

INTRODUCTION

Many surgical procedures and diagnostic examination in horses are performed under general anaesthesia in order to enhance their accuracy and maximize personal safety (Yamashita *et al.*, 2007). Equine practitioners are often required to perform surgical procedures under field conditions and although these surgical procedures are often similar to those performed in a hospital setting, management of general anaesthesia may be quite different (Bohart, 1997). Intravenous anaesthesia is safe, simple to perform and do not require expensive or bulky equipments for its employment. As well as it is less cardiopulmonary depressant than clinically used inhalational anaesthetic regimes (Luna *et al.*, 1996, Yamashita *et al.*, 2007).

There is no available anaesthetic drug which can provide proper anaesthesia alone nowadays. Therefore, combinations of sedatives and other anaesthetics have been widely used in animal practice. The anaesthetic combination should congregate different characteristics, having adequate sedation and a deep unconsciousness state, enough muscle relaxation without greatly changing the patient's physiologic parameters (Alma *et al.*, 2002).

A variety of methods can be used for induction of anaesthesia for different sizes and breeds of donkeys exist in the world depending on availability of drugs, size and condition of donkey and familiarity with different protocols (Matthews and van Dijk, 2004). In USA the preferred method for induction is to sedate with Xylazine (1.1 mg/kg, IV) then

to induce anaesthesia with Ketamine (2.2 mg/kg, IV). Addition of butorphanol (0.01-0.02 mg/kg, IV) or diazepam (0.1-0.3 mg/kg, IV) may provide additional sedation and muscle relaxation. These drugs will generally provide 15-20 min of anaesthesia in most donkeys, however, miniature donkeys are inadequately anaesthetized even for a short procedure, with these doses of drugs; they show lots of muscle rigidity and excitatory effects (Matthews and van Dijk, 2004). Recent study of Abakar and his colleagues (2014), suggested that the addition of diazepam at different doses i.e. 0.1, 0.2, and 0.3 mg/kg IV to Ketamine (3 mg/kg, IV) in donkeys pre-medicated with Xylazine 1.5 mg/kg will produce safe and acceptable induction of anaesthesia, muscle relaxation and recovery. Detomidine (0.04 mg/kg, IV) followed by Ketamine (2.2 mg/kg, IV) is another combination which works well in donkeys (Matthews *et al.*, 1992c). This combination provides about 10 min more anaesthesia than Xylazine and Ketamine.

Thiopental (5 mg/kg, IV) produces rapid and smooth induction; since it does not provide analgesia, it should be used with an effective sedative/opioid premedication. Anaesthesia can be maintained for a short period (<25 min) with thiopental, but respiration must carefully monitored since thiopental may produce apnoea (Radi *et al.*, 2012). It is not advised unless intubation and artificial ventilation can be performed (Matthews and van Dijk, 2004).

Maintenance of anaesthesia using injectable agents can be carried out through repeated injection (top-up) of the

anaesthetic or using continuous infusion (triple drip). Compared to repeated injection continuous infusion decrease the labour and insure consistency in the concentration of the flow of the anaesthetic. The combination of guaifenesin, Ketamine and α_2 -adrenoceptor agonists (α_2 -agonists: Xylazine, Detomidine, Romifidine) have been used for the prolongation of anaesthesia in horses for a long time (McCarty *et al.*, 1990, Young *et al.*, 1993, McMurphy *et al.*, 2002). Combinations of guaifenesin with thiopental or Ketamine have been used successfully in donkeys; however, these should be used with caution. Donkeys appear to be more “sensitive” to guaifenesin, donkey will become recumbent with approximately 60% of the dose required to produce recumbency in horses (Matthews *et al.*, 1997). However, donkeys metabolize Ketamine more rapidly than horses do, so the combination of guaifenesin-Ketamine-Xylazine (GKX or “triple drip”) commonly used in horses may not work well in donkeys (Matthews and van Dijk, 2004). Unfortunately, there are no commercially available pharmaceutical preparations of guaifenesin in Sudan.

Although very similar to horses, donkeys are not the same. The anaesthetist should expect to encounter subtle differences which may affect the anaesthetic management. Physiologically, donkeys are known to have different fluid-balance and partitioning of fluids than does the horse (Maloiy, 1970). This affects the way they distribute drugs, including anaesthetics. Matthews and Taylor (2000), suggest that donkeys also metabolize some drugs faster than horses,

which affects anaesthetic drug duration. Research data concerning the anaesthetic regimens in Mammoth asses, mules and horses has proved that donkeys and mules do not respond similarly to horses when anaesthetized with the same protocols (Abd-Almaseeh, 2008). The pharmacological variations implicate different strategies for anaesthesia in donkeys and mules when, for example, α 2-agonists or Ketamine are indicated (Matthews *et al.*, 1992a; Matthews *et al.*, 1992b; and Mostafa *et al.*, 1995).

Taking into consideration the differences between horses and donkeys, unavailability of accommodation for inhalation agent, availability of injectable anaesthesia this study was designed with the following objectives:

1. Prolongation of the duration of anaesthesia induced with Ketamine protocols with acceptable components.
2. Assessment of some ketamine protocols on donkeys health
3. Quantitative and qualitative comparison of the investigated protocols.
4. Investigating the efficiency of Ketamine protocols to perform surgical operations.

CHAPTER ONE LITERATURE REVIEW

1.1 Ketamine hydrochloride:

Ketamine is classified as a dissociative anaesthetic agent and exerts its effects through the interruption of the cerebral association pathways, with relative sparing of the reticular and limbic systems and depression of the thalamic cortical system (Lin, 1996). Ketamine is the most commonly used agent to anaesthetize different animal species. It has a rapid onset of action after IV or IM administration. It can be administered repeatedly to maintain anaesthesia (Mckelvey and Hollingshead, 2003). Despite of the problem of muscular rigidity caused by the drug which can be overcome by usage of some pre-anaesthetic medications, it is considered to be a very good and safe drug for intravenous anaesthetic practice in equine (Hall and Clarke, 1991).

1.1.1 Chemistry and pharmacology:

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). It is available commercially in the form of 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.

1.1.2 Chemical name:

Ketamine has the chemical name of (2-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride (WHO, 2006).

1.1.3 Chemical formula:

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

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

1.1.4 Structural formula:

The structural formula of Ketamine is present in Figure (1.1).

1.1.5 Mode of action:

Ketamine acts on the central nervous system (CNS) and has local anaesthetic properties. Its effects are mediated primarily by non-competitive antagonism at the *N*-methyl-d-aspartate (NMDA) receptor Ca^{2+} channel pore. NMDA channel block appears to be the primary mechanism of the anaesthetic and analgesic action of Ketamine (at the CNS and also at spinal cord receptors). In addition, it reduces the presynaptic release of glutamate. The *S* (+) enantiomer has a three- to four-fold greater affinity for the NMDA receptor than the *R*(–) form (White *et al.*, 1985)

Furthermore, there is an interaction with the opioid receptors μ and sigma (James *et al.*, 1984), the muscarinic receptors and the calcium channels (Hirota and Lambert, 1996). This analgesic effect is due to reduction of nociceptive reflexions of the spinal medulla (Kitahata *et al.*, 1973) that are otherwise activated in response to pain.

1.1.6 Physiological effects of Ketamine:

The cardiovascular actions of Ketamine include increases in heart rate and cardiac output which are

attributed to increase in centrally mediated sympathetic tone, release of catecholamines from peripheral storage sites, inhibition of neural, extra-neural uptake of catecholamines and inhibition of baroreceptor reflex activity (Muir, 1991b, Lin, 1996, Muir *et al.*, 2000). Ketamine also produces direct vasodilatation of vascular smooth muscle and an inotropic effect on the myocardium (Lin, 1996). The cardiovascular stimulating effects induced by Ketamine are blunted or prevented by prior administration of benzodiazepines and α_2 -agonists (Lin, 1996).

Although, Ketamine increases heart rate and mean arterial pressure, stimulates cardiovascular functions (Haskins *et al.*, 1985), it is important to note that Ketamine has direct myocardial depressant effects independent of

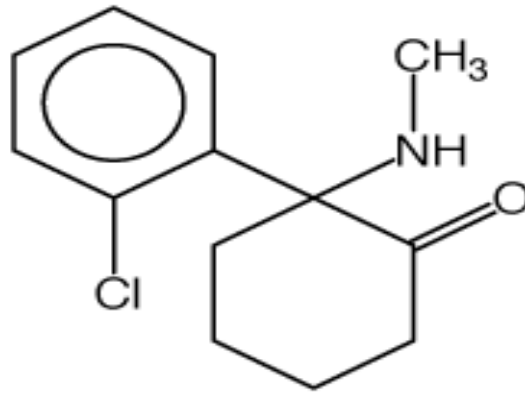


Figure 1.1: Ketamine structure

heart rate and should therefore be avoided in animals with compromised cardiovascular function (Ingwersen *et al.*, 1988). Ketamine is a potentially arrhythmogenic, it may decrease or increase myocardial contractility and may decrease or increase or has no effect on cardiac output (Muir, 1998). In female donkeys in combination with detomidine/diazepam or detomidine/midazolam Ketamine resulted in non significant changes in the heart rate as reported by Ali (2013). Similar result of no significant effect of Ketamine on heart rate in Sudanese local breed donkeys was reported by Abakar *et al.*, (2014).

Ketamine has desired effects such as maintenance and stimulation of respiration, bronchodilator, maintenance of functional residual capacity and achievement of equivalent minute ventilation rates both in spontaneously breathing individuals and in those wide awake (Tokics *et al.*, 1987). Ketamine had also unwanted respiratory effects such as increase in respiratory secretions (Morse *et al.*, 2004; Von Ungern-Sternberg *et al.*, 2007).

Infusions of racemic Ketamine generally cause minimal respiratory depression with only mild hypercapnia and in humans may reverse the hypoventilation produced by opioids (Persson *et al.*, 1999). However, transient apnoea has been reported after administration of a single bolus of racemic or S-Ketamine to horses anesthetized with inhaled agents (Serteyn *et al.*, 1987; Larenza *et al.*, 2007).

Induction of anaesthesia with Ketamine combinations in female donkeys may cause significant increase in the

respiratory rate for a short duration (Ali, 2013). Other researchers reported a contradictory result which showed in form of significant decrease in respiratory rate as a result of using Ketamine combinations in local Sudanese donkeys (Abakar *et al.*, 2014).

Although Ketamine was reported to have no significant effect on rectal temperature (Davison *et al.*, 2007) and Abakar *et al.*, (2014), other researchers claimed a significant drop in rectal temperature as a result of using some Ketamine combinations in donkeys (Ali, 2013), similar results of significant hypothermia was reported in donkeys as a result of using Ketamine combinations (Albozachri *et al.*, 2012).

1.1.7 Blood biochemical effects of Ketamine:

Effect of Ketamine alone or in combination with other drugs on glucose and kidney function in term of urea level was studied by different researchers who reported different or contradictory results. Ketamine/Detomidine combination has no significant effect on glucose and urea concentration in donkeys (El-Kammar *et al.*, 2014). On the other hand Amin *et al.*, (2012a) reported significant increase in serum glucose in female donkeys as a result of using some Ketamine combinations for induction of anaesthesia in female donkeys. Later, Okwudili *et al.*, (2014), reported that blood urea was significantly increased as a result of using Ketamine in combination with Xylazine anaesthesia in dwarf goats

Donkeys anaesthetized with Ketamine in combination with Detomidine or Romifidine, midazolam together with or

without infusion with zolazepam exerted no significant effect on ALT activity (El-Kammar and Gad, 2014, and Amin *et al.*, 2012a), while AST was significantly decreased following intravenous injection of Ketamine in combination with Detomidine in donkeys (El-Kammar *et al.*, 2014). Amin *et al.*, (2012a) reported significant decrease in AST activity in female donkeys as a result of using Romifidine, Ketamine and midazolam for induction together with infusion with zolazepam with Ketamine in female donkeys. Late elevation of AST concentration was noticed 3 days after induction of anaesthesia with Ketamine in combination with Tramadol, and Xylazine, but it was decreased at time 25 minutes in Diazepam, Ketamine and Xylazine (Albozachri *et al.*, 2012).

1.1.8 Anaesthetic effects of Ketamine:

Ketamine produces profound analgesia (Hall *et al.*, 2001). Good analgesia was also reported to occur as a result of using Ketamine in combination with Romifidine and midazolam (Amin *et al.*, 2012c). Mild to moderate analgesia was noticed as a result of using Ketamine in combination with butorphanol and Detomidine in donkeys (Amin and Najim, 2011). Ketamine does not abolish the pineal and pedal reflexes, nor the photic, corneal, laryngeal or pharyngeal reflexes (Susan and Donald, 2003).

Induction of the anaesthesia in donkeys produced by intravenous injection of Ketamine hydrochloride in Detomidine, butorphanol premedicated animals caused rapid induction, and the animals fall down slowly and gradually

step by step. Then, the animal laid on to lateral recumbency with some signs of stiffness and spasm in the limbs few minutes after injection (Amin and Najim, 2011). Excellent induction was observed in horses premedicated with Romifidine ad diazepam or premedicated with Xylazine diazepam and anaesthetized with Ketamine (Kerr *et al.*, 1996). The quality of induction with Ketamine, Xylazine ad diazepam combination was studied by Abakar *et al.*, (2014) and they reported that satisfactory induction was observed in the whole group of animals as a result of using Ketamine for induction of anaesthesia.

The quality of recovery from anaesthesia is almost always good in donkeys, unless there has been no provision for analgesia or other major problems occur (i.e., seizures, respiratory difficulty). Because of their quiet, stoic nature, it is not usually necessary to sedate them for recovery, but it is likely that recovery will be somewhat longer than what is expected for a similar procedure in the horse (Matthews, 2002). Donkeys anaesthetized with Ketamine, Detomidine combination needed about 30-40 minutes to attain full recovery. The fore and hind pedal reflexes were observed at 30 minutes, and the animals required some effort to regain sternal recumbency 35 minutes later, finally standing position at 40 minutes (Amin and Najim, 2011). Excellent recovery was observed in horses anaesthetized with Ketamine when premedicated with Romifidine/diazepam or with Xylazine /diazepam (Kerr *et al.*, 1996). Recovery from Ketamine anaesthesia in donkeys already premedicated with

Xylazine and diazepam exhibited variable range of qualities and it ranged from excellent to good (Abakar *et al.*, 2014).

Ketamine lead to increase of saliva production and saliva may obstruct air way (Hall *et al.*, 2001). Mild to increased salivation was seen in Deer after the administration of Ketamine/acepromazine combination; the amount of salivation gradually decreased and became mild. However, salivation still continued even after full recovery (Ahmed *et al.*, 2009). Profound salivation was observed in pigs as a result of using combination of Ketamine/ Xylazine (Rana *et al.*, 2013).

Ketamine produces no muscle relaxation and tonic clonic spasms of limb muscles may occur even in the absence of surgical or other stimulation (Hall *et al.*, 2001). Muscle relaxation ranged between excellent to very good as a result of using Ketamine with diazepam, Xylazine combination (Abakar *et al.*, 2014). Good muscle relaxation, using Ketamine in combination with Romifidine and midazolam was also reported to occur (Amin *et al.*, 2012). Muscle relaxation ranged from minimal to moderate degree as a result of using Ketamine in combination with butorphanol and Detomidine in donkeys (Amin and Najim, 2011).

1.2 Xylazine:

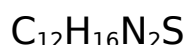
The α_2 -adrenoceptor agonist drugs have been recognized as of worldwide use in veterinary medicine for their sedative, analgesic and muscle relaxation properties in large and small animals. The commonly α_2 agonists which

used in veterinary practice are Xylazine, Detomidine, medetomidine and Romifidine (Luna *et al.*, 2000). 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 α_2 -adrenergic receptors located in various tissues (Kobinger, 1978) and it exerts its effect accordingly.

1.2.1 Chemistry and pharmacology:

Xylazine was first synthesized in 1962 and given the name Bay Va1970. Chemically it is 2-(2,6-dimethylphenylamino)-6,7-dihydro-1,3-thiazine (Prys-Poberts, 1991). Pharmacologically Xylazine is classified as analgesic, sedative and muscle relaxant (Booth, 1988). It is popular and reliable pre anaesthetic medication in a wide range of animal species (Hall and Clarke, 1991).

1.2.2 Molecular formula:



1.2.3 Structural formula:

The structural formula of Xylazine is presented in Figure (1.2).

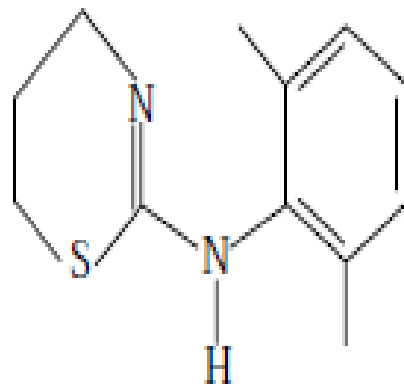
1.2.4 Mode of action:

Xylazine is a typical α_2 -adrenoceptor agonist; it acts on the central nervous system by activation or stimulation of α -adrenoceptors. Xylazine stimulates α_1 and α_2 hence its central and peripheral effects. Affecting the central nervous system Xylazine induces analgesia and sedation (Thurmon *et al.*, 1996). Xylazine also produces muscle relaxation by inhibition of intraneuronal transmission of impulse at the

central level of central nervous system (Booth, 1988; Thurmon *et al.*, 1996).

1.2.5 Some sedative effects of Xylazine:

Xylazine reported to have obvious sedative effect in donkeys (Jordan, 1986; Mbiuki and Mogoia, 1994; Mogoia *et al.*, 1994). The sensitivity to Xylazine between animal species differs (Thurmon *et al.*, 1996). Higher doses of Xylazine have been recommended than what is normally used in the



Xylazine, M_r 220

Figure 1.2: Xylazine structure

horse, the doses of Xylazine normally used are in the range of 0.5 -2mg/kg (Mbiuki and Mogo, 1994; Mogo *et al.*, 1994). Administration of Xylazine 2 mg/kg bwt with Ketamine 4.4 mg/kg bwt intramuscularly has been shown to be effective for producing anaesthesia in donkeys (Mbiuki and Mogo, 1991).

The sedative effect of α_2 adrenergic agonist follows a similar pattern regardless of the agent used. The change seen in the horse as follow: initial apprehension followed by lowering of the head, drooping of the eyelids and lower lip and the horse becomes rapidly ataxic (McCrackin *et al.*, 1994). Abakar *et al.*, (2014) indicated that Immediately, following intravenous injection of Xylazine in donkeys, main signs observed were dropping of the head, lowering the lip, ears, abduction of the legs, protruding of the penis, sometimes ataxia and the animal fell down or adopt sternal recumbancy. Signs of sedation following intramuscular injection include lowering of head and neck, partial drooping of eyelids, muscular in-coordination and staggering gait in goats (Saleh, 1993), similar effects of Xylazine in horses has been reported (Hall and Clarke, 1991).

α_2 agonist require quite environment without any stimulation for it to achieve its full effect (Taylor, 1985). Horses sedated with Xylazine remain very sensitive to touch and the apparently well sedated horse may, if disturbed, respond with a very sudden and accurate kick (Hall *et al.*, 2001).

Prajapathi *et al.* (1994) reported that the duration of sedation and recovery times were dose dependent, being significantly longer with the higher doses. When given as an intravenous infusion over a wide dose range it was shown that Xylazine - induced dose dependent and that the onset of sedation was 2-8 minutes with full recovery varying from 1 to 3 hours.

Xylazine was reported to produce prolong sedation, muscle relaxation and analgesia in different animals species (Greene and Thurmon, 1988). Xylazine has been reported to be associated with production of good analgesia in goats (Dehghani *et al.*, 1991; Saleh, 1993; Aithal *et al.*, 1996), in cattle (Fayed *et al.*, 1989) and in horses Seo *et al.*, (2011). There are reports that Xylazine has only moderate analgesic action in the distal extremities (Mogoa, 1990).

Administration of Xylazine through different routes resulted in salivation which ranged between moderate to profuse watery salivation in ruminants (Booth, 1988), in goats (Neophytou, 1982, and Saleh, 1993) and cattle (Fayed *et al.*, 1989). Following intravenous infusion of Xylazine in goats salivation started to drip few minutes after infusion and continued for 30 to 60 minutes (Kokkonen and Eriksson, 1987). Bader and AL-kattan (2010) reported excessive salivation with drooling after injection of Xylazine in donkeys.

Xylazine was also reported to cause good to excellent muscle relaxation when used in combination with butorphanol/guaifenesin and Ketamine (Thakur *et al.*, 2011)

Booth (1988) reported that intravenous injection of Xylazine induces hypotension, bradycardia and heart block. Joseph *et al.*, (1982), also reported bradycardia in different animal species. Significantly decreased heart rate was reported also as a result of intravenous injection of Xylazine in horses Seo *et al.*, (2011). Significantly decreased heart rate, increased incidence of atrioventricular block, and decreased cardiac output together with mean arterial

pressure was significantly reduced in horses (Wagner *et al.*, 1991). Usage of Xylazine in combination with some anaesthetic may lead to different result as reported by Albozachri *et al.*, (2012) where tachycardia was evident as a result of using Xylazine in combination with tramadol and Ketamine or in combination with diazepam and Ketamine.

Respiratory rate may be affected negatively as a result of using Xylazine via intravenous route which translated in term of a significantly decreased respiratory rate in horses, rams and donkeys as reported by Seo *et al.*, (2011), Khan *et al.*, (2004) and Bader and AL-kattan (2010) respectively.

Hypothermia observed to occur in rams as a result of using Xylazine intravenously (Khan *et al.*, 2004), also significant decrease in rectal temperature was observed to occur in donkeys when Xylazine was used in combination with Tramadol Ketamine or diazepam Ketamine combinations as reported by Albozachri *et al.*, (2012). Similar results were obtained in donkeys ([Molinaro](#) Coelho *et al.*, 2014) as a result of using Xylazine alone or in combination with guaifenesin-Ketamine.

Urination following administration of Xylazine is a common occurrence in goats, and polyurea was observed after injection of Xylazine (Mohammed and Yelwa, 1993). In cattle, Thurmon *et al.*, (1978) reported increased urine output lasting for several hours accompanied by presence of glucose in urine. In mules urination was noted in minutes after the administration of Xylazine as reported by Latzel (2012).

1.2.6 Blood biochemical effects of Xylazine:

Blood glucose level usually increased in different animal species as a result of using Xylazine alone or in combination with other drugs as reported by Ismail *et al.*, (2010) in goats, Camekrten *et al.*, (2013) in Greyhound, Okwudili *et al.*, (2014), in dwarf goat and Kullmann *et al.*, (2014) in horses, when used in combination with Ketamine. Contradictory results were reported in literature concerning the effect of Xylazine on blood urea level. Significant decrease in urea level was reported to occur as a result of using Xylazine in mares Kullmann *et al.*, (2014); non significant elevation was reported by Ismail *et al.*, (2010) in mares, in greyhounds as reported by Camekrten *et al.*, (2013). Significant increase in blood urea was reported in dogs and dwarf goat (Ünsürenl *et al.*, 1986) and (Okwudili *et al.*, 2014).

Albozachri *et al.* (2012) reported significant increase in ALT level as a result of induction of anaesthesia with Xylazine in combination with Tramado/Ketamine while using Xylazine in combination with diazepam/Ketamine resulted in significant drop in ALT level in donkeys. Non significant changes in ALT level were reported to occur as a result of using Xylazine /Ketamine combination in Greyhound dogs as reported by Camekrten *et al.*, (2013). AST serum level was found to be significantly increased as a result of induction of anaesthesia with Tramadol HCL/Ketamine/Xylazine or Diazepam /Ketamine/ Xylazine respectively as reported by Albozachri *et al.*, (2012) in donkeys. On the other hand usage of Xylazine in combination with Ketamine, and diazepam,

resulted in non significant changes in AST level in sheep and goat as reported by Ismail *et al.*, (2010).

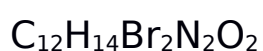
1.3 Detomidine:

Detomidine HCl (Domosedan) is a potent sedative and analgesic for use in veterinary practice Hall *et al.*, (2001). Detomidine has similar effects to Xylazine but Detomidine produces sedation and analgesia of a greater magnitude and a longer duration than Xylazine. Sedation effects become apparent within two to five minutes after intravenous injection (Daunt, 1995).

1.3.1 Chemistry and pharmacology:

Detomidine is a 4 - (2, 3 - dimethylphenyl) methyl - 1H - imidazole hydrochloride, it is an imidazole derivative which has been developed as a sedative/analgesic for animals. It supplies in multi dose bottles at concentration of 10 mg/ml and may be administered via intramuscular or intravenous routes (Virtanen, 1986).

1.3.2 Molecular formula:



1.3.3 Structural formula:

The structural formula of Detomidine is present in Figure (1.3).

HCl

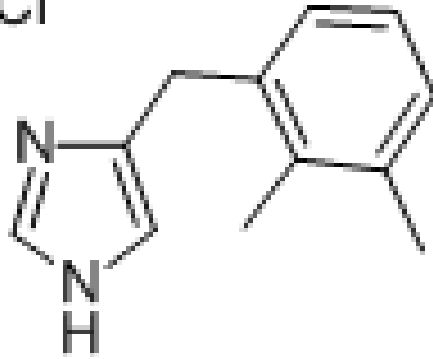


Figure 1.3: Detomidine structure

1.3.4 Mode of action:

Detomidine exerts its action which is CNS depression by stimulating both presynaptic and postsynaptic α_2 - adrenoceptors in the CNS and periphery leading to decrease of norepinephrine release centrally and periphery and reduce ascending nociceptive transmission with net result is a decrease in circulating catecholamines and other stress related factors (Muir and Hubbell, 2013).

1.3.5 Physiological effects of Detomidine:

Detomidine has a suppressive effect on the heart it was reported to induce bradycardia (Vainio, 1982) or to cause second degree atrio-ventricular block (Short *et al.*, 1984; Vainio, 1985) or even bradycardia together with atrio-ventricular block in horses (Short *et al.*, 1986). Bradycardia induced by Detomidine was observed to occur within seconds to 5 minutes after intravenous injection and it might occur at a wide range of doses and it seems to be dose dependent (Short *et al.*, 1984). El-Kammar and Gad, (2014) reported occurrence of significant bradycardia in donkeys as a result of using Detomidine. Also decreased heart rate was reported to occur in other species of animals like Egyptian *Baladi* goats as a result of injection of Detomidine (El-Kammar *et al.*, 2014).

Detomidine has an adverse effect on the respiratory rate which shown to be in form of significant decrease in respiratory rate in donkeys (El-Kammar and Gad, 2014). Also El-Kammar *et al.*, (2014) reported that significant reduction in respiratory rate was noted in goats as a result of

intravenous usage of Detomidine. On the other hand respiratory rate was reported to be none significantly affected as a result of using Detomidine in combination with acepromazine in horse (Taylor *et al.*, 2001).

Body temperature generally decreases as a result of using α_2 adrenoceptors although high doses of Detomidine in horses have been reported to induce hyperthermia (England and Clarke, 1996). In donkeys intravenous injection of Detomidine was reported to decrease rectal temperature significantly (El-Kammar and Gad, 2014). Similar results of significant reduction of rectal temperature were reported in goats after injection of Detomidine (El-Kammar *et al.*, 2014)

1.3.6 Blood biochemical effects of Detomidine:

Although some researchers reported the significant increase in Serum glucose level as a result of injection of Detomidine (Thurmon *et al.*, 1982. and Ambrosio *et al.*, 2012) in horses, other researchers reported different results which is non significant change in serum glucose level in donkeys as a result of injection of Detomidine (El-Kammar and Gad, 2014).

As reported by El-Kammar *et al.*, (2014) serum urea concentration was observed to decrease significantly as a result of intravenous injection of Detomidine in goats. On the other hand serum urea concentration was found to be none significantly affected as a result of injection of Detomidine in donkeys as reported by El-Kammar and Gad (2014). Premedication of donkeys with Detomidine before induction of anaesthesia with midazolam/Ketamine or diazepam/

Ketamine reported to cause significant increase in blood urea (Ali, 2013).

Most of the anaesthetic drugs are metabolized in the liver so it is logical to expect increase in liver enzymes as a result of using any drug which usually metabolized in the liver in spite of that some researchers reported no significant alteration in ALT activity in donkeys as a result of using Detomidine via intravenous route (El-Kammar and Gad, 2014). Contradictory results were reported by El-Kammar *et al.*, (2014) in goats where the ALT activity was found to be significantly increased as a result of intravenous injection of Detomidine. Intravenous injection of Detomidine induced no significant increase in AST level in donkeys (El-Kammar and Gad, 2014); while in goats the level of AST was found to be significantly increased as a result of using Detomidine through intravenous route as reported by El-Kammar *et al.*, (2014). In goats El-Kammar *et al.*, (2014) reported occurrence of frequent urination following the use of Detomidine alone or in combination with butorphanol. Also Detomidine in donkeys caused frequent watery urination (Elkhenany, 2011)

1.3.7 Some sedative effects of Detomidine:

EL-Kammar *et al.*, (2014) reported that different dose rate of Detomidine in combination with butorphanol caused watery salivation in baladi goat. Salivation was also seen in horses during recovery from Detomidine/chloral hydrate anaesthesia (Khan *et al.*, 2003).

Marked signs of sedation and ataxia observed in baladi goat treated with Detomidine (El-Kammar et al., 2014). Similar results were obtained in donkeys as a result of intravenously injection of Detomidine (Ali, 2013). Detomidine is classified as a good analgesic agent and its analgesic power has been shown in number in pain models (Virtanen, 1985 and Clarke, 1988). Detomidine cause analgesia affecting nearly the whole body (El-Kammar et al., 2014) in goats. Also it was reported to cause analgesia when used in combination with diazepam/Ketamine or midazolam/Ketamine (Ali, 2013). Amin and Najim, (2011), reported occurrence of muscle relaxation as a result of using Detomidine in combination with Butorphanol and Ketamine in donkeys. Induction of anaesthesia with Detomidine, midazolam/ diazepam Ketamine combination protocol provided a good muscles relaxation with complete unconsciousness in horses (Ali, 2013).

1.4 Romifidine:

Romifidine is a recent α -2 adrenoceptor agonist marketed for use in horses (Muir et al., 2005). It has been used successfully for sedation, analgesia, and premedication in horses in several countries since 1988 (Martnell and Nyrnan, 1996).

1.4.1 Chemistry and pharmacology:

Romifidine developed from clonidine and it has a typical α 2 adrenoceptor agonist effects, it has gone clinical trials as

a sedative and premedicant in horses (Clarke *et al.*, 1991 and Young, 1992). Chemically it is N-(2-bromo-6-fluorophenyl)-4,5-dihydro-1H-imidazol-2-amine.

1.4.2 Molecular formula:



1.4.3 Structural formula:

The structural formula of Romifidine is presented in Figure (1.4).

1.4.4 Mode of action:

Romifidine is the latest of the α_2 -adrenergic agonists to be developed as an equine sedative and pre anaesthetic agent (Kerr *et al.*, 1996).

1.4.5 Physiological Effects of Romifidine:

Romifidine was reported to cause different effects on the respiratory rate. Amin *et al.*, (2012b) reported significant increase in the respiratory rate in she donkeys as a result of using Romifidine in combination with midazolam and Ketamine. Taylor *et al.*, (2001) and Kerr *et al.*, (2004) reported a non significant effect of Romifidine on respiratory rate in horses. A different effect of Romifidine on the respiratory rate was reported by El-Kammar *et al.*, (2014) in goats and De-Rossi *et al.*, (2009) in horses and Shekidef *et al.*, (2007) where they stated that Romifidine had induced a significant decrease in respiratory rate. The obvious cardiovascular effect of Romifidine reported in literature is bradycardia which was found to be of a short time (10 minutes) as reported by Amin *et al.*, (2012- b) in she donkeys, for 15 minutes as reported by El-Kammar *et al.*,

(2014) in goats or for a longer duration as reported by (Pypendop and Verstegen, 2001), Shekidef *et al.*, (2007) in calves and in horses De-Rossi *et al.*, (2009).

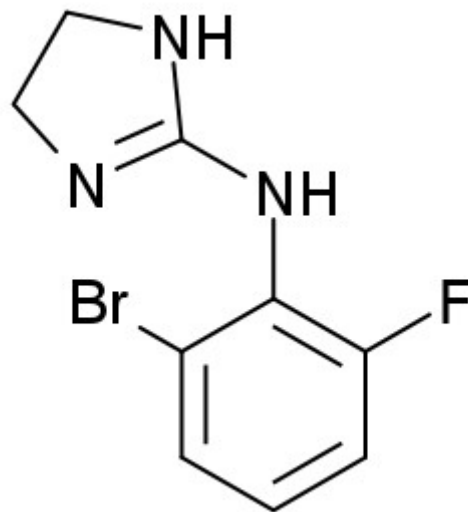


Figure 1.4: Romifidine structure

Significant hypothermia was an evident in donkeys as a result of using Romifidine in combination with midazolam and Ketamine in donkeys as reported by Amin *et al.*, (2012). Similar results of significant decrease in body temperature in goats were reported in goats (El-Kammar *et al.*, (2014).

1.4.6 Blood biochemical effects of Romifidine:

Romifidine causes significant increase in serum glucose level as a result of using it alone (El-Maghraby *et al.*, 2005) or in combination with other drugs (Amin *et al.*, 2012) as in combination with Ketamine and midazolam together with infusion with zolazepam with Ketamine for induction of anaesthesia in female donkeys. Also significant increase in glucose level was reported to occur in calves and goats as a result of using Romifidine through intravenous injection as reported by Shekidef *et al.*, (2007) and El-Kammar *et al.*, (2014) respectively.

Intravenous injection of Romifidine caused significant increase in serum urea level in buffalo calves (Shekidef *et al.*, 2007) while the change was found to be of no significant value in goats (El-Kammar *et al.*, 2014). El-Maghraby *et al.*, (2005) reported that the effect of Romifidine on urea level is dose dependent, they found that injection of Romifidine at dose of 35 and 70 μ g/kg resulted in no significant change in

urea level while the dose of 100µg/kg caused a significant increase in urea level at 60 and 90 minutes after injection of Romifidine.

In she donkeys no significant change in ALT activity was reported to occur as a result of using Romifidine-Ketamine-midazolam for induction together with infusion with zolazepam with Ketamine (Amin *et al.*, (2012), similar result was reported to occur in goats receiving Romifidine intravenously (El-Kammar *et al.*, 2014).

Amin *et al.*, (2012) reported significant decrease in AST activity in female donkeys as a result of using Romifidine- Ketamine-midazolam for induction together with infusion with zolazepam with Ketamine in female donkeys. In buffalo calves and goats significant increase in AST level was reported to occur (Shekidef *et al.*, 2007, and El-Kammar *et al.*, 2014).

1.4.7 Some sedative effects of Romifidine:

The sedation achieved with Romifidine was significantly shallower and shorter-lived than with Detomidine at the recommended doses. The results obtained with the highest dose of Romifidine were in some cases significantly inferior and shorter-lived than those obtained with the medium dose ([Hamm](#) *et al.*, (1995). Marked signs of sedation were found to onset rapidly and continued for 137.33 ± 10.60 minutes in baladi goats (E-Kammar *et al.*, 2014). 100 µg/kg produce sedation for 90- 100 minutes (El-Maghraby *et al.*, 2005). Romifidine has been used successfully for sedation, analgesia, and premedication in horses in several countries

since 1988 (Martnell and Nyran, 1996). Analgesia was observed following intravenous injection of Romifidine (El-Kammar *et al.*, 2014) in baladi goat. Good or excellent analgesia was reported in donkeys as a result of using Romifidine at different dose rates (El-Maghraby *et al.*, 2005).

Frequent urination was observed to occur as a result of using Romifidine alone or in combination with butorphanol in *Baladi* goat (El-Kammar *et al.*, 2014). In donkeys Romifidine at different dose levels caused increased urination (El-Maghraby *et al.*, 2005). Romifidine produces sedation, muscle relaxation reluctance to move and reduced responsiveness to environmental stimuli (Freeman *et al.*, 2002). Mild muscle relaxation and mild analgesia were recorded in buffalo calves as a result of using Romifidine (Shekidef *et al.*, 2007)

Watery salivation was observed to occur as a result of using Romifidine alone or in combination with butorphanol in baladi goat (El-Kammar *et al.*, 2014). Also excessive salivation was observed in all over the period of sedation induced by Romifidine in buffalo calves (Shekidef *et al.*, (2007).

CHAPTER TWO

Materials and Methods

2.1 Materials:

2.1.1 Study location and housing:

The anaesthetic part of this study was carried out at the farm of the College of Veterinary Medicine, Sudan University

of Science and Technology, Hillat Kuku, Khartoum North, Sudan. The surgical evaluation of the anaesthetic protocols was conducted in the farm of Faculty of Veterinary Medicine, University of Albutana, Tampool.

2.1.2 Experimental animals:

A total of 36 healthy local breed donkeys, 24 males and 12 females were used in this study. Their age was between 3-5 years with average body weight of 90 ± 10 kg. The animals were kept in closed pens in College of Veterinary Medicine Farm, Sudan University of Science and Technology throughout the duration of the study. The animals were fed on green fodder, hay and supplemented with concentrates with free access to water. The animals were kept for two weeks to get acclimatized before starting experiments. Thorough clinical examination was conducted before starting experimental work, after each experiment and routinely through the course of the study.

2.1.3 Handling:

Protective bedding made of empty sacks or sandy ground was used to protect the animals during induction, maintenance of anaesthesia and during recovery.

2.1.4 Drugs:

One anaesthetic was used in this study together with three α_2 -adrenocetor agonists' pre-anaesthetic medications as follows:

1. Ketamine Hcl 5% (Troika pharmaceuticals Ltd Thol-382728 Gujarat, India).

2- Xylazine Hcl 2% (Ceva Tiergesundheitb GmbH- Kanzlerstr. 4-40472 Dusseldorf)

3- Detomidine 1% (Orion pharma.13483-2).

4- Romifidine 1% (Boehringer Ingelheim Vetmedica GmbH Blinger 173 55216 Ingelheim).

2.1.5 Monitoring tools:

Disposable syringes 5, 10 and 20 (Nirma limited health care division Sachana Gujarat 382150, India) were used and intravenous catheters (18 G) were used for intravenous injection of drugs. Micro dripper 500 ml/hr was used for infusion (company).

Stethoscope and digital thermometer were used to monitor heart rate and rectal temperature, respectively. Stop watch was used to determine the duration of different phases of anaesthesia.

2.2 Methods:

2.2.1 Anaesthetic protocols:

The following anaesthetic protocols were evaluated in this study:

1- Xylazine 2% (2mg/kg) + Ketamine 5% (4mg/kg).

2- Xylazine 2% (2mg/kg) + Ketamine 5% (4mg/kg) + infusion with saline drip containing Xylazine 2% (2mg/kg) + Ketamine 5% (6 mg/kg).

3-Detomidine 1% (50µg/kg) + Ketamine 5% (4mg/kg).

4- Detomidine 1% (50µg/kg) + Ketamine 5% (4mg/kg) + Infusion with saline drip containing Detomidine 1% (50µg/kg) + Ketamine 5% (6mg/kg).

5- Romifidine 1% (100µg/kg) + Ketamine 5% (4mg/kg).

6- Romifidine 1% (100µg/kg) + Ketamine 5% (4mg/kg) + Infusion with saline drip containing Romifidine 1% (100µg/kg) + Ketamine 5% (6mg/kg).

2.2.2 Pre-anaesthetic preparation:

Animals were fasted from food overnight and water was withheld for 6- 8 hours prior to anaesthesia.

2.2.3 Experimental work:

2.2.3.1 Pilot studies:

Two pilot studies were carried out to determine the suitable dose of Romifidine and Detomidine to be used with Ketamine:

A.1. First pilot study:

Six animals were used in this study. The animals were divided into two groups. Detomidine was injected intravenously at dose rate of 30 and 50µg respectively. 10 minutes later each animal in the two groups received Ketamine at dose rate of 4mg/kg intravenously. The sedative effects of Detomidine were studied. The muscle rigidity resulted from injection of Ketamine was monitored.

A.2. Second pilot study:

Another six animals were used in this study. The animals were divided into two groups. Romifidine was injected intravenously at dose rate of 60 and 100 µg respectively. 10 minutes later each animal in the two groups received Ketamine at dose of 4mg/kg intravenously. The

sedative effects of Romifidine were studied. The muscle rigidity resulted from injection of Ketamine was monitored

2.2.3.2 Anaesthesia Experiments

B.1 First experiment: Six animals were used in this experiment they were anaesthetized with the following two protocols with an interval of two weeks between each successive injection as washing out period.

1- Xylazine 2% (2mg/kg) + Ketamine 5% (4mg/kg).

2- Xylazine 2% (2mg/kg) + Ketamine 5% (4mg/kg) + infusion with saline drip containing Xylazine 2% (2mg/kg) + Ketamine 5% (6 mg/kg).

Following injection of Xylazine animals were monitored for 10 minutes to describe on the signs and characteristics of per-medication injection.

B.2 Second experiment: Six animals were used in this experiment they were anaesthetized with the following two protocols with an interval of two weeks between each successive injection.

1- Detomidine 1% (50µg/kg) + Ketamine 5% (4mg/kg).

2- Detomidine 1% (50µg/kg) + Ketamine 5% (4mg/kg) + Infusion with saline drip containing Detomidine 1% (50µg/kg) + Ketamine 5% (6mg/kg).

Following injection of Detomidine animals were monitored for 10 minutes to describe on the signs and characteristics of per-medication injection.

B.3 Third experiment: Six animals were used in this experiment they were anaesthetized with the following two

protocols with an interval of two weeks between each successive injection.

1- Romifidine 1% (100µg/kg) + Ketamine 5% (4mg/kg).

2- Romifidine 1% (100µg/kg) + Ketamine 5% (4mg/kg). + Infusion with saline drip containing Romifidine 1% (100µg/kg) + Ketamine 5% (6mg/kg).

Following injection of Romifidine animals were monitored for 10 minutes to describe on the signs and characteristics of per-medication injection.

2.2.3.3 Evaluation of selected anaesthetic protocols for surgical lapratomy:

A- Anaesthesia: 18 animals were used in this part of the study. They were divided into three groups, each group consist of six animals. The three groups of animals were anaesthetized using the following protocols respectively:

1- Xylazine 2% 2mg/kg + Ketamine 5% 4mg/kg + infusion (Xylazine 2% 2mg/kg + Ketamine 5% 6 mg/kg).

2- Detomidine 1% (50µg/kg) + Ketamine 5% (4mg/kg) + Infusion Detomidine 1% (50µg/kg) + Ketamine 5% (6mg/kg).

3- Romifidine 1% (100µg/kg) + Ketamine 5% (4mg/kg) + Infusion Romifidine 1% (100µg/kg) + Ketamine 5% (6mg/kg).

B- Monitoring of different parameters: Physiological, anaesthetic and biochemical parameters were monitored using the same methods described for anaesthesia without surgery except for the phase of analgesia which was monitored in this part by moving of limbs three times or more in response to suturing of skin or by responding positively to gentle touch on the sutured skin.

C- Laparotomy: Slandered method for performing laparotomy was used in this study according to the following steps:

- Incision of skin of about 10-15 cm in the right flank region.
- Time for skin incision 4- 6 minutes after induction of anaesthesia.
- Time for incision of muscles 6-8 minutes after induction of anaesthesia.
- Time for start suturing of muscles 20-33 minutes after induction of anaesthesia
- Time for finishing suturing of muscles 26-38 minutes after induction of anaesthesia.
- Time of starting suturing of skin 28- 35 minutes after induction of anaesthesia.
- Time for finishing suturing of skin 32- 44 minutes after induction of anaesthesia.

2.2.4 Criteria for scoring the quality of anaesthetic induction, muscle relaxation and recovery:

The quality of induction, and recovery were scored according to the criteria enlisted in the Table (2.1). While quality of muscle relaxation was enlisted according to the criteria in the Table (2.2)

Table 2.1: Criteria for scoring the quality of anaesthetic induction, muscle relaxation and recovery using some selected Ketamine protocols

Score	Qualit	Character
y		
Induction quality		
1	Smoot	Gradual falling to the ground with no

2	h Fair	paddling and no stiffness of limbs Gradual falling to the ground with mild
3	Rough	paddling and no stiffness of limbs Gradual falling with vigorous paddling and strong stiffness of limbs

Muscle relaxation

1	Excellen t	Complete relaxation (jaws, neck, abdomen and limbs)
2	Good	Relaxation of neck, abdomen and limbs
3	Poor	Rigidity in muscles of jaws, neck, abdomen and limbs

Recovery

1	Smoot h	Donkey capable of standing at first attempt - mild ataxia
2	Fair	Donkey remained calm and needed two- three attempts to stand - clear ataxia
3	Poor	Donkey remained calm but assisted to stand
4	Very poor	Donkeys excitement during recovery - assisted and supported

Table 2.2: Criteria for scoring the quality of abdominal muscle relaxation during performance of surgery

Score	Quality	Character
1	Excellent	Complete relaxation of abdominal muscles
2	Satisfact ory	Partial relaxation of abdominal muscle do not prevent surgical procedure
3	Poor	Rigidity of muscles , prevent surgical

4 Normal procedure

Muscles regained normal tonocity

Body muscle relaxation was assessed subjectively as follows: jaws muscle relaxation by opening and closure of the jaws, neck and abdomen muscle was assessed by gentle pressure on neck muscles and limb muscle relaxation was assessed by flexion and extension of the limbs.

2.2.5 Definitions and monitoring of anaesthetic phases:

Induction of anaesthesia: Was considered subjectively as the period taken by the animal to fall to the ground, showed signs of unconsciousness, respond negatively to painful stimuli and paddling and stiffness of limbs stopped if it present.

Analgesia phase: Was assessed subjectively as the period during which the animal shows signs of unconsciousness and responds negatively to noxious or painful stimuli (pinprick in the perineal and scrotal region).

Lateral recumbency: Was considered subjectively as the duration at which the animal respond positively to painful stimuli, muscles regained their tonicity and the animal is incapable of adopting sternal position.

Sternal recumbency: It was considered subjectively as the period during which the animal could adopt sternal recumbency without falling to lateral recumbency and without adopting standing position (Ghurashi *et al.*, 2008).

Standing phase: It is the stage at which the animal stood but unable to walk ten steps (Ghurashi, 1999).

Recovery: The animal was considered to be recovered from anaesthesia when it is capable of supporting itself in

standing position and walk for ten steps without falling down (Ghurashi *et al.*, 2008).

Total recovery: Total recovery time was considered as the total time calculated from the time of induction of anaesthesia until recovery was attained (Nuha, 2004).

Analgesia during surgery: Was taken subjectively as the duration of time from induction of anaesthesia until the animal respond by moving of limbs and raising of head as a result of surgical interference.

2.2.6 Physiological parameters:

Respiratory rate (cycle/min.): Respiratory rate was recorded using slandered methods described by (Kelly, 1984)

Heart rate (beat/min): Heart rate was recorded by counting the heart beats over the cardiac area using a stethoscope through a whole minute of time as described by (Kelly, 1984)

Rectal temperature ($^{\circ}$ C): Rectal temperature was recorded using a clinical digital thermometer from the rectum. The rectum usually emptied from faeces and the thermometer lubricated before insertion in the rectum (Kelly, 1984).

2.2.7 Blood samples collection:

Blood samples were collected from the jugular vein using 10 ml syringes and transferred into tubes coated with fluoride oxalate as anti-coagulant (AFCO- DISPO, Jordan). The blood in the tubes was immediately and thoroughly mixed with the anticoagulant by gently inverting the tube several times, placed in ice, transported to the laboratory and

centrifuged for five minutes at 5×1000 round/minute using tube centrifuge (EBA20- Hettich zentrifugen, Germany). The separated plasma in each tube was harvested in labelled eppendorf tubes and was kept at -20°C until analysed.

Sampling schedule:

To investigate the level of each of the biochemical values under investigation glucose, urea, ALT and AST four samples were collected during anaesthesia with each tested protocols namely base line sample, 30, 60 and 90 minutes after induction of anaesthesia.

2.2.8 Blood biochemical methods:

2.2.8.1 Glucose:

Glucose is the major carbohydrate present in the blood and it is the major source of cellular energy in the body and the remaining is converted to glycogen for storage in the liver or to fatty acids for storage in adipose tissue. Elevation in blood glucose level occurs in case of diabetes mellitus due to deficiency in insulin secretion or action. Elevation occurs secondary to pancreatitis, thyroid dysfunction, renal failure and liver disease. Hypoglycaemia is less observed and caused by variety of conditions such as hypopituitarism and insulin induced hypoglycaemia.

Assay principle:

Glucose was measured using commercial kit (Vitro Scient-Egypt). Enzymatic method was firstly described by Keilin and Hartree (1948) using glucose oxidase and later, this method was modified by Keston, (1956), using glucose oxidase/peroxidase system and o-dianisidine chromogen

system. Glucose was determined using enzymatic colorimetric method using glucose oxidase and 4-aminoantipyrine according to Trinder, (1969) method modified from Keston (1956). In this method glucose was oxidized by glucose oxidase to gluconic acid and hydrogen peroxide which coupling the phenol and 4- aminoantipyrine to form quinoneimine, a red dyestuff. The optical density of the developing colour was measured at 500 nm using Spectrophotometer (Jenway 6305 U. V. /vis. Spectrophotometer, U. K.).

2.2.8.2 Urea:

Urea is the major end product of protein nitrogen metabolism. It is synthesized in the liver and excreted mostly by the kidney and minimal amount excreted in sweat and degraded in the intestine by bacterial action. Determination of urea is a screening test for renal function; pre renal elevations are seen in shock, inadequate renal perfusion, and diminished blood volume. Renal causes of elevations are chronic nephritis, tubular necrosis, nephrosclerosis. The main cause of post renal elevations is urinary tract obstruction.

Assay principle:

Urea was measured using commercial kit (Vitro Scient-Egypt) according to enzymatic colorimetric method described firstly by Marshall (1913) who added urease enzyme and measured the liberated ammonia with titration with an acid, this method has been used and modified and later modified by Fawcett and Scott (1960). In this modified method urea is hydrolyzed by urease to form ammonium and

carbonate, the ammonium ions react with the salicylate and hypochlorite to form a green coloured indophenol. The optical density of the developing colour was measured at 578 nm using Spectrophotometer (Jenway 6305 U. V. /vis. Spectrophotometer, U. K.).

2.2.8.3 Aspartate aminotransferase (AST) (Glutamic-Oxaloacetic transaminase (GOT)

AST belongs to the group of transaminase enzymes which catalyze the conversion of amino acid to α -Keto acid via the transfer of amino acid group and reverse process. AST is commonly found in tissues presented in both cytoplasm and mitochondria and significant activities seen in cardiac and skeletal muscles, liver, kidney, gastric mucosa and adipose tissue. Elevated AST levels found in liver disease associated with some degree of hepatic necrosis, muscular myopathies, damage of internal organs and myocardial infarction.

Assay principle

AST was analyzed in accordance with kinetic ultraviolet method. Karmen *et al.*, (1955) described the first kinetic method using a couple reaction of MDH and NADH in 1960 this method modified by Henry *et al.* (1960). AST was analyzed using commercial kit (Vitro Scient-Egypt) as described by Barham and Trinder (1972). Vitro reagent is based on the recommendation of the IFCC (IFCC, 1986) where the amino group is enzymatically transferred by AST present in the specimen from aspartate to the carbon atom of 2-oxoglutarate yielding oxaloacetate and L-glutamate.

Oxaloacetate is reduced to malate by LDH present in the reagent with the simultaneous oxidation of NADH to NAD. The rate of oxidation of the coenzyme NADH is proportional to the AST activity in the specimen and it was determined by measuring the decreases in absorbance at 340 nm using Spectrophotometer (Jenway 6305 U. V. /vis. Spectrophotometer, U. K.).

2.2.8.4 Alanine aminotransferase (ALT) (Glutamate Pyruvate transaminase (GPT)

Alanine aminotransferase (ALT) is a soluble cytosolic enzyme that catalyzes the reversible transamination of L-alanine and 2-oxoglutarate to pyruvate and glutamate. Hepatic ALT activity in horses, cattle, sheep, goats, and pigs is very low, which precludes its use for detecting liver disease in these species (Duncan *et al.*, 1994).

Assay principle

The Vitro ALT Kits is based on the recommendations of the IFCC (IFCC, 1986). The series of reactions involved in the assay system are as follows:

1. The amino group is enzymatically transferred by ALT present in the specimen from alanine to the carbon atom of 2-oxoglutarate yielding pyruvate and L-glutamate.
2. Pyruvate is reduced to lactate by LDH present in the reagent with the simultaneous oxidation of NADH to NAD.

Glutamic - Pyruvic Transaminase (GPT) was measured using kits (Randox laboratories Ltd., United Kingdom, BT29 4QY) by monitoring the concentration of pyruvate hydrazone formed with 2, 4- dinitrophenylhydrazine according to Reitman and

Frankel (1957). The formed colour was measured at 530 nm using Jenway spectrophotometer (Jenway 6105 U. V. /vis. Spectrophotometer, U. K).

2.3 Statistical analysis

T- Test was used to compare data between the different anaesthetic phases, while ANOVA was used to compare data for physiological parameters. GraphPad Prism 5.0 (GraphPad Software) was used to perform these analytical operations. A descriptive statistics value (percentage) was used to compare subjective data (i.e. induction, analgesia, muscle relaxation and recovery).

CHAPTER THREE

RESULTS

3.1 Induction and maintenance of anaesthesia with Xylazine/Ketamine protocols:

3.1.1 Signs and observations following injection of Xylazine:

Within 10 minutes after intravenous injection of Xylazine 2mg/kg in donkeys, main signs observed were dropping of the head, lowering of the lip, abduction of the legs, protruding of the penis, profound ataxia and continuous nose blowing and rubbing of the upper lip and gum with the foot or even the ground.

Salivation was observed to occur in the whole animals subjected to anaesthesia using the two protocols under investigation in this study and it usually started from induction of anaesthesia until at least the end of analgesia phase. The different protocols used in the study resulted in frequent urination by the animals under investigation. Each animal did urinate at least three times during the time of anaesthesia started from induction of anaesthesia until full recovery was attained.

3.1.2 Quality of induction, muscle relaxation and recovery:

Induction of anaesthesia with XK caused smooth induction in 33.3% and fair induction in 66.4% of the animals. Induction and maintenance of anaesthesia with XKI resulted in smooth induction in 66.6% and fair induction in 33.3% of the animals used in the study. Rough induction was

not observed to occur as a result of using XK or XKI for induction or induction and maintenance of anaesthesia (Table 3.1.1).

Induction of anaesthesia with XK caused muscle relaxation for 20 minutes only. Induction and maintenance of anaesthesia using XKI resulted in muscle relaxation which lasted for more than 40 minutes. Immediately after induction of anaesthesia with XK good muscle relaxation occurred in 83.3% of the animals, while poor muscle relaxation resulted in 16.7% of the animal used in the study. At 10 minutes following induction of anaesthesia with XK good muscle relaxation was observed in only 50% animals. By 20 minutes following induction of anaesthesia using XK, poor muscle relaxation was observed in all members of the group anaesthetized with XK.

Immediately after induction and maintenance of anaesthesia using XKI poor muscle relaxation was observed only in 16.7% of the animal used in the study, while good muscle relaxation was observed in 66.6% of the animals, and only 16.7% exhibited excellent muscle relaxation out of the total number of the animals used in the study. At 10 and 20 minutes after induction and maintenance of anaesthesia with XKI good muscle relaxation was observed in 83.3% of the animals and excellent muscle relaxation resulted in 16.7% of the animals out of the total number of animals used in the study. At 30 minutes after induction of anaesthesia still good muscle relaxation was available in 83.3% of the animals, while 16.7% of animal used in the study showed poor muscle

relaxation. The whole animals regained their muscle tonicity 50 minutes after induction of anaesthesia with XKI as shown in Table (3.1.2).

Table (3.1.3) shows the effect of induction of anaesthesia with XK and induction and maintenance of anaesthesia with XKI on recovery quality. Results obtained indicated that smooth recovery was observed in 33.3% and 16.6%, fair recovery was observed in 33.3% and 16.6% respectively, while poor recovery was observed in 16.6% and 66.6% of the animal following the use of XK and XKI, respectively.

Table 3.1.1: Induction quality following induction and maintenance of anaesthesia with Xylazine/Ketamine protocols (XK)

Animals	Rough		Fair		Smooth		Scale Protocol
	Animals	%	Animals	%	Animals	%	
6	--	66.7%	4	33.3%	2		XK
6	--	33.3%	2	66.6%	4		XKI

XK= Xylazine/Ketamine

XKI=Xylazine /Ketamine/Infusion

Table 3.1.2: Muscle relaxation quality following induction and maintenance of anaesthesia with Xylazine/Ketamine protocols (XK)

50			40			30			20			10			0			Time
Animals			Animals			Animals			Animals			Animals			Animals			
E	G	P	E	G	P	E	G	P	E	G	P	E	G	P	E	G	P	Scale
0	0	6	0	0	6	0	0	6	0	0	6	0	3	3	0	5	1	XK
0	0	6	0	5	1	0	5	0	1	5	0	1	5	0	1	4	1	XKI

P= poor, G= good, E = excellent

XK= Xylazine/Ketamine.

XKI=Xylazine /Ketamine/Infusion.

Table 3.1.3: Recovery quality following induction and maintenance of anaesthesia with Xylazine/Ketamine protocols (XK)

Scale Protocol	Smooth		Fair		Poor		Very poor	Total no. of animals
	No. of animals	%	No. of animals	%	No. of animals	%	No. of animals	
XK	2	33.3%	2	33.3%	2	33.3%	0	6
XKI	1	16.6%	1	16.6%	4	66.6%	0	6

XK= Xylazine/Ketamine

XKI=Xylazine /Ketamine/Infusion

3.1.3 Anaesthetic phases:

Table (3.1.4) illustrate the effect of induction of anaesthesia with XK and induction and maintenance of anaesthesia with XKI on the different phases of anaesthesia. Results obtained revealed that induction and maintenance of anaesthesia with XKI resulted in a significant increase ($p \leq 0.05$) in the duration of analgesia phase compared to the duration produced following induction of anaesthesia with XK. Another prolongation of the duration of the lateral recumbancy phase observed to occur as a result of induction and maintenance of anaesthesia with XKI which is significantly longer ($p \leq 0.05$) than the duration of lateral recumbancy resulted from induction of anaesthesia with XK. No significant difference was observed in sternal recumbancy between the two groups following induction of anaesthesia with XK or induction and maintenance of anaesthesia with XKI. Non-significant difference was also found to occur in the duration of standing phase resulted from induction of anaesthesia with XK and XKI. The duration of the total recovery time resulted from induction and maintenance of anaesthesia with XKI was found to be significantly longer ($p \leq 0.05$) than the duration of the total recovery time occurred as a result of induction of anaesthesia with XK.

Table 3.1.4: Duration of different anaesthetic phases (mins.) following induction and maintenance of anaesthesia with Xylazine/Ketamine protocols (XK).

Phase	Analgesia	Lateral recumbancy	Sternal recumbancy	Standing phase	Total recovery time
XK	9.00 ±1.54 a	24.17 ±10.55 a	9.33 ±6.22a	2.17±1.17a	37.33±8.38 a
XKI	39.00±8.00 b	47.00±9.30 b	14.17±5.46a	4.83±3.25a	66.83±14.55 b

XK= Xylazine/Ketamine.

XKI=Xylazine /Ketamine/Infusion.

Different letters on the same column indicate significant difference ($p \leq 0.05$).

Time in minutes.

3.1.4 Physiological parameters:

Induction of anaesthesia with XK resulted in a drop in the respiratory rate for about 30 minutes after induction of anaesthesia. A significant drop ($p \leq 0.05$) in the respiratory rate was observed at 10 minutes after injection of Xylazine, immediately after induction of anaesthesia and at 10 and 20 minutes after induction of anaesthesia. Non-significant change in the respiratory rate was observed to occur at 40 and 50 minutes after induction of anaesthesia as shown in Figure (3.1.1). In case of using XKI for induction and maintenance of anaesthesia caused a noticeable non significant drop in the respiratory rate 10 minutes after injection of Xylazine. Also non significant drop in the respiratory rate resulted immediately after induction of anaesthesia and a significant decrease ($p \leq 0.05$) in the respiratory rate was observed 10 minutes after induction of anaesthesia when compared to the baseline values.

Heart rate: The effect of induction of anaesthesia with XK or induction and maintenance of anaesthesia with XKI on the heart rate was elaborated in Figure (3.1.2). Results obtained revealed that both induction or induction and maintenance of anaesthesia were observed to cause slight drop in heart rate 10 minutes after injection of Xylazine and noticeable but non-significant increase in the heart rate immediately after induction of anaesthesia.

Rectal temperature: Induction of anaesthesia with XK resulted in a significant drop ($p \leq 0.05$) in rectal temperature 10 minutes after injection of Xylazine, also immediately after

induction of anaesthesia rectal temperature was found to be significantly decreased ($p \leq 0.05$) compared to the base line values (Figure 2.1.3).

Induction and maintenance of anaesthesia with XKI resulted in a significant decrease ($p \leq 0.05$) in the rectal temperature 10 minutes after injection of Xylazine and it remained at a significantly decreased level ($p \leq 0.05$) after induction and maintenance of anaesthesia until 60 minutes after time of induction of anaesthesia.

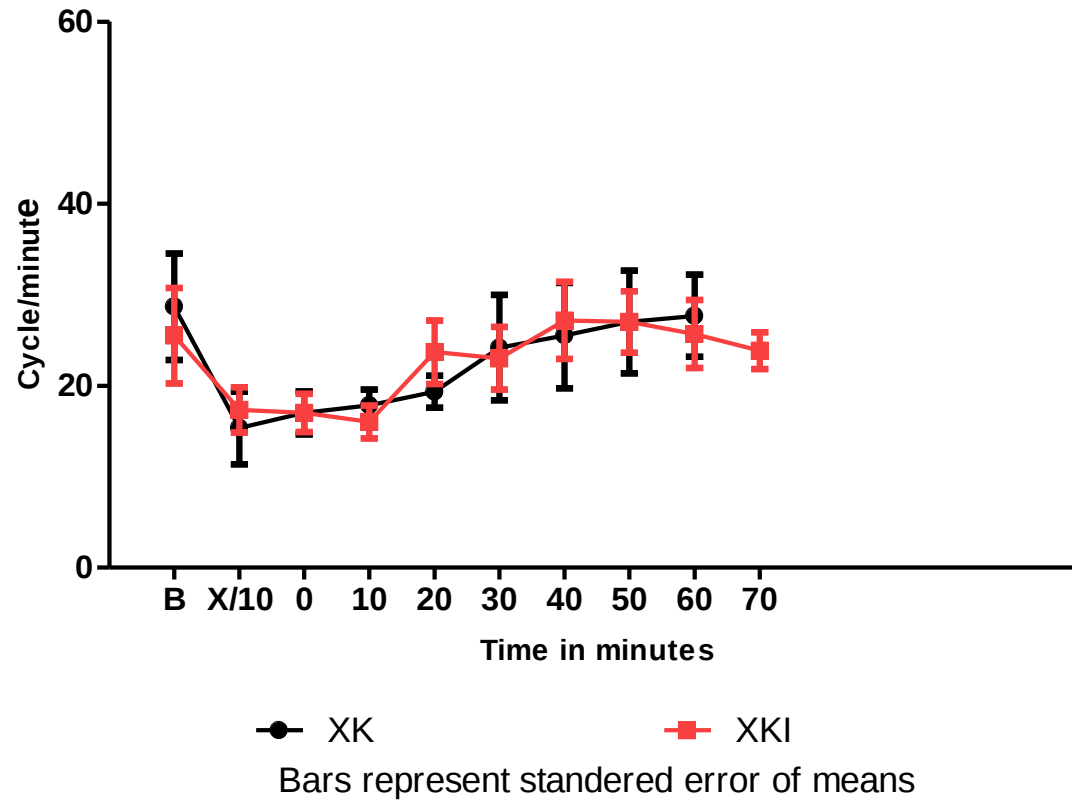


Figure 3.1.1: Effects of induction and maintenance of anaesthesia with Xylazine/Ketamine protocols (XK) on respiratory rate

XK= Xylazine/Ketamine

XKI=Xylazine /Ketamine/Infusion

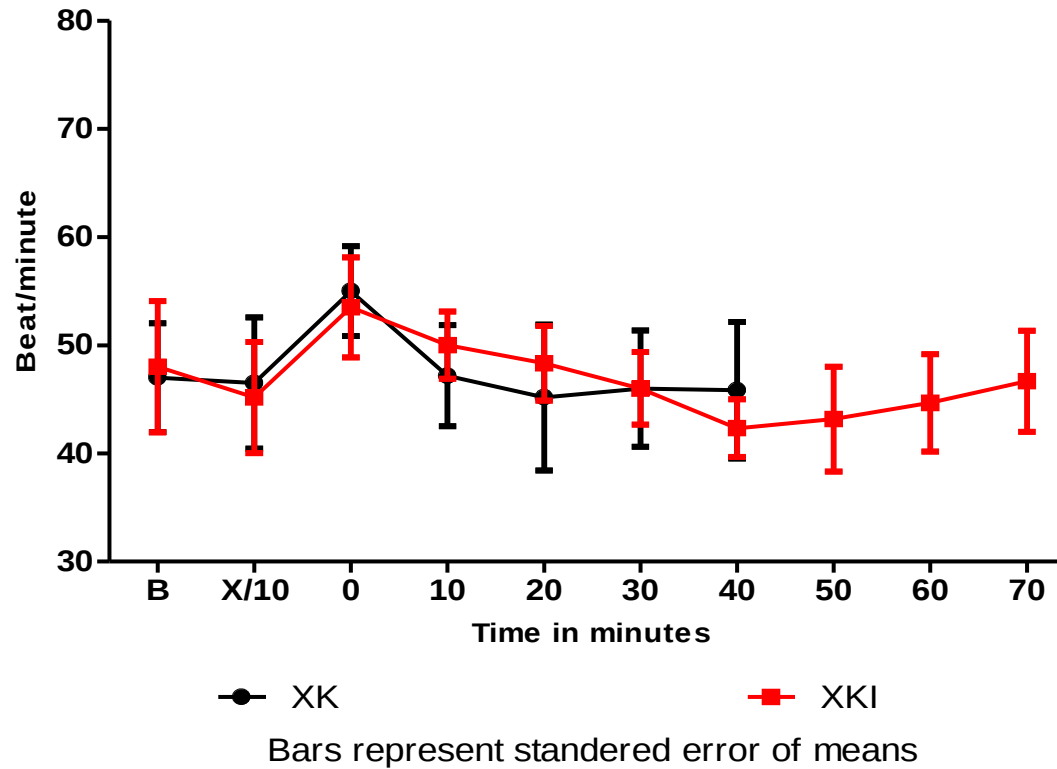


Figure 3.1.2: Effects of induction and maintenance of anaesthesia with Xylazine/Ketamine protocols (XK) on heart rate

XK= Xylazine/Ketamine

XKI=Xylazine /Ketamine/Infusion

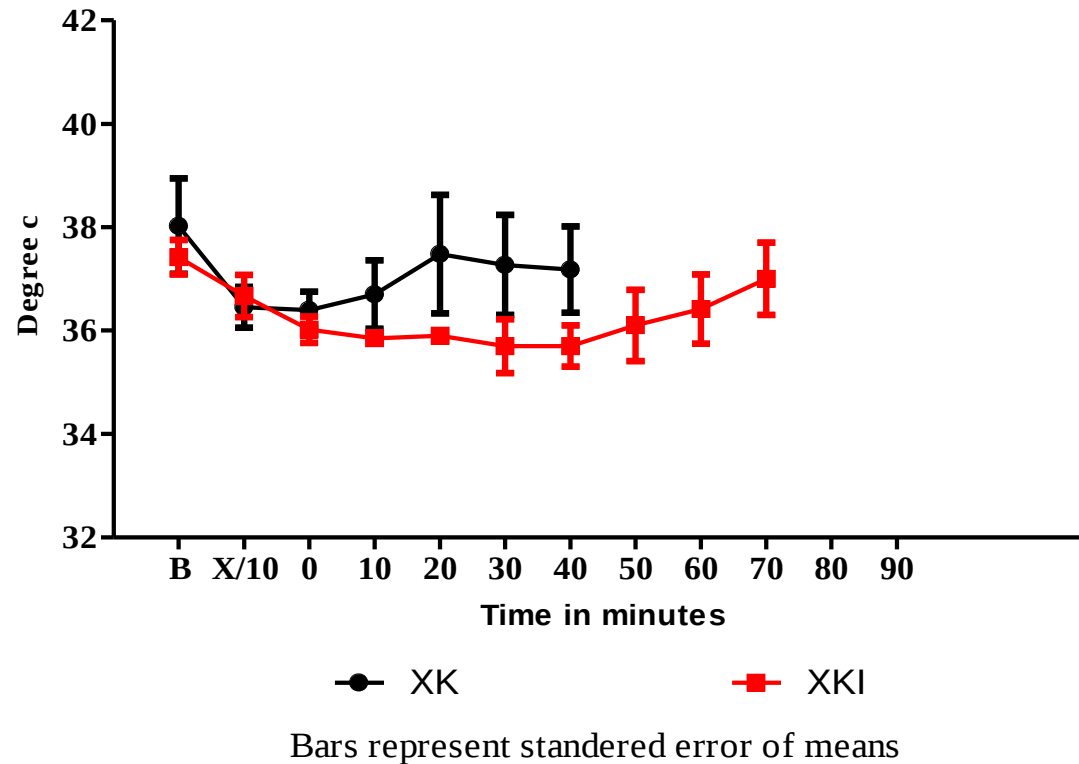


Figure 3.1.3: Effects of induction and maintenance of anaesthesia with Xylazine/Ketamine protocols (XK) on rectal temperature

XK= Xylazine/Ketamine

XKI=Xylazine /Ketamine/Infusion

3.1.5 Blood biochemistry:

Results obtained indicated that induction of anaesthesia with XK resulted in non-significant changes in urea concentration. Induction and maintenance of anaesthesia with XKI resulted in significant increase ($p \leq 0.05$) in urea level at 30, 60 and 90 minutes following induction of anaesthesia compared to the base line values (Table 3.1.5).

Also in Table (3.1.5) it could be observed that, induction of anaesthesia with XK resulted in a significant increase ($p \leq 0.05$) in glucose level at 30, 60 and 90 minutes following induction of anaesthesia when compared with the base line values. Glucose level at 30, 60 and 90 minutes after induction of anaesthesia with XKI was found to be significantly increased ($p \leq 0.05$) compared with the level at base line values. A prominent significant increase in glucose level was observed at 30 minutes following induction and maintenance of anaesthesia with XKI.

Induction of anaesthesia with XK or induction and maintenance of anaesthesia with XKI exhibited non-significant change in ALT level throughout the monitoring period (Table 3.1.5). Also as it could be observed in Table (3.1.5) that AST level exhibited non significant fluctuation in the two protocols tested.

Table 3.1.5: Effects of induction and maintenance of anaesthesia with Xylazine/Ketamine protocols (XK) on some selected blood biochemical constituents

Parameters	Protocol	Base	30	60	90
	S				
Urea (mmol/l)	XK	2.71±0.40 a	3.60±1.71 a	3.99±1.39 a	4.13±1.33 a
	XKI	2.73±0.17a	5.06±0.68b	4.51±0.59b	4.34±0.35b
Glucose (mmol/l)	XK	2.96 ±0.59 a	5.97±0.97 b	6.81±1.15 b	6.92±1.53 b
	XKI	3.61±1.09 a	7.18±0.913 b	5.94±1.74 bc	5.88±1.01c
AST (UI)	XK	80.54±21.16 a	80.21±25.46 a	82.86±22.14 a	83.90±27.50 a
	X KI	104.0±50.80 a	96.35±44.80 a	77.32±17.17 a	78.53±21.19 a
ALT (UI)	XK	4.32±0.48 a	5.12±1.76 a	4.65±0.83 a	5.12±2.07 a
	XKI	7.68±2.45 a	7.10±3.82 a	8.25±3.20 a	7.79±2.49 a

Different letters in the same raw indicate significant difference ($p \leq 0.05$).

XK= Xylazine/Ketamine.

XKI=Xylazine /Ketamine/Infusion.

3.2: Induction and maintenance of anaesthesia with Detomidine/ Ketamine protocols:

3.2.1 Pilot study:

Results obtained following injection of Detomidine at dose rate of 30 µg/kg resulted in mild muscle relaxation, lowering of head, mild ataxia and partial relaxation of penis. Induction of anaesthesia with Ketamine 4mg/kg following premedication with Detomidine 30 µg/kg resulted in rough induction of anaesthesia together with exaggerated muscle rigidity and limb movements and laboured respiratory movements.

Injection of Detomidine at dose rate of 50µg/kg resulted in good muscle relaxation, obvious ataxia and complete protrusion of penis. Induction of anaesthesia with Ketamine at dose rate of 4mg/kg after premediation with Detomidine at dose rate of 50 µ/kg resulted in good induction with no muscle rigidity, no limb movement and no respiratory distress.

The study revealed that the dose of 30 µg/kg of Detomidine is not enough to tolerate the muscle rigidity caused by Ketamine. The dose of 50 µg/kg of Detomidine was chosen for the study.

3.2.2 Signs and observations following injection of Detomidine:

Following intravenous injection of Detomidine 50µ/kg in donkeys, main signs observed were dropping of the head, lowering the lip, abduction of the legs, protruding of the penis, profound ataxia and continuous nose blowing and

rubbing of the upper lip and gum with the foot or even the ground .

3.2.3 Quality of induction, muscle relaxation and recovery:

Table (3.2.1) illustrate the effect of induction of anaesthesia with DK and induction and maintenance of anaesthesia with DKI on induction quality. It revealed that Induction quality observed to occur as a result of anaesthesia with DK was rated as smooth in 50% and fair in the other 50% of the total number of animals used in the study. Smooth induction was observed to occur in 66.6% of total number of animals anaesthetized with DKI while fair induction observed in 33.3% of the group.

Table (3.2.2) shows the effect of induction of anaesthesia with DK and induction and maintenance of anaesthesia with DKI on muscle relaxation and it revealed that induction of anaesthesia with DK resulted in muscle relaxation for 10 minutes while induction and maintenance anaesthesia with DKI resulted in muscle relaxation for more than 40 minutes. Immediately after induction of anaesthesia with DK good muscle relaxation was observed to occur in 50% of the total animals used in the study. Immediately after induction of anaesthesia with DKI good muscle relaxation was observed to occur in 66.6% while poor muscle relaxation was observed to occur in the other 33.3% of the animals used in the study.

Good muscle relaxation was observed in the whole group of animals anaesthetized with DKI 10 minutes after

induction of anaesthesia and this good relaxation lasted for more than 40 minutes following induction of anaesthesia. Poor muscle relaxation was observed in all animals anaesthetized with DK 20 minutes following induction of anaesthesia. All animals anaesthetized with DKl lost their muscle relaxation 50 minutes after induction of anaesthesia and poor muscle relaxation occurred in the whole group of animals used in the study.

As illustrated in Table (3.2.3) it could be observed that recovery from induction of anaesthesia with DK was smooth in quality in 50% and fair in the other 50% of the total animals used in the study. Recovery from anaesthesia with DKl was poor in quality in 50% and very poor in the other 50% of the total animals used in the study.

Table 3.2.1: Induction quality following induction and maintenance of anaesthesia with Detomidine/Ketamine protocols (DK)

Total No. of animals	Rough Animals		Fair Animals		Smooth Animals		Scale Protocol
	%	No.	%	No.	%	No.	
	6	-	0	50%	3	50%	
6	-	0	33.3%	2	66.6%	4	DKI

DK=Detomidine/Ketamine

DKI=Detomidine/Ketamine/Infusion

Table 3.2.2: Muscle relaxation quality following induction and maintenance of anaesthesia with Detomidine /Ketamine protocols (D/K)

50			40			30			20			10			0			Time
E	G	P	E	G	P	E	G	P	E	G	P	E	G	P	E	G	P	Scale
0	0	6	0	0	6	0	0	6	0	0	6	0	4	2	0	3	3	DK
0	0	6	0	6	0	0	6	0	0	6	0	0	6	0	0	4	2	DKI

P= poor, G =good, E= excellent

DK=Detomidine/Ketamine

DKI=Detomidine/Ketamine/Infusion

Table 3.2.3: Recovery quality following induction and maintenance of anaesthesia with Detomidine /Ketamine protocols (D/K)

Scale	Smooth		Fair		Poor		Very poor		Total
Protocol	No.	%	No.	%	No.	%	No.	%	Animals
DK	3	50%	3	50%	0	-	0	-	6
DKI	0	-	0	-	3	50%	3	50%	6

DK= Detomidine +Ketamine.

DKI= Detomidine+Ketamine and maintenance with Detomidine and Ketamine.

3.2.4 Anaesthetic phases:

Table (3.2.4) elaborates the effect of induction of anaesthesia with DK and induction and maintenance of anaesthesia with DKI. It reflected that a significant difference ($p \leq 0.05$) was observed between the duration of analgesia phase resulted from induction of anaesthesia with DK and the duration of analgesia phase resulted from induction and maintenance of anaesthesia with DKI where the later was found to be significantly longer ($p \leq 0.05$). Lateral recumbancy phase resulted from induction and maintenance of anaesthesia with DKI was found to be significantly longer ($p \leq 0.05$) than the duration of lateral recumbancy phase resulted from induction of anaesthesia with DK. Sternal recumbancy phase duration resulted from induction with DK and induction and maintenance with DKI were found to be non-significantly different from each other. Standing phase and total recovery time resulted from induction and maintenance of anaesthesia with DKI were found to be significantly longer ($p \leq 0.05$) than the duration of same phases resulted from induction of anaesthesia with DK.

Table 3.2.4: Duration of different anaesthetic phases (mins.) following induction and maintenance of anaesthesia with Detomidine/Ketamine protocols (D/K)

Phase (min)	Analgesia	Lateral recumbancy	Sternal recumbancy	Standing phase	Total recovery time
DK	11.50±3.78	22.00±4.71 a	11.6±2.50a	3.83±1.72a	37.67±6.47a
DKI	41.17±4.91 a	79.67±3.40 b	18.17±6.40a	16.33±4.68b	114.2±10.21b
	b				

DK=Detomidine/Ketamine.

DKI=Detomidine/Ketamine/Infusion.

Time in minutes.

Different letters in the same row indicate significant difference ($p \leq 0.05$).

3.2.5 Physiological parameters:

As illustrated in Figure (3.2.1) induction of anaesthesia with DK resulted in a non significant drop in the respiratory rate 10 minutes after injection of Detomidine while the decrease in the respiratory rate was found to be of significant value ($p \leq 0.05$) immediately after induction of anaesthesia and 10 minutes following induction of anaesthesia compared to the base line values. Induction and maintenance of anaesthesia with DKI resulted in a significant decrease ($p \leq 0.05$) in the respiratory rate occurred 10 minutes after injection of Detomidine and it remained at significantly decreased level ($p \leq 0.05$) until 30 minutes following induction of anaesthesia. At 40 minutes after induction of anaesthesia a significant ($p \leq 0.05$) increase in the respiratory rate was observed to occur and it remained at high level until full recovery was attained.

Non- significant change in the heart rate was observed to occur as a result of induction of anaesthesia with DK and induction and maintenance of anaesthesia with DKI as illustrated in Figure (3.2.2).

As we could observe in Figure (3.2.3) induction of anaesthesia with DK resulted in significant drop ($p \leq 0.05$) in rectal temperature 10 minutes after injection of Detomidine and it remained so up to 10 minutes following induction of anaesthesia. Induction and maintenance of anaesthesia with DKI in the second group resulted in significant drop ($p \leq 0.05$) in rectal temperature 10 minutes after injection of Detomidine and remained at significantly decreased level

($p \leq 0.05$) until 30 minutes following induction and maintenance of anaesthesia with DKI.

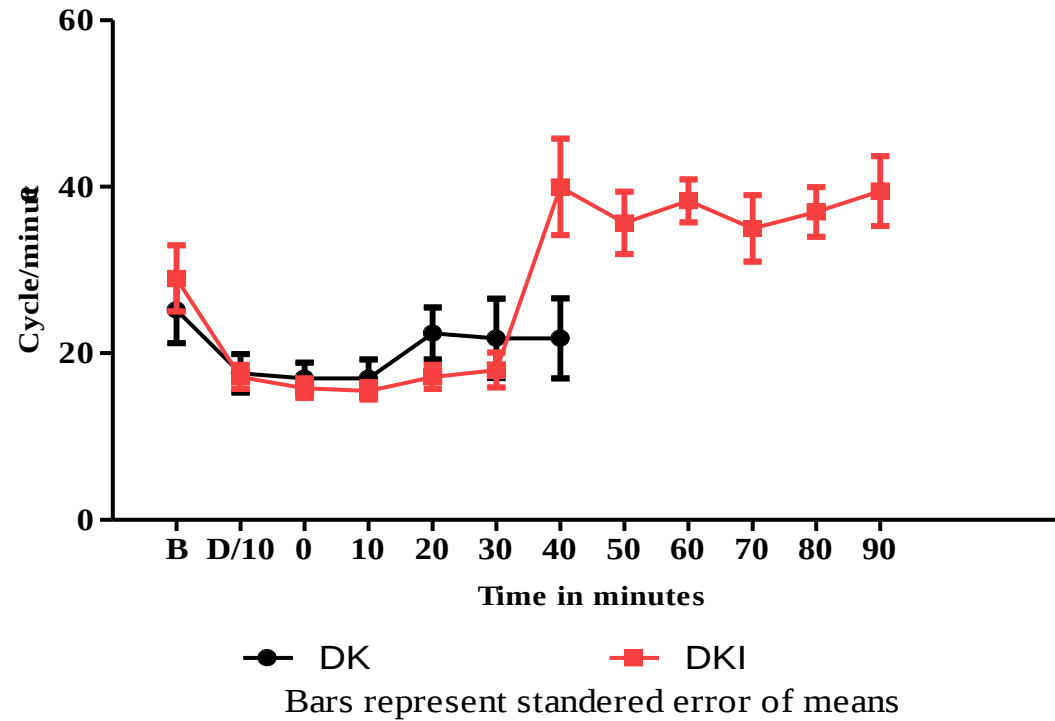


Figure 3.2.1: Effects of induction and maintenance of anaesthesia with Detomidine/Ketamine protocols (DK) on respiratory rate.

DK=Detomidine/Ketamine
 DKI=Detomidine/Ketamine/Infusion

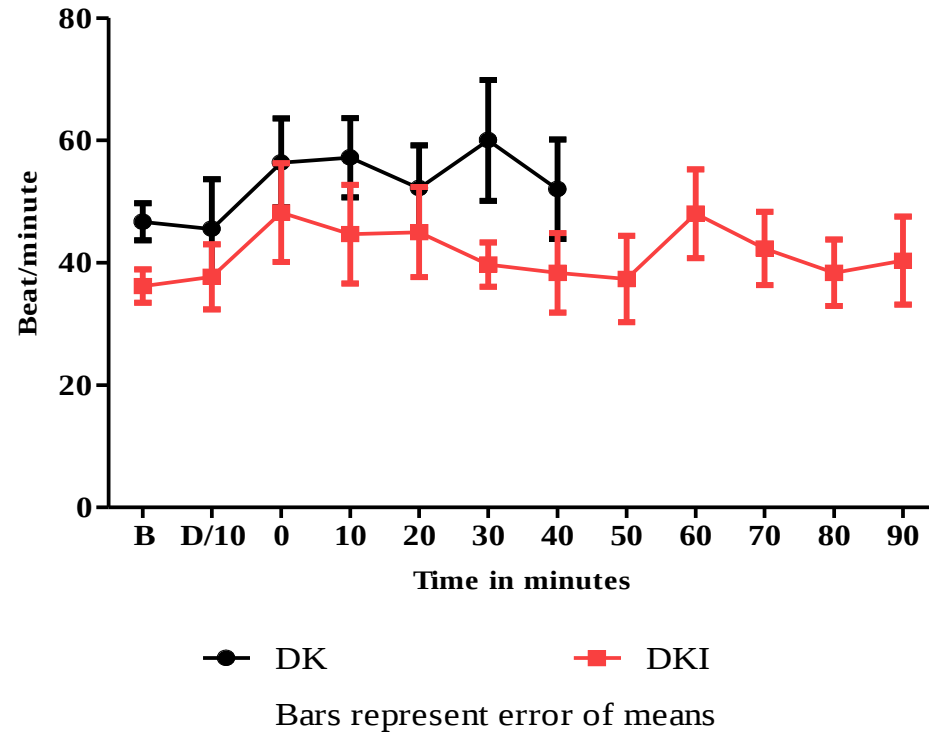


Figure 3.2.2: Effects of induction and maintenance of anaesthesia with Detomidine/Ketamine protocols (DK) on heart rate

DK=Detomidine/Ketamine
 DKI=Detomidine/Ketamine/Infusion

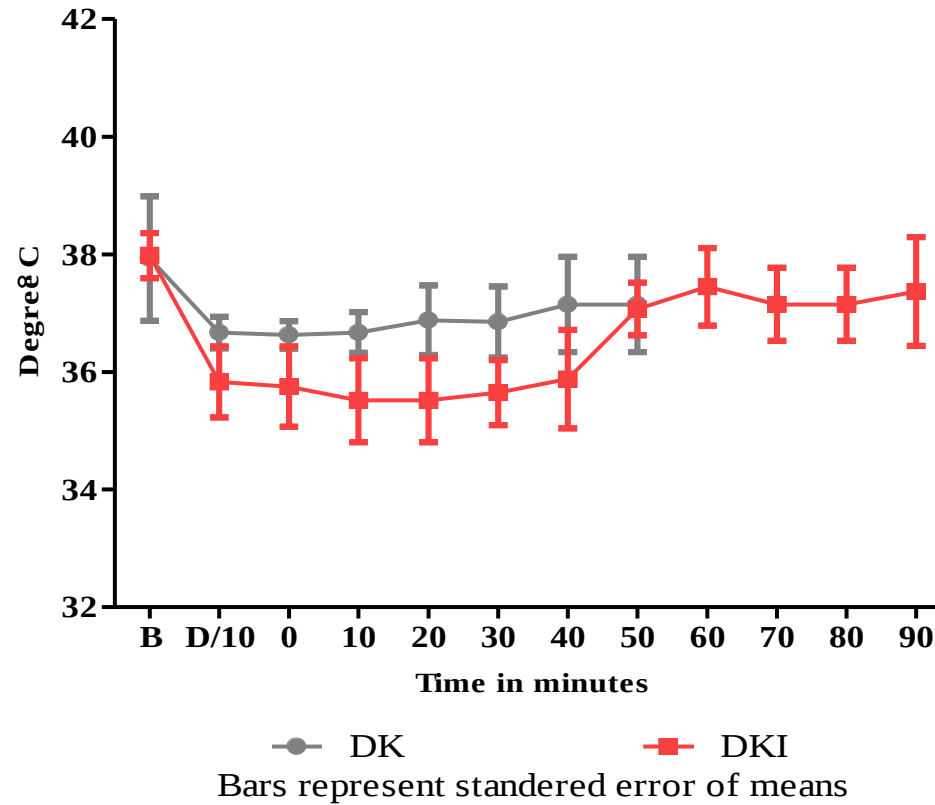


Figure 3.2.3: Effect of induction and maintenance of anaesthesia with detomidine/Ketamine protocol (DK) on rectal temperature

DK=Detomidine/Ketamine
DKI=Detomidine/Ketamine/Infusion

3.2.6 Blood biochemistry:

Table (3.2.5) show the effect of induction of anaesthesia with DK or induction and maintenance of anaesthesia with DKl on some blood biochemical constituents.

Results obtained indicated that induction of anaesthesia with DK resulted in non-significant change in the concentration of urea. While induction and maintenance of anaesthesia with DKl resulted in significant change ($p \leq 0.05$) in urea level at 30, 60 and 90 minutes following induction of anaesthesia when compared to the base line values.

Significant increase ($p \leq 0.05$) in glucose level was observed only at 90 minutes following induction of anaesthesia with DK when compared to the base line values. It is worth to mention that, this increase is of no significant difference when compared with the values reported at 30 and 60 minutes following induction of anaesthesia in the same group. A significant ($p \leq 0.05$) increase in glucose level resulted following induction and maintenance of anaesthesia with DKl at 30, 60 and 90 minutes when compared to the base line values of plasma glucose.

Non-significant change was observed in ALT activity following induction of anaesthesia using DK and induction and maintenance of anaesthesia with DKl in both groups, respectively. AST activity exhibited non-significant change as a result of induction of anaesthesia and induction and maintenance of anaesthesia with DK and DKl, respectively.

Table 3.2.5: Effects of induction and maintenance of anaesthesia with Detomidine/Ketamine protocols (D/K) on some selected blood biochemical constituents

Parameters (unit)	Protocols	Time (minutes)			
		Base	30	60	90
Urea (mmol/l)	DK	2.93 ±0.48a	3.62±0.82a	3.98±0.97a	4.49±1.17a
	DKI	3.16 ±0.69a	5.36±0.47b	5.32±0.35b	5.54±0.48b
Glucose (mmol/l)	DK	4.49 ±0.08a	4.72 ±0.44ab	5.33 ±1.20ab	7.12 ±1.65b
	DKI	3.16 ±0.56a	5.89 ±1.91ab	5.99 ±2.56ab	7.24 ±2.64b
ALT (UI)	DK	3.84 ±1.40 a	5.35 ±1.61 a	4.37 ±1.39 a	5.49 ±2.05 a
	DKI	7.68 ±2.45 a	7.10 ±3.82 a	8.25 ±3.20 a	7.79 ±2.49 a
AST (UI)	DK	87.95 ±35.67a	84.04 ±18.26a	103.5 ±31.09a	101.5 ±29.57a
	DKI	91.14 ±18.60a	110.7 ±33.96a	117.6 ±36.65a	129.1 ±39.60a

DK= Detomidine 50µg/kg + Ketamine 4mg/kg (DK)

DKI= Detomidine 50µg/kg + Ketamine 4mg/kg + Infusion (Detomidine 50µg/kg + Ketamine 6mg/kg) in saline solution (DKI).

Different letters in the same raw indicate significant difference ($p \leq 0.05$).

3.3 Induction and maintenance of anaesthesia with Romifidine/Ketamine protocols:

3.3.1 Pilot study:

Results obtained from the second pilot study revealed that injection of Romifidine at dose rate of 60 µg/kg resulted in mild muscle relaxation, the animals did not stop moving, did not stop eating, mild ataxia, partial protrusion of penis. Induction of anaesthesia with Ketamine 4mg/kg after premedication with Romifidine 60 µg/kg resulted in very rough induction with excitement, exaggerated limb movement and laboured respiration. Injection of Romifidine at dose rate of 100µg/kg resulted in obvious muscle relaxation, no movement of the animal, penis relaxation, ataxia, and lowering of head. Induction of anaesthesia with Ketamine 4mg/kg after premedication with Romifidine 100µg/kg minimal muscle rigidity and very slight limb movement.

The study revealed that the dose of 60 µ/kg of Romifidine is not enough to tolerate the muscle rigidity caused by Ketamine. The dose of 100 µ/kg of Romifidine was chosen for the study.

3.3.2 Signs and observations following injection of Romifidine:

Following intravenous injection of Romifidine 100µ/kg in donkeys, main signs observed were dropping of the head, lowering the lip, abduction of the legs, protruding of the penis, sometimes ataxia and sometimes nose blowing and

rubbing of the upper lip and gum with the foot or even the ground .

3.3.3 Quality of anaesthetic induction, muscle relaxation and recovery:

Smooth induction of anaesthesia was observed in 66.6%, while fair induction was observed to occur in 33.3% of the total number of animals anaesthetized with RK (Table 3.3.1). Induction and maintenance of anaesthesia with RKI resulted in smooth and fair induction to occur at the same percentage namely 50% in the total number of the animals used.

As could be observed in Table (3.3.2) immediately following induction of anaesthesia with RK quality of muscle relaxation was found to be good in 66.6% and poor in 33.3% of the total animals used in the study. 10 minutes after induction of anaesthesia good muscle relaxation was observed to occur in the whole group of animals used in the study. 20 minutes after induction of anaesthesia poor muscle relaxation was found to occur in the whole group of animals used in the study.

Induction and maintenance of anaesthesia with RKI resulted in poor muscle relaxation in 50% animals and good muscle relaxation in the other 50% of the animals used in the study immediately after induction of anaesthesia. 10 minutes after induction and maintenance of anaesthesia with RKI poor muscle relaxation observed in 16.6% while good muscle relaxation occurred in 83.3% of the animals used in the study. 50 minutes after induction and maintenance of

anaesthesia with RKI poor muscle relaxation occurred in all of the animals used in the study.

Table (3.3.3) elaborate the effect of induction of anaesthesia with RK and induction and maintenance of anaesthesia with RKI on quality of recovery. It reflected that induction of anaesthesia with RK resulted in smooth recovery in 66.6% and fair recovery in 33.4% of the total number of animals used in the study. Induction and maintenance of anaesthesia with RKI resulted in smooth recovery in 33.3%, fair recovery in 33.3% and poor recovery in 33.3% of the total number of animals used in the study. Very poor recovery was not found to occur as result of using RKI for induction and maintenance of anaesthesia.

Table 3.3.1: Induction quality following induction and maintenance of anaesthesia with Romifidine/Ketamine protocols (R/K)

Total animals	Rough		Fair		Smooth		Scale Protocol
	%	No.	%	No.	%	No.	
6	-	0	33.3%	2	66.7%	4	RK
6	-	0	50%	3	50%	3	RKI

RK=Romifidine/Ketamine.

RKI= Romifidine/Ketamine Infusion.

Table 3.3.2: Muscle relaxation quality following induction and maintenance of anaesthesia with Romifidine/Ketamine protocols (RK)

50			40			30			20			10			0			Time			
Animals			Animals			Animals			Animals			Animals			Animals						
E	G	P	E	G	P	E	G	P	E	G	P	E	G	P	E	G	P	E	G	P	Scale
0	0	6	0	0	6	0	0	6	0	0	6	0	0	6	0	4	2	0	4	2	RK
0	0	6	0	5	1	0	5	1	0	5	1	0	5	1	0	3	3	0	3	3	RKI

P= poor, G= good, E=excellent

RK=Romifidine/Ketamine.

RKI= Romifidine/Ketamine Infusion.

Table 3.3.3: Recovery quality following induction and maintenance of anaesthesia with Romifidine/Ketamine protocols (RK)

Scale	Smooth		Fair		Poor		Very poor		Total Animals
Protocol	No.	%	No.	%	No.	%	No.	%	
RK	4	66.6	2	33.4	0	--	0	0	6
RKI	2	33.3	2	33.33	2	33.3	0	0	6

RK=Romifidine/Ketamine.

RKI= Romifidine/Ketamine/Infusion.

3.3.4 Anaesthetic phases:

Table (3.3.4) elaborate the effect of induction of anaesthesia with RK and induction and maintenance of anaesthesia with RKI on different phases of anaesthesia. It shows that a significant increase ($p \leq 0.05$) in the duration of analgesia phase was observed as a result of using RKI for induction and maintenance of anaesthesia when compared to analgesia phase resulted from induction of anaesthesia with RK.

Induction and maintenance of anaesthesia with RKI resulted in lateral recumbancy phase that was found to be significantly longer ($p \leq 0.05$) in duration when compared to the lateral recumbancy phase resulted from induction of anaesthesia with RK. Also the duration of sternal recumbancy phase resulted from induction and maintenance of anaesthesia with RKI was significantly longer ($p \leq 0.05$) in duration when compared with that resulted from induction of anaesthesia with RK. Induction and maintenance of anaesthesia with RKI resulted in standing phase which was found to be significantly longer ($p \leq 0.05$) when compared to the standing phase resulted from using RK for induction of anaesthesia. Total recovery time needed by the animals anaesthetised with RKI was found to be significantly longer ($p \leq 0.05$) than the time needed by the animals anaesthetised by RK to get full recovery.

Table 3.3.4: Duration of different anaesthetic phases (mins.) following induction and maintenance of anaesthesia with Romifidine/Ketamine protocols (R/K)..

Phase	Analgesia	Lateral recumbancy	Sternal recumbancy	Standing phase	Total recovery time
RK	12.33±	16.83±1.53a	3.33±1.63a	2.83±1.84a	23.00±2.76a
RKI	5.27a 39.00±	51.50±4.82b	11.50±4.50b	9.00±3.07b	78.00±15.76b
	4.24b				

RK=Romifidine/Ketamine

RKI= Romifidine/Ketamine/Infusion

Time in minutes

Different letters in the same column indicate significant difference ($p \leq 0.05$).

3.3.5 Physiological parameters:

Induction of anaesthesia with RK resulted in a significant decrease ($p \leq 0.05$) in the respiratory rate 10 minutes following injection of Romifidine. The respiratory rate returned to the normal rate 10 minutes after induction of anaesthesia (Figure 3.3.1). Induction and maintenance of anaesthesia with RKI resulted in a significant decrease ($p \leq 0.05$) in the respiratory rate at 10 minutes following injection of Romifidine and at 10, 20 and 30 minutes following induction of anaesthesia.

Induction of anaesthesia with RK and induction and maintenance of anaesthesia with RKI were found to cause non-significant changes in the heart rate as shown in (Figure 3.3.2).

As we could observe in Figure (3.3.3) induction of anaesthesia with RK resulted in significant decrease ($p \leq 0.05$) in the rectal temperature 10 minutes after injection of Romifidine. Induction and maintenance of anaesthesia with RKI resulted in significant decrease ($p \leq 0.05$) in rectal temperature 10 minutes after injection of Romifidine and it remained at significantly decreased ($p \leq 0.05$) level until 50 minutes after induction of anaesthesia.

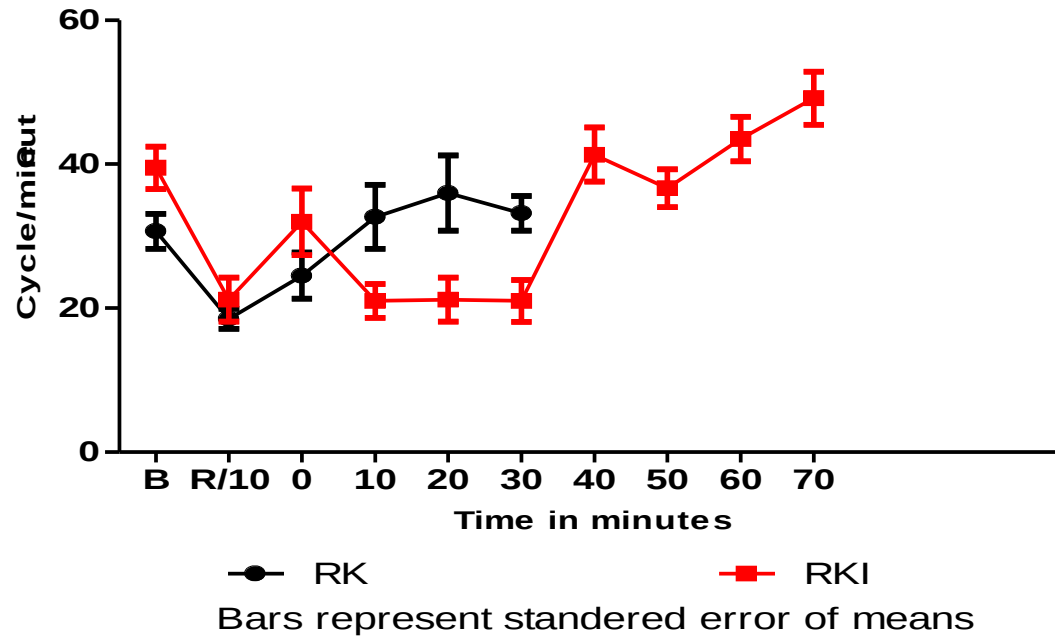


Figure 3.3.1: Effects of induction and induction and maintenance of anaesthesia with Romifidine/Ketamine protocols (RK) on respiratory rate

RK=Romifidine/Ketamine
 RKI= Romifidine/Ketamine/Infusion

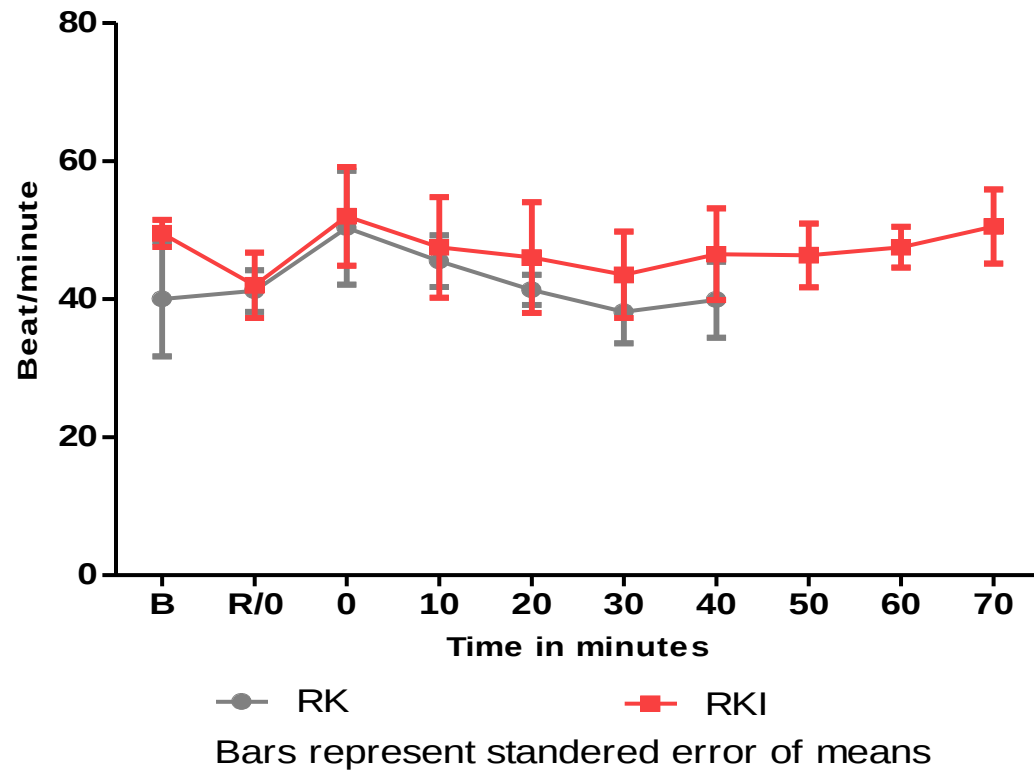


Figure 3.3.2: Effects of induction and maintenance of anaesthesia with Romifidine/Ketamine protocols (RK) on heart rate.

RK=Romifidine/Ketamine.
RKI= Romifidine/Ketamine/Infusion.

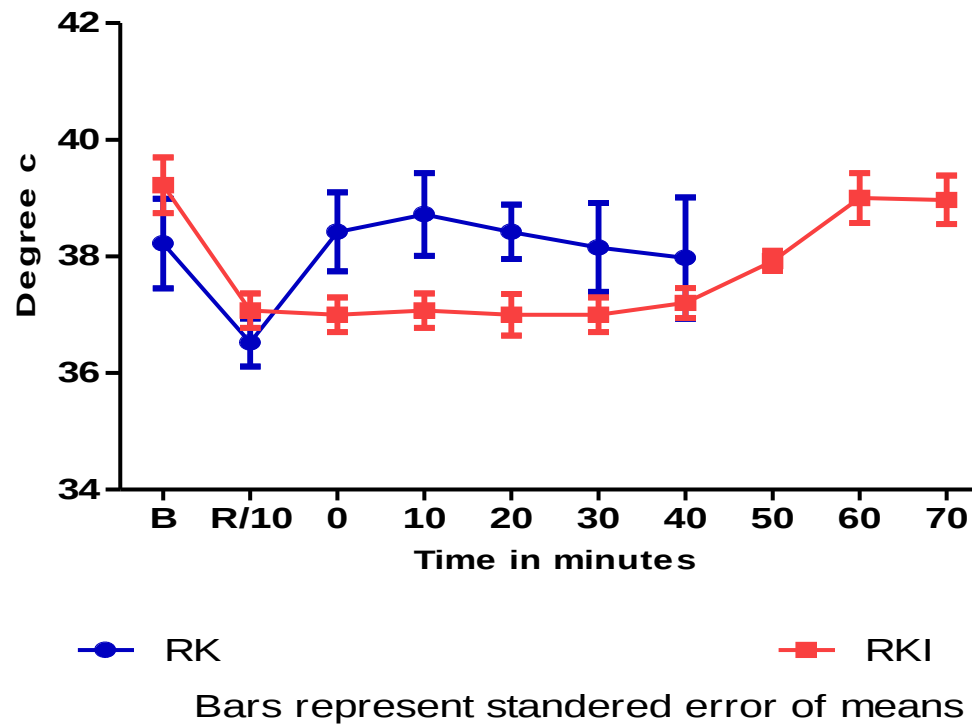


Figure 3.3.3: Effects of induction and maintenance of anaesthesia with Romifidine/Ketamine protocols (RK) on rectal temperature.

RK=Romifidine/Ketamine.

RKI= Romifidine/Ketamine/Infusion.

3.3.6 Blood biochemistry:

Table (3.3.5) shows the effect of induction of anaesthesia with RK and induction and maintenance of anaesthesia with RKI on some blood biochemical constituents.

Induction of anaesthesia with RK and induction and maintenance of anaesthesia with RKI resulted in significant increase ($p \leq 0.05$) in urea level at 30, 60 and 90 minutes following induction of anaesthesia when compared to the base line values.

Glucose level exhibited non-significant change following induction of anaesthesia and induction and maintenance of anaesthesia with RK and RKI, respectively.

ALT activity showed non-significant change as a result of induction of anaesthesia with RK and induction and maintenance of anaesthesia with RKI. Also non-significant change was observed to occur in AST activity as a result of induction or induction and maintenance of anaesthesia with RK or RKI respectively.

Table 3.3.5: Effects of induction and maintenance of anaesthesia with Romifidine/Ketaminr protocols (RK) on some selected blood biochemical constituents

Parameters (unit)	Protocols	Time (minutes)			
		Base	30	60	90
Urea (mmol/l)	RK	3.98±0.52a	5.46±0.57b	5.55±0.73b	5.51±0.89b
	RKI	3.49±0.77a	5.02±0.66b	5.02±0.89b	4.94±0.88b
Glucose (mmol/l)	RK	3.77±1.28a	4.47±1.73a	5.43±2.11a	5.48±2.37a
	RKI	3.20±0.97a	4.26±1.31a	5.67±1.491a	5.83±2.60a
ALT (UI)	RK	6.83±3.63 a	6.78±1.59 a	6.52±1.26 a	6.15±1.52 a
	RKI	7.90±1.34 a	7.68±0.756 a	8.35±1.46 a	9.50±2.18 a
AST (UI)	RK	81.13±5.51 a	82.99±6.23 a	80.19±8.57 a	77.40±8.83 a
	RKI	84.62±11.03 a	79.96±6.94 a	79.94±19.08 a	84.44±7.93 a

Different letters in the same raw indicate significant difference ($p \leq 0.05$).

RK=Romifidine/Ketamine.

RKI= Romifidine/Ketamine/Infusion.

3.4: Evaluation of total intravenous anaesthesia (TIVA) for surgical interference (laparotomy):

3.4.1 Quality of anaesthetic induction, muscle relaxation and recovery:

Table (3.4.1) shows the effect of induction and maintenance of anaesthesia with Xylazine / Ketamine /Infusion (XKIS), Detomidine/ Ketamine/Infusion (DKIS) and Romifidine/Ketamine/Infusion (RKIS) together with performing surgery on the quality of induction of anaesthesia. Results obtained revealed that smooth induction was observed to occur in 66.7%, 33.3% and 33.3% as a result of using XKIS, DKIS and RKIS , respectively. Fair induction was observed to occur in 33.3%, 66.6% and 66.6% as a result of using XKIS, DKIS and RKIS, respectively. Muscles of the abdominal was found to be satisfactory relaxed and none of the surgeons complained from muscle rigidity during performing laparotomy.

Table (3.4.2) illustrate the effect of anaesthesia with XKIS, DKIS and RKIS together with performance of surgery on abdominal muscle relaxation. It revealed that usage of XKIS resulted in excellent and satisfactory muscle relaxation in 66.6% and 33.4% respectively in the whole group of animals at the beginning of surgery. Ten minutes after induction of anaesthesia the whole group of animals exhibited excellent muscle relaxation. At 20 minutes after induction of anaesthesia excellent and satisfactory muscle relaxation was observed to occur in 66.65 and 33.4% of the animals used in the study respectively. At 30 minutes after induction of

anaesthesia 33.3% of the tested group showed excellent muscle relaxation and 66.6% showed satisfactory muscle relaxation. After 40 minutes from induction of anaesthesia excellent, satisfactory and normal muscle relaxation occurred at equal percentages. Usage of DKIS for anaesthesia and surgery resulted in excellent muscle relaxation in the whole group at animals at the beginning of surgery and at 10 minutes after induction of anaesthesia. Excellent and satisfactory muscle relaxation observed to occur in 66.6% and 33.4% of the animals used in the study respectively up to 40 minutes after induction of anaesthesia. Usage of RKIS resulted in excellent and satisfactory muscle relaxation in 66.6% and 33.4% respectively in the whole group of animals at the beginning of surgery. Ten minutes after induction of anaesthesia the whole group of animals exhibited excellent muscle relaxation. At 20 minutes after induction of anaesthesia excellent and satisfactory muscle relaxation observed to occur in 33.4% and 66.6% of the animals used in the study respectively. At 30 minutes after induction of anaesthesia 66.6% of the tested group showed excellent muscle relaxation and 33.3% showed satisfactory muscle relaxation. After 40 minutes from induction of anaesthesia excellent, satisfactory and normal muscle relaxation occurred at equal percentages.

Table (3.4.3) elaborate the effect of induction and maintenance anaesthesia with the above mentioned protocols together with performing of laparotomy on recovery quality. It reflected that smooth and fair recovery

following anaesthesia induction and maintenance with XKSI together with performance of surgery was observed to occur in 33.3% and 66.6% of the investigated animals, respectively. Using DKIS for induction and maintenance of anaesthesia and performing surgery resulted in fair recovery in 33.3% and poor recovery in 66.7% of the animals in this group, respectively. All the donkeys anaesthetized with RKIS for surgery showed smooth recovery.

Table 3.4.1: Induction quality following induction and maintenance anaesthesia with XKIS, DKIS and RKIS

Rough		Fair		Smooth		Scale
%	No.	%	No.	%	No.	Protocol
00	00	33.3%	2	66.6%	4	XKIS
00	00	66.6%	4	33.3%	2	DKIS
00	00	66.6%	4	33.3%	2	RKIS

- XKIS=Xylazine/Ketamine/Infusion with performing laparotomy
- DKIS= Detomidine/Ketamine/Infusion with performing laparotomy
- RKIS= Romifidine/Ketamine/Infusion with performing laparotomy

Table 3.4.2: Effects of induction and maintenance of anaesthesia with XKIS,DKIS and RKIS during performance of laparotomy on abdominal muscle relaxation muscle relaxation

50				40				30				20				10				0				Time				
Animals				Animals				Animals				Animals				Animals				Animals								
P	N	S	E	P	N	S	E	P	N	S	E	P	N	S	E	P	N	S	E	P	N	S	E	P	N	S	E	Scale
-	10	-	-	-	-	-	-	33.	33.	33.	-	-	-	66.	33.	-	-	33.	66.	-	-	-	10	-	-	33.	66.	XKIS
	0							4	4	4				6	4			4	6				0			4	6	
-	10	-	-	-	-	-	-	-	-	33.	66.	-	-	33.	66.	-	-	-	10	-	-	-	10	-	-	-	100	DKIS
	0									4	6			4	6				0				0					
-	10	-	-	-	-	-	-	33.	33.	33.	-	-	-	33.	66.	-	-	-	10	-	-	-	10	-	-	33.	66.	RKIS
	0							4	4	4				4	6				0				0			4	6	

E= Excellent, S= Satisfactory, N = Normal, P=Poor

XKIS= Xylazine/Ketamine/Infusion +Surgery

DKIS= Detomidine/Ketamine/Infusion +Surgery

RKIS= Romifidine/Ketamine/Infusion +Surgery

Zero time= time of starting of surgery

10=10 minutes after induction of anaesthesia

Table 3.4.3: Quality of recovery resulted from induction and maintenance of anaesthesia with XKIS, DKIS and RKIS during performance laparotomy

Total Animals	Very poor		Poor		Fair		Smooth		Scale
	%	No.	%	No.	%	No.	%	No.	Protocol
6	00	0	00	0	66.6	4	33.3	2	XKIS
6	00	0	66.6	4	33.3	2	00	0	DKIS
6	00	0	00	0	00	0	100	6	RKIS

- XKIS=Xylazine/Ketamine/Infusion with performing laparotomy
- DKIS= Detomidine/Ketamine/Infusion with performing laparotomy
- RKIS= Romifidine/Ketamine/Infusion with performing laparotomy

3.4.2 Anaesthetic phases:

Table (3.4.3) elaborate the effect of induction and maintenance of anaesthesia with XKIS, DKIS and performing surgery on the different anaesthetic phases. It reflected that analgesia phase resulted from using DKIS was found to be significantly longer ($p \leq 0.05$) than the duration of analgesia phase resulted in the animals anaesthetised with XKIS and RKIS. The duration of analgesia phase and the analgesia depth resulted from using of each of the three protocols was found to be enough to perform surgery in the whole group of animals used in the study. Lateral recumbancy phase resulted from induction and maintenance of anaesthesia with DKIS was found also to be significantly longer ($p \leq 0.05$) compared with the duration of lateral recumbancy phase resulted from induction and maintenance of anaesthesia with XKIS and RKIS.

Sternal recumbancy phase duration occurred as a result of induction and maintenance of anaesthesia with RKIS was found to be significantly shorter ($p \leq 0.05$) than the duration of the same phase resulted from induction and maintenance of anaesthesia with XKIS and DKIS. Standing phase resulted from using DKIS for induction and maintenance of anaesthesia was found to be significantly longer ($p \leq 0.05$) compared to the duration of the phase recorded as a result of induction and maintenance of anaesthesia with XKIS and RKIS.

The total recovery time duration observed to occur as a result of induction and maintenance of anaesthesia with DKIS

was found to be significantly longer ($p \leq 0.05$) compared to the duration of the total recovery time resulted from induction and maintenance of anaesthesia with XKIS and RKIS.

Table 3.4.4: Duration of the different anaesthetic phases (mins.) following of induction and maintenance of anaesthesia with XKIS, DKIS and RKIS during performance laparotomy.

Phase	Analgesia	Lateral recumbancy	Sternal recumbancy	Standing phase	Total recovery time
XKIS	36.67 _a				58.00 ± 7.89a
	2.58ab	36.00 ± 4.73 a	11.00 ± 0.89a	6.67 ± 2.73a	
DKIS	39.33 ± 2.58				100.7 ± 4.59b
	b	63.97 ± 9.81 b	15.67 ± 3.65a	20.83 ± 2.04b	
RKIS	31.33 ± 2.60				49.00 ± 6.75a
	a	38.17 ± 4.58 a	6.33 ± 3.60b	7.00 ± 5.36a	

- Time in minutes
- Different letters in the same column indicate significant difference ($p \leq 0.05$).
- XKIS=Xylazine/Ketamine/Infusion with performing laparotomy
- DKIS= Detomidine/Ketamine/Infusion with performing laparotomy
- RKIS= Romifidine/Ketamine/Infusion with performing laparotomy

3.4.3 Physiological parameters:

Induction and maintenance of anaesthesia with XKIS, DKIS and RKIS together with performing of surgery caused different changes on the respiratory rate as elaborated in Figure (3.4.1). Induction and maintenance of anaesthesia with XKIS resulted in a significant decrease ($p \leq 0.05$) in the respiratory rate 10 minutes after injection of Xylazine and 10 minutes after induction of anaesthesia. A significant increase ($p \leq 0.05$) in respiratory rate occurred at 40 minutes after induction and maintenance of anaesthesia with XKIS. While, induction and maintenance of anaesthesia with DKIS resulted in non significant decrease in respiratory rate 10 minutes after injection of Detomidine and at 0, 10, 20 and 30 minutes after induction of anaesthesia. Induction and maintenance of anaesthesia with RKIS resulted in a significant decrease ($p \leq 0.05$) in respiratory rate 10 minutes after injection of Romifidine and immediately after induction of anaesthesia.

No significant change in the heart rate was observed following induction of anaesthesia and performing of surgery using XKIS, DKIS and RKIS (Figure 3.4.2).

As we could observe in Figure (3.4.3) induction and maintenance of anaesthesia with XKIS resulted in significant drop ($p \leq 0.05$) in rectal temperature 10 minutes after injection of Xylazine and it remained at significantly decreased ($p \leq 0.05$) level until 40 minutes after induction of anaesthesia. Induction and maintenance of anaesthesia with DKIS resulted in significant decrease ($p \leq 0.05$) in rectal temperature 10 minutes after injection of Detomidine and it

remained at a significantly decreased level up to 50 minutes after induction of anaesthesia. Induction and maintenance of anaesthesia with RKIS resulted in significant decrease ($p \leq 0.05$) in rectal temperature 10 minutes after injection of Romifidine, immediately after induction of anaesthesia and 10 minutes after induction of anaesthesia.

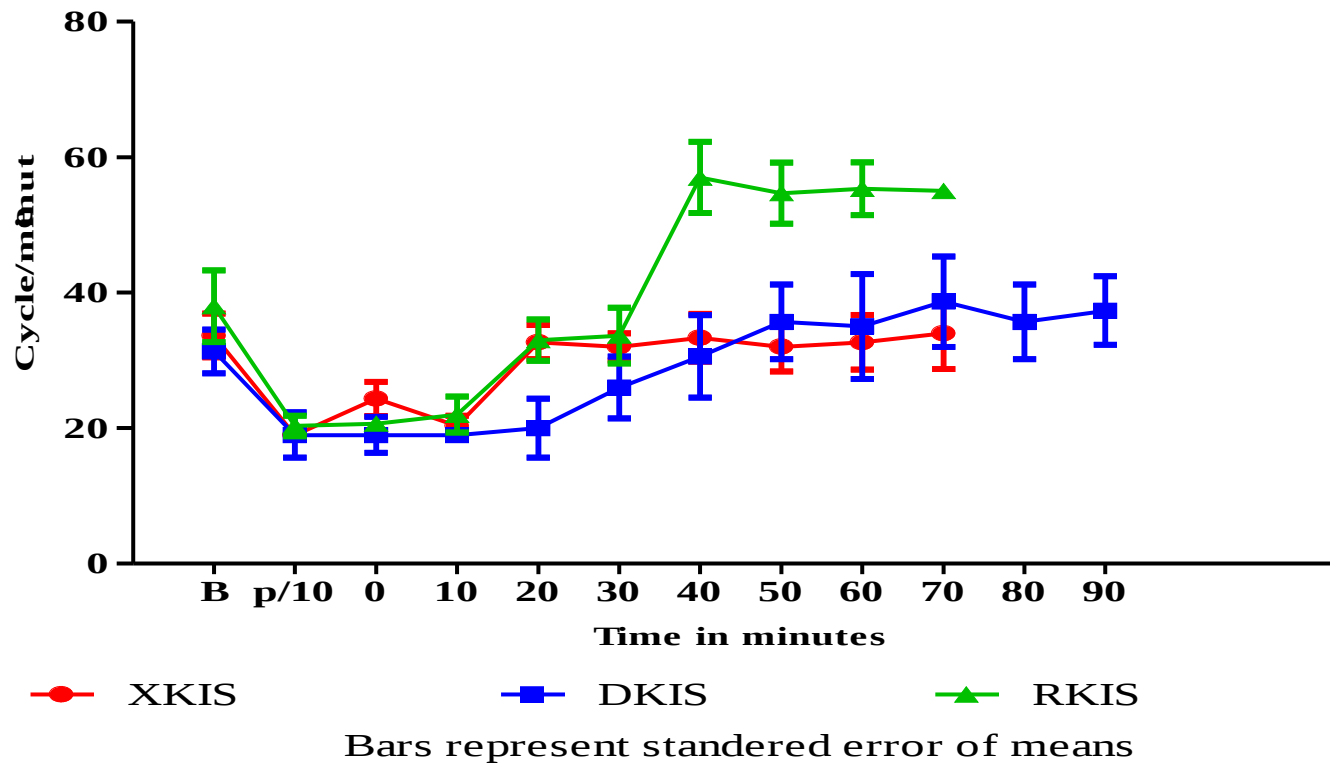


Figure 3.4.1: Effects of induction and maintenance of anaesthesia with XKIS, DKIS and RKIS during performance of laparotomy on respiratory rate

- XKIS=Xylazine/Ketamine/Infusion with performing laparotomy
- DKIS= Detomidine/Ketamine/Infusion with performing laparotomy

- RKIS= Romifidine/Ketamine/Infusion with performing laparotomy

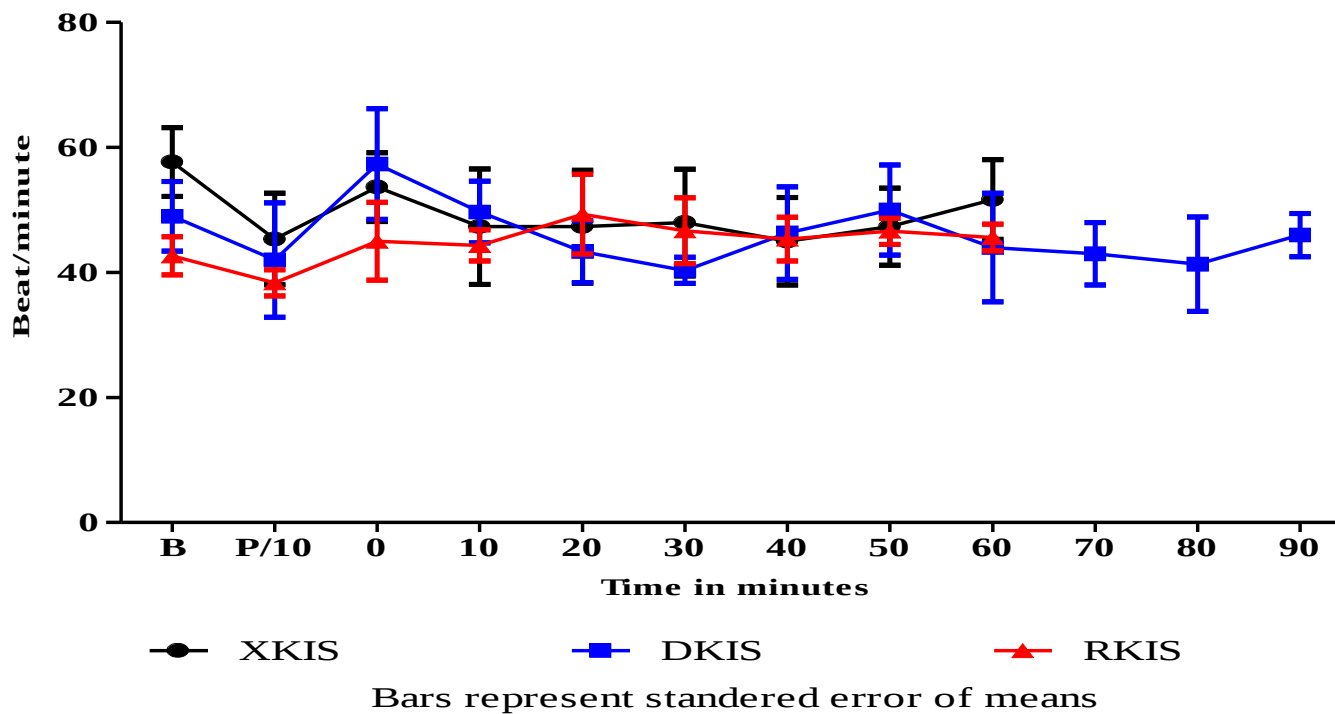


Figure 3.4.2: Effects of induction and maintenance of anaesthesia with XKIS, DKIS and RKIS during performance of laparotomy on heart rate

- XKIS=Xylazine/Ketamine/Infusion with performing laparotomy
- DKIS= Detomidine/Ketamine/Infusion with performing laparotomy
- RKIS= Romifidine/Ketamine/Infusion with performing laparotomy

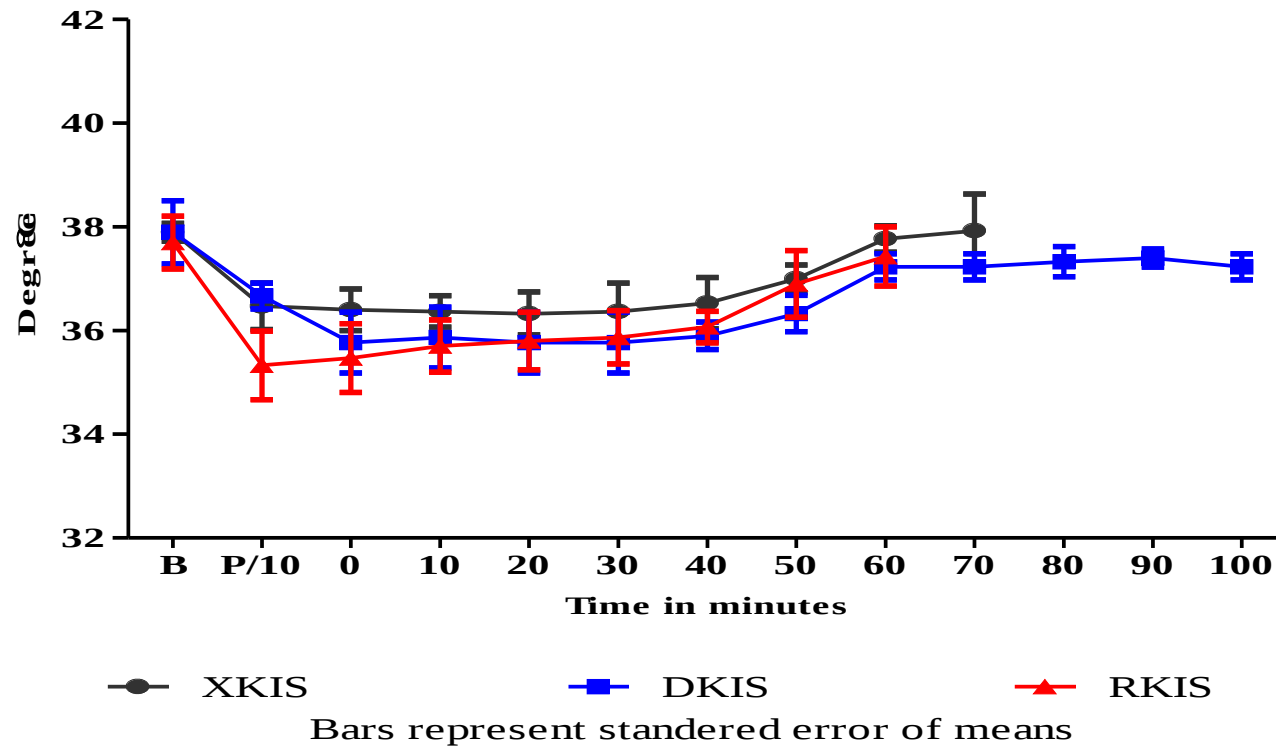


Figure 3.4.3: Effects of induction and maintenance of anaesthesia with XKIS, DKIS and RKIS during performance of laparotomy on rectal temperature

- XKIS=Xylazine/Ketamine/Infusion with performing laparotomy
- DKIS= Detomidine/Ketamine/Infusion with performing laparotomy
- RKIS= Romifidine/Ketamine/Infusion with performing laparotomy

3.4.4 Blood biochemistry:

Table (3.4.3) show the effect of XKIS, DKIS and RKIS and performing surgery on some blood biochemical constituents. Significant change ($p \leq 0.05$) in urea concentration was detected as a result of using XKIS, DKIS and RKIS. The increased level of urea was observed at 30 minutes after induction and it remained until 90 minutes after induction of anaesthesia as shown in Table (3.4.3).

Also significant increase ($p \leq 0.05$) in glucose level resulted at 30, 60 and 90 minutes following induction of anaesthesia with XKIS and performing surgery when compared to the base line values. Induction and maintenance of anaesthesia with DKIS and RKIS and performing surgery resulted in non significant changes of glucose level during the course of anaesthesia and surgery until recovery was attained as illustrated in Table (3.4.3).

No significant change was observed to occur in ALT activity as a result of using the above mentioned protocols for induction and maintenance of anaesthesia and performing surgery. Another non-significant change was observed to occur in the AST activity following induction and maintenance of anaesthesia and performing surgery using the above mentioned protocol as shown in Table (3.4.3).

Table 3.4.4: Effects of induction and maintenance of anaesthesia with XKIS, DKIS and RKIS during performance of laparotomy on some selected blood biochemical constituents

Parameters (unit)	Protocols	Time (minutes)			
		Base	30	60	90
Urea (mmol/l)	XKIS	2.70±0.35a	4.97±0.71b	4.250±0.44b	4.66±0.11b
	DKIS	2.69±0.52a	4.67±0.18b	4.25±0.63b	4.49±0.73b
	RKIS	2.84±0.60a	4.65±0.98b	5.16±0.33b	5.50±0.35b
Glucose (mmol/l)	XKIS	2.32±0.73a	5.32±1.74b	5.73±1.86b	5.41±2.08b
	DKIS	4.09±2.85a	5.00±1.38a	5.02±0.60a	5.16±1.67a
	RKIS	4.05±0.92a	4.86±1.34a	4.80±1.79a	4.85±0.41a
ALT (UI)	XKIS	6.59±0.66a	7.02±1.49a	5.40±1.32a	4.74±0.46a
	DKIS	6.84±1.60a	6.71±1.70a	6.12±1.38a	6.69±1.52a
	RKIS	5.23±1.01a	5.04±0.33a	6.21±2.20a	5.20±1.70a
AST (UI)	XKIS	89.00±38.57a	84.63±37.17a	94.13±41.85a	82.50±22.25a
	DKIS	123.3±49.17a	149.7±9.07a	154.3±25.11a	158.3±30.07a
	RKIS	97.00±19.70a	94.33±25.42a	97.67±32.62a	103.0±13.11a

- Different letters in the same row indicate significant difference ($p \leq 0.05$).

CHAPTER FOUR

DISCUSSION

Following intravenous injection of Xylazine 2mg/kg in donkeys, main signs observed were dropping of the head, lowering the lip, abduction of the legs, protrusion of the penis, profound ataxia and continuous nose blowing and rubbing of the upper lip and gum with the foot or even the ground. Same observations were reported by Abakar *et al.*, (2014) following intravenous injection of Xylazine 1.1 mg/kg in donkeys. Initial apprehension followed by lowering of the head, drooping of the eyelids and lower lip and the horse becomes rapidly ataxic (McCrackin *et al.*, 1994). In goats, intramuscular injection of Xylazine, resulted in lowering of head and neck, partial drooping of eyelids, muscular in-coordination and staggering gait (Saleh, 1993).

The technique of TIVA using mixture of Guaifenesin, Ketamine and Xylazine has been used and promoted for several decades as a method of producing equine anaesthesia. Our data indicate that using each of the two protocols (XK and XKI) resulted in induction quality which found to be either smooth or fair which are considered to be safe and acceptable quality of induction because they are free from excitement with gradual falling to the ground with minimal paddling of limbs and no muscle stiffness. Abakar and his colleagues (2014) reported satisfactory quality of induction of anaesthesia following intravenous injection of Xylazine, Diazepam and Ketamine in donkeys. Ketamine produces no muscle relaxation and tonic clonic spasms of

limb muscles may occur even in the absence of surgical or other stimulation (Hall *et al.*, 2001). Hence the muscle relaxation observed to occur in this study may be due to Xylazine muscle relaxant effect induced by inhibition of the transmission of neural impulses in the central nervous system (Delehant *et al.*, 2003). Most of the animals anaesthetized with XK showed smooth to fair recovery while fair to poor recovery was the dominant scale observed as a result of using XKI and this may be attributed to the increase of the dose where the dose of the second protocol is double the dose in the first protocol, this finding is supported by Hall and Clarke, (1991) and Elise and Hunter, (1979) who reported the dose dependent effect of Xylazine and Ketamine.

The significant prolongation in the duration of analgesia, lateral recumbancy and total recovery observed in case of XKI compared to XK could be attributed mainly to the increase of the dose of the major anaesthetic and to the increase in the dose of the preanaesthetic medication; bearing in mind that the effect of Ketamine and Xylazine are affected both in magnitude and duration by the dose (Hall *et al.*, 2001)

Anaesthesia with either XK or XKI resulted in a significant decrease in respiratory rate for different durations of time. A result that is considered in the same line with that obtained by other researchers (Khan *et al.*, 2004, Bader and AL-kattan 2010 and Seo *et al.*, 2011), who reported drop in respiration as a result of using Xylazine, since Ketamine has

no depressive effect on respiratory rate or even some time might have stimulatory effect (Tokics *et al.*, 1987, Morse *et al.*, 2004; Von Ungern--Sternberg *et al.*, 2007). Ketamine has different effects on heart rate; no significant effect was reported by Ali (2013) and Abakar *et al.*, (2014), stimulatory effect was reported by (Haskins *et al.*, 1985, Brady and Koritnik, 1985). Cardiogenic effect of Xylazine was reported by Booth, (1988), Seo *et al.*, (2011). In our study the combination of Xylazine/ Ketamine lead to no significant effect on heart rate, bearing in mind the stimulatory effect of Ketamine and depressive effect of Xylazine on heart rate there might be some sort of physiological antagonism between the two drugs which translated in term of no significant effect of the combination on the heart rate. The noticeable no significant increase in heart rate after induction may be attributed partially to the high dose of Ketamine and partially to the excitement which may occur during induction of anaesthesia. The significant decrease in rectal temperature following induction and maintenance of anaesthesia with the two protocols is in line with the finding of Mogoia (1997), who reported significant hypothermic effect of Ketamine/Xylazine combination in donkeys. Also our finding is supported by the observations of Afshar *et al.*, (2005) who used the combination in goats Albozachri *et al.*, (2012) who used Ketamine Xylazine combination with either tramadol or diazepam in donkeys.

In this investigation blood glucose was found to be significantly elevated above the base line values in the two

protocols used. Ketamine was reported to have no direct effect on glucose profile Brady and Koritnik (1985). So the increase in glucose level observed in this study may be attributed to the effect of Xylazine and this finding is supported by the findings of other researchers (Ismail *et al.*, 2010, Çamkrten *et al.*, 2013, Kullmann *et al.*, 2014, and Okwudili, *et al.*, 2014) when they used Xylazine in combination with Ketamine. Using the combination of Xylazine and Ketamine in this study reflected contradictory results. The first protocol XK resulted in a no significant change in urea which is supported by the findings of Camekrten *et al.*, (2013), while the protocol of XKI lead to a significant increase in urea level which supported by the finding of Ünsürenl *et al.*, (1986) and Okwudili *et al.*, (2014). The different effects of the two protocols observed in this study may be due to the dose, where the dose of the components of the second protocol is double the dose of the first protocol. The high dose may interfere with function of the kidney.

Both protocols (XK and XKI) have no significant effect on AST activity, this finding is supported by the findings of El-Kammar and Gad, (2014) who used Ketamine Detomidine combination. Also our finding is supported by the findings of Ismail *et al.*, (2010) Camekrten *et al.*, (2013). ALT level was found to be none significantly affected this finding is supported by the results obtained by El-Kammar and Gad, (2014) and Amin *et al.*, (2012a) who used Ketamine combinations with other drugs in donkeys. Also our finding is

supported by the findings of Camekrten *et al.*, (2013), who used Ketamine Xylazine combination in Greyhounds.

In the second study where another α_2 -agonist (Detomidine) was used instead of Xylazine for premedication before anaesthesia in donkeys, Clinical signs and observations induced following injection of Detomidine in donkeys was similar to that induced following injection Detomidine in goats (El-Kammar *et al.*, 2014) or after injection of of Xylazine (α_2 -adrenocetor agonist in donkeys (Abakar *et al.*, 2014). McCrackin *et al.*, (1994), reported initial apprehension followed by lowering of the head, drooping of the eyelids and lower lip and the horse becomes rapidly ataxic. In goats, intramuscular injection of Xylazine, resulted in lowering of head and neck, partial drooping of eyelids, muscular in-coordination and staggering gait (Saleh, 1993).

The diuresis induced by Detomidine in the current study was suggested to be associated with increased glomerular filtration rates, inhibition of anti-diuretic hormone release, and inhibition of antidiuretic hormone effect on the renal tubules and increased release of atrial natriuretic factor (Duthie and Nimmo, 1987, England and Clarke, 1996). Voiding of urine observed in donkeys in the current study may be attributed to the sympathomimetic effect of Detomidine that is in agreement with observations of Joubert *et al.*, (1999). The mechanisms responsible for this are similar to those described for alpha2 adrenergic agonists.

The smooth to fair quality of induction observed in both protocol DK and DKI , is acceptable quality and may be due

to the muscle relaxing effect of Detomidine reported by Matthews *et al.*, (2008) and Amin and Najim, (2011), as Ketamine is expected to cause rough induction due to its effect on muscles (Hall *et al.*, 2001). Ketamine produces no muscle relaxation and tonic clonic spasms of limb muscles may occur even in the absence of surgical or other stimulation (Hall *et al.*, 2001). Muscles relaxation observed in this study is in agreement with previous results obtained by Matthews *et al.*, (2008) and Amin and Najim, (2011), who reported occurrence of good muscle relaxation in horses and donkeys, respectively following induction of anaesthesia using Detomidine/Ketamine combination.

Alpha 2 adrenoceptor agonists improve the quality of recovery in horses (Santos *et al.*, 2003), this finding is in line with recovery quality observed following induction of anaesthesia using the first protocol (DK) where recovery was found to be smooth and fair in quality. In this study recovery from anaesthesia with DK1 was found to be of poor or very poor quality and this may be attributed to the effect of high dose of Ketamine and high dose of Detomidine where in need of a longer duration of time to be metabolized (Hall *et al.*, 2001)

Induction and maintenance of anaesthesia (DK1) resulted in significant ($p \leq 0.05$) prolongation in the duration of analgesia, lateral recumbancy, standing phase and total recovery time compared with the same phases resulted from anaesthesia with DK. The significant difference in the duration of the phases observed in this study between the

two protocols may be attributed to the difference in the dose where in the second protocol the dose is almost double the dose in the first protocol. Ketamine and Detomidine were reported to have a dose dependent effect (Hall *et al.*, 2001)

A significant depression in respiratory rate was observed following the use of DK or DK1 at 10 minutes and 20 minutes respectively. Ketamine is reported to have no depressive effect or even stimulatory effect on respiratory system (Morse *et al.*, 2004; and Von Ungern- Sternberg *et al.*, 2007). So the depressive effect on the respiratory rate may be attributed to the depressive effect of Detomidine on respiration (El-Kammar and Gad, 2014 and El-Kammar *et al.*, 2014). Although, opioids and alpha2 adrenergic agonists are known to depress ventilation and alter arterial partial pressures of carbon dioxide and oxygen, none of the donkeys in the current study showed any symptoms of respiratory failure a result that is in agreement with previous observation of Joubert *et al.*, (1999).

Anaesthesia with either DK or DK1 resulted in no significant change on heart rate. A finding that is in line with the findings of Ali (2013) who reported the non significant effect of Detomidine/diazepam or Detomidine/midazolam Ketamine bearing in mind that diazepam or zolazepam have no effect on heart rate. Vainio, (1982) reported the suppressive effect of Detomidine on heart rate , this effect did not appear in during this study and it might be antagonised by the stimulatory effect of Ketamine on heart rate reported by Haskins *et al.*, (1985). The cardiovascular

actions of Ketamine include increases in heart rate and cardiac output which are attributed to increase in centrally mediated tone, release of catecholamines from peripheral storage sites, inhibition of neural, extra-neural uptake of catecholamines and inhibition of baroreceptor reflex activity (Muir, 1991, and Muir *et al.*, 2000). Ketamine also produces direct vasodilation of vascular smooth muscle and an inotropic effect on the myocardium (Lin, 1996). The cardiovascular stimulating effects induced by Ketamine are blunted or prevented by prior administration of benzodiazepines and α_2 -agonists (Lin, 1996).

After intravenous injection of alpha2 adrenergic agonists, the following cardiovascular effects have been described. Blood pressure initially increases rapidly due to direct stimulation of peripheral alpha1 receptors, which increases systemic vascular resistance, usually within 2-5 minutes of administration. This is accompanied by a significant fall in heart rate due to a baroreceptor response (Vähä-Vahe, 1991, and Daunt, 1995). The heart rate usually returns to normal within a few minutes (Duthie and Nimmo, 1987). The cardiovascular side effects are dose-dependent and reach their maximum effect 15-30 min after intravenous injection (Duthie and Nimmo, 1987).

Duthie and Nimmo, (1987), Daunt, (1995), and England and Clarke, (1996), reported that, heart rates decreased significantly over the first minute. This correlates well with what has been reported in equines treated with Detomidine with or without butorphanol, and with the single account of

the use of Detomidine in donkeys. After the initial drop, the heart rate tended to return to baseline values. It is well-known that after administration of alpha₂ adrenergic agonists the heart rate tends to return to normal, usually within 20–30 min.

Therefore, we considered that the cardiovascular changes observed in the current study in donkeys anaesthetized with DK or DKI were a result of the additive and synergistic effects of Detomidine and Ketamine.

DK and DKI caused a significant drop in rectal temperature after injection of Detomidine and after induction of anaesthesia for 10 minutes and 30 minutes respectively. The significant hypothermia observed in this study may be attributed to the suppressive effect of Detomidine on rectal temperature as reported by (England and Clark, 1996, El-Kammar and Gad.2014, and El-Kammar *et al.*, 2014).

In this study DK was found to have no significant effect on blood urea concentration this finding is in agreement with previous results obtained by El-Kammar and Gad, (2014), who reported the no significant effect of the same protocol on urea in donkeys. DKI was found to cause a significant increase in urea level this finding is in line with the finding of Ali, (2013) who reported significant increase in urea level as a result of using Ketamine combinations which may be due to the high dose of Detomidine and Ketamine.

In this study DK and DKI caused significant increase in blood glucose level during the whole course of anaesthesia, this finding is supported by the findings of Amin *et al.*,

(2012a) and Ambrosio *et al.*, (2012) who reported the same results in donkeys and horses, respectively.

Both DK and DKI were found to cause no significant effect on ALT and AST activity, this finding is supported by the results obtained in donkeys by El-Kammar and Gad, (2014) who used Ketamine/Detomidine combination and it is partially supported by Amin *et al.*, (2012b), in she donkeys who used Ketamine combinations. Khan and his colleagues (2003), evaluated the effects of Detomidine (a novel veterinary sedative and analgesic) on blood chemistry and electrolyte profile in buffalo calves, injected intravenously at the dosage rate of 50 µg/kg body Serum glutamic oxaloacetic transaminase weight.

In the third experiment where Romifidine was used as a pre-anaesthetic medication, signs and observations reported following injection of Romifidine was similar to that induced following injection of Xylazine (Abakar *et al.*, 2014), and Detomidine (Juliana, *et al.*,2005) in donkeys. Watery salivation was observed to occur as a result of using Romifidine alone or in combination with butorphanol in baladi goat (El-Kammar *et al.*, 2014). Also excessive salivation was observed in all over the period of sedation induced by Romifidine in buffalo calves (Shekidef *et al.*, (2007).

Increase in urine production observed in the current study is in agreement with the observations of White (2006) who showed that α_2 -adrenoceptor agonists (Xylazine-Detomidine) produce bradycardia and an increase in urine production.

Using of each of the protocols RK or RKI resulted in induction quality that ranged between smooth and fair. Ketamine was reported to cause no muscle relaxation or even sometimes it might cause muscle rigidity or even muscle spasm (Hall *et al.*, 2001). Consequently, the smooth and fair quality of induction observed in this study is attributed to the muscle relaxation effect of Romifidine (Freeman *et al.*, 2002, and Shekidef *et al.*, 2007). Abakar *et al.*, (2014) suggested that muscular rigidity and spasms are considered components of unsatisfactory and unacceptable induction. To this end Romifidine is considered as good pre-anaesthetic medication to be used before Ketamine in donkeys. Muscle relaxation was observed to occur in both protocols. RK caused muscle relaxation for less than 20 minutes, while DKI resulted in muscle relaxation for 40 minutes. Excellent scale of muscle relaxation was not found to be attained in both protocols. Ketamine produces no muscle relaxation and tonic clonic spasms of limb muscles may occur even in the absence of surgical or other stimulation (Hall *et al.*, 2001). So muscle relaxation observed in both groups may be due to the effect of Romifidine. Investigating the quality of recovery as result of using RK of RKI revealed smooth to fair recovery following induction of anaesthesia with RK. While, in the second protocol (RKI) the recovery quality ranged between smooth, fair and poor. The three scales are acceptable because they do not predispose the animal to the risk of injury during recovery. Appearance of poor recovery in case of RKI which is translated in term of

increasing of attempts to stand and ataxia may be due to the high dose of Romifidine and Ketamine which were reported to have a dose dependent effect (Naccarato and Hunter, 1997, and Figueiredo, *et al.*, 2005).

Donkeys generally recover from anaesthesia without excitement which horses may experience if good analgesia has been provided (Matthews and van Dijk, 2004). The recovery times in donkeys are slower from most anaesthetics, than in horses. Donkeys do not generally stand up until fully recovered, unlike the horse, which may make attempts to stand before it is ready. It is also unusual for donkeys to stand up,, hind end first, as a cow would, while balancing on a front knee (Matthews and van Dijk, 2004).

Donkeys rarely get hysterical about anything, so recoveries from anaesthesia are almost quiet and smooth. It is generally impossible to make a donkey get up before it is ready. Occasionally, young donkeys may need a boost on the tail to stand; sometimes they will get up with rear-legs first, like a cow (Matthews and Taylor, 2000).

Comparing the effect of the two protocols used in this study on the different anaesthetic phases reflected significant prolongation in the duration of the different phases measured. This prolongation may be attributed to the increase in the dose of both the pre-medication and anaesthetic drugs. Here, Romifidine is almost double the dose in the first protocol. Several results indicated dose dependent effect of Romifidine (Lemke, 1999, and Brown, *et al.*, 2015).

A reduction in respiratory rate is observed following the use of Romifidine in horses (Figueiredo *et al*, 2005), a result that is in agreement with the observed decrease in heart and respiratory rates following injection of Romifidine in this study. Since Ketamine has been reported to have maintenance or stimulatory effect on respiratory system (Tokics *et al.*, 1987 (Morse *et al.*, 2004 and Von Ungern-Sternberg *et al.*, 2007). Therefore, the significant decrease in the respiratory rate may be due to the effect of Romifidine which was reported to cause a depressive effect on respiratory rate (Shekidef *et al.*, 2007, De-Rossi. *et al.*, 2009, and El-Kammar *et al.*, 2014).

Several reports indicated bradycardiogenic effect of Romifidine (Pypendop and Verstegen, 2001, Shekidef *et al.*, 2007, De-Rossi *et al.*, 2009, Amin *et al.*, 2012- b, and El-Kammar *et al.*, (2014). The increase in the heart rate observed in the current study as a result of using Romifidine/Ketamine may be attributed to the excitement that might occur during induction of anaesthesia. While, the non significant drop in heart rate is partially supported by the findings of Lemke (1999), who reported bradycardia as a result of using Romifidine. Usage of high dose of Ketamine could be the factor which leads to the no significant effect on heart rate knowing that Ketamine might have stimulatory effect on heart rate (Haskins *et al.*, 1985),

The significant drop in rectal temperature following injection of Romifidine is in agreement with the findings of Lemke, (1999) who reported a hypothermic effect of

Romifidine in dogs. A significant drop in rectal for 30 minutes observed in the second protocol (RKI) is in line with the findings of Amin *et al.*, (2012c) and El-Kammar *et al.*, (2014) who reported hypothermia due to anaesthesia with the same protocol. RK resulted in hypothermia for short time and body temperature returned to the normal values and this could be due to recovery of the animal from anaesthesia.

Both protocols caused significant increase in blood urea which observed during the whole course of anaesthesia, a finding that is in line with the findings of Shekidef *et al.*, (2007). Also our finding may be attributed to the high dose of Romifidine which was reported to have a dose dependent effect on urea level (El-Maghraby *et al.*, 2005).

The noticeable non significant increase in glucose level observed in the current study is partially in agreement with previous results that showed significant increase in glucose level following Romifidine injection (Shekidef *et al.*, 2007, Amin *et al.*, 2012c, and El-Kammar *et al.*, 2014).

The no significant effect of Romifidine on ALT and AST activity may indicate a minimum effect of the drug on the liver function and muscles myopathy. A similar observation was reported in shedonkeys anaesthetized with Ketamine/Romifidine combination (Amin *et al.*, 2012c), and in goats (El-Kammar *et al.*, 2014).

In the fourth part of the study the three anaesthetic protocols were evaluated for their safety and efficacy in maintaining laparotomy in donkeys. Results obtained indicated that induction and maintenance of anaesthesia

with XKIS, DKIS or RKIS resulted in smooth and fair induction. Ketamine is reported to have no muscle relaxation effect or even it might cause muscle spasm or tonic clonic seizures (Hall *et al.*, 2001). Xylazine, Detomidine and Romifidine being members of the α_2 -adrenoceptor agonist they are reported to have muscle relaxant effect (Freeman *et al.*, 2002, Thakur *et al.*, 2011, and Amin and Najim, 2011) who worked on the three drugs separately. So the smooth and fair induction observed in this study may be due to the effect of the three premedications used in the study rather than the anaesthetic itself. The quality of recovery resulted from using XKIS and RKIS ranged between smooth and fair. Poor and very poor recovery was not seen as a result of using either XKIS or RKIS. Quality of recovery resulted from using DKIS ranged from fair to poor. Very poor recovery was not observed to occur as a result of using any of the above tested protocols. Detomidine was reported to have longest duration of action (Yamashita *et al.*, 2000) and the longest duration of ataxia among the alpha 2 adrenoceptor agonists (Hamm *et al.*, 1995, and England *et al.*, 1992). So the poor and very poor recovery resulted from DKIS in this study may be due to the long duration of action and the long duration of ataxia caused by Detomidine compared to Xylazine and Romifidine.

Results obtained indicated that the protocol DKIS resulted in phases of anaesthesia which were found to be longer in duration than the phases resulted from using XKIS or RKIS. That prolongation in the different phases whether it

is significant or non significant could be attributed to the higher affinity of Detomidine to the receptors which translated in prolongation of the duration of action of Detomidine compared to Xylazine and Romifidine (England and Clarke, 1996, and Bueno, 1999). Also the exaggerated effect of Detomidine which appear in the different phases excluding the analgesia phase may be due to the longest ataxic effect of Detomidine compared to Xylazine and Romifidine as reported by (Hamm *et al.*, 1995, and England *et al.*, 1992).

Being an important component of surgery, effects of XKIS, DKIS and RKIS on abdominal muscle relaxation were studied. The three mentioned protocols were found to have either excellent or satisfactory abdominal muscle relaxation. The degree of abdominal muscle relaxation recorded was found to be enough in terms of quality and durations for laparotomy as indicated by the satisfaction of the surgeons. Since Ketamine was reported to have no positive effect on muscle relaxation or even sometimes it leads to muscle rigidity (Hall *et al.*, 2001), so the muscle relaxation occurred here in this study may be attributed to the muscle relaxing effect of the premedications used (Greene and Thurmon, 1988; Ali, 2013; and Freeman *et al.*, 2002).

Using each of three protocols resulted in decrease in respiratory rate. This decrease was found to be of significant value in case of XKIS and RKIS. The decrease in the respiratory rate was found to be of no significant value in case of DKIS but it is still a noticeable decrease. Being

members of alpha 2 adrenoceptor agonists the three drugs are expected to cause a drop in the respiratory rate as reported by Luna *et al.*, (2000). Ketamine was reported to have no significant effect on respiratory rate (Tokics *et al.*, 1987, Morse *et al.*, 2004, and Von Ungern-Sternberg *et al.*, 2007), so the drop in the respiratory rate could be attributed to the respiratory depressing effect of the pre-anaesthetic medications used in the study. Xylazine, Detomidine and Romifidine were reported to have a brady-cardiogenic effect as reported by (Vainio, 1982, Joseph *et al.*, 1982, [Booth, 1988](#), Seo *et al.*, 2011; and Amin *et al.*, (2012b). These observations strongly support results obtained in the current study, where the three premedications resulted in a drop in the heart rate 10 minutes after their injection. Using XKIS, DKIS or RKIS for induction and maintenance of anaesthesia in this study resulted in no significant change in heart rate. The stimulatory effect of Ketamine reported by Haskins *et al.*, (1985) might have an antagonising effect on the bradycardiogenic effect of the pre-anaesthetic medications, hence the no significant effect of the combinations on heart rate.

Rectal temperature was monitored during anaesthesia and surgery with XKIS, DKIS and RKIS. Each of the three protocols caused a significant drop in body temperature. Ketamine was reported to have no effect on body temperature (Davison *et al.*, 2007, and Abakar *et al.*, 2014). Body temperature generally decreases as a result of using α_2 adrenoceptors (England and Clarke, 1996). Xylazine,

Detomidine and Romifidine were reported to have a hypothermic effect (Khan *et al.*, 2004, Amin *et al.*, 2012b, and El-Kammar and Gad, 2014). So the hypothermia resulted in this study may be due to the effect of the three drugs on body temperature. Anaesthesia for a long time may affect basal metabolic rate which might cause hypothermia.

The effect of the three protocols XKIS, DKIS and RKIS on kidney function was studied by measuring blood urea level. The three protocols were observed to cause significant increase in blood urea. Our finding is supported by the findings of Ali, (2013), Okwudili *et al.*, (2014) and El-Kammar *et al.*, (2014) who reported similar results following the use of the same protocols. El-Maghraby *et al.*, (2005) reported that the effect of Romifidine on urea level is dose dependent. Using any of the three protocols resulted in increase in blood glucose. Blood glucose level usually increased in different animal species as a result of using Xylazine alone or in combination with other drugs as reported by Kullmann *et al.*, (2014) in horses, Ismail *et al.*, (2010) in sheep and goats. Studying the effect of Detomidine on blood glucose level in horses Thurmon *et al.*, 1982; and Ambrosio *et al.*, 2012 reported the significant increase in blood glucose as a result of using Detomidine. Romifidine was also reported to cause significant increase in serum glucose level as a result of using it alone (El-Maghraby *et al.*, 2005) or in combination with other drugs as reported by Amin *et al.*, (2012). Serum glucose level was reported to be non significantly affected in donkeys as a result of using Ketamine in combination with

Detomidine (EL-Kammar and Gad, 2014). On the other hand Amin *et al.*, (2012a) reported a significant increase in serum glucose in female donkeys as a result of using some Ketamine combinations for induction in female donkeys.

Effect of different protocols of Ketamine had been studied by different researchers. Xylazine/Ketamine combination in Greyhound (Camekrten *et al.*, 2013), Detomidine/Ketamine (El-Kammar and Gad, (2014) and Romifidine/Ketamine (Amin *et al.*, (2012a) and (El-Kammar *et al.*, 2014). All those combinations of Ketamine protocols investigated in literature reflected no significant effect on ALT. These findings are in line with the results obtained in this study. Induction and maintenance of anaesthesia with each of the three protocols XKIS, DKIS or RKIS resulted in no significant changes on AST level. Our findings in case of XKIS and DKIS are supported by the findings of Kammar and Gad, 2014 and the findings of Ismail *et al.*, (2010) and Camekrten *et al.*, (2013) who reported no significant effects of Xylazine, Detomidine or Ketamine on AST.

CHAPTER FIVE

CONCUSIONS AND RECOMENDATIONS

The study was carried out to fulfil four objectives, and it can be concluded that:

1- Induction of anaesthesia with Ketamine protocols (X, D, or R/K) resulted in duration of anaesthesia which was found to be not enough for surgical interference.

2- Usage of Ketamine infusion drips in combination with Xylazine, Detomidine or Romifidine resulted in significant prolongation of the anaesthetic effect in the three protocols used for an extent suitable for short to medium surgical interference.

3- The protocols used in this study were found to have minimal or tolerable effects on physiological parameters studied (respiratory rate, heart rate and rectal temperature.

4 -The protocols used in this study were found to have non effects on liver functions.

5- Kidney function was affected significantly as a result of using some Ketamine combinations during this study.

6- The three protocols XKI, DKI and RKI can be used safely and efficiently to perform short to medium surgery in donkeys in neck region, limbs or abdomen.

7- Special consideration should be taken in case of recovery from anaesthesia with DKI or DKIS in term of duration and quality of recovery, since it was noticed that it had the longest and toughest duration of recovery.

RECOMINDATIONS:

- 1- The three protocols assessed in this study must be tested for use other species of animals.
- 2- Further studies must be carried out to investigate the effects of high doses of Ketamine and α_2 - adrenoceptor agonists on kidney functions.
- 3- The three protocols assessed in this study are strongly recommended to be used in donkeys.

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