication) is recommended in patients over 60 years of age. [35]

The paediatric dose is somewhat higher. This is illustrated by the recommended induction does of 2.5 to 3.0 mg/kg of propofol in unpremedicated children ages 3-12 years. [104]

Premedication with an opiate and or a benzodiazepine tend to markedly reduce the induction dose. [105]

Debilitated, or ASA III/IV patients require approximately 1. to 1.5mg/kg (20mg every 10 sec) of propofol for induction of anesthesia due to the reduced clearance and higher blood concentration. A rapid bolus should not be used as this will increase the likelihood of undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction and/or oxygen desaturation.

Onset of anesthesia is rapid (one arm-brain circulation). The duration of hypnosis is does dependent, being 5 to 10 minutes following 2 to 2.5mg/kg .[67]

Numerous studies have examined the induction characteristic of propofol. Following a single bolus or a bolus followed by a continuous infusion, quality of induction reported to be smooth with few excitatory effects such as hypertonous, tremor, hiccup, or spontaneous movement.[106-110]

In a study done by Huma Phares, the induction time ranged from 20 to 40 seconds. Induction of anaesthesia with propofol was on overall smooth and more rapid than that of thiopentone in that, with over 66% of patients were unconscious in 20 to 30 seconds while with thiopentone 60% became unconscious in 31 to 40 seconds. In both groups all patients went unconscious by the 40th second. Apnea (defined in this study as the absence of spontaneous respiration for a period if time greater than 20 seconds) during induction occurred in 23% of the propofol group compared to 10% in thiopentone group. Hiccups (9.5%) and muscle movements (14.2%) during induction of anaesthesia occurred in the same percentage of patients in both groups with quality of anaesthesia being graded as good and adequate in all patients in both groups.[107]

Those induction characteristics were also found in other studies. When propofol compared to thiopentone, etomidate and methohexitone, there were no statistically significant difference when measuring the induction time from beginning of injection to loss of eyelash reflex or to loss of counting.[108-111] However, there were important differences between groups with regard to complication on induction. In regard to excitatory effect following propofol are relatively low in frequency ranging from 0-20%, 0 to 6.7% in thiopentone, up to 45% in methohexitone and 64% in the etomidate. [54, 111]

Effect of speed of injection on induction of anesthesia was studied by Rolly et al. The rate of injection had a significant influence on induction time. Mean induction time increased from 21.5 to 34.7 and 50.5 seconds when injection time was increased from 5 to 20 to 60 seconds respectively. An indication that deeper anaesthesia was achieved with the fastest injection was seen in the assessment of eyelash reflex, although the differences between the three groups were not significant. No significant differences and decrease of arterial pressure or apnea were observed.[47]

Because of its pharmacokinetics, propofol provides a rapid recovery and is thus superior to barbiturates for maintenance of anaesthesia, and it appears equal to enflurane and isoflurane.

For maintenance propofol can be given as intermittent boluses or as a continuous infusion. Following a satisfactory induction dose, a bolus of 10 to 40 mg is needed every few minutes to maintain anaesthesia. As these doses need to be given frequently it is more suitable to administer propofol as a continuous infusion. For this purpose drop counter syringe pumps or volumetric pumps are recommended.

Several infusion schemes have been used to achieve adequate plasma concentration of propofol. The infusion rate varies between patients and in somewhat dependent on the use of analgesic and muscle relaxants.

Following induction dose, an infusion of 0.1 to 0.2mg/kg/min usually needed the infusion rate then is titrated to individual requirement and the surgical stimulus. [26]

Morphine, fentanyl or alfentanyl when combined with propofol reduces its required infusion rate and concentration.

For maintenance, propofol has been used a single mixture with alfentanil, containing 1mg of alfentanil (2ml) to 400mg of propofol (40 ml). When this mixture was administered at infusion rate commonly used for propofol, (i.e. 0.166mg/kg/min for 10 min, 0.133 mg/kg/min for 10 min and 0.1mg/kg/min thereafter) it provided an outcome equal to that obtained by using the two drugs as separate infusions. [112]

For total intravenous anaesthesia, Camu et al recommend an initial infusion of 0.1mg/kg/min to 0.3mg/kg/min for about 30 min following induction of propofol, 2mg/kg, followed by a maintenance infusion of 0.05mg/kg/min. [113]

Numerous studies have commented on the recovery aspect a propofol, characterized by rapid, pleasant, with minimum side effects.

Recovery was superior in propofol group when compared to thiopentone and methohexitone. Recovery time was assessed by the crude indice of eye opening, repeating date of birth and by the sophisticated tests of psychomotor function [54,114,115]. The difference was not statistically significant on the recovery characteristics between propofol group and etomidate group. [111]

Sedation for intensive care unit (ICU)

In the management of patient in the intensive care unit, sedation plays a special role, the patients are sedated to support long term mechanical ventilation of to facilitate the procedures e.g. cardioversion, endoscopy as well as well as to provide postoperative sedation.

Propofol by continuous infusion provides a readily titratables level of sedation and rapid recovery once infusion is terminated irrespective of the duration the infusion. [116,117].

In a study of patient sedated in ICU for 4 days with propofol, recovery to consciousness was rapid (about 10 minutes). Both the rate of recovery and decrease in plasma concentration were similar at 24 and at 96 hours, when the infusion was discontinued. Also the plasma concentration required for sedation and for awakening was similar at 24 and 96 hours, which implies that tolerance to propofol did not occur. [118]

When midazolam or propofol was given by infusion to sedate patients after cardiac surgery, patients recovered consciousness more rapidly after propofol infusion. In mechanically ventilated patients, more rapid recovering translates to more rapid extubation when sedation is terminated. Sedation following propofol infusion was easily controlled and there was little cardiovascular depression. [63]

A potential advantage for propofol for ICU patients is that it appears to possess antioxidant properties.[119]

In one study it has been shown that propofol protects endothelial cells against the toxicity of $ONOO^-$ (peroxinitrite). The antioxidant property can be partially attributed to its scavenging effect on peroxinitrite, a property that might be relevant in pathological situations involving a significant contribution of pexoxynitrite to tissue damage. [120]

A 1992 report has linked propofol with several deaths in children requiring sedation for mechanical ventilation secondary to upper respiratory tract infections.[122] The likelihood of propofol being the primary cause has been challenged. However, propofol is not yet approved for ICU sedation in children.[26]

Supplementation of regional blockade

A significant number of patients refuse or are dissatisfied with regional anaesthesia because they do not want to be "wide awake during surgery".

Labat, a surgeon and the "father of regional anaesthesia" comments on the importance of supplementation of regional anaesthesia relating to excessive noise in the operating room. Unnecessary conversation that might be interpreted by the patient and avoidance of the surgeon asking the patient if he feels this or that stimulus. [122]

Infusion rate of propofol required for sedation to supplement regional anesthesia in healthy patients are half or less of those required for general anesthesia (i.e. 0.3 to 0.6mg/kg/min). In elderly patients (over 65 years) and sicker patients the infusion rate that are necessary are markedly reduced. [68]

Wilson and co-workers compared propofol and midazolam in orthopaedic surgery under spinal anaesthesia and pointed out that immediate recovery and

restoration of higher mental function were significantly faster following propofol. (P less than 0.001). Amnesia for immediate postoperative period was significantly greater after midazolam (P=0.0001).[123]

When used for sedation in outpatient oral surgery, no cardiovascular depression or airway problems occurred. Recovery time was faster after propofol than diazepam, also propofol provided better amnesia compared to diazepam. [124]

The safety and effectiveness of patient control sedation (PCS) with propofol has been assessed in phobic dental patients undergoing routine dental extraction. The technique used successful with no cardiorespiratory complications. There was good anxiolysis and for many patients, the ability to adjust their level of sedation provides increased acceptability. [125]

As an antiemetic and antipruritis

Propofol possesses significant antiemetic activity at low (sub hypnotic) doses. [126] It has been used successfully to treat postoperative nausea – (in a bolus of 10mg) and vomiting in hyperemesis gravidarum. Infusion of 1mg/kg/h. provide excellent antiemetic action following chemotherapy. [127]

Nausea and vomiting are infrequent in patient receiving propofol.[128] Nevertheless, the antiemetic effect of lipid emulsion portion of propofol has not been documented.[129]

It has also been reported that propofol at sub hypnotic doses relieve cholestatic pruritus as well as pruritus induced by spinal opiates.[130]

Warnings and precautions

For general anesthesia or during sedation, patients should be continuously monitored and facilities for maintenance of a patent airway, artificial ventilation

and oxygen enrichment and circulatory resuscitation must be immediately available.

In the elderly, debilitated or ASA II/IV patients, rapid bolus administration should not be used during general anaesthesia or sedation in order to minimize undesirable cardiorespiratory depression including hypotension apnea, airway obstruction and/or oxygen desaturation.

Propofol injection should not be co-administered through the same intravenous catheter with blood or plasma because compatibility has not been established.

Strict aseptic technique must always be maintained during handing. Propofol injection is a single – use parenteral product, contains no antimicrobials preservatives and can support rapid growth or microorganisms. Administration should commence promptly and completed within 6 hours after the ampoules or vials have been opened. Any unused portion should be discarded.

When proposal injection is diluted prior to administration, 5% Dextrose should be used and it should not be diluted to a concentration less than 2mg/ml because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic.

Propofol injection has been shown to be compatible when administered with the following intravenous fluids: lactated Ringers, Lactated ringers and 5% Dextrose, 5% Dextrose and 0.45% Sodium chloride, 0.9% Sodium chloride. [18]

Since the drug is formulated in an oil-in-water emulsion, elevation in serum triglycerides may occur when propofol is administered for extended periods of time. Patients at risk of hyperlipidemia should be monitored for increases in serum triglycerides or serum turbidity. Administration of the drug should be adjusted if fat is being inadequately cleared from the body. A reduction in the quantity of concurrently administered lipids is indicated to

compensate for the amount of lipid infused as part of the propofol formulation:1 ml of propofol contains approximately 0.1g of fat (1.1k cal).[18]

Contraindications

Propofol is contraindicated in patients with a know hypersensitivity to the drug or its components, or when general anesthesia or sedation are contraindicated. [18]

Drug interactions

Propofol like (thiopentone) does not potentiate neuromuscular blockade produced by both nondepolarizing and depolarizing neuromuscular blocking agent. [1, 18, 131]

The effect of fentanyl administration on propofol pharmacokinetics is controversial. Some studies suggest that fentanly may reduce both intercompartmental and total body clearance rates as well as volume of distribution.[132] In a separate study fentanyl did not alter propofol pharmacokinetics following a single dose of both drugs.[133]

In respect with interaction with volatile anesthetics, when full total intravenous anaesthesia doses of propofol are infused reduction of MAC up to 100% have been reported. [17]

No significant adverse interactions with commonly used premedications, analgesics and local anesthetic agents have been observed. [18]

Adverse reaction

Propofol is frequently associated with pain on injection. Previous studies reported higher incidence of pain, up to 50%, due to use of small veins on the dorsum of the hand. [4,134] With the use of veins in the antecubital fossa, pain is reduced by fewer than 10%. [107,135] The cause of pain may be due to release of

local kininogens and non-steroidal anti-inflammatory drugs may inhibit this pathway. [136]

The incidence of thrombosis or phlebitis after intravenous injection is usually less than 1%. [137,138]

An accidental injection of propofol into the radial artery was accompanied by severe pain in the hand but no evidence of vascular compromise or sequelae were reported. [139]

The most significant side effect on induction is the decrease in systemic blood pressure. Addition of an opiate just prior to induction of anaesthesia appear to augment this effect.[56.]

Apnea is common following propofol induction. The addition of an opiate increases the incidence of apnea, especially prolonged apnea.

Risk of laryngospasm and bronchospasm is less than that caused by thiopentone.

Myotonic effect ranging from minor, such as twitches of hands and feet to major, resembling a convulsion or opisthotonus may occur after anesthesia.

Nausea and vomiting are 1 – 2% less than with other induction agents.

Drug abuse and dependence

Rare cases of self administration of propofol by health care professionals have been reported, including some fatalities. The drug should be managed to prevent the risks of diversion including restriction of access and accounting procedures as appropriate to the clinical setting.

Overdosage

If overdosage occurs, propofol administration should be discontinued immediately. Overdosage is likely to cause cardiorespiratory depression.

Respiratory depression should be treated with artificial ventilation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patient's leg, increasing the flow rate of intravenous infusion and administration of pressor agent and/or anticholinergic agents.

Special settings

Propofol in porphyria:

Propofol has been used safely on two separate occasions to a patient suffering from acute intermittent porphyria. [140]

In malignant hyperthermia:

Propofol does not trigger malignant hyperpyrexia and is probably the anaesthetic of choice in patient with this condition.[141, 142]

In myotonic dystrophy:

Study shows that propofol has been successfully used in thirteen patients with myotonic dystrophy. No. perioperative respiratory complications were encountered. [143]

Propofol in paediatric population

Studies evaluating the usefulness of propofol in paediatric patients are limited. In comparison studies between propofol and thiopentone, authors suggest that propofol is a useful alternative as an induction agent in children.[109,144]

In those studies there were no statistically significant difference between two drugs (propofol – 2- 2.5mg/kg, thiopentone 4-5mg/kg) in respect with induction time, <45 seconds in both groups) pain on injection (24% propofol group, 10% in thiopentone group), respiratory upset (43% - propofol group, 28%

thiopentone group), excitatory effects (33% - propofol group, 16% thiopentone group) or apnea.

A similar decrease (10%) in mean arterial pressure was observed with both agents after induction but propofol showed better suppression of haemodynamic response to tracheal intubation. Heart rates were stable or deviated from the baseline values by roughly 5 to 10% with both agents. After intubation the heart rate increased more with thiopentone than with propofol. Recovery time were similar in both propofol and thiopentone group.[144]

Propofol is not recommended for use in children of less 3 year of age.[18]

Propofol in pregnancy and puerperium

Several studies have been performed to evaluate the value and safety of propofol as an induction agent in comparison with thiopental in parturient undergoing caesarean section. Opinions on the safety of using propofol in parturient undergoing caesarean section are divided. Neonatal outcome is satisfactory although one group of researchers has consistently preferred thiopentone to propofol. Other centers concluded that propofol (1.5-2.5mg/kg) is a suitable alternative to thiopentone for caesarean section. [6-13]

A rapid and reliable intravenous anesthetic agent should rapidly cross the blood/brain barrier, an this feature is usually followed by rapid placental transfer[145.] The mean foetal/maternal ratio for thiopentone and propofol has been reported to be in the range of 0.4–1.0 and 0.62–086 respectively, demonstrating that both drugs diffuse across the placenta efficiently.[146, 147] As propofol is highly lipophylic compound and is extensively bound to plasma protein, changes in concentration of protein such as albumin may have considerable effect on placental permeability of unbound drug which is the pharmacologically active form. .

He and coworkers indicated that binding to foetal albumin is a determining feature in the control of the placental transfer of propofol and the pharmacological effects of the drug on the foetus can be expected to be fairly constant and predictable from the maternal propofol [148]. In another study it has been shown that uterine and umbilical blood flows also have effect on placental transfer. [149]

The neonatal condition as appraised by Apgar score, blood gas analysis and neurological adaptive capacity score (NACS) has been reported to be comparable with thiopental induction in most studies, but there have been some reports of lower Apgar Score, muscular hypotonus and transient somnolence after propofol administration .[150,151]Total body clearance of propofol was found to be increased in patients undergoing caesarean section compared with non-pregnant patients undergoing laparascopic operation. [152] The increase in clearance may have been caused by removal of fetal and placental tissues at operation, or by the physiological changes of pregnancy, with increased cardiac output or enzyme induction leading to increased metabolism of propofol.

The use of propofol infusion coupled with nitrous oxide has proved to be a satisfactory technique for caesarean section. After induction of anaesthesia with propofol 2mg/kg, patients received propofol 6mg/kg/hr and nitrous oxide 50% in oxygen, best haemodynamic stability and faster recovery time were found in this group compared to those who received thiopentone 4mg/kg and nitrous oxide 50% in oxygen. [153] In another study, no statistically significant cardiovascular depression was found after induction of anaesthesia with propofol or thiopentone for caesarean section. [7] Neonatal outcome were similar in both groups. In fact various researchers have documented on the safety of low infusion rate of propofol in patients undergoing caesarean section. [154,155,156]

Patients in the immediate postpartum period possess many of the physiological changes of pregnancy. [156,157] Some of which take up to 6 weeks to return to normal. Pharmacokinetics variables for propofol in patients undergoing caesarean section were similar to those in patients during immediate postpartum period. There was reduced protein binding of propofol in fetal plasma compared with maternal plasma. The concentration of propofol in the neonate exceeded that in the mother by 2 hours and this suggest that the elimination of propofol was slower in the neonate than in the mother. [147]

PART TWO

CLINICAL STUDY

Introduction:

Propofol, the most recent intravenous induction agent, was compared to Thiopentone in healthy obstetric patients. This study involved 102 patients who received Thiopentone and 104 patients who received propofol, for elective caesarean section. The study evaluated the suitability and safety of propofol as an alternative induction agent by comparing its induction characteristics, the haemodynamic changes, adverse effects on mother and neonate as well as recovery characteristics with STP (sodium thiopentone) in obstetric patients.

Objectives:

The main objective of this study was to compare propofol and Thiopentone as an alternative induction agent in obstetric anaesthesia.

Specific objectives:

The specific objectives of this study were:-

- To compare the mean induction time between propofol and thiopentone.
- To compare the incidence of smooth and non-smooth/disturbed induction between the two induction agents.
- To determine haemodynamic changes associated with induction of anaesthesia, and during tracheal intubation, as well as after delivery.
- To compare haemodynamic changes between propofol group and Thiopentone group.
- To compare incidence of side effects during induction and recovery between two groups.

- To compare incidence of neonatal depression between propofol and thiopentone group.
- To compare recovery time between propofol group and thiopentone group.

Rationale of the study

The ideal induction agent for obstetric anaesthesia should be capable of producing rapid smooth induction, coupled with optimal surgical condition, causing no neonatal depression, short recovery time and minimal postoperative complications.

Propofol was introduced in the Department of Anaesthesia at Muhimbili National Hospital in 1994 and studied in surgical patients. In our Medical Institute, propofol has not been studied and used for induction of anaesthesia in obstetric patients. There was a need to carry out such study to evaluate its effectiveness and suitability as well as safety to mother and the new born.

METHODOLOGY

Study design:

A clinical trial study design was used.

Study area:

This study was done at Muhimbili National Hospital (MNH) in Dar es Salaam, the largest hospital in Tanzania, is the tertiary referral and University teaching hospital in the country where the author is doing her residency.

Sample size estimation

Study Power 80%; Confidence level 95%.

The required number of patients for each drug, n; is given by the following formula

$$n = \frac{P_1 \times (100-P_1) + P_2 \times (100-P_2)\, f(\alpha,\beta)}{(P_2-P_1)^2}.$$

Where P_1-proportion with smooth induction with propofol.

P_2-proportion with smooth induction with thiopental.

$f(\alpha,\beta)$- is a function of α, (significance level) and β (study power).

For 95% significance level unstudy power 80% $f(\alpha,\beta) = 7.9$.

The sample size is estimated to be 103 female patients in each group. So 103 x 2 = 206.

Anaesthetic protocol (patients, materials, procedure and data collection)

Patients

Two hundred and six female patients were randomly selected to receive either thiopentone or propofol.

Inclusion criteria:

This study involved healthy women who presented to the department of anaesthesiology for elective caesarean section and were at least 36 weeks' pregnant. An informed written consent was obtained from all of them.

Exclusion criteria:

Patients with other complications of pregnancy and emergency caesarean

section did not included as they could interfere with the study. Patients with previous history of allergy to anaesthetics were also excluded.

Materials

The principal drugs used for this study were propofol 1% and sodium thiopentone 2.5%. Monitor: HP Viridia automatic monitor model 24CT manufactured by Hewlett-Packard was used for measurement of haemodynamic parameters mainly systolic blood pressure, diastolic blood pressure, mean blood pressure and heart rate. A stop watch was used for measurement of induction time, induction to delivery time and recovery period.

Anaesthetic procedure and data collection.

Patient's physical and obstetric characteristics like age, weight, height, gestation age and parity were recorded in the questionnaire from their antenatal cards. All patients included in this study fasted overnight and were unpremedicated. They were placed on the operating table in the left lateral tilt position and a peripheral intravenous cannula was inserted preferably at the dorsum of the hand and an infusion of lactated Ringer's solution was commenced. A blood pressure cuff and ECG electrodes for the monitor were applied and baseline blood pressures and heart rate were recorded. Patients were preoxygenated for 3 minutes prior to induction of anaesthesia, during the whole procedure 100% oxygen was given.

Anaesthesia was induced using propofol or thiopentone, given over a period of 10sec. Patients were allocated by using tables of random numbers to receive either 2.5% thiopentone sodium (5mg/kg) or 1% propofol (2.5mg/kg). The calculated dose was titrated till induction of anaesthesia, i.e. the loss of eyelash reflex was attained. Additional amount 10-20% was given depending on

the individual patient's reaction or needs. The induction time was noted as the time taken from start of injection of induction agent to the time the eyelid reflex disappeared.

During the induction period, pain at the site of injection was evaluated by either movement of the arm with the intravenous line and by looking at the patients face for changes in expression indicating pain sensation.

Anaesthesia was induced by rapid sequence induction. Suxamethonium 1mg/kg to facilitate intubation was used following the induction dose, 0.5% halothane was used for maintenance.

Haemodynamic changes after induction (before surgical stimulation) and after tracheal intubation were noted.

Quality of induction was assessed by the investigator. Smooth induction of anaesthesia was determined by absence of respiratory upsets (cough and hiccups) and excitatory phenomenon (involuntary muscle movement).

Induction to delivery time was noted and was considered as the time from induction of anaesthesia to clamping of the umbilical cord.

After delivery pethidine 1mg/kg was given intravenously to provide analgesia during surgery. Muscle relaxation was continued with pancuronium 0.1mg/kg and further half of the initial dose were given if required. Residual myoneural block was reversed at the end of the procedure by using neostigmine 0.04mg/kg and atropine 0.01 mg/kg.

To avoid interference with haemodynamic changes atropine was not used as premedicant in this study.

Neonatal assessment by using Apgar Score at 1 minute and 5 minutes after delivery was recorded and method of resuscitation was also noted.

Blood pressure and heart rate were measured indirectly using a non-invasive technique with an automated monitor. The blood pressure and heart rate

as baseline, after induction, after intubation, and 10 minutes after induction (i.e. post delivery) were measured and recorded in the study questionnaire for use in the evaluation. These parameters were continuously monitored after every 5 minutes throughout the procedure and during the recovery period.

The mean duration of anaesthesia was calculated from the time of induction of anaesthesia to the time of cutting off halothane.

The recovery period was determined as the time from the cutting off the inhalation agent (halothane) to the time the patient was able to open her eyes on command every 30 seconds.

The occurrence of nausea or vomiting during recovery, apnea or cardiac arrest were noted. In addition any other side effect during induction or recovery like headache, dizziness, flush/rash was also noted in the questionnaire. All patients were visited 24 – 48hrs post operatively to ascertain any side effects.

Data analysis

The data collected was computerized from the questionnaire. EPI INFO 6 was used in the analysis of the results obtained from this study. The differences between means were analyzed by t – tests to compare the mean values for continuous variables. Chi – square test was used to compare categorical variables. Correlation between variables was determined by correlation analysis and use of t – test for testing significance of correlation coefficient "r".

Ethical issues/consideration

In this study, patients were treated under the usual circumstances. It was important to ensure that informed consent was obtained and that the subjects were aware that participation was voluntary. They were told that information obtained in the course of the research would be only used for the purpose of the research.

Real names would not be used during presentation of the results. The proposal was submitted to ethical clearance to Muhimbili University College of Health Science ethical committee and was approved.

Study limitations:

- There were no facilities in theatre to re-weigh the patients and the last weight from antenatal card had to be used.
- Those parameters were recorded by the same investigator who also knew the drug given to the patient. This could have resulted in bias. Ideally different research assistance would have been assigned for this purpose.
- There were no laboratory facilities that would allow further detailed studies on mother and neonatal assessment.
- Study funding was not adequate to meet all the study requirements

RESULTS:

Out of the 206 patients involved in this study 102 (49.5%) received Thiopentone and 104 (50.5%) received propofol after being randomly allocated. Their physical and obstetric characteristics were comparable (Table 1). The differences between the groups with respect to age, weight, height, parity and gestation age were not statistically significant.

Induction characteristics.

In this study, the dose of induction agent was based on the body weight, 5mg /kg and 2.5 mg /kg for thiopentone and propofol respectively. However 20 patients (19.6%) of thiopentone group required additional 10-20 % of the induction dose.

Both drugs were given intravenously over a period of 10 seconds. The mean induction time in this study was found to be 31.59 ± 2.22 with a range of 25–43 seconds in thiopentone group and for propofol group the mean induction time was found to be 25.5 ±-4.00 with a range from 20 – 40 seconds.

The mean difference in induction time between two groups was statistically significant; $p < 0.05$ (Table II) No induction failure were encountered in this study and all patients became unconscious by the end of 43 seconds.

Induction was found to be smooth in the majority of patients included in this study, 157 patients (76.2%). In propofol group 84 patients (80.8%) and thiopentone group 73patients (71.6%) had smooth induction. The difference between the groups was not statistically significant $p > 0.05$ (Table III).

Involuntary movements occurred in 14(13.5%) patients who received propofol while 8 (7.8%) who received thiopentone. Problems with cough or hiccup at induction occurred in 8(7.8%) and 23(22.5%) of propofol and thiopentone group respectively. There was no statistically significant difference

between the groups in respect with excitatory phenomenos but the difference in respiratory upsets during induction of anaesthesia was statistically significant. (TableXIII).

Apnea during induction was not evaluated because a muscle relaxant was administered immediately after induction of anaesthesia in these obstetric patients.

Pain at injection was noted to be the major adverse effect, in propofol group, out of 104, 30(28.8%) patients experienced pain and only 3(2.9%) in thiopentone group .The difference was statistically significant; $p<0.05$. (TableXIII).

Neither laryngospasm nor cardiac arrest occurred in this study.

Haemodynamic changes:

Heart rate change

The mean heart rate at baseline of propofol group was 87.86 ± 11.51 while for thiopentone group was 86.13 ± 9.39 with a range of 60 – 120 beats/min for the whole group. The difference was not statistically significant; p – value > 0.05 (Table IV).

The mean change in heart rate between basal and after induction for those who received thiopentone was 20.32 compared to 15.5 for those induced with propofol. This change was not statistically significant between groups; $p>0.05$ (Table V).

The mean change in heart rate between basal and after intubation for thiopentone compared to propofol group was found to be 37.68 and 34.08 respectively, which was not statistically significant; $p>0.05$ (Table.V1).

The mean change in heart rate between basal and 10 minutes after induction (post delivery) was not statistically significant between groups. For

thiopentone group, was 20.59 compared to propofol group, 18.8. $p > 0.05$(Table VII). (For more details of heart rate see Figure 1)

Blood pressure

The mean systolic blood pressure at baseline between thiopentone group 122.58 ± 12.59 and propofol group 122.97 ± 12.66 showed no statistically significant difference; $p>0.05$ Table IV.

The difference in mean diastolic blood pressure at baseline compared for two groups of patients was found to be not statistically significant. $p >0.05$ (TableIV). For thiopentone group, the mean diastolic pressure was 70.93 ± 9 .18 and for propofol group was 69.64 ±11.02.

The mean of mean arterial blood pressure at baseline was not statistically significant between the groups.

The mean change in systolic blood pressure from baseline to after induction was not statistically significant between thiopentone and propofol group; $p.>0.05$. (Table V). (For more details of blood pressure see Figure 2, 3, and 4.)

However the mean change in diastolic blood pressure and mean arterial pressure after induction observed in thiopentone group compared to propofol group, the change was statistically significant $p<0.05$ (Table V).

The difference was not statistically significant when the mean change in systolic blood pressure from baseline to after intubation were compared between two groups; $p>0.05$ (Table VI).

The mean change in diastolic blood pressure and mean arterial pressure from baseline to after tracheal intubation was statistically significant between two groups. $P<0.00$ (Table VI).

The change in mean systolic blood pressure and Mean Arterial pressure between baseline and 10 minutes after induction were observed to be not statistically significant between the groups. $P > 0.05$ (Table VII).

However the mean change in diastolic blood pressure from baseline to 10 minutes after induction were compared between the two groups and was statistically significant; $p<0.05$ (Table VII).

.Five patients induced with propofol and 2 patients from thiopentone group had a fall of systolic blood pressure of less than 100mm Hg after induction of anaesthesia. Both patients responded well after being treated with fast running intravenous infusion fluid, further left lateral tilt of the bed and use of vasoconstrictor.

Neonatal outcome

The mean Apgar scores at 1 minute after delivery was compared between groups which was not statistically significant; p value >0.05. (Table VIII).

The mean Apgar score at 5 minute after delivery was not found to be statistically significant when two groups of patients were compared. $p>0.05$. (Table IX).

Two infants of propofol group had Apgar score of 4 and 9 at 1 and 5 min respectively. One in thiopentone group score 5 and 9 at 1 and 5 min respectively. No infant required tracheal intubation or drug therapy other than oxygen by mask.

The mean induction to delivery time was not statistically significant between propofol and thiopentone group p value > 0.05. (Table X).

Recovery characteristics

In this study a total of 206 patients were given muscle relaxant (pancuronium 1mg/kg) after intubation and addition of inhalation agent,

halothane and pethidine 1mg /kg intravenously to facilitate provision of good condition for surgery.

The mean time for duration of anaesthesia was not significant statistically between the two groups, P.>0.05 (Table XI).

The mean recovery period for propofol group was 2.77 with a range of 2 – 10 min, compared to thiopentone group of 4.64 with a range of 2-6 min. The difference between groups was statistically significant p <0.05. (Table XII).

The incidence of adverse effects observed during induction or the recovery period considered statistically significant between the groups were pain (discussed under induction characteristics, page 37), and nausea/vomiting. p < 0.05.Results shows higher incidence of nausea/vomiting in thiopentone group, 15 (14.7%) while 3(2.9%) in propofol group. Others, like headache, dizziness, restlessness, flush/rash, the differences were not statistically significant between the groups. (Table XIII).

TABLES OF RESULTS

TABLE 1

PHYSICAL AND OBSTETRIC CHARACTERISTICS, MEAN (SD)

	THIOPENTONE	PROPOFOL
AGE, YEARS	28.87 (5.26)	28.09 (4.61)
WEIGHT, KG	69.34 (11.73)	69.10 (12.68)
HEIGHT, CM	156.74 (7.09)	154.11 (12.51)
GESTATION AGE, WEEKS	37.83 (0.81)	37.95 (1.09)
PARITY, N	1.71 (1.35)	1.88 (1.22)

TABLE II

DISTRIBUTION OF MEAN INDUCTION TIME (SECONDS)

DRUG	MEAN	STD DEV	RANGE
THIOPENTONE	31.59	2.22	25 - 43
PROPOFOL	25.55	4.00	20 - 40

F. statistics = 178.39 p.0.00

TABLE III

INCIDENCE OF SMOOTH AND DISTURBED INDUCTION BETWEEN THIOPENTONE AND PROPOFOL GROUP

	PROPOFOL	THIOPENTONE
SMOOTH INDUCTION	84 (80.8%)	73 (71.6%)
DISTURBED/INDUCTION	20 (19.2%)	29 (28.4%)
TOTAL	104	102

$Chi^2 = 2.40$ $P = 0.121$

TABLE IV

COMPARISON OF MEANS (SD) OF HAEMODYNAMIC VALUES AT BASELINE BETWEEN THIOPENTONE AND PROPOFOL GROUP

	THIOPENTONE MEANS (SD)	PROPOFOL MEANS (SD)	p - value
SBP	122.58 (12.59)	122.97 (12.66)	0.81
DBP	70.93 (9.18)	69.64 (11.02)	0.63
MAP	88.69 (9.62)	87.93 (10.73)	0.59
HR	86.13 (9.39)	87.86 (11.51)	0.24

TABLE V

HAEMODYNAMIC CHANGES IN THIOPENTONE GROUP AND PROPOFOL GROUP AFTER INDUCTION

THIOPENTONE GROUP (N = 102)	MEAN BASELINE	MEAN AT INDUCTION	MEAN CHANGE $p = (X_2 - X_1)$
SBP	122.58	123.67	1.09
DBP	70.93	71.62	0.69
MAP	88.69	89.76	1.07
HR	86.13	106.45	20.32
PROPOFOL GROUP (N = 104)			
SBP	122.97	120.20	-2.77
DBP	69.64	66.37	-3.27
MAP	87.93	84.71	-3.22
HR	87.86	103.36	15.5

SBP F.statistic = 2.99 p. = 0.08

DBP F.statistic = 8.43 p. = 0.00

MAP F.statistic = 8.32 p. = 0.00

HR F.statistic = 1.73 p. = 0.19

TABLE VI

HAEMODYNAMIC CHANGES IN THIOPENTONE AND PROPOFOL GROUP AFTER INTUBATION

THIOPENTONE GROUP (N = 102)	MEAN BASELINE	MEAN AT INTUBATION	MEAN CHANGE $p = (X_2 - X_1)$
SBP	122.58	148.06	25.48
DBP	70.93	92.79	21.86
MAP	88.69	112.49	23.8
HR	86.13	123.81	37.68
PROPOF0L GROUP (N = 104)			
SBP	122.97	143.98	21.01
DBP	69.64	82.02	12.38
MAP	87.93	102.94	15.01
HR	87.86	121.94	34.08

SBP F.statistic = 2.66 p. = 0.10

DBP F.statistic = 21.49 p. = 0.00

MAP F.statistic = 19.22 p. =0.00

HR F.statistic = 0.55 p. = 0.53

TABLE VII

HAEMODYNAMIC CHANGES IN THIOPENTONE AND PROPOFOL GROUP AFTER 10 MINUTES (POST DELIVERY)

THIOPENTONE GROUP (N = 102)	MEAN AT BASE	MEAN AT 10 MINUTES	MEAN CHANGE $d = (X_2 - X_1)$
SBP	122.58	128.77	6.19
DBP	70.93	70.00	-0.93
MAP	88.69	90.23	1.54
HR	86.13	106.72	20.59
PROPOFOL GROUP N=104			
SBP	122.97	130.06	7.09
DBP	69.64	66.00	-3.64
MAP	87.93	87.59	-0.34
HR	87.86	106.66	18.8

SBP F.statistic = 0.51 p. = 0.52

DBP F.statistic = 5.67 p. = 0.02

MAP F.statistic = 2.99 p. = 0.08

HR F.statistic = 0.00 p. = 0.98

TABLE VIII DISTRIBUTION OF MEAN NEONATAL APGAR SCORES AT 1 MINUTE AFTER DELIVERY IN THIOPETONE AND PROPOFOL GROUP

	MEAN	RANGE	CASES
PROPOFOL	7.9	4 – 9	104
THIOPENTONE	7.9	5 – 9	103

F statistic = 0.158 p value = 0.69

TABLE IX DISTRIBUTION OF MEAN NEONATAL APGAR SCORE AT 5 MINUTES AFTER DELIVERY IN THIOPENTONE AND PROPOFOL GROUP

	MEAN	RANGE	CASES
PROPOFOL	9.6	8 – 10	104
THIOPENTONE	9.6	8 – 10	102

F statistic = 0.627 p value = 0.28

TABLE X

DISTRIBUTION OF MEAN INDUCTION TO DELIVERY TIME (IN MINUTES) BETWEEN THIOPENTONE AND PROPOFOL GROUP

	MEAN	RANGE	CASES
PROPOFOL	4.7	3 – 10	104
THIOPENTONE	4.7	3 – 8	102

F statistic = 0.014 p. value = 0.90

TABLE XI

DISTRIBUTION OF MEAN DURATION OF ANAESTHESIA (IN MINUTES) IN THIOPENTONE AND PROPOFOL GROUP

	MEAN	STD	CASES
PROPOFOL	39.44	6.03	104
THIOPENTONE	40.72	4.60	102

F statistics = 2.936 p – value = 0.09

TABLE XII.

DISTRIBUTION OF MEAN RECOVERY PERIOD (IN MINUTES) IN THIOPENTONE AND PROPOFOL GROUP.

	MEAN RECOVERY TIME	STD DEV	CASES
THIOPENTONE	4.64	0.91	102
PROPOFOL	2.77	1.14	104

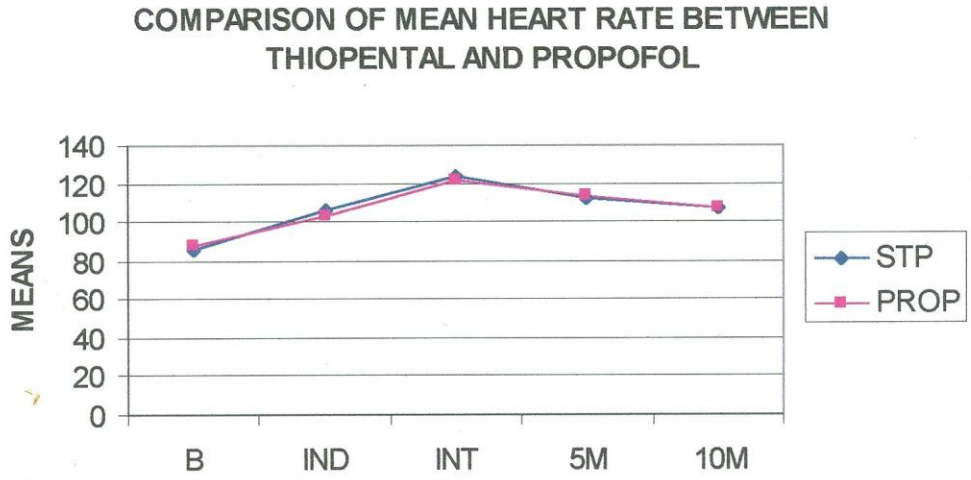
F statistics = 168.122 P= 0.00

TABLE XIII :INCIDENCE OF SIDE EFFECTS DURING INDUCTION AND RECOVERY OF ANAESTHESIA OF PROPOFOL COMPARED TO THIOPENTONE

SIDE EFFECT	THIOPENTONE N = 102	PROPOFOL N = 104	TOTAL	p-value Chi^2
PAIN	3 (2.9%)	30 (28.8%)	33 (16.0%)	p = 0.00 Chi^2=26.42
EXCITATORY PHENOMENON	8 (7.8%)	14 (13.5%)	22 (10.7%)	p = 0.19 Chi^2 = 1.79
NAUSEA& VOMITING	15 (14.7%)	3 (2.9%)	18 (8.7%)	p =0.006 Chi^2=10.18
APNEA	0	0		
LARYNGOSPASM	0	0		
CARDIAC ARREST	0	0		
HEA DACHE	8 (7.8%)	6(5.8%)	14 (6.8%)	p = 0.49 Chi^2 = 1.40
DIZZINESS	4(3.9%)	3(2.9%)	7(3.4%)	p = 0.55 Chi^2 = 1.20
RESTLESSNES	1(1.0%)	7(6.7%)	8(3.9%)	p = 0.06 Chi^2 = 5.53
FLUSH/RASH	4(3.9%)	2(1.9%)	6(2.9%)	P = 0.41 Chi^2 = 1.77
RESPIRATORY UPSET	23(22.5%)	8(7.8%)	31(15.0%)	p = 0.003 Chi^2 = 8.89

GRAPHS

Figure 1



B = Baseline

IND = Induction

INT = Intubation

5M = 5 Minutes after induction

10M = 10 Minutes after induction

STP = Thiopentone

PRO = Propofol

Figure 2

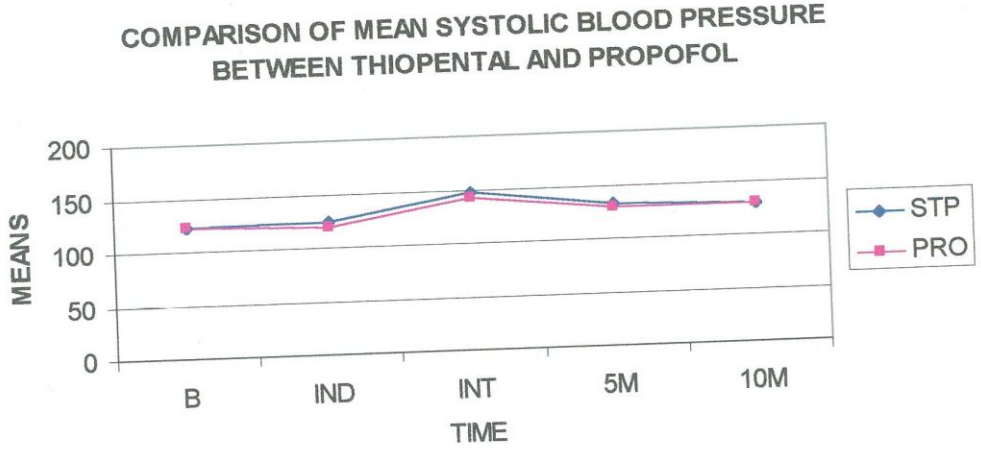


Figure 3

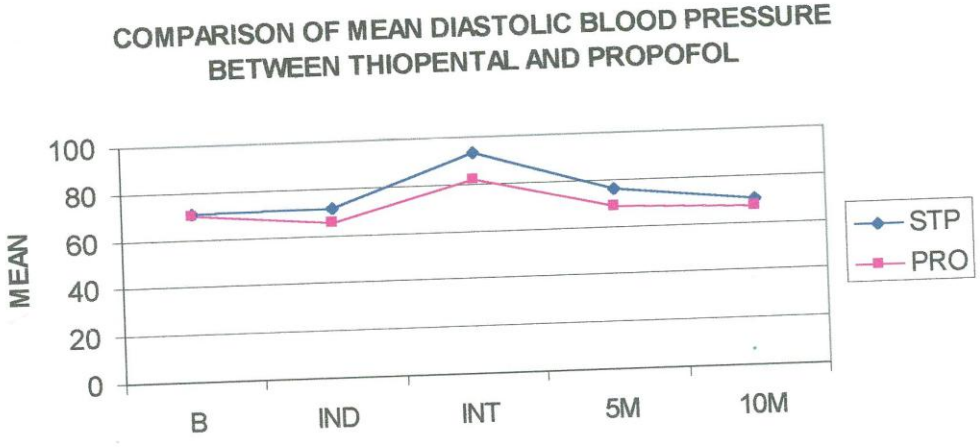
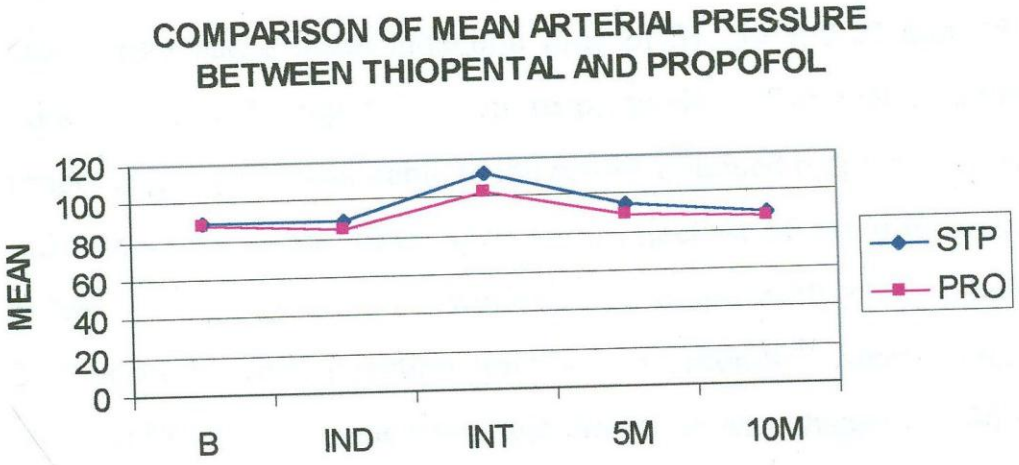


Figure 4


COMPARISON OF MEAN ARTERIAL PRESSURE
BETWEEN THIOPENTAL AND PROPOFOL
MEAN
120
100
80
60
40
20
0
B
IND
INT
5M
10M
STP
PRO

DISCUSSION:

This study involved 206 healthy obstetric patients randomly allocated to receive either thiopentone 5mg/kg or propofol 2.5mg/kg. The induction of anaesthesia had a mean induction time of 31. 59 ± 2.22 and 25.55 ± 4.00 for thiopentone and propofol group respectively. The mean induction time for propofol group is comparable to the results obtained by other authors who defined induction time as the time taken from injection of the drug to loss of eyelash reflex[7,107,111.] Rolly and Co-workers had significantly shorter induction time of 21.5 seconds when injection time was 5 seconds.[47] Mean induction time was increased to 50.5 seconds when injection time was changed to 60 seconds. Thus showing the rate of injection had influence on induction time. De Groom PMRM et al found longer induction time of 39.1 sec and 52.4 sec using stop counting and negative eyelash reflex method respectively, when induction dose was 2mg/kg.[158] A smaller induction dose of 2mg/kg induced anesthesia in only 80% of unpremedicated patients [103] No statistically significant differences were found when propofol compared with thiopentone, etomidate or methohexitone by using either loss of counting or interval between injection of induction agent and loss of eye lash reflex [54,111,158] .In general, induction of anaesthesia is considered to be rapid if it occurs within one arm-brain circulation time (< 60 sec) Differences of few seconds within that time might not be of any clinical significance. Thus the induction time of 25.55 ± 4.00 seconds obtained in this study shows that propofol is accepted as alternative induction agent compared to thiopentone in obstetric anaesthesia. This induction time is considered shorter when compared to thiopentone, that is, the difference is statistically significant $p<0.05$.

A part from rapidity of action the induction with propofol was generally found to be smooth in the majority of patients 80.8%, with the incidence of disturbed induction being 19.2%. This was comparable to thiopentone group with

smooth induction of 71.6% while disturbed induction of 28.4%.These results are comparable with other studies [54].[144] Higher incidence of respiratory upsets found in thiopentone group contributes to high number of patients with disturbed induction.

Incidence of excitatory phenomenon was 13.5% and 7.8% for propofol and thiopentone group respectively. The difference was not statistically significant between groups $p>0.05$. These results are comparable with other studies. [54,107] Lower incidence of excitatory phenomenon after propofol induction has been reported [6,159,160] However the incidence in this study was low compared to that reported by Health PJ (25%) for propofol, where in his study supplement of the same induction agent was used for maintenance instead of inhalation agent. [161] Thus probably most of the movement they were seeing was because the patients were recovering from anaesthesia due to rapid elimination of propofol.

In comparison with other induction agents, the incidence of excitatory phenomenon occurred in 45% of patients who received methohexitone and in thiopentone group range 0-6%. [54,160.]

Incidence of respiratory upsets i.e. cough and hiccups was 7.8% and 22.5% for propofol and thiopentone group respectively. The difference was statistically significant, $p <0.05$. Incidence of respiratory upset in this study was found to be higher in thiopentone group compared to propofol group. This is comparable to the finding by other studies. [54,144] This could be explained that the dose of 5mg/kg was inadequate for all patients. Additional 10-20% of the induction dose was required in 19.6% of the patients. Low incidence of respiratory upset in propofol group is contributed to its property of not inducing histamine release.

In this study incidence of pain was found to be 28.8% and 2.9% for propofol and thiopentone group respectively. The difference was statistically

significant $p<0.05$ This compared favourably with the work of other authors.[7,54,144]

In this study all patients had intravenous line for injection of induction agent on the dorsum of the hand; this explains the high incidence of pain.

Incidence of pain on injection is associated with the site and size of the veins. Injection of anaesthesia agent in small veins of the dorsum of the hand is associated with high incidence of pain.[106,144,158.]

Different measures have been suggested in order to reduce the incidence of pain on injection during induction of anesthesia with propofol.

Authors who used antecubital fossa for the injection of anaesthetic agents reported lower incidence of pain, less than 10%.[107]

Use of lignocaine immediately before propofol injection or premixed with propofol reduced pain from 28.50% to 8.8%.[161,162]

Other strategies have also been used to minimize pain, including use of an opioid as premedication, diluting the drug with an equal volume of saline or cooling the drug.[17,163]

Other studies reported that pain on injection after propofol is less or equal to that with etomidate and equal to that with methohexitone but greater than thiopentone.[54,93]

Induction of anaesthesia with propofol and thiopentone in this study was associated with changes in haemodynamic parameters heart rate, systolic, diastolic and mean arterial pressure. These changes were analyzed in comparison with two drugs in respect with preinduction, after induction, after intubation and post delivery.

The mean heart rate for patients of propofol group at baseline i.e. preinduction values was comparable to that of thiopentone group.

After induction the mean change of heart rate between groups were not statistically significant. This change was found to be an increase of heart rate from baseline values of 15.5 beats/min to 20.32 beats/min. The heart rate changes in propofol anaesthesia is usually variable and not uniform. No change in heart rate a decrease and an increase have all been reported. [40,48 54 ,106 ,111 ,144.]

After intubation the mean change of heart rate between groups was not statistically significant p>.0.05. There was a rise of heart rate from baseline values of 34.08 beats/min to 37.68 beats/min. This finding is consistent with findings in other studies which can be explained by sympathetic stimulation of laryngoscope and endotracheal intubation. [7,144]

The mean change in heart rate at 10 minutes after induction i.e. after delivery was not statistically significant between thiopentone and propofol group. There is tendency to return to their baseline values. (Figure 1) This explains no significance difference in heart rate change during induction and maintenance of anaesthesia between the groups.

The mean of systolic Blood Pressure, diastolic blood pressure and mean arterial pressure were comparable between thiopentone and propofol group at baseline i.e. pre-induction values were not statistically significant.

After induction the mean change of systolic blood pressure from baseline value was found an increase of blood pressure 4.12 mmHg to 4.68 mmHg. No significant difference between groups. These results i.e. slight increase in systolic blood pressure were comparable with other studies in obstetric patients. In non obstetric patients, propofol caused more marked decrease in systolic arterial pressure after induction range between 18mmHg to 39mm H. [54]

This decrease was more pronounced in those patients with higher systolic blood pressure initially. (> 130mm Hg) compared in those with lower initial pressure.

In this study the mean systolic blood pressure at baseline in both groups was less than 130mm Hg. The lower initial systolic blood pressure in this group of patient is contributed to physiological changes during pregnancy i.e. reduction in peripheral resistance.

After intubation the mean change in systolic blood pressure was not statistically significant between the groups. There was an increase of 21.01 to 25.48 mmHg of blood pressure from baseline values. This is comparable with other studies. [6]

This change in mean systolic blood pressure found in this study was high in comparison with that found in non obstetric patient. Mwami reported increase of 7.11 mmHg in intubated patients who had undergone minor gynecological operation. This hypertensive response to tracheal intubation is common in light anesthetized obstetric patients and could be important if hypertension or intracranial vascular lesions are present.

In non obstetric use propofol was shown to attenuate the increase in arterial pressure and heart rate associated with larygoscopy and intubation.

. Therefore it is proposed, as suggested by Moore et al that pre-existing hypertension may be an indication for use of propofol.[6]

The change in mean systolic blood pressure 10 minutes after induction i.e. post delivery was comparable between thiopentone and propofol group. An increase of blood pressure of 6.19mm Hg to 7.09 mmHg was found in this study. This minimum change is comparable with the finding in other studies. [6,7]

In this study the mean change in diastolic blood pressure after induction, intubation and 10 minutes after induction were significantly at lower levels in propofol group in comparison with thiopentone group. A decrease in diastolic blood pressure of 3.27 mmHg after propofol induction was statistically significant compared to increase in diastolic blood pressure of 0.69 mmHg in thiopentone

group. After intubation an increase in mean change in diastolic blood pressure after propofol induction was 12.38 mmHg which was comparatively lower than that after thiopentone induction of 21.86 mmHg. At postdelivery, reduction of mean change of 3.64mmHg after propofol was considerably higher than 0.93 after thiopentone.

These haemodynamics changes i.e. reduction in diastolic and mean arterial pressure result from a decrease of systemic vascular resistance. Addition of an opioid post delivery also contributes to this effect. These findings are comparable to those observed by other workers. [6,7]

A fall in mean of diastolic blood pressure and mean arterial pressure after induction with propofol was found to be less in this study in comparison with non obstetric patient. Huma Phares reported a mean fall of 7.5 mmHg of MAP 2 minutes after induction when Halothane 2% was used, premedication with an opioid gave the same result.[164]

Changes in systemic arterial pressure were tolerated in the majority of patients. Five patients in propofol group and 2 patients in thiopentone presented with systolic blood pressure of less than 100mmHg after induction i.e. pre-delivery.

All patients responded to further left tilt of the operating bed, fast running intravenous fluid and use of vasoconstrictors.

Episode of hypotension, (as defined as by a systolic blood pressure below 100 mmHg) during the induction to delivery interval were significantly less after thiopentone.

As the risk of hypotension exits, the dose should be carefully titrated against the response, patients be well hydrated and monitored their blood pressure carefully especially during the first 10 minutes after induction.

There were neither significant difference in mean Apgar score at 1 minute after delivery nor do 5 minutes post delivery between groups.

Mean neonatal Apgar score at 1 minute after delivery was 7.9 and at 5 minutes post-delivery were 9.6 for both groups.

The mean induction to delivery time was 4.7 minutes for both groups with a range of 3-10 minutes in propofol group and 3-8 minutes in thiopentone group. There was no difference between the groups.

The mean neonatal Apgar scores found in this study were comparable with other studies with induction to delivery times ranged from 5 to 14 minutes. Similar and satisfactory Apgar scores were reported in the propofol group compared to thiopentone. [13.]

Other methods used for neonatal assessment, like Neurologic and Adaptive capacity scores and umbilical cord blood gas analysis were similar and satisfactory between propofol and thiopentone group. [13].

Apgar scores were higher with shorter induction to delivery time. Lower neurologic and Adaptive capacity scored were reported when induction to delivery times are long. [8,155]

Other authors comment the incision of uterus to delivery time seems to be more important to neonatal outcome than induction of anaesthesia to delivery interval. Lower Apgar score at 1 minute and acidosis were reported in cases which the uterine incision to delivery time intervals exceeds 180 seconds where as anaesthesia up to 30 minutes before delivery appears to have no adverse effects on the infant. [165].

In this study the induction dose of 2.5mg/kg of propofol gave similar result of satisfactory Apgar score reported by other authors who used the same dose.[6,144]

Lower Apgar score were reported when higher dose of propofol had been used.[150]

In addition of the time from induction to delivery, the induction dose would probably have important effects on the concentration of propofol in the fetus.

Plasma levels in the newborn at the time of delivery depend on the level in the maternal plasma, and therefore on the time lapsed between the administration of the drug and the delivery of the fetus on the dose used for induction.

In this study two infants of propofol group had Apgar score of 4 and 9 at 1 and 5 minutes. One infant in thiopentone group score 5 and 9 at 1 and 5 min. No. infant required tracheal intubation or drug therapy other than oxygen by mask. They all were well after 5 minutes.

These infants belong to those mothers who had hypotension pre-delivery.

In this study no significant neonatal depression was indicated by Apgar score in either the propofol or the thiopentone group. But it should be taken in consideration the possible risk of some unwanted residual effect on neonate when propofol is used. Placental transfer of propofol depends on placental blood flow and the concentration gradient between the mother and fetus. Therefore maintenance of placental blood flow and hence maintenance or rapid restoration (in case of hypotension) of blood pressure is of vital importance. The dose of the induction agent should also titrated against the patients responses.

The supine position (causing aortocaval compression by the gravid uterus during the caesarean section) has been shown to reduce maternal PO_2 by an average of 13mmHg and may affect placental perfusion. Therefore attempts should be made to maintain the parturient in semi lateral position.

The concentration of propofol returning to the placenta in umbilical arterial blood is determined by the drug concentration and in umbilical venous and fetal drug uptake although some non placental drug transfer is also possible.

possible to differentiate between those two times especially in patients induced with propofol.

No significant difference was found in this study in respect with the mean time for duration of anaesthesia compared between groups. The mean time for duration of anaesthesia for both groups range 32.20 ± 4.61 minutes to 40.72 ± 5.85 , P> 0.05 . This shows that the technique used in this study and short duration of the procedure allowed the greatest advantage of propofol, i.e. rapid recovery to be appreciated.

The difference of postoperative nausea / vomiting between groups was statistically significant. In thiopentone group the incidence was 15(14.7%) compared to 3(2.9%) of propofol group.

Huma phares reported no patient had vomiting in propofol group neither in thiopentone group when those drugs were compared in non obstetric patients who were only premedicated with atropine.

All patients had opioid intraoperatively, in addition to that, physiological changes (e.g. delayed gastric emptying) in this population may explain the high incidence of nausea/ vomiting encountered in this study.

Other studies in obstetric patients showed no difference in incidence of nausea/vomiting between thiopentone and propofol group. This may be contributed to the use of antiemetics agents.[6,7]

Low incidence of nausea/vomiting in propofol group found in this study is comparable with other studies. [54,107,161] Less than 2% incidence of nausea/ vomiting has been reported. The antiemetic effect of propofol may contribute to this result.

The better way to reduce this adverse effect in risky patients like obstetric is to use anaesthetic technique which involve induction agent with less incidence of nausea/vomiting in combination with antiemetic agent.

When compared the incidence of other side effects between groups no statistically significant were observed. Incidence of headache, dizziness restlessness and flush / rash were comparable to other studies.[6,7] The low incidence of these adverse effects can be attributed to smooth induction of anaesthesia with propofol and thiopentone as induction agent.

CONCLUSION AND RECOMMENDATION.

From this study propofol has been shown to be a rapid acting intravenous agent, causing no significant cardiovascular depression in obstetric patients with neonatal outcome comparable to thiopentone. At the induction dose used in this study, induction of anaesthesia was found to be smooth with minimum side effects. These desirable properties of the drug offer an advantage to obstetric patients having in consideration that regurgitation of gastric contents associated with aspiration is a well known risk at induction of anaesthesia for caesarean section and to minimize drug effect on the fetus is another problem. Thus propofol appears to be a suitable alternative induction agent for obstetric anaesthesia.

The main side effect was pain, care should be taken with regard to this. Excitatory phenomenon was comparable to thiopentone, as this occurs after loss of consciousness they may not be perceived by the patient. Usually their duration of effect is less than 1 minute and they are a mild annoyance.

A risk of hypotension should be taken into account. A vigilant blood pressure monitoring is vital during its use.

It is recommended that another study should be carried out to evaluate its effectiveness in pre-existing hypertension (pre-eclampsia).

When facilities are available, it is suggested that detailed study should be done for neonatal assessment using other methods than Apgar score.

High incidence of respiratory upset in thiopentone group put emphasis on the community difference in drug response to be taken in consideration.

The high cost of the drug make many anaesthestists continue to use thiopentone in preference to propofol. However the saving may be minimal when the overall cost of operation and post operative care are taken into account.

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