Sudan University of Science and Technology

College of Graduate Studies and Scientific Research

A comparison of two intramascular doses of Xylazine-Ketamine combination in Sudanese dogs

مقارنة بين جرعتي تخدير عضلي من تركيبة زيلازين وكيتامين في الكلاب السودانية

By

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قَالَ تَعَالَىٰ: ﴿وَيَسْـَٔلُونَكَ عَنِ ٱلرُّوحِ ۖ قُلِ ٱلرُّوحُ مِنْ أَمْرِ رَبِّى وَمَآ أُوتِيتُم مِّنَ ٱلْعِلْمِ إِلَّا قَلِيلًا ﴿٨٥﴾﴾ صدق الله العظيم

الإسراء: الآية (85)

Declaration

I here by declare that this research work was carried out in the department of Veterinary Medicine and Surgery, College of Veterinary Medicine, Sudan University of Science and Technology under the supervision of Dr. Ahmed Abdullah Ahmed Sanhori

DEDICATION

This work is dedicated to the most important persons in my life my dear mother and father, also to my sister, my brothers and to every person encourage me to complete this work

With great lov*e*

ACKNOWLEDGEMENTS

My all thanks to God, then my great thanks to my supervisor, **Dr. Ahmed Abdullah Ahmed** for his continuous guidance, valuable advice and unfailing help. Thanks are also extended to my colleagues in the Masters programme(Mohammed Abass Elbashire,Jumaa Ahmed Abaker,Ahmed Mohammed Ameen and Khidir Abdeen Alkhidir) for their support and for kind help throughout the entire course of the study. I am also indebted to many other colleagues and technicians in the department of Veterinary Medicine and Surgery, College of Veterinary Medicine, Sudan University of Science and Technology for their help and support. Also, I wish to extend my special gratitude to Mortada Mohammed and Abubakar Saied Ali for their great assistance in the completion of this work. The endless thanks are to all whom helped me at time or other during my research.

Abstract

The purpose of this study was to determine the effects of Safe and effective aneasthesia of different protocols of Xylazine-Ketamine on clinical and anaesthesia parameters in attempts to produce safe and satisfactory total intramascular anaesthesia in dogs(10 local breed dogs were used in this study 5dogs for each group)..

In this study two protocols were used: Protocol Xylazine 1mg/kg-ketamine 15mg/kg i/m for group 1 and Protocol Xylazine 1.5 mg/kg-ketamine 15mg/kg i/m for group 2

All anaesthitic protocols produced satisfactory induction and rapid smooth recovery and there were significant increase in the duration of anaesthesia during protocol two compared to protocol one .

In the duration of lateral recombency, sterna recombenc, standing position and total recovery time was monitoring during course of anaesthesia. induction of anaesthesia, muscle relaxation and recoveries were satisfactory in both protocols used.

The clinical and anaesthetic parameters were measure before, during and after anesthesia at interval 10, 20, 30,40,50,60 minutes throughout the duration of the experiment.

The heart and respiratory rates were significantly depressed ($p \leq 0.05$) value of 86.40±33.54 beat /minutes (group1), 120.40±25.74 beat /minutes (group2) 86.40±33.54 beat /minutes (group1), 120.40±25.74 beat /minutes (group2) twenty minutes post induction of aneasthetic protocol and 86±33.97 beat /minutes (group1) and 120±22.14 beat /minutes (group2) fifty minutes post induction of the aneasthetic protocol. The respiratory was 14±4.85 breath/ minute (group1) and 16.80±5.40 breath/ minute (group2) ten minutes post induction of aneasthetic protocol.

Moderate aneasthesia and muscle relaxation was evident into the aneasthesia 1.60±0.89 minutes (group1) and 2±0 minutes (group2). Postoperative care was given to body temperature, degree of sedation and appropriate analgesia.

All reflexes disappeared 54±8.94Minutes (group1) and 56±11.40Minutes (group2). It is concluded that both protocols didn't cause any harmful effect to both cardio pulmonary systems therefore, both protocols can be used in the local breed dogs and they proof to be efficient with good analgesia and good muscle relaxation, and with wide margin of safety.

الخلاصة

الغرض من هذه الدراسة هو تحديد آثار مخدر آمن وفعال من بروتوكولات مختلفة من زيلازين- الكيتامين على المعايير السريرية والتخديريه في محاولات لإنتاج إجمالية تخدير عضلي آمن وفعال في الكلاب (تم استخدام 10كلاب من سلاله محليه في هذه الدراسة 5 كلاب لكل مجموعة).

في هذه الدراسة تم استخدام اثنين من البروتوكولات : بروتوكول زيلازين 1 ملجم /كجم - الكيتامين 15 ملجم /كجم حقن عضلي للمجموعة 1 ، وبروتوكول زيلازين 1.5ملجم /كجم - الكيتامين 15 ملجم/كجم حقن عضلي للمجموعة 2.

أنتجت جميع بروتوكولات التخدير المستخدمه في التجربة تحريض تخديري فعال وتعافي سلس سريع، وكانت هناك زيادة كبيرة في مدة التخدير خلال بروتوكول رقم اثنين مقارنة مع بروتوكول رقم واحد.

تم مراقبة فترة الاستلقاء الوحشي، الاستلقاء القصي ، وضع الوقوف ووقت التعافي الكامل من التخدير أثناء سير التخدير. كانت عمليه التخدير والإسترخاء العضلات والتعافي من المخدر فعال في كل من البروتوكولات المستخدمة.

وتم قياس المعايير السريرية والتخديريه قبل وأثناء وبعد التخدير في الفاصل الزمني 10، 20، 30،40،50، 60 دقيقة طوال مدة التجربة.

معدل ضربات القلب والجهاز التنفسي منخفضة معنويا ($P < 0.05$) قيمة 33.54 ± 86.40 ضربات /دقيقة (مجموعه رقم 1)، 25.74 ± 120.40ضربات /دقيقة (مجموعه رقم 2) 33.54 ± 86.40 ضربات /دقيقة (مجموعه رقم 1) ، 25.74 ± 120.40ضربات /دقائق (مجموعه رقم 2) آخر عشرين دقيقة تحريض بروتوكول التخدير و 33.97 ±86 ضربات/ دقيقة (مجموعه رقم 1) و 22.14 ±120ضربات /دقيقة(مجموعه رقم 2) خمسين دقيقة بعد تحريض بروتوكول التخدير وكان الجهاز التنفسي 4.85 ± 14التنفس /دقيقة(مجموعه رقم 1) و 5.40 ± 16.80 /التنفس الدقيقة (مجموعه رقم 2)عشرة دقيقة بعد تحريض بروتوكول التخدير.
كان التخدير معتدلاو الاسترخاء العضلي واضحا في التخدير 0.89 ± 1.60 دقيقة (مجموعه رقم 1) و 2±0 دقيقة. (مجموعه رقم 2) أعطيت رعاية ما بعد الجراحة لدرجة حرارة الجسم، ودرجة من التخدير وتسكين الألم المناسب.

كل ردود الفعل اختفت (مجموعه رقم 1)8.94 ± 54 دقيقه و40.11.± 56 دقيقه . (مجموعه رقم 2) ويستنتج من ذلك أن كلا من البروتوكولان لم يسبب أي تأثير ضار على كل من الجهازين القلبي والتنفسي وبالتالي، كلا البروتوكولين يمكن أن تستخدم لسلالات الكلاب المحلية، وأنها تعطي تخدير جيد وفعال بالإضافة للتسكين والاسترخاء العضلي الجيد ، ومع هامش واسع من السلامة .

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NMDA	N-Methyl-D-Aspartate (NMDA) receptors
CNS	Central Nervous System
GABA	Gamma amino butyric acid
HPA	Hypothalamus Pituitary Adrenocortical axis
CAD	Coronary Artery Disease
ANOVA	Analysis Of Variance
SPSS	Statistical Package for Social Science

INTRODUCTION AND OBJECTIVE

Domestic dog *Canis lupus familiaris (*Dewey 2003) and *Canis lupus* dingo(Mammal Species of the World 2010) is a domesticated type of the gray wolf, the member of the family *Canidae* of the order *Carnivora*. This term is also used for feral as well as pet varieties. Dog is thought to be the first animal to be domesticated about 15,000 years ago from gray wolves. (Savolainen, P., Zhang, Y.P., Luo J, Lundeberg, J., Leitner, T. (2002). The term "dog" may also mean the male of a canine species, as opposed to the word "bitch" for the female of the same species as defined by the English dictionary. Their importance to early human settlements led to them quickly becoming global across world cultures. Dogs are accomplish many roles for people, such as hunting, herding, pulling loads, protection, assisting police and military, companion ship, and, more recently, aiding handicapped individuals. This effect on human society has given them the nickname "Man's Best Friend". Due to the censuses in 2001, there were 400 million dogs approximately in the world. (Coppinger, et al., 2001).

General anesthesia administrated in dogs and other animal species to provide a state of reversible unconsciousness with adequate analgesia and muscle relaxation for surgical procedures in such a way that it does not threaten the patient's health. A general anesthetic to a fit healthy dog should bear slight risk to the animal's vital functions. However, although the mortality rate is very low, morbidity due to anesthesia, was more or less, ignored, is very common (Lyon 2006).

Xylazine is a potent hypnotic alfa2-adrenoceptor agonist which had been widely used in veterinary medicine (Tranquili *et al*., 1992). It is **a** colonide analoque acts in presynaptic and post synaptic receptors of both preferal and central nevous system as α-2 adrenergic agonist causing inhibition of most of postganglionic nerve stimulation.

Xylazine produce analgesic, sedative and muscle relaxant effects by combining with CNS α_2-adrenoreceptors. It also potentially produces marked cardiopulmonary depression. Xylazine can produce significant cardiac dysrhythmia. Respiratory and heart rate decrease after administration of Xylazine(1mg/kg b.w) It induces vomiting in about 25 % of dogs.(Dart, *et al,*. 1999; Haskins, *et al*., 1986; Paddleford, et al., 1999Tranquili, *et al* 1992). Xylazine is water soluble and can be mixed with the standard ketamine solution without precipitation (Green, *et al.*, 1981). Ketamine hydrochloride is a no barbiturate, dissociative anesthetics agent (Hall, *et al*., 1991). It interacts with N-methyl-D-aspartate (NMDA) receptors, opoid receptors, monoaminergic receptors, muscarinic receptors and voltage sensitive Ca ion channels. Unlike other general anaesthetic agents, ketamine does not interact with Gamma Amino Butyric Acid (GABA) receptors. Ketamine had been developed in 1962, as a fast acting general anesthetic (Jansen, *et al.*, 2000). Ketamine produces profound analgesia without muscle relaxation and tonic-colonic spasm of limb muscles (Hall, *et al.*, 1991; Haskins, *et al.*, 1986**)**. When used in normal clinical dose, most pulmonary function tests remain within normal limits (Hartsfield, *et al*., 1992; Short, *et al*., 1987).It can be given intramuscularly with a wide margin of safety, thus reducing the need for accurate weight estimation. The main disadvantages of ketamine are that it often enhances muscle tone to the extent that tremors or even tonic-colonic convulsions are produced, it causes a marked increase in salivation, and there is wide variation in response between species and among individuals (Green, *et al*., 1981).

The objectives of this study are:

1. To study the effects of two different doses of xylazine(1mg/kg B.W) (1.5mg/kg B.W) in combination with ketamine that would produce a safe and acceptable compare and contrast between the selected anaesthetic doses for cardiopulmonary changes, muscle relaxation, duration of recumbency and quality of recovery total intramuscular anaesthesia in dogs.
2. To study the effects of the anaesthetic protocol tested in some physiological parameters of local breeds of dogs.
3. To detect what the suitable dose used for local breed dogs.
4. the study is designed to provide guidance for practioners engaged in small animal surgery and anaesthesia.

CHAPTER ONE
LITERATURE REVIEW

1.1 The dog

The endogenous breeds of dogs in the Sudan which is considered by our society important, and that's because of their use in the guarding and hunting purposes(A C F), the nomads also known them for decades to herd their sheep and goats in certain rural areas of the country. Their socio economic potential couldn't be ignored, however, they received very little attention in the past,.

Fraser and Broom (1990), defined welfare as the state of animal as attempt to cope with its environment. It is therefore, becomes essential to investigate the various anaesthetic drugs such as α2 adrenoceptors in an attempt to abolish the negative consequences of the stress responses by using suitable non invasive pain relieving mechanisms. Suffering is defined as state of enduring pain, misery or loss. While pain is an unpleasant sensory experience it is very necessary means to survival maintain a responsive hypothalamus pituitary adrenocortical axis (HPA) during anaesthesia and surgery (Sanhori et al., 1991). Pain teach an animal to avoid potentially harmful stimuli and to recognize them in the future. Pain also inhibits any action that may delay the healing process due to supresed of immune.

Now days scientists have established that animals possess a similar neuron anatomy to man but whether they feel pain with the same degree of intensity is open to question, since response to pain is both physical and emotional, and the emotional response cannot be measured directly (Flecknell, 1999). However it can be assumed that an

animal does feel pain and indication of this wa shown in the change of behavioral, physiological markers and response to analgesia.

By action on the autonomic and central nervous system (C.N.S) α2-adrenoceptor agonists, produce sedation, analgesia, and muscle relaxation. This due to distribution of the receptors and their presence at diversities in the central and peripheral (C.N.S) including brain stem nuclei (e.g. locus coerleus), spinal cord laminae, and sensory afferent terminals and various organs (Doherty, 2006).α2-adrenoceptor agonists used clinically in the various veterinary procedures (Clarke, *et al*., 1969). They cause long lasting hypotension, vasoconstriction, control nor epinephrine release from sympathetic nerves and the adrenal gland, decrease heart rate (bradycardia by increase vagal tone), respiratory depression with high doses, increase urine output, hyper glycaemia and uterine contractions in late pregnancy in cattle, sheep and horses. (Doherty, *et al*., 1980; Knight 1980; Doherty 2006; Symonds 1976; shehata *et al*., 1981; Thurmon *et al*., 1982. Hall, *et al*., 2001). They were used in dog and cats before the introduction of medetomidine a more potent α_2 drug.

1.2 Xylazine(Hcl):

1.2.1 Definition:

Xylazine is a clonidine analoque. It acts on presynaptic and postsynaptic receptors of the central and peripheral nervous systems as an α_2-adrenergic agonist. It is used primarily for sedation, anaesthesia, analgesia and muscle relaxation but it has numerous other pharmacological effects, Xylazine inhibits the effects of postganglionic nerve stimulation (Elbahir ,M.A (2012)

1.2.2 Commercial (trade) name:

Xylazine hydrochloride, Rompun hydrochloride

1.2.3 Chemical name:

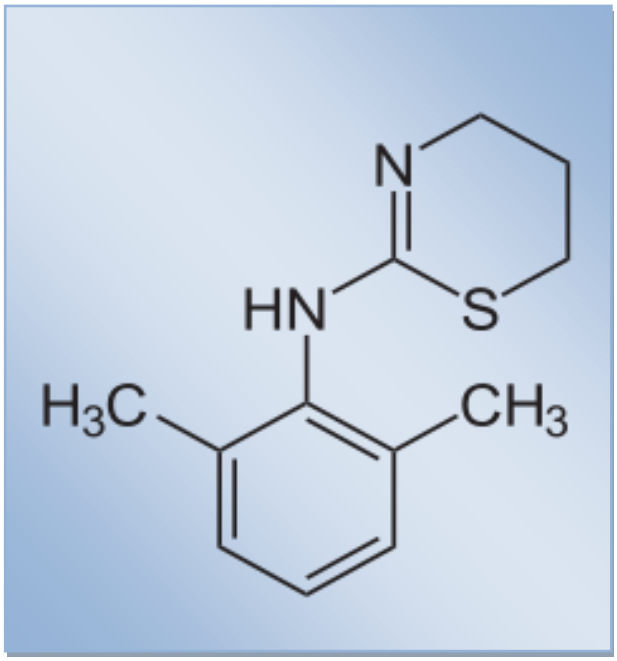
N-(2,6-dimethylphenyl)-5,6-dihydro-4*H*-1,3-thiazin-2-amine(IUPAC name)

N-(2,6-dimethylphenyl)-5,6-dihydro-4H-1,3-thiazine-2-amine hydrochloride (C.A.S. name)

1.2.4 Formula:

$C_{12}H_{16}N_2S$

1.2.5 Structure:



Xylazine has anaesthetic and muscle relaxing proprieties and the extents of these effects showed variable responses and intensity primarily depending on the dose and route of administration (Kollias,

et al., 1993; Cuvelliez *et al.*, 1995). Previous attempts to control pain perception with xylazine and ketamine in donkeys and mules tend to require significantly higher anaesthetic doses to achieve an effective level of sedation. (Koshy, *et al*., 2003).

1.2.6 Mode of action of Xylazine:

Xylazine act upon the central nervous 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-adrenoceptors induces both analgesia and sedation. This result from binding of xylazine to the α_2-adrenoceptors in the presynaptic membrane resulting 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 to excitatory in put (Thurmon *et al*., 1996).

1.2.7 Effects of Xylazine:

1.2.7.1 Cardiovascular and pulmonary effect of Xylazine:

Within 15seconds of administration of Xylazine a profound hypertensive response was recorded. Cardiac minute work was depressed, mechanical index of myocardial oxygen demand and coronary blood flow was also depressed. In different animal species an immediate decrease in heart rate, respiratory rate and cardiac output was produced by sedative dose of xylazine (Campbell *et al*.,1979; Kumar and Thurmon 1979). An early decrease in blood pressure after xylazine administration is attributed to bradycardia which was immediately followed by a sharp small rise in cortisol concentrations recorded by Sanhouri *et al.*, (1991). Bradycardia occurs initially due to a reflex response to the transient hypertension seen immediately after

injection (Sanhouri *et al*., 1991). The hypertension caused via the post synaptic α2-adrenoceptors which increase the peripheral vessels (knight 1980). This gives way to a mild hypotension presumably as stimulation of central presynaptic α2-adrenpceptors which inhibit noradrenaline release by acting on interneurons in the vasomotor relay nuclei to decrease efferent outflow (kobinger, 1978).

1.2.7.2 Effects of Xylazine on physiological parameters:

While decrease in blood pressure observed at later times is attributed to the vasodilatation (Rings and Muir 1982). Prior xylazine treatment prevented the increase in heart rate, xylazine produces noticeable decrease in pulse and respiratory rate, in goats, xylazine (0.01mg/kg) causes decrease in respiratory and heart rate within 5 minutes of drug administration even more, xylazine administrated 8minutes before short transport prevented the transport induced increase in heart rate (Sanhouri *et al.,* 1991). It also suppressed the increased values of respiratory rates induced by transport (Sanhouri *et al.,* 1991). Following xylazine administration alone, the respiratory rate decreased for about 35minutes in accordance with reports from sheep (Stranb 1971; Aziz and Carlyle 1978). The respiratory rate 55minutes into a 2 hours journey increases markedly but suppressed for 60minutes after xylazine administration even though the stress intensity continued to be high.

1.3 Ketamine Hcl (Ketalar)

Ketamine is a dissociative anaesthetic agent because its mechanism of action is thought to interrupt the cerebral association pathways, with relative sparing of the reticular and limbic systems and depression of the thalamic cortical system (Lin., 1996). It is one of the very few general anaesthetic agents that can be administered by more than one route (i.e. IV and IM). In addition, it is probably the only general anaesthetic agent with substantial analgesic effects (Hall et al., 2001). It is a short acting

anaesthetic agent being widely used in recent years. In man, S (+) Ketamine has an anaesthetic-analgesic effect two to four times greater than racemic ketamine (Lauretti et al. 2000), and its hypnotic effect is more potent than that of the R (-) isomer (Terra et al. 1999), allowing the use of lower doses of S (+) ketamine compared to racemic ketamine. Ketamine is used for premedication, sedation, induction and maintenance of general anaesthesia (Huai-Chia et al., 2009).

Ketamine is used commonly for induction of anaesthesia in horses, usually in combination with diazepam or guaifenesin and is also used for maintenance of anaesthesia by incremental dosages (Rossetti et al., 2008).

1.3.1 Identity

Ketamine(2-(2-chlorophenyl)-2-(methylamino)cyclohexanone) is an aryl cyclo alkyl amine structurally related to phencyclidine (PCP). Ketamine hydrochloride is water-soluble, white crystalline and has a pKa of 7.5 (PH at which the solution contains equal proportion of charged and uncharged molecules) (Budavari et al., 1989). 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.

1.3.2 Proprietary names

Katalar, Ketalor, Ketavet, (ECDD) (eScience for Cheminformatics and Drug Discovery 2006) .

1.3.3 Chemical name

(2-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride;(WHO., 2006)

2-(O-chlorophenyl)- 2-(methylamino) cyclohexanone hydrochloride (Blackburn et al., 2006)

(Methylamino)-2-(2-chlorophenyl) cyclohexanone hydrochloride; (Methylamino)-2-(o-chlorophenyl) cyclohexanone hydrochloride (WHO., 2006).

1.3.4 Molecular formula

Free base: $C_{13}H_{16}ClNO$

Hydrochloride salt: $C_{13}H_{17}Cl_2NO$ (WHO, 2003)

1.3.5 Structural formula

Ketamine contains a chiral centre at the C-2 carbon of the cyclohexanone ring, so that two enantiomeres exist S-(+)-ketamine and R-(-)-ketamine. The S-one being the pharmacologically more active one. More and more the S-(+) enantiomere is used in the commercially available preparations (ECDD) (eScience for Cheminformatics and Drug Discovery 2006) .

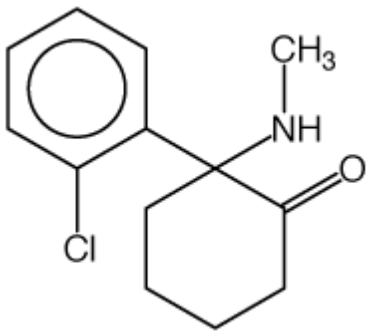


Figure (1) structure of ketamine

1.3.6 Mode of action

The hypnotic and anaesthetic actions of Ketamine are thought to be via N-methyl-D-aspartate (NMDA) receptors (Muir and mason 1993). NMDA antagonism results in blockage of spinal nociceptive reflexes (Hara et al. 1993), by blocking the conduction of painful impulses to the thalamus and to areas of the cortex (White et al. 1982). This makes ketamine a non-competitive N-methyl-D-aspartate (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 depolarisation of the neurone. The N-methyl-D-aspartate (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 centres of the CNS, with the emotional response to these stimuli, and with the process of learning and memory (Bergman, 1999).

Furthermore, there is an interaction with the opioid receptors μ and sigma (James et al., 1984; Parsons et al., 1998), the muscarinic receptors and the calcium channels (Hirota and Lambert, 1996). Blockage of NMDA receptors with low doses of Ketamine is desirable for a good analgesic effect (Ryder et al., 1978). This analgesic effect is due to reduction of nociceptives reflections of the spinal medulla (Kitahata et al., 1973) that are otherwise activated in response to pain.

Ketamine is a neuroleptic anaesthetic agent in clinical use since the 1960's (Maria, et al., 2005). It is a dissociative short acting anaesthetic agent being widely used in recent years for veterinary and human purposes (Lim, 2003). When it was first introduced in the clinical use, it was regarded as an ideal and complete anaesthetic drug, since it provides all the required components of surgical anesthesia, pain relief, immobility, amnesia and loss of consciousness. Ketamine is generally preferred in many of these instances because it does not have as deep a sedative effect as other medications (Dotson, et, al 1995). Ketamine is one of the very few general anaesthetic agents that can be administered by more than one route (i.e. IV, IM, or or PO). In addition, it is probably the only general anaesthetic agent with substantial analgesic effects (Hall et al., 2001). Ketamine is used for premedication,

sedation, induction and maintenance of general anaesthesia (Huai-Chia et al., 2009).

Ketamine is considered to be 'the nightmare of the anesthetist' owing to its complex mechanism of action (Lois, et al., 2008). Since the 1980s the mechanism of action has been considered to be mainly a non competitive antagonism of the N-methyl-D-aspartic acid (NMDA) receptor (Chizh, 2007). N-methyl-D-aspartic acid 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 neuron. 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).It also has been reported to interact with opioid, monoamine, cholinergic, purinergic and adenosine receptor systems as well as having local anesthetic effects (Lois, et al., 2008; Chizh 2007). Lately ketamine has also been shown to inhibit tumor necrosis factor-alpha (TNF alpha) and interleukin 6 (IL-6) gene expressions in lipopolysaccharide (LPS)-activated macrophages. It has even been speculated that the antiproinflammatory effects may be responsible for antihyperalgesic effects of ketamine (De, et al., 2007).Ketamine is a rapid-acting general anaesthetics. Quickly cross the blood-brain barrier (Cotsen, et al., 1997).Producing an anaesthetic state characterized by profound analgesia, normal pharyngeal-laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, cardiovascular and respiratory stimulation, and occasionally a transient and minimal respiratory depression. Ketamine is indicated as the sole anaesthetic agent for

diagnostic and surgical procedures that do not require skeletal muscle relaxation.

One of the advantages of ketamine is that it can be administered via many different routes. It has been delivered via the intravenous, intramuscular, rectal, subcutaneous, transdermal, topical, oral, intranasal, and sublingual, trans-mucosal, epidural, and intra-thecal routes. It has been gargled, locally infiltrated(AS lidocaine), and used in intravenous regional anesthesia. As the oral bioavailability of ketamine is low, the topical and transdermal routes would seem important to investigate for longer term pain management. (Persson, 2010).

1.3.7 Cardiovascular and pulmonary effect of Ketamine:

Ketamine is differ from other anaesthetic drugs in that is not a depressor of the cardiovascular system and is usually associated with increase in blood pressure, heart rate and cardiac output. Increase of blood pressure begins shortly after administration, reaches a maximum within few minutes and usually returns to pre-anaesthetic values within 15 minutes. The cardiovascular stimulation is associated with increase in cardiac work and myocardial oxygen consumption. In animals with coronary artery disease (CAD) and hypertension, ketamine should be avoided because tachycardia and increased blood pressure may cause myocardial ischemia. The stimulating effect of ketamine seems to be central because it inhibits postsynaptic NMDA receptors and presynaptic afferent processes in medial nucleus tractus solitarius. There seems to be also a peripheral action, through the inhibition of the intraneuronal uptake of catechol amines (cocaine-like effect). The rise in noradrenaline levels is detectable in the blood after ketamine administration and the pressure response is blocked by α- and ß-

adrenoceptor antagonists and by sympathetic ganglion blockade (Huai-Chia *et al*., 2009)..

Ketamine was experimented in septic shock and it preserves the cardiovascular function and have the least deleterious effect on hypoxic tissues if compared to other anesthetics (halothane, isoflurane, alfentanil). In infected parturient, ketamine should be considered anaesthetic of choice for induction and maintenance of anesthesia because of maternal hemodynamic stability and maintenance of uteroplacental blood flow (Kuczkowski, *et al*., 2003). Respiration is generally well-maintained under ketamine anesthesia and minimally affects central respiratory effort. Low-dose of ketamine has even been shown to antagonize opioid-induced hypoventilation in healthy volunteers (Persson, *et al*. 1999). There were limited warnings (Miller, *et al*. 2009), however, salivation can be a problem, and high concentrations can induce apnea. In pediatrics the ventilators effects of intravenous versus intramuscular administration have been discussed (Melendez and Bachur 2009). Recent review reported that the risks involved are probably equal for the two paths of administration (Green, *et al.* 2009).

CHAPTER TWO
MATERIALS AND METHODS

2.1 Place of study

This study was carried out at Sudan University of Science and Technology, College of Veterinary Medicine, Department of Veterinary Medicine and Surgery in Hilat kuku located in east Nile locality.

2.2 Experimental animals

This study was carried out using ten local breeds' dogs (females and males) five for each group from urban area . The dogs were healthy and with no congenital or acquired abnormalities, they were subjected to deworming by Ivermectine and Albendazole. They were fasted for 12hours and allowed free access of drinking water. The dog's body weight range between 3-10 kg and their age range between 5-10 months.

2.3 Drugs

One pre-anaesthetic medication and one anaesthetic were used in this study, as follows:

1. Ketamine Hcl 5% (Troika pharmaceuticals Ltd Th-382728 Gujarat, India).
2. Xylazine Hcl (Rompun 2%, alfasan, Holland).

They received xylazine and ketamine by intramuscular route. Pulse, respiratory rate, rectal body temperature, reflexes (spinal, pedal, ear, tail) were recorded on a formatted paper before applying medication. The doses were calculated according to body weight estimation.

2.4 Injection set

Disposable syringes 1ml, 3ml and 5ml (18 gauges) were used for intramuscular injection of drugs.

2.5Monitoring tools

Stethoscope and digital thermometer were used for the monitoring of physiological parameters (heart rate and rectal temperature) respectively, respiratory rate was estimated by observing the flank region. Stop watch was used to determine the time of different phases of anaesthesia and monitoring reflexes.

2.6 Anaesthetic protocols

Tow anaesthetic protocols were used for anaesthetizing the animals as follows:

1- Xylazine 2% 1mg/kg + Ketamine 5% 15 mg/kg.
2- Xylazine 2% 1.5mg/kg + Ketamine 5%15 mg/kg.

2.7 Pre-anaesthetic preparations

Animals were fasted for 12hours and water was withheld for 4hours prior to anaesthesia to allow reduction of gastric fill in an effort to limit compression of the diaphragm by the hindgut and decrease ventilation/perfusion mismatching.

2.8. Experimental design

Experiment(1) injection of xylazine 1mg/kg +ketamine 15 mg/kg i/m. Five healthy dogs as The first group received xylazine 1mg/kg and ketamine 15 mg/kg i/m. Clinical parameters were recorded immediately before injection of anesthetics, and following administration of anaesthesia at zero time (injection time) and the sampling interval of 10 minutes n=8.

Experiment(1) injection of xylazine 1.5 mg/kg +ketamine 15 mg/kg i/m.

The protocol for experiment(1) was repeated except (xylazine 1.5mg/kg i/m.

After animals casting on lateral recumbency ,xylazine was injected intra muscular and after 5 minutes ketamine was injected and this was closed monitoring of different alteration in the injected dogs.

2.9Quality of induction

Quality of induction of anaesthesia was rated as follow:

1- Satisfactory: rapid and smooth with little danger to animal or personnel **(**Nora et al., 2002).
2- Unsatisfactory; prolonged period of muscle incordination or fasciculation (Nora et al., 2002).

2.10Quality of muscle relaxation:

Muscle relaxation was investigated as follows: The nociceptive response was scored as "0" normal response, "1" reduced response and "2" no response.

2.11Quality of recovery

A score, ranging from 1 to 5 as per method of (Ringer et al., 2007) was used for assessment of quality of recovery from anaesthesia.

Score card for quality of recovery:

1. Excellent: Dog capable of standing at first attempt.
2. Very good: Dog remained calm and needed two attempts to stand.
3. Good: Dog remained calm but needed more than two attempts to stand.
4. Poor: Excitement during recovery with danger of injury and needed more than two attempts to stand.
5. Very poor: Severe excitement during recovery with injury.

2.12 Physiological parameters

Physiological parameters had been monitored before induction of anesthetic and at zero time and 10 minute interval using standard method as follows:

2.12.1. Heart rate (beats /minute):

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

2.12.2. Respiratory rate (breaths/ minute)

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

2.12.3. Rectal temperature

Rectal temperature was recorded using a clinical digital thermometer into the rectum.

2.13 Phases of anaesthesia

2.13.1. Induction phase

It is the state or condition in which the animal becomes unconscious, respond negatively to painful stimuli with disappearance of selected reflexes

2.13.2. Anaesthetic phase

Was measured as the period during which the animal was unconsciousness, no reflexes, with negative response to painful stimuli

2.13.4. Lateral recumbency

Was measured as the duration at which the animal opened its eyes and reflexes were regained but it is unable to adopt sternal position.

2.13.5. Sternal recumbency

It was measured as the period during which the animal could adopt sternal recumbency without falling to lateral recumbency and without adopting standing position.

2.13.6. Standing phase

It is the stage at which the animal stood but unable to walk.

2.13.7. Recovery

The animal was considered to be recovered from anaesthesia when it is capable of supporting itself in standing position and walk without falling down.

2.13.8. Total recovery

Total recovery time was measured as the total time intended from the time of induction of anaesthesia until recovery was attained.

2.14 Reflexes

2.14.1 Tongue reflex

It 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.

2.14.2 Spinal reflex

It was assessed by pinching skin using head of needle over shoulders, the back or abdominal area.

2.14.3 Jaw relaxation

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 unwilling to open its mouth (Subjective).

2.14.4 Pedal reflex

Pedal reflex was assessed by pinprick on pedal area between digitals. If the animal moves its leg or leg muscle, the reflex was considered positive

2.14.5 Anal reflex

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

Statistical analysis:

ANOVA was used to compare data for physiological parameters (Respiratory rate, Heart rate and Rectaltemperature), and to compare and contrast between the different anaesthetic phases and reflexes, statistical package for social science (SPSS) using System computer package.

CHAPTER THREE
RESULTS

Protocol No. (1):

Dose(1) Xylazine 1mg/kg (i/m) – Ketamine15mg/kg (i/m), number of dogs 5 dogs

One to three minutes post injection of anesthetic protocol (protocol 1) all dogs were in lateral recumbency and unconscious, except dog number (3) which lost consciousness after seventeen minutes of injection, dogs showed loss of spinal, pedal, tail and anal reflexes. Jaw muscles and motor muscles relaxation and protrusion of tongue were also evident during the same time. Two to six minutes post injection defecation and urination were observed in two dogs. Twelve minutes post injection dog number (4) moved his head and ears but all reflexes were still absent, motor muscles and jaw muscles were still in considerable degree of relaxation also tongue was still protruded. Twenty to sixty minutes post injection anal, tail, spinal and pedal reflexes were returned to normal, muscle and jaw relaxation disappeared and tongue returned into mouth. Swimming movement had been seen at thirty two minutes post injection and 45minutes post injection in dog number (1) which is also known for its variability and exception for that it has no tongue protrusion (like all the other) and no muscle jaw relaxation. Dog number three showed different behavior such as absence of tongue protrusion and no jaw relaxation. Twenty to thirty minutes the same dog showed an alternate attitude of tail reflex (appeared, disappeared). Forty nine to sixty minutes post injection all dogs moved their heads, ears and tails, and unsuccessfully attempted to attain sternal recumbency. Forty seven to

seventy minutes post injection all dogs gained sternal recumbency. Fifty nine to seventy six minutes post injection all dogs stood up and walked.

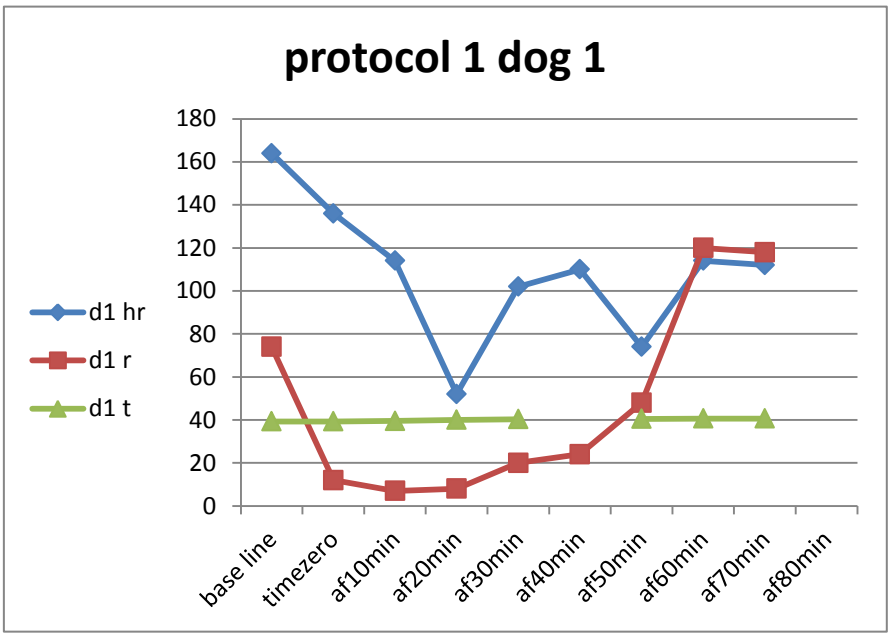


Figure 3.1 Effect of (Xylazine 1mg/kg- Ketamine 15mg/kg body wt) on clinical parameters in dog number (1)

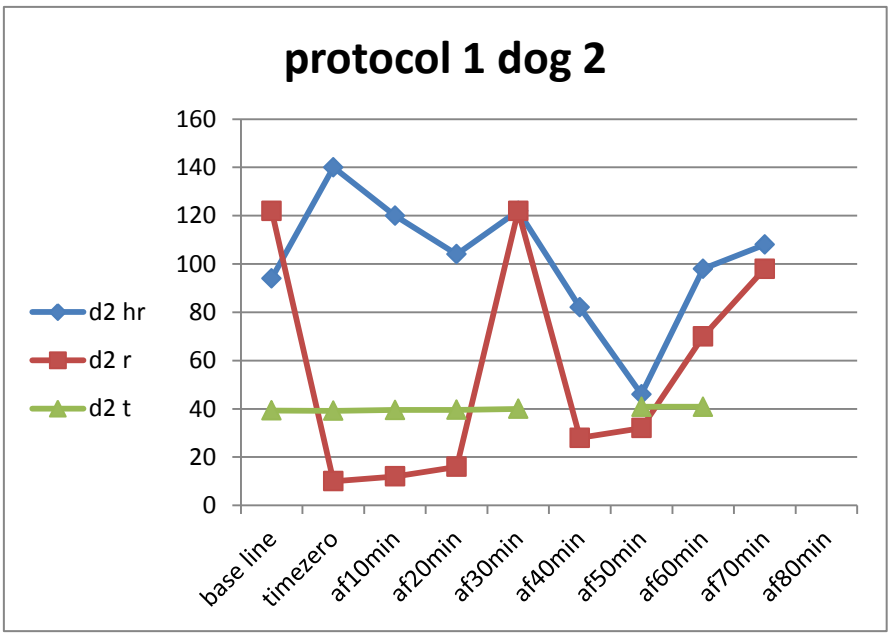


Figure 3.2 Effect of (Xylazine 1mg/kg- Ketamine 15mg/kg body wt) on clinical parameters in dog number (2)

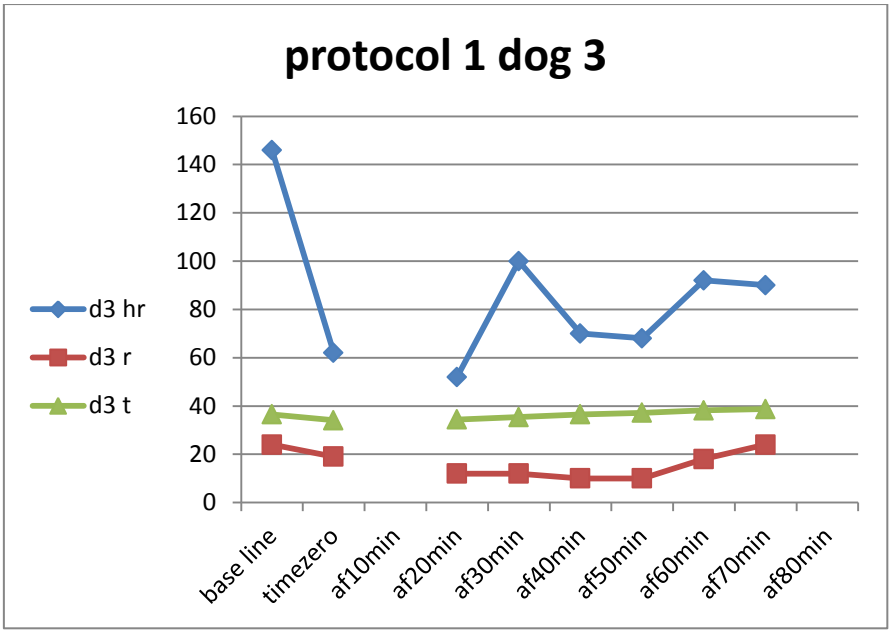


Figure 3.3 Effect of (Xylazine 1mg/kg- Ketamine 15mg/kg body wt) on clinical parameters in dog number (3)

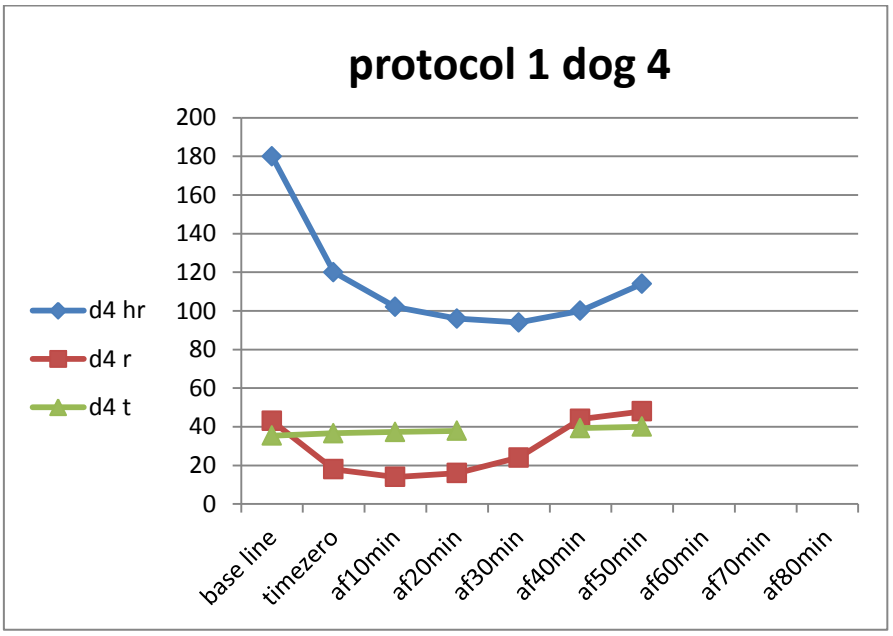


Figure 3.4 Effect of (Xylazine 1mg/kg- Ketamine 15mg/kg body wt) on clinical parameters in dog number (4)

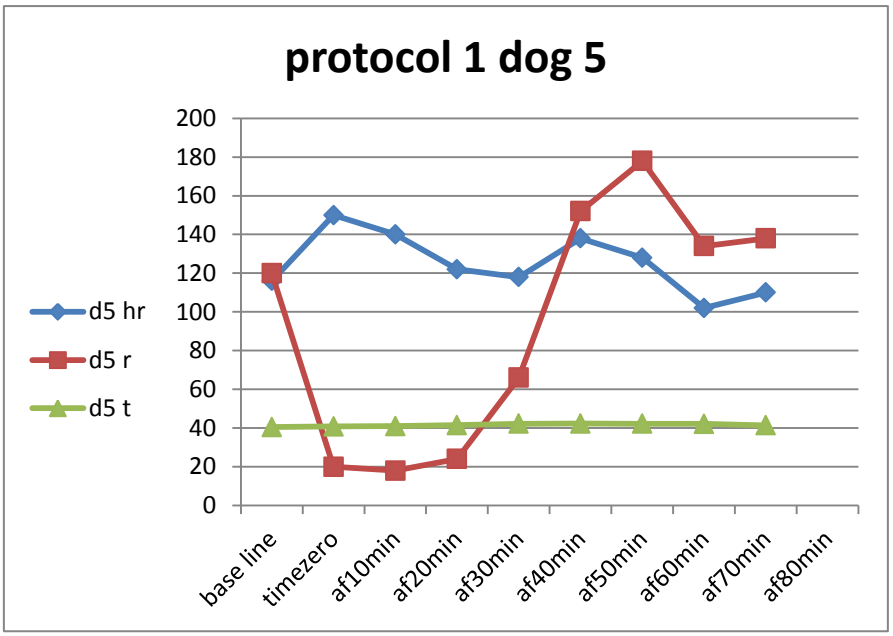


Figure 3.5 Effect of (Xylazine 1mg/kg- Ketamine 15mg/kg body wt) on clinical parameters in dog number (5)

Protocol No. (2):

Dose (2) : Xylazine 1.5mg/kg (i/m) – Ketamine 15mg/kg (i/m) numbers of animals 5 dogs.

Two to four minutes after injection of anaesthetic protocol, all the dogs were in lateral recumbency and became unconscious, they showed loss of spinal, pedal, anal and tail reflexes, jaw and motor muscles showed considerable relaxation and tongue became protruded. Thirty minutes post injection the anal reflex in some dogs, started to wane off, but the spinal, pedal, and tail reflexes still absent. Thirty to forty minutes post injection good muscle relaxation still attained but the tail reflex returned to normal and jaw muscles lost its relaxing mode. Thirty to fifty minutes post injection all reflexes returned to normal, chewing movements were observed and animals pulled their tong inside their mouth. Sixty to seventy minutes post injection dogs had assisted sternal recumbency. Fifty nine to ninety one minutes is the time range when all the anaesthetized dogs stood up and started to walk or eat.

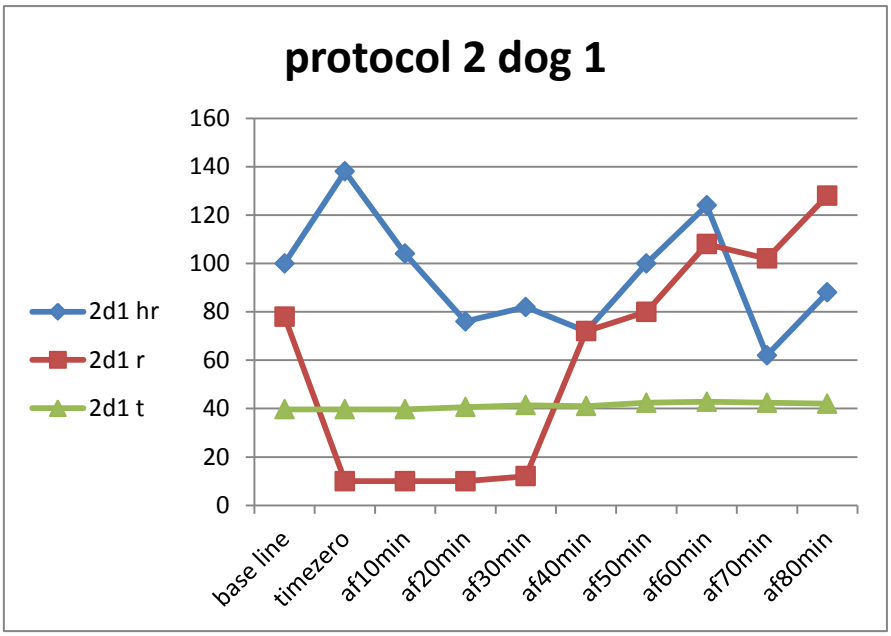


Figure 3.6 Effect of (Xylazine 1.5mg/kg- Ketamine 15mg/kg body wt) on clinical parameters in dog number (1)

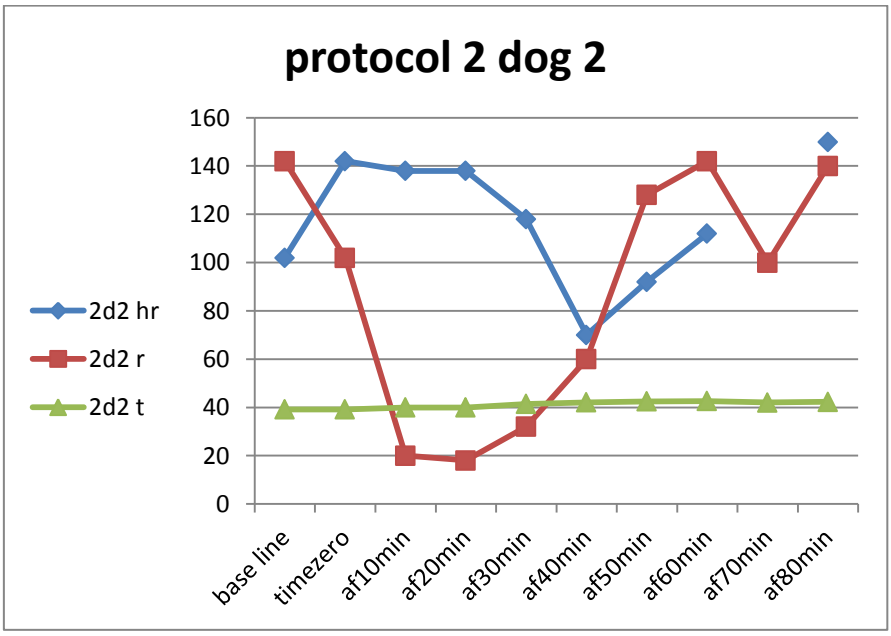


Figure 3.7 Effect of (Xylazine 1.5mg/kg- Ketamine 15mg/kg body wt) on clinical parameters in dog number (2)

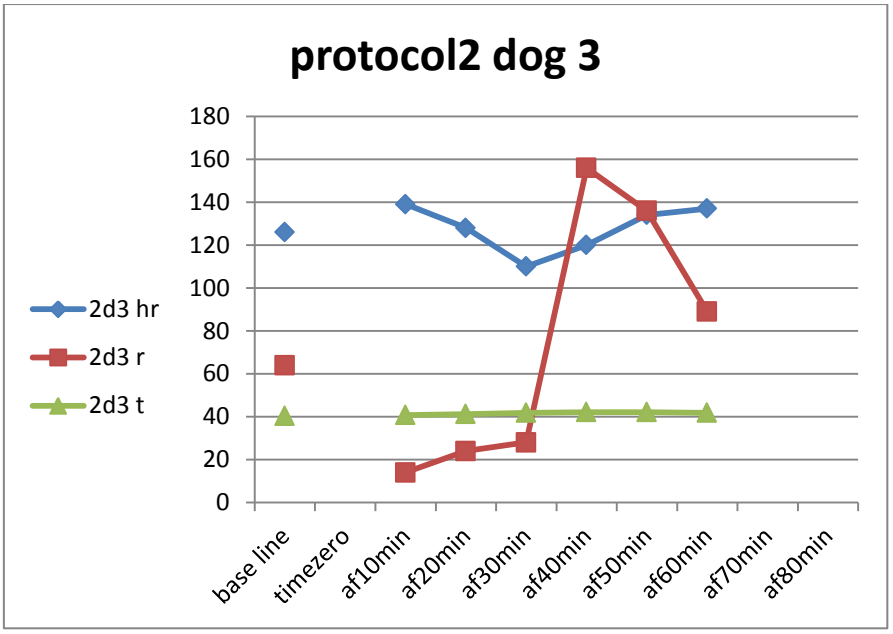


Figure 3.8 Effect of (Xylazine 1.5mg/kg- Ketamine 15mg/kg body wt) on clinical parameters in dog number (3)

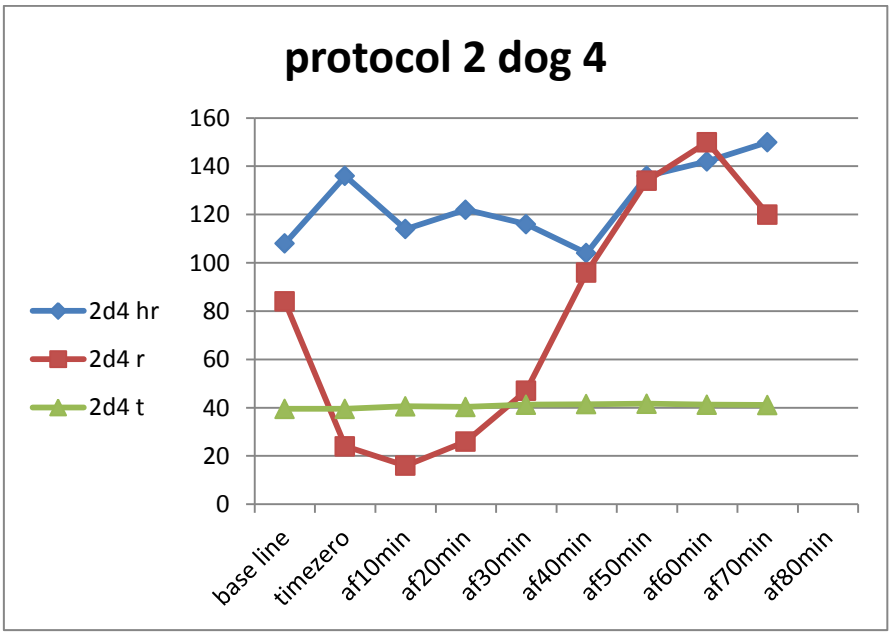


Figure 3.9 Effect of (Xylazine 1.5mg/kg- Ketamine 15mg/kg body wt) on clinical parameters in dog number (4)

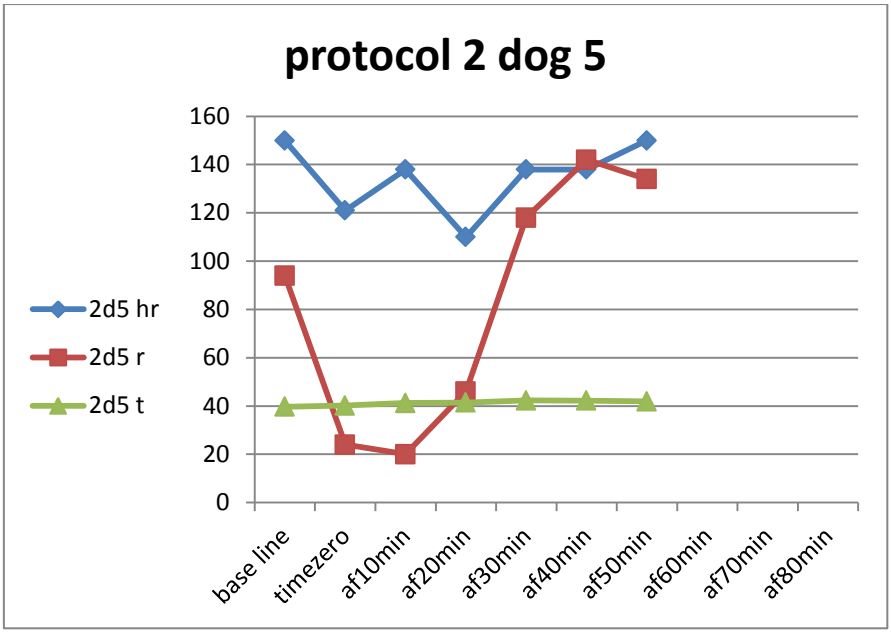


Figure 3.10 Effect of (Xylazine 1.5mg/kg- Ketamine 15mg/kg body wt) on clinical parameters in dog number (5)

The heart rate

Base line values shown on table number (1) mean ± standard deviation (minutes) 140 ± 35 beats/minute (group1: 1mg/kg Xylazine15 mg/kg ketamine) and 125±20.21beats/minute (group2: 1.5 mg/kg Xylazine – 15mg/kg Ketamine). It then dropped to 107.6± 28 and 122.60±14beats/minute respectively, however the difference was not significant. On the other hand, values in group1 sixty minutes post injection were 101.50±9beats/minute compared to 133±15beats/minute which is a remarkable difference ($p \leq 0.5$). The rest of the values showed either increase or decrease but a non-significant variation was recorded.

The respiratory rate

Base line values in group1 were 76.60±44 breaths/minute in group2 84.40±14breaths/minute. 10 minutes post injection 14 ±4 breaths/minute in group1, 16.80±5breaths/minute in group 2. Twenty minutes post injection 15±5 breaths/minute in group1 and 19.60±6breaths/minute in group 2, also the remarkable depression shown during anesthesia time and starts regaining base line values or even higher 85.50±52 breaths/minute compared to 129±25breaths/minute in group2, also, the statistical analysis showed no significant change. However, remarkable decrease in respiratory rates took place during anesthesia and regaining base line values during struggling of awakening but no significant variation among between the two groups.

Temperature

The overall picture of the temperature in both groups and their changed respective base line values showed no significant difference. Values remained 38.20± 2.15^{o}c in group1 and the corresponding values in group2 were 39.52±0.60^{o}c. A rise of up to 42^{o}c was evident in some dogs in group2.

Table (1) showed the effects of both groups on heart rates, respiratory rates and temperature.

Parameters / Treatments	Time (minute)	1 mg/kg Xylazine-15mg/kg ketamine (Protocol 1)	1.5 mg/kg Xylazine-15mg/kg ketamine (Protocol 2)	Significant
Heart rate	Zero	140±35.01	125.20±21.38	NS
	10	107.60±28.96	122.60±14.48	NS
	20	86.40±33.54	120.40±25.74	NS
	30	107.20±12.13	107.20±14.53	NS
	40	100±26.30	100.80±29.75	NS
	50	86±33.97	120±22.14	NS
	60	$101.50±9.29^{b}$	$133±15.07^{a}$	**
	70	105±10.13	70.67±75.37	NS
Respiratory rate	Zero	76.60±44.29	84.40±14.66	NS
	10	14±4.85	16.80±5.40	NS
	20	15.20±5.93	19.60±6.23	NS
	30	26.80±22.52	33±14.42	NS
	40	51.60±57.42	90.40±45.55	NS
	50	63.20±66.04	124±25.10	NS
	60	85.50±52.72	129±25.24	NS
	70	94.50±49.76	107.33±11.02	NS
Temperature	Zero	38.20±2.15	39.52±0.60	NS
	10	30.12±1.70	40.26±0.44	NS
	20	38.68±2.71	40.66±0.54	NS
	30	31.58±1.78	41.44±0.22	NS
	40	23.62±2.16	41.78±0.55	NS
	50	32.04±1.8	42.16±0.35	NS
	60	38.93±4.53	42.06±0.65	NS
	70	30.16±2.02	41.83±0.67	NS

**: Significant at $P \leq 0.01$
NS: No Significant
Different superscript letters within the same row means significant difference at $P < 0.05$

Table (2) showed the effects of the different protocols on selected reflexes in experiment dogs

Experimental animal / Doses / Reflexes	Group(1) of thedogs	Group(2) of the dogs	
	1 mg/kg Xylazine15mg/kg ketamine (protocol 1)	1.5 mg/kg Xylazine15 mg/kg ketamine (protocol 2)	Significant
No. of dogs	5	5	
Spinal absence	2.20±0.45	2±0	NS
Spinal appearance	54±8.94	52±21.68	NS
Pedal absence	2±0	2±0	NS
Pedal appearance	44±11.40	48±20.49	NS
Anal absence	2.40±1.34	2±0	NS
Anal appearance	28±16.43	34±11.40	NS
Tail absence	1.60±0.89	2±0	NS
Tail appearance	32±21.68	36±15.17	NS
Muscle relaxation appearance	1.60±0.89	2±0	NS
Muscle relaxation absence	34±21.91	54±19.49	NS
Tongue relaxation appearance	1.60±0.89	2±0	NS

NS: No significant

Non significant $P<0.05$

Table (3) Duration of anesthesia in protocol No.(1) Xylazine 1mg/kg-ketamine 15mg/kg I/M

Dogs numbers	Duration of aneasthesia
Dog no.1	54 minutes
Dog no.2	50 minutes
Dog no.3	60 minutes
Dog no.4	55 minutes
Dog no.5	54minutes
Mean	54.6±3.75 minutes

Table (4) Duration of anesthesia in protocol No.(2) Xylazine 1.5mg/kg-ketamine 15mg/kg I/M

Dogs numbers	Duration of aneasthesia
Dog no.1	60 minutes
Dog no.2	60 minutes
Dog no.3	60 minutes
Dog no.4	60 minutes
Dog no.5	52 minutes
Mean	58.4±3.75 minutes

Table (5) The effects of both protocols on onset and recovery time

dose / Time	Group1 Xylazine 1mg/kg-ketamine15mg/kg	Group2 Xylazine 1.5mg/kg-ketamine15mg/kg
Time of onset of action of aneasthesia (minutes)	2±0.707	2.6±1.12
Time of first movement(minutes)	48.2±8.49	48.6±18.57
Time of sternal position(minutes)	60.6±9.01	51.2±21.55
Time of standing position(minutes)	67.6±6.42	73±18.99

CHAPTER FOUR
DISCUSSION

Group 1 and 2:

Group (1) Xylazine 1mg/kg- ketamine 15mg/kg i/m, group (2) xylazine 1.5mg/kg- ketamine 15mg/kg i/m, heart rate, respiratory rate, rectal temperature, duration of anesthesia and reflexes were monitored for each animal at zero time which is the injection time, 10 minutes, 20 minutes, 30minutes, 40 minutes, 50 minutes,60 minutes, 70minutes and 80 minutes respectively. In protocol 1 (group1) ranging from 52-60 minutes(from zero to 70min) through the anesthesia time this protocol produced profound sedation except for dog no.3 which showed first sign of sleep 17 minutes post injection. The mean time of anesthesia was 54.6 minutes compared to range of 52-60 minutes, mean 58.4 minutes through the anesthesia time in protocol number 2. Aprofound decrease in heart rate from mean 140±35 as base line to 107.6±28 in protocol (1) in comparison to 125±20.21 to 122.60±14 in protocol (2). However the decrease of heart rate was not significant according to the (ANOVA) program. Sixty minutes post injection values in protocol (1) were 101.50±9 compared to 133±15 in protocol (2) which is a remarkable difference and therefore it seems to agree with the results of Atalan *et al.*, (2002) for depression of heart rate.

Respiratory rate as depicted in the results base line values 70.60±44 minutes in protocol(1) compared to 84.40±10 minutes through the anesthesia decreased to14±4 in protocol (1) compared to16.80±5 in protocol (2) which was a remarkable difference regained base line values higher, 85.50±52 breaths/min compared to129±25 in protocol (2), although, the statistical analysis showed no significant change, a remarkable decrease was evident and it totally agrees with the results of Atalan *et al.*, 2002).

The rectal temperature the overall picture as shown in the results showed no significant change. However, post operative care safe guarded and evaluated by rise or fall in temperature.

Both aneasthetic techniques produced stable cardiopulmonary functions and can be considered safe.

The study also revealed that combination of xylazine and ketamine produced good muscle relaxation which ketamine seen to lack when used alone this agree by (Hall and Clark 1991).

RECOMMENDATION AND CONCLUSION

Recommendations

Each of two protocols,prescribed doses wre found very safe and could be used without any difficulties in sudanses local breed dogs,with regard to their different anaesthetic periods and their availability and the fact that if overdose or any accidental increase in dosage happen,their effects should be reversed by their very well know antagonist.

The both prptocols are used as data base for practitioners and researchers for future work.

Conclusion

Because of minimal effect on vital organs and considerable long anesthesia time as monitored by the reflexes of both protocols was found more practical and useful in these local breed dogs.

Therefore the presser and cataleptic effect of ketamine was abolished by the depressor, sedative and the muscle relaxing effects of xylazine.

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