EFFECT OF EPHEDRINE AND 4 - AMINOPYRIDINE - YOHIMBINE COMBINATION IN REVERSING THE KETAMINE – XYLAZINE ANAESTHESIA IN RABBITS

By

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THESIS

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DECLARATION

I hereby declare that the thesis entitled **"EFFECT OF EPHEDRINE AND 4-AMINOPYRIDINE-YOHIMBINE COMBINATION IN REVERSING THE KETAMINE-XYLAZINE ANAESTHESIA IN RABBITS"** is a bonafide record of research work done by me during the course of research and that the thesis has not previously formed the basis for the award to me of any degree, diploma, associateship, fellowship or other similar title, of any other University or Society.

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Certified that the thesis, entitled **"EFFECT OF EPHEDRINE AND 4-AMINOPYRIDINE-YOHIMBINE COMBINATION IN REVERSING THE KETAMINE-XYLAZINE ANAESTHESIA IN RABBITS"** is a record of research work done independently by Kumari. Chandra Rajeswari, K., under my guidance and supervision and that it has not previously formed the basis for the award of any degree, fellowship or associateship to her.

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K Chandra Rajeswari

CHANDRA RAJESWARI.K

To my loving parents
and brothers

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Introduction

INTRODUCTION

Modern anaesthesia in Veterinary practice is achieved by the "balanced technique" in which combination of drugs are used specifically to produce analgesia, unconsciousness, muscle relaxation and also to promote margin of safety. Among the injectable general anaesthetics, dissociative anaesthetic agents have become the integral part of the "balanced anaesthetic regimen".

Ketamine hydrochloride is a member of dissociative anaesthetics group and was synthesized in 1963. Ketamine hydrochloride (CI-581) is a congener of phencyclidine and chemically is 2-(0-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride.

As an anaesthetic agent, ketamine provide advantages of intramuscular administration, rapid induction and wide margin of safety. Muscular hypertonicity, prolonged and violent recovery are exhibited as side effects. Xylazine, in combination with ketamine not only counteract these side effects of ketamine, but also potentiates its anaesthetic property.

Xylazine (2-(2, 6-dimethyl phenyl amino)-4H-5, 6-dihydro-1, 3-thiazine HCl) an alpha-2 adrenergic agonist, is a centrally acting non-narcotic sedative, analgesic and muscle relaxant. The first successful application of ketamine-xylazine mixture was reported by Amend *et al.* (1972) in cats. Since then the combination of xylazine and ketamine has been used for chemical restraint, induction of anaesthesia and production of surgical anaesthesia in domestic

(Nowrouzian *et al.*, 1981; Rings and Muir, 1982; Sharma *et al.*, 1997), laboratory (Green *et al.*, 1980; Vanpelt, 1977) and wild animals (Jacobson, 1983; Cheeran *et al.*, 1989).

Rabbits are known to be one of the most difficult experimental animals to anaesthetize safely. Requirements of special equipments, expertise of anaesthesist, difficulty with endotracheal intubation and narrow safety margin of barbiturates, limit the use of inhalant and intravenous anaesthetics in rabbits.

Ketamine-xylazine combination was reported to be an effective, easily administered and cost efficient agent for producing surgical anaesthesia in rabbit (White and Holmes, 1976). The severe central nervous system (CNS) depression induced by this combination often leads to prolonged recovery period in rabbit.

Rapid recovery from prolonged ketamine-xylazine anaesthesia is often desirable to minimize post anaesthetic complications like, hypothermia, respiratory depression, hypotension and bradycardia.

Use of an appropriate reversing agent which antagonizes the prolonged ketamine-xylazine anaesthesia when a surgical procedure is completed can effectively shorten the recovery period and reduce the incidences of anaesthetic complications.

Yohimbine hydrochloride, an alpha-2 adrenergic antagonist, has been shown to reverse the CNS depressant effect of xylazine (Hsu, 1981). Yohimbine

hydrochloride also partly antagonized the anaesthetic effects of ketamine (Hatch and Ruch, 1974).

4-Aminopyridine (4-AP) is a nonspecific CNS stimulant which acts by modifying the turnover of acetylcholine and other neurotransmitters and believed to be a partial antagonist of number of CNS depressant drugs (Hatch, 1973; Agoston *et al.*, 1980; Booth *et al.*, 1982).

Combination of 4-aminopyridine and yohimbine was found to antagonize xylazine sedation in dog and cattle (Hatch *et al.*, 1982; Kitzman *et al.*, 1982), ketamine anaesthesia in cats (Hatch, *et al.*, 1983) and xylazine-ketamine anaesthesia in geldings (Kitzman *et al.*, 1984).

Although the combination of 4-AP and Yohimbine has been reported to produce rapid arousal from xylazine-ketamine anaesthesia, it failed to antagonize hypothermia induced by the same in rats (Komulainen and Olson, 1991). It was found to induce convulsion, muscle tremor and hyperaesthesia during recovery (Kitzman *et al.*, 1984; Usha *et al.*, 1990). In addition to this, the cost and non-availability of this mixture limits its practical application in field condition.

Ephedrine hydrochloride, a mixed acting sympathomimetic agent, was tried in the present study as a reversing agent of xylazine-ketamine anaesthesia in an attempt to develop an alternative to yohimbine and 4-AP combination.

Ephedrine hydrochloride (α-hydroxy-β-methyl amino propyl benzene HCl) is a CNS stimulant which acts by stimulating cerebral cortical and medullary

respiratory centres. Ephedrine has been reported to reverse the narcolepsy and respiratory depression induced by morphine (Innes and Nickerson, 1975) and anaesthesia produced by barbiturates (Musser and O' Neill, 1969). Reports are scarce about the rapid antagonism of xylazine-ketamine anaesthesia by ephedrine. Cheeran *et al.* (1998) observed effective reversal of xylazine-ketamine anaesthesia by ephedrine in rats.

The present study was therefore undertaken with the following objectives;-

1. To study the reversing effect of ephedrine on xylazine-ketamine anaesthesia in rabbits, and

2. To compare the reversal effects of ephedrine with that of a combination of 4-AP and yohimbine.

Review of Literature

REVIEW OF LITERATURE

2.1 Xylazine-ketamine anaesthesia

Amend *et al.* (1972) used xylazine pre-medication to eliminate muscular hypertonicity in cats during ketamine anaesthesia. Cats were injected intramuscularly with xylazine followed by ketamine hydrochloride. Xylazine eliminated muscular hypertonicity, prolonged the duration of analgesia of ketamine and produced sedation of sufficient duration to ensure smooth recovery.

Karl *et al.* (1974) reported that in cats intramuscular injection of 2% xylazine solution (0.5 mg/kg) followed 20 min. later by ketamine (20 mg/kg I/M) produced general anaesthesia for about 25 to 50 min.

White and Holmes (1976) reported that in rabbits, xylazine and ketamine combination (5 mg/kg and 35 mg/kg respectively I/M) produced better analgesia, muscle relaxation and surgical anaesthesia lasting for 20-75 min. than, ketamine alone (44 mg/kg).

Muir *et al.*, 1977). reported that simultaneous injection of xylazine and ketamine in adult horses (1.1 mg/kg and 2.2 mg/kg respectively I/V) produced no significant effect on cardiac output, arterial blood pressure and pulmonary arterial pressure. There was mild respiratory acidosis at the time of peak anaesthesia. Administration of large doses of ketamine (6.6 mg/kg) following sedation with

xylazine (1.1 mg/kg I/V) was found to result in, muscular tremor, rigidity, mydriasis, oculogyric movement, sweating, hypertension and tachycardia.

The responses of two inbred strains of rats to intramuscular doses of ketamine and xylazine, singly and in combination were studied (Vanpelt, 1977). Neither ketamine nor xylazine resulted in adequate anaesthesia when given alone. A synergistic effect was observed with the simultaneous administration of these two drugs (ketamine - 87 mg/kg and xylazine - 13 mg/kg) i.e., surgical anaesthesia with extended analgesia lasting 15 to 30 min., followed by long period of immobility (mean 3.8 hours). This combination in rats caused minimal bleeding in the surgical field.

Kumar *et al.* (1979) reported that intramuscular administration of xylazine (0.22 mg/kg) and ketamine (10 mg/kg) in dogs produced surgical anaesthesia ranging from 30 to 36 min. Time taken for recovery was 90 to 110 min. In animals requiring more time for surgery, supplemental administration of ketamine at the rate of 2-4 mg/kg prolonged the duration of anaesthesia by 14 to 22 min. and recovery by 20 to 25 min. There was a transient decrease in respiration, heart rate and rectal temperature which was compensated in 24 hours.

Beverly and Varga (1980) studied the anaesthetic effect of ketamine-diazepam and ketamine-xylazine combination in guinea pigs. The two combination were used in the following dosages. 44 mg/kg ketamine with 5 mg/kg xylazine and 25 mg/kg ketamine with 0.1 mg/kg diazepam. The drugs were mixed and injected intramuscularly. Both combinations abolished signs of

pain from all animals. Recovery time was prolonged with ketamine-xylazine than with ketamine diazepam combination.

Green *et al.* (1980) observed in their 10 year experiments that combination of ketamine (22 mg/kg I/V) and xylazine (3 mg/kg I/V) in rabbits produced effective surgical anaesthesia for 30 min. Xylazine enhanced the value of ketamine as an anaesthetic by its muscle relaxant, sedative and analgesic properties.

NewZealand White rabbits were anaesthetized with intramuscular injection of 5 mg/kg xylazine and 50 mg/kg ketamine and evaluated for its effect on blood pressure, heart rate and respiratory rate (Sanford and Colby, 1980). Anaesthesia was induced within 10 min and it lasted for 45-60 min. Heart and respiratory rates were reduced by 19 per cent and 77 per cent respectively. All the parameters returned to normal base line value within 6 hours of anaesthetic induction.

Nowrouzian *et al.* (1981) evaluated the anaesthetic properties of ketamine and a combination of ketamine, xylazine and atropine in sheep. The results showed that intramuscular administration of atropine (0.2 mg/kg) and xylazine (0.2 mg/kg) followed 15 min. later by intravenous injection of ketamine (22 mg/kg) produced anaesthesia lasted for 67 min. Pre-medication with atropine and xylazine counteracted some undesirable effects of ketamine such as muscle rigidity, salivation and insufficient suppression of reflexes.

Rings and Muir (1982) could not observe any significant changes in the heart rate, central venous pressure and cardiac output, when they used xylazine-ketamine combination in dairy calves. Significant reduction in partial pressure of oxygen necessitated supplemental oxygen therapy to calves receiving this drug combination.

Ketamine (8 to 9 mg/kg I/M) - xylazine (0.5 mg/kg I/M) combination was found effective for immobilizing springbok (Jacobson, 1983). The onset and duration of immobilization ranged from 3 to 10 min. and 1 to 2 hours respectively.

Waterman (1983) studied the effect of pre-medication with xylazine on the uptake, distribution and metabolism of intramuscularly administered ketamine in cats. He found that xylazine significantly increased the duration of ketamine anaesthesia by prolonging plasma half life of ketamine and delaying the production of primary metabolite of ketamine.

Byagagaire and Mbiuki (1984) described the influence of route of administration (intravenous or intramuscular) on duration of xylazine/ketamine induced analgesia (Ketamine 11 mg/kg and xylazine 0.22 mg/kg). Intramuscular injection of these combination produced longer duration of analgesia.

Silverman and Ingram (1986) stated that ketamine alone (100 mg/kg I/M) in deer mouse produced inadequate analgesia. The combination of ketamine and xylazine both at dose levels of 50 mg/kg induced adequate anaesthesia and analgesia.

Ludders *et al.* (1987) employed xylazine (3 mg/kg)-ketamine (40 mg/kg) combination as an anaesthetic technique for repeated collection of blood from NewZealand White rabbits. This technique permitted repeated and consistent collection of an average of 40 ml of blood without using special bleeding devices. Analgesia and adrenergic receptor effects associated with xylazine resulted in decreased circulatory catecholamine thereby facilitating arterial catheterization.

White *et al.* (1987) observed the effects of intramuscularly administered, xylazine (0.25 mg/kg), ketamine (5.5 mg/kg) and a mixture of xylazine and ketamine (0.15 mg/kg and 2.5 mg/kg) on sedation, analgesia, cardiac and respiratory rates in dromedary camel. The mixture of xylazine and ketamine was found superior to either of the drugs used alone. Xylazine reduced the side effects of ketamine without affecting its anaesthetic properties.

Peeters *et al.* (1988) induced general anaesthesia in NewZealand White rabbits by simultaneous intramuscular injection of xylazine and ketamine (5 mg/kg and 50 mg/kg respectively). The surgical anaesthesia lasted for about 33 min. Complete recovery occurred by 51.5 min.

Lipman *et al.* (1990) stated that the administration of acepromazine along with ketamine-xylazine combination in rabbits resulted in longer duration of anaesthesia than ketamine-xylazine combination alone.

Palmore (1990) observed an unusual case of fatal response to usually safe xylazine-ketamine (5 mg/kg and 35 mg/kg respectively I/M) anaesthetic regimen

in a group of rabbits. Five out of seven rabbits died of a mixed respiratory alkalosis-metabolic acidosis.

Popilskis *et al.* (1991) had reported that the ketamine (35 mg/kg) and xylazine (5 mg/kg) combination administered intramuscularly in rabbits produced a safe surgical anaesthesia for 35 to 40 min. and recommended for various surgical procedures.

Chakraborty and Das (1993) tried this drug combination (ketamine (10 mg/kg)-xylazine (1.33 mg/kg) to anaesthetize Siberian tiger (*Panthera tigeris altaica*). The induction time was 10 min. and complete recovery occurred after 3 hours.

Palomares *et al.* (1994) immobilized coypus (*Myocastor coypus*) using ketamine-xylazine (doses ranging from 2.33 to 6.25 mg/kg and 0.25 to 0.86 mg/kg respectively). Best results i.e., satisfactory immobilization and quick recovery were obtained with dose of 4 mg/kg ketamine and 0.5 mg/kg xylazine.

Belant (1996) reported that muskrats can be effectively immobilized with ketamine-xylazine mixture in 20:1 ratio. A dose of 15 mg/kg ketamine and 0.75 mg/kg xylazine provided about 10 min. of handling time and recovery occurred in less than 60 min.

Ghanawat and Mantri (1996) made a comparative study of two anaesthetic protocols in cats: ketamine (25 mg/kg) plus xylazine (1 mg/kg), ketamine (25 mg/kg) plus diazepam (0.5 mg/kg). Ketamine-xylazine was found superior to

ketamine-diazepam, with respect to muscle relaxation, duration of anaesthesia and recovery.

Sharma *et al.* (1997) conducted clinical studies on ketamine-xylazine (5-10 mg/kg and 1-2 mg/kg respectively I/M) induced anaesthesia in canines. The combination was administered in a single syringe after pre-medicating the animals with 0.04 mg/kg of atropine sulphate. From the results, it was concluded that this combination can safely be used to produce balanced surgical anaesthesia in canines under field condition.

Fifteen NewZealand White rabbits were used to study the effects of different anaesthetic combinations (Dutt *et al.*, 1998). Ketamine-xylazine combination with or without pre-medication in rabbit produced significant reduction of rectal temperature, pulse and respiration rate. Ketamine alone produced the shortest anaesthetic period, while diazepam-xylazine-ketamine combination produced longest period of anaesthesia. Head stamping, rolling, ataxia were observed during recovery from xylazine-ketamine anaesthesia.

Chitale *et al.* (1998) studied the haematological effects of ketamine-xylazine anaesthesia in goats. Significant reduction in PCV, Hb concentration and total erythrocyte count, neutrophilia and lymphocytopaenia were observed at half an hour to one hour after the induction of ketamine-xylazine anaesthesia.

2.2 Reversal of xylazine-ketamine anaesthesia with the combination of yohimbine-4-aminopyridine

Hatch and Ruch (1974) conducted experiments on antagonism of ketamine anaesthesia in cats by using adrenergic (l-amphetamine), serotonergic (yohimbine) and cholinergic (Physostigmine, oxotremorine) stimulants. A mixture of l-amphetamine and yohimbine at a dose rate of 1 mg/kg and 0.125 mg/kg respectively I/V, antagonized ketamine anaesthesia almost immediately. Post recovery side effects of the antagonist mixture were apparent anxiety, withdrawal from approach, fearfulness, defensive behaviour, hyperesthesia. Ketamine induced cataleptic motor impairment was not antagonized by the mixture.

The CNS depressant effect of xylazine and reversing effect of adrenergic antagonists having alpha-2 blocking activity such as piperoxan, phentolamine, tolazoline and yohimbine on xylazine induced CNS depression were tested in mice and newly hatched chickens (Hsu, 1981). Among these antagonists yohimbine was found to be most effective since at higher dose (1 mg/kg) it completely abolished the depressant effect of xylazine, while other agents enhanced it.

Kitzman *et al.* (1982) proved that the combination of 4-AP and yohimbine produced marked antagonism of xylazine sedation in cattle. Animals were injected intramuscularly with xylazine HCl (0.2 to 0.3 mg/kg). These animals were grouped into four, when maximally sedated, group I was given isotonic saline solution, group II was given 4-AP (0.3 mg/kg, I/V), group III was given

yohimbine (0.125 mg/kg, I/V), and group IV with 4-AP plus yohimbine in the same dose as mentioned above. This combination decreased the standing time from 94 min. (control) to 7.4 min. But the recovery period was not significantly affected.

Wallner *et al.* (1982) reported that xylazine-atropine induced immobility in dogs can be antagonized with yohimbine and 4-AP. Dogs were given xylazine (2.2 mg/kg I/M). When fully sedated animals received a large dose of atropine (0.5 mg/kg I/V), when fully immobilized the dogs were injected intravenously with saline (control), 4-AP (0.3 mg/kg), yohimbine (0.125 mg/kg) or a combination of both. They noticed a mean walk time of 76 min. for the control, 25.4 min. for 4-AP administered group, 8.7 min. for those given yohimbine and 4.8 min. for those given 4-AP and yohimbine: Mean total recovery time was 3.8, 2.5, 1.1 and 1.6 hours respectively.

Cronin *et al.* (1983) also studied the reversing action of 4-AP, yohimbine in xylazine-acepromazine combination in dogs. Atropinized dogs were injected intramuscularly with a dose of xylazine-acepromazine combination (2.2 mg/kg and 0.5 mg/kg respectively). Loss of righting reflex was considered as point of maximal sedation. On maximal sedation, dogs were injected intravenously with 4-AP (0.5 mg/kg) plus yohimbine (0.25 mg/kg). Combination of 4-AP and yohimbine significantly reduced the walking time from the control value of 43.1 min. to 1.9 min.

Combination of yohimbine-4-AP could partially antagonized the ketamine anaesthesia. This was observed by Hatch *et al.* (1983). Two groups of cats were injected intramuscularly with anaesthetic dose of ketamine (20 mg/kg). On loss of righting reflex, group I and II were given intravenous injection of saline and a mixture of 4-AP (0.6 mg/kg) and yohimbine (0.25 mg/kg) respectively. 4-AP and yohimbine shortened the mean arousal time to 4.1 min. (control - 16.3 min.) and mean walk time to 29.5 min. (control - 45.6 min.). However, ketamine induced catalepsy was not antagonized by this combination.

Hsu (1983) observed that yohimbine prevented xylazine (1 to 10 mg/kg) induced CNS depression at low dose (0.1 mg/kg, I/V) and reversed the CNS depressant effect of xylazine at doses ranging from 0.1 to 1 mg/kg body weight. He concluded that yohimbine can be used safely as an antagonist at a dosage of 0.1 mg/kg to control the duration and depth of xylazine induced CNS depression in dogs.

Mule deer was immobilized with ketamine-xylazine at a dose rate of 5.8 to 14.5 mg/kg and 0.44 to 0.92 mg/kg respectively I/M. Recumbency and ambulatory time was 95 and 150 min. respectively in control. Mule deer became ambulatory in 1 to 17 min. after yohimbine administration (0.125 mg/kg I/V). 4-AP was not used, as it produced convulsion in mule deer (Jessup *et al.*, 1983).

Antagonism of xylazine-ketamine anaesthesia by yohimbine in cat was reported by Hsu and Lu (1984). Twelve cats were anaesthetized with two intramuscular doses of xylazine and ketamine (2.2 mg/kg plus 6.6 mg/kg and

4.4 mg/kg plus 6.6 mg/kg respectively) and it produced approximately 60 and 100 min. of anaesthesia respectively in control cats. When yohimbine was given intravenously 45 min. after ketamine (0.1 mg/kg) administration, cats regained consciousness within 3 min. They were ambulatory 1 to 2 min. after regaining consciousness.

Kitzman *et al.* (1984) studied the antagonistic effect of 4-AP and yohimbine on xylazine-ketamine anaesthesia in geldings. Animals when maximally sedated were given saline solution, 4-AP (0.2 mg/kg) plus low dose yohimbine (0.075 mg/kg) and 4-AP plus large dose yohimbine (0.15 mg/kg). Mean standing time was significantly decreased in groups given combination of antagonists (10.3 ± 2 min. and 8.3 ± 2.6 min. respectively) compared with that of control group (24.3 ± 9.2 min.). Emergence phenomena like muscle twitching, hypersensitivity to noise and visual stimuli were observed in both groups given yohimbine plus 4-AP combination.

Hsu *et al.* (1985) compared the antagonistic effect of 4-AP, doxapram and yohimbine on cardiovascular actions of xylazine in dogs. Xylazine (1 mg/kg I/V) caused a decrease in heart rate accompanied by sinus arrhythmia. Yohimbine (0.1 mg/kg I/V) antagonized the hypertension, hypotension and bradycardia induced by xylazine. Doxapram potentiated xylazine induced hypotension and 4-AP failed to antagonize the cardiovascular effects of xylazine.

Reversal effects of yohimbine on combined xylazine-ketamine induced sedation and immobilization in juvenile African elephants has been studied by

Jacobson *et al.* (1985). Elephants were given a combination of xylazine (0.14 ± 0.03 mg/kg) and ketamine (1.14 ± 0.21 mg/kg) as a single intramuscular injection. Mean immobilization time was 11.6 ± 6.9 min. Twelve of the 14 elephants immobilized with a single dose combination of xylazine and ketamine were given yohimbine (0.13 ± 0.03 mg/kg I/V) and the remaining two elephants were allowed to recover spontaneously. The elephants given yohimbine had a mean standing time of 2.4 ± 1.1 min.

Kitzman and Hatch (1985) compared the antagonistic effect of yohimbine, 4-AP and doxapram on xylazine (2.2 mg/kg I/M) sedation in dogs. At recumbency, the dogs were given yohimbine (0.05, 0.1 and 0.2 mg/kg), 4-AP (0.3, 0.6 mg/kg) and doxapram (0.9 mg/kg). Of the antagonists tested yohimbine was found to be most effective for an overdose of xylazine.

Lynch and Line (1985) found that, yohimbine failed to reverse ketamine anaesthesia in rhesus monkey. Animals were given an intravenous dose of either 0.5 mg/kg yohimbine HCl or saline 10 min. after administration of ketamine HCl (10 mg/kg I/M). There was no difference in the duration of anaesthesia between the yohimbine and saline treated animals.

Mckelvey and Simpson (1985) evaluated the usefulness of yohimbine (0.2 mg/kg) and 4-AP (0.4 mg/kg) for reversing the effects of xylazine (1 mg/kg) and xylazine/ketamine (1 mg/kg and 5 mg/kg respectively) in red deer. Animals became alert and raised their heads within two min. and regained the standing

position within 14.9 ± 3.5 min. after injection of antidote combination. The mean time for standing in controls were 242 ± 39.3 min.

Ramsay *et al.* (1985) reported that immobilization induced by xylazine-ketamine in polar bears can be effectively reversed by administering 0.029 to 0.198 mg/kg of yohimbine HCl intravenously. Mean recovery time was 10 min. Convulsions and muscle twitching occurred in some animals. Median respiration rate and heart rate increased from 5 to 12 breaths/min and from 51 to 79 beats/min respectively.

Renecker and Olsen (1985) used a combination of yohimbine and 4-AP to antagonize xylazine (0.63 to 1.29 mg/kg body weight I/M) induced immobilization in four captive moose, four mule deer and five white-tailed deer. In this study, the maximal sedation of moose and mule deer was reversed by successive injection of yohimbine (0.15 mg/kg) and 4-AP (0.26 to 0.29 mg/kg). These produced sternal recumbency to arousal intervals of 1 to 15 min and recumbency to walking intervals of 1 to 24 min.

Failure of yohimbine to reverse ketamine has been reported by Kreeger and Seal (1986). Grey wolves were given yohimbine (0.2 mg/kg, I/V) 15 min. after immobilization with ketamine (25 mg/kg). Although animals given yohimbine raised their head significantly earlier than controls, there was no difference in time taken to walk.

Lipman *et al.* (1987) demonstrated the reversal of ketamine/xylazine anaesthesia in the rabbit with yohimbine. Six Newzealand White rabbits were anaesthetized with I/M ketamine (50 mg/kg) and xylazine (10 mg/kg). Fourteen days later each rabbit was subjected to same anaesthetic regimen followed 30 min. later by the intravenous administration of yohimbine (0.2 mg/kg). Yohimbine treated animal regained the palpebral, hindlimb pedal and righting reflexes within 34.6 ± 1.6, 34.2 ± 1.6 and 46.2 ± 4.4 min. respectively. While in control these values were 72.5 ± 13.8, 65.2 ± 11.0 and 104.5 ± 8.4 min. respectively.

Seal *et al.* (1987) employed ketamine at different dose levels to immobilize six tigers (*Panthera tigris tigris*). Yohimbine at 5 to 15 mg/kg effectively reversed 50 to 150 mg of xylazine within 4.8 min.

Breghi *et al.* (1989) tried yohimbine-4-AP combination to antagonize ketamine anaesthesia in dogs. The injection of 4-AP (0.3 mg/kg I/V) and yohimbine (0.125 mg/kg I/V) 15 min. after ketamine-diazepam administration significantly reduced the recovery time.

Rao (1989) used yohimbine to antagonize the depression caused by diazepam-ketamine. Rabbits were given yohimbine (0.2 mg/kg I/V) 30 min. after administration of atropine sulphate (1 mg/kg I/M), diazepam (5 mg/kg I/M) and ketamine (30 mg/kg I/V). Yohimbine effectively reduced the total anaesthetic time by about 40%. Increased head, eye movements and gnawing were noticed in the rabbits after yohimbine administration.

Usha *et al.* (1990) studied the reversing effect of yohimbine (2 mg/kg I/V) administered 15 min. after the administration of xylazine (2 mg/kg I/M) and ketamine (15 mg/kg I/M) in dog. From the results, it was found that yohimbine significantly reduced the duration of anaesthesia, sternal recumbency time, mean standing time and total recovery time. Untoward effects exhibited after yohimbine injection were salivation, panting and hyperaesthesia during recovery.

Antagonism of ketamine-xylazine anaesthesia in rats with a combination of yohimbine and 4-AP was reported by Komulainen and Olson (1991). This combination reduced the time to appearance of corneal and pedal reflexes and also reversed the respiratory depression caused by xylazine-ketamine anaesthesia. But anaesthetics induced hypothermia was not antagonized.

Heaton and Brauth (1992) anaesthetized budgerigars (*Meloprittacus undulaus*) with a combination of ketamine (40 mg/kg) and xylazine (10 mg/kg), 45 min. later yohimbine hydrochloride was administered at dosages of (0.0, 0.11, 0.275 or 0.44 mg/kg I/M) in a 0.7% saline vehicle. From the study they found that yohimbine at a dose of 0.275 mg/kg significantly reduced the duration as well as recovery from anaesthesia.

Rats were used to study the reversing effect of 4-AP on ketamine-xylazine anaesthesia (Nair *et al.*, 1993). Two intramuscular doses of xylazine and ketamine (10 mg/kg xylazine plus 20 mg/kg ketamine and 10 mg/kg ketamine plus 20 mg/kg xylazine) caused approximately 37.6 and 49.8 min. of anaesthesia respectively. Treatment groups were given 4-AP (2.5 mg/kg I/M) 15 min. after

induction of anaesthesia. There was significant reduction in duration of anaesthesia and recovery period in 4-AP treated rats.

Yang (1995) administered yohimbine to rabbits at doses of 0.0625, 0.125, 0.25 or 5 mg/kg I/V, 30 min., after injection of xylazine (5 mg/kg I/M) and ketamine (35 mg/kg I/M). Control group was given saline solution. Yohimbine treated rabbits regained the righting reflex within 0.9-2.2 min. in a dose dependant manner (saline treated group 28.3 ± 2.6 min.).

Yang *et al.* (1998) induced general anaesthesia in civet (*Paguma larvata*) with xylazine and ketamine and studied its antagonism by yohimbine. After intramuscular administration of xylazine (5 mg/kg)-ketamine (20 mg/kg), the atropinized animals became incoordinated and lost their righting reflex in 2.2 ± 0.2 and 4.0 ± 0.3 min. respectively. Corneal, palpebral and needle prick reflexes disappeared after 5 min. of dosing. Duration of anaesthesia was 49-78 min. Civets that received yohimbine (0.0625, 0.125, 0.25 mg/kg I/V) showed significant dose dependant shortening of recovery from anaesthesia.

2.3 Reversal of xylazine-ketamine anaesthesia with ephedrine

Ephedrine was first isolated by Nagai in 1887 from *Ephedra equistina* - a plant (Mahuang) used as medicine by Chinese since antiquity.

Ephedrine has been found to stimulate medullary respiratory centre directly and is used as an analeptic to combat respiratory depression caused by hypnotic drugs (Musser and O'Neill, 1969).

It is one of the mixed acting sympathomimetic agents that stimulate sensory area of cerebral cortex and medullary reticular activating system. This cortical stimulation has been utilized to antagonize narcotic depression caused by many CNS depressant drugs like barbiturates, morphine and scopalamine (Innes and Nikerson, 1975).

McGrath (1984) reported that large doses of xylazine along with ketamine as an anaesthetic for caesarean section in large animals impede uterine blood flow and arterial oxygenation which resulted in severe foetal hypoxemia. Ephedrine at the dose of 0.2 mg/kg I/V was found to increase uterine blood flow, systemic vascular tone, cardiac output and counteract the hypotensive state induced by xylazine.

Cardiopulmonary effects of intravenously administered ephedrine during halothane anaesthesia was studied in eight horses (Grandy *et al.*, 1989). Animals were instrumented after inducing anaesthesia with halothane. Baseline measurements of cardiac output, arterial blood pressure, pulmonary artery pressure, and heart rate, etc., were made. Ephedrine was then administered (0.06 mg/kg) and these measurements repeated at 10, 20, 30, 45 and 60 min. after injection. There was a significant increase in mean arterial pressure, cardiac output, stroke volume and a decrease in total peripheral resistance and heart rate.

Wagner *et al.* (1993) studied the effects of ephedrine on cardiovascular function and oxygen delivery in *isoflurane anaesthetized dogs. The dogs were* anaesthetized with isoflurane and instrumented for hemodynamic studies.

Baseline values were recorded. After that ephedrine (0.25 mg/kg) was administered intravenously. Values were again recorded at 5, 10, 15, 30 and 60 min. after injection. Ephedrine caused significant increase in mean arterial pressure, cardiac index, stroke volume and decrease in heart rate. Ephedrine injection also resulted in pronounced increase in haemoglobin concentration.

Chan *et al.* (1997) compared the efficacy of prophylatic ephedrine infusion over fluid preloading in prevention of maternal hypotension during spinal anaesthesia for caesarean section. There was a lower incidence of severe hypotension in the ephedrine group compared to the other group.

Materials and Methods

MATERIALS AND METHODS

3.1 Experimental animals

Study was conducted in thirty two adult healthy inbred strain of NewZealand White rabbits of either sex, weighing between 1.50 and 2 kilograms, obtained from Small Animal Breeding Station, College of Veterinary and Animal Sciences, Mannuthy. The health status of the animals were assessed and were housed separately in cages under identical conditions of feeding and management. Food was withheld for 12 hours before each experimentation to avoid over-estimating the real body weight and to enhance the respiration during anaesthesia. Water was given *ad libitum*. Rabbits were randomly divided into four groups of eight animals each.

3.2 Drugs used in the study

Ketamine injection[1]: 10 ml vial containing 50 mg ketamine hydrochloride/ml.

Xylazine injection[2]: 5 ml vial, each ml containing 20 mg xylazine hydrochloride.

Yohimbine plus 4-Aminopyridine injection[3]: 20 ml vial each ml containing 2 mg 4-aminopyridine plus 1.25 mg yohimbine hydrochloride.

Ephedrine solution[4] was prepared by dissolving 100 mg ephedrine hydrochloride in 5 ml distilled water.

3.3 Preparation of animals

Animals were weighed before the experiment and the dose was calculated according to the body weight. Before the commencement of the experiment, rectal temperature, pulse and respiration rate were recorded and venous blood was collected from the marginal ear vein for evaluation of haematological parameters.

3.4 Experimental design

Drugs were administered in each group as detailed below:

Group 'C' - Control group

Xylazine was administered intramuscularly (lateral thigh muscle) at the rate of 5 mg/kg body weight. After 15 minutes, ketamine was administered intramuscularly (50 mg/kg body weight).

Group T_1

Xylazine-ketamine combination was given as in group 'C'. After 30 minutes of induction of anaesthesia (i.e., at the middle of anaesthesia, as the mean duration of anaesthesia was calculated from control group) a combination of

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1. KETMIN - Themis Chemicals Limited, Hyderabad.
2. XYLOCAD - Cadila Pharmaceuticals Limited, Ahmedabad.
3. ANTAGOZIL SA - Troy Laboratories PTY Limited, Australia.
4. EPHEDRINE HYDROCHLORIDE - CDH Laboratories.

4-aminopyridine and yohimbine (Antagozil-SA) was administered intravenously in the marginal ear vein. (0.2 mg/kg and 0.125 mg/kg body weight respectively).

Group T_2

Xylazine-ketamine combination was given as in group 'C'. Thirty minutes after the induction of anaesthesia (i.e., at the middle of anaesthesia) ephedrine was administered intravenously at the rate of 10 mg/kg body weight.

Group T_3

Xylazine-ketamine combination was given as in group 'C'. After 30 minutes of induction of anaesthesia (i.e., at the middle of anaesthesia) ephedrine was administered at the rate of 20 mg/kg body weight intravenously.

3.5 Main items of observation

3.5.1 Anaesthesia

3.5.1.1 Reflex studies

Time of injection of xylazine/ketamine, loss and regaining of righting reflex, (Lateral recumbency with head down and head up position respectively) onset of Zwangsnagen reflex, time of sitting were recorded.

After xylazine-ketamine administration, the sequence and time of disappearance and reappearance of following reflexes were observed and recorded.

Corneal and palpebral reflex (manifested by closure of eyelids, when the cornea and medial canthus of the eye were touched with the tip of the cotton soaked in normal saline).

Pedal reflex evinced by sudden withdrawal of leg when the interdigital skin is pinched with fingers.

Ear-twitch reflex shown by twitch of ear, when the ear tip was pinched.

The loss of hindlimb pedal reflex was taken as the criteria for deciding the onset of anaesthesia.

3.5.1.2 Anaesthetic studies

3.5.1.2.1 Induction time

Time from administration of ketamine to the disappearance of hindlimb pedal reflex.

3.5.1.2.2 *Duration of anaesthesia*

Time interval between the disappearance and the reappearance of hindlimb pedal reflex.

3.5.1.2.3 Arousal time

Time from administration of reversing agent (in control - time from administration of ketamine) to regaining of righting reflex.

3.5.1.2.4 Recovery time

Time from reappearance of hindlimb pedal reflex to sitting on its all four legs.

3.5.2 Physiological observations

The physiological parameters like rectal temperature, pulse and respiration rate were recorded before and at 5, 10, 20, 30, 45, 60, 75, 90, 105, 120, 150 minutes after xylazine administration and also after complete recovery.

3.5.2.1 Rectal temperature

Rectal temperature was recorded using an electronic digital clinical thermometer.

3.5.2.2 *Respiration rate*

Respiratory rate was counted by observing the respiratory movements of abdominal wall.

3.5.2.3 Pulse rate

The pulse rate was recorded by the palpation of central auricular artery.

3.5.3 Haemogram

Haematological parameters such as total RBC count, total and differential leucocyte count, haemoglobin concentration, packed cell volume were studied for

blood samples collected before the administration of xylazine, during anaesthesia and after recovery from anaesthesia, using disodium EDTA as an anticoagulant.

3.5.3.1 Total erythrocyte count

Total red blood cells were counted by using haemocytometer (Benjamin, 1978). Half (0.5) ml of blood was diluted with* Hayem's fluid upto 101 mark in the erythrocyte diluting pipette and transferred to the Neubauer Counting chamber. Erythrocytes were counted in 5 small central squares under high power (x40).

3.5.3.2 Packed cell volume (PCV)

Packed cell volume was estimated by filling the Wintrobe haematocrit tubes using spinal needle and centrifuging at the speed of 6000 rpm for 15 minutes (Wintrobe *et al.*, 1981).

3.5.3.3 Haemoglobin

Haemoglobin concentration was estimated by acid hematin method.

3.5.3.4 Total leucocyte count

The total white blood cells were counted by standard dilution technique using **Thomas fluid and haemocytometer (Benjamin, 1978).

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* Hayem's fluid: Prepared by dissolving the following salts in 200 ml of distilled water.

Sodium chloride - 1g
Sodium sulphate - 5 g
Mercuric chloride -0.5 g

Half (0.5) ml of blood was diluted with Thomas fluid upto '11' mark in the leucocyte diluting pipette. After charging the counting chamber with diluted fluid, leucocytes were counted in four large corner squares under low power (x10).

3.5.3.5 Differential count

Blood smears were prepared with freshly drawn blood (without anticoagulant) by using slide method. After staining with ***Wrights stain, the differential leucocyte count was done by counting and classifying 200 leucocytes under oil immersion (Benjamin, 1978).

3.6 Statistical analysis

Statistical analysis using the CRD for comparison between groups and paired-t test for assessing between stages difference in the same group.

** Thomas fluid – By dissolving 2 ml glacial acetic acid and 1 ml Gentian violet (1% aqueous) in 100 ml of distilled water.

*** Wright's stain: Prepared by dissolving 0.5 g Wright's Stain powder in 300 ml of methanol.

Results

RESULTS

The data obtained during the course of investigation are presented in Tables 1 to 10 and Figures 1 to 5.

Average weight of the animals used in the groups C, T_1, T_2 and T_3 were 1.8 ± 0.07, 1.8 ± 0.06, 1.9 ± 0.09 and 1.7 ± 0.07 kilograms respectively (Table 3). There is no significant variation in weight of the animals among four groups.

4.1 Anaesthesia

4.1.1 Reflex studies

4.1.1.1 Sequence of disappearance of reflexes

After ketamine administration, the righting reflex disappeared first, followed by hindlimb pedal, corneal, palpebral reflexes and ear-twitch reflex.

4.1.1.2 Mean time for disappearance of reflexes (Table 1)

Righting reflex lost within a mean time of 1.7 ± 0.23 min. for the control group and 1.2 ± .07, 1.4 ± 0.1 and 1.4 ± 0.15 min. for the groups T_1, T_2 and T_3 respectively after the administration of ketamine. Statistical analysis revealed no significant difference in the loss of righting reflex among the four different groups.

The time of abolition of corneal reflex for the groups C, T_1, T_2 and T_3 were 5.3 ± 0.54, 4.6 ± 0.25, 4.2 ± 0.39 and 3.8 ± 0.21 min. respectively. The values showed no significant variation among the groups.

The mean time of disappearance of palpebral reflex for the groups C, T_1, T_2 and T_3 respectively 5.4 ± 0.57, 4.5 ± 0.25, 4.3 ± 0.38 and 3.8 ± 0.21 min. The variation among the groups were marginal.

Abolition of ear-twitch reflex was observed at 5.1 ± 0.46, 5.0 ± 0.41, 4.6 ± 0.24 and 3.8 ± 0.34 min. for the groups C, T_1, T_2 and T_3 respectively. The variation among the groups were marginal.

4.1.1.3 Sequence of reappearance of reflexes

The onset of Zwangsnagen reflex (Chewing movement of jaws) was the first indication of reversal of xylazine-ketamine anaesthesia, both in control group and in the treatment groups. This was followed by reappearance of corneal, palpebral, ear-twitch and hindlimb pedal reflexes.

4.1.1.4 Mean time for reappearance of reflexes (Table 2, Fig.1 and 1a)

Beginning of Zwangsnagen reflex was noticed at 22.4 ± 2.15 min. after 30 min. of induction of anaesthesia (30 min. after the induction of anaesthesia was taken as zero) for the control group and at 1.0 ± 0.02, 0.9 ± 0.03 and 0.5 ± 0.04 min. after the administration of reversing agents for groups T_1, T_2 and T_3 respectively. These values were significantly ($P<0.05$) greater in control than the treated groups.

Rabbits in control group regained corneal, palpebral, ear-twitch and hindlimb pedal reflexes within 23.2 ± 2.3, 23.3 ± 2.35, 24.0 ± 2.23 and 30.6 ± 1.51 min. respectively after 30 min. of the induction of anaesthesia..

Following the administration of reversing agents corneal and palpebral reflexes were regained within 1.1 ± 0.01 and 1.1 ± 0.02 min. and 1.1 ± 0.1 and 1.1 ± 0.1 min. respectively for the groups T_1 and T_2. The corresponding values for the group T_3 were 0.5 ± 0.09 and 0.5 ± 0.08 min. respectively.

Mean time for the reappearance of ear-twitch reflex after administration of antagonist was 1.9 ± 0.12, 1.3 ± 0.11 and 0.7 ± 0.02 min. respectively for the groups T_1, T_2 and T_3.

Rabbits in the groups T_1, T_2 and T_3 were regained the hindlimb pedal reflex with in 3.7 ± 0.22, 4.4 ± 0.36 and 1.4 ± 0.09 min. respectively after receiving reversing agents.

On statistical analysis highly significant difference ($P<0.05$) was found to exist between control and treated groups in the time of reappearance of corneal, palpebral, ear-twitch and hindlimb pedal reflexes. There was no significant variation between different treated groups in the time of reappearance of corneal, palpebral, and ear-twitch reflexes. Mean time for reappearance of hindlimb pedal reflex was significantly shorter for group T_3 when compared to T_1 and T_2.

4.1.2 Anaesthetic studies (Table 3 and Fig.2)

The time of induction, duration of anaesthesia, arousal and recovery time are presented in Table 3 and Fig.2.

Induction time (time from injection of ketamine to the disappearance of hindlimb pedal reflex) for the different groups C, T_1, T_2 and T_3 was 4.2 ± 0.27, 3.7 ± 0.22. 3.6 ± 0.23 and 3.4 ± 0.18 min. respectively. Statistical analysis revealed no significant difference in the induction of anaesthesia among the four groups.

The duration of xylazine-ketamine anaesthesia for the groups C, T_1, T_2 and T_3 were 60.6 ± 1.22, 33.6 ± 0.35, 34.2 ± 0.23 and 31.1 ± 0.13 min. respectively.

Statistical analysis revealed no significant difference between the groups T_1 and T_2 in duration of anaesthesia and it was found to be significantly ($P<0.05$) shorter in group T_3 when compared to T_1 and T_2.

Time of arousal and the recovery time for the group C were 103.85 ± 1.4 and 86.9 ± 2.5 min. respectively. The corresponding values for the group T_1 were 9.1 ± 0.83 and 65.4 ± 1.1 min., for the group T_2 were 35.5 ± 0.87 and 56.0 ± 0.63 min. and for group T_3 were 21.3 ± 2.11 and 41.5 ± 1.33 min. respectively. All the four groups differ significantly ($P<0.05$) from each other in the arousal and recovery time. The shortest arousal and recovery time were observed in groups T_1 and T_3 respectively.

The mean duration of absence of corneal, palpebral, ear-twitch and righting reflexes for the control group were 52.1 ± 1.8, 52.3 ± 2.1, 52.6 ± 1.95 and 102.2 ± 1.36 min. respectively (Table 4). The corresponding values for the group T_1 were 30.0 ± 0.34, 30.1 ± 0.24, 30.4 ± 0.3 and 41.3 ± 1.01 min., for the group T_2 were 30.3 ± 0.49, 30.3 ± 0.49, 30.1 ± 0.57 and 67.7 ± 0.73 min. and for the group T_3 were 29.4 ± 0.20, 29.5 ± 0.18, 29.5 ± 0.18 and 52.6 ± 2.29 min. respectively.

Statistical analysis revealed no significant difference in duration of disappearance of corneal, palpebral and ear-twitch reflexes between the groups T_1, T_2 and T_3, but highly significant ($P<0.05$) difference could be seen, to exist between the control and treated groups in mean duration of aforementioned reflex loss.

Duration of absence of righting reflex showed significant variation between four groups and it is significantly ($P<0.05$) shorter in group T_1 when compared to T_2 and T_3.

4.2 Physiological observations

4.2.1 Rectal temperature (Table 5 and Fig.3)

The rectal temperature showed a significant decrease from mean base line values of 39.5°C, 39.4°C, 39.4°C and 39.7°C respectively for the groups C, T_1, T_2 and T_3 to mean values of 39.1°C, 38.8°C, 38.9°C and 39.1°C respectively in 10

min. time. Transient increase in temperature to 39.4°C, 39.2°C, 39.3°C and 39.5°C for the groups C, T_1, T_2 and T_3 respectively was noticed in 20 min. time.

There after, the rectal temperature decreased progressively from 38.9°C in 30 min. to 36.6°C in 150 min. for the control group.

For the T_1 group the rectal temperature showed a significant increase from 38.9°C in 30 min. to near base line value of 39.4°C in 75 min. time. After that the temperature decreased slowly from 39.1°C in 90 min. to 38.7°C in 150 min. but remained within the normal range reported for rabbits. For the group T_2 the temperature showed a significant increase from 38.9°C in 30 min. to 39.3°C in 150 min.

For the group T_3 the temperature which was 39.1°C in 30 min. showed a significant increase to 39.7°C in 90 min. and a nonsignificant decrease to 39.4°C in 150 min.

Statistical analysis revealed no significant difference in the rectal temperature between the different groups from 5 min. to 30 min. time. From 45 min. to 75 min., increase in temperature was significantly ($P<0.05$) greater for the groups T_1 and T_3 when compared to T_2.

From 90 min. to 150 min., there was a significantly ($P<0.05$) greater increase in temperature for the groups T_2 and T_3 when compared to T_1.

After complete recovery the temperature returned to near base line value of 39.1°C, 39.3°C, 39.4°C and 39.6°C respectively for the groups C, T_1, T_2 and T_3.

Statistical analysis revealed no significant difference between four groups in rectal temperature after complete recovery.

4.2.2 Respiration rate (Table 6 and Fig.4)

The respiration rate which was 130, 131, 133 and 133 breaths/min. respectively for the groups C, T_1, T_2 and T_3 in 'O' min. (mean base line value) showed a gradual decrease to 42, 41, 41 and 40/min. respectively in 10 min. time. Further significant decrease to 25, 23, 23 and 23 breaths/min. respectively was recorded in 30 min. time. Statistical analysis revealed no significant difference among the four groups in respiration rate from 5 min. to 30 min. after xylazine administration.

For the control group, respiratory rate gradually increased from 23 breaths/min. in 45 min. to 57 breaths/min. in 150 min. time.

From 45 min. onwards, these values showed a significant ($P<0.05$) increase from 40, 53 and 63/min. respectively for the groups T_1, T_2 and T_3 to 66, 71 and 96 breaths/min. respectively in 150 min. time.

Highly significant ($P<0.05$) difference in respiration rate was found to exist between the four groups at 45, 60, 75, 90, 105, 120 and 150 min. during recovery.

A more profound decrease in respiratory rate (23/min.) was observed in control group at 45 min. when compared to T_1, T_2 and T_3 groups and increase in these values were significantly ($P<0.05$) greater for group T_3 when compared to T_2 and T_1.

Statistical analysis revealed no significant difference in respiration rate between the four groups after complete recovery.

4.2.3 Pulse rate (Table 7 and Fig.5)

Pulse rate decreased progressively from mean base line values of 253, 253, 251 and 248/min. respectively for the groups C, T_1, T_2 and T_3 to mean values of 112, 110, 113 and 111/min. respectively in 10 min. time. A sudden increase in these values to 158, 154, 157 and 157/min. respectively were observed at 30 min. Pulse rate between four groups did not differ significantly at the 5 to 30 min. intervals after xylazine administration. For the control group, the pulse rate showed a significant ($P<0.05$) decrease from 130/min. in 60 min. to 119/min. in 105 min., then it increased gradually to 150/min. in 150 min. time.

Pulse rate showed a significant increase to near base line values of 195, 227 and 238/min. respectively for the groups T_1, T_2 and T_3 in 60 min., with significantly ($P<0.05$) greater increase was recorded for the group T_2 and T_3 when compared to T_1. Thereafter the pulse rate increased to 223 and 239/min. respectively for the group T_1 and T_2 in 75 min. There was no statistically

significant difference between the groups T_1, T_2 in pulse rate at 90 min. After that it remain increased to 208/min. in 150 min. time for the T_1 group, but started decreasing from 183/min. in 105 min. to 175/min. in 150 min. for the group T_2.

After its marked rise to 238/min. in 60 min., the pulse rate for the group T_3 decreased gradually from 209/min. in 75 min. to 173/min. in 150 min. time.

Highly significant ($P<0.05$) difference in pulse rate could be seen to exist between four groups at 45, 60, 75, 105, 120 and 150 min. time. From 105 min. onwards T_3 group showed a significantly ($P<0.05$) greater decrease in pulse rate when compared to T_2 and T_1 groups.

4.3 Haematology (Table 8, 9 and 10)

The RBC count before xylazine administration, during anaesthesia and after recovery for the group C were 6.7, 5.2 and 6.3 millions/mm^3 respectively. The corresponding values for the group T_1 were 7.1, 6.0 and 7.0 millions/mm^3 respectively, for the group T_2 were 6.7, 5.4 and 6.9 millions/mm^3 respectively and for the group T_3 were 6.9, 5.6 and 7.1 millions/mm^3 respectively.

The mean values for haemoglobin for the four groups before anaesthesia were 12.5, 12.6, 12.7 and 12.3 g/dl respectively, during anaesthesia were 10.8, 10.6, 10.8 and 10.8 g/dl respectively and after recovery were 11.8, 12.5, 12.8 and 12.5 g/dl respectively. The corresponding values for PCV were 46.4, 48.1, 48.0

and 47.6 per cent respectively for the four groups before xylazine administration, 39.5, 40.8, 39.3 and 40.6 per cent respectively during anaesthesia and 42.8, 48, 49 and 49.5 per cent respectively after recovery from anaesthesia.

The total WBC count before xylazine injection, during anaesthesia and after recovery from anaesthesia were 8.2, 7.1 and 7.8 thousands/mm^3 respectively for the control group, 8.4, 7.0 and 8.3 thousands/mm^3 respectively for the T_1 group, 8.3, 7.1 and 8.4 thousands/mm^3 respectively for the group T_2 and 8.3, 7.3 and 8.3 thousands/mm^3 respectively for the group T_3.

On statistical analysis RBC count, Hb, PCV were found to show a significant ($P<0.05$) decrease during anaesthesia and this was present in all the four groups. After recovery these values showed a slight increase for the control group, increased to near base line value for the T_1 group and increased significantly ($P<0.05$) above the mean base line value for the groups T_2 and T_3.

WBC count, which showed a significant decrease during anaesthesia, returned to near base line value in groups T_1, T_2 and reached within the normal range in groups 'C' and T_3.

Differential leucocyte count

Heterophils count of group C, T_1, T_2 and T_3 showed a significant increase from 32, 33, 32 and 32 per cent respectively before xylazine administration to 54, 48, 49 and 50 per cent respectively during anaesthesia.

After recovery, these values returned to mean base line values. Lymphocyte count showed a significant ($P<0.05$) decrease from 62, 62, 63 and 62 per cent respectively for the four groups before anaesthesia to 38, 45, 44 and 42 per cent respectively during anaesthesia. There was no significant variation in lymphocyte count between before anaesthesia and after recovery. Monocyte and basophil count showed a more or less uniform picture during anaesthesia, but there was a significant ($P<0.05$) increase in eosinophil per cent during anaesthesia.

Table 1. Mean time (in minutes) for the disappearance of reflexes in rabbits anaesthetized with xylazine-ketamine combination (5 mg/kg-50 mg/kg)

n = 8

Groups	Disappearance of reflexes after ketamine injection			
	Righting	Corneal	Palpebral	Ear-twitch
C	1.7 ± 0.23	5.3 ± 0.54	5.4 ± 0.57	5.1 ± 0.46
T_1	1.2 ± 0.07	4.6 ± 0.25	4.5 ± 0.25	5.0 ± 0.41
T_2	1.4 ± 0.10	4.2 ± 0.39	4.3 ± 0.38	4.6 ± 0.24
T_3	1.4 ± 0.15	3.8 ± 0.21	3.8 ± 0.21	3.8 ± 0.34

Table 2. Mean time (in minutes) for the reappearance of reflexes in rabbits anaesthetized with xylazine-ketamine followed by administration of reversing agents

n = 8

Groups	30 minutes after induction of anaesthesia is taken as zero time				
	Zwangsnagen	Corneal	Palpebral	Ear-twitch	Hind limb pedal
C	22.4 ± 2.15^{A}	23.2 ± 2.3^{A}	23.3 ± 2.35^{A}	24.0 ± 2.23^{A}	30.6 ± 1.51^{A}
T_1	1.0 ± 0.02^{B}	1.1 ± 0.01^{B}	1.1 ± 0.02^{B}	1.9 ± 0.12^{B}	3.7 ± 0.22^{B}
T_2	0.9 ± 0.02^{B}	1.1 ± 0.1^{B}	1.1 ± 0.1^{B}	1.3 ± 0.11^{B}	4.4 ± 0.36^{B}
T_3	0.5 ± 0.04^{B}	0.5 ± 0.09^{B}	0.5 ± 0.08^{B}	0.7 ± 0.02^{B}	1.4 ± 0.09^{C}

C – Xylazine-ketamine (5 mg/kg – 50 mg/kg)

T1- Xylazine-ketamine (5 mg/kg-50 mg/kg) , Yohimbine – 4-Aminopyridine combination (0.125 mg/kg-0.2 mg/kg)

T2 – Xylazine-ketamine (5 mg/kg-50 mg/kg), Ephedrine (10 mg/kg)

T3 – Xylazine-ketamine (5 mg/kg – 50 mg/kg), Ephedrine (20 mg/kg)

Mean bearing different superscripts in a row differs significantly ($P<0.05$)

Table 3. Effects of xylazine-ketamine anaesthesia and its reversing agents on anaesthetic parameters in rabbits

n = 8

Mean ± S.E.

Groups	Weight of animal in kg	Time in minutes			
		Induction time	Duration of anaesthesia	Arousal time	Recovery time
C	1.8 ± 0.07	4.2 ± 0.27	60.6 ± 1.22 ^{A}	103.85 ± 1.4 ^{A}	86.9 ± 2.5 ^{A}
T_1	1.8 ± 0.06	3.7 ± 0.22	33.6 ± 0.35 ^{B}	9.1 ± 0.83 ^{D}	65.4 ± 1.1 ^{B}
T_2	1.9 ± 0.09	3.6 ± 0.23	34.2 ± 0.23 ^{B}	35.5 ± 0.87 ^{B}	56.0 ± 0.63 ^{C}
T_3	1.7 ± 0.07	3.4 ± 0.18	31.1 ± 0.13 ^{C}	21.3 ± 2.11 ^{C}	41.5 ± 1.33 ^{D}

Mean bearing different superscripts in a row differs significantly ($P<0.05$)

Table 4. Effect of xylazine-ketamine anaesthesia, and its reversing agents on mean duration of absence of reflexes in rabbits

n = 8

Groups	Mean duration of absence of reflexes (time in minutes)			
	Corneal	Palpebral	Ear twitch	Righting
C	52.1 ± 1.80^{A}	52.3 ± 2.10^{A}	52.6 ± 1.95^{A}	102.2 ± 1.36^{A}
T_1	30.0 ± 0.34^{B}	30.1 ± 0.24^{B}	30.4 ± 0.30^{B}	41.3 ± 1.01^{D}
T_2	30.3 ± 0.49^{B}	30.3 ± 0.49^{B}	30.1 ± 0.57^{B}	67.7 ± 0.73^{B}
T_3	29.4 ± 0.20^{B}	29.5 ± 0.18^{B}	29.5 ± 0.18^{B}	52.6 ± 2.29^{C}

Means bearing different superscripts in a row differs significantly ($P<0.05$)

Table 5. Effect of xylazine-ketamine anaesthesia and its reversing agents on mean rectal temperature (°C) in rabbits

n = 8

Groups	0	5	10	20	30	45	60	75	90	105	120	150	Complete recovery (CR)
C	39.5 ± 0.12	39.3 ± 0.12	39.1 ± 0.12	39.4 ± 0.10	38.9 ± 0.05	38.6^{C} ± 0.05	38.4^{C} ± 0.02	38.0^{C} ± 0.06	37.6^{C} ± 0.03	37.3^{C} ± 0.02	36.9^{C} ± 0.06	36.6^{C} ± 0.02	39.1^{AB} ± 0.10
T_1	39.4 ± 0.11	39.1 ± 0.11	38.8 ± 0.09	39.2 ± 0.10	38.9 ± 0.06	39.2^{A} ± 0.07	39.3^{A} ± 0.08	39.4^{AB} ± 0.12	39.1^{B} ± 0.09	39.0^{B} ± 0.07	38.8^{B} ± 0.03	38.7^{B} ± 0.02	39.3^{AB} ± 0.11
T_2	39.4 ± 0.10	39.1 ± 0.09	38.9 ± 0.08	39.3 ± 0.08	38.9 ± 0.06	38.8^{BC} ± 0.08	39.1^{B} ± 0.06	39.3^{B} ± 0.08	39.5^{A} ± 0.09	39.3^{A} ± 0.09	39.2^{A} ± 0.09	39.3^{A} ± 0.10	39.4^{AB} ± 0.11
T_3	39.7 ± 0.11	39.4 ± 0.11	39.1 ± 0.10	39.5 ± 0.11	39.1 ± 0.10	39.0^{AB} ± 0.14	39.4^{A} ± 0.11	39.6^{A} ± 0.11	39.7^{A} ± 0.11	39.5^{A} ± 0.10	39.3^{A} ± 0.10	39.4^{A} ± 0.10	39.6^{A} ± 0.10

Mean bearing different superscripts in a row differs significantly ($P<0.05$)

Table 6. Effect of xylazine-ketamine anaesthesia and its reversing agents on mean respiration rate (breaths/minute) in rabbits

n = 8

Groups	0	5	10	20	30	45	60	75	90	105	120	150	Complete recovery (CR)
C	130 ± 2.16	49 ± 0.83	42 ± 0.42	29 ± 0.37	25 ± 0.55	23^{D} ± 0.37	28^{D} ± 0.37	34^{D} ± 0.53	38^{D} ± 0.52	43^{D} ± 0.62	50^{D} ± 0.59	57^{D} ± 0.44	59 ± 1.55
T_1	131 ± 2.63	50 ± 0.53	41 ± 0.29	29 ± 0.50	23 ± 0.45	40^{C} ± 0.90	54^{C} ± 1.37	60^{C} ± 1.11	68^{C} ± 0.65	70^{C} ± 0.44	68^{C} ± 0.80	66^{C} ± 0.53	60 ± 1.29
T_2	133 ± 2.22	50 ± 0.50	41 ± 0.38	27 ± 0.52	23 ± 0.46	53^{B} ± 0.88	64^{B} ± 0.67	80^{B} ± 0.65	74^{B} ± 1.08	73^{B} ± 1.42	72^{B} ± 2.32	71^{B} ± 3.27	59 ± 1.07
T_3	133 ± 3.18	49 ± 0.60	40 ± 0.42	27 ± 0.46	23 ± 0.50	63^{A} ± 0.65	111^{A} ± 2.44	98^{A} ± 2.09	98^{A} ± 0.77	96^{A} ± 1.53	97^{A} ± 0.80	96^{A} ± 0.71	63 ± 1.07

Mean bearing different superscripts in a row differs significantly ($P<0.05$)

Table 7. Effect of xylazine-ketamine anaesthesia and its reversing agents on mean pulse rate (pulsations/minute) in rabbits

n = 8

Groups	0	5	10	20	30	45	60	75	90	105	120	150	Complete recovery (CR)
C	253 ± 2.81	122 ± 0.71	112 ± 0.87	147 ± 0.58	158 ± 0.59	139^{D} ± 0.87	130^{D} ± 0.82	127^{D} ± 0.80	122^{C} ± 0.86	119^{D} ± 0.53	137^{D} ± 0.87	150^{D} ± 0.82	202^{C} ± 2.23
T_1	253 ± 2.58	122 ± 0.87	110 ± 0.49	147 ± 0.50	154 ± 0.53	184^{C} ± 1.27	195^{C} ± 0.93	223^{B} ± 3.03	204^{A} ± 0.80	195^{A} ± 0.80	195^{A} ± 0.90	208^{A} ± 0.56	217^{A} ± 1.63
T_2	251 ± 2.34	124 ± 0.94	113 ± 1.02	146 ± 0.99	157 ± 0.59	206^{B} ± 1.18	227^{B} ± 0.88	239^{A} ± 0.88	204^{A} ± 0.92	183^{B} ± 0.80	172^{B} ± 0.84	175^{B} ± 0.72	196^{C} ± 1.77
T_3	248 ± 2.98	122 ± 0.92	111 ± 0.97	145 ± 0.64	157 ± 0.50	221^{A} ± 1.07	238^{A} ± 0.97	209^{C} ± 0.85	183^{B} ± 0.93	164^{C} ± 1.04	160^{C} ± 0.44	173^{C} ± 0.73	208^{B} ± 1.95

Mean bearing different superscripts in a row differs significantly ($P<0.05$)

Table 8. Effect of xylazine-ketamine anaesthesia and its reversing agents on the haematological parameters in rabbits

n = 8

Mean ± S.E.

Parameters	Groups	Before anaesthesia	During anaesthesia	After recovery
RBC 10^6/mm^3	C	6.7 ± 0.11 ^{a}	5.2 ± 0.15 ^{b}	6.3 ± 0.1 ^{cB}
	T_1	7.1 ± 0.06 ^{a}	6.0 ± 0.11 ^{b}	7.0 ± 0.1 ^{aA}
	T_2	6.7 ± 0.15 ^{a}	5.4 ± 0.19 ^{b}	6.9 ± 0.15 ^{cA}
	T_3	6.9 ± 0.12 ^{a}	5.6 ± 0.18 ^{b}	7.1 ± 0.12 ^{cA}
PCV (%)	C	46.4 ± 1.34 ^{a}	39.5 ± 0.76 ^{b}	42.8 ± 0.90 ^{cB}
	T_1	48.1 ± 0.69 ^{a}	40.8 ± 0.88 ^{b}	48.0 ± 0.73 ^{aA}
	T_2	48.0 ± 0.57 ^{a}	39.3 ± 0.75 ^{b}	49.0 ± 0.60 ^{cA}
	T_3	47.6 ± 0.65 ^{a}	40.6 ± 0.88 ^{b}	49.5 ± 0.46 ^{cA}
Hb (g/dl)	C	12.5 ± 0.23 ^{a}	10.8 ± 0.14 ^{b}	11.8 ± 0.22 ^{cB}
	T_1	12.6 ± 0.23 ^{a}	10.6 ± 0.14 ^{b}	12.5 ± 0.21 ^{cA}
	T_2	12.7 ± 0.24 ^{a}	10.8 ± 0.35 ^{b}	12.8 ± 0.27 ^{cB}
	T_3	12.3 ± 0.19 ^{a}	10.8 ± 0.14 ^{b}	12.5 ± 0.23 ^{cA}

Mean bearing different superscripts (small letters) in a column differs significantly ($P<0.05$)

Mean bearing different superscripts (capital letters) in a row differs significantly ($P<0.05$)

Table 9. Effect of xylazine-ketamine anaesthesia and its reversing agents on the haematological parameters in rabbits

n = 8

Mean ± S.E.

Parameters	Group	Before anaesthesia	During anaesthesia	After recovery
WBC $10^3/mm^3$	C	8.2 ± 87.67 ^{a}	7.1 ± 133.42 ^{b}	7.8 ± 71.45 ^{cB}
	T_1	8.4 ± 165.79 ^{a}	7.0 ± 154.43 ^{b}	8.3 ± 149.65 ^{aA}
	T_2	8.3 ± 127.33 ^{a}	7.1 ± 108.53 ^{b}	8.4 ± 133.31 ^{aA}
	T_3	8.3 ± 155.41 ^{a}	7.3 ± 136.28 ^{b}	8.3 ± 154.23 ^{cA}
Heterophils (%)	C	32.0 ± 0.80 ^{a}	54.0 ± 1.18 ^{b}	35.0 ± 0.44 ^{c}
	T_1	33.0 ± 0.58 ^{a}	48.0 ± 1.43 ^{b}	33.0 ± 0.46 ^{a}
	T_2	32.0 ± 0.60 ^{a}	49.0 ± 1.46 ^{b}	33.0 ± 0.60 ^{c}
	T_3	32.0 ± 0.59 ^{a}	50.0 ± 0.68 ^{b}	33.0 ± 0.50 ^{a}
Lymphocytes (%)	C	62.0 ± 0.87 ^{a}	38.0 ± 1.12 ^{b}	59.0 ± 0.49 ^{c}
	T_1	62.0 ± 0.94 ^{a}	45.0 ± 1.19 ^{b}	62.0 ± 0.63 ^{a}
	T_2	63.0 ± 0.85 ^{a}	44.0 ± 1.49 ^{b}	61.0 ± 0.63 ^{a}
	T_3	62.0 ± 0.65 ^{a}	42.0 ± 0.65 ^{b}	62.0 ± 0.46 ^{a}

Mean bearing different superscripts (small letters) in a column differs significantly ($P<0.05$)

Mean bearing different superscripts (capital letters) in a row differs significantly ($P<0.05$)

Table 10. Effect of xylazine-ketamine anaesthesia and its reversing agents on the haematological parameters in rabbits

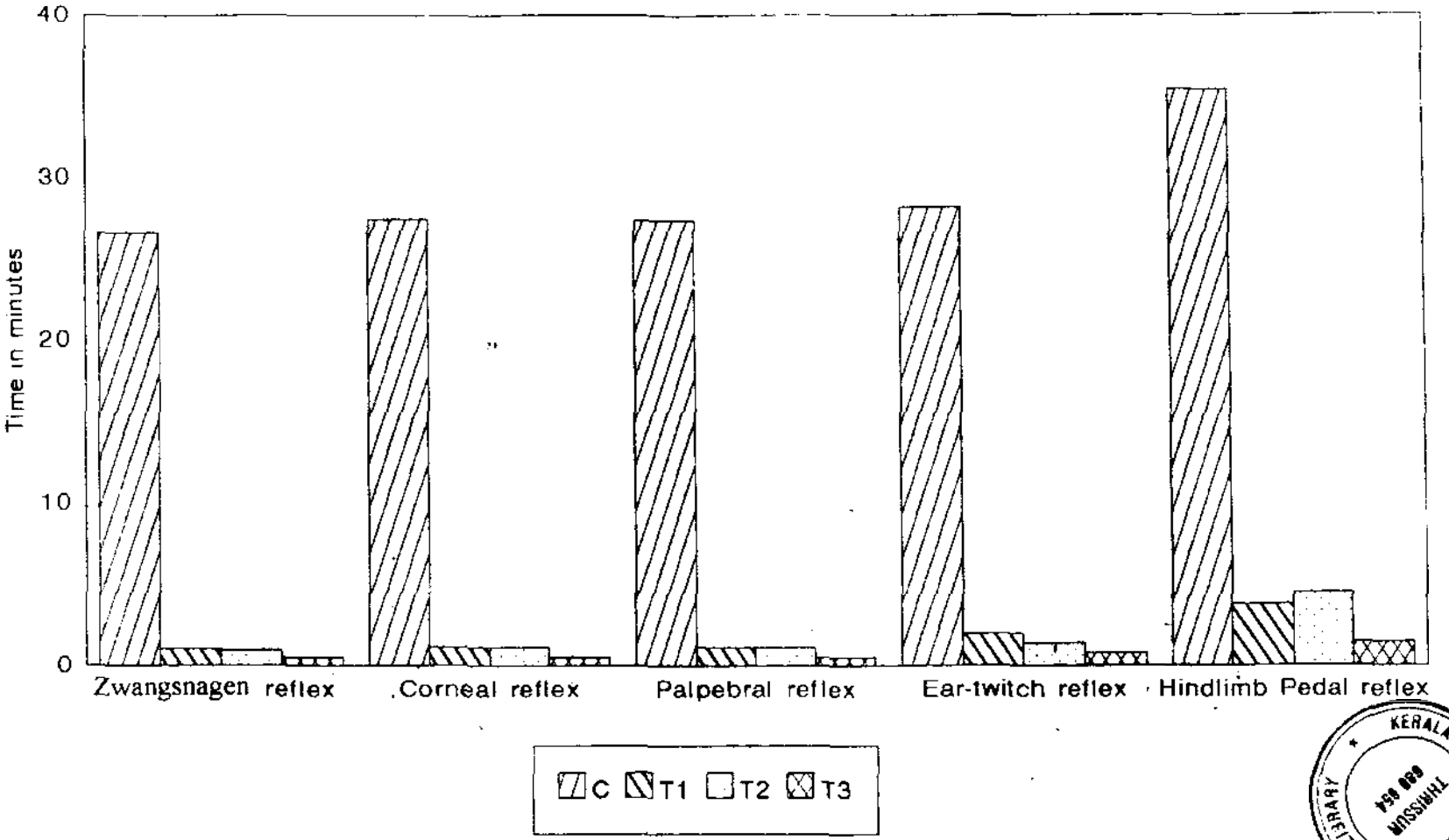
n = 8

Mean ± S.E.

Parameters	Groups	Before anaesthesia	During anaesthesia	After recovery
Monocytes (%)	C	3 ± 0.09 [a]	2 ± 0.06 [b]	3 ± 0.07 [a]
	T_1	3 ± 0.06 [a]	1 ± 0.06 [a]	2 ± 0.12 [a]
	T_2	2 ± 0.09 [a]	1 ± 0.08 [b]	2 ± 0.09 [a]
	T_3	3 ± 0.06 [a]	1 ± 0.11 [b]	2 ± 0.09 [a]
Basophils (%)	C	2 ± 0.11 [a]	1 ± 0.06 [b]	2 ± 0.07 [a]
	T_1	1 ± 0.11 [a]	1 ± 0.11 [a]	2 ± 0.11 [a]
	T_2	2 ± 0.12 [a]	2 ± 0.06 [a]	3 ± 0.00 [a]
	T_3	2 ± 0.06 [a]	2 ± 0.07 [b]	2 ± 0.05 [a]
Eosinophils (%)	C	1 ± 0.09 [a]	5 ± 0.06 [b]	1 ± 0.08 [a]
	T_1	1 ± 0.10 [a]	5 ± 0.08 [b]	1 ± 0.00 [a]
	T_2	1 ± 0.08 [a]	4 ± 0.04 [b]	1 ± 0.06 [a]
	T_3	1 ± 0.08 [a]	5 ± 0.05 [b]	1 ± 0.00 [a]

Mean bearing different superscripts in a column differs significantly ($P<0.05$)

Fig.1 MEAN TIME FOR THE REAPPEARANCE OF REFLEXES IN RABBITS ANAESTHETIZED WITH XYLAZINE-KETAMINE FOLLOWED BY ADMINISTRATION OF REVERSING AGENTS



C- Xylazine-Ketamine (5mg/kg-50mg/kg). T1-Xylazine-Ketamine (5mg/kg-50mg/kg),Yohimbine-4-AP combination (0.125mg/kg-0.2mg/kg). T2-Xylazine-Ketamine (5mg/kg-50mg/kg), Ephedrine (10mg/kg) T3- Xylazine-Ketamine (5mg/kg-50mg/kg), Ephedrine (20mg/kg)

Fig.1a EFFECT OF REVERSING AGENTS ON MEAN TIME FOR THE REAPPEARANCE OF REFLEXES IN XYLAZINE-KETAMINE ANAESTHETIZED RABBITS

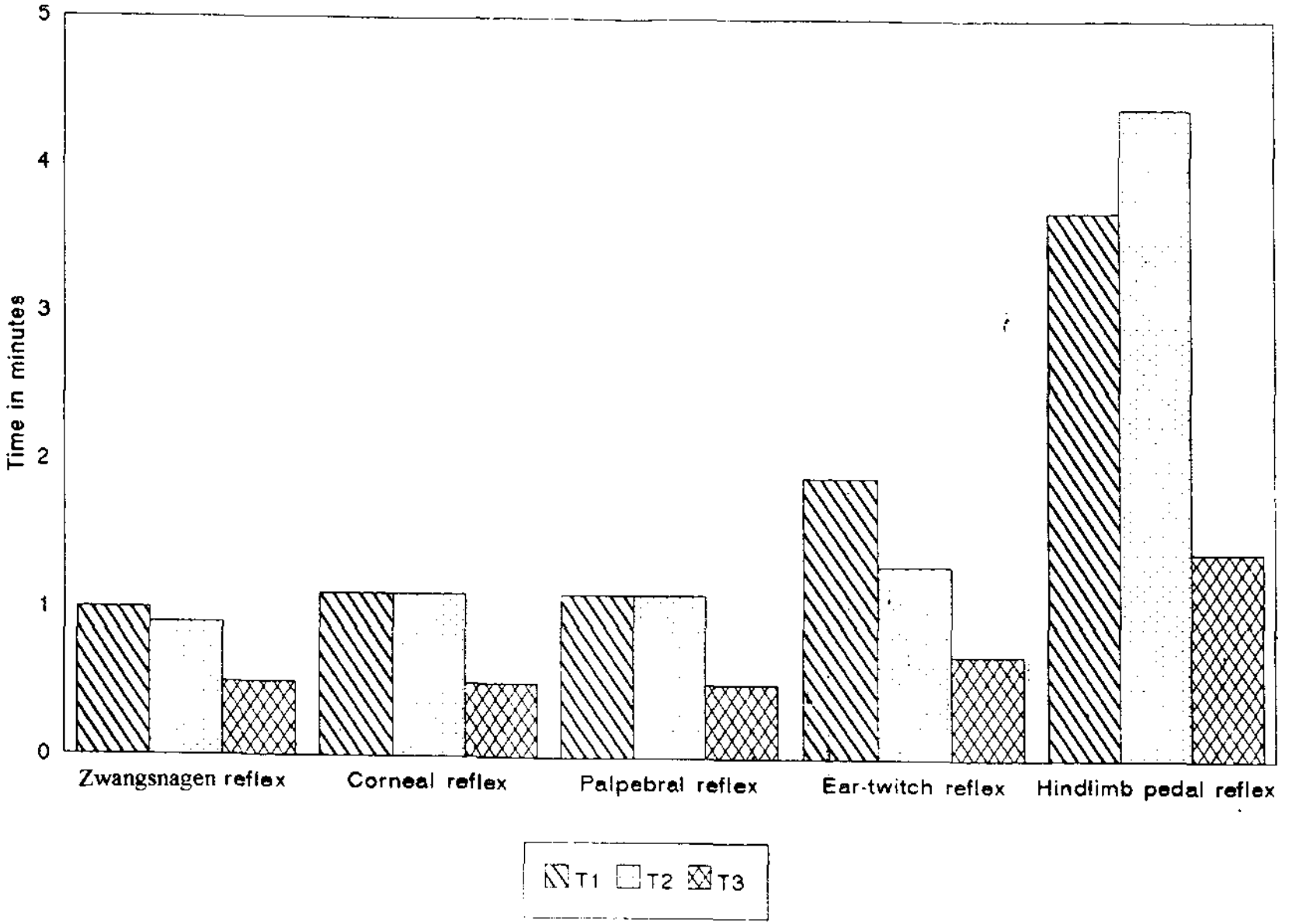


Fig.2 EFFECT OF XYLAZINE-KETAMINE ANAESTHESIA AND ITS REVERSING AGENTS ON ANAESTHETIC PARAMETERS IN RABBITS

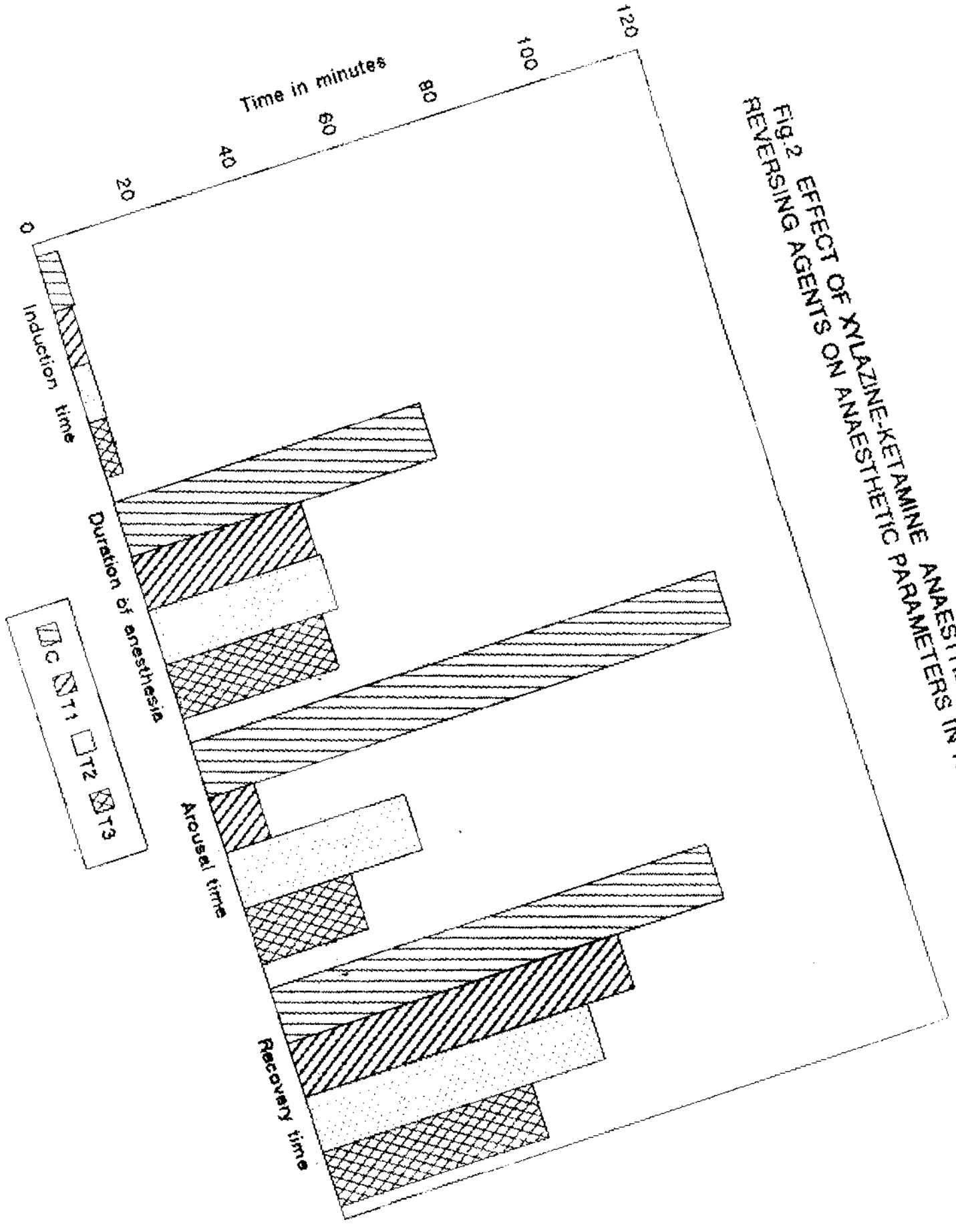


Fig.3 EFFECT OF XYLAZINE-KETAMINE ANAESTHESIA AND ITS REVERSING AGENTS ON MEAN RECTAL TEMPERATURE IN RABBITS

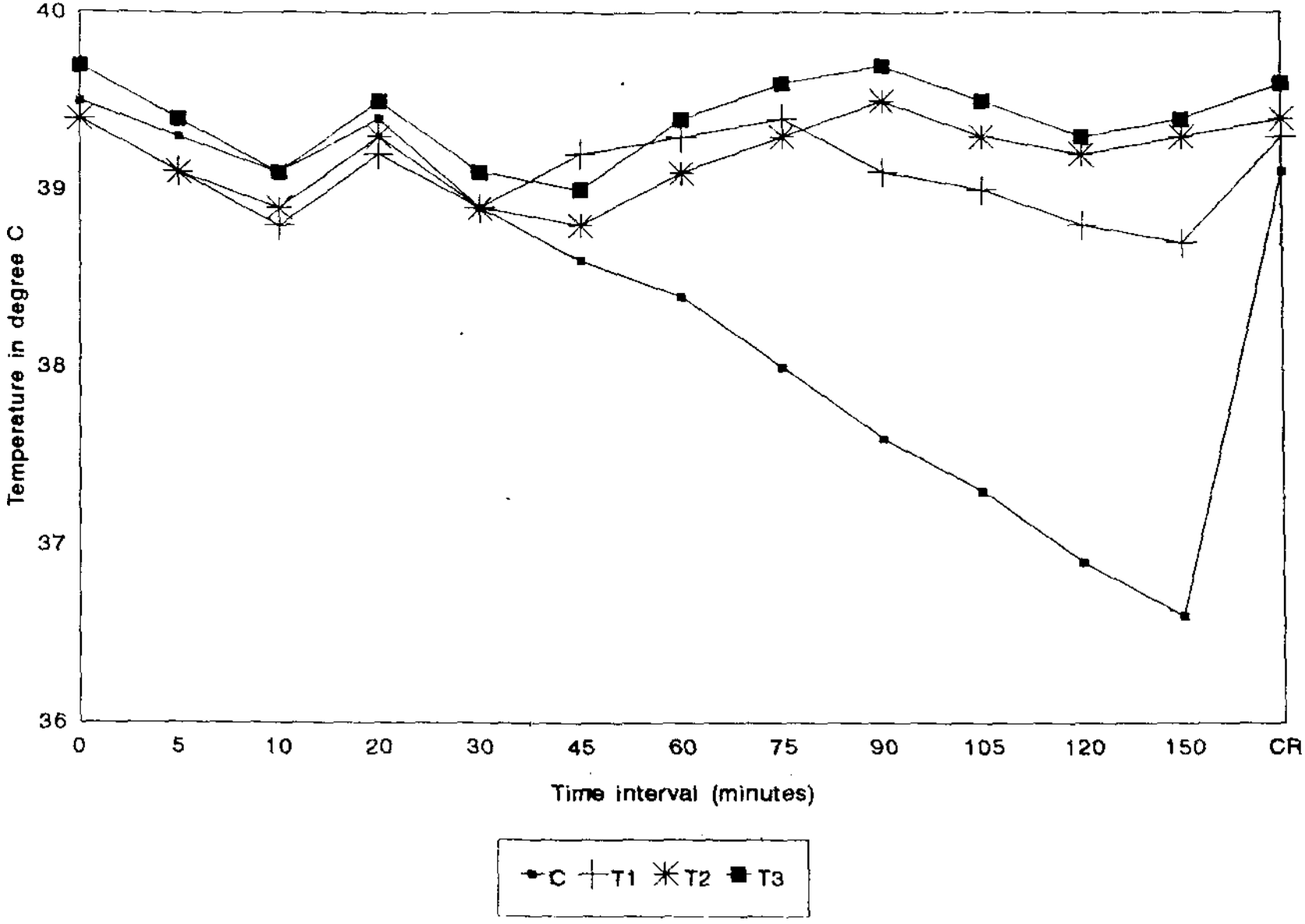


Fig.4 EFFECT OF XYLAZINE-KETAMINE ANAESTHESIA AND ITS REVERSING AGENTS ON MEAN RESPIRATION RATE IN RABBITS

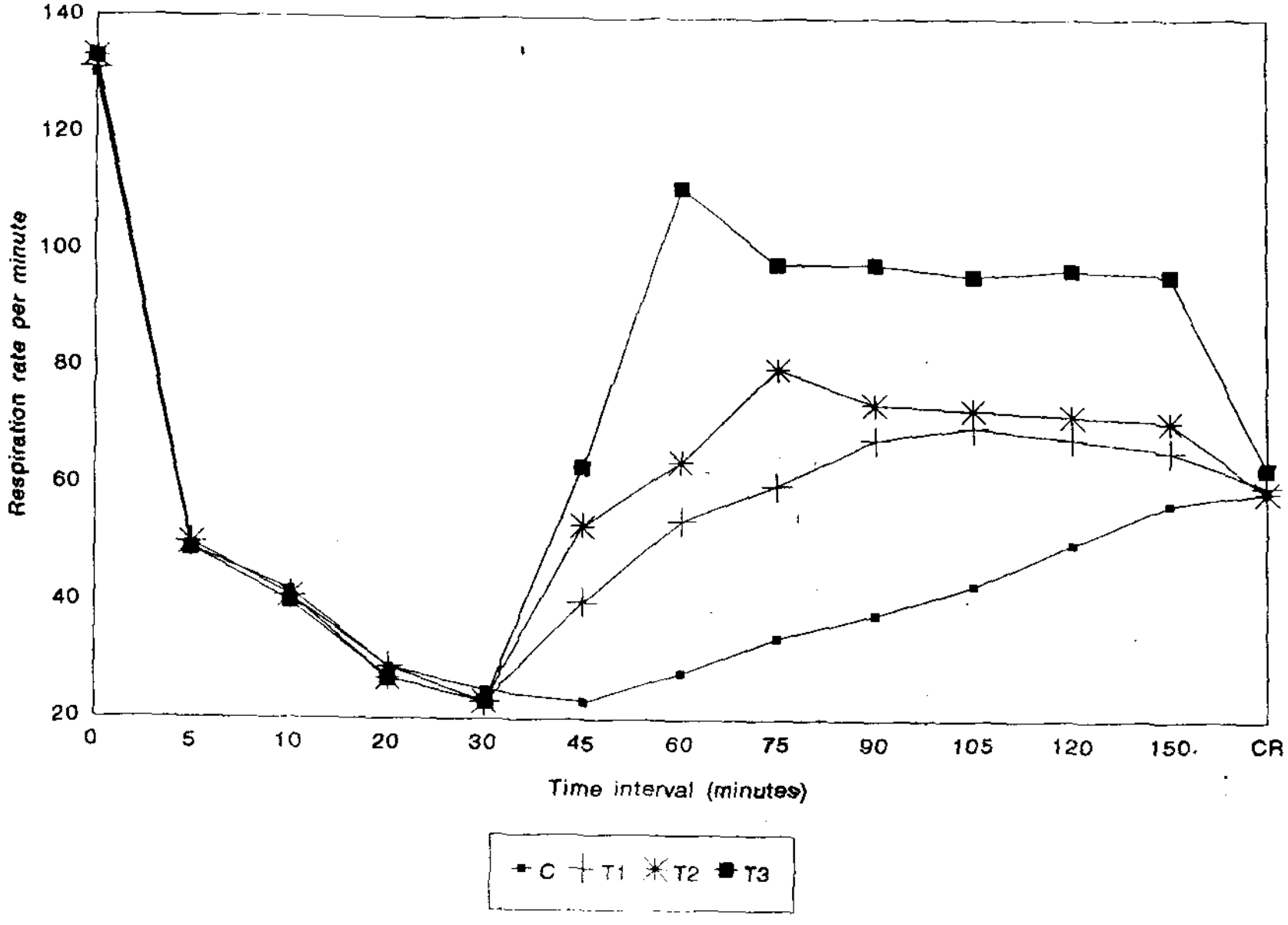
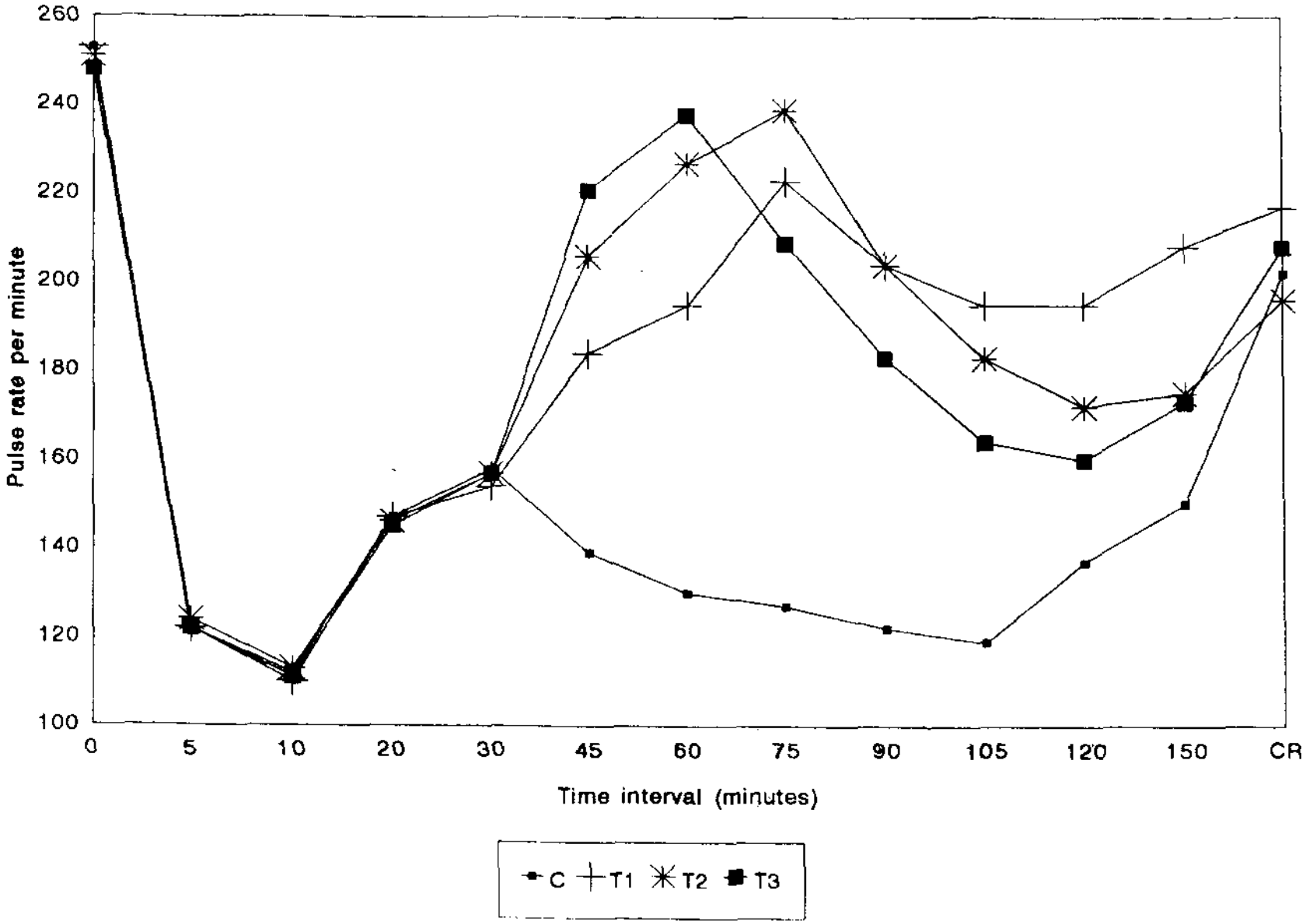


Fig.5 EFFECT OF XYLAZINE-KETAMINE ANAESTHESIA AND ITS REVERSING AGENTS ON MEAN PULSE RATE IN RABBITS



Discussion

DISCUSSION

The objectives of the study were

1) to evaluate the reversing action of ephedrine on xylazine-ketamine anaesthesia in rabbits, and

2) to compare the reversal effects of ephedrine with that of yohimbine-4-aminopyridine (4-AP) combination.

5.1 Anaesthesia

5.1.1 Reflex studies

In the present study, rabbits in all four groups were anaesthetized with xylazine-ketamine combination (5 mg/kg and 50 mg/kg respectively) administered intramuscularly at 15 min. interval.

Clinical responses noticed in rabbits after xylazine administration were, marked lowering of head, incoordination and sternal recumbency within 5 to 10 min. of xylazine administration. Renecker and Olsen (1985) also observed similar responses to xylazine injection in moose and deer.

Subsequent administration of ketamine resulted in disappearance of righting reflex, followed by hindlimb pedal, corneal, palpebral and the ear-twitch reflexes in sequence. Righting reflex lost within 1.4 min. of ketamine injection. The onset of anaesthesia (induction time) was indicated by loss of reactivity to

pinching the interdigital skin of hindlimbs and it was achieved within 3.4 to 4.2 min. of ketamine administration in different groups. This is also in agreement with the observation made by Nowrouzian *et al.* (1981) in sheep (3.2 min.) and by Tiwari *et al.* (1994) in dogs (3-5 min.) after xylazine-ketamine administration. Rapid onset of anaesthesia could be attributed to the high lipid solubility and increased distribution rate of ketamine (Waterman, 1984).

Absence of response to corneal, palpebral and ear-twitch reflexes were observed within 4.5, 4.5 and 4.6 min. respectively of ketamine administration (Table 1). Lipman *et al.* (1987) also noticed loss of palpebral reflex within 5 min. of xylazine-ketamine administration in rabbits.

A feature which indicate regaining of consciousness or reversal from xylazine-ketamine anaesthesia was the onset of Zwangsnagen reflex. The jaws of the rabbits started moving in a chewing fashion as like the process of eating and occasionally the tongue would flick in and out in a lapping motion.

Group 'C' was used as control, in which animals were not given any reversing agent.

In the middle of anaesthesia ie., at 30 min. after anaesthetic induction (as the mean duration of anaesthesia calculated from control group was 60.6 min.) treatment group T_1 received a combination of yohimbine and 4-AP (0.125 mg/kg and 0.2 mg/kg respectively I/V), group T_2 was given ephedrine at a dose rate of

10mg/kg body weight I/V and group T_3 received ephedrine at a dose rate of 20 mg/kg body weight I/V.

Rabbits in treatment groups T_1, T_2 and T_3 showed the Zwagnagen reflex within 1.0 ± 0.02, 0.9 ± 0.03 and 0.5 ± 0.04 min. respectively when compared to control group (22.4 ± 2.15 min.). Thirty min. after induction of anaesthesia was taken as zero time both in control as well as in treatment groups.

Mean time for appearance of Zwangsnagen, corneal, palpepbral and ear-twitch reflexes were significantly reduced in groups T_1, T_2 and T_3 when compared to control group (Table 2, Fig.1 and 1a). The mean time for reappearance of aforementioned reflexes were not statistically significant between groups T_1, T_2 and T_3.

In T_1 group animals regained hindlimb pedal reflex within 3.7 ± 0.22 min. of administration of yohimbine and 4-AP combination. Similar response was reported by Lipman *et al.* (1987), after the administration of yohimbine in xylazine-ketamine anaesthetized rabbits.

Ephedrine significantly reduced the time for reappearance of reflexes at both the dosages studied, but animals in T_3 group (20 mg/kg ephedrine) regain the hindlimb pedal reflex in significantly shorter time as compared to T_2 group (10 mg/kg ephedrine). This indicates rapid recovery of reflexes after ephedrine administration.

5.1.2 Anaesthetic studies

In control group, anaesthesia last for the mean duration of 60.6 ± 1.22 min. *White and Holmes (1976) observed* 20-75 min. of surgical anaesthesia in rabbits when ketamine-xylazine combination (35 mg/kg and 5 mg/kg respectively I/M) was used.

Lipman *et al.* (1987) reported a significant reduction in the duration of anaesthesia in yohimbine treated rabbits (34.2 min.) as compared to controls (65 min.). This is in agreement with the present study (Table 3, Fig.2).

Xylazine has been reported to produce sedation and analgesia by stimulating central presynaptic alpha-2 adrenoceptors. When these receptors are activated, it inhibit norepinephrine release from adrenergic nerve terminals possibly by inhibiting the calcium influx that occur during the action potential (Langer, 1981). Cholinergic, serotonergic, dopaminergic and opiate receptors also are involved in the mechanism of xylazine induced sedation (Kitzman *et al.*, 1982).

Yohimbine is a selective, alpha-2 adrenergic antagonist of xylazine, which competitively blocks alpha-2 receptors and potentiate norepinephrine release (Gross and Tranquilli, 1989).

Antagonism of ketamine may occur by release of central neuronal dopamine and norepinephrine (Booth and McDonald, 1982). Yohimbine has also been reported to stimulate acetylcholine, serotonin and dopamine release from

their respective neurons, which could be attributed to its partial antagonist action on ketamine anaesthesia (Hatch *et al.*, 1983).

Booth *et al.* (1982) reported that, 4-AP accelerates recovery from a number of CNS depressants by selectively blocking potassium current of repolarisation after an action potential, thereby facilitating calcium influx which evoked the release of acetylcholine and other neurotransmitters from prejunctional nerve endings.

In the present study ephedrine at the dose rate of 10 mg/kg body weight (T_2 group) shortened the anaesthetic duration to 34.2 min. and this was not statistically significant from T_1 group indicating that ephedrine at 10 mg/kg is equally effective as yohimbine -4-AP combination in shortening the duration of xylazine-ketamine anaesthesia.

Anaesthetic duration was reduced significantly to 31.1 ± 0.13 min. in (animals received 20 mg/kg ephedrine) T_3 group as compared to T_1 and T_2 groups (33.6 ± 0.35 and 34.2 ± 0.23 min. respectively). But tachycardia, panting type of respiration and pupillary dilatation (Mydriasis) were more pronounced in T_3 group as compared to T_2 group.

In control group, animals regained the righting reflex (arousal time) in 103.85 ± 1.4 min. All the reversing agents tested (yohimbine-4-AP combination, ephedrine 10 mg/kg and 20 mg/kg) significantly decreased the arousal time

(Table 3). The mean arousal time of treated groups T_1, T_2 and T_3 was significantly different from each other with the greatest decrease in T_1 group. This indicates that with respect to arousal time yohimbine-4-AP combination is better than ephedrine as a reversing agent.

Since yohimbine acts on many of the same receptor mechanisms as xylazine and selective antagonism on central alpha-2 adrenoceptor produced early arousal from xylazine-ketamine anaesthesia. This is in accordance with the observations made by Cronin *et al.* (1983) and by Hsu and Lu (1984) in cats.

Both doses of ephedrine significantly shortened the arousal time when compared to controls, with greater decrease in T_3 group (21.3 ± 2.11 min.) i.e., in animals that received 20 mg/kg ephedrine as compared to T_2 group (35.5 ± 0.87 min.). The arousal effect of ephedrine on xylazine-ketamine anaesthesia could be attributed to its capability of facilitating adrenergic synaptic function by enhancing dopamine and norepinephrine release.

According to Tiwari *et al.* (1994) complete recovery was seen after 90 ± 3.75 min. with xylazine-ketamine anaesthesia in dogs. This is in agreement with the present observation in rabbits in control group (86.9 ± 2.5 min.) (Table 3 and Fig.2).

In a comparison of recovery time in the control and treatment groups C, T_1, T_2 and T_3, all were significantly different from each other. Yohimbine-4-AP

combination significantly reduced the recovery time to 65.4 ± 1.1 min. in T_1 group as compared to controls (86.9 ± 2.5 min.).

Among the treated groups, T_3 (ephedrine 20 mg/kg) showed the shortest recovery time (41.5 ± 1.33 min.). This suggests that ephedrine at the dose rate of 20 mg/kg body weight is more effective than 10 mg/kg ephedrine or yohimbine-4-AP combination, in producing rapid recovery from xylazine-ketamine anaesthesia.

In control group, corneal, palpebral and ear-twitch reflexes were abolished for 52.1 ± 1.8, 52.3 ± 2.1 and 52.6 ± 1.95 min. respectively. These values were significantly decreased in treatment groups T_1, T_2 and T_3 (Table 4).

Righting reflex disappeared for 102.2 ± 1.36 min. in control group. A similar finding was reported by Lipman *et al.* (1987) who recorded 104.5 ± 8.4 min. in rabbits anaesthetized with xylazine-ketamine combination.

The three treatment groups differ significantly from each other in duration of absence of righting reflex and this was more in T_2 group followed by T_3 and T_1 (Table 4).

The present study suggested that yohimbine-4-AP combination was a better reversing agent with respect to regaining of righting reflex.

Ephedrine is one of the sympathomimetic amine with CNS stimulant property. Ephedrine was found to stimulate cerebral cortex and reticular activating system in brain, by increasing firing of noradrenergic neurons in these

areas. By this action, it produces arousal or wakefulness from CNS depressant drugs like morphine and barbiturates. Ephedrine also facilitates monosynaptic and polysynaptic transmission in spinal cord and promotes righting movements and postural activity (Innes and Nickerson, 1975).

Since inhibition of norepinephrine release in CNS is the major contributing factor for xylazine induced sedation, ephedrine can effectively antagonize it by potentiating release of central catecholamines located both outside and within the storage granules in the cytoplasm of dopaminergic and noradrenergic neurons (Usdin and Forrest, 1976).

5.2 Physiological parameters

5.2.1 Rectal temperature

A significant reduction in temperature was recorded in all four groups within 10 min. of xylazine administration (Table 5 and Fig.3). Chitale *et al.* (1998) reported that xylazine produced this centrally mediated hypothermia through activation of hypothalamic alpha-2 adrenoceptors, inhibiting the heat conserving mechanism.

After ketamine administration, the rectal temperature showed a transient increase in 20 min. time. This could be due to sympathomimetic effect of ketamine. A similar response was observed after ketamine injection by Thurmon *et al.* (1973) in sheep.

Progressive fall in temperature throughout the 150 min. period recorded in control group might be due to prolonged depressant effect of xylazine on the compensatory mechanisms of thermoregulatory centre such as shivering and tachypnoea (Ponder and Clark, 1980). Another contributing factor may be the high susceptibility of rabbits to radiative and conductive heat losses during anaesthesia because of their high body surface area/body weight ratio (Huerkamp, 1995). A similar hypothermia was reported during xylazine-ketamine anaesthesia by Hobbs *et al.* (1991) in rabbits. The rectal temperature increased to pre-anaesthetic value within 45 min. of receiving yohimbine and 4-AP combination in T_1 group. Takase *et al.* (1987) reported that yohimbine and to a lesser extent 4-AP prevented the hypothermia induced by xylazine-ketamine combination in dogs. This response could be attributed to the alpha-2 antagonistic effect of yohimbine on xylazine induced hypothermia and subsequent elevation of metabolic rate.

There was a gradual rise in rectal temperature after ephedrine administration in the groups T_2 and T_3. This shows effective reversal of xylazine-ketamine induced hypothermia by ephedrine. Increase in temperature after ephedrine administration may be due to its stimulating effect on sympathetic centres in posterior hypothalamus which resulted in peripheral vasoconstriction and potentiation of norepinephrine release with subsequent increase in metabolic rate and heat production (Guyton and Hall, 1996). On comparison it is evident

that group T_2 and T_3 performed better than T_1 in keeping up the body temperature in rabbits.

5.2.2 Respiration rate

In the present study, base line respiration rates in all four groups were higher than normal values reported for rabbits (Table 6 and Fig.4). Physical restraint alone has been shown to increase the respiration rate (Popilskis *et al.*, 1991). Breathing rate decreased significantly after xylazine administration and decreased further after ketamine was given. In control group the respiratory rate remain depressed until the return of pedal reflex and rose gradually until recovery. This change in respiratory rate during xylazine-ketamine anaesthesia concurs with the findings of Haskins *et al.* (1986) in dogs.

Respiratory depression observed in the present study could be due to direct inhibitory action of xylazine on medullary respiratory centre (Lele and Bhokre, 1985) and desensitization of baroreceptors by the pressor response of ketamine. Desensitization of baroreceptor could affect the respiratory rate because these special neurons were the excitation points for respiration (Tenney, 1977).

In group T_1 mean respiratory rate increased significantly after the administration of yohimbine and 4-AP combination. Yohimbine had been reported to reverse the xylazine-ketamine induced respiratory depression in cats (Hsu and Lu, 1984) in mule deer (Jessup *et al*, 1983) and in rabbits (Lipman *et al*, 1987). The antagonistic action of yohimbine and 4-AP combination on respiratory

depression could be attributed to their stimulant effect on ventilation (Komulainen and Olson, 1991).

Rapid respiration rate during recovery was observed in groups T_2 and T_3. Panting type of respiration (hyperventilation) indicates effective reversal of respiratory depression by ephedrine. This reversing effect of ephedrine on respiratory depression appears to be in response to direct stimulation of medullary respiratory centre in brain by increased firing of noradrenergic neurons, innervating the medulla (Adams, 1988).

Ephedrine was reported to be used as an analeptic agent in treatment of morphine and barbiturate poisoning (Levy and Ahlquist, 1971). The result indicates that ephedrine is equally effective as yohimbine-4-AP combination in reversing the respiratory depression due to xylazine-ketamine anaesthesia in rabbits.

5.2.3 *Pulse rate*

Marked bradycardia and significant reduction in pulse rate were observed within 10 min. of xylazine administration. Then the pulse rate showed a transient increase for 15 min. after ketamine injection (Table 7 and Fig.5). Pulse rate among the four groups did not differ significantly at 5 to 30 min. interval. In control group, there was a gradual reduction in pulse rate from 45 to 105 min. time which showed a tendency to reach normal range by 120 min., eventhough not returned to baseline values. Similar observations were reported after ketamine-

xylazine anaesthesia by Haskins *et al.* (1986) in dogs and by Ludders *et al.* (1987) in rabbits.

Xylazine induced bradycardia and decrease in pulse rate could be attributed to the activation of pre and postsynaptic central and peripheral alpha-2 adrenoceptors which resulted in decreased sympathetic outflow from the CNS, increased vagal tone due to facilitation of baroreceptors reflex and decreased release of norepinephrine from sympathetic nerve endings (Hsu and Lu, 1984; Hsu *et al.*, 1985). Transient increase in pulse rate after induction with ketamine was probably due to direct depression of baroreceptor activity, causing a centrally mediated, reflex increase in sympathetic tone (Wright, 1982).

Chitale *et al.* (1998) suggested that the prolonged and predominant depressant action of xylazine on cardiovascular system attributed to the decrease in pulse rates observed in subsequent recording times in control group.

In group T_1, a significant increase in pulse rate was recorded within 15 min. and was continuous for about 45 min. of administration of yohimbine-4-AP combination. The similar response to yohimbine was reported during xylazine-ketamine anaesthesia by Lipman *et al.* (1987) in rabbits.

This reversal effect of yohimbine and 4-AP combination probably are due mainly to the yohimbine component, since 4-AP alone was reported to be ineffective in antagonizing cardiovascular effect of xylazine (Hsu *et al.*, 1985).

Yohimbine reversed the xylazine induced bradycardia and decrease in pulse rate by promoting the sympathetic outflow from the CNS and inhibiting baroreceptor activities (Hsu *et al.*, 1985).

There was a dose dependant increase in pulse rate upto 30 min. of ephedrine administration in groups T_2 and T_3. A significant increase of pulse rate by ephedrine might be due to its both direct sympathomimetic action on alpha receptors in blood vessels and indirect action through increased release of norepinephrine from central and peripheral noradrenergic neurons.

Marked decrease in pulse rate (within normal range) was observed after 45 min. of reversal with ephedrine in both groups T_2 and T_3. This significant decrease in pulse rate appears to be in response to activation of compensatory vagal reflex activity (Hoffman and Lefkowitz, 1996).

In all the treatment groups T_1, T_2 and T_3 eventhough the pulse rate has decreased after 45 min. of administration of reversing agent it has not gone below normal as in case of control. Both doses of ephedrine is found to be equally effective as yohimbine-4-AP combination with respect to reversing cardiovascular effect of xylazine-ketamine.

Haematology

In the present study, haematological parameters like PCV, Hb concentration and total erythrocyte count showed a significant decrease during xylazine-ketamine anaesthesia in all four groups (Table 8).

The changes in haemogram and leukogram, observed during xylazine-ketamine anaesthesia in this study were comparable to those observed by Nowrouzian *et al.* (1981) in sheep, by Usha *et al.* (1990) in dogs and by Chitale *et al.* (1998) in goat. The temporary anaemia during xylazine-ketamine anaesthesia might be due to alpha-2 agonist action of xylazine by which, it reduced the sympathetic tone, thereby resulting in pooling of circulatory erythrocytes in spleen. Another contributing factor for the haemodilution could be due to intercompartmental fluid shift (migration of interstitial fluid into the vascular compartment) (Reddy *et al.*, 1991).

The significant decrease in total leukocytes and lymphocytes (lymphocytopaenia) with a subsequent rise of heterophils (heterophilia) and eosinophils (eosinophilia) in all the four groups during anaesthesia (Table 9 and 10) might be attributed to the adrenocortical stimulation and subsequent effect of glucocorticoids on circulating heterophils and lymphocytes (Schalm *et al.*, 1965). Steffy *et al.* (1979) reported these changes as the classic stress leucogram.

In control group, all the blood parameters, increased, but not returned to the pre-administration levels even after complete recovery. In T_1 group these values

returned to pre-anaesthetic levels after complete recovery, which could be attributed to the yohimbine induced increased release of epinephrine through its alpha-2 blocking property (Kathirvel, 1997).

Mean haemoglobin, PCV and total erythrocyte count increased significantly above the pre-anaesthetic level after ephedrine administration in groups T_2 and T_3. Wagner *et al.* (1993) observed a similar response to ephedrine in isoflurane anaesthetized dogs. Ephedrine produced this response by potentiating release of epinephrine, which reduces circulatory plasma volume by loss of protein freefluid to extracellular space, and also by contraction of spleen (Hoffman and Lefkowitz, 1996).

Comparing the reversing effect of ephedrine with the yohimbine and 4-AP combination, ephedrine is proved to be an easily available and cost effective alternative to yohimbine and 4-AP combination in reversing xylazine-ketamine anaesthesia in rabbits.

Summary

SUMMARY

The experiment was conducted to assess and compare the reversing action of ephedrine with some of the recently developed antagonists combination, like yohimbine and 4-AP in xylazine-ketamine anaesthesia in rabbits.

Thirty two NewZealand White rabbits divided into four groups of eight each were used for the study. Group 'C' was kept as control which received xylazine (5 mg/kg I/M) and 15 min. later ketamine (50 mg/kg I/M). Groups T_1, and T_2 and T_3 served as treatments which received the anaesthesia scheduled as in group'C'.

In the middle of anaesthesia i.e., 30 min. after induction of anaesthesia (as the mean duration of anaesthesia calculated from group 'C' was 60.6 min.) animals in T_1 group were given yohimbine and 4-AP combination (0.125 mg/kg and 0.2 mg/kg respectively I/V), T_2 group animals received ephedrine (10 mg/kg I/V) and T_3 group animals were administered ephedrine (20 mg/kg I/V).

The anaesthetic parameters like the sequence and time of disappearance and reappearance of righting, corneal, palpebral, ear-twitch and hindlimb pedal reflexes were recorded for all four groups. Time of onset of Zwangsnagen reflex, duration of anaesthesia and time of sitting were also noticed for all groups. The rectal temperature, pulse rate and respiration rate were recorded before and at 5, 10, 20, 30, 45, 60, 75, 90, 105, 120, 150 min. after xylazine administration and

also after complete recovery. The haemogram was also studied before, during anaesthesia and after complete recovery for all four groups.

Peripheral reflexes disappeared in the following sequence: righting, hindlimb pedal, corneal, palpebral reflexes and then ear-twitch reflex.

Disappearance of righting reflex was noticed at 1.7, 1.2, 1.4 and 1.4 min. respectively for the four groups after the administration of ketamine. There was no significant difference in these values among the four groups. Similarly, the meantime for disappearance of corneal, palpebral and ear-twitch reflexes also showed no significant difference among groups.

Induction time (mean time for the disappearance of hindlimb pedal reflex) for the groups C, T_1, T_2 and T_3 was 4.2, 3.7, 3.6 and 3.4 min. respectively. Statistical analysis revealed no significant variation among the four groups as the same anaesthetic schedule was adopted for all four groups.

Animals regained consciousness with the beginning of Zwangsnagen reflex, followed by reappearance of corneal, palpebral, ear-twitch and hindlimb pedal reflexes. Onset of Zwangsnagen reflex was noticed at 22.4 min. (i.e., after 30 min. of induction of anaesthesia) in control and at 1, 0.9, 0.5 min. after the administration of reversing agents respectively in three treatment groups. These values were found to be significantly different between control and treatment groups T_1, T_2 and T_3. Similarly the mean time for reappearance of corneal, palpebral, hindlimb pedal and ear-twitch reflexes proved significant variation

between control and treatment groups. There was no significant difference between three treated groups in time of reappearance of aforementioned reflexes except hindlimb pedal reflex which was significantly shorter in T_3 group when compared to groups T_1 and T_2.

The duration of xylazine-ketamine anaesthesia was 60.6, 33.6, 34.2 and 31.1 min. respectively for groups C, T_1, T_2 and T_3. These values were found to be significantly different between control and treatment groups and also between T_3 and T_1, T_2 groups. These values were not statistically significant between treatment groups T_1 and T_2.

The time taken to regain the righting reflex (arousal time) and the time of sitting (recovery time) showed significant difference between four groups C and T_1 and T_2 and T_3. The mean values for the time of regain of righting reflex were 103.85, 9.1 35.5 and 21.3 min. respectively and for the time of sitting were 86.9, 65.4, 56.0 and 41.5 min. respectively.

Mean duration of absence of corneal, palpebral and ear-twitch reflexes showed significant difference only between control group and three treatment groups. There was no significant difference between T_1, T_2 and T_3 for these parameters.

Duration of absence of righting reflex showed significant difference between four groups and it was 102.2, 41.3, 67.7 and 52.6 min. respectively.

The rectal temperature showed a similar pattern of variation in all groups at 5 to 30 min. after xylazine administration i.e., significant decrease of about 0.4 to 0.6°C after xylazine injection and then a transient increase to near pre-xylazine values after 5 min. of ketamine administration.

In control group, the temperature decreased progressively in subsequent recording times and returned to normal range after complete recovery.

Rectal temperature was found to be significantly increased in all treatment groups after administration of reversing agents. From 45 to 75 min., increase in temperature was significantly greater for the groups T_1 and T_3 when compared to T_2. From 90 to 150 min., there was a significantly greater increase in temperature for the groups T_2 and T_3 when compared to T_1.

The respiratory rate decreased to a mean value of 41/min. in 10 min. of xylazine administration and later decreased gradually to a below normal value of 23/min. in 30 min. time in all the four groups. In control group, the respiratory rate (28/min.) remain decreased upto 60 min. time which showed a tendency to reach normal range by 90 min. time (38/min.). Highly significant difference in respiration rate was found to exist between the four groups at 45, 60, 75, 90, 105, 120 and 150 min. respectively during recovery. In groups T_1, T_2 and T_3 respiration rate showed a significant increase from 40, 53 and 63/min. respectively in 45 min. to 66, 71 and 96/min. respectively in 150 min. time. Increase in respiration rate was found to be greater for T_2 and T_3 when compared to T_1.

Pulse rate also showed a similar pattern in all the four groups at 5 to 30 min. time i.e., aprogressive decrease from a mean baseline value of 253/min. to about 111/min. in 10 min. time and then a transient increase to a mean value of 156/min. in 30 min. time.

Thereafter the pulse rate decreased gradually to 119/min. in 105 min. time in control group then it increased to 150/min. in 150 min. time. Highly significant difference in pulse rate could be seen to exist between four groups at 45, 60, 75, 105, 120 and 150 min. time and the decrease was greater for the control group when compared to treatment groups.

In treatment groups pulse rate showed a significant increase (195, 227 and 238/min.) in 60 min. time and the increase was greater for the groups T_2 and T_3 when compared to T_1 . After that the pulse rate remain decreased to 208/min. in 150 min. time in T_1 group. Pulse rate showed a slight decrease from 75-105 min. time in T_2 and T_3 group.

From the study of haemogram it was observed that the total RBC count, Hb concentration, PCV and total WBC count showed a significant decrease during anaesthesia in all the groups. Differential leucocyte count showed heterophilia, lymphocytopaenia and eosinophilia during anaesthesia in all four groups.

After complete recovery, these changes in haematological parameters reached within the normal range in control group, increased to preanaesthetic values in T_1 group and increased above the baseline values in T_2 and T_3 groups.

Following conclusions could be drawn from the results of the experiment:

1. Ephedrine at both doses studied (10 mg/kg and 20 mg/kg) are equally effective as yohimbine and 4-AP combination in reducing the time for reappearance of peripheral reflexes in xylazine-ketamine anaesthetized rabbits.

2. Ephedrine at dose rate of 10/mg/kg is equally effective as yohimbine and 4-AP combination in shortening the duration of xylazine-ketamine anaesthesia in rabbits.

3. Yohimbine and 4-AP combination was found to be more effective than ephedrine in reducing the arousal time.

4. Ephedrine at the dose rate of 20 mg/kg body weight (T_3 group) produced shortest recovery time among the reversing agents tested and it is followed by ephedrine 10 mg/kg and yohimbine 4-AP combination.

5. There was a dose dependent shortening of duration of anaesthesia and recovery time in ephedrine treated groups (T_2 and T_3 groups) and are significantly shorter in animals received 20 mg/kg ephedrine than in animals received 10/mg/kg ephedrine.

6. Cardiopulmonary depression and hypothermia associated with xylazine-ketamine anaesthesia were effectively reversed following the treatment with yohimbine and 4-AP combination (T_1 group) and ephedrine at dosages of 10 mg/kg and 20 mg/kg body weight.

7. Haematological studies proved that all reversing agents tested completely reversed the haematological changes observed during xylazine-ketamine anaesthesia.

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EFFECT OF EPHEDRINE AND 4 - AMINOPYRIDINE - YOHIMBINE COMBINATION IN REVERSING THE KETAMINE – XYLAZINE ANAESTHESIA IN RABBITS

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ABSTRACT OF A THESIS

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ABSTRACT

An attempt was made to assess the efficacy of ephedrine as a reversing agent in comparison with the known antagonists combination, yohimbine and 4-AP in xylazine-ketamine anaesthesia in rabbits.

The study was conducted in thirty two NewZealand White rabbits divided into four groups of eight each. All the four groups (C, T_1, T_2 and T_3) were anaesthetized with 5 mg/kg xylazine and 50 mg/kg ketamine administered intramuscularly at 15 min. interval. Group 'C' served as control, groups T_1, T_2 and T_3 served as treatments. In the middle of anaesthesia i.e., 30 min. after induction of anaesthesia, group T_1 received yohimbine and 4-AP combination (0.125 mg/kg and 0.2 mg/kg respectively I/V), group T_2 were given ephedrine (10 mg/kg I/V) and group T_3 received with ephedrine (20 mg/kg I/V).

The anaesthetic parameters like the sequence and time of disappearance and reappearance of righting, corneal, palpebral, ear-twitch and hindlimb pedal reflexes, duration of anaesthesia, arousal and recovery time were observed for all groups. The rectal temperature, pulse rate and respiration rate were recorded at 0, 5, 10, 20, 30, 45, 60, 75, 90, 120, 150 min. during anaesthesia and also after complete recovery. Haemogram was also studied before, during and also after complete recovery from anaesthesia. The sequence and time of disappearance of reflexes are as follows. Righting reflex was the first to disappear (1.4 min.)

followed by hindlimb pedal, corneal, palpebral and ear-twitch reflexes disappeared at 3.7, 4.5 and 4.6 min. respectively after ketamine administration in all the four groups. The mean time for disappearance of aforesaid reflexes showed no significant variation among the different groups as the same anaesthetic schedule was adopted for all the groups. Animals regained consciousness with the onset of Zwangsnagen reflex, followed by reappearance of corneal, palpebral, ear-twitch and hindlimb pedal reflex. Time for appearance of Zwangsnagen, corneal, palpebral and ear-twitch reflexes were significantly reduced in treatment groups when compared to control and there was no significant difference between treatment groups for these parameters. Time for reappearance of hindlimb pedal reflex was significantly shorter for group T_3 when compared to groups T_1 and T_2.

In comparison with control group (60.6 min.) the mean duration of anaesthesia was significantly reduced for treatment groups T_1, T_2 and T_3 (33.6, 34.2 and 31.1 min. respectively). This decrease was significantly greater in T_3 when compared to T_1 and T_2 . Statistical analysis showed no significant difference between T_1 and T_2 in duration of anaesthesia.

All the four groups differ significantly from each other in the arousal and recovery time. Shortest arousal time was recorded in T_1 group (9.1 min.) followed by T_3 (21.3 min.) and T_2 (35.5 min.). Arousal time in control group was 103.85 min. The duration of time taken for recovery was greater for control group

(86.9 min.) followed by groups T_1 and T_2 (65.4 and 56.0 min. respectively). These values were found to be significantly shorter for the group T_3 (41.5 min.).

The rectal temperature, pulse and respiration rates were significantly decreased below normal values during xylazine-ketamine anaesthesia. These parameters were found to be increased significantly after administration of reversing agents in all treatment groups when compared to control group. The study of haemogram showed that Hb, PCV, total RBC and total leucocyte counts were significantly decreased during anaesthesia. These haematological changes were completely reversed by administration of reversing agents in treatment groups. From the results of the present study it could be concluded that ephedrine can be used as an alternative to yohimbine and 4-AP combination in reversing the anaesthesia produced by xylazine-ketamine combination in rabbits.