TITLE:

EVALUATION OF DRUG COMBINATIONS IN TOTAL INTRAVENOUS ANAESTHESIA IN WEST AFRICAN DWARF GOAT

A DISSERTATION

SUBMITTED TO THE SCHOOL OF POSTGRADUATE STUDIES OF THE UNIVERSITY OF NIGERIA, NSUKKA IN PARTIAL FULFILLMENT FOR THE AWARD OF THE DEGREE OF MASTER OF SCIENCE IN VETERINARY SURGERY.

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DEDICATION

This work is dedicated to God Almighty.

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Abstract

The physiological, biochemical and anaesthetic effects of the drug combinations were studies in West African Dwarf goat. In protocol I, there was a significant ($p < 0.05$) increase in the HR of GP I goats at 10 mins post-induction (PI), which significantly ($p < 0.05$) decreased from 30 min PI. The HR significantly decreased ($p < 0.05$) at 20 min in GP IV goats, and at 10 min GP II goats, and returned to the pre-anaesthetic value at 40 min PI. However, HR decreased significantly ($p < 0.05$) between 10 - 50 mins PI in GP A and B and between 40-80 min PI in GP D. The RR decreased significantly ($p < 0.05$) at 10 and 20 mins PI in GPs A and B respectively, till 40 min PI and at 30 mins PI in GP D. These changes normalized at 40 min PI when compared to the pre-anaesthetic values in protocol I. The RR decreased significantly ($p < 0.05$) between 10 - 80 mins, 10 - 50 mins, 30 - 80 mins PI in GPs A, B, and D respectively, but significantly increased at 20 min PI in GP C. The RT of the goats dropped significantly ($p < 0.05$) between 10 - 40 mins PI in GP I and GP II. However, there was significant ($p < 0.05$) decrease in RT between 20 - 30 mins and 10 - 30 mins PI in GPs A, and B respectively. The induction was good and smooth in GPs II, IV, B and D, slightly excitment in GPs I, III, A and C. The quality of recovery was fair in GPs I and A, good in GPs II and III, B and C, good and rapid in GP IV and D. Side effects such as salivation, coughing, ataxia, apnoe, snoring and phonation were observed in both protocols. There was significant ($p < 0.05$) decrease in PCV at 30 min PI in GPs I, III, IV and D. The mean HB decreased significantly ($p < 0.05$) at 30 min PI in GPs III, IV and A, and at 1440 min PR in GP II, while the values increased significantly ($p < 0.05$) at 120 min PR in GP A. Significant ($p < 0.05$) decrease in RBC was recorded in GP II at 30 min PI, and between 120 -1440 min PR. The mean pre-anaesthetic blood glucose levels (BGL) were 75.00 ± 1.29,

68.50 ± 2.84, 48.50 ± 3.23, and 53.50 ± 4.69 mg/dl for GPs I, II, III and IV, respectively. These values significantly ($p < 0.05$) increased at 30 mins PI in all the GPs and returned to pre-anaesthetic value at 120 min post-recovery (PR) in GPs I and IV, decreased significantly ($p < 0.05$) from 120 -1440 min PR in GP II. The BGL values increased significantly ($p < 0.05$) at 30 min PI in GPs A, B C and D. It remained consistent at 120 min PR in GPs B, C and D and returned to base line value in all these GPs at1440 min PR. The cortisol level significantly ($p < 0.05$) decreased at 30 min PI in GP II but increased significantly ($p < 0.05$) at 120 min PR in GPs I, II, III and IV compared to pre-anaesthetic values. There was a significant decrease ($p < 0.05$) in the cortisol level at 30 min PI in GP B only and increased significantly ($p < 0.05$) at 102 min PR in GPs A, C, and D, and at 1440 min in GP B.

It was concluded that the anaesthetic drug combinations resulted in the smooth and uneventful induction with mild cardiopulmonary depressions and rapid recovery. Their effects on haematological values as well as biochemical values were also mild. The xylazine + ketamine + propofol, xylazine + ketamine and xylazine + propofol combinations produced sufficient surgical anaesthetic durations both in single injection and maintenance procedures and may be used successfully in both short and long surgical procedure without an incident of untoward side effects. The ketamine + propofol combination produced greater haemodynamic stability than other combinations but with shortest duration of surgical anaesthesia.

Therefore, the use of the drug combinations is promising especially in good quality anesthesia, rapid onset and rapid recovery

CHAPTER ONE

1.0 INTRODUCTION

Goats are essential domestic animals in Nigeria and beyond. Many householdsô rear goats and majority of them practice traditional free-range system. The free-range system often predisposes sheep and goat to injuries like fractures and matchet cut (Eze and Nlebedum, 2007). Some of the injuries need urgent and immediate surgical treatment. Most of the surgical cases, (Eze and Idowu, 2002), in major veterinary hospitals and state clinic in Nigeria (arising from dystocia, castration, fracture and sadism), ranks third among cases reported.

In any surgical case, good choice of anaesthetics especially in ruminant cannot be over emphasized. The practice of combining two or more drugs is common and has become a technique to achieve a balanced anaesthesia. The purpose of a balanced anesthetic technique is to achieve all of the components of general anesthesia while minimizing the negative aspects of individual drugs on cardiopulmonary function (Mama, 2000). It is quite obvious that continuous search for proper drug combination that will offer good quality anaesthesia, analgesia and fast recovery with mild or no side effect is ongoing.

Propofol (2, 6-diisopropylphenol) is a phenolic compound unrelated to any other general anesthetics. It is a non-barbiturate, non dissociative and non cumulative intravenous anesthetic agent (Hall *et al.,* 2001). It has good quality anesthesia, rapid onset and short duration of action, with rapid recoveries making the drug potentially useful in ruminants, in which these features are particularly desirable (Nikitas *et al*., 2005). Hall *et al*., (2001) stated that propofol has been accepted as most useful anesthetic agent in all domestic animals but

its use in large animals is hampered by the cost. It is used alone and in combination with other drugs in dogs, cat, cattle, horse, ponies and goats (Lin *et al*., 1997; Mama, 2000; Lerch *et al.,* 2000; Hall *et al.,* 2001, and Steffey *et al.,* 2009.). Reports on the use of propofol for induction and maintenance of anaesthesia have indicated its suitability in goats (Hall *et al.,* 2001; Prassinos *et al.,* 2005, and Khan 2006). Propofol has been shown to be compatible with wide range of drugs used for premedication, inhalation anesthesia and neuromuscular block (Hall *et al.,* 2001). Since it has little or no analgesic property, it is recommended to combine propofol with an analgesic agent (opoid or alpha-2-adenoreceptor agonist) for painful procedure.

Xylazine is an alpha-2-adenoreceptor agonist, is non opoid group with analgesic, sedative and muscle relaxant effects and is used commonly in veterinary practice (Fereidoon *et al.,* 2005). Xylazine is a commonly used sedative in ruminants but there are concerns about the threat of hypoxaemia associated with its use in small ruminants (Dzikit *et al.,* 2009). It has been used in combination with propofol in sheeps (Khan 2006) and with ketamine in intravenous general anaesthsia in goat. (Udegbunam and Adetunji, 2007). Ketamine is a dissociative anaesthetic agent which is licensed for use in dogs intravenously. It produces stable haemodynamics during anaesthesia as a result of its stimulatory effect on the sympathetic nervous system, which counteracts the depressant effects of other drugs used during anaesthesia (Lerch *et al.,* 2000). It produces profound analgesia without muscle relaxation and tonic-clonic spasms of limbic muscles may occur even in the absence of surgical or other stimulation (Hall *et al.,* 2001). However, it can be used for anesthesia in sheep and goat without the fear of causing convulsion (Fereidoon *et al.,* 2005),

According to Mayer *et al*., (1990), ketamine causes an increase in mean arterial pressure (MAP) and cardiac index (CI) while propofol an intravenous hypnotic, in contrast, produces a reduction in both mean arterial pressure (MAP) and cardiac index (C I) . Ketamine and propofol appear to counter each other's adverse effects, conferring several advantages including haemodynamic stability (Rapeport *et al.,* 2009). Ketamine-propofol combination allows a reduction in the hypnotic dose of propofol and a decrease in the cardiovascular depression induced by this drug (Tatiana *et al.,* 2008). According to Lerche *et al.,* (2000) the major side effects of propofol (reduced haemodynamics during induction) and ketamine (psychic disturbances and cardiovascular stimulation) were absent and respiratory function post-surgery was adequate in ketamine-propofol anaesthesia. Ketamine-propofol offer haemodynamic stability while ketamine-xylazine produces long surgical anaesthetic duration (Udegbunam and Adetunji, 2007). It will thus be useful to study the combination of the three drugs to explore their synergistic effect expecting haemodynamic stability, longer surgical anaesthetic time and fast, smooth recovery.

1.1. **OBJECTIVE OF THE STUDY**.

To evaluate the physiological effect and anaesthetic properties of propofol and its drug combinations in West African Dwarf goat.

1.1.1. **SPECIFIC OBJECTIVES OF THE STUDY**;

This study was therefore designed with the following specific objectives;

A. To compare the effect of the total intravenous administration of different drug combination of propofol, xylazine, ketamine on heart rate, respiratory rate, rectal temperature, blood cell count and serum biochemistry in WAD goat.

B. To study the nature of induction, indices of anesthesia, and the quality of recovery following the administration of these drug combinations.

C. To observe any incidence of side effects associated with the use of these drug combinations.

1.2. JUSTIFICATION OF THE STUDY

A. This study would help achieve the objective of total intravenous anesthesia (TIVA) without the use of inhalation anesthetic agents.

B. Information generated from this study would be of immense importance to some veterinary hospitals and clinics that have no functional anesthetic machines and good post operative monitoring protocol.

C. This study was designed to achieve reduction in dosage of the individual agents in the combination thereby reducing side effects.

1.3. NULL HYPOTHESES

A. Different drug combination of propofol, ketamine and xylazine has no different effect on vital parameters ï heart rate, respiratory rate and rectal temperature.

B. There is no observable effect on the blood count and serum biochemistry as a result of administration of the different drug combination.

C. The different drug combinations of propofol, xylazine and ketamine offer no synergistic effect.

D. There is no side effect associated with the use of these drug combinations.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 INTRAVENOUS ANAESTHESIA

Anesthesia is an indispensible prerequisite to most of the surgical interventions, both in humans and animals (Muhammad *et al.,* 2009). Anesthesia is divided into two broad type; local and general anesthesia. General anesthesia is reversible generalized depression of the central nervous system (CNS) which includes amnesia, loss of consciousness (hypnosis), and immobility, often associated with analgesia and suppression of autonomic reflexes (Hemming, 2010,). Bajwa *et al.* (2010) opine that general anesthesia should provide quick and pleasant induction, predictable loss of consciousness, stable operating condition, minimal adverse effect; rapid and smooth recovery of protective reflex and psychomotor functions. General anaesthesia can be achieved through inhalation method and intravenous route. Before the development of intravenous anaesthetics, and till recently, induction of general anaesthesia and maintenance of anaesthesia require inhalation of gases and vapour (including nitrous oxide, ether, and chloroform) that often resulted in slow, unpleasant, and occasionally dangerous inductions and pollution of operation room environment which is a big hazard (Bajwa *et al*., 2010).

The development of intraveneous anaesthetics followed the late 19th century introduction of hollow needle, syringe and intravenous fluid therapy, which provided direct access to the bloodstream for the rapid administration of drugs. These innovations paved way for the introduction of rapidly acting intravenous anaesthetics (Hemming 2010). Intravenous anaesthesia implies inducing general anaesthesia by anaesthetic agents administered

intravenously. It has some advantages which include rapid and smooth induction of anaesthesia, little equipment requirement (syringes, needles, catheters), and easy administration of drugs. Ideally, an intravenous anaesthetic supposed to has certain pharmacodynamic, pharmacokinectic and physicochemical properties. Such properties include hypnosis, amnesia, analgesia, neuroprotection, cardioprotection, rapid onset, and rapid metabolism to inactive metabolite, minimal cardiovascular and respiratory depression. Also include are absent of hypersensitive reaction, no untoward neurologenic effect, nonmutagenic, nontoxic, noncarcinogenic, nonpyrogenic, nonirritant, painless on injection, small volume needed for induction, antimicrobial preparation, water soluble, and stable formulation (Hemming 2010). Practically, no single drug can provide all the characteristics of an ideal intravenous agent (Bajwa *et al.,* 2010), despite the availability of many intravenous anaesthetics.

Following the development and the availability of many intravenous anaesthetics, the concept of ñbalance anaesthesiaò was introduced by Lundy in the year 1926 to describe a poly pharmaceutical combination of premedication, local anaesthesia and general anaesthesia to reduce the dose of each agent and thereby improve safety. This concept has evolved to include the combination of various intravenous drugs including hypnotics, analgesics, sedatives, and muscle relaxants, often with inhaled anaesthetics (Hemming, 2010).

Modification and improvement on general anaesthesia over the time has resulted to total intravenous anaestheasia (TIVA). This implies induction as well as maintenance of anesthesia with intravenous agents using intravenous routes only. This method can be used not only in well-equipped hospital setting but also at remote location with only oxygen and ventilation facilities. Veterinary practices located outside the major cities and training

institutions that do not have anaesthetic machines employ a total intravenous anaesthesia (TIVA) to carry out even major surgical procedures on animal patients (Adetunji *et al*., 2002). Various drugs have been tried from time to time in total intravenous anaesthesia and several drugs are used in different combinations to provide balanced anaesthesia in total intravenous anaesthesia (Bajwa *et al*., 2010). The use of propofol, ketamine and xylazine in different combinations to achieve balanced intravenous anaesthesia, reduce dosage and decrease adverse effect of individual drugs on cardiopulmonary functions formed the bases of this study. Hence the review of both the chemical and anaesthetic properties as well as the adverse effect of the individual drugs became imperative.

2.2 PROPOFOL

Propofol (2, 6-diisopropylphenol) non dissociative and non cumulative intravenous anesthetic agent. It is a short-acting intravenous general anaesthetic agent that can be used for both induction and maintenance of anaesthesia. It has both sedative and hypnotic properties. It has good quality anaesthesia but poor analgesic quality (Hall *et al.,* 2001).

2.2.1 CHEMICAL PROPERTIES

Propofol is chemically described as 2, 6-diisopropylphenol and has a molecular weight of 178.27g. Propofol is slightly soluble in water and, thus, is formulated in a white, oil-in-water emulsion. The pKa is 11. The octanol/water partition coefficient for propofol is 6761:1 at a pH of 6 to 8.5. The pH is adjusted with sodium hydroxide. The propofol injectable emulsion is isotonic and has a pH of 7 to 8.5. It is available as a 1% w/v in 20 mL, 50 mL and 100 mL glass vials for single infusion only. Each vial contains 10 mg/mL of propofol for intravenous administration. In addition to the active component ópropofolô, the formulation also contains

soybean oil (100mg/mL), glycerol (22.5 mg/mL), egg phosphatide (12 mg/mL) and disodium edetate (0.055 mg/mL) and water for injection with sodium hydroxide to adjust pH (Branson and Gross, 1994). Disodium edetate or disodium metabisulfite is added to retard the growth of microorganisms; however, these are still not antimicrobially preserved products (De cosmo *et al*., 2005). Propofol may be stored between 2° and 25°C or at room temperature. Propofol emulsion is a highly opaque white fluid due to the scattering of light from the tiny (~150 nm) oil droplets that it contains. A water-soluble prodrug form, propofol phosphate (fospropofo), has recently been developed and tested with positive results. Propofol Phosphate (fospropofol) is rapidly broken down by the enzyme alkaline phosphatase to propofol and nontoxic inorganic phosphate (Mariusz *et al*., 2002).

2.2.2 PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES

Propofol is a popular agent used for induction of anaesthesia and long-term sedation, owing to its favourable pharmacokinectic profile which ensure a rapid recovery even after prolonged administration (Murthy, 2008). It is highly lipid soluble, short-acting intravenous general anaesthetic agent. The pharmacokinetics is characterized by a three compartment open model, with rapid distribution from blood into the highly perfuse tissues (half-life 2-3 minutes), rapid metabolic elimination from blood (half life 30-60 minutes) and slower final phase, during which propofol is eliminated from poorly perfused tissue (Hall *et al.,* 2001; Favetta *et al*., 2002; and De cosmo *et al*., 2005). Following the initial bolus dose, propofol as a lipid soluble substances, easily passes the blood-brain barrier and is distributed to the highly perfuse central nervous system (spinal cord and brain) resulting to loss of consciousness within the time of one arm-brain circulation about 20 seconds depending on the cardiac output (Hemming, 2010). At this time equal level of concentration is maintained

between the plasma and the brain. Plasma levels, however, decline quickly as a result of high metabolic clearance and prompt distribution to the lean vessel-rich tissues (muscles) and less perfused tissues (fats) (Fulton *et al* 1995; De cosmo *et al*., 2005; and Prassino, *et al* 2005.). These properties account for propofol's rapid onset and short duration of action. Mean onset time was 30 to 40 seconds in human patients after a 2.0 to 2.5 mg/kg bolus (De cosmo *et al*., 2005) while in goat, the induction was 15 to 30 seconds after 3 mg/kg bolus (Prassinos *et al.,* 2005).

Propofol is metabolized via hepatic conjugation to inactive metabolites which are excreted in the urine through the renal system (Hall *et al.*, 2001). The hepatic conjugation of the parent drug forms propofol-glucoronide (PG), 4-(2, 6-diisopropyl-1, 4-quinol)-sulphate (4-QS), and 1-, or 4-(2, 6-diisopropyl-1, 4-quinol)-glucuronide (1-QG and 4-QG). The last two are sulfo- and glucuro-conjugation of the hydroxylated metabolite form (Sneyd, *et al*., 1994; Simons *et al*., 1998; Favetta *et al*., 2002). In human, 4-QS, 1-QG, 4-QG and PG were identified as the main metabolites (Favetta *et al*., 2000). Propofol has a high hepatic extraction and thus, hepatic blood flow is a major determinant of its hepatic elimination (Lange *et al*., 1990; and Favetta *et al*., 2002). Clearance exceeds hepatic blood flow, so extrahepatic metabolism must occur (Vanlersberghe and Camu, 2008). Propofol has a clearance rate of 23-50ml/kg/minute. The presence of hepatic cirrhosis or renal insufficiency does not appear to significantly alter its pharmacokinetics (Favetta *et al.,* 2002).

2.2.3 EFFECTS ON ORGAN SYSTEMS

2.2.3.1 Central Nervous System

Propofol is a hypnotic agent (Sneyd 1992; Li Volti *et al*., 2006) that provides a dose-dependent suppression of awareness from mild depression of responsiveness to obtundation (De cosmo *et al.*, 2005). It has both anxiolytic and amnesic properties. Likely targets of anaesthetic actions are neurons within the spinal cord dorsal horn, since they are invoved in the transmission of stimuli to other central nervous systems. Propofol depresses dorsal horn neuronal responses to innocuous and noxious stimuli (Namiki *et al*., 1980; Kishikawa *et al*., 1995). Experimental finding in goat showed that propofol directly depresses dorsal horn neuronal responses to noxious mechanical stimulation, with little or no indirect effects occurring at supra spinal sites (Antognini *et al*., 2000). Propofol induces its effect on CNS by mechanisms involving facilitation of inhibitory neurotransmission mediated by g-aminobutyric acid (GABA) type A receptor (Veselis *et al*., 2002). It has been interpreted that propofol directly activates the (GABA) receptor and potentiates the GABA evoked responses, neuronal hyperpolarization and slows the channel closing time (Sneyd *et al.*, 1992; Krasowsk *et al*.; 2002; Murthy 2008). It has been shown that propofol produce an allosteric modulation of the GABA recognition site thereby enhancing GABA-ergic transmission (Concas *et al*., 1990). It also blocks the sodium channel (Haeseler and Leuwer, 2003) and inhibits excitatory glutamate release by a presynaptic mechanism (Ratnakumari and Hemming, 1997; Murthy 2008) and decreases cerebral metabolism. Propofol decreases cerebral blood flow (CBF), cerebral metabolic rate of oxygen consumption ($CMRO_2$), and cerebral blood volume (CBV) in adult healthy human subject. The reported reductions in CMRO2 were greater than the one observed after the administration of thiopental with less

cerebral vasoconstriction and reduction of CBF (Waelbers *et al*., 2010). Similar to its effect in man, propofol was reported to decrease CBF and CMRO2 in dogs with preservation of the vasoconstrictor reflex to hypocapnia. However, the autoregulation was impaired, but only at high propofol concentrations (Artru *et al.*, 1992). Propofol also decreased the intracranial pressure (ICP) in an experimental model of cerebral edema in cats, (Waelbers *et al.,* 2010). It has been used in neurosurgical patients to reduce elevated intracranial pressure (ICP) (Krzych *et al.,* 2009). It can cause a critical reduction in cerebral perfusion pressure (CPP) and has been found to decrease intraocular pressure by as much as 60% (De cosmo *et al.,* 2005).

Many studies have proved that propofol has potential neuroprotective properties both in experimental models and clinical practice. The nuerogenic effect of propofol such as reduction in cerebral blood flow, reduction in the cerebral metabolic rate for oxygen consumption ($CMRO_2$), inhibition of glutamate release, mitigation of intracranial pressure and production of electroencephalographic burst suppression, may make it a possible beneficial agent against cerebral ischemia (Kawaguchi *et al*., 2005, and Koerner *et al.,* 2006). Adembri *et al*. (2006) in a study in rat showed that propofol reduced pyramidal cell death, possibly by preventing an increase in neuronal mitochondrial swelling when selective neuronal injury was experimentally induced by a short exposure to oxygen glucose deprivation (OGD) due to permanent middle cerebral artery occlusion. Therefore, it has ability to postpone neuronal death and allow intervention with other decisive pharmacologic strategies (Murthy, 2008). Ishii *et al.* (2002) demonstrated the effect of propofol on glucose metabolism stating that high doses of propofol (60 mg/ kg/ h) attenuate both oedema formation and lactate accumulation. During propofol anaesthesia, cerebral auto regulation

and CO_2 responsiveness are maintained in human patient (Fox *et al.,* 1992). These demonstrate its neuroprotective properties.

Propofol produces electroencephalographic (EEG) burst suppression (Sneyd, 1992; Hugh 2010). It is not likely to induce EEG seizure in healthy individuals but can shorten the duration of convulsion after electroconvulsive therapy, which can be a therapeutic disadvantage (Dwyer *et al*., 1988; Rampton *et al.,* 1988; Rouse*.,* 1988; Simpton *et al.,* 1988; Sneyd, 1992). It has been used to control seizure that had proven refractory to other agents such as phenytoin, phenobarbitone and diazepam confirming its anticonvulsant effect (Wood *et al.,* 1988; Sneyd 1992)

2.2.3.2 Cardiovascular System

The intravenous injection of propofol may cause significant reduction in the arterial blood pressure especially in the hypovolemic patient. It decreases arterial blood pressure by 15% to 40% (Hemming, 2010) leading to hypotension. This is mainly as a result of propofolôs induced significant reductions in the systematic vascular resistance, cardiac filling and cardiac muscle contractility. Propofol resets baroreceptor reflex control of heart rate, resulting in an unchanged heart rate despite reduction of blood pressure (Hemming, 2010). In the other hand, it impairs the normal arterial baroreflex respond to hypotension, particularly in the condition of normocarbia or hypocarbia (De cosmo *et al.,* 2005; Hemming, 2010). Stowel *et al.* (1992) found out in an experimental in vitro study that propofol moderately depressed cardiac function and markedly attenuated autoregulation by causing coronary vasodilation. In this study, at concentrations below 10µmol/L, no significant changes were observed, but beyond 50µmol/ L, propofol caused progressive but differential

decreases in the heart rate, artrioventricular conduction time (leading to atrioventricular dissociation), left ventricular pressure, + LVdp/dT max (change in maximal positive derivative of the left ventricular pressure), percent oxygen extraction and myocardial oxygen consumption of isolated hearts. Myocardial oxygen consumption is decreased by propofol and myocardial oxygen supply-demand ratio is preserved, so it may be useful in patient with ischemic heart disease.

The multiple biological mechanism linking propofol with cardiac depression are thought to involve modulation of central sympathetic control (Krassioukov *et al.*, 1993; Stadnicka *et al.*, 2009), inhibition of the local vascular sympathetic activity (Pensado *et al.*, 1993) and direct modulation of vascular smooth muscle leading to vasodilatory effect (Stadnicka *et a.,* 2009 and Krzych *et al.*, 2009).

At molecular level, they include modification of Ŭ- and ɓ- adrenoceptor binding and L-type calcium cardiac inhibition (Zhou *et al*., 1997; Lejay *et al*., 1998; Zhou *et al*., 1999; Sprung *et al*., 2001). It was found that propofol acts as calcium channel blocker and had a direct impact on calcium channel proteins to diminish voltage-dependent L-type calcium current (Zhou *et al.*, 1997). Propofol also antagonized ɓ-adrenoceptor binding and alter receptor responsiveness to catecholamines in dose dependent and competitive manner (Zhou *et al.*, 1999).

The effect of propofol on heart is variable among individuals in human and animal model probably due to genetic differences. Stadnicka *et al.*, (2009) in their study showed that propofol causes greater hyperpolarization of mensenteric arterial smooth muscle in parental Dalh salt-sensitive (SS) rat than in Brown Norway (BN) rats, and this effect is related to gene

on the chromosome 13. The study suggested that chromosome 13-associated genes may be responsible for differential cardiovascular sensitivity to propofol and that propofolï induced hyperpolarisation is as a result of involvement of and activation of voltage-activated potassium (BK). Similarly, in pharmacological study of the effect of propofol on isolated coronary arteries, Klockgether- Radke *et al*., (2004) suggested that propofol-induced vasodilation is mediated by activation of BK channels.

Several studies have pointed out the cardioprotective effect of propofol. There were reports of propofolôs role in the reduction of cardiac troponin I concentration in clinical investigation (Xia *et al.*, 2006; Zou *et al.,* 2007; Krzych *et al.*, 2009), and myocardial protection by the activation of protein kinase C (Kohro *et al.*, 2001; Kanaya *et al.*, 2001; Wickley *et al.,* 2006). Kanaya *et al.* (2001) and Wickley *et al*. (2006) suggested that propofol increases the sensitivity of myofibrillar actinomyosin ATPase to calcium by increasing intracellular pH via protein kinase C-dependent activation of NA^+ -H^+ exchange. The infusion of the propofol has been reported to cause a significant reduction in the number of in vitro apoptotic cell (Choi *et al.*, 2007) and prevented dopamine-induced apostosis of heart cell after ischemia in rat (Lejay *et al*., 1998). In the studies carried out by Tsuchiya *et al*. (2002), propofol increased erythrocytes membrane fluidity, thereby increasing their resistance to physical and haemodynamic stress. Moreover, propofol may also protect erythrocyte membrane against oxidative and physiological stress suggesting its efficacy and usefulness as an antioxidant. This protective effect of propofol on oxidation in red blood cell membrane was enhanced by another antioxidant, ascorbic acid (Tsuchiya *et al*., 2002).

Propofol produces a minimal increase in plasma histamine levels. It is not arrythmogenic and does not sensitize the heart to catecholamines (Hall *et al*., 2001; Hemming, 2010).

2.2.3.3 Respiratory System

Propofol is a profound and potent respiratory depressant, and produce apneic period of 30 to 60 second following normal induction dose (De cosmo *et al*., 2005; Krzych *et al*., 2009; Hemming, 2010; Mehrdad *et al*., 2010). Propofol infusion inhibits hypoxic ventilator drive and depresses the normal response to hypercarbia. It depresses the laryngeal reflexes preventing the occurrence of Hiccough, cough and laryngospasm. This can be proving helpful during intubation or laryngeal mask placement in the absence of paralysis (De cosmo *et al*., 2005). Propofol causes bronchodilation even in sedation type doses which makes it useful agent in patients with asthma, hyperactive airways, or chronic obstructive pulmonary disease (De cosmo *et al*., 2005; Hemming, 2010).

2.2.4 OTHER PROPERTIES

Propofol has significant antiemetic activity even at subanaesthetic doses. However, blood propofol concentration of 200µg/ml is required for the effect to be achieved (De cosmo *et al.,* 2005 and Hugh, 2010). It has not been shown to cause malignant hyperthermia and this may be used safely in patient with malignant hyperthermia (Mckenzie *et al.,* 1992). It is an effective antipruritic. It has been effective in relieving pruritis associated with spinal opiates and cholestasis (Hugh, 2010; De cosmo *et al.,* 2005). It has also been found to have antioxidant activity both in vitro and in vivo (De cosmo *et al.,* 2005; Li Volti *et al.,* 2006). Li Volti *et al.,* (2006), pointed out that propofol posses antioxidative and anti-apoptotic properties and involve important enzymatic system such as heme oxygenase-1 (HO-1), in exerting its effects thus providing an important and powerful strategy for protection during anaesthesia.

2.2.5 USES, ANAESTHESIA AND ANALGESIA

Propofol is use for induction and maintenance of anaesthesia both in man and in animals. It is also used to sedate individuals who are receiving mechanical ventilation. In critically ill patients, propofol has been found to be superior to lorazepam both in effectiveness as well as overall cost (Cox *et al*., 2008). Propofol is also used for procedural sedation, for example during endoscopic procedures. Its use in these settings results in a faster recovery compared to midazolam (McQuaid and Laine, 2008). Propofolôs rapid clearance and short half time also make it useful for maintainance of anaesthesia by continous infusion without significant cumulative effects and the concentrations of the propofol often decreases rapidly when the infusion is terminated (Hemming, 2010). Propofolôs pharmacokinectic properties and low incidence of nausea and vomiting make it particularly useful for shot procedures and ambulatory surgery (Smith *et al*., 1994). Propofol has good quality anesthesia, rapid onset and short duration of action, with rapid recoveries making the drug potentially useful in ruminants, in which these features are particularly desirable (Prassinos *et al*., 2005). Hall *et al*. (2001) stated that propofol has been accepted as most useful anaesthetic agent in all domestic animals. It has being use alone and in combination with other drugs in dogs, cat, cattle, horse, ponies and goats (Lin *et al.*, 1997; Mama 2000; Lerch *et al.,* 2000; Hall *et al.,* 2001; Steffey *et al.,* 2009). Propofol, at dose range of 3 mg/kg to 7mg/kg body weight provided a smooth and uneventful induction of anaesthesia, combined with satisfactory condition for rapid tracheal intubation and smooth transition to inhalation anaesthesia in unpremedicated goats and sheep (Reid *et al.,* 1993; Pablo *et al*.; 1997, Hall *et al*., 2001; Prassinos *et al.,* 2005)

Reports on the use of propofol for induction and maintenance of anaesthesia have indicated its suitability in goats (Hall *et al.,* 2001; Khan 2006; Prassinos *et al.,* 2005). Propofol has been shown to be compatible with wide range of drugs used for premedication, inhalation anesthesia and neuromuscular block (Hall *et al.,* 2001). It has good muscle relaxant property but little or no analgesic properties.

2.2.6 SIDE EFFECTS

Propofol causes pain at the site of injection. However, the pain can be alleviated with local anaesthetic pretreatment at the site of injection and warming of the emulsion to 37 ^{o}C before the administration (De cosmo *et al.,* 2005). Propofol causes apnea after induction, hypotension, bradycardia and opistothonus (Hall *et al.,* 2001; Adetunji *et al*., 2002; De cosmo *et al*., 2005; Hugh, 2010). It caused dystonia and mild myoclonic movement in man (Schramm and Orser, 2002). Administration of propofol over time (infusion for period exceeding three days) may produce propofol infusion syndrome (PRIS) which is characterized by severe metabolic acidosis, renal failure and rhabdomyolysis associated with progressive myocardial failure as a result of progressive increase in the level of serum lipids, particularly triglycerides. The syndrome appears to be duration and dose-related. It is more frequent in young than adult patient (Vasile *et al.*, 2003; De cosmo *et al*., 2005; Murthy, 2008; Krzych *et al* 2009; Hemming, 2010).

2.3. KETAMINE

Ketamine, a cyclohexanone derivative is a non-barbiturate whose pharmacological action is distinctly different from those other intraveneous anaesthetic. It is classified pharmacological as an N-methyl-D-aspartate receptor anatagonist (Harison *et al*., 1985). It is

a racemic compound with R and S stereisomer. The S-ketamine has about four times greater affinity for phencyclidine site of the N-methyl-D-aspartate (NMDA) receptor than R-ketamine (Hirota *et al*., 1999; Narita *et al.,* 2001). The S-ketamine also has greater analgesic effect and less hallucinogenic side effects making it preferred for use in medical procedure (Zarate *et al*., 2006). Ketamine causes a state of dissociative anaesthesia in which the patient appears awake but is unconscious and does not feel pain (Hall *et al*., 2001, Aliu 2007). It has hypnotic, profound analgesic and amnestic properties (Tomlinson 1994; Hall *et al*., 2001). It produces dose related unconsciousness and analgesia (Cohen *et al*., 1973). It has no muscle relaxant effect and tonic clonic spasms of limbic muscle may occur even in the absence of surgical or other stimulation (Hall *et al.*, 2001),

2.3.1 CHEMICAL PROPERTIES

The systematic (IUPAC) name of ketamine is 2-(2-chlorophenyl-2-methylamino-cyclohexan-1-one) with chemical formular $CH_{13}H_{16}C_1NO$. It has Synonyms as ketaject®, ketaset®, vetalar®, ketalar®. It has a molar mass of 237.725g/mol. Ketamine is a chiral compound either in powered or liquid form. It is a white crystalline substance readily soluble in water and its solution has a pH of just over 4.0. This solution is non irritant both on intravenous and intramuscular injection (Virtue, 1967). Ketamine is synthesized from 2-chlorobenzonitrite, which reacts with Grignard reagent, cyclopentyl-magnesium bromide to give 1-(-2-chlorobenzoyl) cyclopentane (Stevens, 1963; Stevens, 1966). The next step after the product of 1-(-2-chlorobenzoyl) cyclopentane, is bromination using bromine to the corresponding bromoketone, which upon reaction with aqueous solution of methylamine form the methylamino derivative. During this reaction a simultaneous hydrolysis of the tertiary bromine atom occurs. On futher heating, the reaction product in decalin, a ring expansion

rearrangement occurs, causing formation of ketamine (Stevens, 1966). Ketamine can be stored in room temperature (15-30 ^{o}C).

2.3.2 PHARMACOKINECTIC AND PHARMACODYNAMIC PROPERTIES

Ketamine is water and lipid soluble. It is absorbable via intravenous, intramuscular, oral and topical routes due to both its water and lipid solubility (Aroni *et al*., 2009). Bioavailability of ketamine following intravenous dose is > 95%, intramuscular is 93%, and intranasal is 25-50%, oral 17-20%, sublingually 30%, and rectally 30% (Idvall, 1976; and Sinner *et al*., 2008). Following the administration, ketamine is rapidly distributed from the blood into the brain and other highly perfused tissue. It is 12% bound in plasma. Redistribution of ketamine from central nervous system to peripheral tissue and hepatic biotranformation terminates its anaesthetic action (Dripps *et al*., 1982). Ketamine is biotransformed in the liver by cytochrome P3A4 (CYP3A4), Cytochrome P2B6 (CYP2B6) and cytochrome P2C9 (CYP2C9) iso-enzymes into norketamine through N-demethylation. It has been reported that cytochrome P3A4 (CYP3A4) is principally responsible for this metabolism in human and cytochrome P3A (CYP3A) in other animals (Capponi *et al*., 2009; Veilleux-Lemieux *et al*., 2012). The norketamine is hydroxylated into 5-hydroxynorketamine by CYP2B6 and CYP2A6. The 5-hydroxylnorketamine can br conjugated to more water-soluble glucuronide derivative and be excreted by kidney (Lankveld *et al.*, 2006). The hydroxylnorketamine metabolites are unstable ex vivo at higher temperature, and were thought to undergo futher oxidation (thermal dehydration) to dehydronorketamine (Lankveld *et al*., 2006; Sinner *et al.,* 2008). Dehydronorkrtamine (DHNK) followed by norketamine is most prevalent final metabolites detected in the serum and urine (Sams and Pizzo 1997; Seay *et al*., 1993; Li *et al*., 2011). Dripps, (1982) reported that norketamine is the major matebolite of ketamine and

is one-third to one-fifth as potent anaesthetically as ketamine. The plasma levels of norketamine are three time higher than ketamine following oral administration (Aroni *et al*., 2009; and Haas *et al*., 1992). The peak plasma concentrations of ketamine are reached within 1 minute intraveneously, 5 to 15 minutes intramuscularly and 30 minutes orally (Quibell *et al*., 2011).

2.3.3 EFFECT ON ORGAN SYSTEM

2.3.3.1 Central Nervous System

The effect of ketamine on central nervous system begins more slowly (1 to 5minute) following intravenous injection compared to other anesthetic agent like thiopentone (30 to 60 seconds) (Tomlison, 1994). The anesthetic state produced by ketamine is dissociative which means that the patient may appear awake and reactive but unconscious and does not respond to sensory stimuli (Tomlison, 1994; Hall *et al*., 2001; Aliu, 2007). It produces dose related unconsciousness and analgesia (Cohen *et al*., 1973). Ketamine is rapidly distributed to the brain following its administration having higher concentration than in the blood (Domine *et al*., 1965). It appears to selectively depress the thalamocortical system, an association region in the cerebral cortex, while stimulating the reticular activating and limbic system. Ketamine also interacts with muscarinic receptors decending monoaminergic pain pathways and voltage gated calcium channel (Hall *et al*., 2001). It is a potent cerebral vasodilator that increases cerebral metabolism, blood flow and cerebral metabolic rate of oxygen consumption ($CMRO_2$) (Hemming 2010; Dawson *et al*., 1971). It increases intracranial pressure in spontaneously breathing patients thus, it is relatively contraindicated in a patient who has sustained a recent head injury and in neurosurgical procedure (Hemming, 2010).

The increase in the intracranial pressure can be attenuated by controlled ventilation, hypocapnia or prior administration of diazepam, thiopental or propotol. Ketamine also produced mydriasis, nystagmus, and excitatory CNS effect. However it does not appear to lower the seizure threshold in patients who have seizure disorder. Ketamine in low doses might control neurogenic pain and reverse the wind-up phenomenon (Hemming, 2010). Ketamine has been well documented as having neuro-protective effect against Ischemic injury and glutamate induced brain injury (Shibuta *et al*., 2006). It blocks the NMDA receptor, which is hightly activated via enhanced excitatory neurotransmitter release during ischaemia (Thompson *et al*., 1985). It also blocks glutamate NMDA receptor to reduce hypnotic neuronal injury to the gray matter (Bruce *et al*., 1990). In vitro studies showed that ketamine can also interfere with transmembrane calcium influx. However, there are evidences of neurodegeneration as a result of prolonged exposure to ketamine. Hughes *et al*. (1993) demonstrated that MK- 801, a potent NMDA receptor antagonist, induced pathomorphological changes and increase brain drived neurotropic factor mRNA (BDNF mRNA) in rat cerebrocortical neuron. Brain derived neurotropic factor (BDNF) is one of the major neurotropic factor that primarily support the growth and survival of cholinergic, dopaminergic, and motor neuron. The BDNF is synthesized by sensory neuron and glia and may have both autocrine and paracrine functions in mediating activity-dependent plasticity (Ibla *et al*., 2009; Ichisaka *et al.,* 2003). Garcia *et al*. (2008) reported that ketamine increased BDNF level in adult rat and induced an anti-depressant state as assessed by a force swin test. Furthermore, Ibla *et al*. (2009) demonstrated that prolonged ketamine administration in neonatal rat induces BDNF experession in whole brain and suggested that the increase in BDNF level is a late response to accelerated neuronal degeneration in the developing rat

brain. Therefore BDNF induced after memantine or ketamine administration, may serve as a compensatory response to brain injury.

2.3.3.2 Cardiovascular System

Ketamine has cardiovascular stimulatory effect. Its stimulatory effect includes increases in systemic and pulmonary arterial vascular resistance and pressure (Wrong and Jenkin, 1974), heart rate, cardiac output, myocardial oxygen consumption, stroke volume index, coronary blood flow and cardiac work (Ivankovich *et al*., 1974; Idvall *et al*., 1979; Tomlinson, 1994, and Hemming, 2010). Ketamine causes increases in cardiac output, heart rate, and arterial blood pressure in goat (Wright, 1982). These cardiovascular effects result primarily from the stimulation of the sympathetic nervous system to produce tachycardia and hypertension. However, the mechanism by which ketamine produces cardiovascular stimulation has been suggested by many authors. Dowdy and Kaya (1968) reported that ketamine produced diminution of frequency response of baroreceptors which, reflexly through the central nervous system, could produce an increase in heart rate and blood pressure and therefore proposed that the pressor effect of ketamine is the result of desensitization of the arterial baroreceptor. Virtue *et al.* (1967) suggested that the stimulatory cardiovascular effects of ketamine could be the result of endogenous release of catecholamines. Traber *et al.* (1970) concluded that the cardiovascular excitatory effects of ketamine are due to stimulation of the sympathetic nervous system and to an atropine-like action on the heart. From a study conducted with goats, Ivankovich *et al.* (1974) concluded that ketamine produces peripheral sympathomimetic effect primarily by direct stimulation of CNS structures, and that when these structures are depressed by pentobarbital; the peripheral effects of ketamine are ameliorated. Apart from sympathominetic effects mediated within the central nervous system

(Ivankovich *et al.,* 1974). Ketamine inhibits neuronal uptake of catecholamines by sympathetic nerve ending (Salt *et al.*, 1979). It increases the plasma epinephrine and norepinephrine within 2 minutes of administration which may return to control level 15 minutes later (Baraka *et al.,* 1973). Ketamineôs interference with the reuptake of norepinephrine no doubt may lead to some of its cardiovascular effects which could be the result of a similar action on the postganglionic adrenergic neuron (Miletich *et al.,* 1973). It produces direct vasodilation of vascular smooth muscle (Altura *et al.,* 1980). It was reported that ketamine increased artrioventricular conduction time and has a direct myocardial depressant effect (Ivankovich *et al.*, 1974). Ketamine causes dose-dependent rise in blood pressure and heart rate (Ivankovich *et al*., 1974; Dundee *et al.*, 1978). However, Tomlinson (1994) argued that the increase in blood pressure and heart rate do not seem to be dose related when more than, 1mg/kg of ketamine is given and larger doses do not necessarily cause a greater increase in blood pressure inhuman subject. Lankveld *et al*. (2006) reported a significant increase in heart rate during early infusion phase but after 20 minutes when the ketamine infusion rate was decreased to 3.6 mg/kg/h from initial dose of 4.8mg/kg/h, the value returned to base line and remained stable for the remainder of the experiment in horses. In goat ketamine causes increase in cardiac output, heart rate and arterial blood pressure (Wright, 1982). Arrhythmia has been reported in cat following the used of ketamine (Hall *et al.,* 2001)

2.3.3.3 Respiratory System

Ketamine stimulates respiratory system rather than depressing it (Adams, 1997). However, respiratory rate may decrease transiently, immediately after induction of anesthesia (Hemming, 2010). Mild respiratory depression has been reported and in clinical practice, this

is usually manifested by an increased rate which does not compensate for a decreased tidal volume (Hall *et al*., 2001). Upper air way reflexes (pharyngeal and laryngeal reflexes) and muscle tone are maintained, so it is possible to perform ketamine anesthesia without protective measure to the air way (Adams, 1997), but increase salivary and tracheobronchial secretion can lead to cough and laryngospasm such that the co-administration of an anti-sialagogue like atropine is recommended (Hemming, 2010). Ketamine rapidly administered intravenously cause apnoea of about 60 seconds, but breath is well maintained or may even increase slightly following slow intravenous induction (Tomlinson, 1994). It produces branchiodilatory effect which is extremely useful in patients with reactive air way disease such as asthma or bronchospasm (Tomlison, 1994; Hemming, 2010). Ketamine is unique in its ability to maintain the functional residual capacity upon induction of anesthesia possibly because of the maintenance of skeletal tone. The direct myocardial depressant effect of ketamine, if unmasked through the depression of the patient CNS by other anaesthetic agents, may result to cardiovascular depression (Ivankovich, 1974). However, the effect is usually masked by sympathomimetic effect of the ketamine when used alone.

2.3.3.4. OTHER EFFECTS

Ketamine causes a rise in the intraocular pressure for a short period of time making its use contraindicated in patient with perforated eye, eye injury or for ophthalmic surgery where a still eye is required (Tomlison, 1994). Diplopia and nystagmus have been noted following ketamine administration. The eye pupil size and reaction to light is usually normal (Grant *et al*., 1981). Ketamine causes a significant increase in serum concentration of liver enzymes as reported in human anaesthesized with a ketamine infusuion (Dundee *et al*., 1978). In dogs given higher intramuscular injection of ketamine (40mg/kg daily for 6 weeks), a transient

increase in liver enzymes was observed (Corseen *et al.,* 1968). It crosses placenta easily and approximately the same concentration was seen in fetus as in the mother (Tomlison, 1994). Studies have shown that ketamine anaesthesia caused a reversible decrease in haemogram of foxes, sheep, vervet and bonnet monkey, and water buffalo (Kirk, 1972; Nowrouzian *et al.*, 1980; Wall *et al*., 1985; Ramasamy *et al*., 2006 and Singh *et al*., 2006).

2.3.5 USES, ANAESTHESIA AND ANALGESIA

Ketamine may be used in small doses as a local anaesthetic agent particularly for the treatment of pain associated with movement and neuropathy pain (Lunchish *et al*., 2005). When combined with opoids, it is effective in relieving cancer pain (Saito *et al.*, 2006). Ketamine is often use in veterinary practice due to its wide safety margin and its anaesthetic and analgesic effect in dogs, cats, rabbits, rats, and other small animals (Hall *et al*., 2001). Ketamine, intramuscularly administered, produces an anaesthetic state characterized by profound analgesia, normal reflexes, and transient cardiac stimulation with minimal respiratory depression in cat (Chen, 1968). Several clinically useful characteristics of ketamine promote its use, including analgesia, bronchodialation and reduced cardiopulmonary depression (Hemming, 2010). The sympathomimetic properties of ketamine give it an important role in the anaesthesia. Ketamine is useful in the rapid induction of anaesthesia in the heamodynamically unstable patient who have acute hypovolemia, hypotension, cardiomyopathy, constrictive pericarditis, or cardiac tamponade and in patient with congenital heart disease or bronchiospastic disease. It may be the agent of choice for rapid induction of anaesthesia in patient with acute asthma, animal in shock and may decrease volatile anaesthetic requirement in animal with shock (Hemming, 2010). A unique advantage of ketamine is the versatility of its administration routes - intravenous,

intramuscular, oral and rectal route. Ketamine is used partly because of its wide therapeutic index, but mainly because it is one of the few agents which do not depress respiratory function at anaesthetic doses (Green *et al*., 1981). Ketamine can be used alone in small animals as a sedative for procedure which do not require muscle relaxation as in radiographic procedure. However, it is commonly combined with other sedative for synergistic effect and to counteract muscle rigidity. Ketamine is usually combined with useful adjunct sedative including xylazine, acepromazine, medetomine, diazepam and midazolam.

2.3.6 SIDE EFFECTS

The side effects of ketamine include increased blood pressure, elevated heart rate, respiratory depression, vocalization erratic and prolonged recovery, spastic jerking movements and muscle tremors. In rare instances, ketamine has shown to induce seizures and causes ataxia. Ketamine often enhances muscle tone to the extent that tremor or even tonic clonic convulsion is produced. It causes a marked increase in salivation and there is wide variation in response between species and between individual (Green *et al*., 1981, and Pablo *et al.,* 1997). Ketamine can stimulate uterine contraction in the first trimester of pregnant but has variable effect in the third trimester in human (Hemming, 2010).

2.4. XYLAZINE

Xylazine, a potent alpha-2-adenoreceptor agonist, is non opoid group with analgesic, sedative and muscle relaxant effects and is used commonly in veterinary practice (Booth, 1988 and Fereidoonz *et al.,* 2005). Based on these known properties of xylazine, it has been used extensively in various species of animals (Hall, 1971). It is a commonly used sedative in ruminants but there are concerns about the threat of hypoxaemia associated with its use in

small ruminants (Dzikit *et al.,* 2009). It has been used in combination with propofol in sheeps (Khan, 2006) and with ketamine in intravenous general anaesthesia in goat (Udegbunam *et al.,* 2007).

2.4.1 CHEMICAL PROPERTIES

Xylazine is chemically described as N-(2, 6-dimethylphenyl)-5,6-dihydro-4H-1,3-thiazine-2-amine hydrochloride. It has a molecular weight of 220.33. It has Synonyms such as BAY VA 1470, Xylazine hydrochloride, and Rompun hydrochloride. The commercial product contains 23.32 mg/ml xylazine hydrochloride in water based injectable solution. Xylazine can be obtained also as pure crystalline powder. It is white or almost white crystalline substance with melting point of 165-168°C. It is freely soluble in water, very soluble in methanol and chloroform, practically insoluble in hexane and ether

2.4.2 PHARMACODYNAMIC AND PHARMACOKINECTIC PROPERTIES

Xylazine can be administered subcutaneously, orally, intravenously, and intramuscularly. Absorption of xylazine is rapid following intramuscular injection, with half-life of 2.8 to 5.4 minute. Though xylazine undergoes incomplete absorption, its bioavailability ranges from 52 to 90% in dog, 17-73% in sheep, 40 - 48 in horse (Garcia-villar, *et al.,* 1981). Studies in rat and cattle have shown that 8% of intact or unchanged drug appeared in the urine of rat while in cattle, less than 1% of the unchanged drug was eliminated in the urine two hours after its administration (Duhm *et al.*, 1969, and Garcia-villar, *et al*., 1981).

The apparent volume of distribution for xylazine is between 1.9 and 2.7 l/kg in the dog, horse, cow and sheep. The peak drug concentration in plasma is reached after 12 to14

minutes in horse, cattle, dog and sheep following intramuscular administration. Xylazine undergoes rapid metabolism yielding about 20 metabolites in rat. The major xylazine metabolites characterized in horses in vivo and rat liver in vitro were identified as 2-(4-hydroxy-2,6-di-methylphenylamino)-5,6-dihydro-4H-,3-thiazine, 2-(3-hydyroxy-2,6-di-methylphenylamino)-5,6-dihydro-4H-1,3 thiazine, N-(2,6-dimethylphenyl)thiourea and 2-(2, 6-dimethylphenylamino)-4-oxo-5,6-dihydro-1,3-thiazine (Mutlib, *et al*., 1992), cattle, peak excretion of metabolite in urine occurs between 2-4 hours following administration of xylazine. This suggests that xylazine is extensively metabolized. The major metabolite excreted in cattle urine in free and conjugated form was identified as 1-amino-2, 6-dimethylbenzene (ADB) also known as 2, 6-xylidine which appears in urine within 4 hour of injection of therapeutic dose of xylazine. ADB probably forms from oxidative or hydrolytic breakdown of the thiazine ring (Putter and Sagner, 1973). The half-life of elimination of xylazine after intravenous administration of single dose is 49.5 minutes in horse, 36.5 minutes in cattle, 23 minute in sheep and 30 minute in dog (Garcia-villar, *et al.,* 1981)

2.4.3 EFFECT ON ORGAN SYSTEMS

2.4.3.1 Central Nervous System

Xylazine acts on presynaptic and postsynaptic receptors of the central and peripheral nervous systems as an alpha-$_2$-adrenergic agonist. It acts upon the central nervous by activation or stimulation of alpha-adrenoreceptors such as alpha-2-adrenergic receptor. Within the central nervous system, activation of alpha-2-adrenoceptors induces both analgesia and sedation. Xylazine binds to the alpha-2-adrenoceptor in the presynaptic membrane associated G-proteins and this leads to activation of potassium channels in the postsynaptic neurons,

causing the cell to loose potassium and become hyperpolarized. This action makes the cell unresponsive to excitatory input (Thurmon *et al*., 1996). Xylazine also produce muscle relaxation by inhibition of intraneuronal transmission of impulse at central level of the central nervous system. It has been reported that alpha-2-agonist and µ-opoid agonist can produce the same pharmacodynamic event (Thurmon *et al*., 1996). This is because the adrenergic and opiod receptors although different, may be found in the same location of the brain, and even the neuron. Furthermore, these receptor types are coupled to the same signal transducer and signal transduction mechanism is linked to the same effector mechanism (Thurmon *et al*., 1996).

2.4.3.2. Cardiovascular System

Intravenously administration of xylazine has been shown to induced bradycardia, hypotension, and heart block in ruminant and other species of animals (Aziz and Carlyle, 1978; Booth, 1988; Dehghani *et al.,* 1991; Saleh, 1993; Hall *et al*., 2001). Xylazine hydrochloride when injected intravenously showed partial cardiac block with decrease conductivity and brandycardia in horse (Hall and Clark., 1991), in sheep (Aziz and Carlyle, 1978) and in dogs (Klide *et al.,* 1975). In ponies, intravenous xylazine has been shown to produce bradycardia, sino-artrial (SA) block and transient atrio-ventricular (AV) block within one minute of its injection. (Garner *et al.,* 1971). Both intravenous and intramuscular administration of xylazine have caused significant reduction in heart rate in goat (Kumar and Thurmon, 1979), calve (Campbell *et al*., 1979), sheep (Aziz and Calyle, 1978) and horse (Hall *et al*., 2001). Brouwer *et al*. (1980) reported that intravenous injection of xylazine in horse was followed by ódropped beatô leading to significant decrease in heart rate which

increased again on the induction of anaesthesia by the injection of the second drug. The epidural injection administration has also produce the same effect in goat and cattle (Aithal *et al*., 1996). Suggestions have been made regarding the decrease in heart rate caused by xylazine hydrochloride. Kumar and Thurmon, (1979) suggested tha xylazine Hcl causes decrease heart rate via central and peripheral suppression of the sympathetic trunk since pre-administration with atropine negated the change in goat. Clark *et al*. (1982) suggested that the decrease in heart rate could be in response to transient hypertension that xylazine hydrochloride induces. It may also be due to the direct depressive action of xylazine on cardiac pacemaker and conductive tissue (Aziz and Carlyle, 1978).

Xylazine has been shown to cause decrease in mean arterial blood pressure in sheep and calve (Celly *et al*., 1997; Campell *et al*, 1979). Aziz and Carlyle *et al.,* (1978) reported initial increase followed by decrease in mean arterial blood pressure in sheep.

Xylazine induces an increase in total peripheral resistance. This increase in total peripheral increase, Green and Thurmon (1988) attributed it to direct alpha-adrenoreceptor stimulation of the peripheral vessels, causing peripheral vasoconstriction.

2.4.3.3 Respiratory System

Xylazine has been shown to cause significant reduction in respiratory rate especially at maximal sedation period in goats and other species (Aziz and Carlyle, 1978; Kumar and Thurmon, 1979). Xylazine administered epidurally has caused a reduced respiratory rate and irregularity in the pattern of respiration in both goat and cattle and concurrent decrease in tidal volume in goat (Mohammed and Yelwa, 1993) and sheep (Aziz and Carlyle, 1978).

Some researchers have attributed these effects of xylazine hydrochloride on pulmonary function to alpha-adrenoreceptor mediated activity which results in respiratory depression (Aithal *et al.,* 1996). Xylazine is a commonly used sedative in ruminant but there are concerns about the treat of hypoxaemia associated with its use in small ruminant (Dzikit *et al*., 2009). Hypoxaemia has been reported in goat, Kumar and thurmon, (1979) reported significant reduction in arterial pH and oxygen tension, 15 minute after intramuscular administration of xylazine. The hypoxeamia seen in small ruminant following xylazine may be attributed to recumbency, as lateral recumbencey during surgery period may cause some mismatching of ventilation and perfusion of lung tissue, and due to hypoventilation during sedation as a result of depression of the respiratory centre. The resultant effect would be low oxygen tension and high carbon-dioxide tension (Kumar *et al*., 1976, Kumar and Thurmon, 1979).

2.4.3.4 Effect on Temperature

The effect of xylazine on rectal temperature of various species of animal has not been stable. In goat, xylazine has shown decreased, increased and sometime no effect on the rectal temperature (Kumar and Thurmon, 1979, Dehghani *et al*., 1991, Mohammed and Yelwa, 1993). Young (1979) reported increase in rectal temperature following xylazine administration in cattle.

2.4.4 OTHER EFFECTS

Xylazine causes polyuria which has been reported in cattle lasting up to 5 hours (Thurmon *et al*., 1978). Polyuria in goat given intramuscular injection of xylazine has been observed at 47.8 ±11.8 minute post injection (Mohammed and Yelwa, 1993). Also Gweba *et al.* (2009) reported polyuria and pronounced salivation in sokoto red goat. Xylazine also causes hyperglycaemia which has been reported in goat (Kumar and Thurmon, 1979). It also causes hypoinsulinaemia (Green *et al.,* 1981). Intravenous injection of xylazine hydrochloride induced profused salivation in ruminants (Booth, 1988). Salivation following administration of xylazine Hcl has been reported in goats and cattle (Fayed *et al*., 1989; Mohammed and Yelwa, 1993 and Sale, 1993). Xylazine caused contraction of the bovine uterus similar to oxytocin and premature birth has been reported following its administration to heavily pregnant cow (Hall *et al*., 2001). Its use is contraindicated in the last trimester of pregnancy.

2.4.5. USES, ANAESTHESIA, ANALGESIA AND SEDATION

Xylzine is commonly administered by practicing veterinarians as a form of chemical restraint and to provide good muscle relaxation and visceral analgesia prior to administration of the main anaesthesia (Eze *et al.*, 2004). It is a drug that is used for sedation, anesthesia, muscle relaxation, and analgesia in animals such as horses, cattle and other non-human mammals. It has been used in various species because of its potent sedative, analgesic and myorelaxant properties (Hall *et al*. 2001). Its use in both domestic and wild animal species either alone or in combination with other tranquilizer and anaesthetic agents has been relatively safe (Knight, 1980). The sensivity to xylazine between animal species varies (Thurmon *et al.,* 1996). Ruminant are highly sensitive to xylazine and goats are much more sensitive to

xylazine than sheep (Taylor, 1991). The doses of 0.1 ï 0.2 mg/kg and 0.05 mg/kg may result in profound deep sedation for long period of time in sheep and goat respectively (Taylor, 1991). Sale *et al*. (1993), reported some sedative signs observed in goat following intramuscular administration of xylazine 0.05mg / kg, which include partial drooping of the upper eyelid, lowering of head and neck, protrusion of nictating membrane and tongue, muscle incoordination and staggering. In goat, xylazine 0.2 mg / kg causes sedation for as long as 96.25 ± 37.04 minute and recovery occurred in 60 to 240 minute. Also Muhammed and Yelwa, (1993) reported recumbency lasting 18.0 ± 11.8 minute and full recovery occurred 78.8 ± 26.47 minute post intramuscular injection of 0.05mg/kg of xylazine hydrochlororide. Similarly, intramuscular administration of xylazine in horses and cattle resulted in sedation 10 to15 minutes post drug administration (Hall *et al*., 2001) while in cat, xylazine given at 2.2 mg/kg body weight produced sedation for 96.25 ± 37.04 and recovery was 44.66 ± 32.0 minutes (Dehghani *et al*., 1991). It was shown that the duration of sedation and recovery time were dose-dependent being significantly longer with the higher dosage as compared to the lower dosage both in intramuscular and intravenous administrations.

Several authors have reported good analgesic effect of xylazine in goats (Dehghani *et al*., 1991; Saleh, 1993 and Aithal *et al.,* 1996), and cattle (Fayed *et al*., 1989). Knight *et al*. (1980) suggested that xylazineôs analgesic action is due to its action on the autonomic and central nervous system (CNS). Xylazine caused insensibility to pin prick and loss of the interdigital reflex in goat following intramuscular injection of xylazine 0.5mg/kg body weight (Saleh, 1993). Xylazine has been shown to have a potent anaesthetic effect when injected locally (Knight, 1980).

2.4.6. SIDE EFFECTS

Xylazine produces significant cardiac arrhythmias in all domestic species, interfering with normal electrical activities in the heart, especially after intravenous administration (Green *et al*., 1981). It abolishes the swallowing reflex so that regurgitation can result in pulmonary aspiration (Hall *et al.,* 2001). Gastro intestinal motility is decreased and bloat may develop, while diarrhea may be observed 12 to 24 hour after sedation (Hopkins, 1972). Xylazine causes the suppression of antidiuretic hormone (ADH) release leading to increase urine production in animal injected with xylazine hydrochloride (Hall *et al.,* 2001). In goat, Gweba, *et al.,* (2009) observed profused salivation, bleating, flexing of neck, polyuria and drastic decreased in ruminal motility, 30-60 minute post administration of xylazine in goat. It causes bradycardia and hypotension in all domestic speciesis phenolic compound unrelated to any other general anesthetics. It is a non-barbiturate,

2.5 HAEMATOLOGY AND BIOCHEMISTRY

Blood is an important and reliable medium for assessing the health status of individual animals. (Ramprabhu *et al.,* 2010). Variation in blood parameters of animal are due to several factors such as altitude, feeding level, age, sex, breed diurnal factors, seasonal variation, temperature, physiologic status and drugs (Mbassa and Poulsen, 2003). Hematological and serum biochemical tests reveal the nutritional, physiological and health status of the animal (Opara, *et al.,* 2010). Hematological and serum biochemical tests are widely used for the diagnosis of serious animal diseases which may lead to economic losses in animal like reduced milk production and meat (Banni *et al*., 2008) or may lead anaesthetic risk.

Pre-anaesthetic check on heamatological and biochemical profile of the animal is very essential except if the clinical examination was adequate (Hall *et al*., 2001). But these analyses when combined with case history and clinical examination of the animal could detect disease state in vast majority of apparently fit healthy animals (Coles, 1986; Hall *et al*., 2001).

Haematological and biochemical values of goats and sheep in Nigeria have been presented to serve as references for clinical interpretation of laboratory result (Opara *et al.,* 2010, Daramola *et al*., 2005; Banni *et al.,* 2008).

2.5.1 PACKED CELL VOLUME (PCV)

Blood is made up of plasma and cells. The relative proportion of red blood cell (erythrocytes) of the whole blood cells to the plasma is called packed cell volume (Reece, 2007). The proportion of erythrocytes always occupies the lower portion of capillary tube, when the blood in the capillary tube is centrifuged at 11000 revolutions per minute (rpm) for 5 minutes. This is as a result of separation of blood into its various component components according to their relative gravity following centrifugation. The buffy coat and plasma occupy the upper layer of capillary tube. PCV is a useful tool in detecting health condition such as anaemia, polycythaemia Vera and monitoring of treatment (Cheesbrough, 2004, Reece, 2007). In cat PCV decreased following ketamine injection (Middleto, 1980). Also, ketamine anaeasthesia produced a decrease in PCV content of sheep (Nowrouzian *et al.,* 1981), monkey (Bonnet macaque) (Ramasamy *et al.,* 1981) and water buffalo (Singh *et al*., 2006). Kumar and Thurmon (1979) reported decrease in haematocrit value in goat caused by xylazine at maximal depth of analgesia. Also, a significant reduction in pack cell volume has

been reported during sedation following administration of xylazine to caprine and feline (Dehghani *et al.,* 1991). This was attributed to the xylazineôs lytic effect on red blood cells

2.5.2. HEAMOGLOBIN (HB) CONCENTRATION

Haemoglobin is the iron-containing oxygen-transporting protein in the red blood cells of vertebrates (Kiran *et al*., 2012). It is made up of four haeme groups joined by one molecule of globin (Reece, 2007). It functions specifically as an oxygen carrying capacity and iron component of red blood cells. The ability of red blood cells to carry oxygen depends on the amount of chemical characteristics of the heamogolobin present (Authur and Gyton, 1976 and Coles, 1986).

Haemoglobin is an acid buffer and can bind with bicarbonate (HCO_3^-), acid-hydrogen ion portion (H^+) of ionized carbonic acid and nitric oxides. It buffers these acids for minimal alteration of blood pH (Cunningham, 2002). The deficiency of HB in the red blood cells decreases the blood oxygen-carrying capability leading to symptoms of anaemia (Kiran *et al*., 2012).

The specific function of HB is interfered by nitrate poisinig and toxins (Cunnigham, 2002). Ketamine has been reported to cause decrease in Hb concentration in sheep and goat (Nowrouzian *et al.,* 1981) and monkey (Ramasamy *et al.,* 2006).

2.5.3. RED BLOOD CELL (RBC) COUNTS

Red blood cells are primarily involved in the transport of oxygen and carbon dioxide and function exclusively within the vascular system. The whole mass of red blood cells and their precussor in the bone marrow is called erythron (Young and Heath, 2000). RBC in animals is

highly adapted for its function of oxygen and carbon dioxide transport. Its biconcave shape, more spherical in goat and its thickness provide large surface area for oxygen diffusion in internal and external surfaces of the cells. RBC is stored in the spleen. It has life span of 120 days and it is removed from the circulation by spleen and liver (Young and Heath, 2000). The RBC value is affected by animal breed, environment, age, sex, handling excitement and apprehension. The normal red blood cell counts in goats of different age, sex and under different management systems have been well documented (Daramola *et al*., 2005; Banni *et al.,* 2008; Olayemi *et al*., 2009; Opara *et al.*, 2010).

Ketamine anaesthesia produced decrease in total erythrocyte in sheep (Nowrouzian *et al.,* 1981). Also xylazine causes a decrease in total number of erythrocytes in goat (Kumar and Thurmon, 1979), in caprine and feline (Dehghani, *et al*., 1991).

2.5.4. TOTAL WHITE BLOOD CELL

White blood cells (WBC) otherwise called leucocytes constitute an important part of the defense and immune system of the body and as such act outside blood vessels in the tissue (Young and Heath, 2000). It is transported to various organs in the body for different functions (Cunningham, 2002). Most of them are transported to inflammatory sites for defensive functions (Athur and Gyton, 1976). Five types of leucocytes are normally present in circulation. They traditionally divided into granulated- neutrophil, eosinophils, basophils and mononuclear leucocytes-lymphocytes and monocytes (Athur and Gyton, 1976; Young and Heath, 2000). The circulating leucocytes in domestic animal numbered about 10,000/µl, while in goat, it is about 8×10^3 / µl. Xylazine has been reported cause a decrease in the total white blood cells count in camel (Mohammed *et al.,* 2001). Decrease in white blood cell has

also been recorded in epidural administration of ketamine in water buffalo (Singh *et al.,* 2006) and in vervet monkey (Wall *et al.,* 1995). However, Gweba *et al.,* (2009) reported a significant increase in the mean white blood cell count in sokoto red goat sedated with xylazine.

2.5.5. BLOOD GLUCOSE

The blood glucose level is the amount of glucose (sugar) present in the blood of human or animals. Glucose is the primary source of energy for the bodyõs cells and blood lipid (inform of fat and oils) are primarily a compact energy store. Glucose is transported from intestine or liver to body cells via blood stream and is made available for cell absorption via the hormone insulin, produced by the body primarily in the pancreas (Daly, 1998). The actual amount of glucose in the blood and body fluid is so small. The reason why this amount is so small is that, to maintain an influx of glucose into the cells. Enzymes modify glucose by adding phosphate or other group to it (USDA, 2009). Normally, in mammals, the body maintains the blood glucose level between about 3.6 and 5.8 mmol/ L or 64.8 and 104.4 mg/dL. The normal blood glucose level in human is about 4mmol/L or 72 mg/dL. However, this fluctuates throughout the day. Glucose levels are usually lowest in the morning before the first meal of the day term ñthe fast levelò, and rise after meal for an hour.

Blood glucose is stable in ruminant most of the time because instead of being directly absorbed from the gut, is mainly derived by gluconeogenesis (Eriksson and Teravainen, 1989). However, Basset (1974), observed in sheep a slow cycle between feeding. After a slight initial decrease, blood glucose level slowly rose and returned to pre-feeding level. In goat, Eriksson and Teravaainen, (1989) reported decreased in blood glucose concentration,

following morning feeding of hay after which pre-feeding level were restored within $2^1/_2$ hour. The normal blood glucose level in goat is between 64 ï 73 mg/dL (Okonkwo *et al.*, 2010), in cattle is between 56 ï 88 mg/dL (Clark, 2003), and in dogs is between 70 ï 180 mg/dL (Kim, 2006).

Blood glucose level outside the normal is a medical condition. A persistently high level is referred as a hyperglycaemia, while low level is referred as hypoglycaemia. Diabetes mellitus is characterized by persistent hyperglycaemia from any several causes and is the most prominent disease related to failure of blood sugar regulation. Drug can increase or decrease glucose levels. Xylazine has been reported to cause temporal hyperglycaemia in cattle, and goats (Fayed *et al*., 1989; Kumar and Thurmon, 1979).

2.5.6. CORTISOL

Cortisol is a steroid hormone or glucocorticoid. It is the major glucocrticoid produced and secreted by the adrenal gland (Bondy, 1980). It is produced in the zona fasciculate, the second of the three layers comprising the outer adrenal cortex. The release of cortisol is controlled by the hypothalamus, a part of the brain. Hypothalamus secretes the corticotropin releasing hormone (CRH) which stimulates the anterior lobe of pituitary gland and triggers the pituitary secretion of the Adrenocorticotropic hormone (ACTH). Adrenocorticotropic hormone carried by the blood to the adrenal cortex where it triggers glucocorticoid secretion and production of cortisol (Brook and Marshall, 2001). Cortisol is released in response to stress and low level of blood glucocorticoids, acting by negative feedback mechanism at the hypothalamic level and neural inputs from other brain centers.

Cortisol secretion increases in response to any stress in the body, whether physical (such as illness, trauma, surgery, temperature extremes and transportation) or psychological. This is because response to stress can increase secretion of ACTH by the pituitary gland (Hucklebridge *et al.,* 1999; Brook and Marshall, 2001). As the level of free cortisol in the blood rises, the release of ACTH is inhibited by the negative feedback effect. Conversely, if cortisol levels are subnormal, the negative feedback decreases, ACTH levels rise and adrenal cortex secrets cortisol until normal blood levels are restored.

Normally during the day, there is fluctuation of cortisol achieving the highest level in the morning and the lowest in the night. This phenomenon is known as diurnal variation or circadian rhythm of plasma cortisol. The circadian rhythm of plasma cortisol has been reported in many species including in growing pigs (De Jong *et al*., 2000), horses (Irvine and Alexander, 1994) and bull (Schmidt *et al.,* 2010). In sheep, cortisol has been reported to have no circadian rhythm (Basset, 1974). It was also reported that cortisol increased at night and was influenced by feeding in sheep (Fulkerson and Tang, 1979; Murayama *et al.,* 1986). In goat, it was reported that cortisol changes were associated with feeding and plasma cortisol peaked both after morning and afternoon feeding (Eriksson and Teravainen, 1989).

The primary function of cortisol are to increase blood sugar through gluconeogenesis, suppress the immune system and aid in fat, protein and carbohydrate metabolism and maintenance of muscle and myocardial integrity (Bondy, 1980). Other functions include reduction of bone formation, regulation of blood pressure and cardiovascular function and production of fetal lung surfactant between weeks 30-32 of pregnancy to promote maturation.

Cortisol measurement is a powerful tool for diagnosis of normal and abnormal state of adrenal function and evaluation of suspected abnormalities in glucocorticoid production. In human, it is used to detect such disease state as Cushingôs syndrome (hyper cortisolism), Addisonôs disease or secondary adrenal insufficiency (Hypocortisolism) (DRG diagnostic, 2006). However in animals, concentration of cortisol in blood is widely used as an indicator of stress response. Some published information on the effect of stress response to transportation in goat (Sanhouri *et al*., 1992) and restraint and isolation in sheep (Moolchandani *et al*., 2008) is available.

Stress response in animals is as results of the hormonal and metabolic changes that follow injury or trauma. The hormonal component of surgical stress response principally involves activation of the sympathetic nervous system and alteration in the level of pituitary, thyroid and adrenal hormones (Kostopanagiotou *et al.,* 2010). Cortisol may improve the stress response by energy mobilization and behavoural changes (Schmidt *et al*., 2010).

Among factors influencing the intra operative stress response are anaesthetic drugs (Kostopanagiotou *et al.,* 2010). The anaesthetic drugs either potentiate or inhibit the cortisol release. This results in increase or decrease of cortisol level in the blood. Decrease in cortisol levels has been documented both in anaesthsized and intensive care patients receiving propofol and in vitro findings suggest a direct inhibitory action of propofol on adrenal steroidogenesis (Lambert *et al*., 1985; Kenyon *et al.,* 1985 and Newman *et al*., 1987). Frangen *et al*. (1987), argue that propofol inhibits cortisol release to stimulatory insult. Pretreatment of goats with xylazine suppressed cortisol concentrations induced by transportion (Sanhouri, *et al.,* 1992). Also, pretreatment of rats with xylazine suppressed cortisol concentrations induced by immobilization and heat stress (Fayed *et al.,* 1994.).

2.5.7. Blood Urea Nitrogen

Urea a nitrogenous compound is a product of amino-acid break down in the liver. (White *et al*., 1973). It is synthesized most probably by the way of the ornithine arginine cycle. The enzyme arginine is found in large quantity in the liver (Baker *et al.,* 2007). In normal animal any excess urea in the circulation is passively filtered out of the plasma by the renal glomeruli in the kidney and passes out into the urine. If the kidney is not properly functioning, the urea cannot be removed from the plasma in sufficient amount resulting in an abnormal rise in plasma urea level, the determination of serum urea nitrogen is presently the most screening test for evaluation of kidney function base on the ability of kidney to remove the nitrogenous waste (urea) from the plasma (Kaplan, 1965). The test is not only valuable in the cases of renal failure but also in wide variety of conditions which are not primarily renal (Baker *et al.,* 2007). In human, the level of urea in the blood varies but ranges from 2.5 to 8.3 mmol/ L (15 ï 49.8mg/dL) for normal person on a full ordinary diet. Any urea level above 8.3 mmol/ L is suggestive of impaired renal function (Baker, *et al.,* 2007). The normal level of serum urea in WAD goat, it ranges from 1.9 -5.6 mmol/L (11.4 ï 34.5 mg/dL) for buck, 2.6 - 6.7mmol/L (15.6 ï 40.1 mg/dL) for doe, 1.4 ï 6.6 mmol/L (8.4 ï 39.6 mg/dL) for buck kid and 3.7 ï 6.25 (22.2 ï 37.5 mg/dL) for doe kid (Daramola *et al*., 2005; Opara *et al*., 2010).

Increase in serum urea nitrogen may be due to pre-renal, renal and post renal causes. Pre-renal causes may include cardiac decompensation, water depletion due to low intake or excessive loss, increase protein catabolism, dehydration, congestive heart failure, blocked urethra and ruptured bladder (Kwen *et al.,* 2000). Among the renal causes are acute glomerulonephritis, chronic nephritis, polycystic kidney, nephrosclerosis and tubular necrosis

(Kaplan, 1965). Post renal causes include all types of obstruction of the urinary tract, stone, enlarged postrate gland and tumor. Decrease could be due to low dietary protein, gross sepsis, anabolic hormonal effect, liver failure, portosystemic shunt (congenital or acquired) and inborn error of urea cycle metabolism (Chaney and Marbach, 1962).

2.5.8 CREATININE

Creatinine a non protein nitrogenous compound is a metabolite of creatine (Coliville and Smith, 1985). It is formed during metabolism that occurs in the muscle. The rate of production of creatinine remains constant provided the physical activity in the muscle remain reasonably constant. The quantity of creatinine formed each day depends on the total body content of creatine which in turn depends on the dietary intake, rate of synthesis of creatine and muscle mass (Coliville and Smith, 1985). Creatinine is released in the blood and removed from the plasma by glomerular filteration and excreted from urine unabsorbed. It is also excreted in feaces, vomitus and sweat and can be decomposed by bacteria (Veniamin, 1970). Creatinine excretion is constant in the absence of disease and less affected by change in diet (Cheesbrough, 2004). Disease of muscle, tissue wasting and extensive muscle destructions can lead to elevated level of serum creatinine and creatinurea (Mohammed and Ahmed, 2008). Ketamine and xylazine/ ketamine anaesthesia has been reported to increase the level of serum creatinine (Hirasawa and Yonezawa, 1975; Gonzalez Gil, 2003; Mavadati *et al*., 2011). Creatinine measurement is used extensively in the assessment of kidney function and the ability of kidney to remove creatinine from the plasma. Most useful endogenous creatinine is regarded as a maker in the diagnosis and treatment of kidney disease. The creatinine level in healthy goat ranges from 0.65 ± 0.04 to 0.9 ± 0.1 mg/dl (Opara *et al.*, 2010).

2.5.9. ALANINE AMINO-TRANSFERASE (ALT)

Serum alanine amino-transferase (ALT) is formerly known as glutamic pyruvic tranaminase (GTP). It is a hepatocellular enzyme that catalyses the reversible transamination of L-alanine and 2-oxoglutamate. It is an enzyme found in the highest amount in liver and typically used to detect liver injury (Pratt, 2010; Kiran *et al*., 2012). It is liver specific hepatocellular enzyme in dog, cat, primate and mice, but not of mature horses, sheep, pigs or cattle, as their livers do not contain significant level of ALT (Boyd, 1962; Nagode *et al*., 1966). The serum half-life of the ALT is from 2-5 hours (Cornelius and Kaneko, 1960). The increase in serum activity of ALT is directly related to the amount of damage that has occurred to the hepatocytes. If the damage is minimal, serum ALT activity will increase slightly but with moderate damage, there will be 3 - 8 fold increase. Severe liver damage will cause greater than 8 fold increases in serum activity (Coles, 1986). If the liver damage is acute and transitory, one would expect the serum level to return to normal fairly rapidly. If however, there is chronic or progressive liver disease, the serum level will remain high. If the value is reduced by half every one to two days, the prognosis is good (Hoe and Harvey, 1961). Alanine amino-transferase concentration may increase in the serum secondary to enzyme induction by drugs such as glucocorticoids and anticonvulsants. Certain chemical agents are known to increase the basal intracellular concentration of this enzyme (Badylak and Vanleet, 1981). Increase in plasma ALT concentration has been observed after xylazine/ketamine administration in rabbits (Wyatt *et al*., 1989; Gonzalez Gil, 2003; Mavadati *et al*., 2011)

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1. PREPARATION OF ANIMAL HOUSE

Animal house was prepared in anticipation of the purchase of the animal. The house was cleaned thoroughly and disinfected with household bleach sodium hypochlorite 3.5% w/v (Hypo hygiene product Ltd. Km 5, Itokin Road Ikorodu, Lagos Nigeria) as disinfectant and fumigated with OPS DDVP ((80% w/w dichlorvos) (Obikason pharmacy and stores Ltd, 17 Aniekwe street Fegge Onitsha, Nigeria) to safeguard against microbial agent and arthropod pests. Grasses around the animal house were cleared, removed, and burnt. Pif paff insecticide powder was spread around the surrounding to keep away soldier ants and rodents. The pen was left for three weeks before it was used for housing the experimental animals.

3.2 ANIMALS AND THEIR MANAGEMENT

Apparently healthy male goats aged between 7 and 9 months were used for the study. They were purchased from the surrounding villages around University of Nigeria Nsukka (Eke Ozzi in Enugu Ezike, Igbo Eze North LGA, Nkwo Ibagwa in Ibagwa, Igbo Eze south LGA, and Afor Opi in Opi, Nsukka LGA). The animals were thoroughly examined for any signs and symptoms of illness. Blood samples were collected and examined for the presence of possible blood parasites. Feacal samples were also collected from each animal and examined for helminths ova. The animals were dewormed with levamisol® injection (Hebei Huarun Pharmacy ltd China). The animals were also treated with antibiotic, oxytetracycline (Kepro, Holland) 20% short acting for 3 consecutive days at 1ml per 10kg intramuscularly as a prophylactic against bacterial infections. The animals were vaccinated on fourth day against

Peste des Petits ruminatum (PPR) virus using PPR vaccine from Vom Jos Plateau State, Nigeria.

Four animals were kept per a pen and fed with freshly cut grasses. The animals were also allowed to graze in the field under controlled tittering. Water was also served. Clinical examination and physiological parameters such as heart rate, rectal temperature, and respiratory rate were taken regularly throughout the period of acclimatization which lasted for 21days.

3.3. ANAESTHETIC DRUGS.

Drugs used in the study were Propofol 10mg/ml injection- 20ml vial (PofolÊ Popular infusion ltd Tongi Bangladesh), xylazine (Kepro Holland) and ketamine (Laborate pharmaceutical, India).

3.4. PILOT STUDY (Establishment of Propofol Dosage in WAD goats).

3.4.1 Animals

Nine goats were used in the study. Goats were randomly divided into three groups of three goats each**.**

3.4.2 Administration of Propofol

Goats were given three different doses of propofol using 5ml syringe and 23 gauge needle through the jugular vein.

In group 1, Propofol was administered to the goats at a dose of 2.5mg / kg body weight.

In group 2, Propofol was administered to the goats at a dose of 5mg / kg body weight.

In group 3, Propofol was administered to the goats at a dose of 7.25mg / kg body weight.

3.5. EXPERIMENTAL PROCEDURE

3.5.1 Animals

The goats were randomly divided into two protocols of sixteen goats each.

Sixteen healthy male goats were randomly assigned into four groups of four goats each in both protocols.

3.5.2. Administration of the drug combinations

Each drug combination was administered intravenously (IV) through the jugular vein. The drugs were combined in the following order in each group;

(1) Xylazine (0.05mg/kg body weight) and ketamine (5mg / kg body weight).

(2). Xylazine (0.05mg/kg body weight) and propofol (5mg / kg body weight).

(3) Ketamine (5mg/kg body weight) and propofol (5mg / kg body weight).

(4) Xylazine (0.05mg/kg body weight) and ketamine (5mg / kg body weight) and propofol (5mg / kg body weight).

3.5.3 Protocol I

Experiment one was a single dose injection procedure. No maintenance dose was given.

In group I; animals were given xylazine (0.05mg / kg body weight) with tuberculin syringe and needle. This was followed immediately with ketamine (5mg / kg body weight) slowly through the jugular vein using 5ml syringe and 23 gauge needle.

Group II animals were given xylazine (0.05mg / kg body weight) followed by propofol® (5mg / kg body weight) using 23 gauge needle and 5mls syringe.

Animals in group III (3) were administered ketamine (5mg / kg body) followed by propofol (5mg/kg body weight) using 23 gauge needle 5 ml syringes.

Animals in group IV were administered xylazine (0.05mg / kg body weight) with tuberculin syringe, followed by ketamine (2.5mg / kg body weight) and propofol (2.5mg / kg body weight) with 23 gauge and 5ml syringe through the jugular vein.

3.5.4. Protocol II.

In this experiment**,** an extended dose procedure which involved both induction and maintenance doses.

In the group A, animals were administered xylazine (0.05mg / kg body weight followed by ketamine 5mg / kg body weight and maintained with ketamine (5mg / kg body) body weight.

Also, in group B, animal were given xylazine 0.05mg / kg body weight followed immediately propofol (5mg / kg body weight) and maintained with repeated injection of propofol 5mg / kg body weight.

Animals in group C were given ketamine 5mg / kg body weight followed by propofol 5mg / kg body and maintained by repeated injection of propofol 5mg / kg body weight.

While animals in group D were administered xylazine (0.05 mg / kg body weight), ketamine (2.5mg / kg body weight) and propofol (2.5mg / kg body weight) simultaneously and maintained with propofol 5mg / kg body weight.

3.6. PARAMETERS MONITORED

The following physiological parameters were monitored; heart rate, respiratory rate and rectal temperature.

3.6.1. Heart Rate (beat/minute)

Heart rate was determined with the aid of stethoscope. The goat was placed on the table and made to lie down on its right side in a complete relaxed manner. Stethoscope was placed over the chest perpendicular to the apex of the heart and the heart beats were listened to through the ear piece. Each heart beat counted while looking at already set stop watch to time the count. The heart beats were counted for one full minute and the result recorded.

3.6.2. Respiratory Rate

This was done by visual observation and counting of thoraco-abdominal movement. Expiration and inspiration movement were counted as one cycle. This was done before induction of the anaesthesia (t = 0) and subsequently at every ten minute interval post induction.

3.6.3 Rectal Temperature (°C)

This was measured with mercury-in-glass clinical thermometer. The clinical thermometer was shaken to return mercury back into its bulb. The thermometer was inserted gently into the rectum in a rotatory manner ensuring that the bulb was in touch with the mucus membrane of the rectum (Nwosu, 2002). Then the thermometer was brought out after two (2) minute and the mercury level was read and recorded. This was done before the induction

time (t 0) of anaesthesia and subsequently at every ten (10) min interval following the induction till the recovery of the animal.

3.7. DETERMINATION OF INDICES OF ANAESTHESIA

A modified method of determination of quality of anaesthesia according to Adetunji *et al*., (2002) was used.

3.7.1. Onset of Flank Analgesia

This was done by recording the time (in minute) of the initial injections of the drugs (t0) and the time of disappearance of flank twitch reflex (tz) the difference between the former and the later gave the time of the onset of flank analgesia.

3.7.2. Duration of Flank Analgesia

This was done by noting the time of disappearance of flank twitch reflex (TD) following the intravenous injection and the time of reappearance of flank twitch. Then the difference between the time of disappearance (TD) and the time of reappearance (TA) of flank twitch reflex gave the duration of flank analgesia time (DA) DA = TA - TD

3.7.3. Duration of Recumbency

This was measured by recording the time when anaesthesia induced recumbency in the animal (goat) and then the time when the goat was able to maintain standing positionown its own following recovery. The difference between the two was taken as the duration of recumbency.

3.7.4. Standing Time

Standing time was calculated by determining the difference between the time when the goat assumed sternal posture as sign of recovery and when the goat finally stood on its own unassisted.

3.7.5 Quality of Induction and Recovery

Some criteria were used to evaluate the quality of induction and recovery (Lin *et al.,* 1997, Carrol *et al*., 1998, and Prassinos *et al.,* 2005). Hence, ñgoodò, ñfairò, or ñpoorò were assigned to the experimental goats in each group according to the criteria depending on the observed signs.

3.7.5.1 Induction quality scoring

Good: smooth induction, rapidly assumes recumbency, no signs of excitement.

Fair: slightly prolonged induction, mild excitation, presence of swallowing reflex

Poor: obvious excitement, jumps or attempt to stand after recumbency, full presence of swallowing reflex.

3.7.5.2 Recovery quality scoring

Good: smooth, easy transition to alertness, a resume sternal position, stands in a reasonable amount of time and is able to walk with minimal ataxia.

Fair: transient excitement or whole body movement, some struggle, hyper-responsiveness that disappears once the goat stands unassisted but with moderate ataxia.

Poor: stereotype behaviour, e.g circling, premature, attempts to stand, prolong struggling.

3.7.6. SIDE EFFECTS

Side effects were observed by watching closely to the goats following induction of the anaesthesia.

3.8. HAEMATOLOGY AND BIOCHEMISTRY

3.8.1. Blood Sample Collection

Blood samples were collected before anaesthesia at time (t 0), at 30 min following induction, 120 and 1440 minutes post recovery. About 3.5ml of blood were collected with 23 gauge needle and 5ml syringe from each goat from jugular vein. About 2mls of blood was preserved into ethylenediamine tetra acetic acid (EDTA) bottle for the determination of packed cell volume, haemoglobin concentration, red blood cell count, and total white blood cell count. While about 1.5mls of blood was placed into non EDTA test tube and allowed to clot and serum harvested for biochemistry.

3.8.2. Packed Cell Volume

Microhaematocrit centrifuge method (Coles, 1986) was used for the determination of packed cell volume. The standard capillary tubes (17 mm long and 1.2 mm wide) were dipped into the EDTA bottle with one end and the tubes were filled ¾ with blood by allowing blood to move into the capillary by capillary action. The filled ends of the tubes were sealed with plastacin and the capillary body wiped with tissue paper. The tubes were securely placed in the spaces inside the micro haemathocrit bench centrifuge (Hawkley, England) with the open pointing at the centre and the sealed end facing outward. The tubes were subsequently

centrifuged at 3000 rpm for five (5) minutes. The PCV of the goats were the read using the standard microhaematocrit reader (Hawkely, England). The results were expressed in percentages.

3.8.3. Haemoglobin Concentration

Haemoglobin concentration was measured using the cyanomethoglobin method to determine the haemoglobin level in the experimental goat (Cole, 1986). The method is based on the dilution of potassium ferricyanide and potassium cyanide to yield the stable heamoglobin derivative cynamethaemoglobin. The potassium ferricyanide converts the haemoglobin to methaemoglobin by the action of potassium cyanide. The absorbance of this solution is read in a colorimeter at a wave-length of 540nm

Clean empty labeled test tubes were arranged in the rack. Five (5) mls of Drabkin solution was pipette into each test tube bottle except in the blank. 20µl of the test blood from each sample was added to the corresponding labeled test tube containing the drabkin solution. The contents were thoroughly mixed by gently shaking and rocking. The mixture was allowed to stand for 5 minutes after which it was transferred into cuvette and placed in electronic controlled colorimter for reading. The colorimeter was first zero using the blank and the absorbance of the standard determined. Subsequently, the absorbances of the samples were recorded. The readings were done at optical density of 540nm. The actual values were then obtained using the Haemoglobin reference table (Boerhringer,Gmbh Diagnostica).

3.8.4. Red Blood Cell (RBC)

Cleaned dried empty test tubes well labelled were arranged in the rack in accordance with test samples. RBC diluting fluid was used to dilute out the blood. 4mls of the diluting fluid

was dispensed into each empty test tube accordingly, using pipette. Twenty micro liters (20µl) of whole blood from each sample was diluted by dispensing it into an appropriate test tube containing the diluents. The Neubaeur counting chamber was filled with small quantity of fluid which was drawn from each sample using capillary tube. The chamber was covered with slide cover and the cells allowed some time to settle. The chamber was placed on stage of light microscope and the cells were counted using 4mm objective and X10-eye piece. The number of red blood cell counted for each sample was multiplied by 10,000 to obtain the red cell count per micro liter of blood (Dacie and Lewis, 1975).

3.8.5 Total White Blood Cell counts

White blood cell diluting fluid was used and 380µl of the dilute was pipette into each of the labelled empty test tube bottles. Then 20µl of the test blood sample was dispensed into the corresponding test tubes containing the white blood cell diluting fluid.

The contents of the tubes were mixed gently to lyz the red blood cell there after a drop of the diluted blood was put on a Neubaeur chamber, covered with cover slip. The preparation was clamped in the microscope and viewed with x10 objective. The total white bloods in the four large cover squares of the Neubaeur were counted. The number of cells counted for each blood sample was multiplied by 50 to obtain the total white blood cell counts per micro liter of blood (Dacie and Lewis, 1975).

3.8.6 Blood Glucose Level

The blood glucose sugar levels of the goats were determined in the morning before the administration of the anaesthetics (pre-anaesthetic value), 30 minutes after induction of the anaesthesia, 120 and 1440 minutes respectively post recovery. The blood glucose

concentrations were measured immediately after blood sample was obtained through jugular vein, using a hand- held glucose meter (Accu-Chek, Roche Diagnostics, Auckland, New Zealand). It was done by dropping blood sample obtained on a glucose test strips inserted in a Glucometer (ACCU-CHEK active serial no GN: 10023338) which instantly displayed the sugar level on the screen. The values obtained were expressed in mg/dl of the blood.

3.8.7 Serum Cortisol Level

Cortisol level in the experimental goat was carried out using cortical Elisa kit with serial number E1A -1887 (DRG Diagnostic, DRG instrument GMBH. Germany frauenber-slra be 18, D-35039 Murbarg). It was done according to the companyôs specifications (DRG Diagnotic userôs manual, 2006) The instruments used were microtiter plate, calibrated reader (450±10nm); calibrated variable precision micropipettes, absorbent paper and aqua dest, microtiter wells (96)

3.8.7.1 Procedure for Cortisol ELISA Assay

1. The required numbers of micro titer wells were secured in the holder

2. 20µl of each standard, control and samples was dispensed into appropriate wells with new disposable tips.

3. 200µl of Enzyme conjugate was dispensed into each well. They were thoroughly mixed for 10 seconds and incubated for 60 minutes at room temperature.

4. The contents were briskly shaken out of the well.

5. The wells were rinsed three times with diluted wash solution (400µl per well).

6. The wells were sharply strike on absorbent paper to remove residual droplets 100µl of

substrate solution was added to each well and inhabited for 15 minutes at room temperature.

7. The enzymatic reaction was stopped by adding 100µl of stop solution to each well.

8. The plates was read with Automatic electronic micro titer plate reader with optic density at 450±10nm within 10 minute after adding the stop solution and the results automatically calculated using 4pl out (4 parameter logistics, curve fit) and printed.

3.8.8 Serum Urea Nitrogen Determination

Urease Berthelot method (Fawcette and Scott, 1960) for quantitative in vitro determination of urea in serum, plasma and urine using Randox urea colorimetric kit (Randox labiratores ltd. Ardmore, Diamond Road, crumlin, Co. Atrim united kingdom) was used. The principle is that urea in serum is hydrolyzed to ammonia in the presence of urease. The ammonia is then measured photometircally by Berthelotôs reaction. The urea colorimetric kit contains three reagent; R1, R2, R3.

3.8.8.1 Procedure for the determination of serum urea

1. Three test tubes were labeled Blank, standard, and test sample separately
2. Into each of the three test tubes, 0.1ml of R1 was added.
3. Into test tube labeled bank, 10ml of distilled, water was added; into the test labeled standard, 10ml of ñstandardò was added, and into the test sample, 10ml of serum sample was added.
4. The contents of each was them mixed carefully and incubated at 37^0c for 10 minute
5. To each of the tubes, 2.5ml of Reagent 2 was added

6. To each of the tubes, 2.5 ml of Reagent 3 was added.
7. The contents were them mixed immediately and incubated at 37^{o}c for 15 minutes.
8. The blank was used to zero the spectrophotometer and thereafter the optical density of the standard and the test sample were read off in the spectrophotometer at the wave length of 540nm

Urea concentration in the serum sample was calculated by dividing the absorbance of serum sample (test) by the absorbance of the standard then multiplied by the concentration of the standard (80mg/dl) thus:

$$\frac{\text{Absorbance of the test sample x concentration of the standard (80mg/dl).}}{\text{Absorbance of standard}}$$

3.8.9 Serum Creatinine Level Determination

Determination of serum creatinine was based on the modified Jaffe method (Fossati, *et al.,* 1983) for in vitro determination of creatinine in serum, plasma or urine using Randox creatinine colormetric method with depolarization (Randox laboratories Ltd. Ardmore, Diamond Road Crumlin, Co. Antrim, United kingdom).The principle of the test is that creatinine in alkaline solution reacts with picrate to form a coloured complex.

3.8.9.1 Procedure for determination of serum creatinine

1. Into 1.0ml of serum in a test tube, 1.ml of trichloroacetic acid was added. The content was mixed well with a glass rod and thereafter centrifuged at 2500 rpm for 10 minutes. The supernatant was then separated off and used subsequently as the test sample. This procedure was done to deproteinize the sample.

2. Equal volumes (5ml each) of picric acid and sodium hydroxide (NaOH) were mixed in a test tube (Reagent mixture). 1.0 ml of this mixture was pipette into each of the three test tubes labelled test, standard, and blank

3. 0.5ml of Trichloroacetic acid was each added into the test tubes labelled ñBlankò and the ñstandardò.

4. Into the test tube labelled ótestôô, 1.0m1 of the treated serum supernatant from 1 above was added. In the test tube labeled ñstandardò, 0.5 ml of standard was added and into the test tube labeled ñBlankò 0.5ml of distilled water was added.

5. The mixture in the three tubes in (4) above were thoroughly mixed and left to stand for 20 minutes at 25^0c. Thereafter, the blank was used to zero the spectrophotometer and then the absorbance of the test sample and the standard were read at the wave length of 500-550nm.

6. The concentration of the serum creatinine (result) is calculated by the formula. Absorbance of the test samples divided by the absorbance of the standard, multiplied by the concentration of the standard.

$$\frac{\text{Absorbance of the test sample X concentration of Absorbance of standard (2mg/dl)}}{\text{Absorbance of standard}}$$

3.8.10 Serum Alanine Aminotransferase (SALT)

Serum alanine aminotransferase was determined using standard colorimetric method of Reitman and frankel, (1957). This is an in vitro method of determining SALT in serum using Randox glutamic-pyruvic Transaminase test kit. (Randox Lab. ltd. Ardmore Diamond Road,

Crumlin Co. Atrim, united kingdom,). The principle is that glutamicï Oxaloacetic Transaminase is measured by monitoring the concentration of Oxaloacetate hydrozone formed with 2, 4- dinitrophenylhydrazine. The kit contains two solutions; solution 1(buffer) and solution 2 (2-4-clinitrophenylhydrazine)

3.8.10.1. Procedure for Serum Alanine Aminotransferase Determination

1. Two test tubes were labeled test sample and blank
2. Into the test tube labelled test, 0.1ml of the serum was added while test tube labelled blank, 0.1ml distilled water was added.
3. 0.5 ml of solution 1 was added into each of the tubes above
4. The contents were mixed and incubated at 37 °C for 30 minutes.
5. Into each of the tubes, 0.5 ml of solution 2 was added.
6. The content were mixed and allowed to stand for 5 minute at room temperature after which the absorbance of the sample was read against the reagent blank at the wave length of 540 nm. The activity of ALT in the test serum was obtained by matching the optical density of the serum sample with the reference table 1:5 dilution reading above 0.50 iu/l and the result multiply by 5.

3.9.0 DATA ANALYSIS

Data were expressed as mean ± standard error of four goats in each four groups. The means of physiological parameter were compared using analysis of variance (ANOVA). The means of hematological data, biochemical analysis and anesthetic indices were also compared. A probability value less than or equal to 0.05 (pÒ0.05) was considered significant in all cases.

CHAPTER FOUR

4.0 RESULTS

4.1.0 PILOT STUDY

4.1.1 PHYSIOLOGICAL VARIABLES

4.1.1.1 Heart Rate

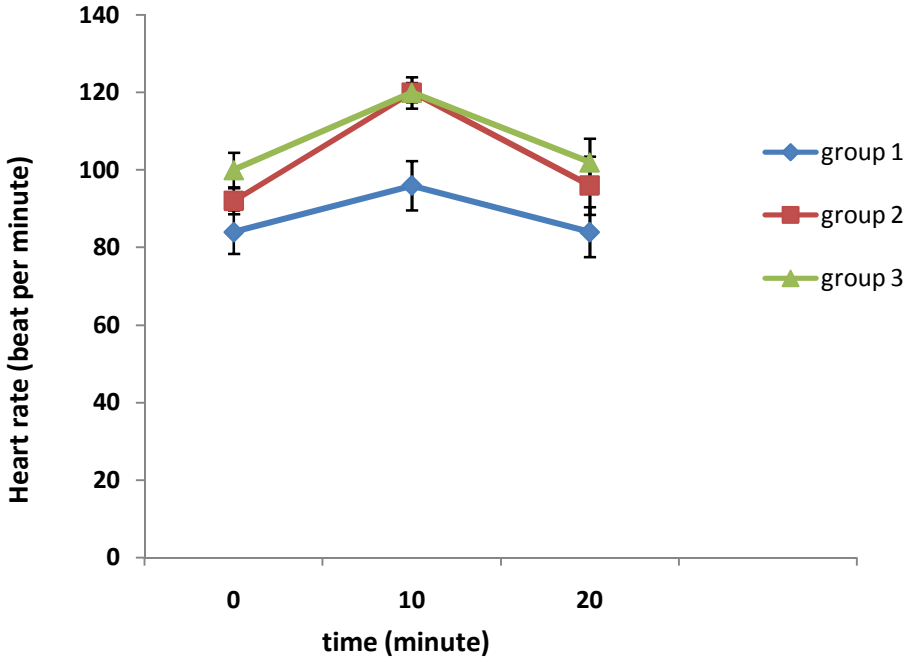
There was significant increased ($p<0.05$) in heart rate of goats in the three groups at 10 min following the administration of different dose of propofol (figure 1).

4.1.1.2 Respiratory Rate

There was significant decreased ($p < 0.05$) in the respiratory rate of the goat in groups 1 and 2, at 10 min, while in group 3 there was no significant change ($p > 0.05$) following the administration of different dose of propofol (figure 3).

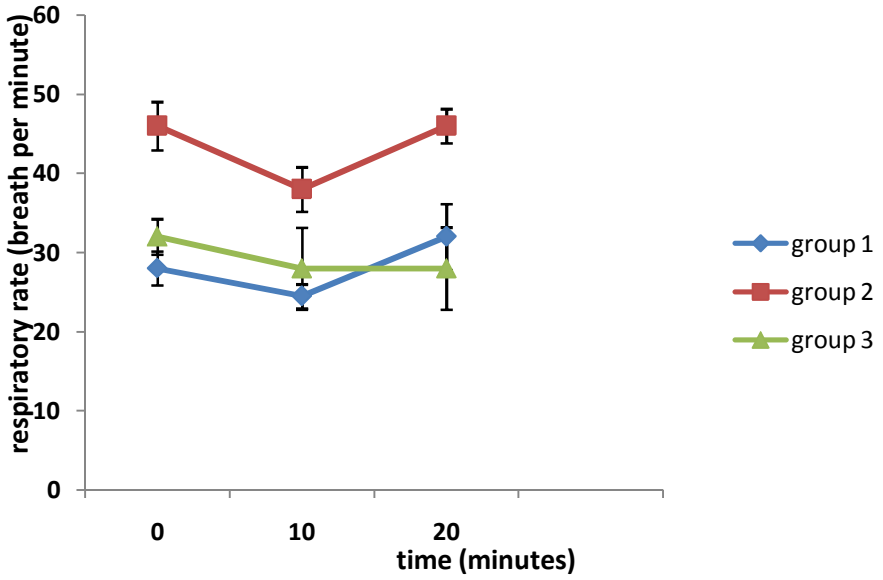
4.1.1.3 Rectal Temperature

There was no significant decreased ($p > 0.05$) in the rectal temperature in all groups following the administration of different dose of propofol (figure 3).



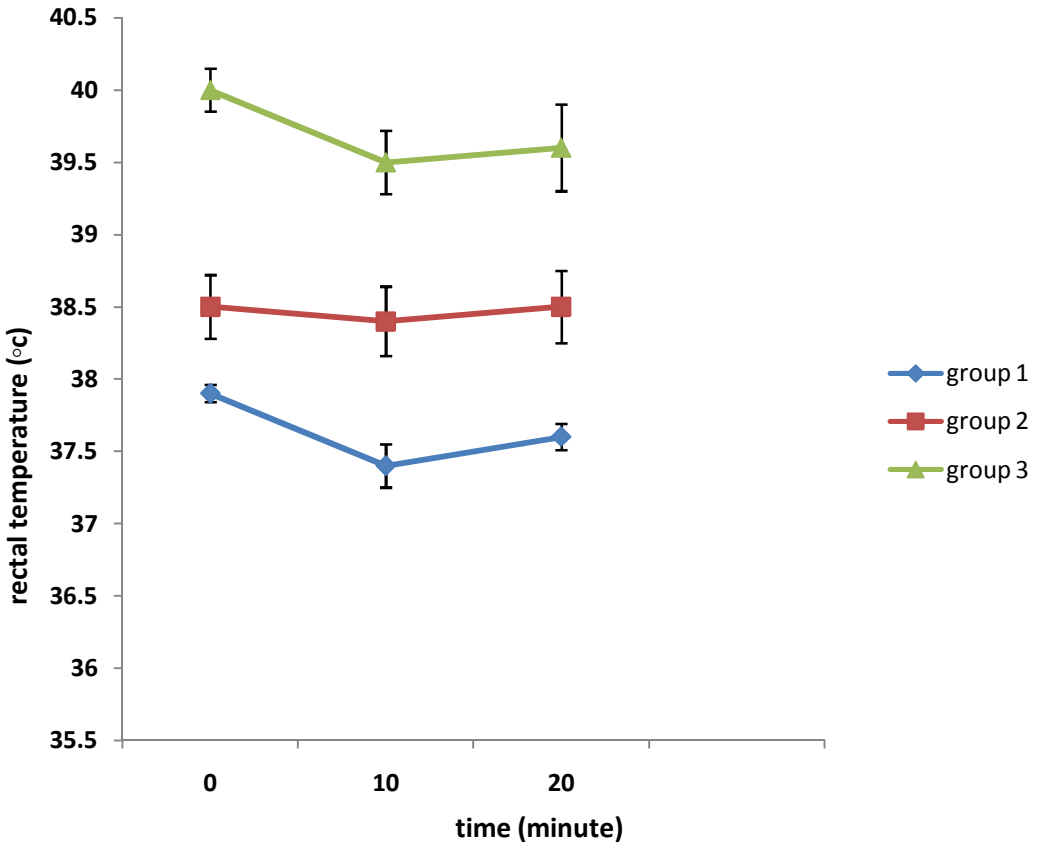
Group I ï propofol 2.5mg/kg body weight
Group II- propofol 5mg/kg body weight
Group III- propofol 7mg/kg body weight

Figure 1: Mean heart rate following intravenous administration of different dose of Propofol.



Group I ï propofol 2.5mg/kg body weight
Group II- propofol 5mg/kg body weight
Group III- propofol 7mg/kg body weight

Figure 2: Mean respiratory rate following intravenous administration of different dose of Propofol.



Group I ï propofol 2.5mg/kg body weight
Group II- propofol 5mg/kg body weight
Group III- propofol 7mg/kg body weight

Figure 3: Mean rectal temperature following intravenous administration of different dose of Propofol.

4.1.2 Anaesthetic indices

4.1.2.1 Onset of Analgesia

The time for onset of anaesthesia was 1.00 ± 0.1, 1.00 ± 0.10 and 0.56 ± 0.30 min for groups 1, 2 and 3 respectively (figure 4)**.**

4.1.2.2 Surgical Anaesthetic Time

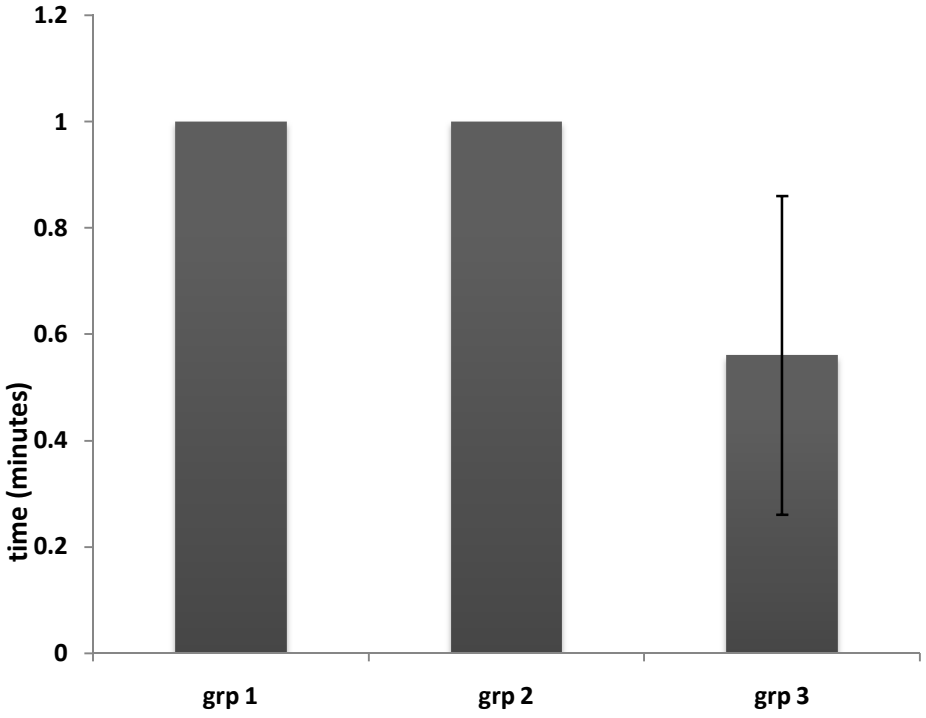
The surgical anaesthetic time was 3.01 ± 1.21, 9.02 ± 2.00 and 16.20 ± 2.2 min for groups 1, 2 and 3 respectively. It was significantly ($p < 0.05$) longer in group 3 when compared to other groups. Anaesthesia was good in group 2 (5mg/kg) and group 3 (7.5 mg/kg) (figure 5).

4.1.2.3 Recumbent Time

Duration of recumbency was 7 ± 2.00, 15 ± 1.00 and 21 ± 2.40 min for groups 1, 2 and 3 respectively. It is significantly ($p < 0.05$) longer in group 3 when compared to other groups (figure 6).

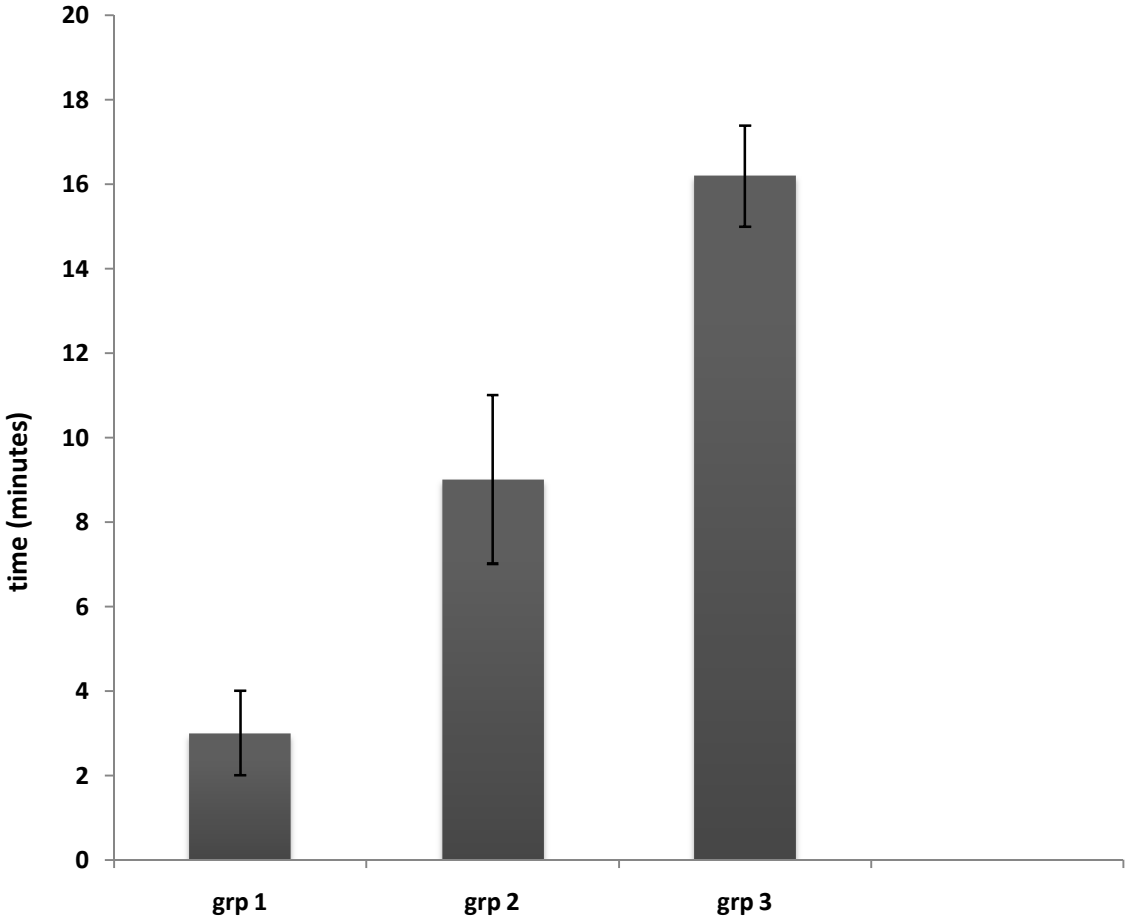
4.1.2.4 Standing Time

Goats in all the groups stood up at 1. 00 min after assumed sternal recumbency during recovery (figure 7).



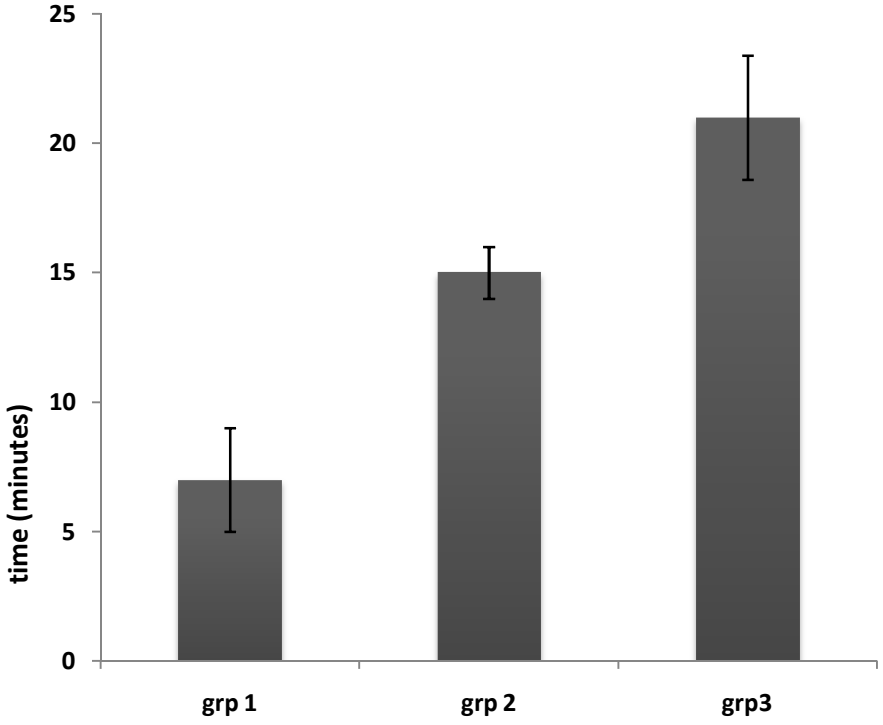
Group I ï propofol 2.5mg/kg body weight
Group II- propofol 5mg/kg body weight
Group III- propofol 7mg/kg body weight

Figure 4: Mean onset of analgesic time following intravenous administration of different dose of Propofol.



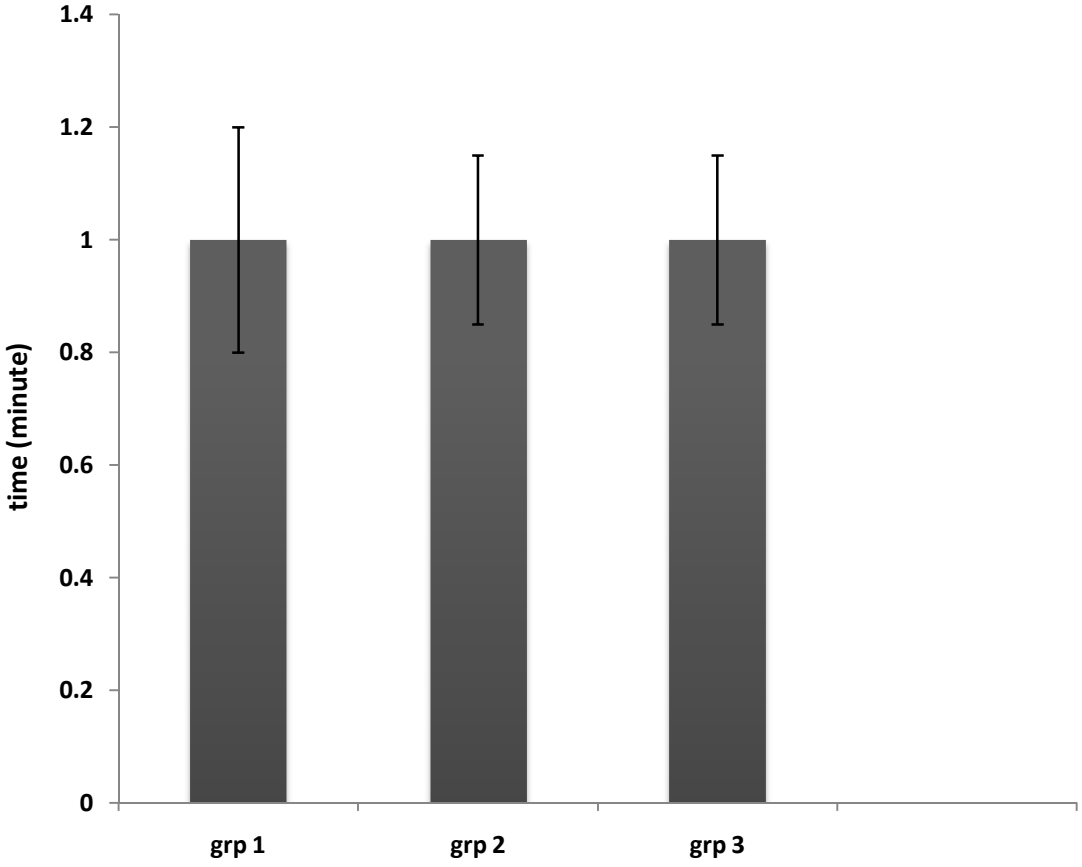
Group I ï propofol 2.5mg/kg body weight
Group II- propofol 5mg/kg body weight
Group III- propofol 7mg/kg body weight

Figure 5: Mean surgical anaesthetic time following intravenous administration of different dose of Propofol.



Group I ï propofol 2.5mg/kg body weight
Group II- propofol 5mg/kg body weight
Group III- propofol 7mg/kg body weight

Figure 6: Mean recumbent time following intravenous administration of different doses of Propofol.



Group I ï propofol 2.5mg/kg body weight
Group II- propofol 5mg/kg body weight
Group III- propofol 7mg/kg body weight

Figure 7: Mean standing time following intravenous administration of different dose of propofol.

4.2 PROTOCOL I:

4.2.1. PHYSIOLOGICAL VARIABLES

4.2.1.1 Heart Rate

In group I, there was significant ($p<0.05$) increase in the heart rate at 10 min post induction which later significantly ($p<0.05$) decreased between 30 to 40 minutes post induction. The heart rate significantly ($p<0.05$) decreased at 10 to 40 minutes and at 10 to 20 minutes in groups II and IV respectively. It returned to the level of pre-induction value at 30 minute post induction in group IV. However, there was significant increased in heart rate in group I at 10 to 40 minutes when compared to other groups (Figure 8).

4.2.1.2 Respiratory Rate

The respiratory rate decreased significantly ($p < 0.05$) at 10 and 20 minutes post induction in groups I and II respectively till 40 minutes post induction and between 20 to 30 minutes post induction in group IV and returned to pre-induction level at 40 minutes post induction when compared to the pre-induction values. There was no significant ($p > 0.05$) change between pre-induction and post induction respiratory rate in group III. The mean respiratory rate is significantly ($p< 0.05$) low in group I between 10 to 20 minutes post induction when compared to other groups. However, at 30 minute post induction, there were no significant ($p > 0.05$) variation in the values of groups I, II, IV though they are significantly ($p < 0.05$) low compared to group III (Figure 9).

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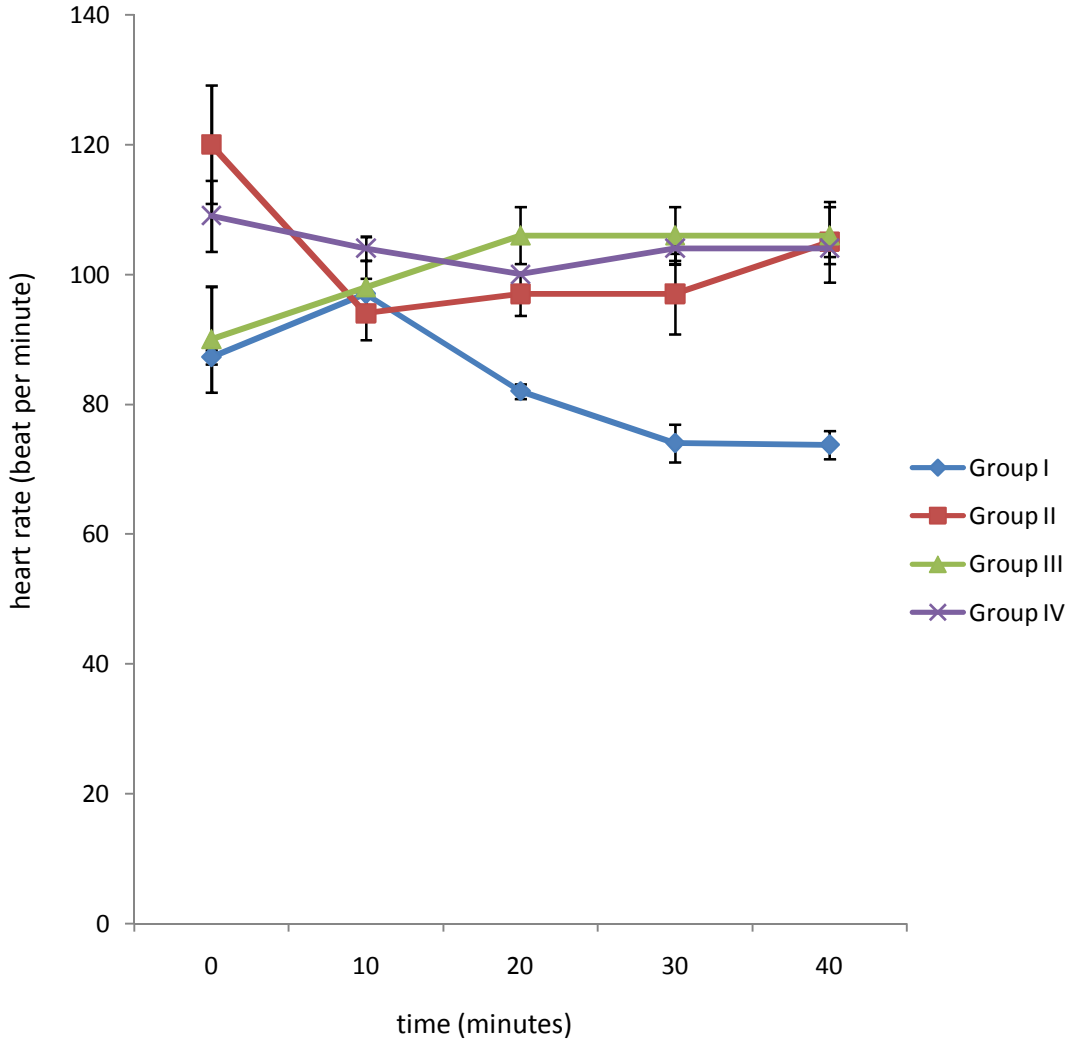
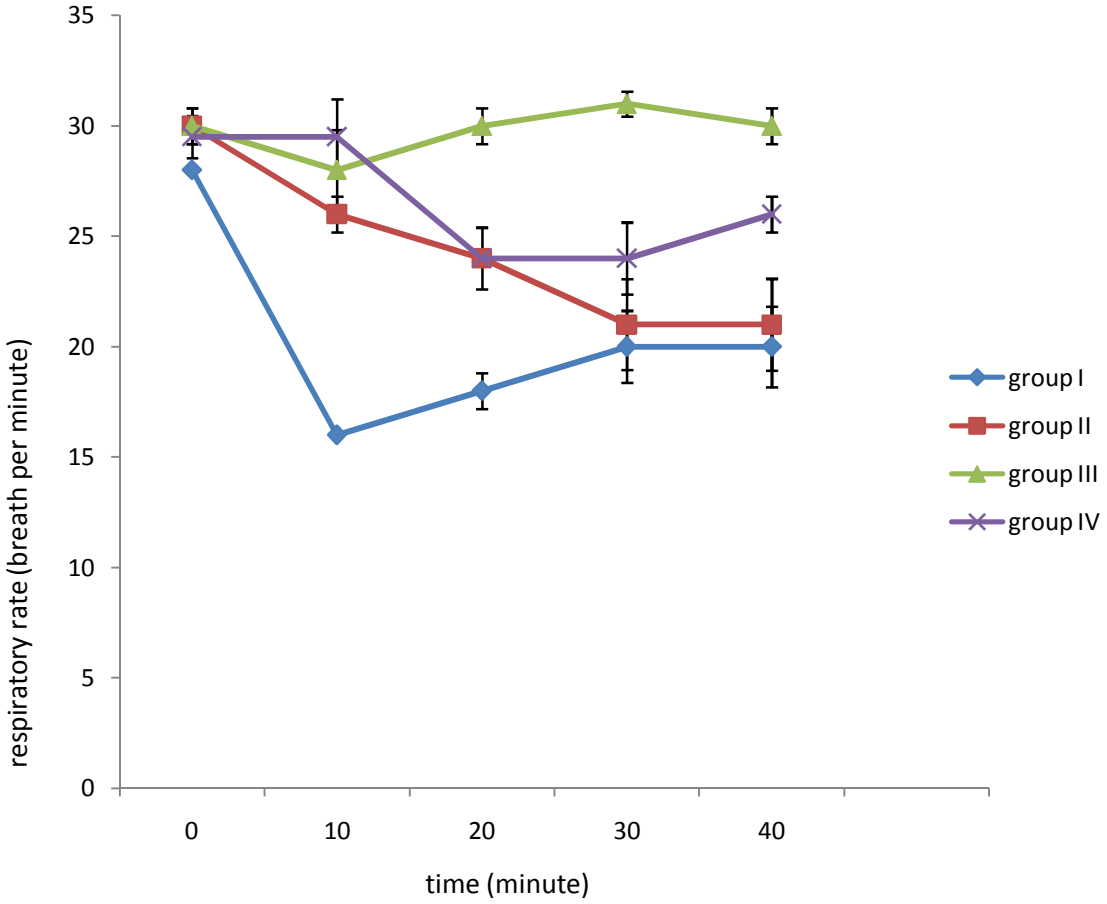


Group I - xylazine/ketamine
Group II - xylazine/propofol
Group III- ketamine/ propofol
Group IV - xylazine/ ketamine/ propofol

Figure 8: Mean heart rate following intravenous administration of anaesthetic drug combinations.

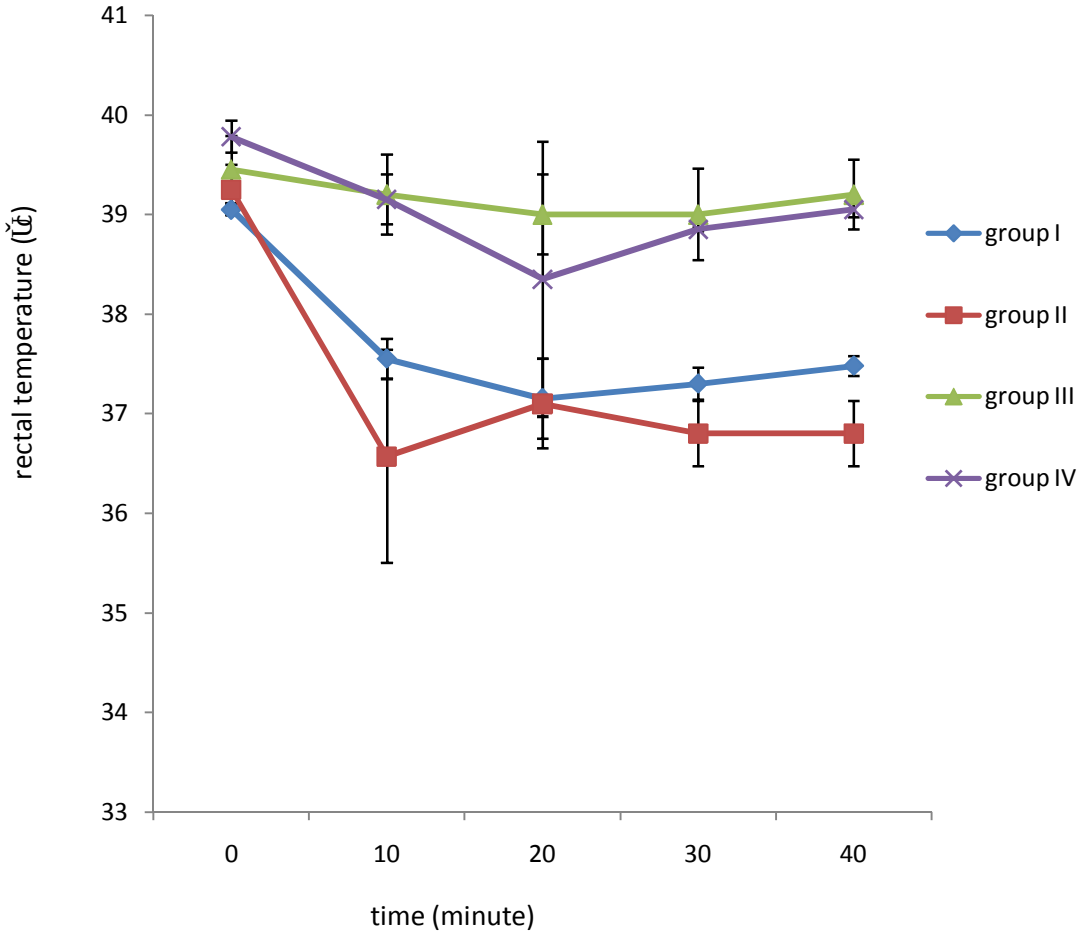


Group I - xylazine/ketamine
Group II - xylazine/propofol
Group III- ketamine/ propofol
Group IV- xylazine/ ketamine/ propofol

Figure 9: Mean respiratory rate following intravenous administration of anaesthetic drug combinations

4.2.1.3. Rectal Temperature ($^{\circ}$C)

The rectal temperature of the goats dropped significantly ($p < 0.05$) at interval of 10 to 40 in groups I and II post induction when compared to pre-induction value. However, the rectal temperature dropped significantly ($p < 0.05$) in group II when compared to other groups (Figure 10).



Group I - xylazine/ketamine
Group II- xylazine/propofol
Group III- ketamine/ propofol
Group IV - xylazine/ ketamine/ propofol

Figure 10: Mean rectal temperature following intravenous administration of the anaesthetic drug combinations

4.2.2 ANAESTHETIC INDICES

4.2.2.1 Onset of Analgesia

Following induction of anaesthesia, analgesia was observed at 4.00 ± 0.41, 2.02 ± 0.47, 2.01 ± 0.02 and 1.00 ± 0.00 in group I, II, III, and IV respectively. Flank and pedal reflexes took more time to disappear in group I and less time in group IV when compared to other groups. There was no significant variation between onset of analgesia between groups II and III (figure 11).

4.2.2.2 Surgical Anaesthetic Time

Duration of surgical anaesthesia was 24.05 ± 4.29 minutes in group I, 21.00 ± 2.27, 12.25 ± 1.25, and 26.05 ± 2.25, for group II, III, and IV respectively. Duration of surgical anaesthesia was significantly ($p<0.05$) low in group III when compared with other groups (Figure 12).

4.2.2.3 Recumbent Time

Duration of recumbency recorded was significantly high in group I, followed by groups IV, II and III respectively. (Figure 13)

4.2.2.4 Standing Time:

Goats in groups I, II and IV stood up following sternal recumbency within the same range of time. There was no significant ($p > 0.05$) variation among the groups. However, standing time was significantly ($p < 0.05$) high in group III when compared to other groups (figure 14).

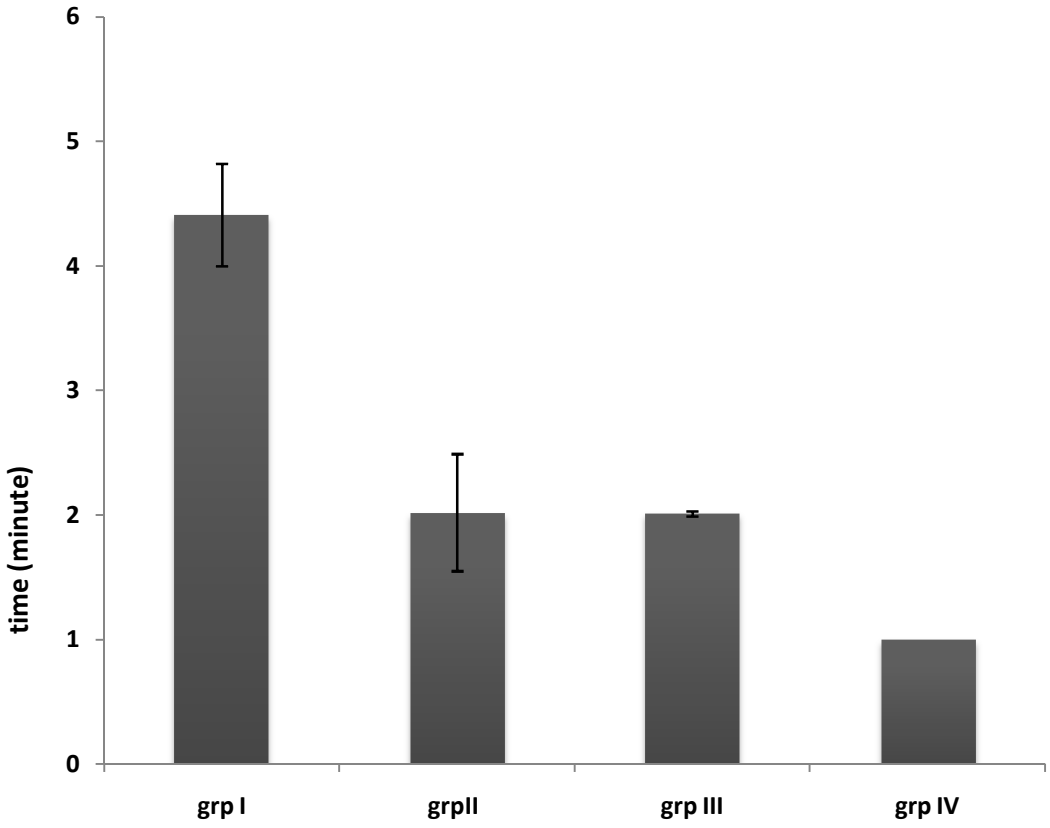


Figure 11: Mean onset of analgesic time following intravenous administration of the anaesthetic drug combinations.

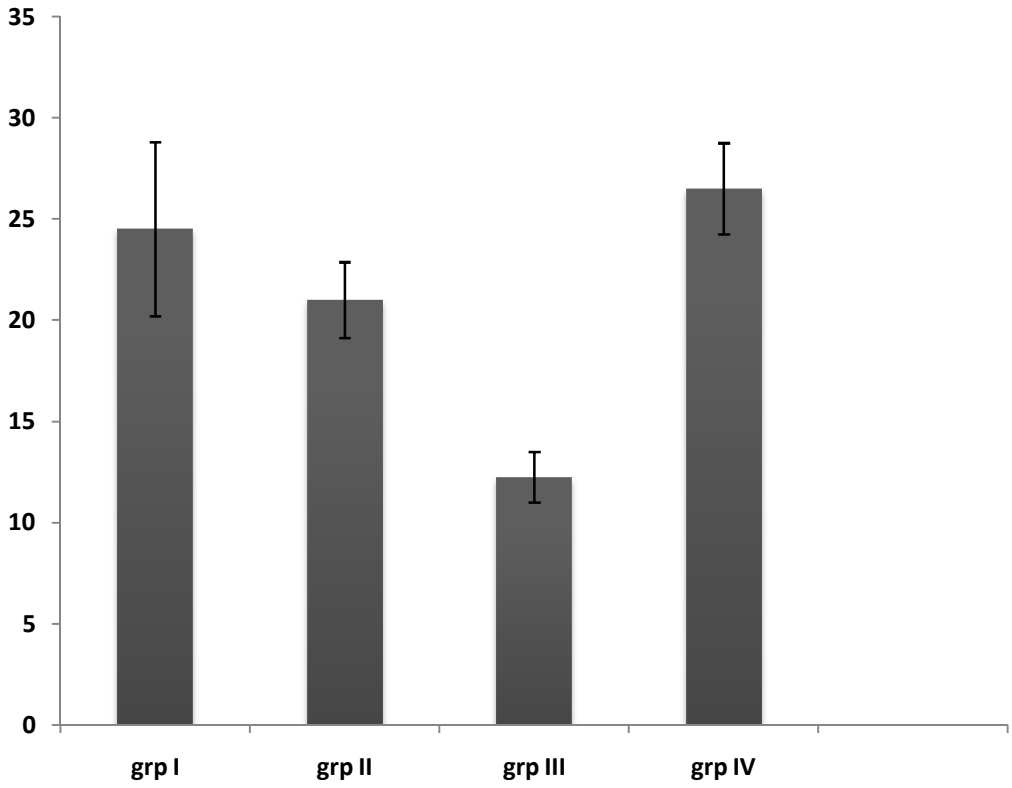


Figure 12: Mean surgical anaesthetic time following intravenous administration of the anaesthetic drug combinations.

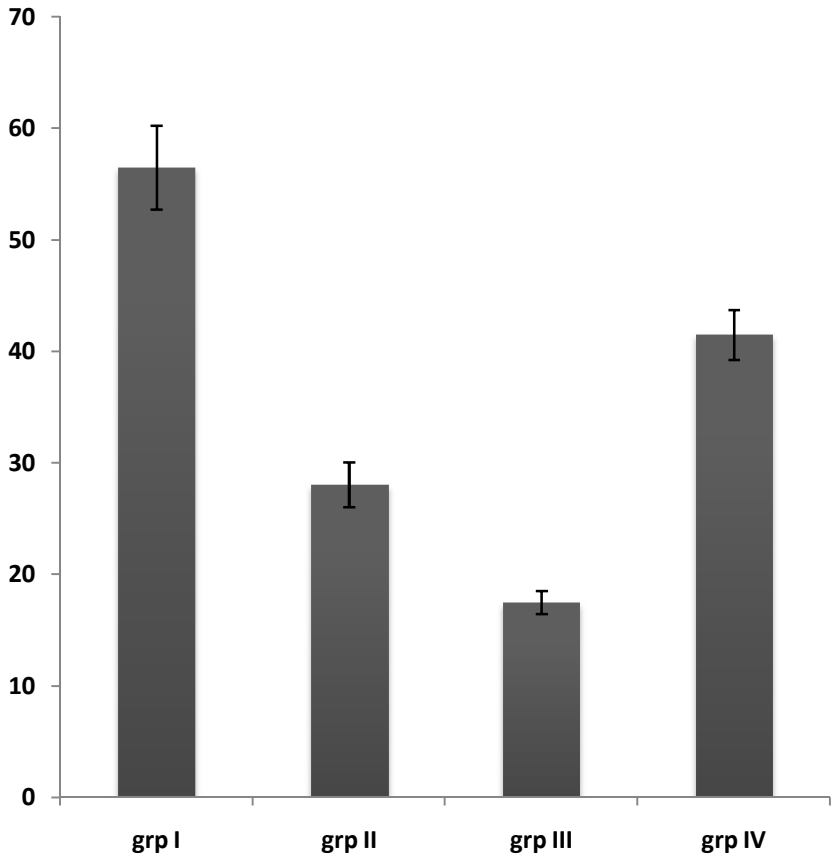


Figure 13: Mean recumbent time following intravenous administration of the drug combinations.

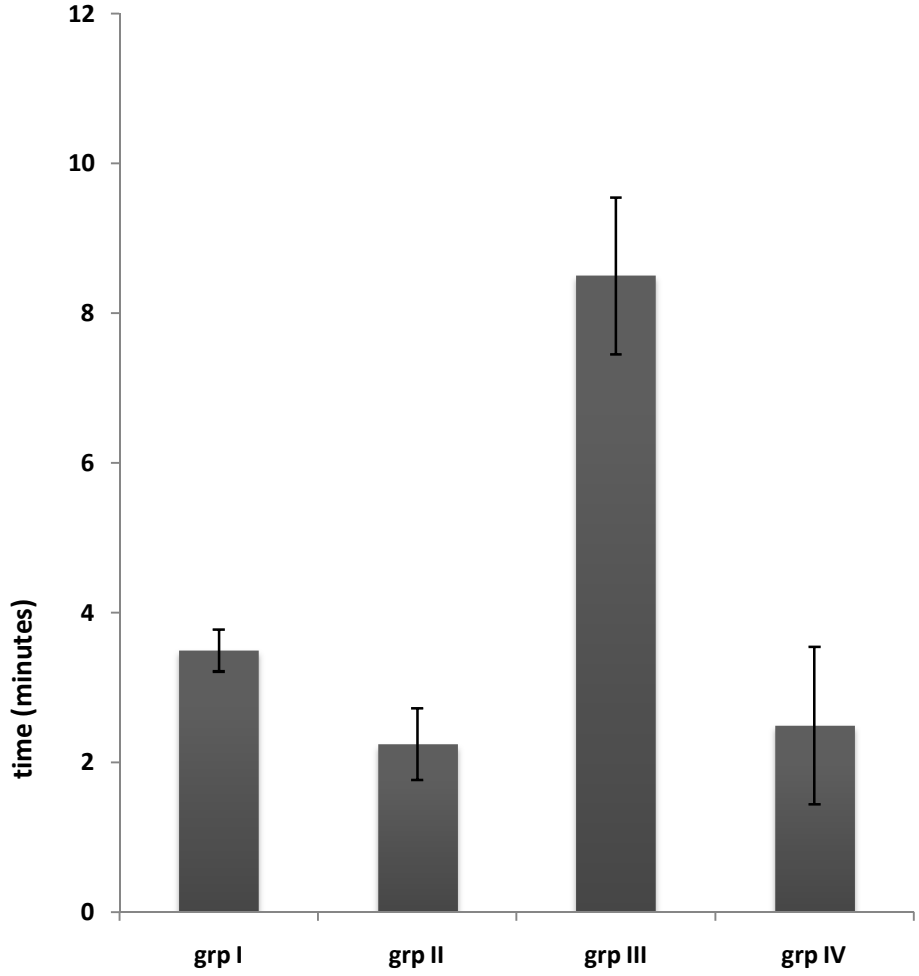


Figure 14: Mean standing time following intravenous administration of the anaesthetic drug combinations.

4.2.2.5 Quality of Induction and Recovery

The induction was smooth in all the goats in groups II and IV and two goats each in group I and II. The goat rapidly assumed recumbency immediately following the induction of anaesthesia. There was no sign of excitement of any form (Table1).

4.2.3 SIDE EFFECTS

Side effects observed include apnoea, labored breathing, irregular breathing, snoring, grunting, coughing, salvation, tail wagging, paddling movement, ataxia and urination. Salivation was observed in all the experimental groups however it was profuse in all the four goats in group I and in three goats in group III. Open eyelid was observed in all goats in groups I and IV, and 2 goats in group IV. Snoring was observed in all groups except group I and it was more intense in group IV. However, all the goats in groups II, III, and IV and two goats in group I, showed apnoea (Table 2).

Table 1: **Summary of induction and recovery qualities (n=4)**

	Group I	**Group II**	**Group III**	**Group IV**
Quality of induction	Good 50%	Good 100%	Good 50%	Good 100%
	Fair 50%		Fair 50%	
Quality of recovery	Good 25%	Good 50%	Good 50%	Good 100%
	Fair 75%	Fair 50%	Fair 50%	

% of animal that show respective signs

Table 2: **summary of side effects observed**.

Side effects	group I	Group II	Group III	Group IV
Apnoea	+ 50%	+ 100%	+ 100%	+ 25%
Dyspnoa	+ 50 %	- 100%	+ 50%	- 100%)
Open eyelid	+ 100%	- 100%	+ 25%	- 100%
Snoring	- 100%	+ 25%	+ 50%	+ 100%
Grunting	+ 50%	- 100%	+ 25%	- 100%
Coughing	- 100%	- 100%	+ 25%	- 100%
Salivation	+ 100%	+ 50%	+ 75%	+ 25%
Tail wagging	+ 50%	- 100%	+ 75%	- 100%
Paddling movement	+ 50%	- 100%	+75%	- 100%
Ataxia	+ 50%	- 100%	+ 100%	- 100%
Urination	+ 25%	+ 50%	+ 50%	+ 100%

-Absence, + present, % of goat affected

4.2.4 HEAMATOLOGICAL AND BIOCHEMISTRY VALUES

4.2.4.1 Packed Cell Volume (PCV)

There was significant ($p < 0.05$) decrease in packed cell volume in groups I, III and IV at 30 minutes post induction when compared to the pre- induction values. However, there as significant ($p <0.05$) decrease in packed cell volume at 30 minutes post induction in group IV when compared to group II (Table 3).

4.2.4.2 Haemoglobin (Hb) Concentration

Haemogolobin concentration dropped significantly ($p < 0.05$) in groups III and IV at 30 minutes post induction, and in group II at 1440 min post recovery, but significantly ($p<0.05$) increased at 2 hours in group I post recovery when compared to pre-induction values. However, there were no significant ($p < 0.05$) differences in haemogolobin concentration values in all the groups at 2 hours post recovery, but the value significantly increased at 24 hours in group I when compared to other groups (Table 4).

4.2.4.3 Red Blood Cell (RBC) Counts

The red blood cell counts significantly ($p<0.05$) increased at 2 hours post recovery in group I when compared to other groups, but significantly ($p < 0.05$) decreased at 24 hours post recovery in group II compared to other groups. Significant ($p < 0.05$) decreased in red blood cell counts were recorded in group II at 30 minutes post induction and between 2 hours to 24 hours post recovery. Also, red blood cell significantly ($p<0.05$) decreased at 2 hours post recovery in group IV (Table 5).

Table 3: **Mean (±SEM) Packed Cell Volume (%) of goats following intravenous administration of anaesthetic drug combinations**.

Time (min)	Group I	Group II	Group III	Group IV
0	27.75 ± 0.32^{b}	22.00 ± 1.47^{a}	31.25 ± 1.11^{c}	23.50 ± 1.04^{a}
30	$25.50 \pm 0.65^{*b}$	23.00 ± 0.41^{b}	$25.50 \pm 2.02^{*b}$	$18.50 \pm 1.04^{*a}$
120	27.00 ± 0.14^{b}	22.00 ± 1.15^{a}	28.00 ± 1.83^{b}	23.00 ± 1.29^{a}
1440	27.00 ± 0.30^{b}	20.50 ± 1.04^{a}	30.50 ± 0.65^{c}	22.00 ± 0.99^{a}

*Data in the same column differ significantly ($p < 0.05$) from the pre-induction value (time 0)

^{abc} figures with different superscripts within row are significantly ($p < 0.05$) different.

Table 4: **Mean (±SEM) Haemoglobin Concentration (g/dl) of goats following intravenous administration of anaesthtetic drug combinations**.

Time (min)	Group I	Group II	Group III	Group IV
0	8.10 ± 0.16^{a}	8.65 ± 0.14^{b}	10.10 ± 0.04^{c}	8.25 ± 0.14^{ab}
30	9.00 ± 0.00^{c}	8.10 ± 0.05^{b}	$7.9 \pm 0.53^{*b}$	$6.65 \pm 0.03^{*a}$
120	$9.35 \pm 0.20^{*a}$	8.10 ± 0.64^{a}	9.40 ± 0.12^{a}	8.10 ± 0.64^{a}
1440	7.55 ± 0.55^{a}	$7.20 \pm 0.46^{*a}$	10.50 ± 0.08^{c}	8.80 ± 0.00^{b}

*Data in the same column differ significantly ($p < 0.05$) from the pre-induction value (time 0)

^{abc} figures with different superscripts within row are significantly ($p < 0.05$) different.

Table 5: Mean (±SEM) Red Blood Cell Counts (x 10^{12} cells/ µl) of goats following intravenous administration of anaesthtetic drug combinations

Time (min)	Group I	Group II	Group III	Group IV
0	13.75 ± 0.94^{a}	13.07 ± 1.25^{a}	12.52 ± 0.72^{a}	10.90 ± 0.46^{a}
30	14.72 ± 0.40^{b}	$9.92 \pm 0.25^{*a}$	12.37 ± 1.78^{ab}	11.17 ± 0.55^{a}
120	15.02 ± 0.35^{c}	$7.77 \pm 0.29^{*a}$	13.5 ± 0.47^{b}	$8.75 \pm 0.44^{*a}$
1440	$13.70 \pm 1.17b^{c}$	$8.07 \pm 1.25^{*a}$	15.62 ± 0.64^{c}	11.55 ± 0.62^{b}

*Data in the same column differ significantly ($p < 0.05$) from the pre-induction value (time 0)

^{abc} figures with different superscripts within row are significantly ($p < 0.05$) different.

4.2.4.4 Total White Blood Cell Counts

There was significant ($p < 0.05$) increase in total white blood cells in group I at 24 hours post recovery. However, it significantly ($p < 0.05$) decreased in in group III at 24 hours post recovery (Table 6).

4.2.4.5 Blood Glucose

Blood glucose levels obtained were 75.00 ± 1.29, 68.50 ± 2.84, 48.50 ± 3.23, and 53.50 ± 4.69 mg/dl for groups I, II, III and IV respectively. These values significantly ($p<0.05$) increased at 30 minutes post induction in all the groups and returned to the level of pre-induction value at 2 hours post recovery in groups I and IV. It decreased significantly ($p<0.05$) from 2 to 24 hours post recovery in group II. The significant ($p<0.05$) increased in group III persisted till 24 hour post recovery. However, the increase was significantly ($p<0.05$) higher in group III at 120 minutes post recovery when compared to other groups (Table 7).

4.2.4.6 Serum Cortisol level

The cortisol level significantly ($p<0.05$) decreased at 30 min post induction in group II, but significantly ($p < 0.05$) increased at 120 min post recovery in all the groups and returned to the pre-induction level at 1440 minutes in all groups except in group III. The increase in group III was significantly ($p<0.05$) higher from 30 minutes post induction to 1440 minutes post recovery when compared to other groups (Table 8).

Table 6: **Mean (±SEM) Total White Blood Cell counts (x 10^9cells/ µl) of goats following intravenous administration of anaesthtetic drug combinations.**

Time (min)	Group I	Group II	Group III	Group IV
0	12.81 ± 0.69^{b}	12.29 ± 1.16^{ab}	10.53 ± 0.20^{a}	10.19 ± 0.27^{a}
30	11.25 ± 0.65^{b}	10.50 ± 0.22^{ab}	10.06 ± 0.13^{a}	10.09 ± 0.07^{a}
120	14.46 ± 0.48^{c}	12.15 ± 0.85^{b}	10.67 ± 0.15^{ab}	10.11 ± 0.07^{a}
1440	$14.94 \pm 0.36^{*c}$	11.4 ± 0.70^{b}	$9.41 \pm 0.14^{*a}$	9.67 ± 0.38^{a}

*Data in the same column differ significantly ($p < 0.05$) from the pre-induction value (time 0)

^{abc} figures with different superscripts within row are significantly ($p < 0.05$) different.

Table 7: **Mean (±SEM) Blood glucose level (mg/ dl) of goats following intravenous administration of anaesthtetic drug combinations .**

Time (min)	Group I	Group II	Group III	Group IV
0	75.00 ± 1.29[a]	68.50 ± 2.84[b]	48.50 ± 3.23[a]	53.50 ± 4.69[a]
30	113.50 ± 12.75*	108.50 ± 4.36*	119.00 ± 1.29*	97.50 ± 11.00*
120	66.00 ± 5.49[a]	57.00 ± 3.11*[a]	115.25 ± 3.68*[b]	63.00 ± 10.11[a]
1440	76.75 ± 6.04[b]	50.50 ± 0.28*[ab]	57.00 ± 0.91*[ab]	44.00 ± 9.31[a]

*Data in the same column differ significantly ($p < 0.05$) from the pre-induction value (time 0)

[abc] figures with different superscripts within row are significantly ($p < 0.05$) different.

Table 8**: Mean (±SEM) Serum Cortisol level (ng/ ml) of goats following intravenous administration of anaesthtetic drug combinations**.

Time	Group I	Group II	Group III	Group IV
0	26.82 ± 5.53[a]	31.78 ± 1.33[a]	30.13 ± 9.79[a]	31.56 ± 13.55[a]
30	21.87 ± 10.58[b]	9.05 ± 2.04*[a]	50.13 ± 11.86[c]	12.17 ± 1.11[a]
120	52.87 ± 5.30*[a]	53.63 ± 2.12*[a]	120.05 ±17.00*[b]	108.50 ± 0.57*[b]
1440	20.96 ± 6.03a	37.82 ± 2.12[a]	66.52 ± 27.88[b]	28.91 ± 18.00[a]

*Data in the same column differ significantly ($p < 0.05$) from the pre-induction value (time 0)

[abc] figures with different superscripts within row are significantly ($p < 0.05$) different.

4.2.4.7 Blood Urea Nitrogen (BUN)

The blood urea nitrogen value significantly ($p < 0.05$) decreased at 30 min post induction in groups III and IV. At 120 min post recovery the value significantly ($p < 0.05$) decrease in group IV but increased ($p < 0.05$) in group III. At 1440 min post recovery, the BUN value decrease significantly ($p < 0.05$) in group II, III and IV respectively (Table 9).

4.2.4.8 Serum Creatinine level

The mean creatinine values significantly ($p < 0.05$) decreased at 30 mins post induction in group III, and at 120 min post recovery in group IV and in groups III and IV at 1440 min post recovery. The decrease in group IV was progressive (Table 10).

4.2.4.9 Serum Alanine Amniotransaminase (SALT)

The ALT value significantly ($p < 0.05$) increased at 1440 min post recovery in groups III and IV when compared to pre-induction values. Also, significant increase was recorded in group II at 2 hour post recovery when compared to the pre induction value. (Table 11)

Table 9**: Mean (±SEM) Blood urea nitrogen (mg/ dl) of goats following intravenous administration of anaesthtetic drug combinations**.

Time (min)	Group I	Group II	Group III	Group IV
0	38.45 ± 0.15^{c}	36.92 ± 1.51^{b}	27.00 ± 0.20^{a}	28.5 ± 0.89^{a}
30	34.86 ± 7.52^{b}	37.90 ± 2.98^{b}	$23.00 \pm 0.73^{*a}$	$24.07 \pm 0.35^{*a}$
120	30.52 ± 7.40^{b}	28.35 ± 1.78^{ab}	$31.00 \pm 0.42^{*ab}$	$21.17 \pm 0.57^{*a}$
1440	31.96 ± 4.60^{b}	$26.40 \pm 5.22^{*ab}$	$24.32 \pm 1.93^{*a}$	$21.17 \pm 1.35^{*a}$

*Data in the same column differ significantly ($p < 0.05$) from the pre-induction value (time 0)

^{abc} figures with different superscripts within row are significantly ($p < 0.05$) different.

Table 10: Mean (±SEM) Serum Creatinine level (mg/ dl) of goats following intravenous administration of anaesthtetic drug combinations.

Time (min)	Group I	Group II	Group III	Group IV
0	1.45 ± 0.06^{c}	1.35 ± 0.65^{c}	1.05 ± 0.03^{b}	0.82 ± 0.07^{a}
30	1.48 ± 0.18^{b}	1.40 ± 0.82^{b}	$0.83 \pm 0.32^{*a}$	0.75 ± 0.06^{a}
120	1.31 ± 0.25^{b}	0.90 ± 0.56^{ab}	0.93 ± 0.03^{ab}	$0.60 \pm 0.04^{*a}$
1440	1.20 ± 0.91^{c}	1.35 ± 0.29^{bc}	$0.75 \pm 0.06^{*ab}$	$0.59 \pm 0.02^{*a}$

*Data in the same column differ significantly ($p < 0.05$) from the pre-induction value (time 0)

^{abc} figures with different superscripts within row are significantly ($p < 0.05$) different.

Table 11**: Mean (±SEM) Alanine Aminotransaminase (ALT) level (iu/ l) of goats following intravenous administration of anaesthtetic drug combinations** .

Time (min)	Group I	Group II	Group III	Group IV
0	15.40 ± 4.82	16.50 ± 0.21	10.50 ± 1.19	10.50 ± 0.20
30	13.72 ± 1.62	18.50 ± 1.75	11.00 ± 0.91	14.00 ± 1.47
120	12.90 ± 2.23	19.50 ± 2.10	8.50 ± 0.65	14.00 ± 1.47
1440	18.85 ± 3.41	19.50 ± 3.75	17.50 ± 0.46*	14.62 ± 2.68*

*Data in the same column differ significantly ($p < 0.05$) from the pre-induction value (time 0)

^{abc} figures with different superscripts within row are significantly ($p < 0.05$) different.

4.3 PROTOCOL II

4.3.1 PHYSIOLOGICAL VARIABLES:

4.3.1.1 Heart Rate

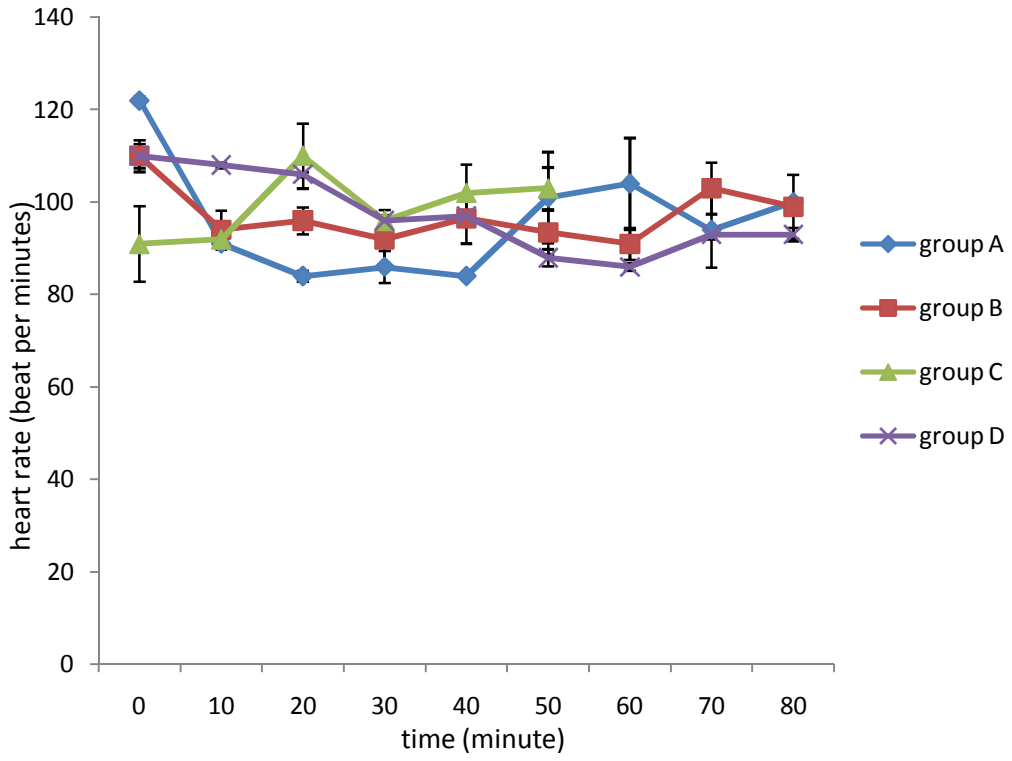
The heart rate significantly ($p<0.05$) decreased between 10 to 50 minutes post induction in group A, between 10 to 60 minutes post induction in group B, and between 40 to 80min minutes post induction in group D. However, the heart rate increased ($p<0.05$) at 20 min post induction in group C (Figure 15).

4.3.1.2 Respiratory Rate

The respiratory rate significantly ($p<0.05$) decreased between 10 to 80 minutes, 10 to 50 minutes, 30 to 80 minutes post induction in groups A, B, and D respectively. There was significant ($p < 0.05$) increased in respiratory rate at 20 minutes post induction in group C which was significantly ($p<0.05$) higher when compared to other groups (figure 16).

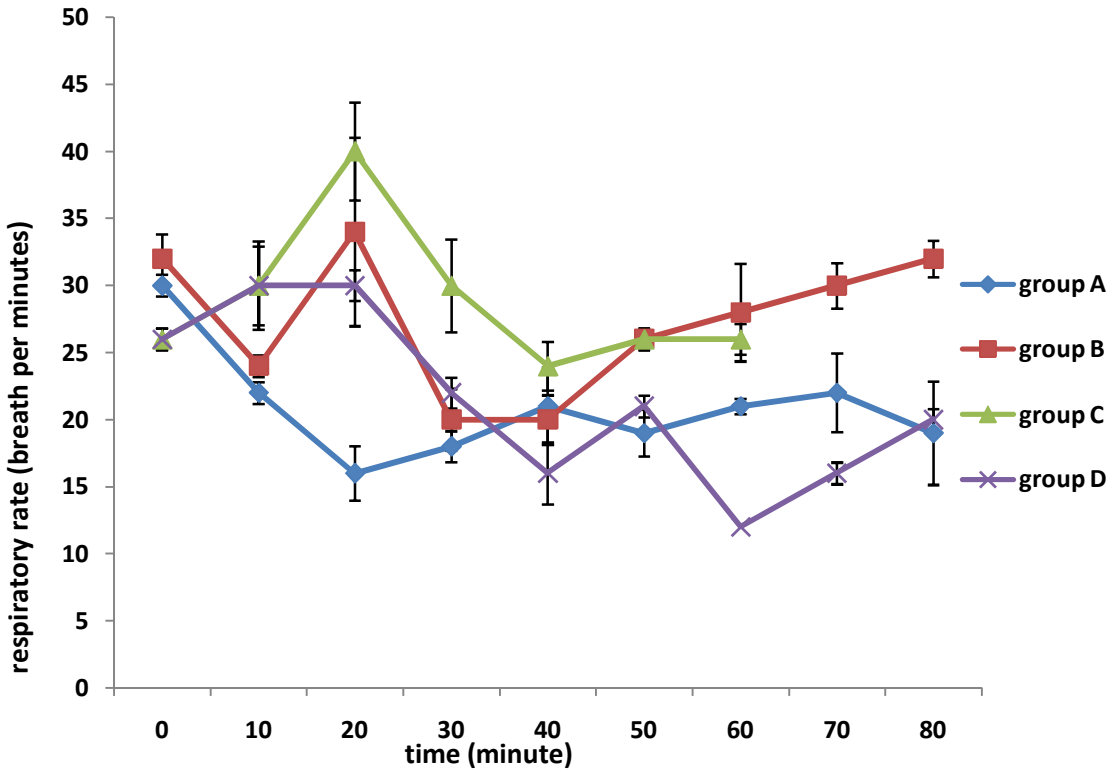
4.3.1.3 Rectal Temperature ($^{\circ}C$)

There was significant ($p < 0.05$) decrease in rectal temperature, between 10 to 20 minutes, and 10 to 40 minutes post induction in groups A, and C, respectively when compared to pre-induction value. However, temperature significantly ($p < 0.05$) increased between 10 to 20 minutes in group D after which it returned to the level of pre-induction value. However, there was significant ($p<0.05$) decreased in rectal temperature from 10 to 40 minutes and 70 to 80 minutes post induction in group B when compared to other groups (Figure17).



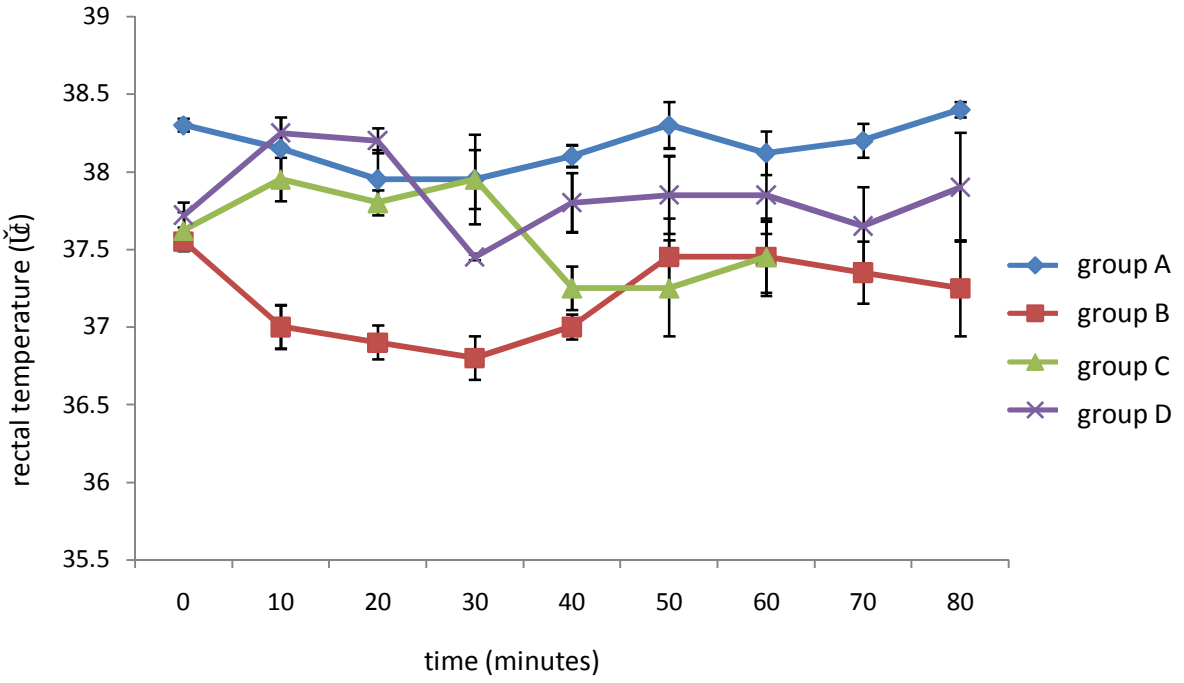
Group A - xylazine/ketamine
Group B- xylazine/propofol
Group C- ketamine/ propofol
Group D - xylazine/ ketamine/ propofol

Figure 15: Mean heart rate following intravenous administration of the anaesthetic drug combinations



Group A - xylazine/ketamine
Group B- xylazine/propofol
Group C- ketamine/ propofol
Group D - xylazine/ ketamine/ propofol

Figure 16: Mean respiratory rate following intravenous administration of the anaesthetic drug combinations



Group A ï xylazine / ketamine
Group B- xylazine / propofol
Group C- ketamine / propofol
Group D - xylazine/ ketamine/ propofol

Figure 17: Mean rectal temperature following intravenous administration of the anaesthetic drug combinations

4.3.2 ANAESTHETIC INDICES

4.3.2.1 Onset of Analgesia

The onset of analgesia (Figure 18), shows that analgesic effect of the anaesthetics combination in group A was observed at 3.57 ± 0.28 minute post induction. This was significantly ($P < 0.05$) high when compared to the onset of analgesia in other groups. Group D goats were observed to have shortest ($p < 0.05$) period of onset of analgesia (1.00 ± 0.00) following induction when compared to other groups.

4.3.2.2 Surgical Anaesthetic Time

The period of surgical anaesthesia lasted for 78 .50 ± 1.04 minutes in group D. This was significantly ($p < 0.05$) longer when compared to other group. Also, the period of anaesthesia lasted for 51.00 ± 11.01 and51.50 ± 5.92 in groups A and B respectively. These were significantly ($p < 0.05$) longer when compared to group C (Figure 19).

4.3.2.3 Recumbent Time

Figure 12 shows the result of recumbent time in four groups of goats. The mean recumbent time following induction was 91.50 ± 3.75 and 91.00 ± 2.08 minutes in groups A and D respectively. These values were significantly ($p < 0.05$) longer when compared to other values obtained for groups B and C (Figure 20).

4.3.2.4 Standing Time

The mean standing time for group A was significantly ($p < 0.05$) longer when compared to other groups (Figure 21).

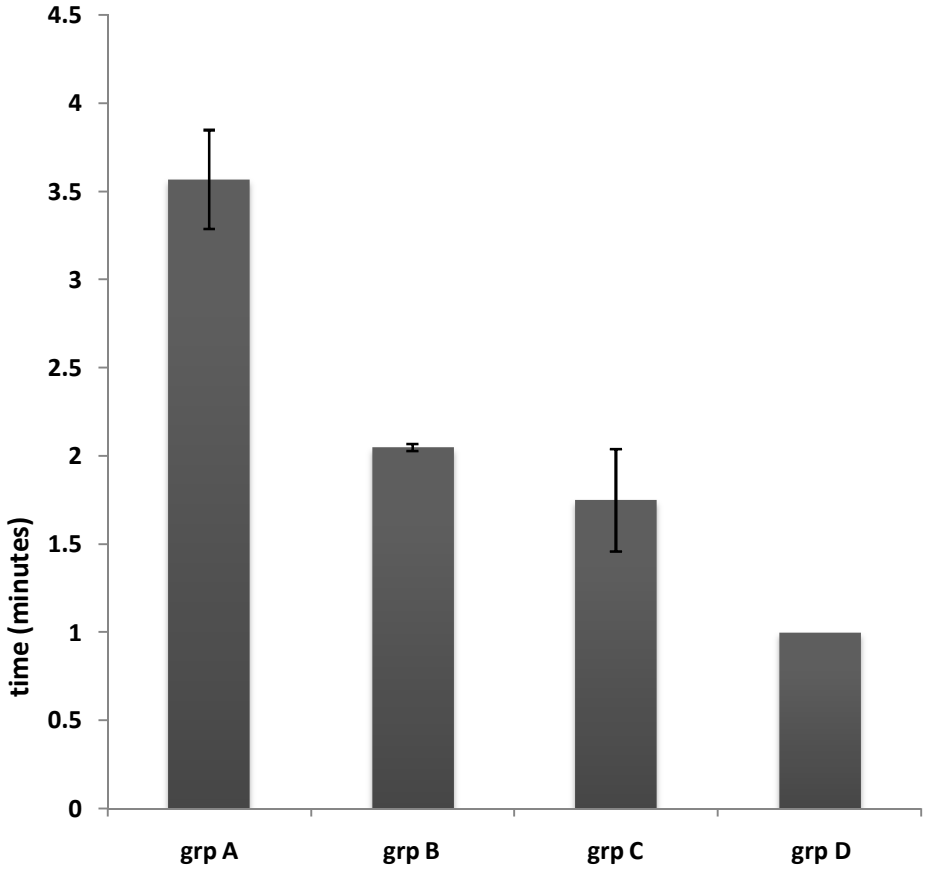


Figure 18: Mean onset of analgesic time following intravenous administration of the drug combinations.

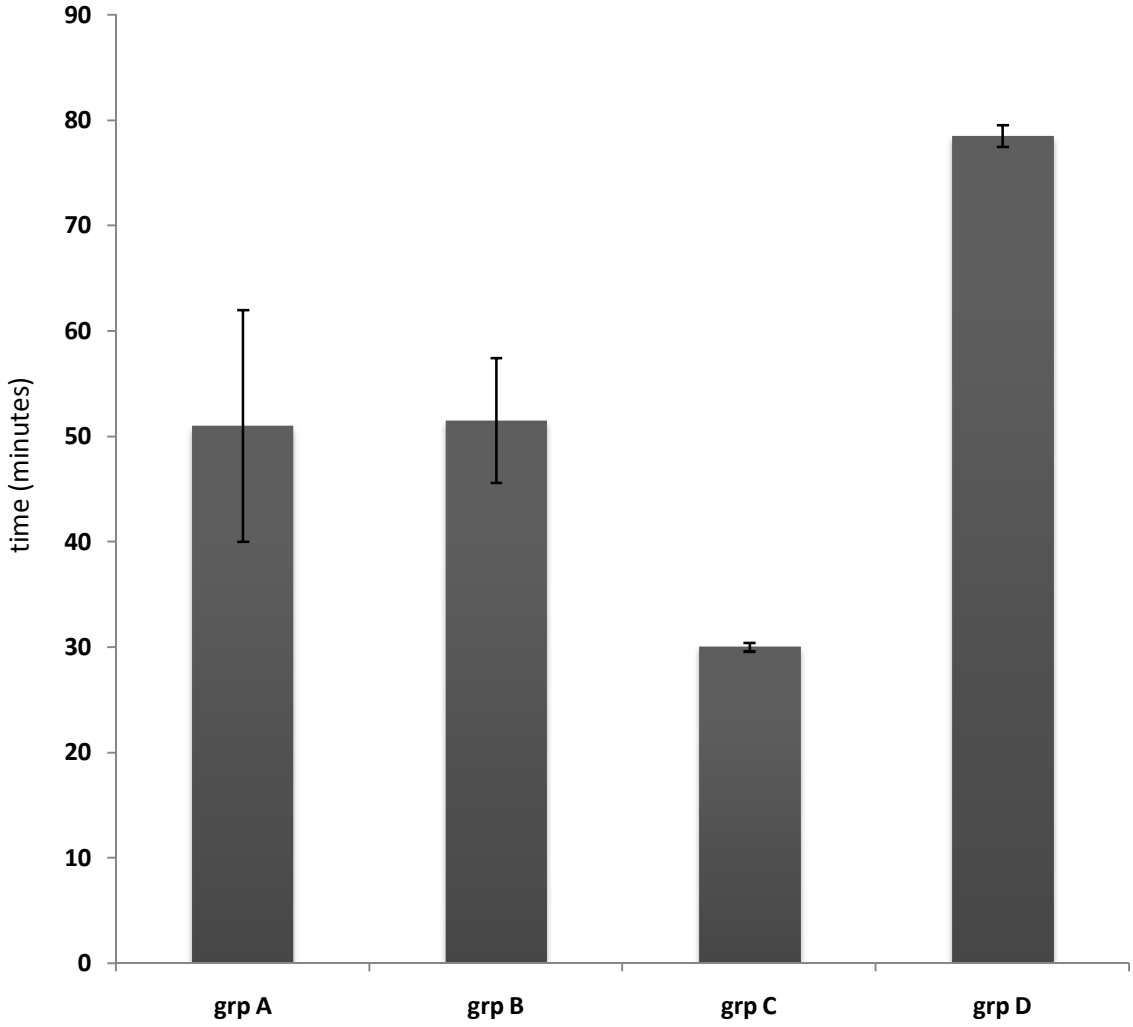


Figure 19: Mean surgical anaesthetic time following intravenous administration of the anaesthetic drug combinations.

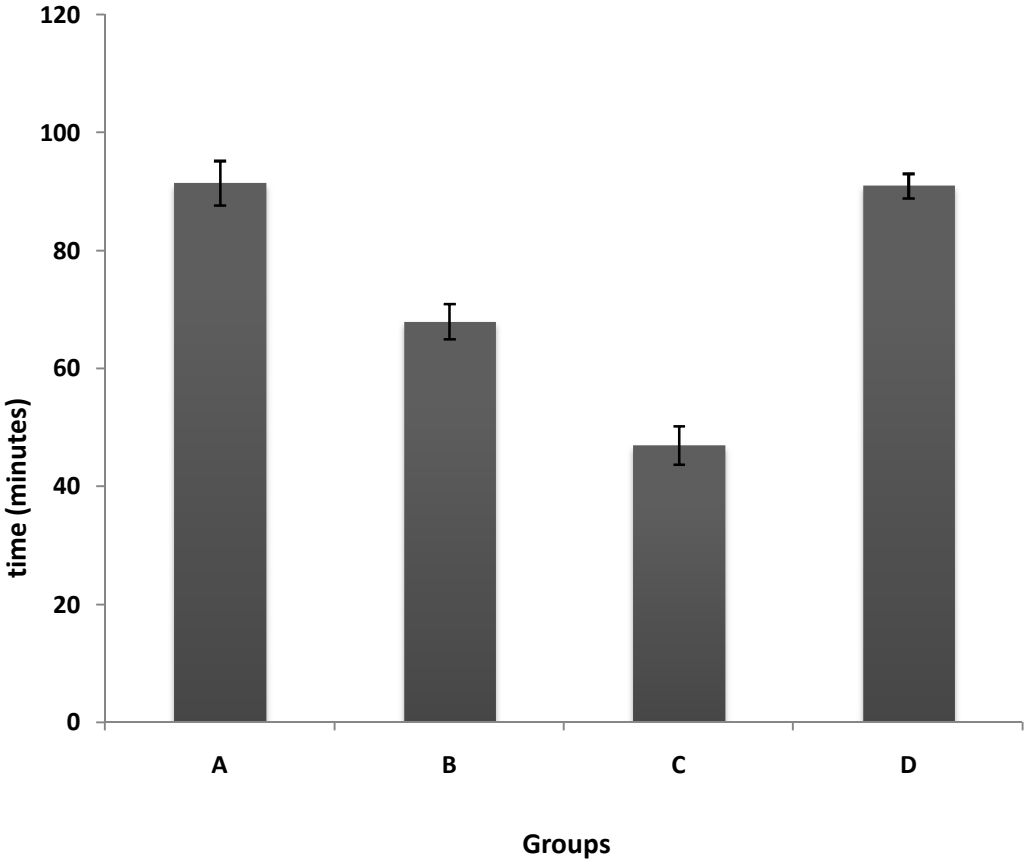


Figure 20: Mean recumbent time following intravenous administration of the anaesthetic drug combinations.

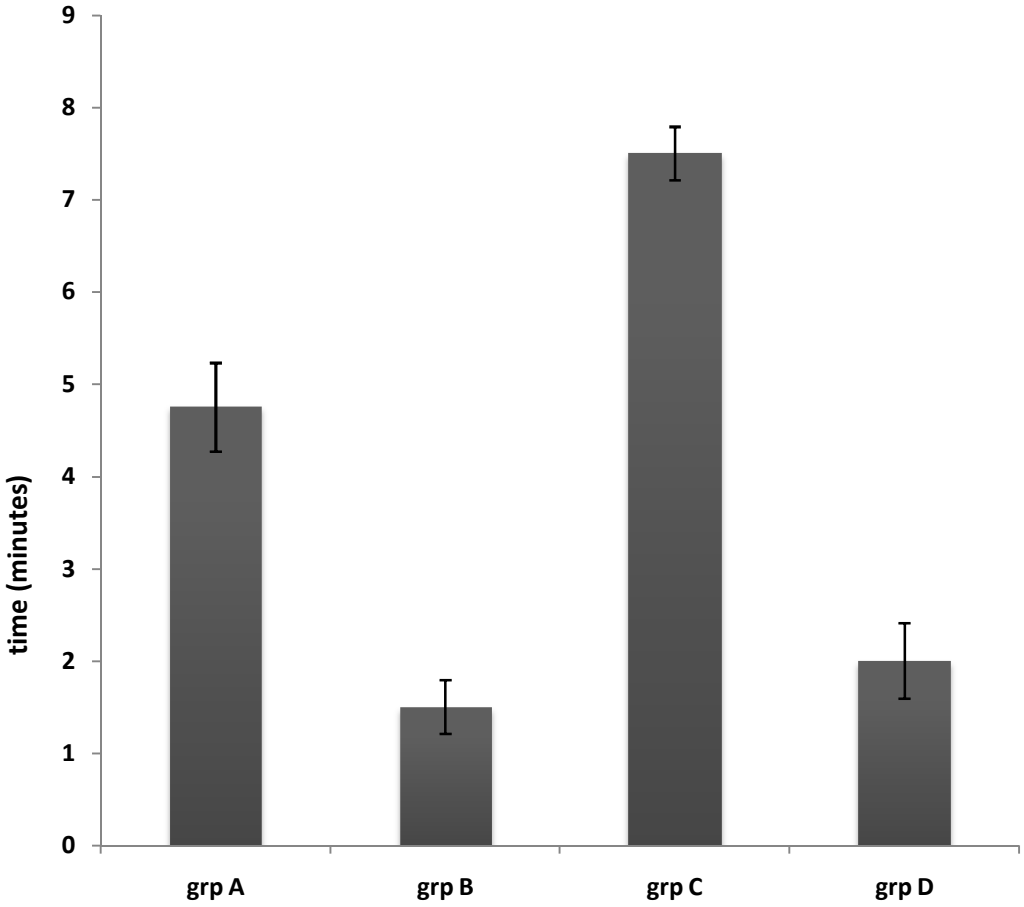


Figure 21: Mean Standing time following intravenous administration of the drug combinations.

4.3.2.5 Nature of Induction and Recovery

Table 12 shows the quality of induction and recovery obtained from the four groups of the goats. Following the administration of anaesthesia, smooth induction was observed in all the goats in groups A and D, and three goats in groups A and C each. The goats rapidly assumed lateral recumbent position and no form of excitement were observed. However, one goat each in groups A and C exhibited slight excitement and the presence of swallowing reflex was observed.

Recovery was also smooth, no hallucination and the goats stood few minutes after assumed sternal recumbency. These were observed in all the goats in group D and three goats in group B and C each. However, transient excitement, struggle to stand and moderate ataxia were observed in all the goats in group A, one goat in group B and two goats in groups C.

4.3.2.6 Side Effects

The side effects observed in this experiment includes apnoea, laboured breathing, snoring, grunting, coughing, salivation, tail wagging, paddling movement, open eye lid, ataxia and urination.

Salivation was profuse in all the goats in groups A and B and two goats in group C, but mild in two goats in group D. Coughing was observed in one goat in group A only and one to three goats in group A, B and C. Ataxia was noticed in goats after standing in Groups A and C, while urination was observed in all the groups. Snoring was present in groups B and C, and highly present in group D. Open eyelids were observed in all goats in group A and two goats in group C. This persisted in group A even after maintainance with ketamine, but the eyes were closed following maintainance in group C with propofol (table 13).

Table 12**: Nature of induction and recovery qualities (n=4)**

	Group A	Group B	Group C	Group D
Quality of induction	Good 75% Fair 25%	Good 100%	Good 75% Fair 25%	Good 100%
Quality of recovery	Fair 100%	Good 75% Fair 25%	Good 50% Fair 50%	Good 100%

% of animal that show respective signs

Table 13**: summary of the side effects observed in different experimental groups**

Side effects	Group A	Group B	Group C	Group D
Apnoea	+ 25%	+ 50%	+75%	+ 100%
Laboured breathing	+25%	+50%	- 100%	- 100%
Open eyelid	+ 100%	- 100%	+ 50%	+ 25 %
Snoring	- 100%	+ 50%	+ 100%	+ 100%
Grunting	+ 50 %	- 100%	- 100%	- 100%
Coughing	+ 25%	- 100%	- 100%	- 100%
Salivation	+ 100%	+ 50%	+ 100%	+ 50%
Tail wagging	+ 75%	- 100%	+50%	- 100%
Paddling movement	+ 75%	- 100%	+ 75%	+ 50%
Ataxia	+ 75%	-100%	+ 100%	- 100%
Urination	+ 25%	+ 75%	+ 50%	+ 100%

- **Absence, + present, (%) No of goats affected.**

4.3.3 HEAMATOLOGICAL VALUES

4.3.3.1 Packed Cell Volume

Table 14 shows packed cell volume of the four experimental goat groups. There was significant ($p < 0.05$) decrease in packed cell volume at 30 minute post induction in group D. Also slight decrease was observed in group A and B at 30 minutes post induction but it was not statistically significant ($p > 0.05$).

4.3.3.2 Haemoglobin Concentration

The mean haemoglobin concentration values significantly ($p < 0.05$) decreased at 30 minutes post induction in groups A. There was slight decrease in groups B, C, and D goats at 30 min post induction but it was not statistically significant ($p > 0.05$) (Table 15).

4.3.3.3 Red Blood Cell Counts

The results of red blood cell count of the four experimental groups are shown in Table 16. There was no significant ($p > 0.05$) change recorded in the red blood cell count as in all the groups.

4.3.3.4 Total White Blood Cell counts

Table 17 shows the results of total white blood cells of the four experimental groups. Significant ($p < 0.05$) decrease in the total white blood cells occurred at 30 min post induction in groups A and D, and at 120 min post recovery in group A and C. The decrease was observed even at 1440 min post recovery in group C.

Table 14**: Mean (±SEM) Packed Cell Volume (%) of goats following intravenous administration of anaesthtetic drug combinations**

Time (min)	Group A	Group B	Group C	Group D
0 minute	20.00 ± 2.04^{a}	24.50 ± 0.65^{b}	29.50 ± 0.65^{c}	24.00 ± 0.57^{b}
30 minutes	17.00 ± 1.47^{a}	21.50 ± 3.01^{a}	30.00 ± 2.04^{b}	$20.00 \pm 1.29^{*a}$
120	18.00 ± 1.47^{a}	26.50 ± 1.75^{b}	30.00 ± 0.82^{c}	26.50 ± 0.65^{b}
1440	21.50 ± 2.32^{a}	23.00 ± 1.47^{a}	31.50 ± 0.65^{b}	24.00 ± 0.75^{a}

*Data in the same column differ significantly ($p < 0.05$) from the pre anaesthetic value (time 0)

^{abc} figures with different superscripts within row are significantly ($p < 0.05$) different.

Table 15**: Mean (±SEM) Haemoglobin concentration (g/dl) of goats following intravenous administration of anaesthtetic drug combinations** .

Time (min)	Group A	Group B	Group C	Group D
0	7.53 ± 0.17^{a}	7.55 ± 0.32^{a}	9.55 ± 1.06^{b}	7.92 ± 0.85^{ab}
30	$5.90 \pm 0.46^{*a}$	5.90 ± 0.65^{a}	9.20 ± 0.80^{b}	7.55 ± 0.68^{ab}
120	6.35 ± 0.37^{a}	7.90 ± 0.60^{b}	10.30 ± 0.45^{c}	6.80 ± 0.12^{ab}
1440	6.52 ± 0.25^{a}	7.26 ± 0.30^{a}	10.90 ± 0.54^{b}	7.41 ± 0.19^{a}

*Data in the same column differ significantly from the pre anaesthetic value (time 0) ($p < 0.05$)

^{abc} figures with different superscripts within row are significantly different ($p < 0.05$)

Table 16**: Mean (±SEM) Red Blood Cell Counts (x 10^{12} cellls/ µl) of goats following intravenous administration of anaesthtetic drug combinations.**

Time (min)	Group A	Group B	Group C	Group D
0	9.87 ± 0.41	9.50 ± 0.18	11.37 ± 0.82	11.62 ± 0.63
30	9.80 ± 1.06	9.80 ± 1.58	9.99 ± 2.15	10.99 ± 0.16
120	9.10 ± 0.61	11.33 ± 1.30	10.90 ± 0.10	12.40 ± 1.43
1440	12.13 ± 1.59	11.72 ± 0.81	11.50 ± 0.21	11.45 ± 2.15

*Data in the same column differ significantly ($p < 0.05$) from the pre anaesthetic value (time 0)

^{abc} figures with different superscripts within row are significantly ($p < 0.05$) different.

Table 17**: Mean (±SEM) Total White Blood Cell counts (10^9cellls/ µl) of goats following intravenous administration of anaesthtetic drug combinations.**

Time (min)	Group A	Group B	Group C	Group D
0	10.66 ± 0.64^{a}	11.83 ± 0.83^{ab}	11.23 ± 0.58^{ab}	12.29 ± 0.22^{b}
30	$9.18 \pm 0.30^{*a}$	9.88 ± 0.55^{ab}	10.88 ± 0.16^{bc}	$11.06 \pm 0.20^{*c}$
120	$9.53 \pm 0.22^{*a}$	12.13 ± 0.86^{bc}	$10.33 \pm 0.16^{*bc}$	11.76 ± 0.21^{c}
1440	10.28 ± 0.14^{a}	12.14 ± 0.84^{bc}	$10.03 \pm 0.49^{*ab}$	11.77 ± 0.24^{c}

*Data in the same column differ significantly ($p < 0.05$) from the pre anaesthetic value (time 0)

^{abc} figures with different superscripts within row are significantly ($p < 0.05$) different.

4.3.3.5 Blood Glucose level

The results of the blood glucose of the four experimental groups are shown in table 18. The values significantly increased ($p<0.05$) at 30 min post induction in all the groups, and remained consistent at 120 min post recovery in groups B, C and D and returned to level of pre-induction values in all the groups 1440 min post recovery.

4.3.3.6 Serum Cortisol Level

Table 19 shows the cortisol levels of the four experimental groups. The cortisol level significantly decreased ($p<0.05$) at 30 minutes post induction in group B only and significantly ($p<0.05$) increased at 2 hours post recovery in groups A, B, and D, and at 24 hours in group B goats.

4.3.3.7 Blood Urea Nitrogen

The results of blood urea nitrogen of the four experiment groups are shown in table 20. There was no significant ($p > 0.05$) variation in blood urea nitrogen value in all the groups.

4.3.3.8 Serum Creatinine level

Table 21 shows the creatinine levels of the four experimental groups. There was significant decrease ($p<0.05$) at 1440 min post recovery in group C when compared to pre induction value. It also decreased significantly ($p<0.05$) in group A at 120 min post recovery when compared to group D.

Table 18: **Mean (±SEM) Blood glucose level (mg/ dl) of goats following intravenous administration of anaesthtetic drug combination**s

Time (min)	Group A	Group B	Group C	Group D
0	57.50 ± 1.04[a]	56.50 ± 3.01[a]	54.00 ± 2.94[a]	76.50 ± 8.21[b]
30	111.00 ± 11.67*	102.00 ± 2.08*	120.00 ± 1.82*	99.50 ± 8.45*
120	79.00 ± 9.06[a]	66.50 ± 4.05*[a]	64.00 ± 1.68*[a]	108.00 ± 4.34*[b]
1440	64.50 ± 2.25[b]	55.00 ± 2.38[a]	58.00 v 1.82[b]	76.00 ± 2.94[c]

*Data in the same column differ significantly ($p < 0.05$) from the pre anaesthetic value (time 0)

[abc] figures with different superscripts within row are significantly ($p < 0.05$) different.

Table 19**: Mean (±SEM) Serum Cortisol level (ng/ ml) of goats following intravenous administration of anaesthtetic drug combinations.**

Time	Group A	Group B	Group C	Group D
0	30.38 ± 7.10[a]	30.16 ± 7.15[a]	30.02 ± 13.05[a]	31.56 ± 14.00[a]
30	28.50 ±10.42[b]	7.44 ± 3.90[a]*	20.45 ± 9.38[b]	10.36 ± 6.88[ab]
120	126.36 ± 4.50*[b]	14.48 ± 2.45[a]	112.39 ± 30.01*[b]	110.45± 36.81*[b]
1440	55.19 ± 25.37[a]	59.66 ± 9.28*[a]	37.01 ± 19.80[a]	23.74 ±10.99[a]

*Data in the same column differ significantly ($p < 0.05$) from the pre anaesthetic value (time 0)

[abc] figures with different superscripts within row are significantly ($p < 0.05$) different.

Table 20: Mean (±SEM) Blood urea nitrogen (mg/ dl) of goats following intravenous administration of anaesthtetic drug combinations.

Time	Group A	Group B	Group C	Group D
0	35.70 ± 2.72[a]	37.77 ± 0.81[a]	30.33 ± 3.15[a]	39.57 ± 0.83[a]
30	32.37 ± 4.33[a]	35.95 ± 0.30[a]	38.92 ± 2.30[a]	36.75 ± 3.37[a]
120	40.42 ± 3.13[a]	34.18 ± 2.86[a]	37.67 ± 6.20[a]	35.95 ± 2.35[a]
1440	29.17 ± 3.16[a]	34.85 ±1.10[a]	32.92 ± 1.72[a]	36.82 ± 0.66[a]

*Data in the same column differ significantly ($p < 0.05$) from the pre anaesthetic value (time 0)

[abc] figures with different superscripts within row are significantly ($p < 0.05$) different.

Table 21**: Mean (±SEM) Serum Creatinine level (mg/ dl) of goats following intravenous administration of anaesthtetic drug combinations.**

Time	Group I	Group II	Group III	Group IV
0	1.70 ± 0.09^{b}	1.20 ± 0.20^{a}	1.75 ± 0.06^{b}	1.90 ± 0.00^{b}
30	1.20 ± 0.35^{a}	1.60 ± 0.06^{ab}	1.60 ± 0.04^{ab}	1.85 ± 0.31^{b}
120	1.95 ± 0.06^{b}	1.35 ± 0.26^{a}	1.65 ± 0.11^{ab}	1.70 ± 0.11^{ab}
1440	1.10 ± 0.13^{a}	1.60 ± 0.09^{bc}	$1.40 \pm 0.15^{*ab}$	1.85 ± 0.06^{c}

*Data in the same column differ significantly ($p < 0.05$) from the pre anaesthetic value (time 0)

^{abc} figures with different superscripts within row are significantly ($p < 0.05$) different.

4.3.3.9 Serum Alanine Aminotransaminase (SALT)

The results of SALT of the four experiment groups are shown in table 22. The SALT value significantly ($p < 0.05$) increased 120 min in group A and 1440 min in group C and D post recovery respectively

Table 22**: Mean (±SEM) Serum Alanine Aminotransaminase (SALT) level (iu/ l) of goats following intravenous administration of anaesthtetic drug combinations**

Time	Group A	Group B	Group C	Group D
0	15.00 ± 0.82	14.00 ± 0.40[a]	14.90 ± 0.81	15.10 ± 0.91
30	14.00 ± 3.4	14.50 ± 0.65[b]	13.50 ± 2.65	14.60 ± 2.19
120	17.20 ± 7.22*	12.50 ± 4.05a	13.00 ± 3.18	15.20 ± 0.65
1400	13.00 ± 6.0	13.77 ± 2.10[b]	16.00 ± 0.51*	19.63 ± 3.31*

*Data in the same column differ significantly ($p < 0.05$) from the pre anaesthetic value (time 0)

[abc] figures with different superscripts within row are significantly ($p < 0.05$) different.

CHAPTER FIVE

5.0 DISCUSSION AND CONCLUSION

5.1 DISCUSSION

The pilot study showed that propofol at the dose of 7.5 mg / kg and 5 mg/kg produced anaesthetic duration of about 18.2 ± 2.2 and 9.02 ± 3 minutes respectively. Propofol at dose of 7.5 mg/kg can be adopted as the normal dose in an unpremedicated West African Dwarf goat. This result agreed with that of Hall *et al*. (2001) who reported that propofol at a dose of 5ï 7 mg /kg intravenous in unpremedicated sheep and goat induced anaesthesia sufficient for endotracheal intubation. Pre-medication with acepromazine, 0.05 mg/kg and papaveretum, 0.4 mg/kg decreased the dose of propofol for intubation to approximately 4 mg /kg (Hall *et al*., 2001). This suggests that drug combination in total intravenous anaethesia reduces the dose of individual drugs in the combination. Based on this, the propofol dose of 5mg / kg body weight was used in combination with other drugs (ketamine and xylazine).

The intravenous injection of the four different combinations of the drugs resulted in the smooth and uneventful induction with rapid recovery. However, their injections were associated with side effects such as apnoea, snoring, salivation, paddling, urination, and ataxia.

The significant increase in the heart rate at 10 minute post induction in group I (xylazine/ ketamine group), protocol I may be attributed to the cardiostimulatory effect of ketamine. Ketamine causes cardiac stimulation by sympathomimetic effects mediated within the central nervous system (Ivankovitch *et al*., 1974; Altura *et al*., 1980; Eze *et al*., 2004). This effect might have over shadowed the bradycadiac effect of the xylazine which at 30 minute

subverted the effect of ketamine resulting in low heart rate that lasted till the end of experiment. However, low heart rate following induction of anaesthesia using xylazine/ ketamine has been reported (Nowrouzain *et al*., 1980; Eze *et al*., 2004; Fereidoon *et al*., 2005 and Udegbunam and Adetunji, 2007). The combination of propofol and xylazine in group II leads to decrease in the heart which lasted for over 30 minute. This may be due to the prevention of stress response by the two drugs and their bradycardia and hypotensive effects (Kumar and Thurmon, 1979). However the combination of three drugs in group IV (Protocol I) lead to slight decrease for only 10 minutes which showed the balance in the pharmacological effects of the individual drugs in the combination and the sympathetic nervous stimulatory effects ketamine which counteracts the depressant effect of other drugs leading to heamodynamic during anaesthesia (Lerch *et al*., 2000). The maintenance dose extended the decrease in heart rate to 50 minute post induction in groups A and B. The significant ($p < 0.05$) increased in heart rate at 20 minute in group C may be as a result of the stimulatory effect of ketamine on the heart and/ or a sign of light anaesthesia or awakening (Hall *et al*., 2001). This necessitated the administration of maintenance dose of propofol that decreased ($p < 0.05$) the heart rate at 30 minute post induction.

The significant decrease in respiratory rate was found in groups I, II and IV. This may be attributed to the effects of xylazine and propofol which are both potent respiratory depressants. The decreased in the respiratory rate in group I (xylazine/ ketamine) was in accordance with the previous finding of Borkowski *et al*. (1990) and Vertegen *et al*. (1991) in rabbit and cat respectively. On the contrary, Eze *et al*. (2004) reported an increase in respiratory rate in goat after xylazine / ketamine administration which was attributed to the overriding effect of ketamine. However, no significant ($p > 0.05$) decrease in respiratory rate

was observed in group III. This showed that administration of ketamine with propofol prevented respiratory depression, which was seen when propofol was used with xylazine (Muhammed *et al*., 2009). Ketamine is said to differ from other anaesthetics because it does not depress ventilatory response to hypoxia (Eze *et al*., 2004). The decreased in respiratory rate was prolonged by maintenance dose in groups A, B and D but not in group C in the second experiment.

The decreased in temperature recorded in groups I and A (Xylazine/ketamine groups) is in accordance with the finding of Eze *et al*. (2004). Also the decrease in groups II and B (xylazine/propofol groups) has been reported by Adetunji *et al*. (2002). The rectal temperature dropped to about 36°C in group II and lasted throughout the period of studies. The maintenance of anaesthesia did not prolong the drop in the rectal temperature beyond 40 minutes in groups A and B. This is probably due to non inclusion of xylazine in the drugs used for the maintainance of anaesthesia in both groups as xylazine has been reported to cause decrease in rectal temperature in goat (Dehghani *et al*., 1991; Mohammed and Yelwa, 1993).

The short onset of analgesia recorded in groups II, III, and IV when compared to that in group I, and in groups B, C and D when compared to group A, may be as a result of effect of propofol in the combinations. This was not seen in xylazine/ ketamine combinations in both experiments. Propofol causes rapid induction within 15 to 30 seconds resulting in unconsciousness (Prassinos *et al*., 2005). The combined effect of the three drugs seems to have reduced the onset of analgesia to almost 1 minute in groups IV and D in both protocols.

It is interesting to note that there was no significant ($p > 0.05$) variation in the value of surgical anaesthetic time among groups I, II and III respectively. This showed that the involvement of xylazine in the drug combination of the three groups potentiated the analgesic and sedative effects of the drugs. Xylazine acts in synergism with ketamine to produce better analgesic effect (Taylor, 1991).

Maintenance of anaesthesia in protocol II produced surgical anaesthetic time of 51.00 ± 11.01, 50.51 ± 7.23, 30.00 ± 0.41 and 78.50 ± 1.04 for groups A, B, C and D respectively. The drug combination in group D produced the longest surgical anaesthetic time than others following maintenance. This can be attributed to the effect of anaesthetic and analgesic synergism of the three drugs in the combination. The combination was more potent since it produced longer duration of surgical anaestheasia than combinations used in other groups. Therefore, this implies that clinically, this particular combination can be used successfully in long surgical procedures. However drug combination in groups A and B produced almost the same surgical anaesthetic time while that of group C produced the least surgical anaesthetic time.

The decrease in the packed cell volume, haemoglobin concentration, red blood cells and total white blood cells was transient and most of the values returned to pre-induction value within 24 hours post recovery. The decrease can be attributed to the haematological effects of xylazine and ketamine. Kumar and Thurmon (1979) reported that xylazine caused a decrease in total number of erythrocytes, leucocytes, haemoglobin concentration, and haematocrit at maximal depth of analgesia. The decrease in haematological values following administration of xylazine might have resulted from pooling of blood in the spleen as has been reported in

other tranquilizers in goat (Monzaly *et al*., 1992). Also, ketamine had caused decrease in all haematological value (Wall *et al*., 1995; Singh *et al*., 2006; Ramasamy *et al*., 2006).

Blood glucose level significantly increased ($p < 0.05$) in all groups at 30 minute post induction. This may be regarded as a stress response (Singh, 2003). However, it was probably caused by hyperglycemic effect of ketamine and xylazine (Saha *et al*., 2005; Suilaman and Hanan, 2009). The elevation in the blood glucose may be a transient effect of the anaesthetics because the blood glucose values returned to the pre-induction value before 1440 minutes post recovery in all groups except in group III in protocol I. It may be that the hyperglycemic effect of the drug combination in group III in protocol I (ketamine-xylazine) has more hyperglycemic effect than the other combinations that it lasted longer post recovery. Hence, the use of the combination in a diabetic patient must be done with caution.

Cortisol level was significantly low in groups II and IV in protocol I, and B in protocol II at 30 minute post induction. This showed the effects of anaesthetics on the cortisol level which may have resulted from the suppression of production and release of cortisol in the blood. This can be attributed to the suppressive and inhibitory action of propofol and xylazine on the adrenal steroidogenesis (Lambert *et al.*, 1985 and Rizk *et al*., 2012). Sanhouri *et al* (1992) reported that pre-treatment of goat with xylazine suppressed cortisol concentration induced by transportation. The combine effect of propofol and xylazine on cortisol concentrations was prominent in groups II in protocol I and B in protocol II at 30 minute which was significantly low when compared to other groups. However there was surge in the concentration at 1440 minutes post recovery when the effect of the anaesthetic must have waned (Konstopanagiotou *et al.*, 2010). The increase was same in groups III, IV, A, C and D

of the two protocols II. It is interesting to note that it returned to pre-induction value in all the groups before 1440 minutes post recovery.

Blood urea nitrogen and creatinine tests revealed the efficiency of renal function, the ability of kidney to excrete these metabolites (Kaplan, 1965 and Gonzalez Gil *et al.*, 2003). Decreases in the blood urea nitrogen and creatinine concentration were observed after propofol-xylazine, propofol-ketamine and propofol-xylazine-ketamine administration. This implies that the kidney stepped up its function in response to elimination of the three drugs. This may have increased glomerular filteration and urine output. Xylazine has been report to cause polyuria in goat (Mohammed and Yelwa, 1993). However, an increase in blood urea nitrogen was observed after propofol-ketamine administration 120 minutes post recovery in group III. This has been reported in rabbit after ketamine-xylazine administration (Mavadati *et al.*, 2001 and Gonzalez Gil *et al.*, 2003).

An increase in ALT was observed after administration of xylazine-ketamine (group A) in protocol II, ketamine-propofol (group C) in protocol II and xylazine- ketamine-propofol (groups IV and D) in protocol I and II respectively. It is possible that hypotension in combination with hypoxemia due to lowered packed cell volume and haemoglobin concentration (Wyatt *et al.*, 1989; Mavadati *et al*., 2001 and Gonzalez Gil *et al*., 2003) may be associated with the release of these enzymes from the heart muscles or liver. Gonzalez Gil *et al*. (2003) reported increase in ALT concentration following the administration of ketamine-xylazine in rabbit.

Those changes in serum BUN, ALT, and creatinine observed after induction of the anaesthetics might be related to possible short term effect of the anaeasthetics on the renal function rather than pathological conditions.

Side effects observed include apnoea, snoring, salivation, paddling, and ataxia, urination, open eyelid, and salivation. Apnoa occurred in all the groups in both protocols. It is possible that the three drugs used (xylazine, ketamine and propofol) are associated with apneustic breathing post administration. Apneustic breathing is characterized by inspiratory holding which last for some minutes. Propofol produced apneic period of 30 to 60 second following normal induction dose (De cosmo *et al*., 2005; Mehrdad *et al*., 2010; Krzych *et al*., 2009). Apnoa has been reported after propofol used in human beings (Langley and Heel, 1988; De cosmo *et al*., 2005). It has also been reported in goat after propofol administration (Pablo *et al.*, 1997; Prassinos *et al*., 2005).

Ketamine alone or ketamine-xylazine caused apnoa in goat (Prassinos *et al.*, 2005; Eze *et al*., 2004; Udegbunam; Adetunji, 2007). It is also the side effect of xylazine (Hall and Clark, 1991).

Salivation was seen in all the groups but it was more profuse in ketamine-xylazine and ketamine- propofol groups in both protocols. Both xylazine and ketamine or ketamine-xylazine combination have been reported to cause salivation in goat under anaesthesia (Mohammed and Yelwa, 1993; Eze *et al*., 2004; Udegbunam and Adetunji, 2007). Bags were used to support the heads of the animal at poll and saliva flowed freely out of the mouth (Taylor, 1991).

Urination was also observed in all the groups in both protocols. However, it was more pronounce in xylazine-propofol and xylazine-ketamine-propofol groups in both experiment. Urination is a means of elimination of the three drugs by the kidney. It is a response of healthy kidney to eliminate these substances in the body. Urination following the administration of xylazine is a common occurrence in goat (Mohammed and Yelwa, 1993;

Aithal *et al.,* 1996). Mohammed and Yelwa, (1993) reported polyuria following administration of xylazine which is thought to be due to prolonged hyperglycaemia which was shown to persist for up to 150 minutes post-xylazine injection in goats. Urination post ketamine-xylazine injection has been reported (Eze *et al*., 2004; Udegbunam and Adetunji, 2007)

5.2 CONCLUSION

Based on the results from this study, the intravenous injection of the four different combinations of the anaesthetic drugs caused smooth and uneventful induction with mild cardiopulmonary depressions and rapid recovery. Their effects on haematological values as well as biochemical values were also mild.

The xylazine-ketamine-propofol combination produced the longest surgical anaesthetic duration in both single injection and maintenance procedures and may be used successfully in both short and long surgical procedure without untoward side effects.

The xylazine-ketamine and xylazineï propofol combinations produced moderate surgical anaesthetic time with mild side effects. The combinations can be recommended for use in some surgical procedures.

The ketamine-propofol combination produced the shortest duration of surgical anaesthesia but greater haemodynamic stability than other combinations. However, its use in long surgical procedure requires that several maintenance doses may be needed before the end of the procedure and may result in severe side effect and waste of drugs.

Apnoea was the major side effect of the combinations more especially in propofol combinations. Therefore, care must be taken when administering these drugs by monitoring the animal closely to know when the apnoea develops. Drug administration should be stopped whenever the apnoea starts and continued when the animal regain its normal regular breathing. An attempt to continue with the injection or infusion of drug once the apnoea develops may lead to respiratory arrest and possible death of the animal.

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APPENDIX

TABLES FOR TRIAL STUDY

Heart rate

Time	Group 1	Group 2	Group 3
0	84 ± 5.57	92 ± 3.42	84 ± 4.51
10	96 ± 6.30*	120 ± 2.5*	96 ± 4.05*
20	84 ± 6.4	120 ± 7.5*	102 ± 6.15*

Respiratory rate

Time	Group 1	Group 2	Group 3
0	28 ± 2.15	46 ± 3.06	32 ± 2.25
10	24.5 ± 1.50 *	38 ± 2.80*	28 ± 5.17
20	32.2 ± 4.15*	46 ± 2.16	28 ± 5.2

Rectal temperature

Time	Group 1	Group 2	Group 3
0	37.9 ± 0.06	38.50 ± 0.22	40.00 ± 0.15
10	37.4 ± 0.15	38.4 ± 0.24	39.50 ± 0.22
20	37.6 ± 0.09	38.5 ± 0.25	39.6 ± 0.30

Onset of analgesia

Group	Time
1	1.00 ± 0.00
2	1.00 ± 0.00
3	0.56 ± 0.30

Surgical anaethetic time

Group	Time
1	3.01 ± 1.00^{a}
2	9.02 ± 2.00^{b}
3	16.20 ± 1.20^{c}

Recumbent time

Group	Time
1	7.00 ± 2.00^{a}
2	15.00 ± 1.00^{b}
3	21.00 ± 2.40^{c}

Standing time

Groups	Time
1	1.0 ± 0.02
2	1.0 ± 0.15
3	1 ± 0.15

TABLES FOR PROTOCOL I

Heart rate (beat/minute)

Time (minutes)	Group I (b/m)	Group II (b/m)	Group III (b/m)	Group IV (b/m)
0	87.25 ±1.11[a]	120.00 ± 9.13[b]	90.00 ± 8.41[a]	109.00 ± 5.45[ab]
10	97.00 ± 2.38*[a]	94.00 ± 4.08*[a]	98.00 ± 4.16[a]	104.00 ±1.83[ab]
20	82.00 ± 1.15[a]	97.00 ± 3.36*[a]	106.00 ± 4.39[c]	100.00 ± 0.00*[c]
30	74.00 ± 2.90*[a]	97.00 ± 6.22*[b]	106.00 ± 4.40[c]	104.00 ± 1.83[c]
40	73.75 ± 2.19*[a]	105.00 ± 6.22[b]	106.00 ± 4.39[c]	104.00 ± 1.30[c]

*Data in the same column differ significantly from the pre-induction value (time 0) ($p < 0.05$)
[abc] figures with different superscripts within row are significantly different ($p < 0.0$

Respiratory rate (breath/minute)

Time	Group I	Group II	Group III	Group IV
0 minute	28.00 ± 0.00[a]	30.00 ± 0.81[a]	30.00 ± 0.81[a]	29.50 ± 0.95[a]
10 minute	16.00 ± 0.00*[a]	26.00 ± 0.81[b]	28.00 ± 1.82[b]	29.50 ± 1.70[b]
20 minute	18.00 ± 0.81*[a]	24.00 ± 1.40*[b]	30.00 ± 0.81[c]	24.00 ± 0.00*[b]
30 minute	20.00 ± 1.63*[a]	21.50 ± 2.06*[a]	31.00 ± 0.57[b]	24.00 ± 1.63*[a]
40 minute	20.00 ± 1.82*[a]	21.00 ± 2.08*[a]	30.00 ± 0.81[b]	26.00 ± 0.81[b]

*Data in the same column differ significantly ($p < 0.05$) from the pre-induction value (time 0) [abc] figures with different superscripts within row are significantly ($p < 0.05$) different

Rectal temperature ($^{\xi}$c)

Time	Group I	Group II	Group III	Group IV
0 minute	39.05 ± 0.06[a]	39.25 ± 0.25[a]	39.45 ± 0.34[a]	39.78 ± 0.16[a]
10 minutes	37.55 ± 0.02*[b]	36.57 ± 1.07*[a]	39.20 ± 0.34[b]	39.15 ± 0.25[b]
20 minutes	37.15 ± 0.40*[a]	37.10 ± 0.45*[a]	39.00 ± 0.40[a]	38.35 ± 1.38[a]
30 minutes	37.30 ± 0.16*[b]	36.80 ± 0.33*[a]	39.00 ± 0.46[b]	38.85 ± 0.02[b]
40 minutes	37.48 ± 0.18*[b]	36.80 ± 0.33*[a]	39.20 ± 0.35[c]	39.05 ± 0.08[c]

*Data in the same column differ significantly ($p < 0.05$) from the pre-induction value (time 0) [abc] figures with different superscripts within row are significantly ($p < 0.05$) different

Onset of analgesia

Group	time (minutes)
I	4.00 ± 0.41[c]
II	2.02 ± 0.47[b]
III	2.01 ± 0.02[b]
IV	1.00 ± 0.00[a]

Duration of analgesia

Groups	Time (minutes)
I	2 4.5± 4.29[b]
II	21.00 ± 1.87[b]
III	12.25 ± 1.25[a]
IV	26.5 ± 2.25[b]

Recumbent time

Group	**time (minutes)**
I	**56.50 ± 3.75[d]**
II	**28.05 ± 2.01[b]**
III	**17.50 ± 1.04[a]**
IV	**41.50 ± 2.25**c

standing time

Groups	**time(minutes)**
I	**3.5** ± 0.28[a]
II	**2.25** ± 0.48[a]
III	**8.50** ± 1.05[b]
IV	**2.50** ± 1.05[a]

TABLES FOR PROTOCOL II

Heart rate (beat/minute),

Time	Group A	Group B	Group C	Group D
0	**122.00** ± 0.82	**110.00** ± 2.58	**91.00** ± 8.18	**110.50** ± 3.40
10	**91.00** ± 0.57*	**94.00** ± 4.16*	**92 .00** ± 1.83	**108.00** ± 0.57
20	**84.00** ± 1.15*	**96.00** ± 2.88*	**110.00** ± 7.02*	**106.00** ± 0.57
30	**86.00** ± 3.46*	**92.00** ± 5.23*	**96.00** ± 2.30	**96.00** ± 0.57*
40	**84.50** ± 0.50*	**96.50** ± 5.43*	**102.50** ± 6.13	**97.00** ± 0.57*
50	**101.00** ± 9.88*	**93.50** ± 4.78*	**103.50** ± 4.56	**88.00** ± 1.83*
60	**104.00** ± 9.93	**91.00** ± 3.42		**86.00** ± 0.82*
70	**94.00** ± 8.08	**103.50** ± 5.56		**93.50** ± 0.95*
80	**100.00** ± 0.00	**99.00** ± 6.95		**93.00** ± 1.47*

*Data in the same column differ significantly ($p < 0.05$) from the pre-anaesthetic value (time 0)
^{abc} figures with different superscripts within row are significantly ($p < 0.05$) different.

Respiratory rate (Breath/Minute).

Time	Group A	Group B	Group C	Group D
0 minute	**30.00** ± 0.81	**32.00** ± 1.82	**26.00** ± 0.81	**26.00** ± 0.81
10 minutes	**22.00** ± 0.82*	**24.00** ± 0.81*	**30.00** ± 3.30	**30.00** ± 2.94
20 minutes	**16.00** ± 2.03*	**34.00** ± 7.02	**40.00** ± 3.65*	**30.00** ± 1.15
30 minutes	**18.00** ± 1.15*	**20.00** ± 2.30*	**30.00** ± 3.46	**22.00** ± 1.15*
40 minutes	**21.00** ± 2.88*	**20.00** ± 1.82*	**24.00** ±1.82	**16.00** ± 2.30*
50 minutes	**19.00** ± 1.73*	**26.00** ± 0.82*	**26.00** ± 0.81	**21.00** ± 0.81*
60 minutes	**21.00** ± 0.57*	**28.00** ± 3.65	**26.00** ± 1.15	**12.00** ± 0.00*
70 minutes	**22.00** ± 2.94*	**30.00** ± 1.70		**16.00** ± 0.81*
80 minutes	**19.00** ± 3.86*	**32.00** ± 1.36		**20.00** ± 0.81*

*Data in the same column differ significantly ($p < 0.05$) from the pre anaesthetic value (time 0)
^{abc} figures with different superscripts within row are significantly ($p < 0.05$) different.

Figure 9: Rectal temperature ($^{\xi}$c),

Time	Group I	Group II	Group III	Group IV
0 minute	**38.30** ± 0.04^{a}	**37.55** ± 0.06^{b}	**37. 62** ± 0.12^{b}	**37.72** ± 0.08^{b}
10 minutes	**38.15** ± 0.02^{b}	**37.00** ±0.14*^{a}	**37.95** ± 0.14^{b}	**38.75** ± 0.10*^{c}
20 minutes	**37.95** ± 0.19*^{c}	**36.90** ±0.11*^{a}	**37.80** ± 0.08^{b}	**38.20** ± 0.08*^{c}
30 minutes	**37.95** ± 0.19*^{c}	**36.80** ± 0.14*^{a}	**37.95** ± 0.29^{b}	**37.45** ± 0.02^{b}
40 minutes	**38.10 ± 0.07**	**37.55** ± 0.08*^{a}	**37.25** ± 0.14^{b}	**37.80** ± 0.19^{c}
50 minutes	**38.00** ± 0.05^{a}	**37.45** ± 0.25^{a}	**37.25** ± 0.31^{a}	**37.85** ± 0.25^{a}
60 minutes	**38.12** ± 0.14^{a}	**37.45** ± 0.23^{a}		**37.85** ± 0.25^{a}
70 minutes	**38.20** ± 0.11^{a}	**37.35** ±0.20^{a}		**37.65** ± 0.25^{a}
80 minutes	**38.40** ± 0.05^{a}	**37.25** ± 0.31^{a}		**37.90** ± 0.35^{a}

*Data in the same column differ significantly ($p < 0.05$) from the pre anaesthetic value (time 0)
^{abc} figures with different superscripts within row are significantly ($p < 0.05$) different.

Onset of analgesia

Group	**time (minutes)**
A	**3.57 ± 0.28[c]**
B	**2.05 ± 0.02[b]**
C	**1.75 ± 0.29[b]**
D	**1.00 ± 0.00[a]**

Duration of analgesia

Groups	Time (minutes)
A	51.00 ± 11.01[b]
B	51.50 ± 05.92[b]
C	30.00 ± 00.41[a]
D	78.50 ± 01.04[c]

Recumbent time

Group	**time (minutes)**
A	**91.50 ± 3.75[c]**
B	**68.00 ± 2.97[b]**
C	**47.00 ± 3.29[a]**
D	**91.00 ± 2.08[c]**

Mean standing time

Group	**time (minutes)**
A	**4.75** ± 0.48[b]
B	**1.50** ± 0.29[a]
C	**7.50** ± 0.29[c]
D	**2.00** ± 0.41[a]