Sudan University of Science and Technology

College of Veterinary Medicine

COMPARATIVE STUDY OF DIFFERENT DOSES OF KETAMINE WITH XYLAZINE IN MONKEYS. IN KUKU ZOO EAST NILE KHARTOUM STATE

(Chlorocebus sabaeus)

دراسة مقارنة لجرعات مختلفة من الكيتامين هيدروكلوريد مع الزايلازين هيدروكلوريد في القرود

A dissertation submitted in partial fulfillment of the requirement of College of Veterinary Medicine for B.V.M

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DEDICATION

To the spring that does not tire of giving, whoever has made my happiness with woven threads from her heart to my dear mothers

To those who seek and share to enjoy the comfort and joy that led me to the path of success and taught me to rise the ladder of life with wisdom and patience to my dear fathers.

To whom I love, who walks in my veins, and preaches in their memories, and I turn to my brothers and sisters

To whom we have traveled together, we are moving together towards success and creativity to our friends

Who taught us letters of gold and words of words and expressions of the highest and most beautiful expressions in science to our dear professors and Doctors

To all those who supported us in completing this research

To Sudan university of science and technology

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List of Abbreviations

K1Z	Ketamine (2.5 mg kg^{-1}) with Xylazine (1 mg kg^{-1})
K2Z	Ketamine (5 mg kg^{-1}) with Xylazine (1 mg kg^{-1})
i. m	Intra-muscular
i.v	Intra-venous
SE	Stander Error
RR	Respiratory Rate
HR	Heart Rate
NS	Not Significant
Sig	Significance
HCL	Hydrochloride
MRI	Magnetic Resonant Imaging
NMDA	N-methyl-D-aspirate
M	Muscatine
C°	Degree centigrade
Kg	Kilogram
Ml	Millitre
SPSS	statistical package for social science
PCP	Phencyclidne
IOP	Intra Ocular Pressure
CO_2	Carbone dioxide

Acknowledgement

We Have Started With More Than One Hand And Many Of Us, And We Have Had Many Difficulties. Today, Thanks To God, We Help Turn This Page And Present The Essence Of Our Journey Between The Depths Of This Humble Work.

To The Lighthouse Of Science And Imam Mustafa To The Illiterate, Who Taught The Learners To The Master Of Creation To Our Noble Messenger, Our Master Muhammad Peace Be Upon Him.

To Whom, Without Her This Work Was Not To Be Created, Whom Formulated For Us From Her Knowledge Letters And Thought Of A Beacon Illuminating The March Of Science And Success To Ours Supervisor DR . Geehan Abdullah Mohamed. Prof. Shadia Abdelatti, Dr. Abubaker, Dr.Ahmed Adam, Motwakel Abdelrhman And Alaa Ahmed For Their Endless Support.

Abstract

This study was conducted to compare between two general anesthetic protocols in monkeys using Ketamine HcL as sole anesthetic agent with Xylazine HcL as premedication drug.

Two intramuscular anesthetic protocols were used to anesthetize eight clinically sound green monkeys. The first intramuscular protocol was achieved by using Ketamine at dose rate (2.5mg kg^{-1}) and the second anesthetic protocol was obtained by using Ketamine (5mg kg^{-1}), both anesthetic protocols were performed in Xylazine (1mg kg^{-1}) premedicated monkeys.

Clinical parameters such as Respiratory rates, heart rates, and rectal temperature were monitored; some anesthesia phases (induction time, Duration of anesthesia and recovery time) were recorded.

The quality of both induction and recovery with the degree of muscle relaxation and some selected anesthetic reflexes were observed.

Both anesthetic protocols were safe, no incidence of apnea was observed, the anesthetic protocol using Ketamine at dose 5mg kg^{-1} with Xylazine (1mgkg^{-1}) showed significant increase in the duration of anesthesia compare with the other protocol. It could be concluded that both intramuscular anesthetic protocol were suitable for many surgical interventions in monkey, however, the protocol using Ketamine in dose rate of 5mg $kg^{-1}$was found to be superior to the other protocol.

Key word: Anesthesia, Ketamine, Xylazine, Monkeys.

خلاصة الأطروحة

أجريت هذه الدراسة للمقارنة بين نوعين من البرتوكولات التخديرية في القرود، باستخدام هيدروكلوريد الكتامين كمخدر اساسي مع هيدروكلوريد الزيلازين كعلاج تمهيدي.

أستعمل بروتوكولين تخديريين عضليين في ثمانية قرود سليمة سريريا، البروتوكول التخديري العضلي الاول تم باستعمال الكتامين بجرعة ٢,٥ ملجم كجم$^{-1}$ والبروتوكول التخديري الثاني بجرعة ٥ ملجم كجم$^{-1}$ من الكتامين في قرود سبق علاجها تمهيديا بجرعة ١ ملجم كجم$^{-1}$ من الزيلازين.

تمت مراقبة القياسات السريرية مثل معدلات التنفس ، ضربات القلب ودرجة حرارة الجسم كما سجلت بعض مراحل التخدير مثل (زمن إحداث التخدير ، ومدة مفعول المخدر و زمن الإفاقة من التخدير).

كما لوحظت نوعية كل من إحداث التخدير والإفاقة منه ودرجات الإرتخاء العضلي وبعض المنعكسات التخديرية.

وجد أن كل من البروتوكوليين التخديريين آمن ولم يلاحظ حدوث لتوقف التنفس، كما وجد أن هنالك زيادة معنوية في زمن مفعول التخدير عند استعمال الكتامين بجرعة ٥ ملجم كجم$^{-1}$ مقارنة بالجرعة الاخري (٢,٥ ملجم كجم$^{-1}$).

استنتج أن كل من البروتوكوليين التخديريين العضليين مناسب لإجراء بعض التدخلات الجراحية بالقرود وأن البروتكول التخديري بإستعمال ٥ ملجم كجم$^{-1}$ من الكتامين يتفوق علي البروتوكول التخديري الآخر.

كلمات مفتاحية: تخدير، كتامين ، زيلازين، قرود.

Introduction

Monkeys are Haplorhineprimates, a group generally possessing tails and consisting of about 260 known living species. There are two distinct lineages of monkeys: New world Monkeys and Catarrhines. Apes emerged within the Catarrhines with the old world monkeys as a sister group. Many monkeys species are tree-dwelling (arboreal), although there are species that live primarily on the ground, such as baboons. Most species are also active during the day (diurnal). Monkeys are generally considered to be intelligent, particularly old world monkeys (Fleagle,zs 2014).

The green monkey *(Chlorocebus sabaeus)*, also known as the Sabaeus monkey or the call Ithrixmonkey (Kingdon, 1997). It is an old world monkey with golden-green fur and pale hands and feet. The tip of the tail is golden yellow as are the backs of the thighs and cheek whiskers. It does not have a distinguishing band of fur on the brow, like other *Chlorocebus* species, and males have a pale blue scrotum (Cawthon, 2006*)*.

Intramuscular injection of selected ratios of Ketamine and Xylazine provided smooth anesthetic induction, wide safety margin, and no significant undesirable side effects. Induction, recovery times, duration of anesthesia, and thermoregulatory ability can be affected by different combinations of Ketamine and Xylazine. The addition of Xylazine to Ketamine increases muscle relaxation, recovery time and duration of anesthesia, while generally decreasing induction time and thermoregulatory ability (Elise *et al.,* 1979).

Objective

The specific aim of this observational clinical study was to:

1. Evaluate the effectiveness and practicability of Ketamine and Xylazine on induction time, duration of anesthesia and recovery time in green monkey under filed condition.
2. Study the effect of two intramuscular anesthetic protocols using Ketamine (2.5mg kg^{-1}) plus Xylazine (1mg kg^{-1}) and Ketamine at dose rate (5mg kg^{-1}) with Xylazine (1mg kg^{-1}) on respiratory, heart rates and rectal temperature as stress biomarkers.
3. Compare and contrast between the two mentioned anesthetic protocols on anesthesia phase (induction time, duration of anesthesia and recovery time).
4. Select the superior satisfactory anesthetic protocol, hence, to provide clinical guidance to veterinary practitioners in term of dosage and rout of administration in green monkeys.

CHAPTER ONE
LITERATURE REVIEW

1.1. Anesthesia in monkey

Chemical immobilization of wild primates is a difficult, risky and hazardous procedure. Besides the risks related directly to the capture itself, several authors have stressed the problem of behavioral disruption of a group following an anaesthetic event, resulting for example in a change in the social status of the darted individual (Chimpanzee Pan troglodytes; S. Unwin personal observations).This can also manifest as an altered response to the human observer (Karesh *et al*., 199^). Procedures for darting small arboreal primates are described by Glander *et al.* (1991), Jones and Bush (1988) and Karesh *et al.* (1998).

When anesthetizing primates, the greatest challenge is to restrain the patients during the induction because of their agility, strength and defensive nature. Different drugs and combinations for immobilizing and anesthetizing primates are recommended, the use of dissociatives for restraint, as preanesthetics and as anesthetics has revolutionized the handling of primates. Inhalation anesthesia produces surgical anesthesia and prevents involuntary movements observed when administering ketamine alone (Schumacher, 1998).

In rhesus monkey study only single ratio (5:1) of Ketamine to Xylazine was used and the effect of Xylazine alone was not evaluated, the addition of Xylazine to Ketamine increased the mean duration of anesthesia as logarithmic function of the Xylazine dose (Elise *et al.*, 1979).

Medetomidine is an alpha-2-adrenergic receptor agonist administered with Ketamine in cruces sedation anesthesia in non-human primates in dose dependent, species-specific manner, Medetomidine. The dose 150microgram/kg per Ketamine 4mg/kg provided anesthesia for handling and restraint within 10 minutes of administration (Theriault *et al.*, 2008). Fowler *et*

al. (2001) used Tiletamine/ Zolazepam and Glycopirolate as premedication, propofol for induction and isofrurane with propofol for maintenances of anesthesia during magnetic resonant imaging (MRI) scanning in rhesus monkeys.

1.2. Ketamine Hydrochloride

Dissociative anesthesia, general anesthetic and tranquilizer is administered intravenously rapid acting general anesthetic producing an anesthetic state characterized by profound analgesia, normal pharyngeal-laryngeal reflex cardiovascular and respiratory stimulation, and occasionally transient and minimal respiratory depression (Haskins *et al.*,1986:Hall and Clarke, 1991)

Ketamine muscle relaxation properties are poor, but are improved with sedatives such as Diazepam or Xylazine (Hall *et al.*, 2001; Hirota and Lambert, 1996).

1.2.1. Commercial Name

Ketalar®,Ketalin®, Ketalor® and Ketaminol®.

1.2.2. Chemical Name

2- (2-Chlorophenyl)-2-(Methyl amino).

1.2.3. Ketamine Formula

Free base: C13H16ClNO

Hydrochloride Salt: C13H17ClNO.

1.2.4. Usage of Ketamine

Ketamine is used as a tranquilizer, antiemetic and analgesia agent for treatment of neuropathic pain syndrome (Rojas, 2012), or as a premedication prior to general anesthesia at high-fully anesthetic level doses, Ketamine has also been found to bind to opioid receptors and sigma receptors and induce a

state of dissociative anesthesia (Chohan, 2010). It has rapid pharmacological action characterized by profound analgesia, mild cardiac stimulation, normal pharyngeal-laryngeal reflexes, mild respiratory depression and markedly increased intraocular pressure. It produces paralysis with some muscle rigidity, good analgesia, and complete amnesia. Ketamine can be used for routine surgical procedures when administered in combinations with Diazepam, Medetomidine, Propofol. or Xylazine for desexing (Baba , 2012). As a sole agent, it can be given for minor procedures such as catheterization associated with urolithiasis. Ketamine is agent of choice in non-human primate

1.2.5. Composition of Ketamine

Ketamine (2-(2-chlorophenyl)-2-(methyl amino) - Cyclohexanone) is an arylcycloalkylamine structurally related to phencyclidine (PCP), it is water-soluble, white crystalline and has a PH of 7.5. Its free base has lipid solubility 10 times than that of thiopentone sodium. The commercially available pharmaceutical form is an aqueous solution for injection of the raceme mixture of the hydrochloride salt (Budavari *et al.*, 1989).

1.2.6. Ketamine Pharmacology and Mode of Action

Ketamine is a dissociative anesthetic, originally, the dissociation component refers to a functional and electrophysiological dissociation of thalamo-neocorticaland limbic systems (Reich and Silvay, 1989; Haas and Harper, 1992). Later, the nature of the sub anesthetic Ketamine experience has led to the use of the term ‘dissociative‘ in a more psychological sense referring to a feeling of dissociation of the mind from the body (Jansen, 1990). Ketamine binds to the so-called PCP-binding site of the N-methyl-D-aspirate (NMDA)-receptor complex, located within the ion channel, thereby blocking the transmembranous influx. This makes Ketamine a non-competitive NMDA-receptor antagonist. NMDA-receptors are calcium-gated channel receptors. The endogenous agonists of this receptor are the excitatory amino acids glutamic

acid, aspartic acid, and glycine. Activation of the receptor results in opening of the ion channel and depolarization of the neurons. The NMDA-receptor is involved incensory input at the spinal, thalamic, limbic and cortical levels. Ketamine would be expected to block or interfere with sensory input to higher centers of the central nervous system (CNS), with the emotional response to these stimuli, and with the process of learning and memory (Bergman, 1999). Awakening from Ketamine anesthesia takes place at plasma concentrations of 0.64-1.12 μg/ml (Reich and Silvay, 1989). Ketamine is rapidly absorbed when administered through the intramuscular (T-max 5-15 min), nasal (T-max 20 min) or oral route as a solution (T-max 30 min).

Bioavailability is low when Ketamine is given orally (17%) or rectally (25%). Extensive first pass metabolism in liver and intestine is largely responsible for this effect. Bioavailability after nasal administration is approximately 50%. This may partly be caused by significant swallowing of the fairly large intranasal deposit. Ketamine has a high lipid solubility and low plasma protein binding (12%), which facilitates rapid transfer across the blood-brain barrier. Initially it is distributed to highly perused tissues, including the brain, to achieve levels 4-5 times those in plasma (distribution half-life after i.v.24 sec.). CNS effects subside, following redistribution to the less well-perfuse tissues (re-distribution half-life 2.7 min.). The predominant route of elimination is by liver metabolism. The high extraction rate (0.9) makes Ketamine clearance susceptible to factors affecting blood flow. The conjugated hydroxyl metabolites are mainly excreted renaly .Terminal elimination half-life are ranging from 100-200 minutes (Malinovsky *et al.*, 1996).

1.2.7. Ketamine Dosage and Route of Administration

Ketamine (dose may range from 1 to 4.5 mg/kg); an intramuscular dose equivalent to 10 mg per kg body-weight usually produces surgical anesthesia

within 3 to 4 minutes lasting for 12 to 25 minutes(Reynolds *et al*., 1989). Analgesia is obtained by administration of 0.2-0.75 mg/kg intravenously (Reich and Silvay, 1989). Sub anesthetic doses inducing psychotropic effects range from 0.1 to 1.0 mg/kg i.v. Clinically, the drug usually is administered by intramuscular or intravenous injection. For analgesia, the intra theca route is used as well. Also, the oral and the rectal routes have been described (Reich and Silvay, 1989).

1.2 .8.Complications of Ketamine

Abdel-Rahman and Ismael (2000) studied the teratogenic potency of Ketamine hydrochloride in CF-1 mice with and without cocaine, was shown that Ketamine (50 mg/kg/day) potentiated the teratogenic effects of cocaine Olney *et al*. (2000) suggested that Ketamine has the potential to delete large numbers of neurons from the developing brain by a mechanism involving interference in the action of neurotransmitters glutamate and gamma amino butyric acid (GABA)at N-methyl-d-aspartate (NMDA) and GABA receptors during the synaptogenesis. Period of pregnancy and the first several years after birth in humans) causes millions of developing neurones to commit suicide (die by apoptosis). Ketamine is highly unlikely to possess any relevant genotoxic properties (Waskell, 1978; Adhvaryu *et al.*, 1986). Neurotoxicity of Ketamine was observed in rats (Olney *et al.*, 1991).

1.2.9. Ketamine Contraindications and Interactions

This drug is contraindicated in canine patients with glaucoma, seizures or chronic renal disease. A number of studies have demonstrated tolerance to the effects of Ketamine (White and Ryan, 1996). This type of acute tolerance is related to changes at the site of action rather than any increase in rate of metabolism. Rats, chronically exposed to Ketamine, exhibited sub cortical withdrawal seizures manifestations for up to 5 days after self-administration was discontinued(White and Ryan, 1996), its use is contraindicated in patients

with significant ischemic heart disease and should be avoided in patients with a history of high blood pressure (Haas and Harper, 1992).

1.2.10. Ketamine in Wilde Life Practice:

In veterinary medicine, Ketamine hydrochloride is usually used in combination with other anesthetic drugs and in mono narcosis as a strong analgesic agent (Wright, 1982; Haskins, 1985). Ketamine hydrochloride in monkeys induces increased in cerebral blood flow, intracranial and cerebrospinal fluid pressure as a result of cerebral vasodilatation, and elevated arterial blood pressure (Thurmon *et al.*, 1996).

1.2.11. The Effects of Ketamine on the Clinical Parameters

Ketamine is a mild respiratory depressant. It causes a shift of the CO_2 dose-response curve to the right, in a dose-related manner, but does not change the slope of the curve; this effect is similar to that of opioids, but dissimilar from most sedative hypnotics and anesthetics, suggesting that opioid receptors may play a role in the respiratory depressant effect. In clinical study the respiratory depression occur after rapid intravenous injection of Ketamine (Reich and Silvay, 1989; White and Ryan, 1996). Ketamine differs from most anesthetic agents in that it appears to stimulate the cardiovascular system, producing changes in heart rate, and blood pressure (Haas and Harper, 1992). On the other hand cardio depressant effects have been noted in critically ill patients, on the other hand, administration of Ketamine/ Xylazine in monkeys did not cause any significant changes in body temperature (Kul *et al.,* 2000).

1.3. Xylazine:

Xylazine is the first alph-2 adrenergic agonist to be used as a sedative as analgesic agent by veterinarians in animals before the advent of Medetomdine, a more specific and potentα-2 adrenergic agonist (Hall *et al*., 2001).

1.3.1. Identity:

Xylazine is an organic base which is administered as an aqueous solution of Hydrochloride salt (Brander *et al.*, 1991).

1.3.2. Proprietary (Trade) Name

Rompun®, Xylazine HCl® and Xyloject®

1.3.3. Chemical Name

2 (2, 6 dimethyl phenylamine) -4-H-5, 6-dihydro-1, 3-thiazine.

1.3.4. Molecular Formula

$C_{12}H_{16}N_2S$.

1.3.5. Uses of Xylazine in Monkeys

Xylazine is often used as a sedative, muscle relaxant, and analgesic (Thurmon *et al.*, 1986*).*

1.3.6. Xylazine Mode of Action and Pharmacology

Xylazine acts upon the central nerves system (CNS) by activation or stimulation of α-adrenergic system e.g. the α-2-adrenergic receptor, because Xylazine has also α1-adrenergic effect, it causes peripheral in addition to central action upon these adrenergic receptor subtypes. Within the central nervous system, activation of α-2-adrenoceptor induces analgesia and sedation, these results from binding of Xylazine to the α-2-adrenoceptor in presynaptic membrane result inactivation of membrane- associated G-protein and this leads to activation of potassium channels in the postsynaptic neurons, causing the cell to lose potassium and become hyperpolarized, this action makes the cell unresponsive excitatory input (Thurmon *et al.*, 1996). Investigation after administration of labeled Xylazine (35S and C14) revealed that, approximately 20% metabolites were detected but not identified; only 8% of the labeled parent compound was recovered. The principle metabolite in urine represented 35% of the total radioactivity. The ratio between the renal and biliary excretion of the radiolabeled compound was 7:3, but the report did not explicitly indicate if the

entire radioactivity was recovered and showed that less than 1% of the parent radiolabel led compounds Xylazine HCl could be recovered in cattle urine (Duhm *et al.*, 1969; Pötter and Sagner 1973).

1.3.7. Xylazine Complications and Contraindications

Xylazine in general is safe, sometimes may cause bradycardia, depression in respiration and gastrointestinal tract. It is increases intra-uterine pressure in pregnant females; accordingly it should not be used in last trimester (Ruiz *et al.*, 2014).

1. 3.8. Xylazine in Wilde Life Practice

Xylazine HCl has a multitude of applications for field use in cervids (fallow deer, mule deer, sake deer, white-tailed deer and elk), other hoof stock, and wildlife including calming of fractious animals, restraint for diagnostic and minor surgical procedures, relief of pain following injury or surgery and as a pre-anesthetic to local anesthesia (Terry *et al.,* 1986).

Xylazine hydrochloride should be used in Cervidae when it is desirable to produce a state of sedation accompanied by a shorter period of analgesia. Other indications and uses are found in peer combined with Ketamine, it has been used extensively in wildlife species and wildlife management applications. Its wide margin of safety and reversibility has made it a useful tool in the hands of wildlife veterinarians and professional wildlife biologists (Terry *et al.,* 1986). It is commonly used in conjunction with etorphine and carfentanil for its muscle relaxation properties to minimize the “opiate rigidity” produced by these two compounds. Yohimbine hydrochloride at a dose rate of 0.2 to 0.3 mg/kg administered intravenously can reverse the effects of Xylazine hydrochloride safely and rapidly. Xylazine can also be reversed with Tolazoline and Atipamezole in most species **(**Terry *et al.*, 1986).

1.3.9. Effects of Xylazine on Clinical Parameters

Combination of Ketamine and Xylazine decreased respiratory rate, heart rate and rectal temperature in the monkeys (England and Clarke, 1989; Pettifer and Dyson, 1993; Atalan *et al.*, 2002; Demirkan *et al.*, 2002; Afshar *et al.*, 2005).

1.3.10. Xylazine in Combination with Ketamine

The combination of Ketamine HCl and Xylazine HCl, has been used to immobilize numerous wild and domestic carnivores (Knight, 1980; Herbstl *et al.*,1985; Terry *et al.*, 1986;Haskins *et al.*, 1986; England and Clarke, 1989; Tranquili and Benson,1992). These drugs usually result in a smooth induction and recovery with the pronounced cataleptic effects of Ketamine HCl being ameliorated by the depressor, sedative and my relaxing effects of Xylazine HCI The combination of Ketamine HCl and Xylazine HCl anesthesia is very useful and safe in monkey, because of invariable status in physiological and hematological function (Parry *et al.*, 1981., Terry *et al.*, 1986).

CHAPTER TWO

Materials and Methods

2.1. Study Site

This study was carried out at kuku Zoo (Hilat Kuku, East Nile. Khartoum –Sudan). All experiments were carried out between 3pm and lasted at 6 pm.

2.2. Experimental Animals

A total number of eight clinically sound green monkeys of both sexes, body weight ranged 2.5-4 kg were used in this experimental study.

2.3. Housing and Management

Monkeys were housed in cage at kuku zoo they were fed bananas, twice daily and allowed free asses to water (Fig 2.1).

2.4. Pre- anesthetic Preparations

Monkeys were not fasted prior to anesthesia; however, recent feeding was avoided before administration of anesthesia to minimize vomiting risk and aspiration of vomits.

2.5. Injection Set and Monitoring Tools

Disposable syringes (1 ml, 21G x 1½˝, Monoinject Syringe, Sudan, 5 ml 21G x 1½˝, CMS-Sudan disposable Syringe, Xuyl Webest medical product Co., LTD, China) were used for anesthesia injection; Stethoscope was used for monitoring of heart beats.

{Fig 2.1}: Housing and Management in Kuku Zoo (East Nile Khartoum -Sudan)

Stop-watch and digital thermometer were used to determine the duration time of different phases of an anesthesia, and the body temperature respectively also induction box was used to control the monkeys during anesthesia injection

2.6. Anesthetic Drugs

The drugs that used in this study include:

1. Ketamine HCL (Ketamine Hydrochloride USP 50MG – 1, Troikaa pharmaceuticals Ltd).
2. Xylazine HCl (Seton2% , Bayer , Turkey)

2.7. Anesthetic Protocols

Two anesthetic protocols were used to anesthetize monkeys as follow.

1 .Xylazine (1 mg $kg^{-1,}$ im) + Ketamine (2.5 mg $kg^{-1,}$ im).

2. Xylazine (1 mg $kg^{-1,}$ im) + Ketamine (5 mg $kg^{-1,}$ im)

2.8. Anesthesia Phases

Phases of anesthesia were obtained by recording induction time, duration of anesthesia and recovery time.

2.8.1. Induction Time

The time from injection until the animal sank from normal posture to lying with his head on the floor of the cage and was unresponsive to pinprick (Elise *et al.*, 1979).

2.8.1.1. Quality of Induction

The quality of induction of anesthesia was rated as follow:

Satisfactory: rapid and smooth with little danger to both animal and personnel (Nora *et al.*, 2002).

Unsatisfactory: prolonged period of incoordination muscle fasciculation (Nora *et al.*, 2002).

2.8.2. Duration of Anesthesia

The time from involuntary recumbence and loss of pinprick until the responses to the pinprick was regained (Elise *et al.*, 1979).

2.8.3. Recovery Time

The time from first positive response to pinprick until the monkey could maintain a sitting posture (Elise *et al*., 1979).

2.8.3.1. Quality of Recovery

A score, ranging from 1 to 5 as described by Ringer *et al*. (2007) was used for assessment of quality of recovery from anesthesia.

Score (1) Excellent: Animal capable of standing at first attempt

Score (2) Very good: Animal remained calm and needed two attempts to stand.

Score (3) Good: Animal remained calm but needed more than two attempt to stand

Score (4) Poor: excitement during recovery with danger of injury and needed more than two attempt to stand

Score (5) Very poor: severe excitement during recovery with injury

2.8.4. Quality of Muscle Relaxation

The quality of muscle relaxation score as follow:

i. Excellent: characterize by complete relaxation

ii. Good: characterized by adequate relaxation of muscle that permit surgery

iii. Moderate: with partial relaxation of neck, head and limb muscle

iv. Poor: characterized by rigidity of neck, head and limb muscle

2.9. Physiological Parameters

Physiological parameters were recorded before administration of anesthesia as base line values and then at 15, 25, 45 and 60 minutes interval after injection of anesthesia in both anesthetic protocols.

2.9.1. The Heart Rate (beat minutes^{-1})

The heart rate (HR) was recorded by counting the heart beats over the cardiac area using stethoscope.

2.9.2. Respiratory Rate (breath minutes^{-1})

Respiratory rate (RR) was recorded by counting thoracic movements.

2.9.3. The Body Temperature (C^{o})

Body temperature (C^{o}) was monitored by using digital thermometer.

2.10. Anesthetic Reflexes

Some selected anesthetic reflexes were tested during anesthesia in both anesthetic protocols such as:

2.10.1. Palpebral Reflex

The reflex was assisted by digital touch on the canthus or eye lashes, if purposeful motor reflex observed, the reflex was considered positive (Batuol, 1990).

2.10.2. Pedal Reflex

Pedal reflex was assisted by pinprick at inter digit space, if the animal moves it´s leg or leg muscle; the reflex was considered positive (William, 2007).

2.11. Statistical Analysis

Statistical analysis were made using T-test, data are presented (Mean ± SE) and significance was detected at ($P<0.01$ and $P<0.05$) using statistical package for social science (SPSS) programme. No statistical evaluation was made for subjective data (i.e. Palpebral and Reflexes).

Chapter Three

Results

3.1. General Observation on Administration of Anesthesia

Immediately after injection of all mentioned anesthetic protocol with Ketamine in combination with Xylazine, the animal exhibited different signs including dropping of head and adoption of lateral recumbencey.

3.2. Induction and Onset of Anesthesia

The quality of induction using Ketamine with Xylazine in monkeys was found to be smooth and excitement free with little danger to both animal and personnel, in addition no evidence in all anesthetic regimes showed involuntary excitement during anesthesia induction in both anesthetic protocols, no apnea occurrence was observed during anesthesia course (Fig.3.1).

3.3. Anesthesia Phases

As illustrated in table 3.1, the phases of anesthesia (minutes) were described as mean ± stander error (SE). Significant increases were observed at induction time, duration time of anesthesia and recovery time from anesthesia in Xylazine- premedicated monkeys that anesthetized using 5 mg kg^{-1} of Ketamine.

Table 3.1:

Mean ± SE of induction time, anesthesia duration time and recovery time (in minutes) in both anesthetic protocols using Ketamine (2.5 mg kg^{-1}) / Xylazine (1 mg kg^{-1}) and Ketamine (5 mg kg^{-1}) / Xylazine (1 mg $kg^{-1)}$ in monkeys .

Anesthesia Phases	**Anesthetic Protocols**		**Sig**
	K_1Z	K_2Z	
Induction	2.92 ± 1.3	4 ± 1.6	*
Anesthesia	68.04 ± 3.9	89.4 ± 3.06	*
Recovery	1 ± 0.25	10.67 ± 2.4	*

N= 8

K1Z = Ketamine (2.5 mg kg^{-1}), Xylazine (1 mg kg^{-1})

K2Z = Ketamine (5 mg kg^{-1}), Xylazine (1 mg kg^{-1})

*= Significant at ($P < 0.05$)

3.4 Quality of induction

The quality of induction in two mentioned anesthetic protocols in green monkeys was described as percentage, the induction quality in monkeys that anesthetized with ketamine (5mg kg^{-1}) and/ or (2.5 mg kg^{-1}), showed 50% of and 75% of satisfactory quality of induction respectively table (3. 2).

3.5 Quality of Muscle Relaxation

The quality of muscle relaxation in both tested anesthetic protocols in green monkeys, ranged from moderate to good according to the previous mentioned described score (Table 3.3).

3.6 Quality of Recovery

The quality of the recovery from anesthesia in both tested anesthetic protocols in green monkeys were found to be good and very good according to the previous mentioned described grades (Table 3.4).

3.7. The Effects of the Anesthetic protocols on Physiological Parameters

3.7.1. Respiratory Rate (RR):

As illustrated in table 3.5, respiratory rate values (breaths min^{-1}) was described as mean ± standard error, no significant difference was observed during the course of anesthesia in the two mentioned anesthetic protocols

3.7.2. Heart Rate (HR):

No significant difference was observed during the course of anesthesia in the two mentioned anesthetic protocols. However, the heart rate values at 15 minutes prior to the administration of anesthesia in both protocols showed significant increased (Table 3.6).

Table {3.2}:

The quality of anesthesia induction as percentage in both tested anesthetic protocols in green monkeys.

protocols	Number of animal	Satisfactory		Unsatisfactory	
		NO	%	NO	%
K_1Z	4	3	75	1	25
K_2Z	4	2	50	2	50

Table (3. 3):

The quality of muscle relaxation as percentage in both tested anesthetic protocols in green monkeys.

Protocols	No of animal	Poor		Good		Moderate		Excellent	
		NO	%	NO	%	NO	%	NO	%
K_1Z	4	0	0	3	75	1	25	0	0
K_2Z	4	0	0	1	25	3	75	0	0

N= 8

K1Z = Ketamine (2.5 mg kg-1), Xylazine (1 mg kg-1)

K2Z = Ketamine (5 mg kg-1), Xylazine (1 mg kg-1

Table 3.4:

Grades of recovery quality in both studied anesthetic protocols in green monkeys.

Protocols	No.of animals	Very poor		Poor		Good		Very good		Excellent	
		No	%	No	%	No	%	No	%	No	%
K1Z	4	0	0	0	0	٣	75	1	25	0	0
K2Z	4	0	0	0	0	1	25	3	75	0	0

N= 8

K1Z = Ketamine (2.5 mg kg-1), Xylazine (1 mg kg-1)

K2Z = Ketamine (5 mg kg-1), Xylazine (1 mg kg-1

Table 3.5:

Mean ±SE of respiratory rates (breaths min^{-1}) during anesthetic protocols using Ketamine (2.5mg kg^{-1}) plus Xylazine (1mg kg^{-1}) and Ketamine (5mg kg^{-1}) with Xylazine (1 mg kg^{-1}) at 0,15,25,45 and 60 minutes intervals in monkeys

anesthetic Protocols	**Time intervals**				
	0	**15**	**25**	**45**	**60**
K_1Z	36.25 ± 3.32	70 ± 3.65	68.5 ± 3.59	64.5 ± 5.12	64.75 ± 4.02
K_2Z	38.7 5± 2.52	63.75 ± 11.07	52.5 ± 5.9	53. 5± 7.41	47.75 ± 4.36
Sig	NS	NS	NS	NS	NS

N=8

K1Z = Ketamine (2.5 mg kg^{-1}), Xylazine (1 mg kg^{-1})

K_2Z= Ketamine (5mg kg^{-1}), Xylazine (1 mg kg^{-1})

NS= not significant

Table 3.6:

Mean ± SE of heart rates (beats min $^{-1}$) during two anesthetic protocol using Ketamine (2.5 mg kg^{-1}) with Xylazine (1mg kg^{-1}) and Ketamine(5 mg kg^{-1}) with Xylazine (1 mg kg^{-1}) at 0. 15, 25, 45 and 60 minutes intervals in green monkeys.

anesthetic Protocols	**Time intervals (min)**				
	0	**15**	**25**	**45**	**60**
K1Z	97.75 ± 5.54	135.5 ± 4.40	90 ± 7.87	83.5 ± 3.12	80.5 ± 3.40
K2Z	88.7 ± 4.32	129 ± 4.50	113.75 ± 2.71	100 ± 6.87	90.25 ± 3.56
Sig	NS	*	NS	NS	NS

N=8

K_1Z= Ketamine (2.5 mg kg^{-1}), Xylazine (1 mg kg^{-1})

K_2Z= Ketamine (5 mg kg^{-1}), Xylazine (1 mg kg^{-1})

*= Significant at ($P < 0.05$)

NS= not significant

3.7.3. Rectal Temperature (C°)

As showed in table 3.7 the temperature degrees were described as mean ± standard error, no significant differences were observed during the course of anesthesia in all mentioned anesthetic protocols, but the temperature values at 45 minutes following the injection of anesthesia in both tested anesthetic protocols revealed significant increased.

3.8. The Effects of Anesthetic Protocols on Selected Reflexes:

3.8.1. Palpebral Reflex:

Palpebral reflex was slow to absent in two anesthetic protocols using Ketamine (2.5mg kg^{-1}) with Xylazine (1mg kg^{-1}) and Ketamine (5mg kg^{1}) with Xylazine (table 3.8 a and b).

.3.8.2 Pedal Reflex:

During this study an absent of pedal was observed in two tested anesthetic protocols using Ketamine (2.5 mg kg^{-1}) with Xylazine (1 mg kg^{-1}) and Ketamine (5 mg kg^{1}) with Xylazine (1mg kg^{-1}), table(3.8 a and b) and figure (3.1).

3.6.3 Pinprick Reflex

Table (3.8 a and b) described the present and absent pinprick reflex in two anesthetic protocols using Ketamine (2.5 mg kg^{-1}) with Xylazine (1 mg kg^{-1}) and Ketamine (5 mg kg^{1}) with Xylazine (1 mg kg^{-1}).

Table 3.7:

Mean ± SE of rectal temperature degrees (C^{o}) during two anesthetic protocol using Ketamine (2.5 mg kg^{-1}) with Xylazine (1 mg kg^{-1}) and Ketamine (5 mg kg^{-1}) with Xylazine (1 mg kg^{-1}) at 0. 15, 25, 45and 60 minutes intervals in green monkeys in Kuku Zoo.

anesthetic Protocol	**Temperature Degrees (C^{o})**				
	0	15	25	45	60
K1Z	35.6 ± 0.95	37.7 ± 0.41	37.45 ± 0.41	36.82 ± 0.41	36.52 ± 0.46
K2Z	36.52 ± 0.97	38.1± 0.15	37.32 ± 0.34	36.87 ± 0.24	36.6 ± 0.19
Sig	NS	NS	NS	*	NS

N=8

K_1Z= Ketamine (2.5 mg kg^{-1}), Xylazine (1 mg kg^{-1})

K_2Z= Ketamine (5 mg kg^{-1}), Xylazine (1 mg kg^{-1})

*= Significant at ($P < 0.05$)

NS= not significant

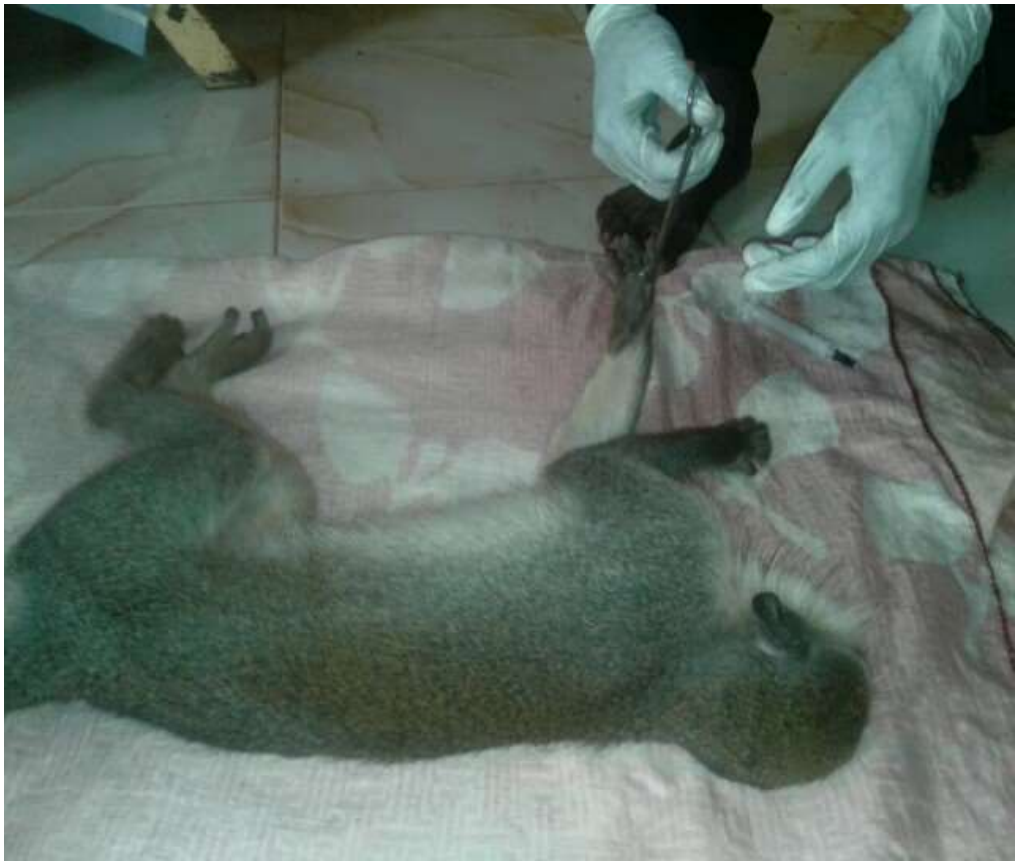

Fig 3.1: Pedal Reflex in Anesthetized Monkey in Kuku Zoo (East Nile Khartoum Sudan).

Table 3.8a:

Effect of anesthetic protocols using Ketamine 5mg $kg^{-1}$with Xylazine (1 mg kg^{-1}) on some selected reflexes at 0, 15, 25, 45, and 60 minutes intervals in green monkeys in Kuku zoo.

Reflexes	**Base**	**15 min**	**25 min**	**45 min**	**60 min**
Palpebral	+	_	_	_	_
Pedal	+	_	_	_	_
Pinprick	+	_	_	_	_

Table (3.8b):

Effect of anesthetic protocols using Ketamine 2.5mg kg^{-1} with Xylazine 1 mg kg^{-1} on some selected reflexes at 0, 15, 25, 45, and 60 minutes intervals in green monkeys in Kuku zoo.

Reflexes	**Base**	**15 Min**	**25 min**	**45 min**	**60 min**
Palpebral	+	_	_	_	_
Pedal	+	_	_	_	_
Pinprick	+	_	_	_	_

CHAPTER FOUR

DISCUSSION

Study of the available literature and databases demonstrated limited information on Ketamine anesthesia in green monkeys. Throughout this study efforts were attempted to keep the experimental conditions as stable as possible. Such precautions were important for the standardization and interpretation of the results.

The selection of appropriate regime of surgical anesthesia would depend, on the duration of the operative procedures and the depth of the required anesthesia.

The chosen doses of Ketamine HCl and Xylazine HCl in this study were based on results of published literature (Elise *et al.*, 1979).

Ketamine had come into the foreground especially during the last decade due to prevention of its side effect by using drug combination and thus expansion of its area of usage (Akeson *et al.,* 1993*).* Preanesthetics drugs like diazepam, Xylazine and atropine can possess hypotensive and hypoxic effects by depression of cardiovascular and respiratory activity, in contrast to most of anesthetic drugs; ketamine has been shown to possess incremental effects on heart rate (Lin *et al.*, 1993).

The results indicate that deep anaesthesia with complete muscle relaxation and a wide safety margin (since respiratory depression is not found) can be achieved in rhesus monkeys by tested combined doses of Ketamine and Xylazine.

Induction was found smooth and satisfactory at both doses of Ketamine except for animals which occasionally became delirious and thrashed about the cage

during the induction period following administration of anesthesia and these results were in accordance of that ketamine usually result in a smooth induction and recovery with the presser and cataleptic effects of ketamine HCl being ameliorated by the depressor, sedative and myo-relaxing effects of Xylazine HCl (Parry *et al.*, 1981; Terry *et al.*, 1986)

The onset time in all Xylazine- premedicated monkeys when injected with 2.5mg kg^{-1} and/ or 5 mg kg^{-1} were occurred within 2.92±1.3 and 4±1.6 minutes respectively. The average of anesthetic duration was 68.04±3.9 minutes (Ketamine 2.5 mg^{-1}) and 89.4±3.06 minutes in anesthesia using Ketamine at dose rate 5 mg kg^{-1} protocols, these results were partially similar to those reported by Elise *et al.*, (1979).

Clinical parameters which have been recorded during this study revealed that the respiratory rates (breathe/ $mint^{-1}$) were found within the normal range following administration of Ketamine and Xylazine in both studied anesthetic protocol, these were in agreement with the findings of Afshar *et al*.,(2005) who was reported that Ketamine/Xylazine anesthesia could not alter respiratory rates in many of animal species.

On the other hand, heart rate values (beat/ min^{-1}) showed significant increase at 15 minute following the injection of Ketamine and Xylazine in both anesthetic protocols. The increase in heart rate following ketamine anesthesia may be contributed to the increase of sympathetic activity and decreased vagal tone, although Xylazine overrides these effects by excitatory carotid baroreceptor reflex induced by hypotension and decreased sympathetic and increased vagal activity, also several investigations have been showed that use of Xylazine result in bradycardia and associated Brady arrhythmias and administration of ketamine increase and correct heart rate (Diamond *et al.*, 1993; Kerr *et al.*, 1994).

In addition the observation of decreasing in rectal temperature values which occurred during the anesthesia in both protocols at 45 minutes interval were in total agreement with that reported by (Demirkan *et al.*, 2002 ; Atlan *et al.*, (2002) ,the decreased in temperature might be due to depression of thermo - regulator center.

CHAPTER FIVE

CONCLUSIONS AND RECOMMENDATIONS

Total intramuscular anesthesia (TIMA) has several potential advantages for the practicing veterinarian acting as surgeon- anesthetist because it is relatively easy to manage, veterinary attendants can be instructed easily in its use, and only comparatively inexpensive apparatus is required for its delivery. Furthermore, TIMA avoids the pollution of the theatre and environment with traces of inhalation anesthetic agents.

Selection of anaesthetic agents depends upon species or breed of the animal, nature of surgical operation, susceptibility of the patient to the action of anesthetic drug and health status of the animal to be anaesthetized.

Ketamine plus xylazine at dose rates(2.5 mg kg-1) and(1 mg kg-1)respectively were a safe and provide satisfactory anesthesia in monkey. Using different dosage of ketamine have not produce significant different on health prameter rather than that usage of large dose of ketamine (5 mg kg-1) prolonged anesthetic phase.

Recommendation:

- further studies will be needed in monkeys to determine the effectiveness of ketamine to find out an ideal regimen including ketamine in combination with other anesthetic drugs.
- a future work needs to be done in larger numbers of subjects
- for deep prolong surgery in monkeys use ketamine (5 mg kg-1) with premedication xylazine (1 mg kg-1) .and for minor surgery use (2.5 mg kg-) and(1 mg kg-1).

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