



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

Sudan University of Science and Technology



Collage of Veterinary Medicine

Study on the Effects of Ketamine with some Premedications in Dogs

دراسة عن أثر الكيتامين مع بعض العلاجات التمهيدية في الكلاب

Dissertation submitted of partial fulfillment of the requirement of B.V.M

Honors Degree in Veterinary medicine

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DEDICATION

FROM OURS HEART TO BE HAPPY WHEN WE MEET HER
KINDERGARTEN TO LOVE THAT GROWS PURER FLOWERS

OURS MOTHER

TO OURS MANHOOD AND SACRIFICE CODE

TO THOSE WHO PUSHED US TO THE FLAG AND HAS INCREASED HONOR

OURS FATHER

TO THOSE WHO ARE CLOSER TO ME THAN THE SPIRITUAL

TO THOSE WHO SHARED WITH ME THE LAP OF THE MOTHER AND THEIR
DERIVED MY PRIDE AND MY INSISTENCE

OURS BROTHER

TO THE COMPANIONABLE IN MY STUDIES AND I SHARED MY CONCERNS

A MEMORIAL AND RECOGNITION

OURS FRIEND

TO THIS SCIENTIFIC EDIFICE YOUTHFUL AND TITAN

SUST

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LIST OF ABBREVIATIONS

TIVA	Total Intravenous Anesthesia
i. m	Intra-muscular
i.v	Intra-venous
Xylazine HCl	Xylazine Hydrochloride
SD	Stander Deviation
RR	Respiratory Rate
HR	Heart Rate
K	Ketamine
Sig	Significance
NS	Not Significance
KZD	Ketamine, Xylazine , Diazepam
KZA	Ketamine, Xylazine, Atropine
BLV	Baseline Line Values
M	Muscarinic
PCP	Phencyclidine
NMDA	N-methyl-D-aspirate
AUC	Area Under the Curve
GABA	Gamma Amino Butyric Acid

C°	Degree centigrade
IOP	Intra ocular pressure
CNS	Central Nervous System
CO ₂	Carbone Dioxide
Bz	Benzodiazepines
PBRS	Peripheral Benzodiazepines Receptors
CBRS	Central Benzodiazepines Receptors
Vd	Volume Distribution
ml	Milliter
Kg	Kilogram
SPSS	statistical package for social science

ABSTRACT

Two Intramuscular anesthetics protocols based on ketamine (I.m) as anesthetic , xylazine (I.m) With either diazepam (I.v) or atropine sulphate (I.v) .for this purpose two groups of dog each group consist of fivesounds male dogs (each dog acted as its own control) .

The first anesthetic protocol was achieved by using ketamine (10mg kg^{-1}) , xylazine (1mgkg^{-1}) and diazepam (0.25mg kg^{-1}) , The second protocol was conducting using ketamine (10mg kg^{-1}) , xylazine (1mgkg^{-1}) and atropine sulphate (0.03mg kg^{-1}) .

Clinical parameter viz : respiratory rate , heart rate and body temperature were monitored , some anesthesia phases (anesthetic phase , lateral recumbency , sternal recumbency , recovery and total recovery time) were recorded , selected anesthetic reflex(Tongue and Jaw Relaxation, Palpebral ,Pedal and Anal Reflexes)were observed. Respiratory rate showed significant increase at 5, 15, 25 and 35 minute following administration of anesthesia with ketamine (10mg kg^{-1}) , xylazine (1mgkg^{-1}) and diazepam (0.25mg kg^{-1}) compared with anesthesia using ketamine (10mg kg^{-1}) , xylazine (1mgkg^{-1}) and atropine sulphate (0.03mg kg^{-1}) in dogs , heart rates were significantly higher at 5,15 and 25 minute after anesthesia compare with other anesthetic protocol .anesthesia phase such as anesthetic , lateral recumbency and total recovery showed no significance difference in both anesthetic protocols , however, sternal recumbency phase and recovery time showed significant differences ;It found that the duration of sternal recumbency and recovery (min) were longer in xylazine , diazepam premeditated dog compared with xylazine , atropine premeditated one .

It could be concluded that anesthesia obtained using ketamine with premedication such as xylazine with either diazepam or atropine sulphate was safe and suitable for many surgical interventions in dogs.

Key words : Ketamine ,Xylazine ,Diazepam , Atropine , Dogs.

خلاصه الاطروحه

اجريت هذه التجربة باستخدام بروتوكولين تخديرين. استعمل الكيتامين والزيلازين عن طريق الحقن العضلي مره مع الديازيبام واخرى مع كبريتات الاتروبيين عن طريق الحقن الوريدي. استعمل لهذا الغرض مجموعتين من الكلاب، كل مجموعة تحتوي على حمسة كلاب ذكور سليمة ولائقة صحيا. (كل كلب كان كمنترول لنفسه).

البروتوكول التخديري الاول كان باستعمال الكيتامين 10 ملجم كلجم⁻¹، زيلازين 1 ملجم كلجم⁻¹ والديازيبام 0.25، ملجم كلجم⁻¹ والبروتوكول التخديري الثاني كان باستخدام الكيتامين 10 ملجم كلجم⁻¹، زيلازين ملجم كلجم⁻¹ والاتروبيين 0.3، ملجم كلجم⁻¹.

تمت مراقبة القياسات الاكلينيكية مثل معدلات التنفس و ضربات القلب ودرجة حرارة الجسم كما سجلت بعض الأطوار التخديرية (الطور التخديري، الإستلقاء الجانبي، الإستلقاء القصي، الافاقه وزمن الافاقه الكلية) كما لوحظت بعض من منعكسات التخدير (منعكس اللسان والأسترخاء الفكي، منعكس الجفون، منعكس القدم ومنعكس الشرج).

اظهر معدل التنفس زيادة ملحوظة عندالدقيقة 5، 15، 25 و 35 من استعمال (الكيتامين 10 ملجم كلجم⁻¹، زيلازين 1 ملجم كلجم⁻¹ والديازيبام 0.25، ملجم كلجم⁻¹) مقارنة مع التخدير باستخدام (الكيتامين 10 ملجم كلجم⁻¹، زيلازين 1 ملجم كلجم⁻¹ والاتروبيين 0.3، ملجم كلجم⁻¹) كما اوضحت معدلات ضربات القلب زيادات ملحوظة عند الدقائق 5، 15 و 25 بعد أحداث التخدير مقارنة مع البروتوكول التخديري الاخر. أما بالنسبة للأطوار التخديرية مثل الطور التخديري والاستلقاء الجانبي والافاقه الكلية لم تظهري تغيرات ملحوظة في كل من البروتوكولين بالرغم من ان طور الاستلقاء القصي وزمن الإفاقه من التخدير اظهرت زيادة ملحوظة حيث وجد ان مدة طور الاستلقاء على الغص وزمن الافاقه (بالدقائق) كانت اطول في الكلاب التي تم تخديرها باستعمال الكتامين، الزيلازين والديازيبام مقارنة مع الكلاب التي استعمل فيها الأتروبيين بدلا من الديازيبام.

استنتج من هذه الدراسة ان التخدير باستخدام الكيتامين والمخدراتالتمهيدية أمثال الزيلازين مع الديازيبام او الاتروبيين كان امنا وملائما لإجراء بعض التدخلات الجراحية في الكلاب.

كلمات مفتاحية : كيتامين , زيلازين , ديازيبام , اتروبيين , كلاب .

Introduction

The domestication of animals is the scientific theory of the mutual relationship between animals with the humans who have influence on their care and reproduction (Zeder,2015). The dog was the first domesticant and was stablished across Eurasia before the end of the late Pleistocene era, well before cultivation and before the domestication of other animals (Larson and Bradley ,2014 ; Larson , 2012 ; Perri and Angela , 2016).

The domestic dog (*canis Lupus familiars* or *canis familiars*) is a domesticated canid which has been selectively bred over millennia for various behaviors, sensory capabilities, and physical attributes (Dewey and Bhagat,2002). Dogs play many roles for people, such as hunting, herding, pulling loads, protection, assisting police and military, companionship and more recently, aiding handicapped individuals. This influence on human society has given them the sobriquet, “man’s best friend” (Rupert,2002).

Anesthesia can be classified according to the type of drug used and/or the route of drug administration. Basically there are two major ways to obtain general anesthesia in veterinary medicine: either via the parenteral injection of anesthetic drugs (subcutaneously,intramuscularly or intravenously) or via inhalation of volatile anesthetic agent’s.An ideal anesthetic produces sleep, amnesia, analgesia and muscle relaxation. As all these characteristics cannot be provided by a sole agent, a combination of drugs is used. This technique is referred to as “balanced anesthesia” (Thurmon and Short, 2007). Balanced intravenous anesthesia can be obtained by administering sedatives and analgesics in the premedication phase, as well as by using different analgesics. Inhalation anesthetics owe their popularity to the predictable and rapid adjustment of anesthetic depth. Additionally, since endotracheal intubation needs to be performed, the administration of a high percentage of oxygen and artificial ventilation becomes possible. These components help minimize patient morbidity and mortality (Dodman,1977). Several disadvantages are inherent to inhalation anesthesia. Inhalant anesthetics require the use of a cumbersome and costly anesthetic machine, including a suitable breathing system and vaporizer (Matthews,2007). Another of the major disadvantages when using volatile anesthetics is the

exposure of operating-room personnel to the pollution in the ambient air. Replacing mask induction for induction of the anesthesia by adapted intravenous agents reduces the occupational exposure of anesthesiologists to anesthetic gases drastically (Hasei *et al.*, 2003) , since the operating room air is contaminated by vaporizer filling, by leaks in the patient breathing circuit and by the spillage of liquid agent (Byhahn *et al.*, 2001; Steffey and Mama ,2007).

Injectable anesthetics are useful in situations where inhalational techniques are not readily available. They are also a suitable alternative when anesthesia must be provided outside of a hospital setting or for quick procedures, such as clinical examinations, diagnostic imaging, and minor surgical procedures (Dugdale, 2010).

An appropriate selection of premedication drugs can significantly improve intraoperative cardiovascular stability, perioperative analgesia and the quality of recovery. Cardiovascular stability is mainly improved by premedication since the quantity of potentially more dangerous drugs used to produce general anesthesia can be decreased. In order to optimize the advantages of premedication, it is important to select drugs based upon the needs of the individual patient and its physical status (Murrell, 2007).

Dissociative anesthetics (eg, ketamine, tiletamine) have a relatively rapid onset of action, a longer duration of effect (20–45 minutes), and are suitable for IV and IM administration. Dissociative anesthetics are preferred for shelter anesthesia protocols (Thurmon *et al.*,2007). This type of anesthesia is characterized by catalepsy, amnesia, profound somatic analgesia, muscle rigidity (spontaneous movements and tremors are possible), the presence of active reflexes (ie, palpebral reflexes, gagging, swallowing), and salivation (Berman and Top, 2010). Ketamine is dissociative anaesthetic widely used in combination with several drugs in dogs, it produces increased motor activity, hyperreflexia and sympathetic activation (Wright, 1982; Haskins *et al.*, 1986). Ketamine is routinely employed in combination with sedatives (eg, benzodiazepines or α -2 agonists) and analgesics to improve muscle relaxation, surgical analgesia (antinociception), and quality of recovery (Belda *et al.*, 2009).

Xylazine HCL is a popular and reliable pre-anaesthetic medication in a wide range of animal species (Hall and Clarke, 1991). It is used as analgesic and muscle relaxant. Xylazine stimulates

directly peripheral alpha-2adrenegic receptors located in various tissues (Kobinger,1978) and it exerts its effect accordingly, a possible central effects was also reported by sanhouri *et al* (1991b) .

Diazepam (Valium) has the chemical formula of 7- chloro- 1, 3-dihydro-1-methyl-5-phenel; it is probably the most widely used of the benzodiazepines. Diazepam induces sedation and hypnosis with minimal effects on the cardiopulmonary activities of the body (Vickers *et al.*, 1984).

Atropine may be used to prevent the xylazine-induced salivation, bradycardia and arrhythmia, (Hall and Clarke 1991).

Objectives:

The specific aims of this prospective clinical experimental study were to:

a. Evaluate the effectiveness and practicability of ketamine and its combination with premedications such as xylazine, diazepam and atropine on induction, duration of anesthesia and recovery in dogs under field condition.

b. Study the effect of two injectable anesthetic protocols using ketamine (10mg kg^{-1}), xylazine (1mg kg^{-1}) with diazepam (0.25mg kg^{-1}) and ketamine (10mg kg^{-1}), xylazine (1mg kg^{-1}) and atropine sulphate (0.03mg kg^{-1}) tested by some physiologic parameters of dogs as stress bio- markers.

c. To Compare and contrast between studied anesthetic regimes on anesthesia phases (anesthetic phases, lateral recumbency, sternal recumbency, recovery and total recovery from anesthesia).

d. To select the superior satisfactory anesthetic regimes in dogs.

e. To provide clinical guidance to veterinary practitioners in term of dosage and route of administration in this in important species.

CHAPTER ONE

LITERATURE REVIEW

1.1. Injectable Anesthesia in Dog

Injectable anesthetic agents are mostly employed in situation where rapid induction of anesthesia is indicated , and some agent are also suitable for maintenance of anesthesia. Important factor for the induction of these agents include onset of action , duration of anesthetic phase , route of administration and cardiorespiratory response (Dugdale,2010).

1.2. Ketamine Hydrochloride

Dissociative anesthesia, general anesthetic and tranquilizer is administered intravenously or intramuscularly (Stoelting ,1999; Hall and Clarke, 1991). The cyclohexane, ketamine is a 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 (Hall and Clarke, 1991; Haskins *et al.*,1986). Ketamine muscle relaxation is poor, but is improved sedatives such as diazepam or xylazine (Hall *et al .*, 2001; Hirota and Lambert, 1996).

1.2.1. Commercial Name

Ketalar[®],Ketalin[®], Ketalor[®] and KetaminolVet[®].

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 μ receptors and sigma receptors and induce a state of dissociative anesthesia (Chohan,2010).Ketamine has a rapid pharmacological action characterized by profound analgesia, mild cardiac stimulation, normal pharyngeal-laryngeal reflexes, mild respiratory depression and markedly increased intraocular pressure (Kovalkuk,2013).This drug causes complex reactions in the brain depressing certain areas and stimulating others, which enables it to anesthetize and cause seizures in overdose (Haskins *et al.*, 1985). It produces paralysis with some muscle rigidity, good analgesia, and complete amnesia. Ketamine can be used for routine surgical procedures when administered in combination with diazepam, medetomidine, propofol (Mannarion , 2012) or xylazine for desexing (Baba , 2012). As a sole agent, it can be given for minor procedures such as catheterization associated with urolithiasis.

1.2.5 . Composition of Ketamine

Ketamine (2-(2-chlorophenyl)-2-(methyl amino) - cyclohexanone) is an arylcycloalkylamine structurally related to phencyclidine (PCP). Ketamine hydrochloride is water-soluble, white crystalline and has a Pka of 7.5. Its free base, ketamine, has lipid solubility 10 times that of thiopentone. The commercially available pharmaceutical form is an aqueous solution for injection of the racemic mixture of the hydrochloride salt. However, in some countries, e.g. the Netherlands the S-enantiomer is marketed (Budavari *et al.*, 1989).

1.2.6. Ketamine pharmacology and mode of action

Ketamine is a dissociative anesthetic (Domino *et al.*, 1966). Originally, the dissociation component refers to a functional and electrophysiological dissociation of thalamo-neocortical and 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-aspartate (NMDA)-receptor complex, located within the ion channel, thereby blocking the transmembranous ion flux. 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 in sensory 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 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 perfused 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 less well-perfused 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 renally. 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 Silvey, 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 thecal route is used as well. Also, the oral and the rectal routes have been described (Reich and Silvey, 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 neurones 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 commitsuicide (die by apoptosis).ketamine is highly unlikely to possess any relevant genotoxic properties (Adhvaryu *et al.*, 1986; Waskell, 1978). No data on the carcinogenic potential of ketamine are available. Neurotoxicity as observed in rats (Olney *et al.*, 1989; 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 subcortical 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 or cerebrovascular accidents (Haas and Harper, 1992).

1.2.10. Ketamine in Veterinary 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 *et al.*, 1985; Hartsfield, 1992; Thurmon *et al.*, 1996). Ketamine hydrochloride in dogs induces increase in cerebral blood flow and intracranial and cerebrospinal fluid pressure as a result of cerebral vasodilatation, and elevated arterial blood pressure (Booth, 1982; Thurmon *et al.*, 1996). Some authors suggest that ketamine and xylazine injection causes increase in intraocular pressure in dogs, but in horses, conversely, results in decrease (Trim *et al.*, 1985; Thurmon *et al.*, 1996).

1.2.11. Effects of Ketamine on Clinical Parameters

Ketamine is a mild respiratory depressant. It causes a shift of the CO₂ 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 administered intramuscularly (Reich and Silvey, 1989; White and Ryan, 1996). Ketamine has a bronco dilatory effect and pharyngeal and laryngeal reflexes are maintained (Reich and Silvey, 1989).

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. This may be due to chronic catecholamine depletion preventing any sympathomimetic effects of ketamine. The cardiovascular effects of ketamine usually do not pose a problem, but its use is contraindicated in patients with significant ischemic heart disease and should be avoided in patients with a history of high blood pressure or cerebro-vascular accidents (Haas and Harper, 1992). Tachycardia was the most common finding upon physical examination (Weiner *et al.*, 2000). On the basis of literature, both ketamine and xylazine may produce hypothermia. The decline in body temperature is in agreement with (Bush *et al.*, 1977), when ketamine was used

in nonhuman primates did not find any significant changes in body temperature after ketamine/xylazine administration in dog (Kul *et al.*, 2000).

1.3. Xylazine:

Xylazine was the first α -2 adrenergic agonist to be used as a sedative as analgesic agent by veterinarians in dogs and cats before the advent of medetomidine, a more specific and potent α -2 adrenergic agonist (Hall *et al.*, 2001).

Xylazine is the first and most widely used α -2 agonist in the horse its used primarily for sedation, anesthesia, analgesia and muscle relaxation, and the extent of these effects may vary intensity depending on the administered dose (Kollias *et al.*, 1993; Cuzelliez *et al.*, 1995).

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[®].

1.3.3. Chemical Name

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

1.3.4. Molecular Formula

C₁₂H₁₆N₂S.

1.3.5. Uses of Xylazine in Dogs

Xylazine is often used as a sedative, muscle relaxant, and analgesic (Thurmon *et al.* , 1988).

1.3.6. Xylazine Mode of Action and Pharmacology

Xylazine acts upon the central nerves system by activation or stimulation of α -adrenergic system e.g. the α -2 adrenergic receptor ,because xylazine has also α -1 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 adrenoceptorin presynaptic membrane result in activation 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 (^{35}S and C^{14}) 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 radiolabelled compound was 7:3, but the report did not explicitly indicate if the entire radioactivity was recovered (Duhm *et al.*, 1969).

Pütter and Sagner (1973) showed that less than 1% of the parent radiolabelled compound as xylazine HCL could be recovered in cattle urine.

1.3.7. Xylazine Complications and Contraindications

Xylazine In cats and dogs: contraindicated in individuals with gastrointestinal obstruction due to emetic effects. in dogs: aerophagia may result in bloat; gaseous stomach distention may interfere with interpretation of radiographs. (Plumb,2002).

1.3.8. Effects of Xylazine on Clinical Parameters

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

1.3.9. 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 myorelaxing effects of xylazine

HCl (Parry., *et al.*, 1981., Terry *et al.*, 1986).The combination of ketamine HCl and xylazine HCl anesthesia is very useful and safe in dog, because of invariable status in physiological and hematological functions.

1.4. Diazepam

Diazepam is probably the most widely use of the benzodiazepine (Hall *et al.*, 2001). It is a potent hypnotic-sedative and produce muscle relaxation; it is long action during to its slow metabolism (Koshy *et al.*, 2003). It has been used for premedication prior to the use of ketamine in dogs and horses and during anesthesia to abolish ketamine – induced convulsion in cats (Short, 1981; Reid and Frank, 1972).

Diazepam alone has not been widely used in large animals, its muscle relaxing properties may be associated with induced panic (Muir and Mason , 1993; Rehm and Schatzmann, 1984). In combination with ketamine, diazepam alleviates unwanted cardiovascular effects of ketamine and demonstrates anticonvulsive, amnestic and muscle relaxant effects via central mechanism (Koshy *et al*, 2003), However, diazepam extremely effective for sedation of young foals, which become recumbent so that ataxia is not a problem. Nevertheless, benzodiazepines, generally diazepam and midazolam are widely used in drug combinations for induction of anesthesia as they cause little cardiovascular depression, although they may enhance respiratory effect (Taylor and Clarke, 2007).

1.4.1. Commercial Name

Valium[®] and Diastast[®].

1.4.2. Chemical Name

7-chloro-1, 3-dihydro-1-methyl-5-phenyl-2H-1, 4-benzodiazepin-2-

1.4.3. Molecular Formula

Diazepam molecular formula is C₁₆H₁₃ClN₂O

1.4.4. Diazepam Mode of Action and Pharmacology

The action of benzodiazepine compounds is thought to be through stimulation of specific benzodiazepine (Bz) receptors (Hall *et al.*, 2001). Their main sedative effect is through depression of the limbic system, and their muscle relaxant properties according to several authors (Hall *et al.*, 2001., Date *et al.*, 1984), are through inhibition of polysynaptic pathway in the spinal cord. The action of diazepam is manifested by facilitation inhibitors synaptic transmission by Gamma amino butyric acid GABA (Atkinson *et al.*, 1987).

Diazepam can be administered intravenously, intramuscularly, orally and rectally via suppository of enema (Forney, 2002). Although the receptor was first identified as a binding site for the benzodiazepine, diazepam, in peripheral organ systems, the peripheral benzodiazepine receptors (PBRs) were subsequently found to be distinct from the central benzodiazepine receptors (CBRs) in terms of their pharmacological profile, structure, sub-cellular location, tissue distribution and physiological functions (Pierre *et al.*, 2002).

Benzodiazepine agonists are best known for their action as anxiolytics, anticonvulsants, antispasmodics and sedative-hypnotics muscle relaxants, leading to their , white spread clinical use, this action is due to depression of sub-cortical levels (primarily limbic, thalamic, and hypothalamic) of central nervous system (CNS) by diazepam (Susan and Donald, 2003). After oral administration diazepam is rapidly absorbed and reached peak plasma levels within 30 minutes to 2 hours. However, it was slower than oral and incompletely absorbed following intramuscular administration (Susan and Donald, 2003).

Diazepam is metabolized by the liver to nor diazepam and other active metabolized which are excreted in the urine (Forney, 2002). These drugs are highly fat soluble (lipophilic), after they gain access to the bloodstream, moves into the central nervous system, though still a function of individual drug of drug lipophilicity, is quite rapid for all benzodiazepines (Arendt *et al.*, 1983).

1.4.5. Diazepam Complications and Contraindications

Use of diazepam should be avoided, when possible, in individuals with ataxia, severe hypoventilation, acute narrow-angle glaucoma, severe hepatic deficiencies, severe renal deficiencies (for example, patients on dialysis), liver disorders, severe sleep apnea, severe depression, particularly when accompanied by suicidal tendencies such as psychosis, pregnancy or breast feeding. (Epocrates, 2008).

Diazepam has a range of side effects common to most benzodiazepines, including Suppression of REM sleep, Impaired motor function, Impaired coordination, Impaired balance, Dizziness, Depression and Reflex tachycardia. (Kay 1970).

1.4.6. Effects of Diazepam on Clinical Parameters

Diazepam has relatively weaker cardiovascular effects when compared with other sedative drugs (Koshy *et al.*, 2003; Muir, 1998). In combination with ketamine, diazepam alleviates unwanted cardiovascular effects of ketamine and demonstrates anticonvulsive, and muscle relaxant effects via central mechanisms (Koshy *et al.*, 2003). Hypothermia was reported in 15% of cases in one series. (Martin, 1985; Hojer *et al.*, 1989).

1.4.7. Uses of Diazepam in Dog

Diazepam is mainly used to treat anxiety, insomnia, panic attacks and symptoms of acute alcohol withdrawal. It is also used as a premedication for inducing sedation, anxiolysis, or amnesia before certain medical procedures (e.g., endoscopy) (Bråthen *et al.*, 2005)

Diazepam is the drug of choice for treating benzodiazepine dependence with its long half-life allowing easier dose reduction. Benzodiazepines have a relatively low toxicity in overdose (Riss *et al.*, 2008).

1.4.8. Combination of Diazepam with Ketamine

The combination of diazepam and ketamine is a commonly described protocol for induction of general anaesthesia in healthy dogs of various ages. It may also be indicated in certain cases

with cardiovascular compromise (Beteg *et al.*, 2010; Boutureira *et al.*, 2007; Fayyaz *et al.*, 2009; Green *et al.*, 1981; Haskins *et al.*, 1986; Hazra *et al.*, 2008; Hellyer *et al.*, 1991; Kolata, 1986; White *et al.*, 2001). The combination of diazepam and ketamine, at a dose range of 0.2 mg/kg - 0.5 mg/kg and 5 mg/kg – 10 mg/kg respectively, has generally been associated with excitement-free induction of anaesthesia in dogs. However, maintenance of pharyngeal and laryngeal reflexes as well as hypersalivation have resulted in difficult intubations being reported (Green *et al.*, 1981; Hellyer *et al.*, 1991; White *et al.*, 2001). Recovery from diazepam-ketamine in dogs has been reported to be free of emergence excitation although it is commonly associated with ataxia (Beteg *et al.*, 2010; White *et al.*, 2001).

1.5. Atropine Sulphate

Atropine is the best known member of a group of drugs known as muscarinic antagonists, which are competitive antagonists of acetylcholine at muscarinic receptors. This naturally occurring tertiary amine was first isolated from the *Atropa belladonna* plant by Mein in 1831 (Weiner, 1985).

1.5.1. Identification

Atropine sulphate found as odorless, very bitter, colorless crystals or white crystalline powder (Parfitt, 1999; Budavari, 1996).

1.5.2. Commercial Name

Atropen[®].

1.5.3 .Chemical Name

1 H,5 H-Tropan-3 -ol (\pm) -tropate.

1.5.4. Molecular Formula

C₁₇H₂₃NO₃.

1.5.5. Atropine Sulphate Mode of Action and Pharmacology

In general, atropine counters the "rest and digest" activity of glands regulated by the parasympathetic nervous system. This occurs because atropine is a competitive, reversible antagonist of the muscarinic acetylcholine receptors (acetylcholine being the main neurotransmitter used by the parasympathetic nervous system). Atropine is a competitive inverse agonist for the muscarinic acetylcholine receptor types M1, M2, M3, M4 and M5. It is classified as an anticholinergic drug (parasympatholytic). (Rang *et al.*, 2003).

Atropine is absorbed irregularly from the gastrointestinal tract, and more slowly than with parenteral dosing (Dollery, 1991). In adults, atropine is absorbed mainly from the duodenum and jejunum rather than the stomach. Maximum radioactivity, using ³H-atropine, was found one hour after an oral dose (Beermann *et al.*, 1971). Absorption of orally administered atropine may be delayed if atropine has been previously administered, 38% increase in small bowel transit time was observed following intramuscular injection of atropine (Hardison *et al.*, 1979).

After intravenous dosing, atropine distributes rapidly with only 5% remaining in the blood compartment after five minutes (Berghem *et al.*, 1980). Initial distribution half-life is approximately one minute (Kanto and Klotz, 1988). Elimination kinetics can be fitted to a two-compartment model after therapeutic doses. The apparent volume of distribution (V_d) is 1-1.7 L/kg with a clearance of 5.9-6.8 ml/kg/minute and a half life of 2.6-4.3 hours in the elimination phase (Kanto *et al.*, 1981; Aaltonen *et al.*, 1984; Virtanen *et al.*, 1982).

Atropine is metabolized in the liver by microsomal monooxygenases. HPLC separation of urine has identified 5 compounds: atropine, noratropine, tropine, atropine-N-oxide (equatorial isomer), and tropic acid (Van der Meer *et al.*, 1983). Thus, atropine is partly metabolized and partly excreted unchanged in the urine, the unchanged portion being approximately 50% (Van der Meer *et al.*, 1986). Since biliary excretion is negligible, the hepatic plasma clearance of 519±147 ml/min represents metabolism. Hepatic blood clearance and extraction ratio were 476±136 ml/min and 0.32, respectively. The elimination of atropine is, therefore, partly flow-dependent (Hinderling *et al.*, 1985). Following an intravenous injection, 57% of the dose is found in the

urine as unchanged atropine and 29% as atropine. Since the renal plasma clearance (656 ± 118 ml/min) was found to approach the renal plasma flow (712 ± 38 ml/min), tubular excretion may occur. Thus, both liver and renal disease can be expected to influence the kinetics of atropine (Hinderling *et al.*, 1985).

1.5.6. The Effects of Atropine sulphate on Clinical Parameters

Injections of atropine are used in the treatment of bradycardia (Rang., 2007). As an antisialogogue when reduction of secretions of the respiratory tract is thought to be needed; its routine use as a preanesthetic agent is discouraged (Field *et al.*, 2010). The effect of atropine sulphate in clinical dose causes no dangerous rise in body temperature (Brit, 1973).

1.5.7. Use of Atropine in Dogs

Atropine is used to anesthesia for surgery to reduce drooling and respiratory tract secretions. Atropine is often administration with many anesthetic agents to prevent slowing of the heart rate and important drug in cardio pulmonary rate. Atropine is an antidote for some insecticide. Atropine is also use to reduce drooling , vomiting and nausea (Dawn , 2015).

Atropine is used in the eye to dilate pupils, this can reduce pain and prevent complication in various eye disease .atropine well antagonize compounds that constrict air ways and cause coughing and used in animals that may have difficulty breathing such as asthma – like conditions (Dawn , 2015).

1.5.8. Atropine in Combination with Ketamine

Ketamine hydrochloride in combination with acetylpromazin with or without atropine sulphate as a pre anesthetic medication Use of atropine sulphate alone decrease tear production from a mean base line. Tear production continues to decrease after the administration of Ketamine hydrochloride (Journal of the American Veterinary Medical Association, 1984).

1.5.9. Atropine Complications and Contraindications

Signs of over-atropinization are infrequent but may include mydriasis, tachycardia and a central Atropine anticholinergic syndrome with restlessness, hyperactivity and delirium. Cyanotic (hypoxic) patients should be oxygenated and if necessary intubated at the same time as

atropine is administered, to avoid ventricular tachyarrhythmias, if an infusion is used, the risk of over-atropinization should be avoided by regular review of the rate of infusion, particularly in patients with liver or kidney disease, in children and in the elderly. In warm environments, patients should be kept cool and body temperature monitored as atropine inhibits sweating (International Programme on Chemical Safety Evaluation, 2002)

CHAPTER TWO

Materials and Methods

2.1. Study Site

This study was carried out at the College of Veterinary Medicine, Sudan University of Science and Technology, located in Hillat Kuku, the duration of this study was 2 months, all experiments were carried out between 3 pm and lasted at 6 pm.

2.2. Experimental Animals

A total number of five clinically sound males' dogs with range age and body weight 2-3 months and 5- 7.5 kg respectively were used.

2.3. Housing and Management

Dogs were housed in special cages located at veterinary teaching hospital at the college of Veterinary Medicine (Hilat Kuku), Sudan University of Science and Technology. All dogs were subjected to clinical examination to ensure their healthy status and parasite free, dogs were fed on chickens, meats and milk twice a day and allowed free access to water(Fig2.1).

2.4. Pre -Anesthetic Preparations

Dogs were fasted for overnight prior to anesthesia, to ensure a safe anesthesia; It is known that recent feeding may affect anesthetic doses by altering the basal metabolic rate. The site of an intravenous cannula was clipped shaved and disinfected.

2.5. Injection Set and Monitoring Tools

Disposable syringes (1ml, 21G× 11/2,Ava-med syringe, Sudan(21G× 11/2,CMS-Sudan disposable syringe ,XuyIwebest medical product CO.,LTD,China),Stethoscope was used for monitoring of heart beat, stop watch was used to determine the duration time of different phases of an aesthesia, thermometer used to gauge the body temperature.

Fig2.1. Animal Hosing and Management in College of Veterinary Medicine (Hillat Kuku).



2.6. Anesthetic Drugs

One anesthetic drug and three pre- anesthetic medications were used in this study, as follows:

1. Ketamine (Ketamine Hydrochloride USP 50MG ML -1 ,Troikaa pharmaceuticals Ltd.)
2. Xylazine (Rompum 2%, Bayer , turkey)
3. Diazepam (Diazepam .5% F.Hoffmann-La Roche Ltd , BSwitzerland by CENEXI SAS , Fontenay-sous Bois , France
3. Atropine (Atropine 1mg -1ml (sulphate) iv scRenaudin)

2.7. Anesthetic Protocols

Two anesthetics protocols were used to anesthetize dogs as follow :

1. Xylazine (1mg kg^{-1} , i.m.) +Diazepam (0.25mg kg^{-1} , i.v) +Ketamine (10mg kg^{-1} , i.m.)
2. Xylazine (1mg kg^{-1} , i.m.) +Atropine (0.03mg kg^{-1} , i.v.) + Ketamine (10mg kg^{-1} , i.m.)

2.8.1. Administration of Anesthesia

All animals were anesthetized by the following anesthetic protocols:

* The first anesthetic protocol was obtained by using of xylazine (i.m.) at dose rate 1mg kg^{-1} , then after the appearance of its signs (3-5 min) diazepam (0.25mg kg^{-1} , i.v.) was injected, ketamine(10mg kg , i.m.) is administered immediately after diazepam.

* The second anesthetic protocol was obtained by using of xylazine (i.m.) at dose rate 1mg kg^{-1} , and then followed by injection of Atropine (0.03mg kg^{-1} , i.v), finally ketamine (10mg kg^{-1} , i.m.) was injected.

2.8.2. Induction of Anesthesia

It is the state or condition in which the animal becomes unconscious, responded negatively to painful stimuli with disappearance of selected reflexes (Jani *et al.*, 1982).

2.8.2.1. Quality of Induction

Quality of induction of an aesthesia was rated as follows:

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

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

2.8.2.2. The Onset Time

The onset time is recorded in all anesthetic regimes by calculating the time from administration of anesthetic regime to the time when animal showed absence of reflexes.

2.8.3. Phases of Anesthesia

Phases of anesthesia were obtained by recording the anesthetic phase, lateral and sternal recumbency phases, recovery time and the total recovery time.

2.8.3.1. Anesthetic Phase (Sleeping Time)

It was considered as the period during which the animal showed sing of unconsciousness, noreflexes, response negatively to pain full stimuli (Tammisto *et al.*,1981).

2.8.3.2. lateral and sternal recumbency phases:

Lateral recumbency was considered as the duration at which the animal response positively to pain full stimuli, muscle regained their tonicity and the animal is incapable of adopting sternal position . Sternal recumbency the duration of time during which the animal was capable to adopt sternal recumbency without falling to the lateral recumbency and without adopting the standing positioning (Ghurashi *et al.*,2008).

2.8.3.3. Recovery Phase

The animal was considered to be recovered from an aesthesia when it is capable of supporting itself in standing position and walk for ten steps without falling down (Ghurashi *et al.*,2008).

2.8.3.3.1 .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 an aesthesia.

- 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 attempts to stand.

- Score (4) poor: Excitement during recovery with danger of injury and needed more than two attempts to stand.
- Score (5) very poor: severe excitement during recovery with injury.

2.8.3.3.2. Total Recovery Time

Total recovery time was considered as the total time recorded from the time of induction of an aesthesia until full recovery was attained (Nuha., 2004).

2.8.4. Quality of Muscle Relaxation

The quality of muscle relaxation scored as followed:

- I. Excellent: characterized by complete relaxation.
- II. Good: characterized by adequate relaxation of muscle that permits surgery.
- III. Moderate: with partial relaxation of neck, head and limb muscle.
- IV. Poor: characterized by rigidity of neck, head and limb muscle.

2.8.5. Physiological Parameters

Physiological parameters were recorded before administration of anesthesia as baseline value and then at 5,15,25,35,45,60and 30 minutes intervals after injection of anesthesia in all anesthetic regimes.

2.8.5.1. Respiratory Rate (Breath Minute⁻¹)

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

2.8.5.2. Heart Rate (Beats Minute⁻¹)

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

2.8.5.3. Body temperature

Body temperature(C°) was monitored by using digital thermometer.

2.8.6. Reflexes of Anesthesia

2.8.6.1. Tongue and Jaw Relaxation Reflexes

These was assessed by pulling the tongue outside the mouth, when the animal was capable to pull its tongue into the mouth, the reflex was considered positive (Nuha.,2004). Persistence of open mouth due to induced jaw retraction was considered to be a positive jaw relaxation reflex. The reflex was considered regained when the animal was reluctant to open its mouth (Subjective).

2.8.6.2. Palpebral Reflex

The reflex was assessed by digital touch on the can thus or eyelashes, if purposeful motor reflex observed, the reflex was considered positive (Batoul ., 1990) .

2.8.6.4. Pedal Reflex

Pedal reflex was assessed by pinprick on the coronary band of the digit. If the animal moves its leg or leg muscle, the reflex was consider positive (William and wyatt ., 2007) .

2.8.6.5. Anal Reflex

Anal reflex was assessed by inducing tension of anal sphincter with two fingers. Positive response was considered when the movement of anal sphincter was noticed (Subjective).

2.8.7. Statistical Analysis

Statistical analysis were made using T-test, data are presented as mean \pm stander deviation ($M \pm S.D$) and significance was detected at ($P < 0.01$ and $P < 0.05$) using statistical package for social science SPSS program me. No statistical evaluation of subjective data (i.e. Tongue and Jaw Relaxation Reflexes, Palpebral Reflex ,Pedal Reflex and Anal Reflex).

CHAPTER THREE

RESULTS

3.1. Induction and Onset of Anesthesia

As showed in fig 3.1, the quality of induction using ketamine (10 mg kg^{-1}) with both xylazine (1 mg kg^{-1}) and diazepam (0.25 mg kg^{-1}) respectively and ketamine (10 mg kg^{-1}) with xylazine (1 mg kg^{-1}) and atropine (0.03 mg kg^{-1}) in dogs was found to be satisfactory (smooth and excitement free with little danger to both animal and personnel).

The mean onset time of anesthesia with both mentioned anesthetic protocols were 70 ± 30 second.

3.2. General Observations on Administration of Anesthesia

Immediately after injection of two studied anesthetic protocols using ketamine, xylazine with either diazepam (0.25 mg kg , i.v.) or atropine sulphate (0.03 mg kg , i.v), animals were exhibit different signs including dropping of head, observed ataxia and adoption of lateral recumbence.

3.3. Anesthesia Phases

As illustrated in table (3.1), the duration of anesthesia phases (minutes) were described as mean \pm standard deviation (SD), the duration of anesthetic phase , lateral recumbency and total recovery of the two studied anesthetic protocols (KZD and KZA) showed no significant differences, however, the duration of the sternal recumbency phase and recovery time showed significant changes at ($p < 0.01$) ; the sternal recumbency (6.80 ± 5.16) and recovery duration (7.40 ± 7.86) were longer in xylazine /diazepam premedicated dogs compared with the duration of sternal recumbency (2.40 ± 2.07) and recovery time (3.60 ± 2.07) in xylazine/ atropine premedicated dogs.

Fig.3.1 The Onset and Induction of Anesthesia in College of Veterinary Medicine (Hillat Kuku).



Table (3.1): Mean \pm SD of anesthetic phase (sleeping time), lateral recumbency, sternal recumbency , recovery time and total recovery time (in minutes) in different anesthetic protocols using ketamine (10mg kg⁻¹) with both xylazine (1mg kg⁻¹) and diazepam (0.25mg kg⁻¹) and ketamine (10mg kg⁻¹) , xylazine (1mg kg⁻¹) and atropine (0.03mg kg⁻¹) in dogs in College of Veterinary Medicine (Hillat Kuku).

Anesthetic phases	Anesthetic regimes		Sig
	KXD	KXA	
Anesthetic phase	36.2 \pm 11.3	34.0 \pm 3.60	N.S
Lateral recumbency	47.6 \pm 19.2	48.0 \pm 11.9	N.S
Sternal recumbency	6.80 \pm 5.16	2.40 \pm 2.07	*
Recovery time	7.40 \pm 7.86	3.60 \pm 2.07	*
Total recovery	60.0 \pm 13.2	54.8 \pm 11.7	N.S

N=5

SD= Standard Deviation

KZD= Ketamine, Xylazine, Diazepam.

KZA= Ketamine, Xylazine, Atropine.

Sig= significant.

N.S= Not significant.

* = Significant at (P < 0.05)

3.4. Quality of Muscle Relaxation and Recovery:

The quality of muscle relaxation in both anesthetic protocols either ketamine, xylazine with diazepam or Ketamine, xylazine with atropine sulphate ganged between good and excellent muscle relaxation. The recovery quality was varied between the different two anesthetic protocols, in the first protocol (KZD) 60% (3 out of the 5 animals) exhibited excellent recovery and the animal stood up in the first attempt and 40% (2 out of the 5 animals) showed very good recovery and the animal needs two attempts with help to stand. In the second group (KZA) 80% (4 out of 5 animals), exhibited very good recovery, while 20% (1 out of the 5 animals) showed good recovery quality (table.3. 2.).

Table 3.2: Grades of recovery quality in the two tested protocols using KZD and KZA in experimental dogs in College of Veterinary Medicine (Hillat Kuku).

Protocols	No.of animals	Very poor		Poor		Good		Very good		Excellent	
		No	%	No	%	No	%	No	%	No	%
KZD	5	0	0	0	0	3	60	2	40	0	0
KZA	5	0	0	0	0	0	0	4	80	1	20

N= 5

KZD = Ketamine (10 mg kg⁻¹, i.m.), Xylazine (1 mg kg⁻¹, i.m) and Diazepam (0.25 mg kg⁻¹, i.v.).

KZA = Ketamine (10 mg kg⁻¹, i.m), Xylazine (0.25 mg kg⁻¹, i.m) and Atropine (0.03 mg kg⁻¹,i.v.).

3.5. The Effects of the Anesthetic Protocols on Physiological Parameters:

3.5.1. Respiratory Rate (RR):

Respiratory rate values (breath min⁻¹) were described as mean ± standard deviation, table (3.3.) showed highly significantly differences at (p<0.01) at 5 and 25 minutes after administration of anesthesia; the respiratory rate values were higher in dogs anesthetized with general anesthesia using KZD compared with those anesthetized with KZA, and significantly differences (p<0.05) at 15 and 35 minutes after administration of the two anesthetic regimes in dogs; also dogs under anesthesia using KZD showed higher respiratory values compared with dogs anesthetized with KZA. Respiratory rates were dramatically increased at 40 and 60 minutes after anesthesia injection, then started to decrease near to the normal values at 90 minutes post anesthesia injection.

Tab3.3: Mean ± SD of respiratory rates (breath min⁻¹) during two anesthetic regimes using ketamine (10mg kg⁻¹), xylazine (1mg kg⁻¹) and diazepam (0.25mg kg⁻¹) and ketamine (10mg kg⁻¹), xylazine (1mg kg⁻¹) and atropine (0.3mg kg⁻¹) at 0, 5, 15, 25, 35, 45, 60 and 90 minutes intervals in experimental dogs.

Anesthetic protocols	Respiratory rates(RR breaths min ⁻¹)							
	BLV	5	15	25	35	45	60	90
KZD	34.6±6.56	27.8±2.71	25.4±2.91	26.8±2.03	29±3.19	38.33±8.88	64±0.00	39.8±7.31
KZA	46.2±10.25	13.2±0.37	17.4±1.12	17.6±0.93	20.4±1.03	36.5±2.50	57±0.00	41.8±1.77
Sig	N.S	**	*	**	*	N.S	N.S	N.S

N=5

KZD= Ketamine, Xylazine, Diazepam

KZA= Ketamine, Xylazine, Atropine

BLV= Baseline Values

Sig= significant

* =significance at (p<0.05)

** = significance at (p<0.01)

3.5.2. Heart Rate (HR):

As depicted in table 3.3, heart rate values (beats min⁻¹), showed highly significant differences (P < 0.01) at 5 and 15 minutes and significant difference (p<0.05) at 25minutes after administration of anesthetic protocols in dogs anesthetized with KZA compared with animals anesthetized using KZD.

Table 3.4 : Mean ±SD of heart rates (HR) of two anesthetic regimes using ketamine (10mg kg⁻¹), xylazine (1mg kg⁻¹) and diazepam (0.25mg kg⁻¹) and ketamine (10mg kg⁻¹), xylazine (1mg kg⁻¹) and atropine (0.3mg kg⁻¹) at 0, 5, 15, 25, 35, 45, 60 and 90minutes intervals in experimental dogs .

Protocols	HR (breath min ⁻¹)							
	BLV	5	15	25	35	45	60	90
KZD	99.2±7.96	15.55±82.4	95.8±7.15	87±7.9	89.6±3.50	105±27.50	84±0.00	103.8±19.88
KZA	105±9.15	127.6±7.81	117.8±5.92	106.4±2.99	92.2±9.97	106.5±5.50	97±0.00	95.64±6.8
Sig	N.S	**	**	*	N.S	N.S	N.S	N.S

No= 5

KZD= Ketamine, Xylazine, Diazepam

KZA= Ketamine, Xylazine, Atropine

BLV= Baseline Values

Sig= significant

* =significance at (p<0.05)

** = significance at (p<0.01)

3.5.3. Temperature

Body temperature was described as mean \pm standard deviation, no significant differences were observed during the course of anesthesia in all mentioned anesthetic protocols (table3.4.).

Tab3.5: Mean \pm SD of temperature (C^o) of two anesthetic regimes using ketamine (10mg kg⁻¹), xylazine (1mg kg⁻¹) and diazepam (0.25mg kg⁻¹) and ketamine (10mg kg⁻¹), xylazine (1mg kg⁻¹) and atropine (0.3mg kg⁻¹) on at 0, 5, 15, 25, 35, 45, 60 and 90minutes intervals in experimental dogs .

Protocols	Temperature (C ^o)							
	BLV	5	15	25	35	45	60	90
KZD	38.52 \pm 0.42	38.04 \pm 0.53	38.3 \pm 0.30	37.92 \pm 0.53	37.96 \pm 0.55	37.93 \pm 0.74	39.9 \pm 0.00	38.2 \pm 0.64
KZA	39.06 \pm 0.22	38.88 \pm 0.10	38.46 \pm 0.18	38.02 \pm 0.13	37.52 \pm 0.19	37.35 \pm 0.55	36.6 \pm 0.00	37.54 \pm 0.41
Sig	N.S	N.S	N.S	N.S	N.S	N.S	N.S	N.S

No= 5

KZD= Ketamine, Xylazine, Diazepam

KZA= Ketamine, Xylazine, Atropine

BLV= Baseline Values

Sig= significant

* =significance at (p<0.05)

** = significance at (p<0.01)

3.6. The Effect of Anesthetic Protocols on Selected Reflexes :

As showed in table 3.5 a &b, selected reflexes such as tongue protruding , palpebral, pedal, anal, jaw relaxation and spinal reflexes were presented as (+ sign which means present of the reflex or – sign that means absent of the selected reflex) during the course of anesthesia in all anesthetic protocols

Table 3.6a: Effect both anesthetic protocols using KZD on some selected reflexes in dogs at 0, 15, 25,35, 45, 60 and 90 minutes intervals

Reflex	Base	0	15	25	35	45	60	90
Tongue	+	-	-	-	+	+	+	+
Palpebral	+	-	-	-	+	+	+	+
Jaw	+	-	-	-	+	+	+	+
Pedal	+	-	-	-	+	+	+	+
Anal	+	-	-	-	+	+	+	+
spinal	+	-	-	-	+	+	+	+

Table 3.6b: Effect both anesthetic protocols using KZA on some selected reflexes in dogs at 0, 15, 25,35, 45, 60 and 90 minutes intervals

Reflex	Base	5	15	25	35	45	60	90
Tongue	+	-	-	-	-	+	+	+
Palpebral	+	+	+	+	+	+	+	+
Jaw	+	-	-	-	-	+	+	+
Pedal	+	-	-	-	-	+	+	+
Anal	+	-	-	-	-	+	+	+
spinal	+	-	-	-	-	+	+	+

0= time of xylazine injection (i.m)

+ = present of the anesthetic reflex

- = absent of anesthetic reflex

Fig3.2. Palpebral ,Tongue and Jaw Relaxation Reflexes



CHAPTER FOUR

DISCUSSION

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). Preanesthetic 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). Ketamine is a rapid-acting general anesthetic producing an anesthetic state characterized by profound analgesia, normal pharyngeal-laryngeal reflexes without muscle relaxation, cardiovascular and respiratory stimulation and occasionally a transient and minimal respiratory depression (Hall and Clarke, 1991; Haskins *et al.*, 1986). These drugs usually result in a smooth induction and recovery with the pressor 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 combination of the α_2 -adrenergic agonist, xylazine HCl and the cyclohexane, ketamine HCl has been used to immobilize numerous wild and domestic carnivores (Knight., 1980; Herbstl *et al.*, 1985; Terry *et al.*, 1986; England and Clarke., 1989; Tranquili and Benson., 1992). Xylazine premedication in healthy dogs has been associated with an increase in mortality rate compared with other pre-anesthetic regimes (Clarke and Hall, 1990; Dyson *et al.*, 1998).

There was not any mortality in this study.

The dose rates chosen in this study was 10 mg kg^{-1} , based on results of published literature (Reynolds *et al.*, 1989). The onset time in all anesthetic protocols using ketamine (10 mg

kg⁻¹) in combination with premedications (xylazine 1mg kg⁻¹), diazepam (0.25mg kg⁻¹) and atropine (0.03mg kg⁻¹) occurred within 70 ±30 seconds .

The effect of administration of two anesthetic protocols using ketamine (10mg kg⁻¹) in combination with premedications (xylazine 1mg kg⁻¹), diazepam (0.25mg kg⁻¹) and atropine (0.03 mg kg⁻¹) provide satisfactory anaesthesia in dogs ,this result was supported by (Brock and Hildebrand., 1990 ; Nigel, 2007).

The average duration of anesthesia (from induction to first movement with conscious) were 47.6±19.2 and 48.0±11.9 minutes in anesthetic protocols using KZD and KZA respectively, these results were similar to those reported an anesthetic duration of 55.25 minutes (Sindak *et al.*, 2010) and the quality of both induction and recovery were satisfactory and smooth also agree with those observed by (Sindak *et al.*, 2010).

The study showed significant decrease in respiratory rate values at 5, 15, 25 and 35 minutes following administration of both anesthesia protocols using KZD and KZA; The noticeable decrease in respiratory rate values is similar to those reported a significant changes at 15, 30 and 60 min after xylazine-ketamine administration in dogs (Kul *et al.*, 2000). Respiratory rate significantly remained lower than baseline throughout the anesthesia (Demirkan *et al.*, 2002; Atalan *et al.*, 2002; Cormick and Hartsfield., 1992; Haskins *et al.*, 1986; Tranquili and Benson, 1992; Hall and Clarke, 1991; Gleed, 1987). On the other hands, using of atropine s/c 10 minutes before pre-anesthesia positively impacts the heart frequency and breathing, (Muir, 1978). In this study the heart rate showed highly significantly decrease at 5, 15 and 25 minutes after administration of anesthesia in both studied anesthetic protocols, and this observation is in total agreement with that reported by Hall *et al* (2001) and Kul *et al* (2000); major side effects of α₂-adrenoreceptor agonists on the cardiovascular system may have contributed to the decreased heart rate in this anaesthetic regimen. Although ketamine may increase the heart rate by the increased sympathetic activity and decreased vagal tone, 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 bradyarrhythmias and administration of ketamine increase and correct heart rate (Diamond *et al.*, 1993; Kerr *et al.*, 1994).

Reduction of the heart rate, atrioventricular block and hypotension are usually observed after the use of α -2 adrenoceptor agonists (Klide *et al.*, 1975). The concomitant use of ketamine probably delayed the arterial hypotension, which was observed only at the end of anaesthesia (Haskins *et al.*, 1986; Wright, 1982).

Body temperature values showed no significant changes during anesthesia courses in all anesthetic protocols, this data also are supported by others authors that the dosis does not affect the temperature, (Thurmon and Benson, 1986). In this study muscle relaxation range between excellent, very good to good .and this agree with (Matthews *et al.*, 2004 , Koshiy *et al .*, 2014).

CHAPTER FIVE

CONCLUSIONS AND RECOMMENDATIONS

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.

Proper anesthetic management means more than a return of the subject to consciousness, it also includes the quality of anaesthesia provided.

Ketamine plus xylazine at dose rates 10 mg kg^{-1} and 0.25 mg kg^{-1} respectively with either diazepam (0.25 mg kg^{-1}) or atropine (0.03 mg kg^{-1}) were a safe and provide satisfactory anesthesia in dogs.

In this study during the anesthesia using KZD or KZA, heart and respiratory rates were decreased and this did not making any life threatening.

The cardio-pulmonary changes caused by ketamine anesthesia with premedications were transient and improved in the latter half of the study as the drug effect wore off.

It could be concluded that anesthesia obtained using ketamine with premedication such as xylazine with either diazepam or atropine sulphate was safe and suitable for many surgical interventions in dogs.

Recommendation:

- further studies will be needed in dogs 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 and with evaluation of other cardio-respiratory parameters, including blood gas analysis and invasive blood pressure measurement.

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