MIDAZOLAM IN COMBINATION WITH GLYCOPYRROLATE AND XYLAZINE AS A PREANAESTHETIC FOR GENERAL ANAESTHESIA IN DOGS

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Thesis submitted in partial fulfilment of the requirement for the degree of

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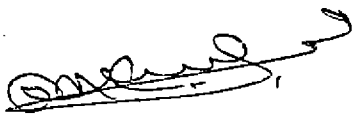
DECLARATION

I hereby declare that this thesis, entitled **"MIDAZOLAM IN COMBINATION WITH GLYCOPYRROLATE AND XYLAZINE AS A PREANAESTHETIC FOR GENERAL ANAESTHESIA IN DOGS"** is a bonafied 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 **"MIDAZOLAM IN COMBINATION WITH GLYCOPYRROLATE AND XYLAZINE AS A PREANAESTHETIC FOR GENERAL ANAESTHESIA IN DOGS"** is a record of research work done independently by **Sri. M.K.Narayanan,** under my guidance and supervision and that it has not previously formed the basis for the award of any degree, diploma, fellowship or associateship to him.

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M.K. NARAYANAN

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Introduction

1. INTRODUCTION

The development in surgery is closely linked with the progress in anaesthesiology, both in men and animals. General anaesthesia is preferred to any other anaesthetic techniques, since it facilitates the refinement in surgical intervention.

In veterinary practice, injectable anaesthetic technique is more preferred due to the inherent peculiarities of animal patients, and the ease of administration of drugs without the need of any sophisticated equipment and facilities. Commonly, drug combinations are being used for the induction and maintenance of anaesthesia, since it reduces the dose requirement and side effects of individual drugs. Now-a-days an injectable anaesthetic regimen with a combination of xylazine and ketamine became very popular and commonly used for short duration surgical procedures. The potential risks of these drugs are being eliminated by adjusting the dose, considering the health status of the patient (Hsu *et al.*, 1985) and with the concurrent use of anticholinergics, like atropine (Watney *et al.*, 1987) and glycopyrrolate (Robertson and Moon, 2003), and midazolam (Tranquilli *et al.*, 1990).

Xylazine resembles tranquilizer in activity producing sedative, analgesic and muscle relaxant effects (Sharma *et al.*, 1983). It has particularly marked hypnotic action on the central nervous system leading to general muscle relaxation which supplements the state of sleep and freedom from pain, but side effects include bradycardia, cardiac arrhythmia, retching and vomiting (Hall, 1985).

Ketamine is a dissociative anaesthetic; it can be administered as a sole agent in dogs, for anaesthesia of short to moderate duration or for induction before gaseous anaesthesia. Ketamine causes marked muscle rigidity and is usually administered in conjunction with either an α_2-agonist such as xylazine or a benzodiazepine such as diazepam (Maddison *et al.*, 2002).

Midazolam is a new benzodiazepine agonist that has got rapid onset of action and safe for critically ill patients (Koc *et al.*, 2002). Midazolam in combination with ketamine provides smooth induction of anaesthesia and facilitate easy endotracheal intubation, since it abolishes the swallowing reflex (Hellyer *et al.*, 1991). Because of advantages like rapid onset and cardio stimulatory properties, ketamine-midazolam combination has been recommended for general anaesthesia (Jacobson and Hartsfield, 1993b).

Natural anticholinergic agents like atropine sulphate or synthetic anticholinergic agent like glycopyrrolate are used to reduce the secretions of salivary gland and mucous glands of the respiratory tract and it also reduces gastric and intestinal motility. Glycopyrrolate was superior to atropine sulphate since it reduces gastric acidity and Mendelson's syndrome in man (Short, 1987).

Maintenance of anaesthesia by use of an inhalant agent has been routinely used in veterinary surgery. However, one of the main concerns is the progressive cardio respiratory depression observed with high doses of inhalation agents such as isoflurane (Steagall *et al.*, 2006). In this situation, a combination of inhalation anaesthetic with an injectable anaesthetic is preferred to achieve balanced anaesthesia, and also it greatly reduces the requirement for the inhalation agent. Isoflurane is an inhalant anaesthetic of choice for prolonged surgeries especially in compromised patients. It has got faster induction and recovery, provides relatively high levels of anaesthesia, marked muscle relaxation and greater margin of safety. Since there is no ideal anaesthetic drug to produce balanced anaesthesia, the search for a better combination will continue and use of injectable anaesthetic for induction and maintenance by inhalation anaesthetics is going to be a preferred choice for relatively long duration surgeries.

Hence the present study was carried out with the following objectives.

1. To assess the pre-anaesthetic effect of midazolam with glycopyrrolate and xylazine

2. To evaluate the anaesthetic effect of ketamine and ketamine-isoflurane anaesthesia with the pre-anaesthetic combination

Review of Literature

2. REVIEW OF LITERATURE

2.1 PREMEDICATION

2.1.1. GLYCOPYRROLATE

Mirakhur *et al.* (1978) evaluated the preanaesthetic effect of glycopyrrolate and found that it could produce powerful antisialagogue effect without undue change in heart rate and the effect was more prolonged than atropine.

Proakis and Harris (1978) reported that glycopyrrolate, as a muscarinic receptor antagonist, had the advantage of not crossing the blood brain barrier and placental barrier, resulting in decreased likelihood of central nervous system and foetal effects.

Preiss and Berguson (1983) reported that intravenous administration of glycopyrrolate significantly increased heart rate in conscious human cardiac surgical patients. In increasing the heart rate glycopyrrolate was approximately twice as potent as atropine.

Hall (1985) reported that glycopyrrolate as an antisialagogue and was five times potent than atropine with little effect on cardiovascular system. It was also claimed that due to little central effect it caused less interference with vision than atropine.

According to Short (1987), glycopyrrolate was superior to atropine in reducing gastric acidity and consequent Mendelson's syndrome, in human beings.

Watney *et al.* (1987) reported that the cardiovascular stability and effective reduction in salivation produced by glycopyrrolate proved to have significant advantage over atropine and hyoscine. It was also reported that

atropine and hyoscine produced tachycardia followed by a fall in pulse rate, but glycopyrrolate maintained the pulse rate at the same level.

Jacobson *et al.* (1994) observed significant increase in heart rate, cardiac index, and significant decrease in stroke index following administration of glycopyrrolate in dogs.

Dyson and Davies (1999) reported that, dogs with less than 10 kg body weight were more resistant to the effects of glycopyrrolate and required a higher dose than the standard (0.01 mg/kg body weight i.v.) to reverse bradycardia in anaesthetized dogs.

Tranquilli (2001) preferred to use glycopyrrolate as an antisialagogue to decrease the effects of excessive vagal tone resulting from traction applied to the uterus. It was reported that glycopyrrolate could not cross the placental barrier as readily as atropine and increased the gastric pH decreasing the likelihood of severe pulmonary pathology following the aspiration of the stomach content.

Robertson and Moon (2003) reported that bradycardia in bitches, other than opioid-induced, could be temporarily alleviated with glycopyrrolate at the dose rate of 0.01 to 0.02 mg/kg intravenously. It was also reported that administration of glycopyrrolate would not result in unnecessary foetal tachycardia since it could not cross the placental barrier.

2.1.2 XYLAZINE

Greene (1972) attributed the hyperglycemia during anaesthesia to decreased membrane transport of glucose, decreased renal excretion and decreased glucose utilization.

Moye *et al.* (1973) reported that when used alone xylazine produced a state of relaxation which was adequate for performing most minor procedures in dogs and cats. A transitory decrease in blood pressure, pulse rate, and respiratory rate was observed during sedation. At high doses emesis had been reported. The

author considered emetic action advantageous, as it empty the stomach, there by eliminating the possibility of aspiration during surgery and post-operatively.

Yates (1973) reported that xylazine could be used as a good sedative along with local anaesthetics. It was suggested that, xylazine could be used to perform cesarean section in dogs under local anaesthesia without depressing the pups.

Klide *et al.* (1975) observed subjective sedative effects like lying down, lack of response to environment, medial rotation of eye ball and prolapse of nictitans in dogs following the intramuscular administration of xylazine (2.2 mg/kg). Any significant change in arterial pH, PaO2 or Pa CO2 was not observed. But the heart rate was significantly decreased without significant change in the aortic blood pressure.

Muir and Piper (1977) reported that following intravenous administration of xylazine (1.1 mg/kg) in dogs, the mean arterial blood pressure from 94 ± 13 increased to 138 ± 17 mm of Hg at ten minutes, and there after it decreased to 89 ± 12 and 84 ± 14 mm of Hg at 30 and 60 minutes respectively.

Peshin *et al.* (1980) observed transient bradycardia and decrease in respiratory rate in dogs following intramuscular administration of xylazine at the rate of 3.0 mg/kg body weight. Xylazine caused a decrease in T wave interval and in the amplitude of 'P' wave interval and QRS complex. The PR and QT intervals decreased during tachycardia and increased during bradycardia. Changes in the T wave along with elevation of ST segment were suggestive of myocardial hypoxia. There was slight decrease in total erythrocyte and leucocytes count, packed cell volume and hemoglobin concentration. There was decrease in lymphocyte count with corresponding increase in neutrophil count following xylazine administration. Significant increase in blood glucose, mild increase in serum sodium and, decrease in potassium and chloride concentrations were also observed.

Wallner *et al.* (1982) reported that xylazine would be useful for minor procedures that require total relaxation and immobilization and need supplementation with local anaesthetic for surgical procedures. The major advantage was its prompt antagonism by 4-aminopyridine and yohimbine.

Sharma *et al.* (1983) studied the effect of xylazine on thiopentone sodium anaesthesia in atropine premedicated dogs and observed decrease in heart rate, respiration rate, mean arterial blood pressure and body temperature. Decrease in erythrocyte and total leukocyte counts, haemoglobin concentration and packed cell volumes were also observed. The duration of anaesthesia was found significantly increased in thiopentone sodium induced anaesthesia when maintained with xylazine.

Hsu *et al.* (1985) administered atropine sulphate (0.04 mg/kg) body weight, im) 15 minutes after pentobarbital (14.0 mg/kg iv) with prior administration of xylazine (2.2 mg/kg body weight im) at an interval of 10 minutes. Atropine sulphate injection did not significantly change the duration of absence of pedal reflex, duration of anaesthesia and the time from return of consciousness to ambulation. Although atropine sulphate antagonized xylazine induced bradycardia, the data indicated that it caused increased respiratory depression in dogs anaesthetized with xylazine and pentobarbital.

2.1.3 MIDAZOLAM

Jones *et al.* (1979) reported certain behavioural depression viz., initial signs of profound weakness, ataxia, transient agitation followed by a period of quiescence following intramuscular administration of midazolam. A normal behavioural pattern returned within two hours of midazolam administration. Hemodynamic stability of midazolam had been reported in clinical trials conducted in canines. It was also stated that, in concentration, necessary for induction of anaesthesia, midazolam maleate had minimum effect on the cardiovascular functions.

Forster *et al.* (1980a) assessed the effect of intravenous administration of midazolam (0.15mg/kg) on the cardiovascular system in eight healthy human volunteers. A statistically significant but clinically unimportant decrease in arterial blood pressure and an increase in heart rate were observed.

Forster *et al.* (1980b) compared the respiratory effect of midazolam with diazepam in eight healthy human volunteers and concluded that both the drugs injected intravenously, in equipotent doses depressed respiration significantly and similarly.

Millar *et al.* (1980) recommended midazolam as a satisfactory alternative to diazepam, being a water soluble agent with less incidence of venous irritation and its short duration of action.

Whitwam *et al.* (1980) observed a decreased mean arterial pressure (MAP) after the administration of midazolam (1mg/kg) in dogs. Maximal effect was observed at 10 minutes when MAP decreased for 164 mm Hg to 116 mmHg, after which recovery occurred. The increase in the heart rate initially from 129 to 149 beat per minute and it progressively decreased to a mean value of 91 beats per minute by one hour.

Kanto *et al.* (1982) reported midazolam to have hypnotic action. The intravenous dose of midazolam recommended for clinical use in human beings was 0.30 mg/kg.

Melvin *et al.* (1982) observed a decreased minimum alveolar concentration (MAC) of halothane in a dose-related fashion with midazolam in human patients. Following the administration of midazolam, the systolic pressure reduced significantly and the pulse rate remained unchanged.

Nugent *et al.* (1982) opined that midazolam maleate, in sufficient dosage produce a profound decrease in cerebral metabolic rate for oxygen than diazepam depression or alteration in the cerebral energy state.

Hall *et al.* (1988) observed that in dogs midazolam produced a dose and concentration-dependent reduction of enflurane minimum alveolar concentration. It was also observed that the degree of suppression of noxious stimulation in the presence of volatile anaesthetic agent by benzodiazepine in human and dogs appeared similar.

Shenoy *et al.* (2002) found that midazolam took significantly longer time to induce sleep and associated with undesirable side effects such as movement of limb in human patients. It was suggested that these effects could be markedly attenuated by premedication with a narcotic drug. Pain and thrombophlebitis were significantly less with midazolam.

Steffey (1996) reported that midazolam at sub-anaesthetic doses, induced sedation and heavy hypnosis in humans. It was recommended as a good alternative to diazepam as it was non- irritating to the tissues and well absorbed following intramuscular injections.

Bishnoi and Saini (2005a) administered midazolam in calves at the rate of 0.5 mg/kg intravenously and reported that sedation of 19 ± 2.61 minutes could be achieved with depression of various reflexes, mild relaxation of the jaw, tail, limbs and abdomen along with a diminished response to external stimuli. There was decrease in temperature, blood pressure, respiratory rate, tidal volume and minute volume. Similarly, changes in heart rate, pulse rate central venous pressure, mean pulmonary artery pressure and ECG parameters were also non-significant.

Bishnoi and Saini (2005b) analysed the blood gas changes after administration of midazolam in calves and observed significant decrease for short duration in pH of arterial as well as mixed venous blood and non significant increase in partial pressure of carbon dioxide ($PaCO_2$ and $PvCO_2$) values indicating a mild respiratory acidosis, but it was compensated by slight increase in bicarbonate (HCO_3 a and HCO_3 v) content in both arterial and mixed venous

blood. The changes in partial pressure of oxygen (PaO_2, PvO_2) and base excess of arterial and venous blood (BEa and BEv) values were not appreciable. But there was a significant decrease in oxygen saturation (SaO_2 and SvO_2) of arterial blood indicating alveolar hypoventilation. Non-significant decrease in sodium, potassium and total protein concentrations up to 60 min and increase in glucose level were also observed.

2.2 ANAESTHESIA

2.2.1 KETAMINE

Parsania *et al.* (1977) observed severe muscle contraction and profuse salivation in dogs when ketamine hydrochloride alone was used. Though different reflexes were persisted, fair to poor muscle relaxation was observed when used along with promazine hydrochloride and variety of operations could be performed with the combinations.

Schulman (1981) induced anaesthesia using combination of ketamine and promazine, (5.5 mg/kg) and (2.75 mg/kg) administered intravenously. Premedication with atropine sulphate (0.045 mg/kg) subcutaneously controlled the extreme salivation associated with ketamine anaesthesia.

Wright (1982) reported that ketamine alone had not proven useful in producing anaesthesia in dogs, primarily because of increased muscle rigidity and occasional convulsions.

Haskins *et al.* (1985) reported that ketamine (10 mg/kg) administered intravenously in dogs, increased the heart rate and mean systemic blood pressure, whereas it decreased the respiration rate. One of the dog exhibited brief tono-clonic seizures after ketamine administration whereas all the dogs salivated profusely. The duration of surgical anaesthesia with a single dose of ketamine was about 13-15 minutes. At the rate of 10 mg/kg body weight anaesthesia produced was unsatisfactory for surgical procedures. Muscle tone was extreme

and exuberant spontaneous movement was virtually continuous after about 15 minutes. It was recommended that dogs should be given adjunctive sedative or tranquilizer premedication when ketamine is to be used, since ketamine is a cardiovascular and metabolic stimulant.

Thiruthalinathan *et al.* (1995) observed convulsion, muscle rigidity and salivation in wild canines when ketamine alone was used.

Thurmon *et al.* (1996) observed muscle rigidity, salivation and convulsion in dogs during ketamine anaesthesia.

2.2.2 ISOFLURANE

Klide (1976) observed decreased cardio pulmonary function to a greater extent with enflurane than isoflurane. But with both the agents, the cardiopulmonary function increased with increasing depth of anaesthesia. Muscle twitching was noticed in all the dogs anaesthetized with enflurane, but not noticed with isoflurane. Induction and recovery from anaesthesia was quite rapid with enflurane though the duration was longer.

Steffey and Howland Jr. (1977) reported that the blood solubility of isoflurane was lower than halothane, enflurane and methoxyflurane. It was also stated that isoflurane did not induce muscle twitching or seizure like activity as seen during enflurane anaesthesia; consequently, isoflurane is not classified as convulsant anaesthetic like enflurane, ketamine or nitrous oxide.

Muir and Piper (1977) reported the relative potency of inhalation anaesthetics in decreasing cardiac contractility in dogs in the following order of: enflurane, halothane, methoxyflurane, isoflurane, cyclopropane and diethyl ether.

Steffey and Howland Jr. (1980) reported that both isoflurane and halothane produced similar dose dependent depletion in circulatory and respiratory functions in young and healthy horses during spontaneous ventilation and controlled ventilation

Zbinden *et al.* (1988) studied the uptake and elimination of halothane and isoflurane and concluded that the rate of uptake of isoflurane was more rapid than that of halothane from the alveolar space to the blood, but from the blood to the brain tissue. The rates of elimination from brain tissue and from blood were found to be similar for both agents.

Tyner *et al.* (1989) reported that administration of butorphanol tartrate at the rate of 02. mg/kg body weight intravenously in isoflurane anaesthetized dogs reduced mean, systolic and diastolic arterial blood pressure and cardiac output. The mean heart rate reduced in five minutes of butorphanol administration, with a maximum decrease at 45 minutes.

Ludders (1992) reported many advantages for isoflurane than over other inhalant anaesthetics such as faster induction and recovery, relatively sparing effect on cardiovascular function and cerebral blood flow auto regulation and negligible metabolism.

Wagner and Bednarski (1992) reported that, with (4 to 7 ml oxygen/kg/ minute) low-flow and closed-system anaesthesia, relatively expensive anaesthetic agents such as isoflurane could be safely and economically used.

Hellyer (1996) recommended that, unstable patients, requiring rapid change in anaesthetic depth, should be anaesthetized with either halothane or isoflurane as both the agents were rapidly acting anaesthetic and provided flexibility to change the depth of anaesthesia. It was also stressed that endotracheal tube should be retained until, normal swallowing reflexes returned and in brachycephalic dogs, it should be removed only if the dog started chewing.

According to Steffey (1996), isoflurane not caused any effect on atrio-ventricular conduction as caused by halothane in dogs. It was reported that isoflurane increased the arterial partial pressure of carbon dioxide ($PaCO_2$) and significantly decreased the arterial pH (pHa) at all anaesthetic concentrations. It

was also found that this magnitude of response was greater with isoflurane than with savoflurane at 1.8 and 2.4 MAC.

Mutoh *et al.* (2001) reported that the upper airway administration (mask induction) of isoflurane induced greater reflex inhibition of breathing in dogs than savoflurane. But topical nebulization of the upper air way with lidocaine abolished the reflex effects of both the anaesthetics.

Galloway *et al.* (2004) compared the anaesthetic index of sevoflurane with that of isoflurane in unpremedicated dogs and suggested that sevoflurane has a higher anaesthetic index in dogs than isoflurane. Sevoflurane and isoflurane caused similar dose-related cardiovascular depression. Although both agents caused dose-related respiratory depression, sevoflurane caused less respiratory depression at higher equipotent anaesthetic doses.

2.3 THE DRUGS UNDER TRIAL IN COMBINATIONS

2.3.1 GLYCOPYRROLATE-XYLAZINE

Dunkle. *et al.* (1986) echo-cardio graphically evaluated the cardiac performance of xylazine alone, xylazine and glycopyrrolate in cats. It was observed that the α–2 adrenergic agonist, xylazine has a marked depressive effect on cardiac performance in the cat, and with glycopyrrolate the bradycardia was minimized, though the cardiac performance was not improved.

Ko and Mc Grath (1997) observed an increase in mean heart rate within five minutes after administration of xylazine-butorphanol-glycopyrrolate combination in dogs. This increase in heart rate was attributed to the anticholinergic effects of glycopyrrolate.

2.3.2 GLYCOPYRROLATE-XYLAZINE-MIDAZOLAM

Tranquilli *et al.* (1990) observed a significantly increased heart rate in dogs when glycopyrrolate was administered along with midazolam-xylazine-butorphanol mixture.

2.3.3 XYLAZINE-KETAMINE

Navarro and Friedman (1975) evaluated the effects of xylazine and ketamine hydrochloride in dogs subjected to caesarean section. The puppies were not seen depressed when xylazine alone was used. From the study it was concluded that the analgesia and muscle relaxation provided by xylazine in conjunction with lidocaine were sufficient to allow surgical delivery of pups and administration of ketamine, after the delivery, complemented the effects of xylazine and made uterine and abdominal closure easy.

Stephenson *et al.* (1978) could achieve the desired plane of anaesthesia in 10 minutes with the combined intramuscular administration xylazine hydrochloride and ketamine hydrochloride (2.0 mg/kg) and (5.5 mg/kg) in dogs premedicated with atropine sulphate (0.25 mg/kg). The anaesthesia persisted for 30 minutes and got fully recovered within one to two hours.

Clark *et al.* (1982) reported that recovery from anaesthesia following the administration of atropine, xylazine and ketamine was marked by clonic head and limb movement, followed by vocalization after painful stimuli. No significant alteration in serum biochemistry following the administration of atropine, xylazine and ketamine were observed. There was significant rise in heart rate, blood pressure and myocardial oxygen demand and significantly reduced arterial oxygen tension following the administration of atropine, xylazine and ketamine for anaesthesia in dogs. Myocardial hypoxia, ECG changes such as ST segment slurring and premature ventricular contraction were also observed. But there was no significant alteration in serum biochemistry.

Wright (1982) reported that ketamine was effective in producing anaesthesia in combination with drugs like xylazine, acetylpromazine, promazine etc.

Jacobson (1983) employed ketamine-xylazine combination for immobilizing springbok (*Antidorcas marsupialis*) and compared the haematologic and serum biochemical values, before and after immobilization. The haematologic serum aspartate transaminase, blood urea nitrogen and chloride values before immobilization were not significantly different from those after immobilization. The serum glucose and alanine transaminase values were found significantly higher in animals after immobilization, whereas potassium value was significantly lower.

Kolata and Rawling (1983) reported that a drug combination of xylazine and ketamine at the rate of 1.1 mg/kg and 11 mg/kg respectively produced hypoventilation, as reflected by increased $PaCo_2$ and a 30 per cent decrease in cardiac index.

Hall (1985) reported that xylazine produced deep sedation with centrally induced muscle relaxation, with the side effects *viz.*, bradycardia, cardiac dysarrhythmia, retching and vomiting, and prolonged sedation lead to hypothermia. It was also reported that xylazine at a dose rate of 1-3 mg/kg intramuscularly reduced the rigidity produced by the dissociative agent such as ketamine.

Trim and Gilroy (1985) reported that the combination of xylazine (1 mg/kg) and ketamine (10 mg/kg) injected intravenously produced excellent immobilization and conditions for surgery in healthy pigs. The recovery of all animals was rapid and uneventful. It was also stated that the decrease in PaO_2 after the administration of xylazine and ketamine was probably a reflection of the decrease in cardiac output.

Haskins *et al.* (1986) evaluated the effects of intravenously administered xylazine (1.0 mg/kg) followed by ketamine (10.0 mg/kg) intravenously in dogs. Xylazine caused significant decrease in heart rate, cardiac output, left ventricular work, breathing rate, minute ventilation, physiological dead space, oxygen transport, mixed venous partial pressure of oxygen and oxygen concentration. It caused significant increase in systemic blood pressure, central venous pressure, systemic vascular resistance, tidal volume and oxygen utilization ratio. Subsequent administration of ketamine was associated with significant increase in heart rate, cardiac out put, transient increase in alveolar-tidal PO_2 and PCO_2.First and second degree atrio-ventricular block were observed after xylazine administration but these changes were eventually reversed following the administration of ketamine. Muscle relaxation was better and salivation was less with xylazine-ketamine combination compared with xylazine alone. The time of ultimate recovery was similar between xylazine-ketamine combination and ketamine alone.

Moens and Fargetton (1990) studied the comparative anaesthetic and physiological effects of meditomidine-ketamine and xylazine-ketamine combinations in dogs. It was reported that all the combinations rapidly induced anaesthetic state that permitted endotracheal intubation, absence of pedal reflex, good muscle relaxation and bradycardia. The effects produced by meditomidine-ketamine combination were comparable to xylazine-ketamine combination, even though the muscle relaxation time and recovery time was significantly longer.

Ramaswamy *et al.* (1991) could achieve rapid induction (44.17 seconds) of anaesthesia in dogs by intravenous or intramuscular administration of a combination of xylazine (at the rate of 0.5 mg/kg) with ketamine (at the rate of 10 mg/kg).

Tiwari *et al.* (1994) reported that administration of xylazine with ketamine produced excellent muscle relaxation, deep sedation and moderate analgesia with loss of righting reflex in dogs. There was increase in blood

glucose level, but the urea nitrogen, sodium and potassium levels remain unaffected.

Thiruthalinathan *et al.* (1995) observed convulsion, muscle rigidity and salivation in wild canines when ketamine alone was used. But when ketamine-xylazine combination was used it did not show any such effects and showed better sedation, good relaxation and faster recovery.

Baniadam *et al.* (2004) studied the effect of xylazine-ketamine on temperature, heart and respiratory rate, arterial blood pressure and blood gases in sheep had reported little depressant effects on the cardiovascular system. It was also observed that the combination was responsible for a little disturbed ventilation, decreased PaO_2, increased $PaCO_2$ and decreased body temperature during anaesthesia.

2.3.4 MIDAZOLAM-XYLAZINE

Tranquilli *et al.* (1990) evaluated the depressant effects of midazolam and xylazine in dogs and concluded that simultaneous administration of the drugs induced a profound level of central nervous system depression. It was also stated that when midazolam was administered prior to xylazine resulted in a moderate dysphoric reaction, but such reactions could be prevented by administration of xylazine prior or simultaneously with midazolam.

Gross *et al.* (1992) administered midazolam-xylazine-butorphanol combination in dogs and found that the mean arterial blood pressure increased above baseline at 60 minutes, but decreased below base line and at the 60 minutes value after the administration of reversal mixture. Heart rate increased above the 60 minutes value after reversal.

2.3.5 MIDAZOLAM-KETAMINE

Hellyer *et al.* (1991) induced anaesthesia in greyhounds with a mixture of diazepam or midazolam (0.28 mg/kg) and ketamine (5.5 mg/kg) and maintained

with halothane. Induction of anaesthesia was considered good (easy transition to unconsciousness, no struggling, vocalization or paddling) with both midazolam-ketamine and diazepam-ketamine. The authors recommended both midazolam-ketamine and diazepam-ketamine as useful anaesthetic combinations, but more rapid intubation was an added advantage of the former combination. It was also state that, midazolam followed by ketamine administration resulted in smooth induction of anaesthesia and facilitated an easy endotracheal intubation suggesting the loss of swallowing reflex in all the animals whereas swallowing reflex was present in animals induced anaesthesia without ketamine.

Jacobson and Hartsfield (1993a) studied the cardiorespiratory effects o intravenous bolus administration and infusion of ketamine-midazolam in dogs and reported that induction of anaesthesia with ketamine-midazolam was good in all dogs, minimal cardiorespiratory effects except for significant increase in mean heart rate in dogs received infusion. Respiratory depression was more in those animals administered ketamine-midazolam as bolus.

Luna *et al.* (1992) observed that intubation was easy in horses administered with a combination of methotrimeprazine, midazolam and guaiphenesin, with ketamine. This combination provided smooth induction, good muscle relaxation and no ataxia or excitement produced while positioning the horse for surgery.

Clutton *et al.* (1997) observed that the induction of anaesthesia with midazolam followed by ketamine resulted in reduction of total dose of thiopentone sodium in pigs and these animals had earlier recovery.

Koc *et al.* (2002) reported mild respiratory depression, decrease in heart rate and body temperature following the administration of midazolam xylazine combination in dogs. But, there was no change in blood pressure arterial pH, PaO_2 and $PaCo_2$.

Kaur and Singh (2004) induced anaesthesia in bovines with midazolam (0.1 mg/kg) followed by ketamine (4.0 mg/kg) administered intravenously and maintained with intravenous thiopentone sodium (5%) "to effect".

2.3.6 MIDAZOLAM-KETAMINE –ISOFLURANE

Faggella and Aronsohn (1993) reported only little analgesia following the administration of midazolam-ketamine combination in cats. But supplementation with isoflurane was resulted in smooth and rapid induction of anaesthesia. It was also reported that being midazolam compatible with ketamine, both could be mixed with same syringe for administration.

Jacobson and Hartsfield (1993b) studied the bolus administration and infusion of intravenous ketamine (10 mg/kg) and midazolam (0.5mg/kg) in isoflurane anaesthetized (1.7% end tidal concentration) healthy dogs. Following the administration of ketamine-midazolam as a bolus and as infusion caused significant reduction in mean systemic blood pressure, cardiac index, stroke volume, base excess, pHa and decrease in heart rate were noticed and returned to the base line values by the end of the study. But the cardiovascular effects were less severe following infusion. Base excess and pHa decreased significantly in the infusion group, although similar changes were observed in both groups. It was also reported that cardio stimulatory properties of ketamine-midazolam combination could be blocked with concurrent use of isoflurane. It was also recommended that ketamine-midazolam should be used judiciously in isoflurane anaesthetized dogs and that an infusion or low doses of ketamine-midazolam were preferred over a rapid bolus injection technique.

2.3.7 XYLAZINE-ISOFLURANE

Steffey *et al.* (2000) reported that administration of xylazine reduced the anaesthetic requirement for isoflurane in horses and increased the blood glucose concentration in a dose-related manner.

Table 1. Normal values of physiological, haematological and serum biochemical parameters of dogs

(Courtesy: Benjamin, 1985 and Chauhan and Agarwal, 2006)

Physiological Parameters	Range	Haematological Parameters	Range	Serum Biochemical Parameters	Range
Rectal temperature (°C)	37.50-39.20	Haemoglobin concentration (g/dl)	12-18	Serum glucose (mg/dl)	55-90
Pulse rate (per min)	90-100	Volume of Packed Red Cells (%)	37-54	Aspartate amino transferase (U/L)	10-62
Respiration rate(per min)	10-30	Erythrocyte Sedimentation Rate (mm/h)	1-6	Alanine amino transferase (U/L)	25-92
Oxygen saturation (SpO_2)(per cent)	>95%	Total leukocyte count ($10^3/mm^3$)	8.2-13.5	Total protein (g/dl)	6.1-7.8
Blood coagulation time (min)	4	Lymphocytes (%)	12-30	Blood urea nitrogen (mg/dl)	10-20
Capillary refill time (sec)	1-2	Neutrophils (%)	60-75	Serum creatinine (mg/dl)	1.0-2.7
Systolic blood pressure (mm Hg)	110 -160	Eosinophils (%)	2-10	Serum sodium (mEq/L)	140-154
Diastolic blood pressure (mm Hg)	70 - 90	Monocytes (%)	3-9	Serum potassium (mEq/L)	3.7-5.8
Mean blood pressure (mm Hg)	80 - 120	Basophils (%)	0-1	Serum chloride (mEq/L)	108-119
Arterial Blood Gas Parameters		pH (pHa)	7.31-7.42	Partial pressure of oxygen (PaO_2) (mm H g)	91-97
		Partial pressure of carbon dioxide ($PaCO_2$) (mm H g)	30-43	Bicarbonate (HCO_3) mEq/L	18-24

Materials and Methods

3. MATERIALS AND METHODS

3.1 SELECTION OF ANIMALS

The anaesthetic study was conducted on 24 female dogs of different breeds subjected to elective surgical procedures (oopherectomies) at the Department of Veterinary Surgery and Radiology of College of Veterinary and Animal Sciences, Mannuthy and the University Veterinary Hospital, Kokkalai.

All the animals were clinically examined and were found apparently healthy. They were randomly divided in to four groups *viz*., Group I, II, III and IV, each consisting of six dogs and were serially numbered, *viz.*

Group I - I_1, I_2, I_3, I_4, I_5 & I_6
Group II - II_1, II_2, II_3, II_4, II_5 & II_6
Group III - III_1, III_2, III_3, III_4, III_5 & III_6
Group IV - IV_1, IV_2, IV_3, IV_4, IV_5 & IV_6

3.2 PREPARATION OF THE ANIMALS

All the dogs were withheld water for 12 hours and food for 24 hours prior to pre- anaesthetic medication.

3.3 PRE ANAESTHETIC MEDICATION (PREMEDICATION) (Plate 1)

Animals of all the groups were administered intramuscularly, glycopyrrolate[1] at the rate of 0.011mg/kg body weight followed by xylazine[2] at the rate of 1.0 mg/kg body weight, at 15 minutes interval. In addition, animals of Group III and IV were also administered intravenously midazolam[3] at the rate of 0.3 mg/kg body weight, 10 minutes after the administration of xylazine.

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1. Pyrolate - Neon Lab, Thane, Maharastra.
2. Xylaxin – Indian Immunologicals, Hyderabad.
3. Mizolam– Neon Lab, Thane, Maharastra.

3.4 ANAESTHETIC TRIALS (Plate 1)

Fifteen minutes after xylazine premedication, the anaesthetic trials were carried out as follows:

Group I: Ketamine hydrochloride[4] at the rate of 10 mg/kg body weight was administered intramuscularly.

Group II: Ketamine hydrochloride at the rate of 10 mg/kg body weight was administered intramuscularly. Anaesthesia was maintained with isoflurane[5] in oxygen delivered by semi-closed anaesthetic circle re-breathing system utilizing Tec-3 Halothane Vapourizer (IOL, Calcutta) (Plate 2).

Group III: Ketamine hydrochloride at the rate of 10 mg/kg body weight intramuscularly was administered.

Group IV: Ketamine hydrochloride at the rate of 10 mg/kg body weight intramuscularly was administered. During surgery, anaesthesia was maintained with isoflurane in oxygen delivered by semi closed anaesthetic circle re- breathing system utilizing Tec-3 Halothane Vapourizer (IOL, Calcutta).

After induction of anaesthesia with ketamine, endotracheal intubation was carried out in dogs to keep the airway patent in Groups I and III and to deliver isoflurane for maintenance of anaesthesia in Groups II and IV. Lignocaine hydrochloride[6] two per cent was used in dogs of Group I for completing the surgery whenever required.

During surgery 5% dextrose saline[7] was administered intravenously to all the dogs.

4.Aniket–.Neon Lab,Mumbai.
5. Forane – Abbott India Ltd, Mumbai.
6. Xylocaine 2% – Astra Zeneca Pharma India Ltd, Bangalore.
7. Dextrose Saline-Baxter, Tamil Nadu.

The physiological observations and collection of blood samples from the cephalic vein for haematological and biochemical evaluations were carried out before the administration of pre anaesthetic combination, immediately before, and at 30 and 90 minutes and at 24 hours after the administration of ketamine. To assess the acid-base balance during anaesthesia, blood samples from the femoral artery from three animals of each group were also collected before induction, during anaesthesia and recovery.

3.5 SURGICAL MANAGEMENT

All the animals were subjected to elective surgical procedures (oopherectomies) under aseptic precautions (Plate 3). The animals were controlled on the left lateral reccumbency. Laparotomy was carried out by right flank approach by putting an oblique incision, 4-5cm long, cutting through the skin, abdominal muscles and peritoneum. The uterine horns were identified, exteriorized and the vessels were ligated anterior and posterior to the ovary. The ovary was removed retaining the bursa. The same procedure was repeated for the removal of other ovary also. The peritoneum and the abdominal muscles were sutured in simple continuous pattern using 1/0 chromic catgut. The skin wound was apposed in vertical mattress pattern using monofilament nylon. Polyvinyl polymer spray[8] was applied over the suture line. Postoperatively, inj.ampicillin-cloxacillin[9] was given intramuscularly for five consecutive days and sutures were removed on the eighth day.

3.6 MAIN ITEMS OF OBSERVATIONS

3.6.1 Clinical Observations

3.6.1.1 ***Clinical signs:*** The salient clinical signs exhibited by the dogs following the premedication, during induction, maintenance and recovery of anaesthesia were recorded.

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8. Healex plus - Shreya Life Sciences Pvt. Ltd., Mumbai.
9. Megapen-Aristo Lab, Maharastra.

3.6.1.2: ***Induction time of anaesthesia:*** Induction time was calculated as the time from the injection of ketamine to the disappearance of the pedal reflex.

3.6.1.3: ***Duration of surgical anaesthesia:*** The time interval between the time of disappearance of pedal reflex following the administration of ketamine and the time of return of pedal reflex.

3.6.1.4 ***Depth of anaesthesia*** It was evaluated during surgery by assessing the extent of analgesia, degree of muscle relaxation and unconsciousness and graded as unsatisfactory, satisfactory, good or very good.

3.6.1.5: ***Muscle relaxation time:*** The time interval between the disappearance and the return of the tone of muscles of lower jaw.

3.6.1.6 ***Degree of muscle relaxation:*** It was rated as excellent (++++), good (+++), moderate (++) and poor (+) depending up on the resistance in opening the jaws manually and by the assessment of relaxation of the muscles of the abdomen during surgery.

3.6.1.7 ***Recovery time:*** It was calculated as the time interval between the return of pedal reflex and the time when the animal could stand up and walk unassisted.

3.6.2 Physiological Observations

The physiological observations were made before and after premedication, and at 30min, 90 min and at 24h after the administration of ketamine.

3.6.2.1 ***Rectal Temperature, pulse rate and respiration rate***

The animals were subjected to recording of rectal temperature, respiration rate and pulse rate.

3.6.2.2 *Colour of visible mucous membrane*

The colour of conjunctival/ buccal mucous membrane was noted through out the period of observation.

3.6.2.3 *Oxygen saturation level (by Pulse Oximetry):* The oxygen saturation (SpO_2) level (%) in the blood was recorded by connecting the transducer of the pulse oximeter (Multi Para Monitor- BM3 Vet, Bionet Co Ltd, Korea) to the ear flap / tongue (Allen, 1992) (Plate 4 and 5).

3.6.2.4 Capillary *refill time*

The capillary refill time was recorded from refilling of the tongue capillary and the mucous membrane of the gums after pressing on it and was recorded in seconds.

3.6.2.5 *Blood coagulation time*

Blood coagulation time was recorded employing capillary tube method (Chauhan and Agarwal, 2006). The time intervals between the appearance of blood during vein puncture and the appearance of the fibrin strands seen across the gap between the ends of the tube was calculated as coagulation time.

3.6.2.6 *Arterial Blood pressure*

Arterial blood pressure (systolic, diastolic and mean) was measured non-invasively by using a Multi Para Monitor (B M3 Vet , Bionet Co Ltd, Korea).

3.6.2.7 *Electrocardiogram*

The electrocardiography was performed in Lead II, at a paper speed of 25 mm/second using a Multi Para Monitor (BM3 Vet, Bionet Co Ltd , Korea).

3.6.3 Hematological Parameters

Blood samples were collected before and after premedication, and at 30 min, 90 min and at 24h after the administration of ketamine for the estimation of haemoglobin (Hb) (Sahli's method), volume of packed red cells (VPRC), erythrocyte sedimentation rate (ESR) (Wintrobe method), total and differential counts (Benjamin, 1985).

3.6.4 Serum Biochemical Parameters

Serum samples were collected before and after premedication, and at 30 min, 90 min and at 24h after the administration of ketamine for the estimation of total protein, creatinine, blood urea nitrogen (BUN), glucose, aspartate amino transferase (AST), alanine amino transferase (ALT), using the chemical kits (Agappe Diagnostics Pvt. Ltd., Eranakulam) by Semi Auto Analyzer (Secomam, France) and sodium, potassium and chloride using Atomic Absorption Spectrophotometer (Perkin Elmer –Model 2380).

3.6.5 Arterial Blood Gas Analysis

Arterial blood was collected from the femoral artery in a sterile heparinized disposable syringe without air bubbles. The collected samples were stored in ice- water bath (Clark *et al.*, 1982 and Gautam and Singh, 1998) until analysis. The blood samples were analysed for pHa, PaO_2, $PaCO_2$ and HCO_3 (AVL Blood Gas Analyser, Bangalore) (Plate 6). The values were interpreted based on the standard suggested by Haskins (1977). Accordingly for the comparison of two successive measurements, the difference must exceeds a value of 0.015 for pH a, 5 mm Hg for PaO_2, 3 mm Hg for $PaCO_2$ and 2 m Eq/L for HCO_3.

3.6.6 Postanaesthetic Observations

All the dogs were observed up to the time of recovery and at 24 hours after the surgery and the signs were recorded. On eighth post operative day, the skin sutures were removed.

3.6.7 Statistical Analysis

Statistical analysis was carried out using Analysis of co-variance (ANACOVA) and student t- test method for all the parameters under investigation to identify the magnitude of changes between the groups and within the group during various stages of anaesthesia (Snedecor and Cochran, 1985).

Results

4. RESULTS

Twenty four female dogs were utilized for the study. The results obtained were statistically analysed and the observations are presented in Tables 2 to 12.

4.1 GROUP- I

4.1.1.Clinical Observations (Table 3)

4.1.1.1. Clinical signs: The common clinical signs, suggestive of sedation, manifested by the dogs following xylazine premedication were winking of eyes, yawning and inco-ordination of movements with lowering of head. The other symptoms noticed were vomiting (I_1, I_2, I_4), licking (I_1, I_3), urination (I_5, I_6), and defecation (I_1, I_5, I_6). All the dogs, assumed the position of sternal reccumbency with head down posture in 3.00 ± 0.78 min.

The dogs assumed the position of lateral reccumbency by 4.50 ± 0.34 min following the administration of ketamine. Out of the six dogs, in four (I_2, I_3 I_4, I_6) endotracheal intubation could be performed only with resistance.

During recovery, shivering and vocalization and urination were noticed in all the dogs.

4.1.1.2. Induction time of anaesthesia: The induction time of anaesthesia was 9.50 ± 0.81 min. (Fig.1).

4.1.1.3. Duration of surgical anaesthesia: The duration of surgical anaesthesia was 31.33 ± 2.97 min. (Fig.1).

4.1.1.4. Depth of anaesthesia: The depth of surgical anaesthesia was satisfactory only in two dogs (I_1, I_5). In others (I_2, I_3, I_4, I_6) the surgery was performed with the supplementation of local infiltration anaesthesia.

4.1.1.5 Muscle relaxation time: The muscle relaxation time was 41.16 ± 2.14 min. (Fig.1).

4.1.1.6. Degree of muscle relaxation: The degree of muscle relaxation was moderate in two dogs (I_1, I_5) and was poor in others (I_2, I_3, I_4, I_6).

4.1.1.7 Recovery time: The recovery time was 71.67 ± 3.07 min. (Fig.1).

4.1.2 Physiological Observations (Tables 4 to 6)

4.1.2.1. Rectal temperature (°C)*:* Rectal temperature was 38.92 ± 0.15 and 38.92 ± 0.14 before and after premedication with glycopyrrolate-xylazine combination respectively. In ketamine anaesthesia it was 38.79 ± 0.21, 38.45 ± 0.18 and 38.71 ± 0.21 at 30 min, 90 min and 24 h. respectively. There was decrease in rectal temperature after premedication, during anaesthesia and recovery. The decrease was significant ($P<0.05$) during recovery, though it increased to near normal value by 24 h. (Fig.2).

4.1.2.2 Pulse rate (per min): Pulse rate was 100.67 ± 6.86 and 106.67 ± 15.76 before and after premedication respectively. In ketamine anaesthesia it was 95.00 ± 1.69, 92.33 ± 1.89 and 90.50 ± 2.42 at 30 min, 90 min and 24 h. respectively. There was increase in pulse rate after premedication, but during anaesthesia and recovery it was decreased (Fig.3).

4.1.2.3 Respiration rate (per min): Respiration rate was 33.67 ± 4.63 and 24.50 ± 2.35 before and after premedication respectively. In ketamine anaesthesia it was 26.67 ± 5.56, 23.83 ± 2.26 and 23.83 ± 2.20 at 30 min, 90 min and 24 h. respectively. There was decrease in respiration rate after premedication and during anaesthesia. The decrease was significant ($P<0.05$) after premedication, at 90min and at 24 h. (Fig.4).

4.1.2.4 Colour of visible mucous membrane : Colour of visible mucous membrane was pale roseate in all animals.

4.1.2.5 Oxygen saturation (SpO_2) level (%): Oxygen saturation level was 92.00 ± 2.05 and 94.00 ± 1.61 before and after premedication respectively. In ketamine anaesthesia it was 94.67 ± 0.42, 95.17 ± 0.70 and 93.67 ± 0.42 at 30 min, 90 min and 24 h. respectively. The SpO_2 level was seen increased throughout the period of observation. The increase was significant ($P<0.05$) after premedication (Fig.5).

4.1.2.6 Capillary refill time (sec): Capillary refill time was 2.00 ± 0.23 and 1.50 ± 0.26 before and after premedication respectively. In ketamine anaesthesia it was 1.50 ± 0.22, 1.50 ± 0.22 and 1.83 ± 0.22 at 30min, 90 min and 24 h. respectively. There was decrease in capillary refill time after premedication and during anaesthesia. Thereafter the variations were marginal (Fig.6).

4.1.2.7 Blood coagulation time (in min): Blood coagulation time was 3.52 ± 0.13 and 3.78 ± 0.20 before and after premedication respectively. In ketamine anaesthesia it was 3.92 ± 0.08, 3.78 ± 0.13 and 3.75 ± 0.11 at 30 min, 90 min and 24 h, respectively. There was gradual increase in coagulation time throughout the period of observation and increase was significant ($P<0.05$) at 30 min. (Fig.7).

4.1.2.8 Systolic blood pressure (mmHg): Systolic blood pressure was 130.67± 3.03 and 158.00 ± 4.73 before and after premedication respectively. In ketamine anaesthesia it was 213.17 ± 5.17, 154.83 ± 4.60 and 132.33 ± 4.89 at 30 min, 90 min and 24 h. respectively. There was significant ($P<0.05$) increase in systolic blood pressure after premedication, during anaesthesia and recovery (Fig.8).

4.1.2.9 Diastolic blood pressure (mmHg): Diastolic blood pressure was 78.33 ± 2.95 and 100.17 ± 2.11 before and after premedication respectively. In ketamine anaesthesia it was 152.33 ± 3.10, 102.17 ± 2.71 and 79.33 ± 2.52 at 30 min, 90 min and 24 h. respectively. There was significant ($P<0.05$) increase in diastolic blood pressure after premedication, during anaesthesia and recovery (Fig.9).

4.1.2.10 Mean arterial blood pressure (mmHg): Mean arterial blood pressure was 99.83 ± 4.50 and 118.67 ± 3.24 before and after premedication respectively.

In ketamine anaesthesia it was 173.00 ± 2.98, 123.00 ± 2.69 and 100.50 ± 4.33 at 30 min, 90 min and 24 h. respectively. There was significant (P<0.05) increase in mean arterial blood pressure after premedication, during anaesthesia and recovery (Fig.10).

4.1.2.11 Electrocardiogram (ECG): All the animals showed normal ECG reading before premedication. The changes noticed after premedication and during anaesthesia were tachycardia, premature ventricular contractions, arrhythmia and sino-atrial block. Increased heart rate and occasional ventricular premature contractions were noticed in one animal (I_3). The increase in heart rate was noticed in animal No.I_5 after administration of glycopyrrolate and it has got corrected after the administration of xylazine (Plate 7). This became normal after a period of 20 minutes. The same animal showed signs of sino-atrial block after xylazine administration and it reduced after the administration of ketamine but sinus arrhythmia persisted. S-T segment depression was also noticed in these animals.

4.1.3 Haematological Parameters (Tables 7 to 8)

4.1.3.1 Haemoglobin concentration (g/dl): Haemoglobin concentration was 11.32 ± 0.36 and 10.48 ± 0.36 before and after premedication respectively. In ketamine anaesthesia it was 10.33 ± 0.40, 10.40 ± 0.46 and 10.80 ± 0.33 at 30 min, 90min and 24 h. respectively. There was a decrease in haemoglobin concentration throughout the period of observation. The decrease was significant (P<0.05) after premedication, during anaesthesia and recovery (Fig.11).

4.1.3.2 Volume of packed red cells (%): Volume of packed red cells was 30.67 ± 0.56 and 31.67 ± 0.33 before and after premedication respectively. In ketamine anaesthesia, it was 30.83 ± 0.70, 31.17 ± 1.01 and 32.04 ± 0.68 at 30 min, 90 min and 24 h respectively. There was significant (P<0.05) increase in volume of packed red cells after premedication and during recovery but during anaesthesia there was significant (P<0.05) decrease (Fig.12).

4.1.3.3 Erythrocyte sedimentation rate (mm/h): Erythrocyte sedimentation rate was 2.83 ± 0 .70 and 2.67 ± 0 .76 before and after premedication respectively. In ketamine anaesthesia it was 2.67 ± 0.42, 2.50 ± 0.67 and 2.83 ± 0.40 at 30 min, 90 min and 24 h. respectively. There was gradual decrease in erythrocyte sedimentation rate following premedication and during anaesthesia .But it increased to the base line value by 24 h. (Fig.13).

4.1.3 .4. Total leukocyte count ($10^3/mm^3$): Total leukocyte count was 13.00 ± 1.25 and 13.00 ± 1.31 before and after premedication respectively. In ketamine anaesthesia it was 12.90 ± 1.32, 13.28 ± 1.23 and 14.93 ± 2.80 at 30 min, 90 min and 24 h. respectively. The variations were marginal (Fig.14).

4.1.3.5 Lymphocyte count (%): Lymphocyte count was 28.83 ± 1.01 and 29.50 ± 0.43 before and after premedication respectively. In ketamine anaesthesia it was 28.83 ± 0.83, 29.17 ± 0.91 and 29.17 ± 1.01 at 30 min, 90 min and 24 h. respectively. The variations were marginal (Fig.15).

4.1.3.6 Neutrophil count (%): Neutrophil count was 69.00 ± 0.73 and 68.83 ± 0.54 before and after premedication respectively. In ketamine anaesthesia it was 69.50 ± 0.76, 69.50 ± 1.09 and 69.83 ± 0.95 at 30 min, 90 min and 24 h. respectively. The variations were marginal (Fig.16).

4.1.3.7 Eosinophil count (%):Eosinophil count was 1.83 ± 0.4 and 1.67 ± 0.33 before and after premedication respectively. In ketamine anaesthesia it was 1.33 ± 0.21, 1.33 ± 0.21 and 1.17 ± 0.17 at 30 min, 90 min and 24 h. respectively. The variations were marginal (Fig.17).

4.1.3.8 Monocyte count(%): Monocyte count was 0.33 ± 0.24 and 0 ± 0 before and after the premedication respectively. In ketamine anaesthesia it was 0.16 ± 0, 0 ± 0 and 0.16 ± 0.24 at 30 min, 90 min and 24 h. respectively. The variations were marginal.

4.1.3 .9 Basophil count (%):Basophil count was 0 ± 0 throughout the period of observation.

4.1.4 Serum Biochemical Parameters (Tables 9 to 11)

4.1.4.1 Total protein (g/dl): Total protein was 7.00 ± 0.28 and 6.53 ± 0.13 before and after premedication respectively. In ketamine anaesthesia it was 6.42 ± 0.21, 6.58 ± 0.11, 6.83 ± 0.18 at 30 min, 90 min and 24 h respectively. There was decrease in serum total protein content after premedication and during anaesthesia and recovery. The decrease was significant ($P<0.05$) after premedication and during anaesthesia (Fig.18).

4.1.4.2 Creatinine (mg/dl): Creatinine was 1.05 ± 0.03 and 0.98 ± 0.13 before and after premedication respectively. In ketamine anaesthesia it was 0.97 ± 0.05, 1.10 ± 0.07 and 1.03 ± 0.06 at 30 min, 90 min and 24 h. respectively. There were marginal decrease in serum creatinine level after premedication and during anaesthesia, but during recovery there was marginal increase (Fig.19).

4.1.4.3 Blood urea nitrogen (mg/dl): Blood urea nitrogen was 31.50 ± 0.34 and 29.17 ± 1.80 before and after the premedication respectively. In ketamine anaesthesia it was 28.83 ± 0.60, 32.00 ± 2.61 and 33.67 ± 2.17 at 30 min, 90 min and 24 h. respectively. There was decrease in BUN level after premedication and during anaesthesia. The decrease during anaesthesia was significant ($P<0.05$) but it increased above the baseline value during recovery (Fig.20).

4.1.4.4. Glucose (mg/dl): Glucose was 87.17 ± 4.50 and 140.00 ± 9.48 before and after premedication respectively. In ketamine anaesthesia it was 147.00 ± 13.64, 221.67 ± 29.25 and 171.50 ± 6.23 at 30 min, 90 min and 24 h. respectively. There was significant ($P<0.05$) increase in serum glucose value after premedication, during anaesthesia and recovery (Fig.21).

4.1.4.5 Aspartate amino transferase (U/L): Aspartate amino transferase was 55.17 ± 2.43 and 44.17 ± 3.61 before and after premedication respectively. In

ketamine anaesthesia it was 48.67 ± 2.35, 39.67 ± 4.24 and 49.00 ± 1.37 at 30 min, 90 min and 24 h. respectively. There was decrease in AST value after premedication and during anaesthesia and the decrease was significant ($P<0.05$) at 90 min. (Fig.22).

4.1.4.6 Aalanine amino transferase (U/L): Aalanine amino transferase was 47.67 ± 3.09 and 37.00 ± 4.63 before and after premedication respectively. In ketamine anaesthesia it was 44.33 ± 4.50, 37.50 ± 4.44 and 44.00 ± 3.53 at 30 min., 90 min. and 24 h. respectively. There was decrease in ALT value after premedication and during anaesthesia (Fig.23).

4.1.4.7 Sodium (mEq/L) : Sodium was 148.00 ± 3.78 and 144.83 ± 2.48 before and after premedication respectively. In ketamine anaesthesia it was 138.00 ± 3.31, 142.83 ± 1.38 and 140.67 ± 1.71 at 30 min, 90 min and 24 h. respectively. There was decrease in serum sodium concentration, but was not significant (Fig.24).

4.1.4.8 Potassium (mEq/L): Potassium was 5.03 ± 0.14 and 5.30 ± 0.14 before and after premedication respectively. In ketamine anaesthesia it was 4.87 ± 0.28, 5.10 ± 0.18 and 4.98 ± 0.19 at 30 min, 90 min and 24 h. respectively. There was marginal variations in serum potassium concentration after premedication and during anaesthesia (Fig.25).

4.1.4.9 Chloride (mEq/L): Chloride was 111.00 ± 2.02 and 108.00 ± 0.89 before and after premedication respectively. In ketamine anaesthesia it was 110.33 ± 0.42, 110.0 ± 1.63, 106.00 ± 1.48 at 30 min, 90 min and 24 h. respectively. There was decrease in serum chloride concentration through out the period of observation and the decrease was significant ($P<0.05$) at 24 h. (Fig.26).

4.1.5. Arterial Blood Gas Analysis (Table 12)

4.1.5.1 pH: The pHa was 7.36 ± 0.02, 7.27 ± 0.03 and 7.28 ± 0.05 before premedication, during anaesthesia and recovery respectively. There was decrease in pHa during anaesthesia and recovery (Fig.27).

4.1.5.2 Partial pressure of oxygen **(PaO_2)** (mm Hg): Partial pressure of oxygen was 92.50 ± 1.15, 102.90 ± 19.65 and 112.37 ± 15.00, before premedication, during anaesthesia and recovery respectively. There was increase in PaO2 during anaesthesia and recovery (Fig.28).

4.1.5.3 Partial pressure of carbon dioxide **($PaCO_2$)** (mm Hg): Partial pressure of carbon dioxide was 26.43 ± 1.02, 36.39 ± 9.36 and 31.23 ± 1.53, before premedication, during anaesthesia and recovery respectively. There was increase in $PaCO_2$ during anaesthesia and recovery (Fig.29).

4.1.5.4 Bicarbonate **(HCO_3)** (m mol/L): Bicarbonate was 13.87 ± 0.18, 12.80 ± 0.40 and 15.93 ± 2.53, before premedication, during anaesthesia and recovery respectively. There was marginal no change in HCO_3 during anaesthesia and recovery (Fig.30).

4.1.6 Postanaesthetic Observations

Following recovery, the dogs were with varying degree of dullness which lasted for three hours and had the normal food intake from the next day onwards.

4.2 GROUP II

4.2.1 Clinical Observations (Table 3)

4.2.1.1. Clinical signs: The common clinical signs, suggestive of sedation, manifested by the dogs following xylazine premedication were winking of eyes, yawning and inco-ordination of movements with lowering of head. The other symptoms noticed were vomiting in all animals, licking (II_1), urination (II_6) and defecation (II_1, II_3, II_6). All the dogs, assumed the position of sternal reccumbency with head down posture in 10.83 ± 0.40 min.

The dogs assumed the position of lateral reccumbency by 4.33 ± 0.42 min following the administration of ketamine. Out of the six dogs, in four (II_2, II_3 II_4, II_6) endotracheal intubation could be performed only with resistance.

During recovery, shivering, vocalization and urination were noticed in all the dogs.

4.2.1.2. Induction time of anaesthesia: The induction time of anaesthesia following the administration of ketamine was 8.83 ± 0.40 min. (Fig.1)

4.2.1.3. Duration of surgical anaesthesia: The duration of surgical anaesthesia was 45.83 ± 3.74 min. (Fig.1).

4.2.1.4. Depth of anaesthesia: The depth of surgical anaesthesia was satisfactory in all the dogs after the administration and subsequent maintenance with isoflurane.

4.2.1.5. Muscle relaxation time: The muscle relaxation time was 49.83 ± 1.85 min. (Fig.1).

4.2.1.6. Degree of muscle relaxation: The degree of muscle relaxation was good in the dogs following the administration of isoflurane.

4.2.1.7. Recovery time: The recovery time was 74.14 ± 3.75 min. (Fig.1).

4.2.2. Physiological Observations (Table 4 to 6)

4.2.2.1. Rectal temperature (°C)**:** Rectal temperature was 39.10 ± 0.07 and 38.99 ± 0.04 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 38.91 ± 0.15, 38.75 ± 0.13 and 38.94 ± 0.08 at 30 min, 90 min and 24 h. respectively. There was a decrease in rectal temperature after premedication and during anaesthesia (Fig.2).

4.2.2.2. Pulse rate (per min)**:** Pulse rate was 91.17 ± 4.12 and 83.17 ± 2.86 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 87.17 ± 2.07, 90.00 ± 2.62 and 86.50 ± 3.24 at 30 min, 90 min and 24 h respectively. There was decrease in pulse rate after premedication and during anaesthesia (Fig.3).

4.2.2.3. Respiration rate (per min)**:** Respiration rate was 24.67 ± 6.70 and 17.33 ± 2.55 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 19.17 ± 4.06, 23.50 ± 6.82 and 33.00 ± 5.79 at 30 min, 90 min and 24 h. respectively. There was decrease in respiration rate following premedication and at 30 min, but at 90min and 24h it was increased (Fig.4).

4.2.2.4. Colour of visible mucous membrane **:** Colour of visible mucous membrane was pale roseate in all animals.

4.2.2.5. Oxygen saturation (SpO_2) level (%)**:** Oxygen saturation level was 82.33 ± 3.48 and 94.33 ± 0.42 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 97.17 ± 0.87, 98.33 ± 0.21 and 95.00 ± 1.37 at 30 min, 90 min and 24 h. There was significant ($P<0.05$) increase in SpO_2 level after premedication and during anaesthesia (Fig.5).

4.2.2.6. Capillary refill time (sec)**:** Capillary refill time was 1.50 ± 0.23 and 1.33 ± 0.22 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 1.83 ± 0.21, 1.50 ± 0.17 and 1.66 ± 0.22 at 30 min, 90 min and 24 h. respectively. There was decrease in capillary refill time after

premedication but it was increased during anaesthesia, thereafter it decreased to the near normal value (Fig.6).

4.2.2.7. Blood coagulation time (in min): Blood coagulation time was 3.85 ± 0.11 and 3.92 ± 0.11 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 4.17 ± 0.10, 4.22 ± 0.11 and 4.18 ± 0.07 at 30 min, 90 min and 24 h. respectively. There was an increase in coagulation time and it was significant ($P<0.05$) after premedication, during anaesthesia and at 24h. (Fig.7).

4.2.2.8. Systolic blood pressure (mm Hg): Systolic blood pressure was 139.83 ± 2.21 and 159.67 ± 2.01 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 181.83 ± 6.36, 168.17 ± 2.47 and 140.83 ± 2.79 at 30 min, 90 min and 24 h respectively. There was decrease in the systolic blood pressure following premedication and with significant ($P<0.05$) increase at 30 min. Thereafter it was decreased (Fig.8).

4.2.2.9. Diastolic blood pressure (mm Hg): Diastolic blood pressure was 84.14 ± 2.03 and 104.50 ± 1.64 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 148.50 ± 1.80, 103.33 ± 1.64 and 84.17 ± 2.29 at 30 min, 90 min and 24 h. respectively. There was increase in diastolic blood pressure after premedication and during anaesthesia. The increase was significant ($P<0.05$) during anaesthesia (Fig.9).

4.2.2.10. Mean arterial blood pressure (mm Hg): Mean arterial blood pressure was 105.00 ± 2.16 and 125.67 ± 2.20 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 167.83 ± 2.27, 124.33 ± 1.89 and 103.17 ± 1.84 at 30 min., 90 min. and 24 h. respectively. There was increase in mean arterial blood pressure after premedication and during anaesthesia. The increase was significant ($P<0.05$) after premedication and during anaesthesia (Fig.10).

4.2.2.11. Electrocardiogram (ECG): All the animals showed normal ECG before premedication. Sino atrial block was observed after the administration of xylazine and persisted up to 10 minutes after ketamine and subsequent isoflurane maintenance. In animal No. II_1 there was a reduction in the height of the R wave. In animal No.II_2 there was a depression of ST segment and the depression persisted throughout the period of anaesthesia. Peaked T wave persisted. In animal No. II_3 the sinus arrhythmia persisted with a negligible increase in the height of the T wave (Plate 8). Mild elevation of ST segment was also noticed in this animal (II_3). Right bundle branch block seen in animal No. II_4, but the condition became normal. The ECG was normal at the beginning in the animal II_5, but the depression of ST segment aggravated. There was only QRS complex indicating tachycardia. The height of R wave reduced with a small or mild P wave. Subsequent to the administration of ketamine showed an increase in the height of the R wave but sinus arrhythmia persisted.

4.2.3. Haematological Parameters (Tables 7 to 8)

4.2.3.1. Haemoglobin concentration (g/dl): Haemoglobin concentration was 10.77 ± 0.37 and 10.48 ± 0.38 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was10.13 ± 0.27 at 30 min, 10.22 ± 0.43 at 90 min and10.20 ± 0.24 at 24 h. There was significant ($P<0.05$) decrease in haemoglobin concentration after premedication and during anaesthesia (Fig.11).

4.2.3.2. Volume of packed red cells (%): Volume of packed red cells was 29.67 ± 0.56 and 29.67 ± 0.56 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 28.83 ± 0.31, 29.00 ± 0.68 and 30.0 ± 1.21 respectively at 30 min, 90 min and 24 h. respectively. There was no variation after premedication, but during anaesthesia it was further decreased (Fig.12).

4.2.3.3. Erythrocyte sedimentation rate (mm/h): Erythrocyte sedimentation rate was 2.17 ± 0.17 and 2.00 ± 0.26 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 1.83 ± 0.17, 1.67 ± 0.33 and 2.00 ± 0.26

at 30 min, 90 min and 24 h. of administration of ketamine. There was decrease in ESR after premedication and during anaesthesia (Fig.13).

4.2.3.4. Total leukocyte count ($10^3/mm^3$): Total leukocyte count was 11.23 ± 5.57 and 11.21 ± 4.79 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 11.16 ± 5.52, 11.46 ± 4.27 and 14.33 ± 2.83 at 30 min, 90 min and 24 h. respectively. The variations were marginal (Fig.14).

4.2.3.5. Lymphocyte count (%): Lymphocyte count was 31.17 ± 1.40 and 32.17 ± 0.75 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 29.00 ± 0.82, 29.17 ± 0.91 and 28.83 ± 0.95 at 30 min, 90 min and 24 h. respectively. The variations were marginal (Fig.15).

4.2.3.6. Neutrophil count (%): Neutrophil count was 67.00 ± 1.15 and 66.17 ± 0.54 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 65.50 ± 0.92, 65.33 ± 1.26 and 66.17 ± 0.87 at 30 min, 90 min and 24 h. respectively. There was decrease in neutrophil count and it was significant ($P<0.0$) at 30 min. and 90 min. (Fig.16).

4.2.3.7. Eosinophil count (%): Eosinophil count was 1.33 ± 0.21 and 1.50 ± 0.34 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 1.17 ± 0.17, 1.33 ± 0.21 and 1.50 ± 0.22 at 30 min, 90 min and 24 h. respectively. The variations were marginal (Fig.17).

4.2.3.8. Monocyte count (%): Monocyte count was 0.20 ± 0.24 and 0.16 ± 0.24 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 0.16 ± 0.24, 0.16 ± 0.24 and 0.16 ± 0.24 at 30 min, 90 min and 24 h. respectively. The variations were marginal.

4.2.3.9. Basophil count (%): Basophil count was 0 ± 0 throughout the period of observation.

4.2.4. Serum Biochemical Parameters (Tables 9 to 11)

4.2.4.1. Total protein (g/dl): Total protein was 7.13 ± 0.35 and 6.35 ± 0.45 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 6.67 ± 0.26, 6.62 ± 0.27, and 6.40 ± 0.13 at 30 min, 90 min and 24 h. There was decrease in total protein after premedication and during anaesthesia and recovery. The decrease was significant ($P<0.05$) after premedication (Fig.18).

4.2.4.2. Creatinine (mg/dl): Creatinine was 1.83 ± 0.26 and 1.30 ± 0.14 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 1.20 ± 0.07, 0.97 ± 0.03 and 1.02 ± 0.14 at 30 min, 90 min and 24 h. There were marginal decreases in serum creatinine level after premedication and during anaesthesia (Fig.19).

4.2.4.3. Blood urea nitrogen (mg/dl): Blood urea nitrogen was 34.33 ± 0.21 and 33.00 ± 1.41 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 44.33 ± 5.57, 36.83 ± 5.18 and 35.17 ± 3.38 at 30 min, 90 min and 24 h. There was a decrease in BUN after premedication. During anaesthesia and recovery, there was significant ($P<0.05$) increase (Fig.20).

4.2.4.4. Glucose (mg/dl): Glucose was 94.33 ± 2.49 and 151.33 ± 7.51 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 155.00 ± 15.24, 175.00 ± 13.29 and 169.67 ± 8.55 at 30 min, 90 min and 24 h. respectively. There was significant ($P<0.05$) increase in the serum glucose concentration after premedication, during anaesthesia and at 24h. (Fig.21).

4.2.4.5. Aspartate amino transferase (U/L): Aspartate amino transferase was 33.67 ± 0.61 and 40.33 ± 1.20 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 45.00 ± 4.84, 34.17 ± 3.75 and 44.33 ± 2.39 at 30 min, 90 min and 24 h. There was an increase in AST value after premedication and during anaesthesia ($P<0.05$) (Fig.22).

4.2.4.6. Alanine amino transferase (U/L): Aalanine amino transferase was 30.67 ± 0.67 and 41.50 ± 1.80 before and after premedication with glycopyrrolate-xylazine combination respectively. In ketamine-isoflurane anaesthesia, it was 45.33 ± 3.49, 29.00 ± 3.98 and 41.33 ± 2.67 at 30 min, 90 min and 24 h. There was increase in ALT value after premedication and during anaesthesia ($P<0.05$) (Fig.23).

4.2.4.7. Sodium (mEq/L) : Sodium was 133.67 ± 6.78 and 148.67 ± 4.80 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 144.00 ± 4.85, 145.67 ± 2.59 and 140.00 ± 3.44 at 30 min, 90 min and 24 h respectively. There was marginal increase in serum sodium concentration after premedication, during anaesthesia and recovery (Fig.24).

4.2.4.8. Potassium (mEq/L): Potassium was 5.67 ± 0.30 and 4.85 ± 0.30 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 5.52 ± 0.37, 5.30 ± 0.35 and 4.43 ± 0.41 at 30 min, 90 min and 24 h. There was a marginal variation in serum potassium concentration after premedication, during anaesthesia (Fig.25).

4.2.4.9. Chloride (mEq/L): Chloride was 104.50 ± 2.31 and 107.00 ± 2.46 before and after premedication respectively. In ketamine-isoflurane anaesthesia, it was 107.17 ± 2.04, 106.83 ± 1.42, 101.50 ± 0.72 at 30 min, 90 min and 24 h. The variations were marginal (Fig.26)

4.2.5. Arterial Blood Gas Analysis (Table 12)

4.2.5.1 pH: The pH of arterial blood (pHa) was 7.22 ± 0, 7.27 ± 0.08 and 7.19 ± 0.07 before premedication, during anaesthesia and recovery respectively. There was increase in pHa during anaesthesia but it was decreased during recovery (Fig.27).

4.2.5.2. Partial pressure of oxygen (PaO_2) (mm Hg): Partial pressure of oxygen was 90.70 ± 0.66, 434.53 ± 21.53 and 134.40 ± 3.59 before premedication, during

anaesthesia and recovery respectively. There was marginal increase in PaO_2 during anaesthesia and recovery (Fig.28).

4.2.5.3. Partial pressure of carbon dioxide ($PaCO_2$) (mm Hg): Partial pressure of carbon dioxide was 38.17 ± 9.04, 36.80 ± 13.83 and 39.27 ± 8.15 before premedication, during anaesthesia and recovery respectively. The $PaCO_2$ level was maintained during anaesthesia and recovery (Fig.29).

4.2.5.4. Bicarbonate (HCO_3) (m mol/L): Bicarbonate was 14.73 ± 0.18, 18.97 ± 1.98 and 17.03 ± 0.65 before premedication, during anaesthesia and recovery respectively. There was increase in HCO_3 during anaesthesia and recovery (Fig.30).

4.2.6. Postanaesthetic Observations

Following recovery, the dogs were with varying degree of dullness which lasted for four hours and had the normal food intake from the next day onwards.

4.3 GROUP III

4.3.1 Clinical Observations (Table 3)

4.3.1.1. Clinical signs: The common clinical signs, suggestive of sedation, manifested by the dogs following xylazine premedication were winking of eyes, yawning and inco-ordination of movements with lowering of head. The other symptoms noticed were vomiting (III_1, III_2, III_3, III_5, III_6) licking (III_4) urination (III_5) and defecation (III_6). All the dogs, assumed the position of sternal recumbency with head down posture in 10.50 ± 0.62 min.

All the dogs were manually controlled on lateral recumbency for the intravenous administration of midazolam and there after the recumbency maintained. Endotracheal intubation could be performed without any resistance.

During recovery, shivering and urination were noticed in all the dogs.

4.3.1.2. Induction time of anaesthesia: The induction time of anaesthesia following the administration of ketamine, was 6.83 ± 0.47 min. (Fig.1)

4.3.1.3. Duration of surgical anaesthesia: The duration of surgical anaesthesia was 37.50 ± 2.14 min. (Fig.1).

4.3.1.4. Depth of anaesthesia: The depth of surgical anaesthesia was satisfactory and the abdominal muscle relaxation was good.

4.3.1.5. Muscle relaxation time: The muscle relaxation time was 41.00 ± 2.31 min. (Fig.1).

4.3.1.6. Degree of muscle relaxation: The degree of muscle relaxation was good in all the dogs.

4.3.1.7. Recovery time: The recovery time was 108.00 ± 8.47 min. (Fig.1).

4.3.2. Physiological Observations (Tables 4 to 6)

4.3.2.1. Rectal temperature (°C)**:** Rectal temperature was 39.08 ± 5.15 and 38.71 ± 0.11 before and after premedication with glycopyrrolate- xylazine and midazolam combination respectively. In ketamine anaesthesia it was 38.57 ± 0.12, 38.43 ± 0.18 and 38.86 ± 0.06 at 30 min, 90 min and 24 h respectively. There was decrease in rectal temperature after premedication and during anaesthesia and it was significant ($P<0.05$) during recovery (Fig.2).

4.3.2.2. Pulse rate (per min)**:** Pulse rate was 104.00 ± 6.21 and 89.33 ± 1.74 before and after premedication respectively. In ketamine anaesthesia it was 90.50 ± 1.71, 98.50 ± 3.40 and 93.67 ± 3.60 at 30 min, 90 min and 24 h. respectively. There was decrease in pulse rate after premedication and anaesthesia. There was significant ($P<0.05$) after premedication (Fig.3).

4.3.2.3. Respiration rate (per min)**:** Respiration rate was 38.67 ± 6.81 and 18.50 ± 1.17 before and after premedication respectively. In ketamine anaesthesia it was 21.00 ± 7.45, 20.83 ± 2.17 and 24.67 ± 6.70 at 30 min, 90 min and 24 h respectively. There was decrease in respiration rate after premedication and anaesthesia. The decrease was significant ($P<0.05$) after premedication and at 90 min. (Fig.4).

4.3.2.4. Colour of visible mucous membrane : Colour of visible mucous membrane was pale roseate in all animals.

4.3.2.5. Oxygen saturation (SpO_2) level (%)**:** Oxygen saturation level was 89.83 ± 2.44 and 93.33 ± 0.76 before and after premedication respectively. In ketamine anaesthesia it was 95.17 ± 0.31, 95.33 ± 0.33 and 95.33 ± 0.21 at 30 min, 90 min and 24 h respectively. There was increase in oxygen saturation level after premedication and during anaesthesia (Fig.5).

4.3.2.6. Capillary refill time (sec)**:** Capillary refill time was 1.50 ± 0.23 and 1.67 ± 0.22 before and after premedication respectively. In ketamine anaesthesia it

was 2.00 ± 0.21, 1.66 ± 0.37 and 1.66 ± 0.17 at 30 min, 90 min and 24 h. respectively. There was increase in capillary refill time after premedication, during anaesthesia and there after it gradually decreased to the near normal value by 24 h. (Fig.6).

4.3.2.7. Blood coagulation time (in min): Blood coagulation time was 3.83 ± 0.22 and 4.23 ± 0.15 before and after premedication respectively. In ketamine anaesthesia it was 4.13 ± 0.22, 4.42 ± 0.16 and 4.28 ± 0.20 at 30 min, 90 min and 24 h. There was increase in CT after premedication, there after the variations were marginal (Fig.7).

4.3.2.8. Systolic blood pressure (mmHg)*:* Systolic blood pressure was 140.17 ± 2.36 and 134.67 ± 2.56 before and after premedication respectively. In ketamine anaesthesia it was 185.00 ± 3.68, 138.33 ± 3.24 and138.50 ± 2.58 at 30 min, 90 min and 24 h respectively. There was significant ($P<0.05$) increase in systolic blood pressure after premedication, during anaesthesia and recovery (Fig.8).

4.3.2.9. Diastolic blood pressure (mmHg): Diastolic blood pressure was 84.83 ± 1.92 and 84.83 ± 2.29 before and after premedication respectively. In ketamine anaesthesia, it was 136.17 ± 2.63, 92.50 ± 2.55 and 89.33 ± 2.30 at 30 min, 90 min and 24 h respectively. There was significant ($P<0.05$) increase in diastolic blood pressure after premedication and during anaesthesia. But it decreased to near normal value by 24 h. (Fig.9).

4.3.2.10. Mean arterial blood pressure (mmHg)*:* Mean arterial blood pressure was 107.00 ± 3.18 and 127.00 ± 2.45before and after premedication respectively. In ketamine anaesthesia, it was 156.67 ± 2.52, 118.17 ± 2.10 and 105.00 ± 2.51 at 30 min, 90 min and 24 h respectively. There was an increase in mean arterial blood pressure after premedication and during anaesthesia. The increase was significant ($P<0.05$), during anaesthesia though it decreased below the normal value by 24h. (Fig.10).

4.3.2.11. Electrocardiogram (ECG): Electrocardiography was normal before premedication in all the animals. This was followed by ST segment elevation and became normal during the period of surgical anaesthesia.

The occurrence of right bundle branch block was significant and then the height of the P wave reduced. This became normal afterwards. After 60 minutes of ketamine administration there was a depression of ST segment with solitary supraventricular premature contractions and animal became normal by the end of anaesthetic period in animals III_4. There was peaked T wave during ketamine anaesthesia (Plate 8).

4.3.3 Haematological Parameters (Tables 7 to 8)

4.3.3.1 Haemoglobin concentration (g/dl): Haemoglobin concentration was 11.57 ± 0.23 and 10.08 ± 0.15 before and after premedication respectively. In ketamine anaesthesia it was 10.73 ± 0.47, 9.82 ± 0.21 and 10.03 ± 0.15 at 30 min, 90 min at 24 h respectively. There was significant ($P<0.05$) decrease in haemoglobin concentration after premedication, during anaesthesia, recovery and at 24 h. (Fig.11).

4.3.3.2. Volume of packed red cells (%): Volume of packed red cells was 33.50 ± 0.92 and 31.00 ± 0.57 before and after premedication respectively. In ketamine anaesthesia it was 29.67 ± 0.42, 30.83 ± 0.31 and 32.33 ± 0.56 at 30 min, 90 min and at 24 h respectively. There was a decrease in VPRC after premedication and during anaesthesia ($P<0.05$), and recovery ($P<0.05$) (Fig.12).

4.3.3.3. Erythrocyte sedimentation rate (mm/h): Erythrocyte sedimentation rate was 2.00 ± 0.25 and 1.50 ± 0.22 before and after premedication respectively. In ketamine anaesthesia it was 2.33 ± 0.33, 1.83 ± 0.30 and 1.83 ± 0.30 at 30 min, 90 min and at 24 h respectively. There was decrease in ESR after premedication and during anaesthesia (Fig.13).

4.3.3.4. Total leukocyte count ($10^3/mm^3$): Total leukocyte count was 18.13 ± 4.84 and 17.91 ± 2.89 before and after premedication respectively. In ketamine anaesthesia it was 18.66 ± 3.00, 18.36 ± 2.99 and 18.38 ± 3.95 at 30 min, 90 min and at 24 h respectively. The variations were marginal (Fig.14).

4.3.3.5. Lymphocyte count (%): Lymphocyte count was 28.67 ± 1.02 and 27.83 ± 1.01 before and after premedication respectively. In ketamine anaesthesia it was 28.33 ± 0.67, 29.33 ± 0.61 and 29.17 ± 0.70 at 30 min, 90 min and at 24 h respectively. The variations were marginal (Fig.15).

4.3.3.6. Neutrophil count (%): Neutrophil count was 69.83 ± 1.11 and 71.05 ± 0.92 before and after premedication respectively. In ketamine anaesthesia it was 70.33 ± 0.61, 69.83 ± 0.60 and 69.83 ± 0.70at 30 min, 90 min and at 24 h respectively. The variations were marginal (Fig.16).

4.3.3.7. Eosinophil count (%):Eosinophil count was 1.33 ± 0.42and 0.66 ± 0.21before and after premedication respectively. In ketamine anaesthesia it was 1.17 ± 0.17, 0.83 ± 0.17 and 1.00 ± 0 at 30 min, 90 min and at 24 h respectively. The variations were marginal (Fig.17).

4.3.3.8. Monocyte count (%): Monocyte count was 0.17 ± 0.24 and 0 ± 0 before and after premedication respectively. In ketamine anaesthesia it was 0.16 ± 0, 0 ± 0 and 0 ± 0 at 30 min, 90 min and at 24 h respectively. The variations were marginal.

4.3.3.9. Basophil count (%): Basophil count was 0 ± 0 throughout the period of observations.

4.3.3. Serum Biochemical Parameters (Table 9 to 11)

4.3.3.1. Total protein (g/dl): Total protein was 6.85 ± 0.45 and 6.40 ± 0.28 before and after premedication respectively. In ketamine anaesthesia it was 6.17 ± 0.35, 6.40 ± 0.30, 6.58 ± 0.30 at 30 min, 90 min and at 24 h respectively.

There was marginal decrease in protein content after premedication and during anaesthesia (Fig.18).

4.3.3.2. Creatinine (mg/dl): Creatinine was 1.35 ± 0.30 and 1.05 ± 0.14 before and after premedication. In ketamine anaesthesia it was 1.00 ± 0.10, 0.93 ± 0.07 and 1.00 ± 0.0 at 30 min, 90 min and at 24 h respectively. There was marginal decrease in serum creatinine level after premedication and during anaesthesia (Fig.19)

4.3.3.3. Blood urea nitrogen (mg/dl) : Blood urea nitrogen was 33.33 ± and 30.33 ± 2.99 before and after premedication respectively. In ketamine anaesthesia it was 30.17 ± 3.08, 27.67 ± 1.98 and 28.67 ± 2.65 at 30 min, 90 min and at 24 h respectively. There was decrease in BUN level after premedication, during anaesthesia and recovery and the decrease was significant ($P<0.05$) during recovery (Fig.20).

4.3.3.4. Glucose (mg/dl): Glucose was 95.50 ± 2.63 and 168.00 ± 7.41 before and after premedication. In ketamine anaesthesia it was 185.50 ± 21.55, 200.50 ± 19.87 and 188.33 ± 9.33 at 30 min, 90 min and at 24 h respectively. There was significant ($P<0.05$) increase in glucose concentration after premedication, during anaesthesia and at 24h (Fig.21).

4.3.3.5. Aspartate amino transferase (U/L): Aspartate amino transferase was 42.17 ± 5.82 and 42.00 ± 2.62 before and after premedication respectively. In ketamine anaesthesia it was 40.67 ± 4.21, 41.33 ± 1.50 and 40.67 ± 2.40 at 30 min, 90 min and at 24 h. respectively. There was marginal decrease in AST value after premedication during anaesthesia and recovery(Fig.22).

4.3.3.6. Aalanine amino transferase (U/L): Aalanine amino transferase was 39.50 ± 5.46 and 35.33 ± 2.92 before and after premedication. In ketamine anaesthesia it was 36.00 ± 4.49, 34.50 ± 3.58 and 33.67 ± 2.75 at 30 min, 90 min and at 24 h respectively. There was marginal decrease in ALT value after premedication and during anaesthesia (Fig.23).

4.3.3.7. Sodium (mEq/L) : Sodium was 135.33 ± 1.61 and 143.50 ± 3.76 before and after premedication. In ketamine anaesthesia it was 137.83 ± 2.18, 139.83 ± 1.08 and 139.83 ± 1.19 at 30 min, 90 min and at 24 h respectively. There was marginal increase in sodium concentration after premedication and during anaesthesia (Fig.24).

4.3.3.8. Potassium (mEq/L): Potassium was 4.78 ± 0.43 and 4.61 ± 0.26 before and after premedication. In ketamine anaesthesia it was 4.38 ± 0.43, 4.55 ± 0.38 and 4.73 ± 0.25 at 30 min, 90 min and at 24 h respectively. The variations were marginal (Fig.25).

4.3.3.9. Chloride (mEq/L): Chloride was 88.17 ± 15.92 and 108.50 ± 0.88 before and after premedication. In ketamine anaesthesia it was 108.67 ± 1.12, 106.0 ± 1.18, 104.17 ± 1.17 at 30 min, 90 min and at 24 h respectively. There was increase in serum chloride level after premedication and during anaesthesia and during anaesthesia the increase was significant ($P<0.05$) at 30 min. (Fig26).

4.3.3. Arterial Blood Gas Analysis (Table 12)

4.3.3.1. pH: The pHa was 7.34 ± 0.02, 7.29 ± 0.01 and 7.31 ± 0.01 before premedication, during anaesthesia and recovery respectively. There was decrease in pHa during anaesthesia and recovery (Fig.27).

4.3.3.2. Partial pressure of oxygen (PaO_2) (mm Hg): Partial pressure of oxygen was 110.73 ± 14.02, 117.87 ± 1.92 and 115.67 ± 19.49 before premedication, during anaesthesia and recovery respectively. There was increase in PaO_2 during anaesthesia and recovery (Fig.28).

4.3.3.3. Partial pressure of carbon dioxide ($PaCO_2$) (mm Hg): Partial pressure of carbon dioxide was 25.53 ± 1.84, 42.33 ± 1.89 and 33.17 ± 5.02 before premedication, during anaesthesia and recovery respectively. There was increase in $PaCO_2$ during anaesthesia and recovery (Fig.29).

4.3.3.4. Bicarbonate (HCO_3) (m mol/L): Bicarbonate was 18.13 ± 1.62, 13.80 ± 1.27 and 17.60 ± 1.58 before premedication, during anaesthesia and recovery respectively. There was decrease in HCO_3 during anaesthesia but during recovery it increased to the near normal value (Fig.30).

4.3.4. Postanaesthetic Observations

Following recovery, the dogs were with varying degree of dullness which lasted for six hours and had the normal food intake from the next day onwards.

4.4. GROUP IV

4.4.1. Clinical Observations (Table 3)

4.4.1.1 Clinical signs: The common clinical signs, suggestive of sedation, manifested by the dogs following xylazine premedication were winking of eyes, yawning and inco-ordination of movements with lowering of head. The other symptoms noticed were vomiting (all the dogs), licking (IV_3, IV_6) and defecation (IV_3, IV_6). All the dogs, assumed the position of sternal recumbency with head down posture in 10.83 ± 0.71 min.

All the dogs were manually controlled on lateral recumbency for the intravenous administration of midazolam and thereafter the recumbency maintained. Endotracheal intubation could be performed without any resistance.

During recovery, shivering and urination were noticed in all the dogs.

4.4.1.2. Induction time of anaesthesia: The induction time of anaesthesia following the administration of ketamine was 6.50 ± 0.43 min. (Fig.1).

4.4.1.3. Duration of surgical anaesthesia: The duration of surgical anaesthesia was 42.33 ± 0.84 min. (Fig.1).

4.4.1.4. Depth of anaesthesia: The depth of surgical anaesthesia was very good.

4.4.1.5. Muscle relaxation time: The muscle relaxation time was 54.66 ± 3.02 min. (Fig.1).

4.4.1.6. Degree of muscle relaxation: The degree of muscle relaxation was excellent in all the dogs after the administration of isoflurane.

4.4.1.7. Recovery time: The recovery time was 91.50 ± 6.42 min. (Fig.1).

4.4.2. Physiological Observations (Tables 4 to 6)

4.4.2.1. Rectal temperature (°C)*:* Rectal temperature was 39.21 ± 0.13 and 38.96 ± 1.74 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 38.65 ± 0.12, 38.53 ± 0.10 and 39.33 ± 0.13 at 30 min, 90 min and 24 h. respectively. There was marginal decrease in rectal temperature through out the period of observation (Fig.2).

4.4.2.2. Pulse rate (per min)**:** Pulse rate was 85.00 ± 6.25 and 80.66 ± 3.87 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 82.83 ± 3.55, 85.17 ± 3.75 and 87.33 ± 3.42 at 30 min, 90 min and 24 h. respectively. There was significant ($P<0.05$) decrease in pulse after premedication and thereafter there was marginal increase (Fig.3).

4.4.2.3. Respiration rate (per min)**:** Respiration rate was 28.17 ± 5.15 and 20.66 ± 5.07 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 26.50 ± 3.34, 27.17 ± 7.73 and 38.67 ± 6.81 at 30 min, 90 min and 24 h. respectively. There was decrease in respiration rate after premedication, but during anaesthesia it gradually increased (Fig.4).

4.4.2.4. Colour of visible mucous membrane : Colour of visible mucous membrane was pale roseate in all animals.

4.4.2.5. Oxygen saturation (SpO_2) level (%)**:** Oxygen saturation level was 86.67 ± 4.03 and 96.00 ± 0.44 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 98.33 ± 0.20, 98.33 ± 0.21 and 94.83 ± 0.91 at 30 min, 90 min and 24 h. respectively. There was significant ($P<0.05$) increase in oxygen saturation level after premedication and during anaesthesia (Fig.5).

4.4.2.6. Capillary refill time (sec)**:** Capillary refill time was 1.50 ± 0.23 and 1.67 ± 0.22 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 1.83 ± 0.21, 1.66 ± 0.31 and 1.66 ± 0.17 at 30 min, 90 min and 24 h. respectively. There was significant ($P<0.05$) increase in capillary refill time

after premedication, during anaesthesia and thereafter it decreased to the near normal value (Fig.6).

4.4.2.7. Blood coagulation time (in min): Blood coagulation time was was 4.25 ± 0.18 and 4.45 ± 0.26 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 4.52 ± 0.20, 4.78 ± 0.22 and 4.37 ± 0.19 at 30 min, 90 min and 24 h respectively. The variations were marginal (Fig.7).

4.4.2.8. Systolic blood pressure (mmHg): Systolic blood pressure was 136.67 ± 3.08 and 130.00 ± 3.64 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 183.17 ± 2.77, 137.00 ± 2.62 and 129.17 ± 1.74 at 30 min, 90 min and 24 h respectively. There was decrease in systolic pressure after premedication but during anaesthesia there was increase and the increase was significant ($P<0.05$) at 30 min. (Fig.8).

4.4.2.9. Diastolic blood pressure (mmHg): Diastolic blood pressure was 81.00 ± 2.59 and 84.50 ± 2.34 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 130.17 ± 4.10, 92.17 ± 1.56 and 89.00 ± 2.98 at 30 min, 90 min and 24 h. respectively. There was decrease in diastolic pressure after premedication and during anaesthesia it was increased (Fig.9).

4.4.2.10. Mean arterial blood pressure (mmHg): Mean arterial blood pressure was 101.67 ± 2.98 and 137.33 ± 1.67 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 151.83 ± 4.60, 113.83 ± 1.79 and 104.00 ± 2.47 at 30 min, 90 min and 24 h respectively. There was decrease in mean arterial pressure after premedication but during anaesthesia there was significant increase ($P<0.05$) (Fig.10).

4.4.2.11. Electrocardiogram (ECG): Electrocardiography was normal before premedication in all the animals. Sinus arrythmia and sino atrial block observed after the administration of xylazine in animal IV_1 and IV_2.

In animal No. IV_2 the sinus arrythmia persisted till the administration of ketamine. This sinus arrythmia connected slowly and was followed by ventricular tachycardia with ventricular premature contractions persisted. Fusion beat (variation of ventricular premature contraction) observed in this animal and subsequently the rhythm became normal. ST segment depression also noticed after 30 min. of ketamine administration and isoflurane maintenance but became normal after 15 min. The animal IV_3 showed peaked T wave. The P wave is equal to R wave and subsequently T wave became more than R wave. The sinus arrythmia persisted. There was signs of sinoatrial block/arrest. Occasional missing of QRS complex indicating second degree heart block. Indications of ventricular tachycardia also observed in animal IV_2.

Signs of sino atrial block/arrest observed in animal IV_2. There was a solitary ventricular premature contraction (spike like ventricular contraction). The heart rate reduced. QT interval widened. Signs of SA block, height of T wave increased and peaking of T wave. The sino atrial block aggravated after 15 minutes became normal after 30 minutes. The animal became perfectly normal and showed ECG recording with normal T wave (Plate 9 to 11).

4.4.3. Haematological Parameters (Table 7 to 8)

4.4.3.1. Haemoglobin concentration (g/dl): Haemoglobin concentration was 11.52 ± 0.18 and 11.06 ± 0.13 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 10.85 ± 0.16, 10.72 ± 0.14 and 11.10 ± 0.77 at 30 min, 90 min and 24 h respectively. There was significant ($P<0.05$) decrease in haemoglobin concentration after premedication and during anaesthesia (Fig.11).

4.4.3.2. Volume of packed red cells (%): Volume of packed red cells was 31.67 ± 0.67 and 29.83 ± 0.47 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 28.83 ± 0.40, 28.50 ± 0.56 and 30.83 ± 0.87 at 30 min, 90 min and 24 h. respectively. There was a decrease in volume of packed

red cells after premedication, during anaesthesia and recovery. The decrease was significant ($P<0.05$) (Fig.12).

4.4.3.3. Erythrocyte sedimentation rate (mm/h): Erythrocyte sedimentation rate was 2.17 ± 0.31 and 1.50 ± 0.22 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 1.67 ± 0.21, 1.83 ± 0.17 and 1.67 ± 0.21 at 30 min, 90 min and 24 h. respectively. There was decrease in ESR after premedication, but during anaesthesia the variations were marginal (Fig.13).

4.4.3.4. Total leukocyte count ($10^3/mm^3$): Total leukocyte count was 14.00 ± 2.47 and 14.51 ± 2.12 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 15.18 ± 1.88, 15.73 ± 1.93 and 14.36 ± 1.89 at 30 min, 90 min and 24 h. respectively. The variations were marginal (Fig.14).

4.4.3.5. Lymphocyte count (%): Lymphocyte count was 28.33 ± 1.12 and 29.50 ± 0.88 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 32.17 ± 0.95, 30.83 ± 1.11 and 30.33 ± 1.43 at 30 min, 90 min and 24 h. respectively. There was an increase in lymphocyte count after premedication and during anaesthesia. The increase was significant ($P<0.05$) during anaesthesia (Fig.15).

4.4.3.6. Neutrophil count (%): Neutrophil count was 69.17 ± 1.14 and 69.50 ± 0.88 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 66.50 ± 0.85, 67.67 ± 1.05 and 68.00 ± 1.15 at 30 min, 90 min and 24 h. respectively. There was no change in neutrophil count after premedication, but during anaesthesia, there was significant ($P<0.05$) decrease (Fig.16).

4.4.3.7. Eosinophil count (%): Eosinophil count was 2.00 ± 0.26 and 1.00 ± 0.00 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 1.00 ± 0.26, 1.33 ± 0.21 and 1.50 ± 0.43 at 30 min, 90 min and 24 h. respectively. There was marginal decrease in eosinophil count after premedication and during anaesthesia (Fig.17).

4.4.3.8. Monocyte count(%):Monocyte count was 0.20 ± 0.24 and 0 ± 0 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 0.33 ± 0, 0.16 ± 0.24 and 0.16 ± 0.24 at 30 min, 90 min and 24 h. respectively. The variations were marginal.

4.4.3.9.Basophil count (%): Basophil count was 0 ± 0 throughout the period of observations.

4.4.4. Serum Biochemical Parameters (Tables 9 to 11)

4.4.4.1. Total protein (g/dl): Total protein was 6.60 ± 0.32 and 6.38 ± 0.32 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 6.10 ± 0.37,6.45 ± 0.27,6.57 ± 0.33 at 30 min, 90 min and 24 h respectively. There was decrease in total protein content after premedication. But during anaesthesia there was significant ($P<0.05$) decrease (Fig.18).

4.4.4.2. Creatinine (mg/dl): Creatinine was 1.28 ± 0.31 and 0.77 ± 0.08 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 0.87 ± 0.11, 0.87 ± 0.08 and 1.02 ± 0.02 at 30 min, 90 min and 24 h. respectively. There was marginal decrease in serum creatinine level after premedication and during anaesthesia (Fig.19).

4.4.4.3.Blood urea nitrogen (mg/dl) : Blood urea nitrogen as 30.33 ± 1.86 and 35.50 ± 5.68 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 26.50 ± 3.39, 26.67 ± 2.84 and 32.67 ± 1.86 at 30 min, 90 min and 24 h. respectively. There was increase in the BUN level after premedication, but during anaesthesia it was decreased (Fig.20).

4.4.4.4 Glucose (mg/dl): Glucose was 94.17 ± 1.17 and 187.50 ± 18.89 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 211.50 ± 20.69, 199.00 ± 8.91 and 185.33 ± 7.93 at 30 min, 90 min and 24 h. respectively. There was a significant ($P<0.05$) increase in glucose concentration after premedication, during anaesthesia and at 24 h. (Fig.21).

4.4.4.5. Aspartate amino transferase (U/L): Aspartate amino transferase was 52.50 ± 6.29 and 43.33 ± 3.11 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 43.33 ± 4.05, 39.83 ± 2.55 and 42.67 ± 3.42 at 30 min, 90 min and 24 h. respectively. There was decrease in AST values after premedication and during anaesthesia (Fig.22).

4.4.4.6. Aalanine amino transferase (U/L): Aalanine amino transferase was 48.33 ± 5.55 and 40.66 ± 3.87 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 40.50 ± 4.63, 35.67 ± 3.04 and 38.00 ± 3.00 at 30 min, 90 min and 24 h. respectively. There was decrease in ALT values after premedication and during anaesthesia (Fig.23).

4.4.4.7. Sodium (mEq/L) : Sodium was 137.83 ± 1.17 and 138.50 ± 1.85 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 141.17 ± 0.83, 140.17 ± 1.08 and 140.00 ± 0.37 at 30 min, 90 min and 24 h. respectively. There was marginal increase in serum sodium concentration after premedication and anaesthesia (Fig.24).

4.4.4.8. Potassium (mEq/L): Potassium was 4.48 ± 0.26 and 4.70 ± 0.27 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 3.97 ± 0.10, 4.33 ± 0.08 and 4.60 ± 0.21 at 30 min, 90 min and 24 h. respectively. There was marginal variations in potassium concentration after premedication, but during anaesthesia there was significant ($P<0.05$) decrease (Fig.25).

4.4.4.9. Chloride (mEq/L): Chloride was 101.50 ± 1.52 and 108.50 ± 0.88 before and after premedication respectively. In ketamine–isoflurane anaesthesia, it was 108.33 ± 0.80, 104.83 ± 1.47, 104.17 ± 0.87 at 30 min, 90 min and 24 h. respectively. There was significant ($P<0.05$) increase in serum chloride after premedication and during anaesthesia (Fig.26).

4.4.5. Arterial Blood Gas Analysis (Table 12)

4.4.5.1. pH: The pHa was 7.23 ± 0.05, 7.22 ± 0.04 and 7.27 ± 0.02 before induction, during anaesthesia and recovery respectively. There was no change in pHa during anaesthesia, though there was an increase during recovery (Fig.27).

4.4.5.2. Partial pressure of oxygen **(PaO_2)** (mm Hg): Partial pressure of oxygen was 94.03 ± 1.97, 414.30 ± 4.53 and 113.67 ± 9.79 before induction, during anaesthesia and recovery respectively. There was marked increase in PaO_2 during anaesthesia and recovery (Fig.28).

4.4.5.3 Partial pressure of carbon dioxide **($PaCO_2$)** (mm Hg): Partial pressure of carbon dioxide was 46.07 ± 4.67, 46.93 ± 5.14 and 36.50 ± 5.29 before induction, during anaesthesia and recovery respectively. The $PaCO_2$ level was maintained during anaesthesia and decreased during recovery (Fig.29).

4.4.5.4. Bicarbonate **(HCO_3)** (m mol/L): Bicarbonate was 18.63 ± 0.27, 17.97 ± 1.04 and 15.87 ± 1.52 before premedication, during anaesthesia and recovery respectively. There was no change in HCO_3 during anaesthesia, though it was decreased during recovery (Fig.30).

4.4.6. Postanaesthetic Observations

Following recovery, the dogs were with varying degree of drowsiness/lethargic/ dullness which lasted for four hours and had the normal food intake from the next day onwards.

Table 2. Body weight and quantities of the drugs administered. (Mean ± SE)

(n=6)

Groups	Body weight (kg)	Glycopyrrolate (ml) (0.20 mg/ml)	Xylazine (ml) (20.0 mg/ml)	Midazolam (ml) (1.00 mg/ml)	Ketamine (ml) (50mg/ml)	Isoflurane
I	14.25 ±1.20	0.78 ±0.16	0.78 ± 0.16	Not administered	3.02 ±0.64	Not administered
II	15.00 ±0.97	0.79 ±0.06	0.79 ±0.06	Not administered	3.05 ±0.23	"To effect"
III	16.17 ±2.29	0.83 ±0.12	0.83 ±0.12	5.17 ±0.76	3.33 ±0.49	Not administered
IV	16.58 ±2.48	0.83 ±0.13	0.83 ±0.13	5.50 ±0.88	3.33 ±0.51	"To effect"

Table 3. Time of induction, duration of anaesthesia, degree of muscle relaxation, depth of anaesthesia, muscle relaxation time and recovery time. (Mean ± SE) (n=6)

Clinical Observations	I	II	III	IV
Time of induction of anaesthesia (Minutes)	9.50 ± 0.72	8.83 ± 0.40	6.83 ± 0.48	6.50 ± 0.43
Duration of surgical anaesthesia (Minutes)	36.70 ± 2.65	45.83 ±1.54	37.50 ± 2.14	42.33 ± 0.84
Degree of muscle relaxation	Moderate	Good	Good	Excellent
Depth of anaesthesia	Satisfactory (in two dogs) Not satisfactory (in four dogs)	Satisfactory	Satisfactory	Good
Muscle relaxation time	41.20 ± 2.14	49.83 ± 1.85	41.00 ± 2.31	54.67 ± 3.02
Recovery time (Minutes)	71.70 ± 4.01	80.00 ± 5.17	108.00±8.47	91.33 ±1.93

Table 4. Observations on rectal temperature, pulse rate and respiration rate- before and after premedication, during anaesthesia and recovery, and at 24h.(Group I-IV) (Mean±SE) n=6

Parameters	Group	Premedication		During anaesthesia (30min)	During recovery (90 min)	At 24 h
		Before	After			
Rectal temperature (°C)	I	38.92± 0.15	38.92± 0.14	[a]38.79 ± 0.21	38.45± 0.18*	38.71±0.21
	II	39.10±0.07	38.99±0.04*	[a]38.91±0.15	38.75±0.13	38.94±0.08
	III	39.08±5.15	38.71±0.14	[b]38.57±0.12	38.43±0.18*	38.86±0.06
	IV	39.21±0.13	38.96±1.74	[b]38.65±0.12	38.53±0.10	39.33±0.13
Pulse rate (per min)	I	100.67±6.86	106.67±15.76	[a]95.00±1.69	92.33±1.89	90.50±2.42
	II	91.17±4.12	83.17±2.86	[b]87.17±2.07	90.00±2.62	86.50±3.24*
	III	104.50±6.21	89.33±1.74*	[b]90.50±1.71	98.50±3.40*	93.67±3.60
	IV	85.00±6.25	80.66±3.87*	[b]82.83±3.55	85.17±3.75	87.33±3.42
Respiration rate (per min)	I	33.67±4.63	24.50±2.35*	26.67±5.56	23.83±2.26	23.83±2.20*
	II	24.67±6.70	17.33±2.55	19.17±4.06	23.50±6.82	33.0±5.79
	III	38.67±6.81	18.50±1.17*	21.00±7.45	20.83±2.17*	24.67±6.70
	IV	28.17±5.15	20.66±5.07	26.50±3.34	27.17±7.73	38.67±6.81

(P<0.05) Significant at 5 per cent level. * Raw means compared to the mean value before premedication
Column means with alphabetic superscripts in common (a, b, c, d) is not statistically significant.

Table 5. Observations on oxygen saturation ,blood coagulation time and capillary refill time - before and after premedication, during anaesthesia and recovery, and at 24h.(Group I-IV) (Mean±SE) n=6

Parameters	Group	Premedication		During anaesthesia (30min)	During recovery (90 min)	At 24 h
		Before	After			
Oxygen saturation (SpO2)(per cent)	I	92.0±2.05	[a]94.0±1.61*	[b]94.67±0.42	[b]95.17±0.70	93.67±0.42
	II	82.33±3.48	[a]94.33±0.42*	[a]97.17±0.87*	[a]98.33±0.21*	95.0±1.37 *
	III	89.83±2.44	[b]93.33±0.76	[b]95.17±0.31	[b]95.33±0.33	95.33±0.21
	IV	86.67±4.03	[a]96.00±0.44*	[a]98.33±0.20*	[a]98.33±0.21*	94.83±0.91
Blood coagulation time (min)	I	3.52 ±0.13	3.78 ±0.20	3.92 ±0.08*	3.78 ± 0.13	3.75 ±0.11
	II	3.85 ±0.11	3.92 ±0.11*	4.17 ±0.10*	4.22 ± 0.11*	4.18 ±0.07*
	III	3.83 ±0.22	4.23 ±0.15	4.13 ± 0.22	4.42 ±0.16	4.28 ±0.20
	IV	4.25 ±0.18	4.45 ±0.26	4.52 ± 0.20	4.78 ±0.22	4.37 ±0.19
Capillary refill time (sec)	I	2.00±0.23	1.50±0.26	1.50±0.22	1.50±0.22	1.83±0.22
	II	1.50 ±0.23	1.33±0.22	1.83±0.21	1.50 ±0.17	1.66 ±0.22
	III	1.50±0.23	1.67±0.22	2.00±0.21	1.66±0.37	1.66±0.17
	IV	1.50 ±0.23	1.67±0.22	1.83±0.21	1.66±0.31	1.66±0.17

($P<0.05$) Significant at 5 per cent level. * Raw means compared to the mean value before premedication
Column means with alphabetic superscripts in common (a, b, c, d) is not statistically significant.

Table 6. Observations on systolic blood pressure, diastolic blood pressure and mean blood pressure (mm Hg) before and after premedication, during anaesthesia and recovery, and at 24h.(Group I-IV) (Mean ± SE) n=6

Parameters	Group	Premedication		During anaesthesia (30min)	During recovery (90 min)	At 24 h
		Before	After			
Systolic blood pressure (mm Hg)	I	130.67±3.03	158.00± 4.73	213.17±5.17	154.83±4.60	132.33±4.89
	II	139.83±2.21	159.67±2.01	181.83±6.36	168.17±2.47	140.83±2.79
	III	140.17±2.36	134.67±2.56	185.00±3.68	138.33±3.24	138.50±2.58
	IV	136.67±3.08	130.00±3.64	183.17±2.77	137.00±2.62	129.17±1.74
Diastolic blood pressure (mm Hg)	I	78.33±2.95	100.17±2.11	152.33±3.10	102.17±2.71	79.33±2.52
	II	84.14±2.03	104.50±1.64	148.50±1.80	103.33±1.64	84.17±2.29
	III	84.83±1.92	84.83±2.29	136.17±2.63	92.50±2.55	89.33±2.30
	IV	81.00±2.59	84.50±2.34	130.17±4.10	92.17±1.56	89.00±2.98
Mean blood pressure (mm Hg)	I	99.83±4.50	118.67±3.24	173.00±2.98	123.00±2.69	100.50±4.33
	II	105.00±2.16	125.67±2.20	167.83±2.27	124.33±1.89	103.17±1.84
	III	107.00±3.18	127.00±2.45	156.67±2.52	118.17±2.10	105.00±2.51
	IV	101.67±2.98	137.33±1.67	151.83±4.60	113.83±1.79	104.00±2.47

($P<0.05$) Significant at 5 per cent level. * Raw means compared to the mean value before premedication
Column means with alphabetic superscripts in common (a, b, c, d) is not statistically significant.

Table 7. Observations on haemoglobin concentration, volume of packed red cells, erythrocyte sedimentation rate and total leukocyte count - before and after premedication, during anaesthesia and recovery, and at 24h.(Group I-IV) (Mean ± SE)

n=3

Parameters	Group	Premedication		During anaesthesia (30min)	During recovery (90 min)	At 24 h
		Before	After			
Haemoglobin concentration (g/dl)	I	11.32 ± 0.36	^{b}10.48 ± 0.36*	^{a}10.33 ± 0.40*	^{a}10.40 ± 0.46*	^{a}10.80 ± 0.33
	II	10.77 ± 0.37	^{ab}10.48 ± 0.38*	^{a}10.13 ± 0.27*	^{a}10.22 ± 0.43*	^{a}b10.20± 0.24
	III	11.57 ± 0.23	^{b}10.08 ± 0.15*	^{a}10.73± 0.47*	^{b}9.82 ± 0.21*	^{b}10.03± 0.15*
	IV	11.52 ± 0.18	^{a}11.06 ± 0.13*	^{a}10.85 ± 0.16*	^{a}10.72 ± 0.14*	^{a}11.10± 0.77
Volume of Packed Red Cells (%)	I	30.67 ± 0.56	31.67 ± 0.33*	30.83 ± 0.70*	31.17 ± 1.01*	32.04 ± 0.68*
	II	29.67 ± 0.56	29.67 ± 0.56	28.83 ± 0.31	29.00 ± 0.68	30.00 ± 1.21
	III	33.50 ± 0.92	31.0 ± 0.57	29.67 ± 0.42*	30.83 ± 0.31*	32.33 ± 0.56
	IV	31.67 ± 0.67	29.83 ± 0.47	28.83 ± 0.40	28.50 ± 0.56	30.83 ± 0.87
Erythrocyte Sedimentation Rate (mm/h)	I	2.83 ± 0.70	2.67 ± 0.76	2.67 ± 0.42	2.50 ± 0.67	2.83± 0.40
	II	2.17 ± 0.17	2.00 ± 0.26	1.83 ± 0.17	1.67 ± 0.33	2.00 ± 0.26
	III	2.00 ± 0.25	1.5 ± 0.22	2.33 ± 0.33	1.83 ± 0.30	1.83± 0.30
	IV	2.17 ± 0.31	1.50± 0.22	1.67 ± 0.21	1.83 ± 0.17	1.67 ± 0.21
Total leukocyte count (10^3/mm^3)	I	13.00 ± 1.25	13.00 ± 1.31	12.90 ± 1.32	13.28 ± 1.23	14.93 ± 2.80
	II	11.23 ± 5.57	11.21 ± 4.79	11.16 ± 5.52	11.46 ± 4.27	14.33 ± 2.83
	III	18.13 ± 4.84	17.91 ± 2.89	18.66± 3.00	18.36± 2.99	18.38 ± 3.95
	IV	14.00 ± 2.47	14.51 ± 2.12	15.18 ± 1.88	15.73± 1.93	14.36 ± 1.89

(P<0.05) Significant at 5 per cent level. * Raw means compared to the mean value before premedication

Column means with alphabetic superscripts in common (a, b, c, d) is not statistically significant.

Table 8. Observations on differential leukocyte count (lymphocytes, neutrophils, eosinophils, monocytes and basophils) before and after premedication, during anaesthesia and recovery, and at 24h. (Group I-IV) (Mean ± SE) n=6

Parameters	Group	Premedication		During anaesthesia (30min)	During recovery (90 min)	At 24 h
		Before	After			
Lymphocytes (%)	I	28.83 ± 1.01	29.50 ± 0.43	^{b}28.83 ± 0.83	29.17 ± 0.91	29.17 ± 1.01
	II	31.17 ± 1.40	32.17 ± 0.75	^{b}29.00 ± 0.82	29.17 ± 0.91	28.83 ± 0.95
	III	28.67 ± 1.02	27.83 ± 1.01	^{b}28.33 ± 0.67	29.33 ± 0.61	29.17 ± 0.70
	IV	28.33 ± 1.12	29.50 ± 0.88	^{a}32.17 ± 0.95*	30.83 ± 1.11	30.33 ± 1.43
Neutrophils (%)	I	69.00 ± 0.73	^{ab}68.83 ± 0.54	^{a}69.50 ± 0.76	69.50 ± 1.09	69.83 ± 0.95
	II	67.00 ± 1.15	^{b}66.17 ± 0.54	^{b}65.50 ± 0.92*	65.33 ± 1.26*	66.17 ± 0.87
	III	69.83 ± 1.11	^{a}71.05 ± 0.9	^{a}70.33 ± 0.61	69.83 ± 0.60	69.83 ± 0.70
	IV	69.17 ± 1.14	^{b}69.50 ± 1.24	^{b}66.50 ± 0.85*	67.67 ± 1.05	68.00 ± 1.15
Eosinophils (%)	I	1.83 ± 0.40	1.67 ± 0.33	1.33 ± 0.21	1.33 ± 0.21	1.17 ± 0.17
	II	1.33 ± 0.21	1.50 ± 0.34	1.17 ± 0.17	1.33 ± 0.21	1.50 ± 0.22
	III	1.33 ± 0.42	0.66 ± 0.21	1.17 ± 0.17	0.83 ± 0.17	1.00 ± 0
	IV	2.00 ± 0.26	1.00 ± 0.0	1.00 ± 0.26	1.33 ± 0.21	1.50 ± 0.43
Monocytes (%)	I	0.33± 0.24	0± 0	0.16± 0	0± 0	0.16± 0.24
	II	0.50± 0.24	0.16 ± 0.24	0.16± 0.24	0.16 ± 0.24	0.16± 0.24
	III	0.17± 0.24	0± 0	0.16±0	0± 0	0± 0
	IV	0.50± 0.24	0 ± 0	0.33±0	0.16± 0.24	0.16± 0.24
Basophils (%)	I, II,III,IV	0± 0	0± 0	0± 0	0± 0	0± 0

($P<0.05$) Significant at 5 per cent level. * Raw means compared to the mean value before premedication
Column means with alphabetic superscripts in common (a, b, c, d) is not statistically significant.

Table 9. Observations on total protein content, serum creatinine and blood urea nitrogen levels - before and after premedication, during anaesthesia and recovery, and at 24h.(Group I-IV) (Mean ± SE)

n=6

Parameters	Group	Premedication		During anaesthesia (30min)	During recovery (90 min)	At 24 h
		Before	After			
Total protein (g/dl)	I	7.00 ± 0.28	6.53 ± 0.13*	6.42 ± 0.21*	6.58 ± 0.11	6.83 ± 0.18
	II	7.13 ± 0.35	6.35 ± 0.45*	6.67 ± 0.26	6.62± 0.27	6.40 ± 0.13
	III	6.85 ± 0.45	6.40 ± 0.28	6.17 ± 0.35	6.40± 0.30	6.58 ± 0.30
	IV	6.60 ± 0.32	6.38 ± 0.32	6.10 ± 0.37*	6.45± 0.27	6.57 ± 0.33
Serum creatinine (mg/dl)	I	1.05±0.03	[ab]0.98±0.13	0.97±0.05*	[a]1.10±0.07	1.03 ±0.06
	II	1.83±0.26	[a]1.30±0.14*	1.20±0.07	[b]0.97±0.03	1.02±0.14*
	III	1.35±0.30	[b]1.05±0.14	1.00±0.10	[b]0.93±0.07	1.00±0
	IV	1.28±0.31	[b] 0.77±0.08	0.87±0.11	[b]0.87±0.08	1.02±0.02
Blood urea nitrogen (mg/dl)	I	31.50±0.34	29.17±1.80	28.83±0.60*	32.00 ± 2.61	33.67±2.17
	II	34.33±0.21	33.00±1.41	44.33±5.57*	36.83±5.18*	35.17±3.38
	III	33.33±1.31	30.33±2.99*	30.17±3.08	27.67±1.98*	28.67±2.65
	IV	30.33±1.86	30.50±5.68	26.50±3.39	26.67±2.84	32.67±1.86

($P<0.05$) Significant at 5 per cent level. * Raw means compared to the mean value before premedication

Column means with alphabetic superscripts in common (a, b, c, d) is not statistically significant.

Table 10. Observations on serum glucose, aspartate amino transferase and alanine amino transferase levels - before and after premedication, during anaesthesia and recovery, and at 24h.(Group I-IV) (Mean ± SE)

n=6

Parameters	Group	Premedication		During anaesthesia (30min)	During recovery (90 min)	At 24 h
		Before	After			
Serum glucose (mg/dl)	I	87.17±4.50	140.00±9.48*	147.00±13.64*	221.67±29.25*	171.50±6.23*
	II	94.33±2.49	151.33±7.51	155.0±15.24	175.00±13.29	169.67±8.55
	III	95.50±2.63	168.90±7.41*	185.50±21.55*	200.50±19.87*	188.33±9.33*
	IV	94.17±1.17	187.50±18.89*	211.50±20.69*	199.00±8.91*	185.33±7.93*
Aspartate amino transferase (U/L)	I	55.17±2.43	44.17±3.61	48.67±2.35	39.67±4.24*	49.00±1.37
	II	33.67±0.61	40.33±1.20	45.00±4.84*	34.17±3.75	44.33±2.39
	III	42.17±5.82	42.00±2.62	40.67±4.21	41.33±1.50	40.67±2.40
	IV	52.50±6.29	43.33±3.11	43.33±4.05	39.83±2.55	42.67±3.42
Alanine amino transferase (U/L)	I	47.67±3.09	37.00±4.63	44.33±4.50	37.50±4.44	44.00±3.53
	II	30.67±0.67	41.50±1.80	45.33±3.49*	29.00±3.98	41.33±2.67
	III	39.50±5.46	35.67±3.20	36.00±4.49	34.50±3.58	33.67±2.75
	IV	48.33±5.55	40.66±3.87	40.50±4.63	35.67±3.04	38.00±3.00

(P<0.05) Significant at 5 per cent level. * Raw means compared to the mean value before premedication
Column means with alphabetic superscripts in common (a, b, c, d) is not statistically significant.

Table 11. Observations on serum sodium, serum potassium and serum chloride concentration- before and after premedication, during anaesthesia and recovery, and at 24h.(Group I-IV) (Mean ± SE)

n=6

Parameters	Group	Premedication		During anaesthesia (30min)	During recovery (90 min)	At 24 h
		Before	After			
Serum sodium (mEq/L)	I	148.00±3.78	[a]144.83 ± 2.48	138.00± 3.31	[a]142.83 ± 1.38	140.67 ± 1.71
	II	133.67±6.78	[ab]148.67 ± 4.80	144.00 ± 4.85	[a]145.67 ± 2.59	140.00 ± 3.44
	III	135.33±1.61	[c]143.50 ± 3.76	137.83 ± 2.18	[b]139.83 ± 1.08	139.83 ± 1.19
	IV	137.83±1.17	[b]138.50 ± 1.85	141.17 ± 0.83*	[ab]140.17 ± 1.08	140.00 ± 0.37
Serum potassium (mEq/L)	I	5.03 ± 0.14	5.30 ± 0.14 *	4.87 ± 0.28	5.10 ± 0.18	4.98 ± 0.19
	II	5.67 ± 0.30	4.85 ± 0.30*	5.52 ± 0.37*	5.30 ± 0.35*	4.43 ± 0.41*
	III	4.78 ± 0.43	4.61 ± 0.26	4.38 ± 0.43	4.55 ± 0.38	4.73 ± 0.25
	IV	4.48 ± 0.26	4.70 ± 0.27	3.97 ± 0.10*	4.33 ± 0.08	4.60 ± 0.21
Serum chloride (mEq/L)	I	111.00 ± 2.02	108.00± 0.89	110.33 ± 0.42	110.00± 1.63	106.00 ± 1.48*
	II	104.50 ± 2.31	107.00 ± 2.46	107.17 ± 2.04	106.83 ± 1.42	101.50 ± 0.72
	III	88.17 ± 15.92	108.50 ± 0.88*	108.67 ± 1.12*	106.00± 1.18	104.17 ± 1.17
	IV	101.50 ± 1.52	108.50 ± 0.88	108.33 ± 0.80*	104.83 ± 1.47	104.17 ± 0.87

(P<0.05) Significant at 5 per cent level. * Raw means compared to the mean value before premedication
Column means with alphabetic superscripts in common (a, b, c, d) is not statistically significant.

Table 12. Observations on arterial pH, partial pressure of oxygen, partial pressure of carbon dioxide and bicarbonate levels before induction, during anaesthesia and recovery. (Mean ± SE)

n=3

Parameters	Groups	Before induction of anaesthesia	During anaesthesia (at 30 min)	During recovery (at 90 min)
Arterial pH (pHa)	I	7.36 ± 0.02	7.27 ± 0.03	7.28 ± 0.05
	II	7.22 ± 0	7.27 ± 0.08	7.19 ± 0.07
	III	7.34 ± 0.02	7.29 ± 0.01	7.31 ± 0.01
	IV	7.23 ± 0.05	7.22 ± 0.04	7.27 ± 0.02
Partial pressure of oxygen (PaO_2) (mm of Hg)	I	92.50 ± 1.15	102.90 ± 19.65	112.37 ± 15.00
	II	90.70 ± 0.66	434.53 ± 21.53	134.40 ± 3.59
	III	110.73 ± 14.02	117.87 ± 1.92	115.67 ± 19.49
	IV	94.03 ± 1.97	414.30 ± 4.53	113.67 ± 9.79
Partial pressure of carbon dioxide ($PaCO_2$) (mm of Hg)	I	26.43 ± 1.02	36.39 ± 9.36	31.23 ± 1.53
	II	38.17 ± 9.04	36.80 ± 13.83	39.27 ± 8.15
	III	25.53 ± 1.84	42.33 ± 1.89	33.17 ± 5.02
	IV	46.07 ± 4.67	46.93 ± 5.14	36.50 ± 5.29
Bicarbonate levels (HCO_3) (m mol /L)	I	13.87 ± 0.18	12.80 ± 0.40	15.93 ± 2.53
	II	14.73 ± 0.18	18.97 ± 1.98	17.03 ± 0.65
	III	18.13 ± 1.62	13.80 ± 1.27	17.60 ± 1.58
	IV	18.63 ± 0.27	17.97 ± 1.04	15.87 ± 1.52

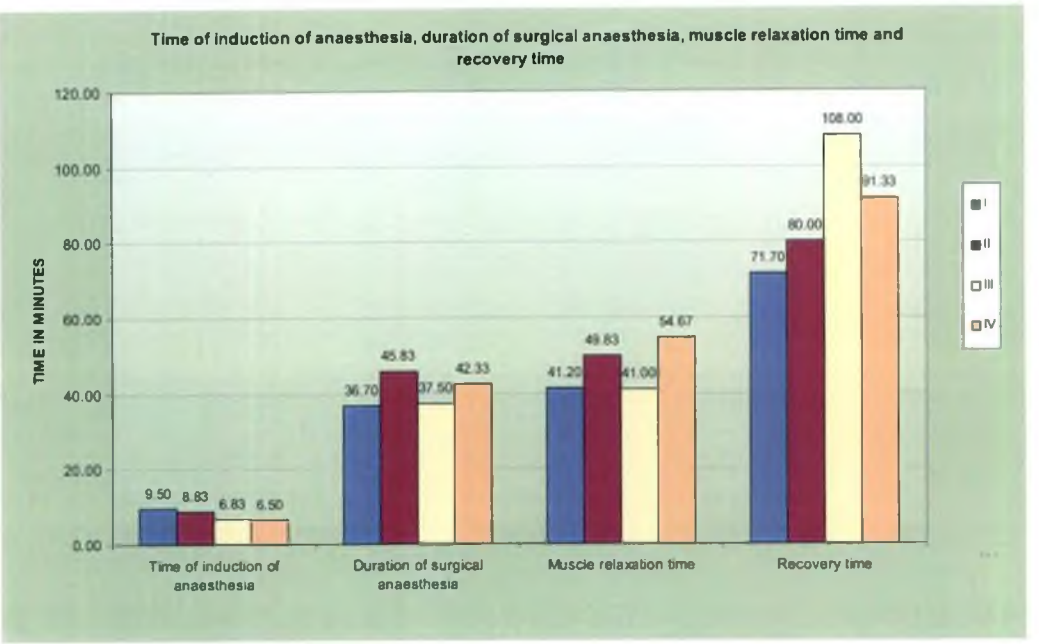


Fig. 1: Mean time of induction of anaesthesia, duration of surgical anaesthesia, muscle relaxation time and recovery time

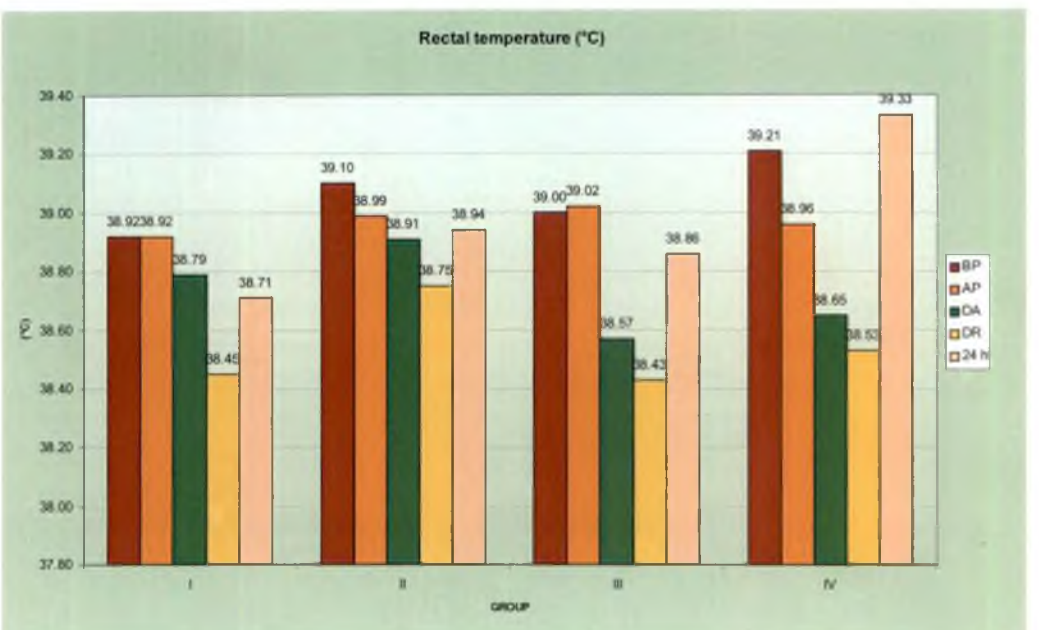


Fig. 2: Mean Rectal Temperature (°C)

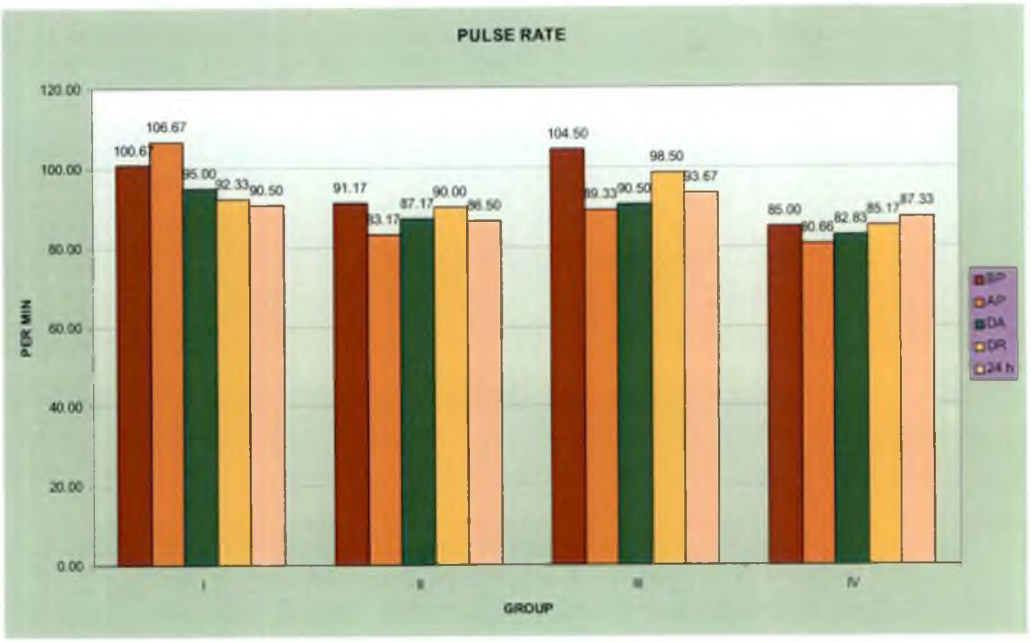


Fig. 3: Mean Pulse Rate

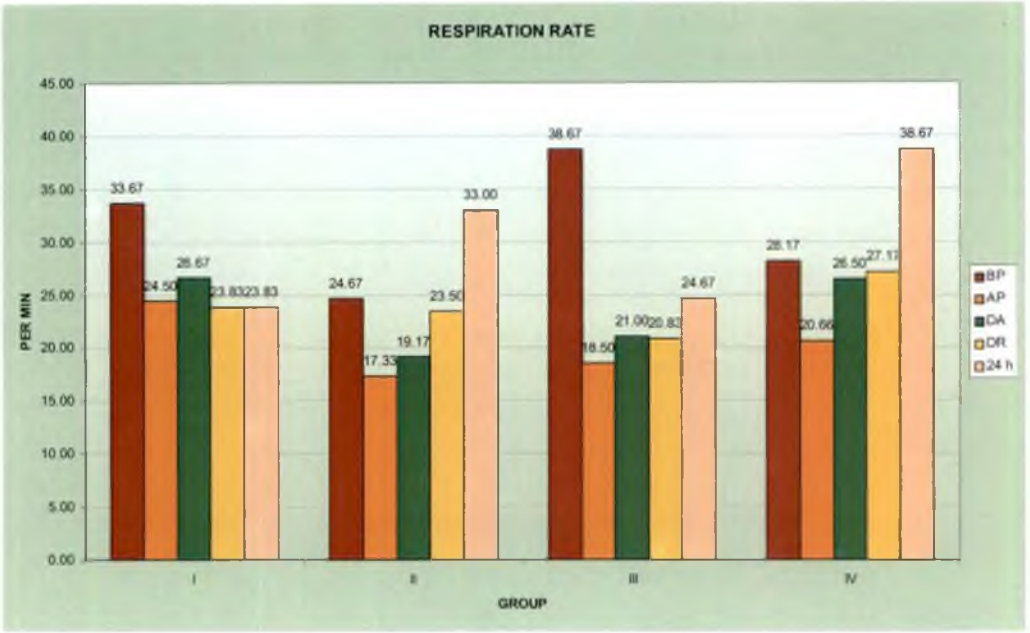


Fig. 4: Mean Respiration Rate

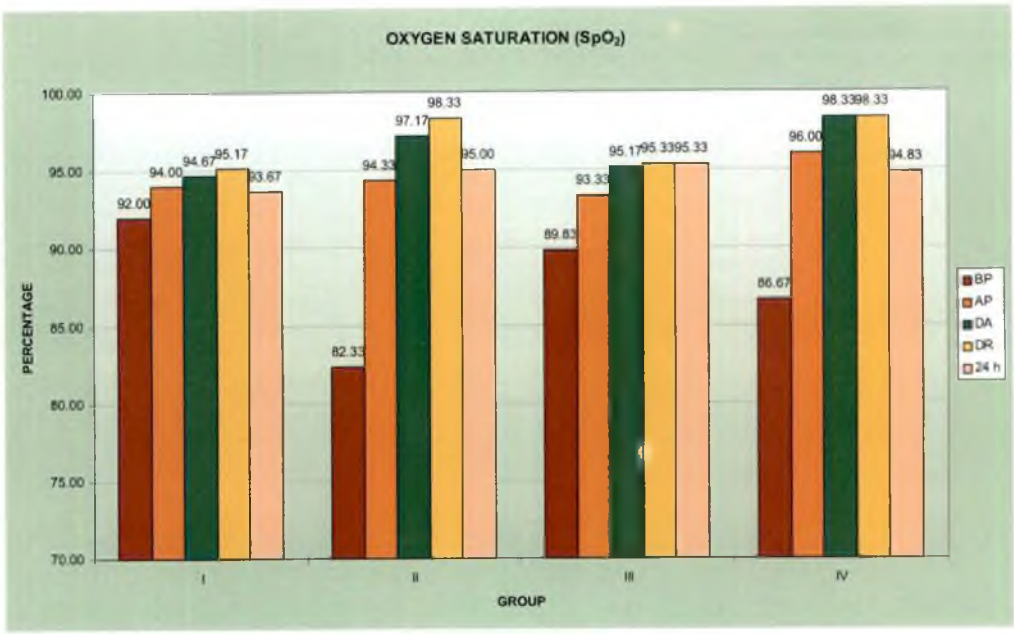


Fig. 5: Mean Oxygen Saturation (SpO_2)

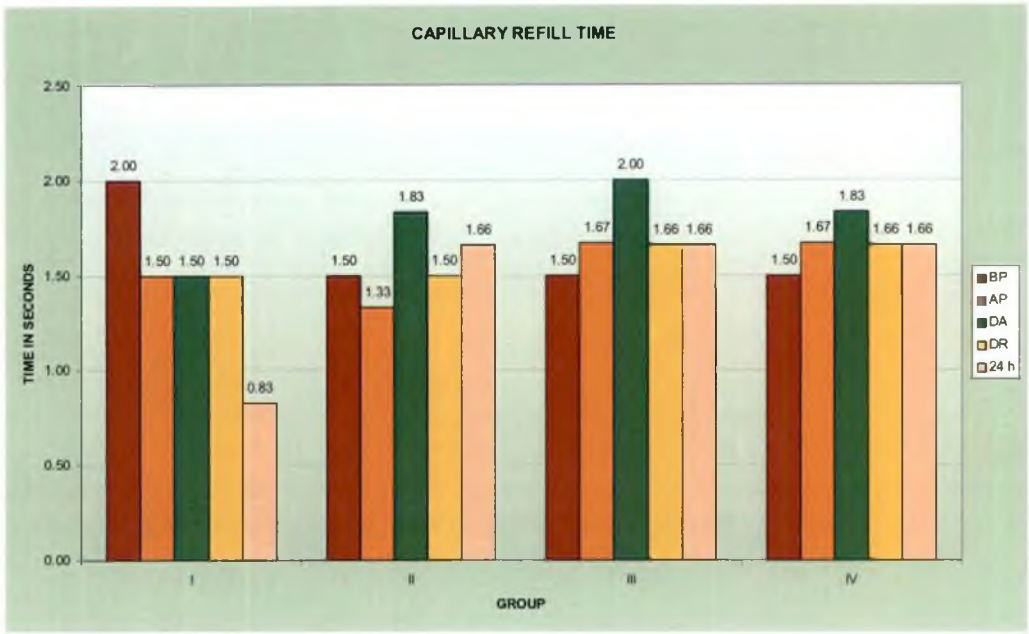


Fig. 6: Mean Capillary Refill Time

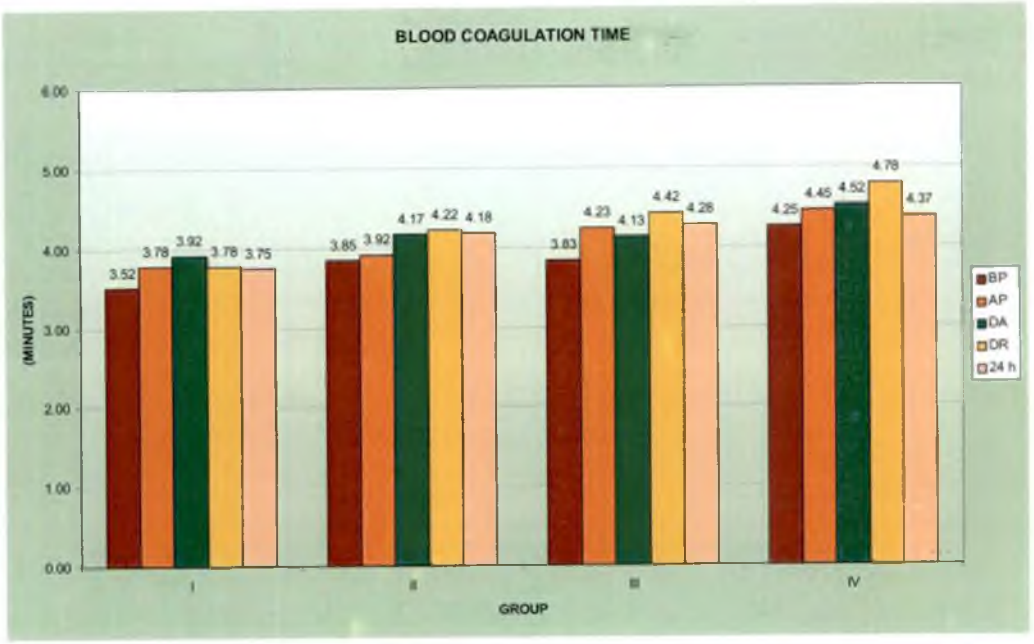


Fig. 7: Mean Blood Coagulation Time

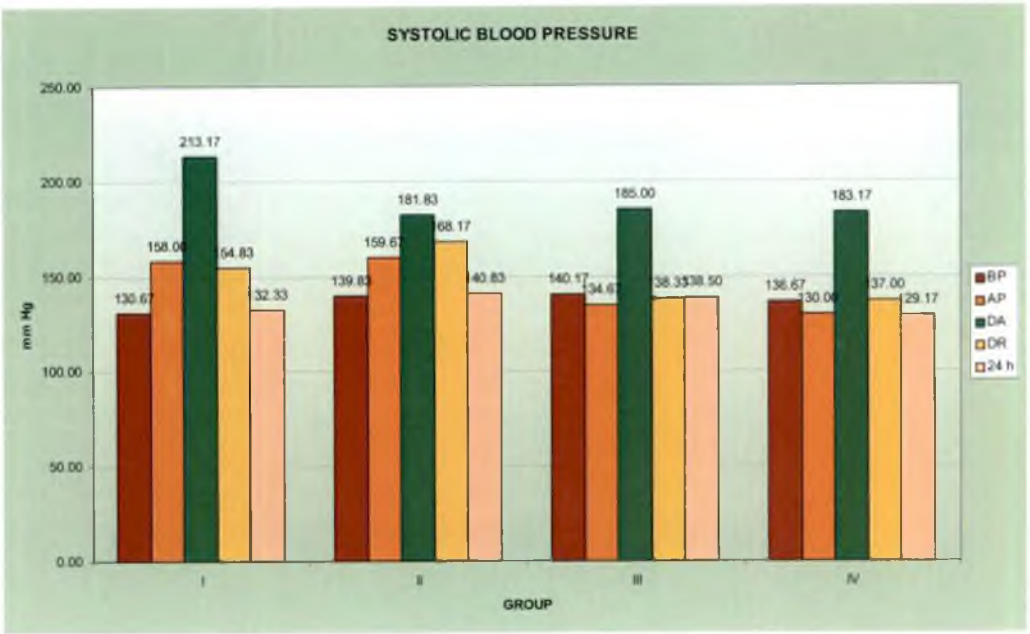


Fig. 8: Mean Systolic Blood Pressure

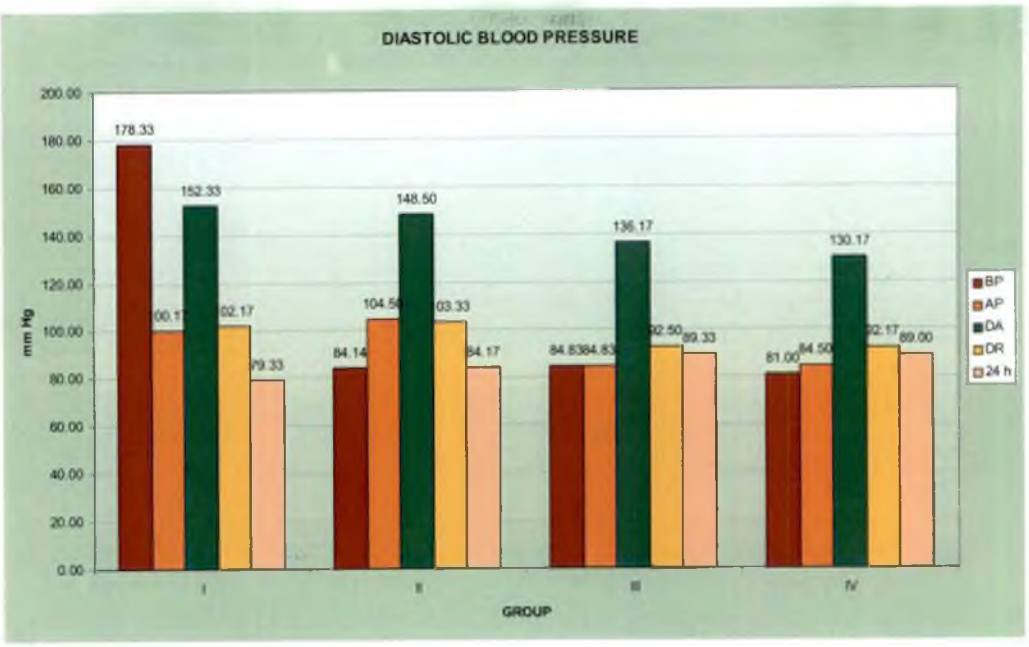


Fig. 9: Mean Diastolic Blood Pressure

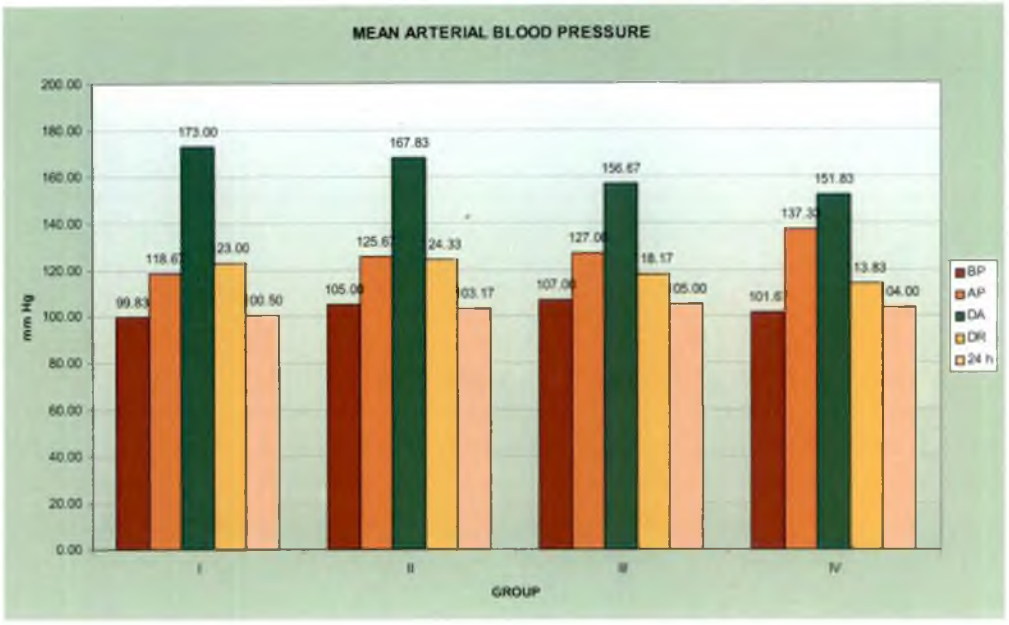


Fig. 10: Mean Arterial Blood Pressure

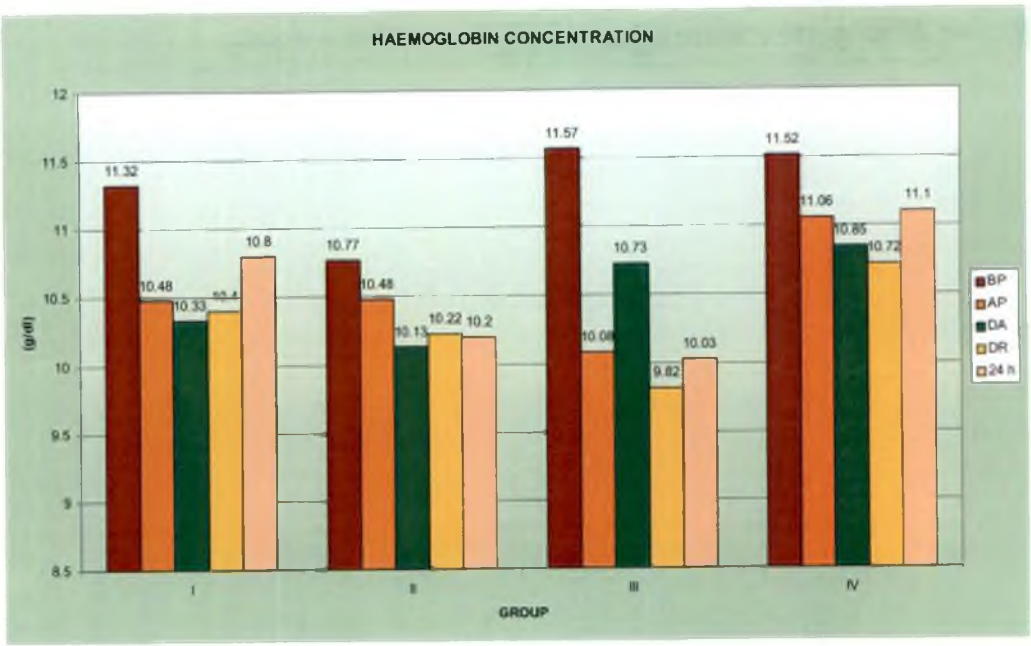


Fig. 11: Mean Haemoglobin Concentration

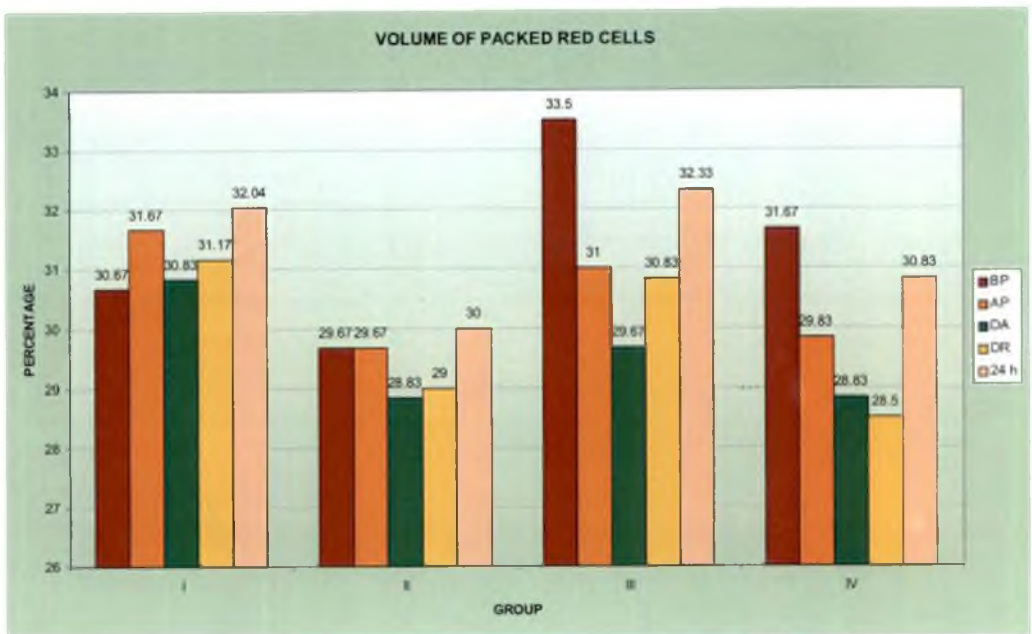


Fig.12: Mean Volume of Packed Red Cells

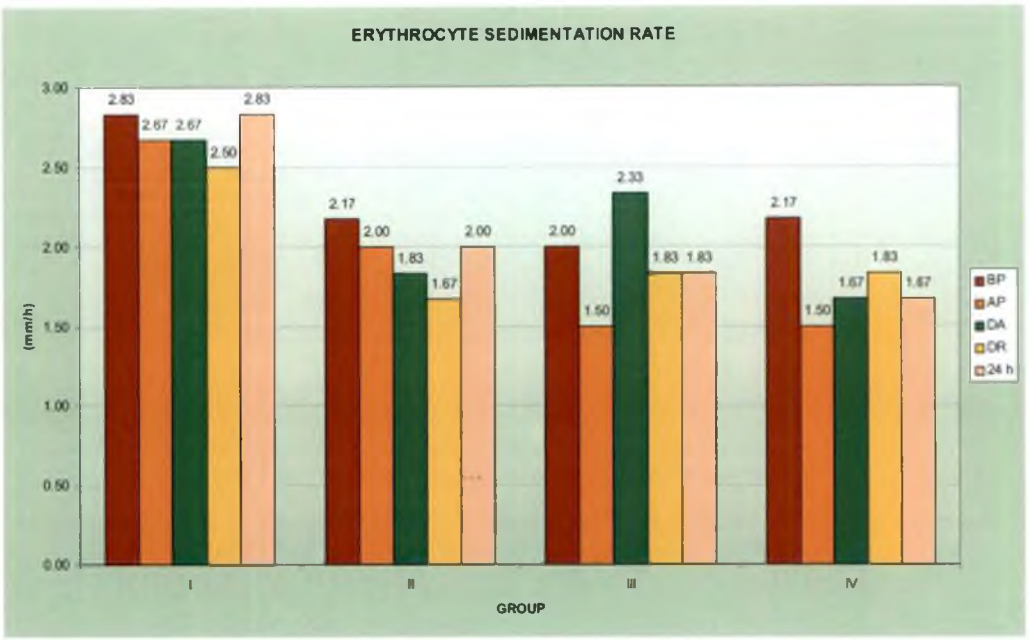


Fig. 13: Mean Erythrocyte Sedimentation Rate

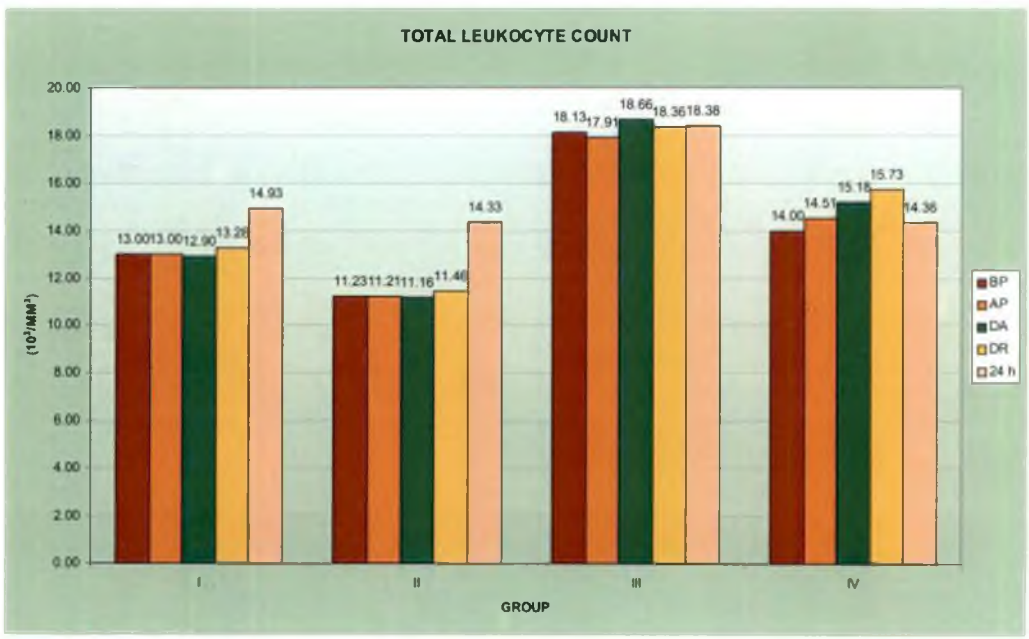


Fig. 14: Mean Total Leukocyte Count

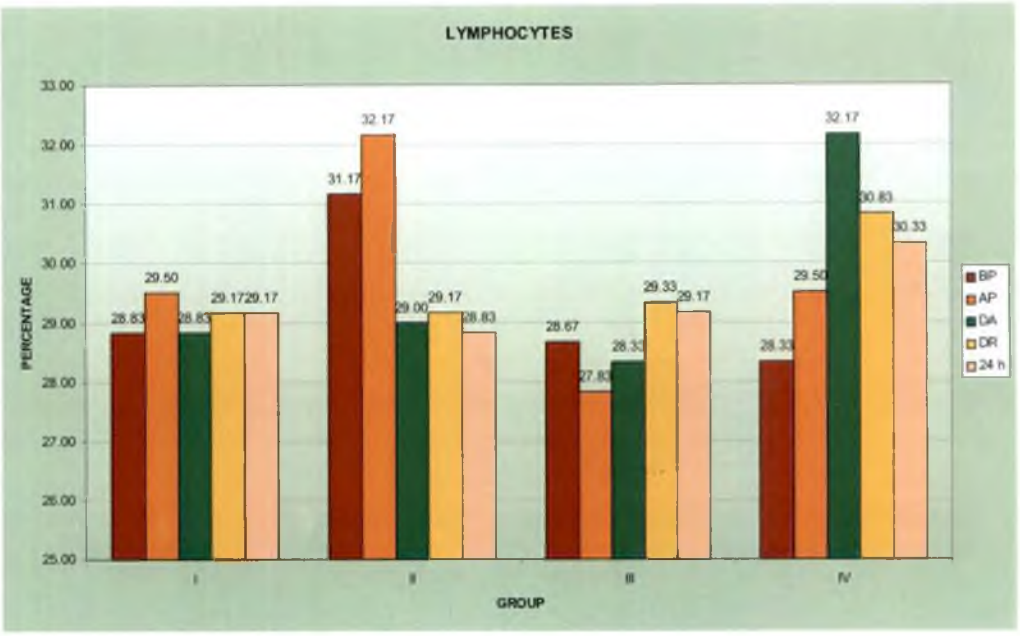


Fig. 15: Mean Lymphocytes

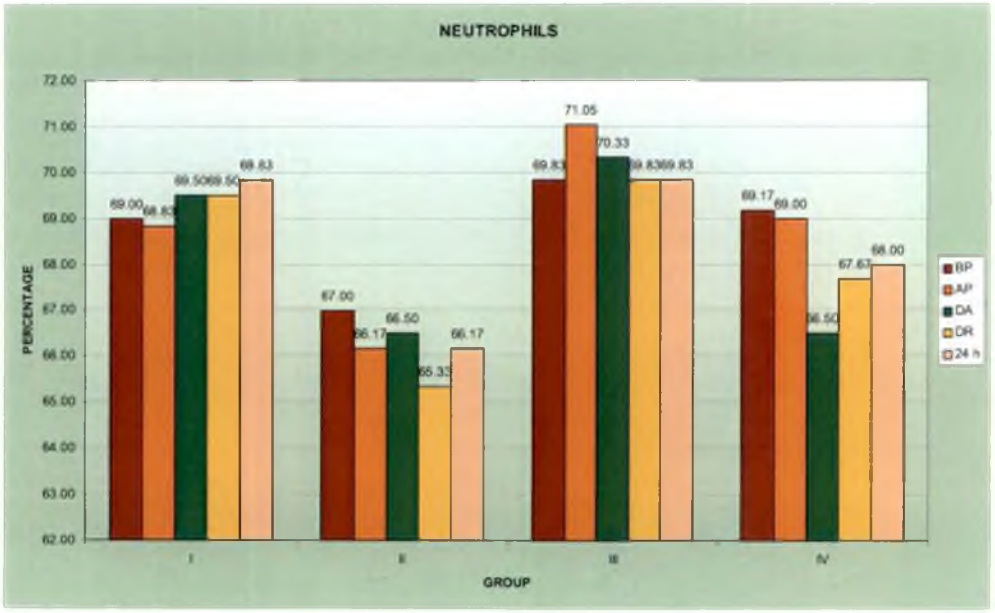


Fig. 16: Mean Neutrophils

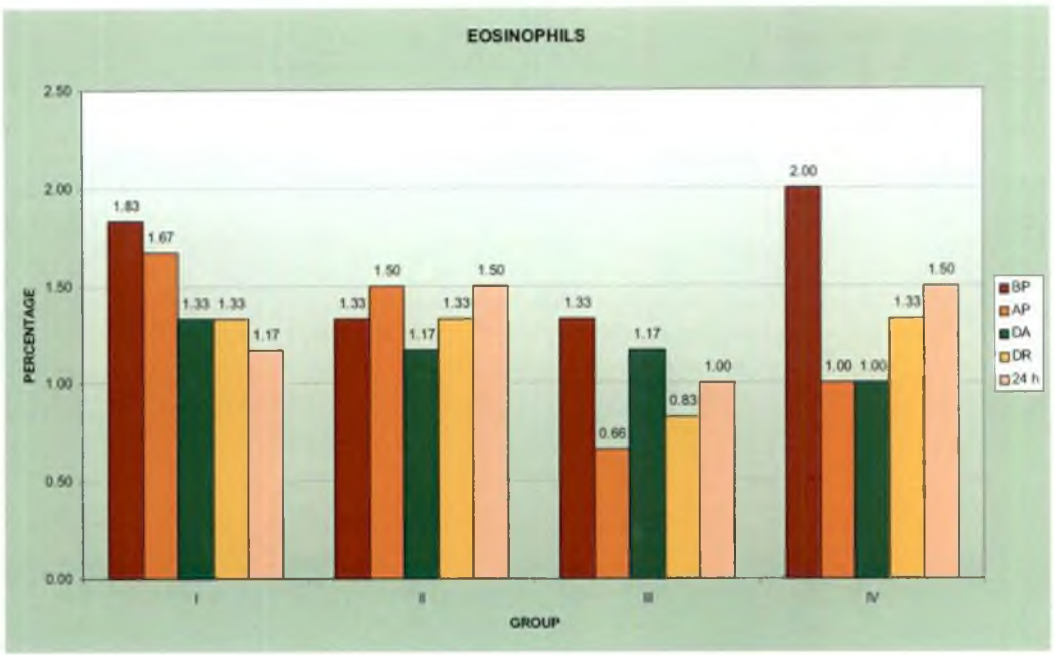


Fig. 17: Mean Eosinophils

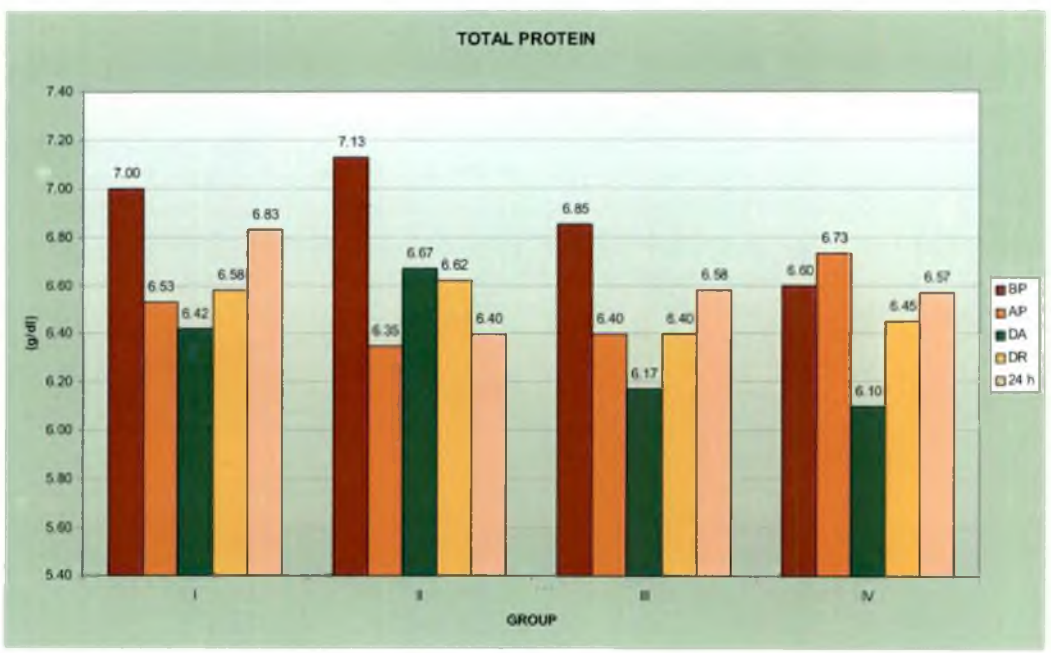


Fig. 18: Mean Total Protein

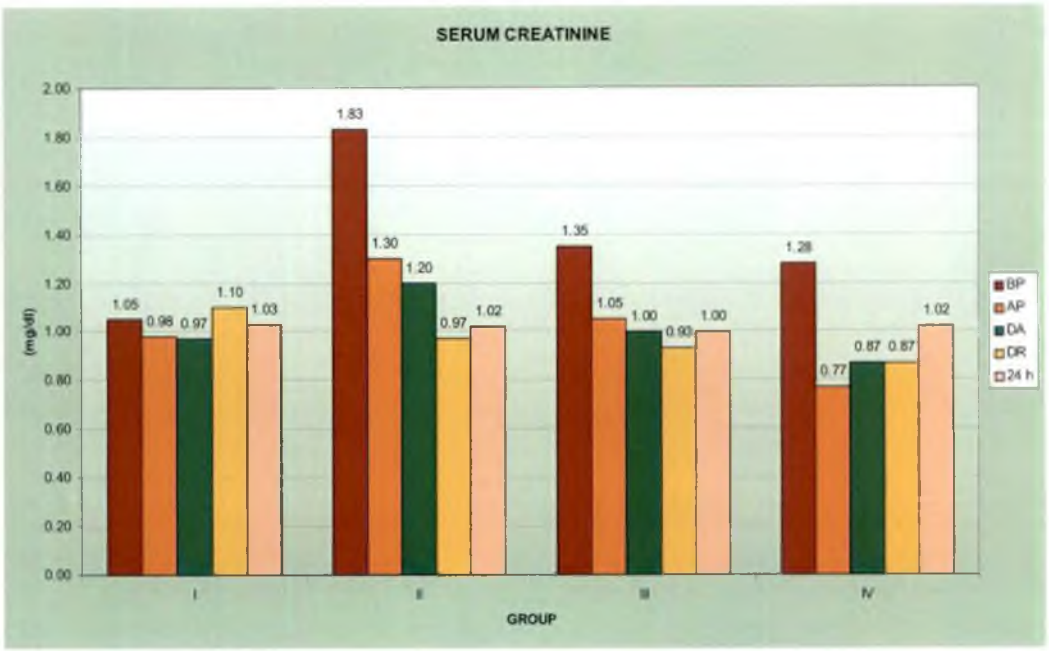


Fig. 19: Mean Serum Creatinine

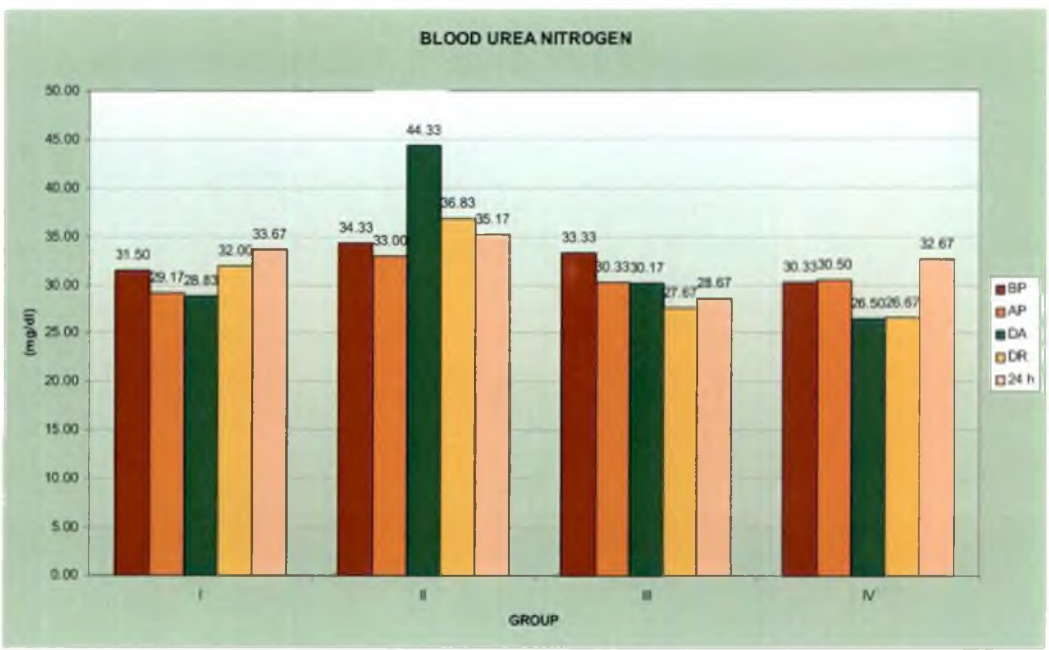


Fig. 20: Mean Blood Urea Nitrogen

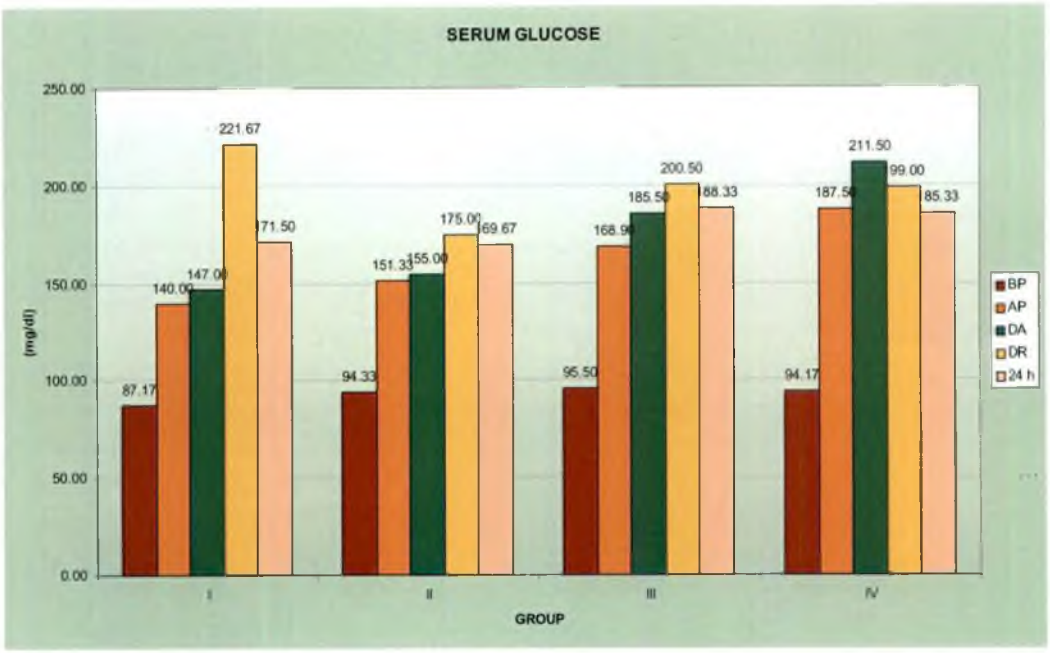


Fig. 21: Mean Serum Glucose

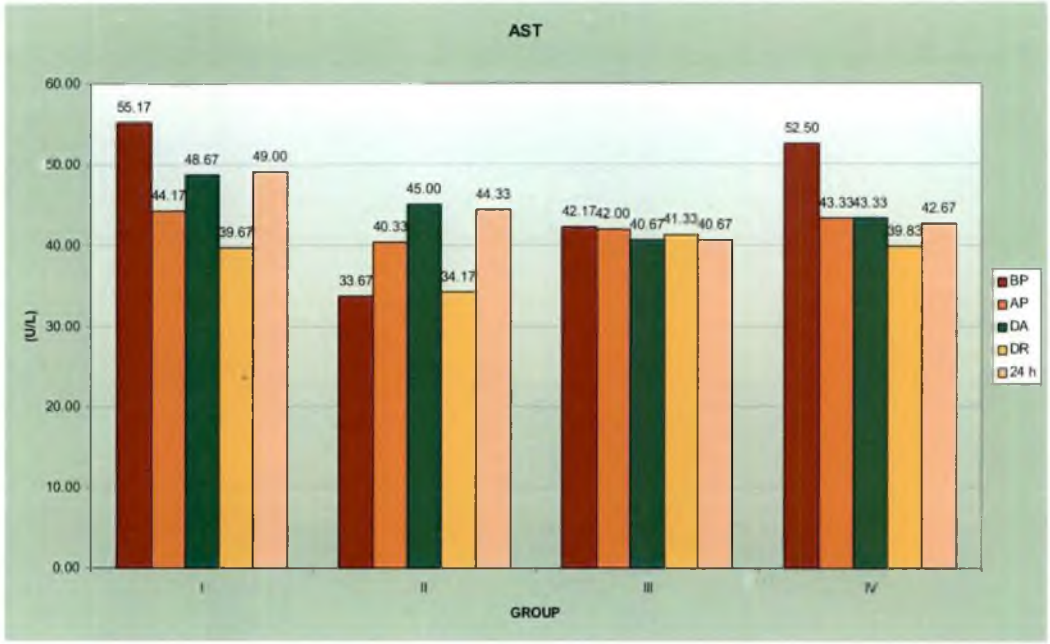


Fig. 22: Mean AST

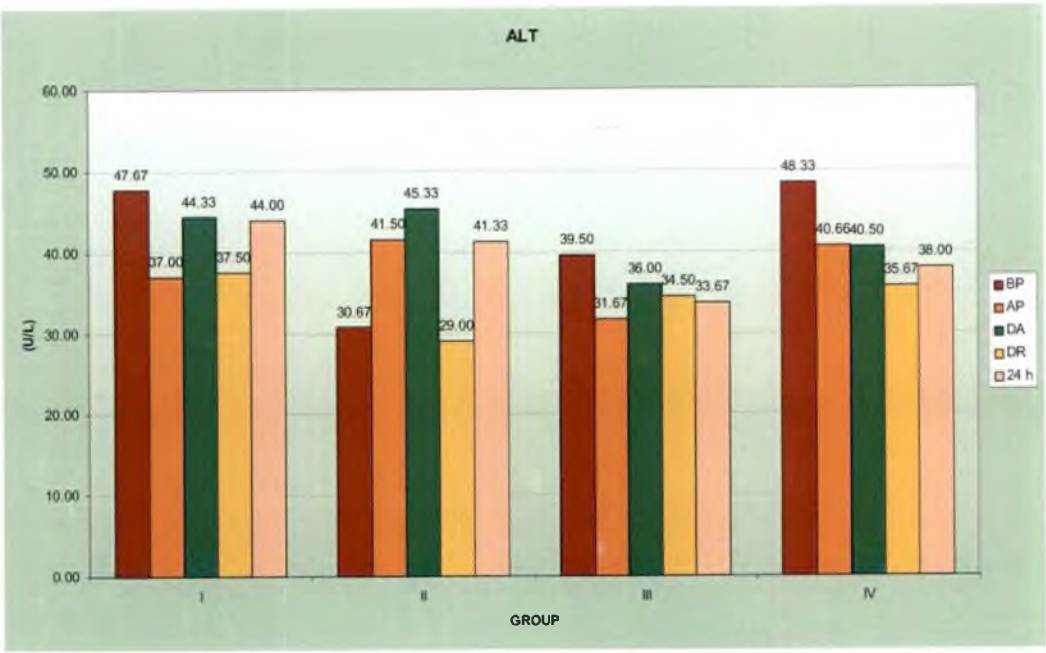


Fig. 23: Mean ALT

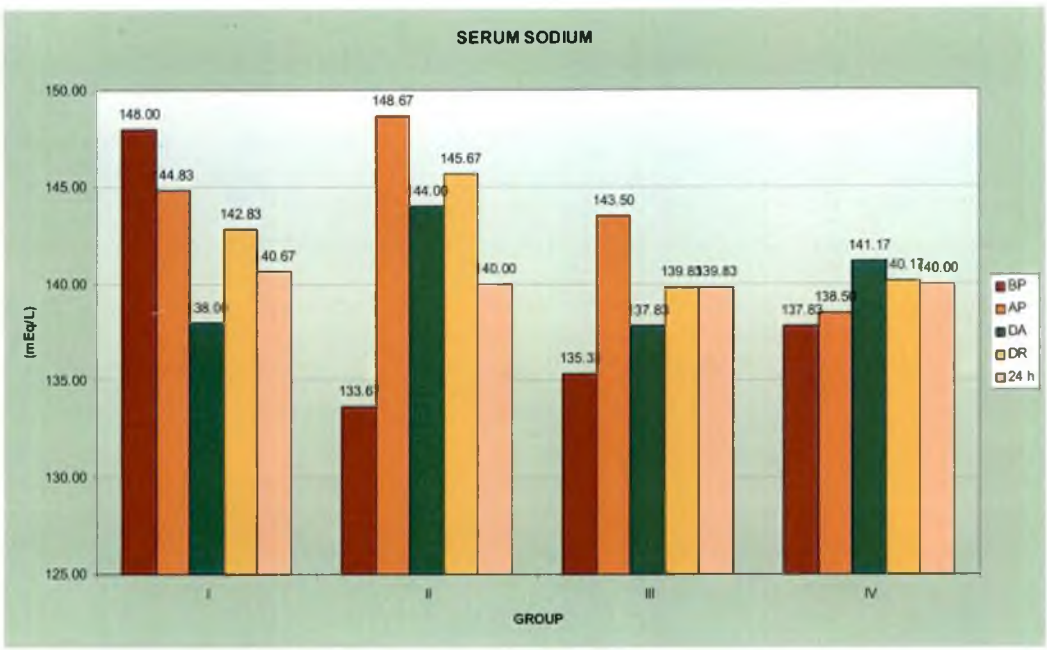


Fig. 24: Mean Serum Sodium

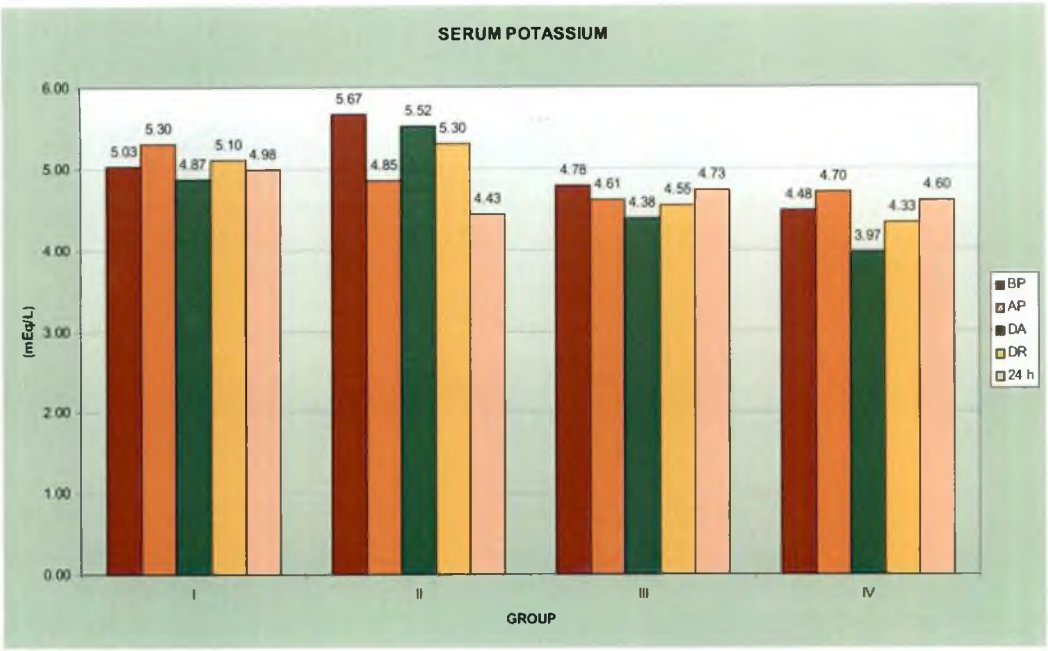


Fig. 25: Mean Serum Pottassium

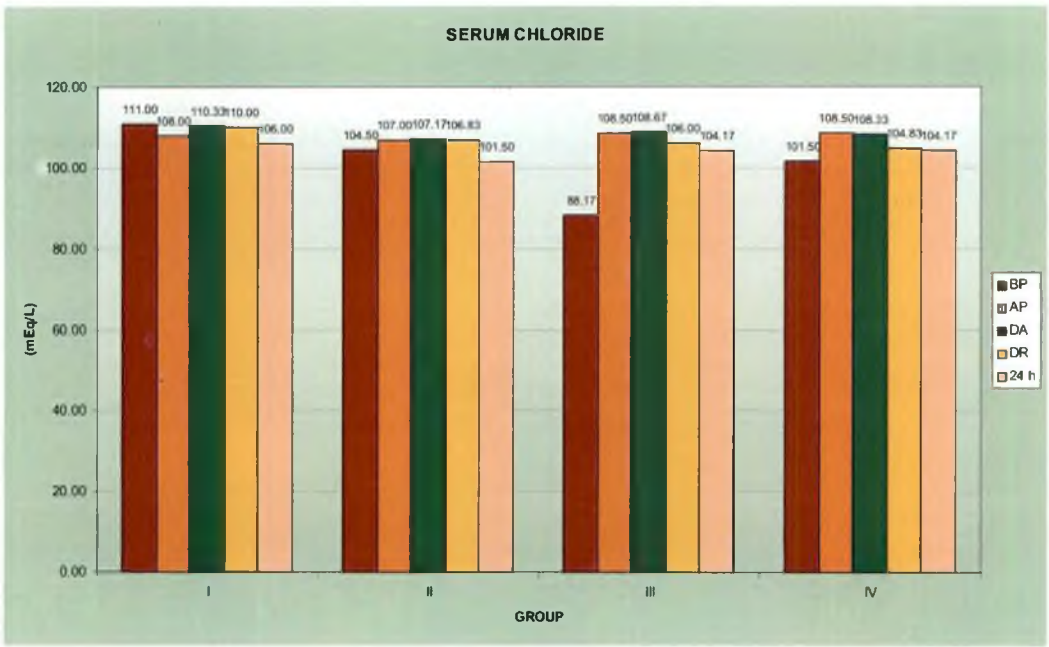


Fig. 26: Mean Serum Chloride

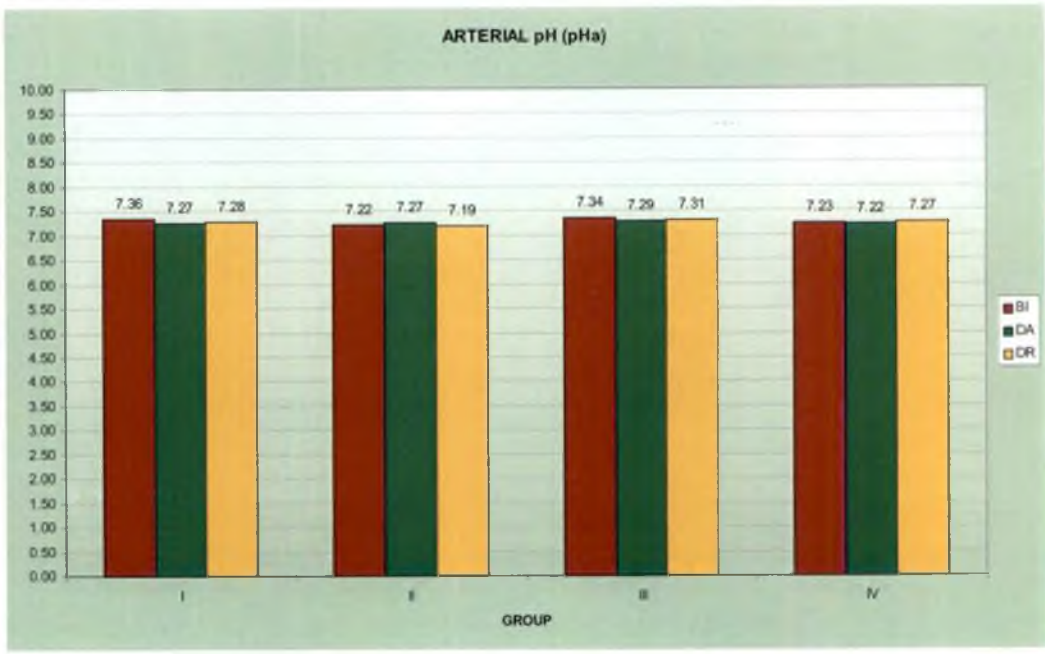


Fig. 27: Mean Arterial pH(pHa)

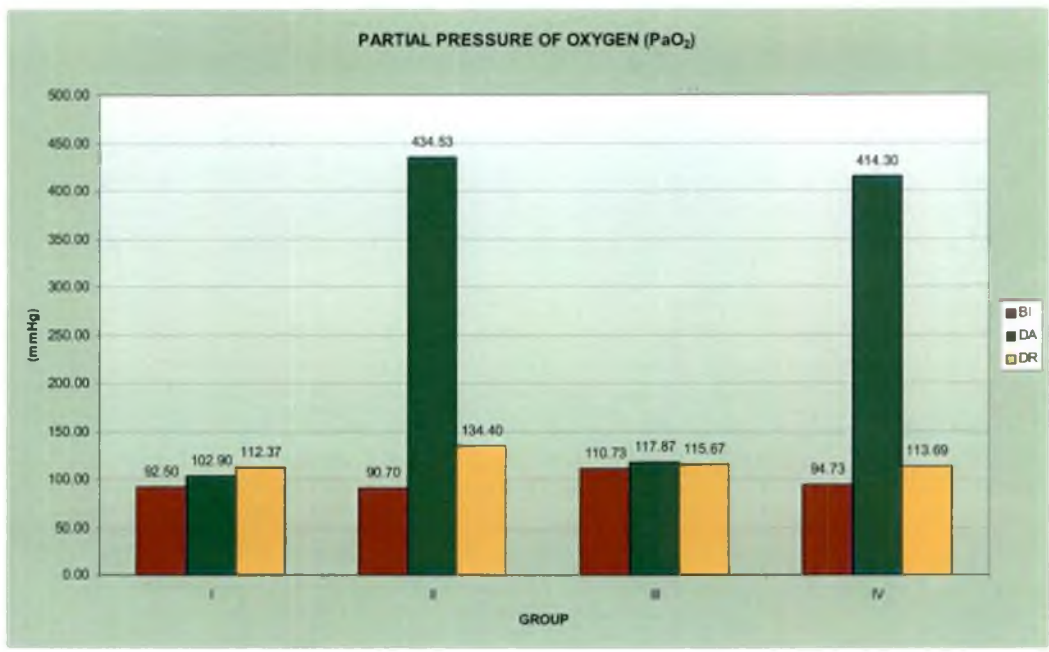


Fig. 28: Mean Partial Pressure of Oxygen (PaO_2)

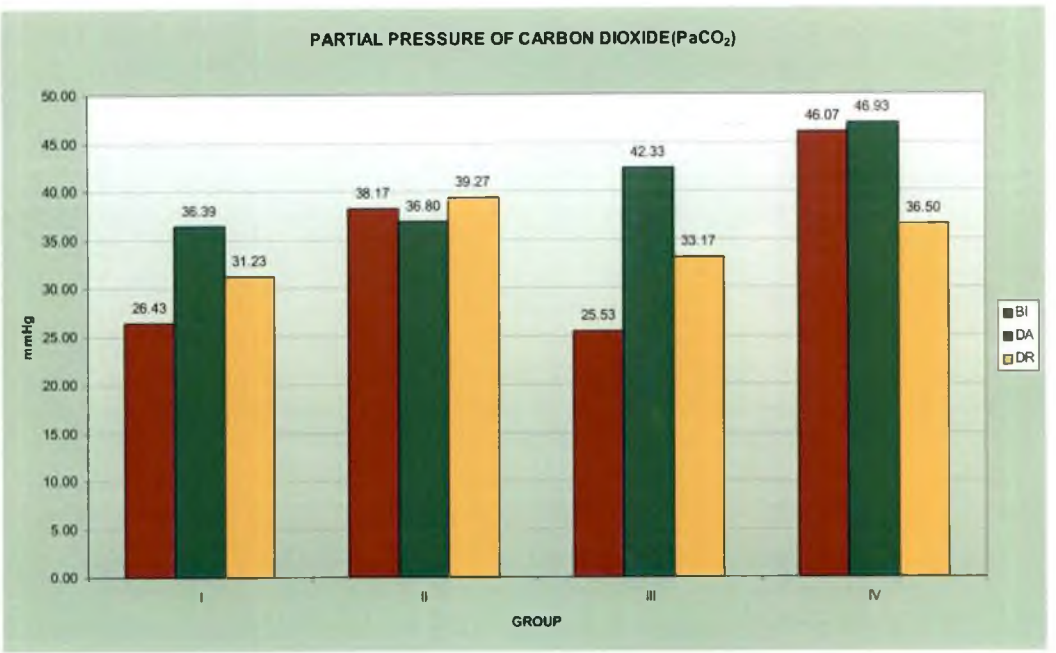


Fig. 29: Mean Partial Pressure of Carbon Dioxide ($PaCO_2$)

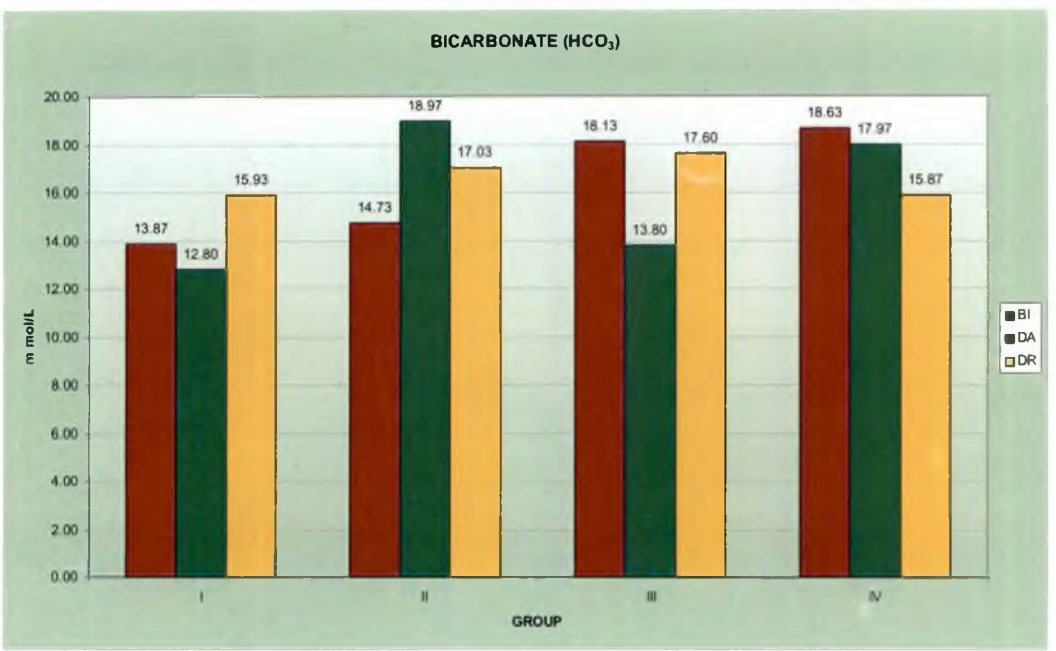


Fig. 30: Mean Bicarbonate (HCO_3)

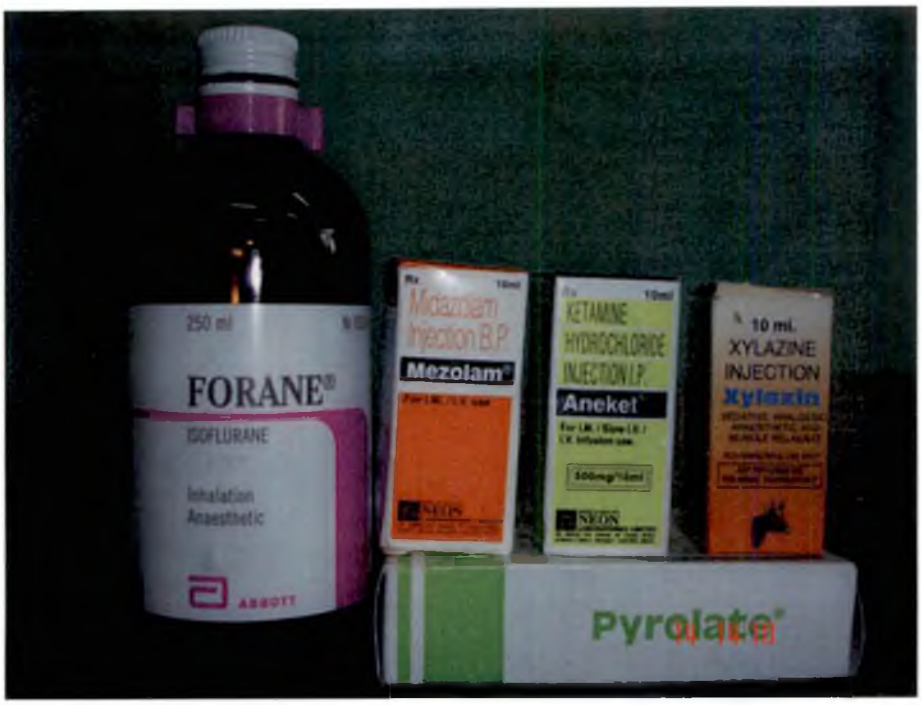


Plate 1. Drugs used for the study

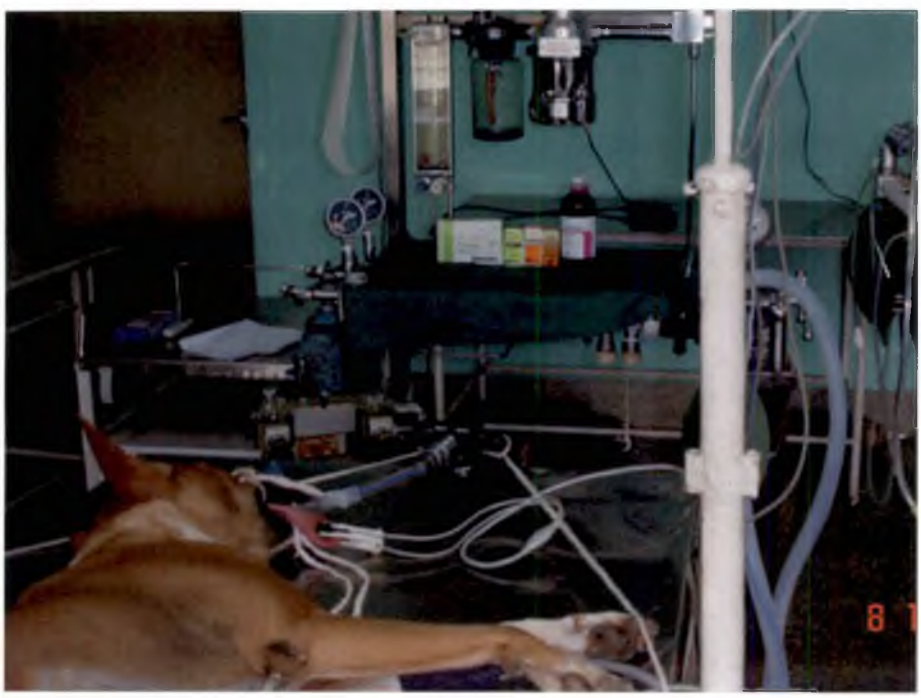


Plate 2. Anaesthesia apparatus and the animal under anaesthesia

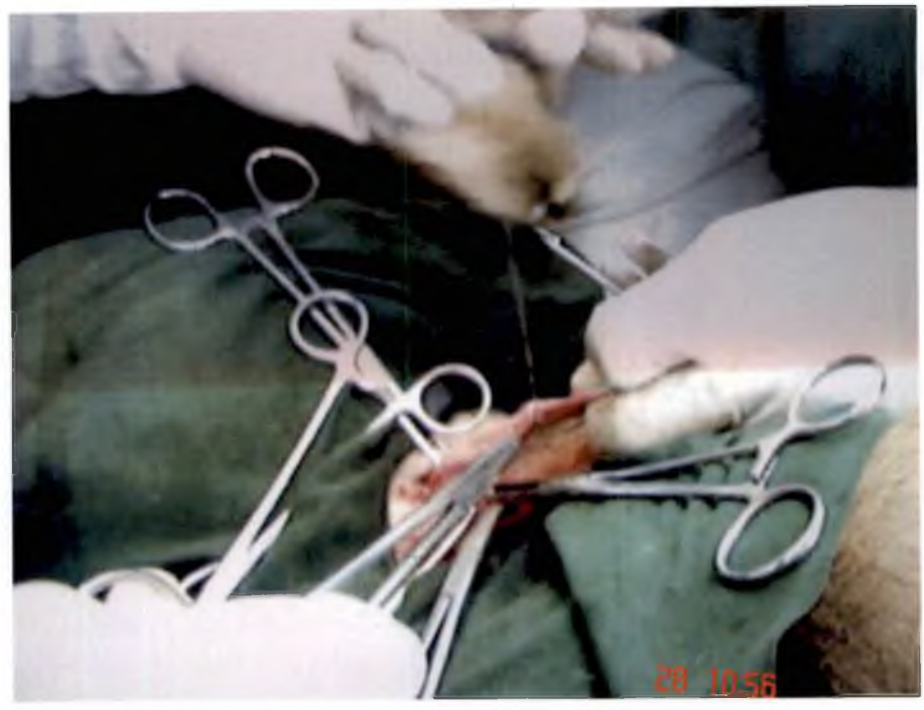


Plate 3. Surgical procedure - oopherectomy

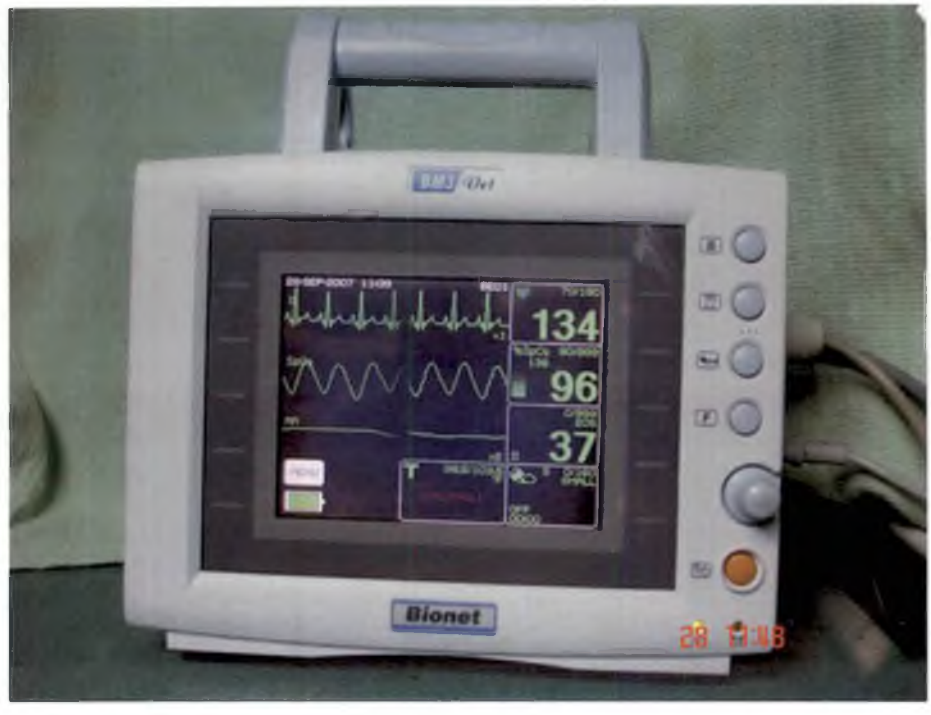


Plate 4. Multi Para Monitor

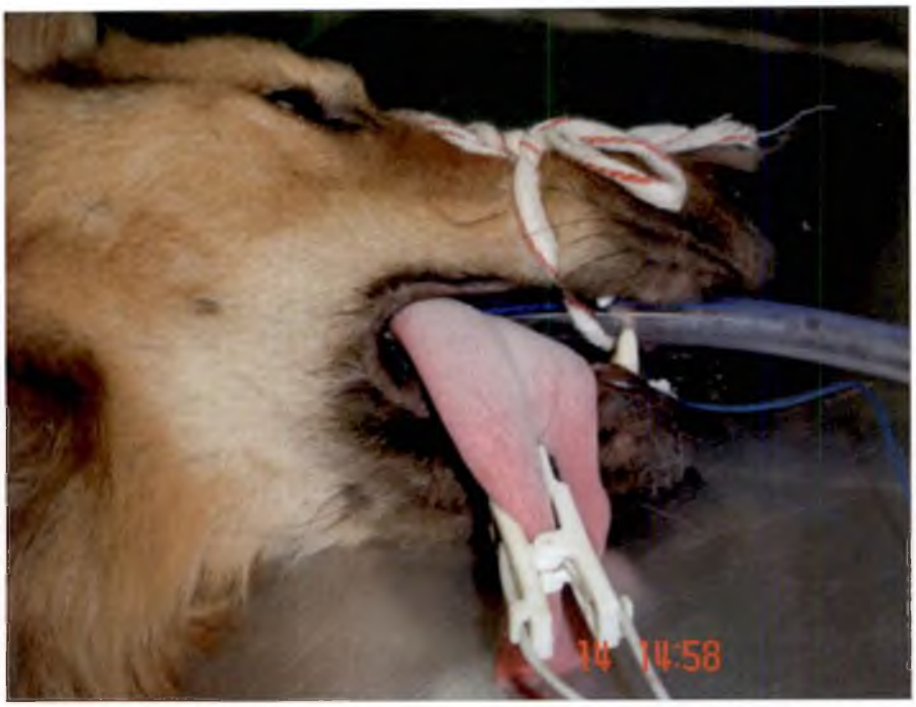


Plate 5. Entotracheal intubation and pulse oximeter transducer on the tongue

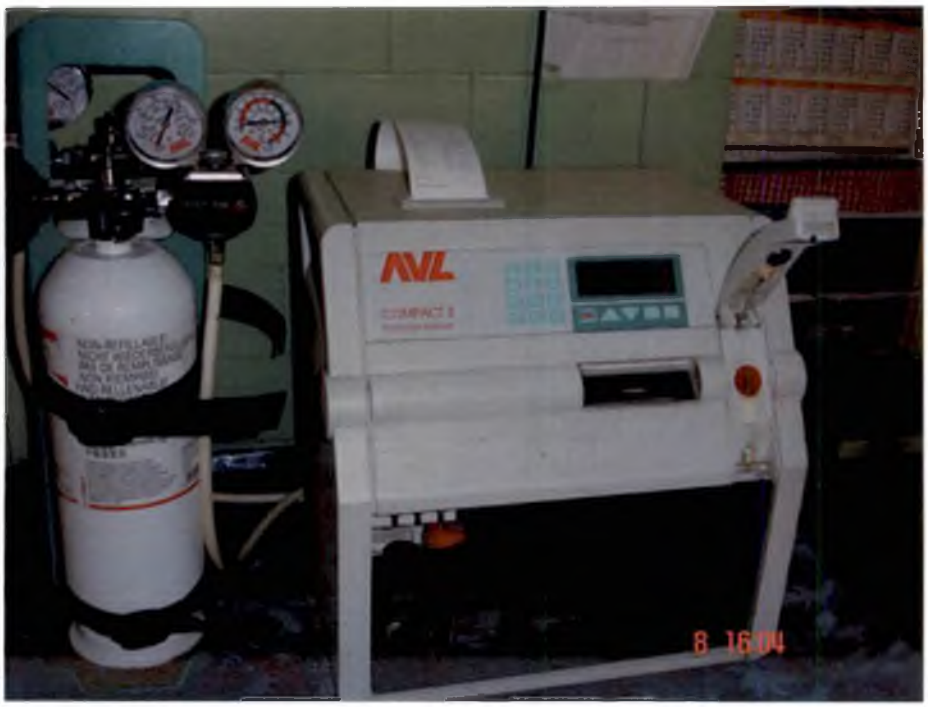
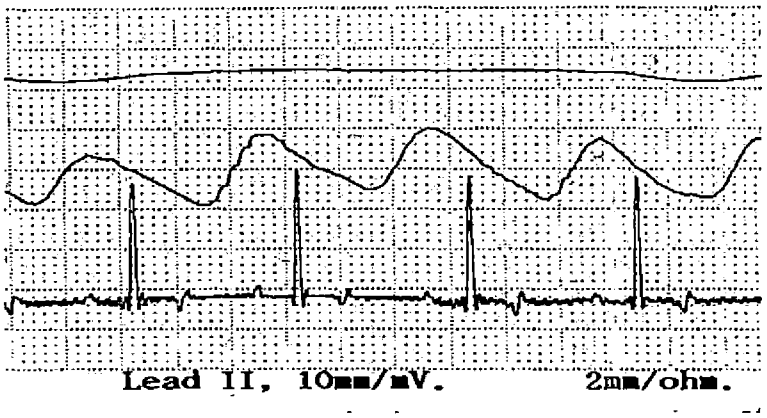
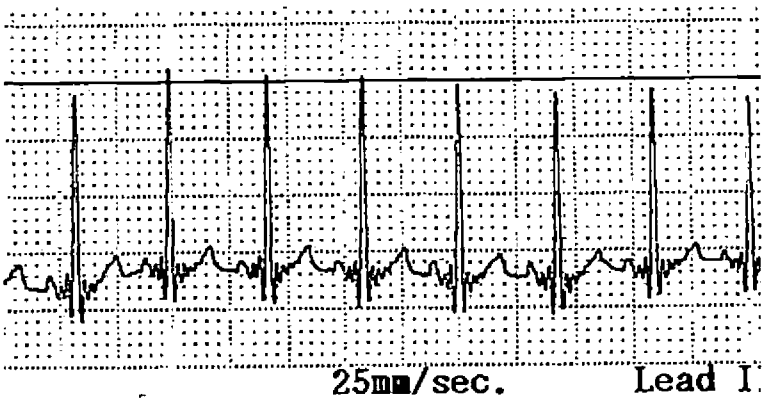


Plate 6. Blood Gas Analyser

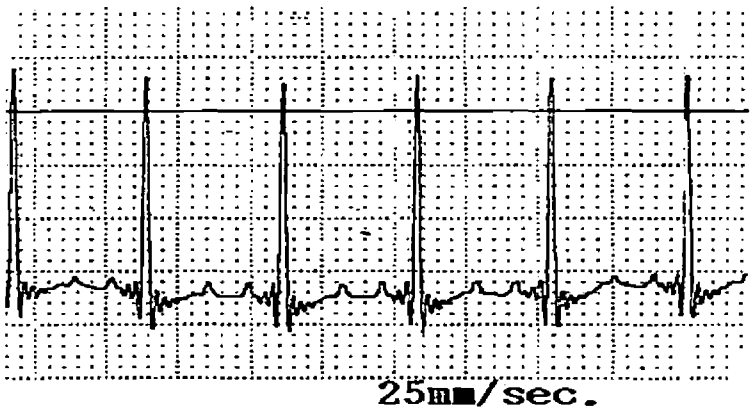
Plate 7



A. Normal electrocardiogram of a dog. (I s)

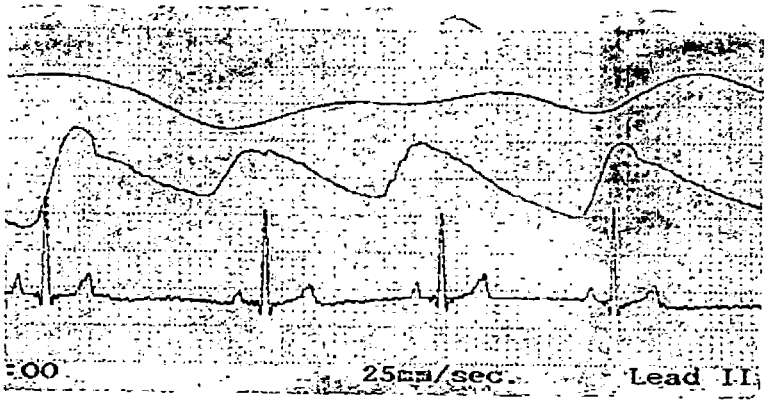


B. Tachycardia - following glycopyrrolate premedication in a dog (I s)

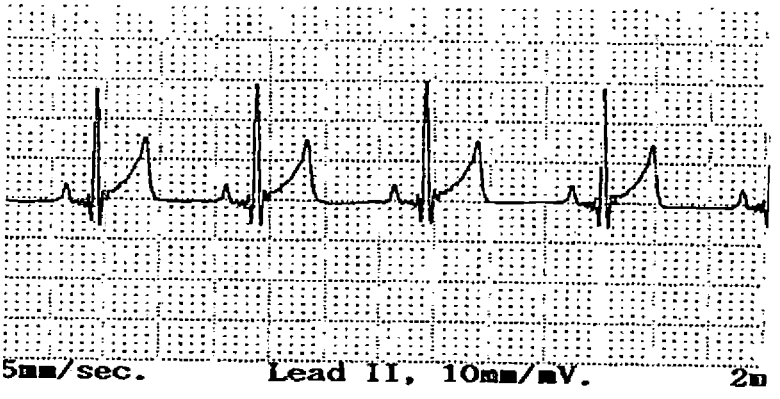


C. Tachycardia-being corrected after xylazine premedication (I s)

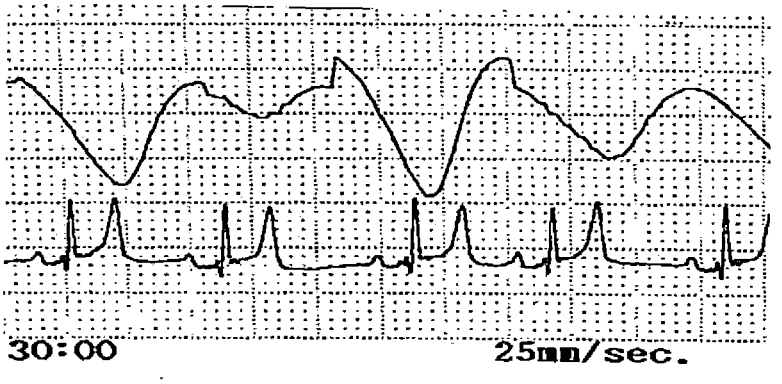
Plate 8



A. Sinus arrythmia during ketamine - isoflurane anaesthesia in a dog (II 3)

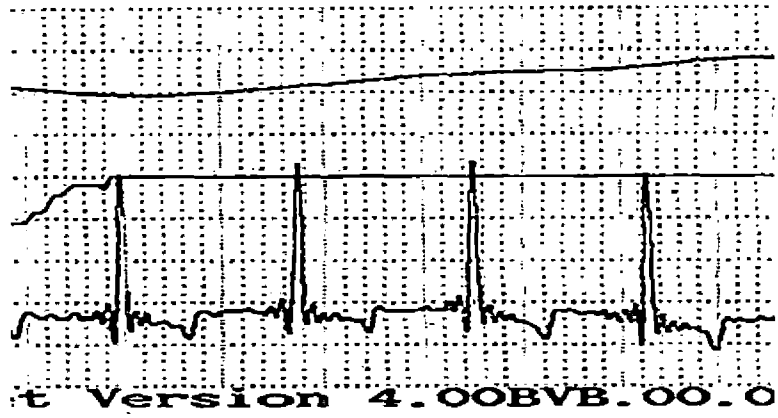


B. ST segment elevation during ketamine anaesthesia with midazolam premedication in a dog (III 5)

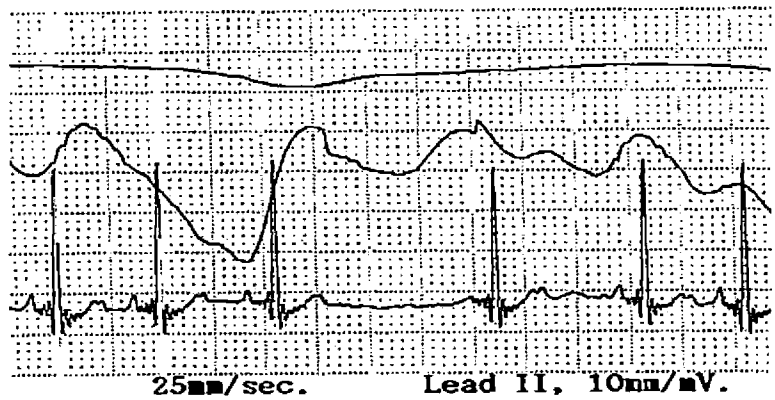


C. Peaked T wave during ketamine anaesthesia with midazolam premedication in a dog (III 4)

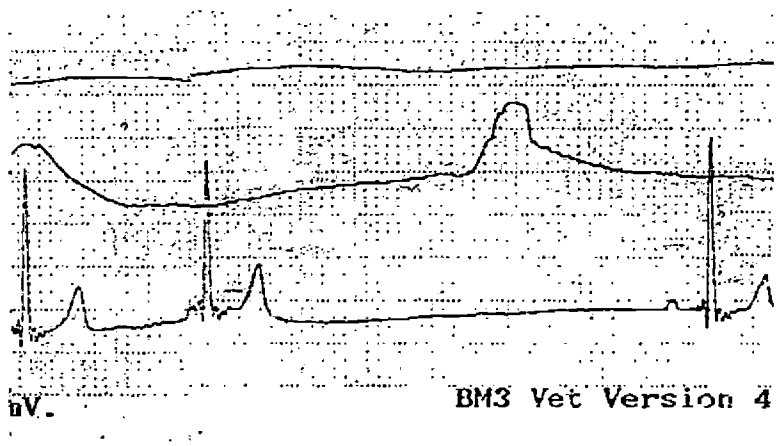
Plate 9



A. ST coving during ketamine anaesthesia in a dog (IV 1)

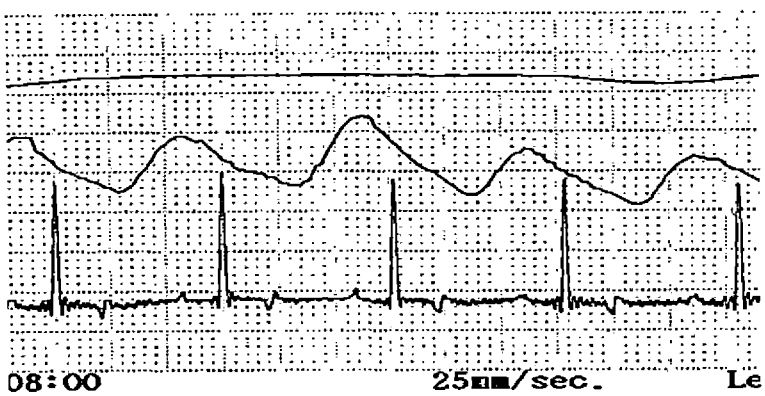


B. S A Block-after midazolam premedication in a dog (IV 1)

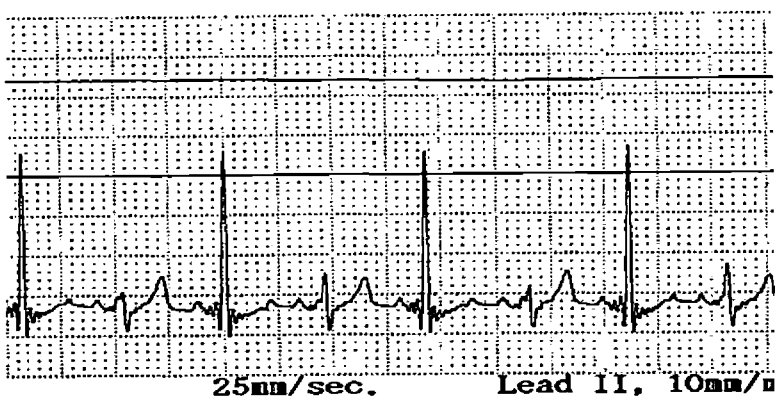


C. SA Arrest -after midazolam premedication in a dog (IV 1)

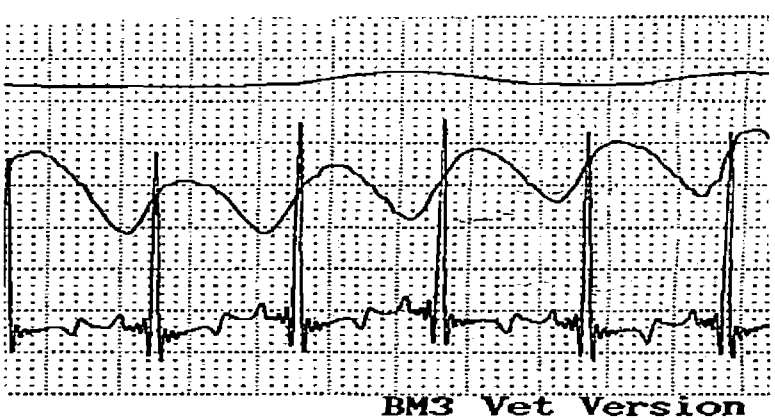
Plate 10



A. SA block-getting corrected during ketamine-isoflurane anaesthesia with midazolam premedication in a dog (IV 1)

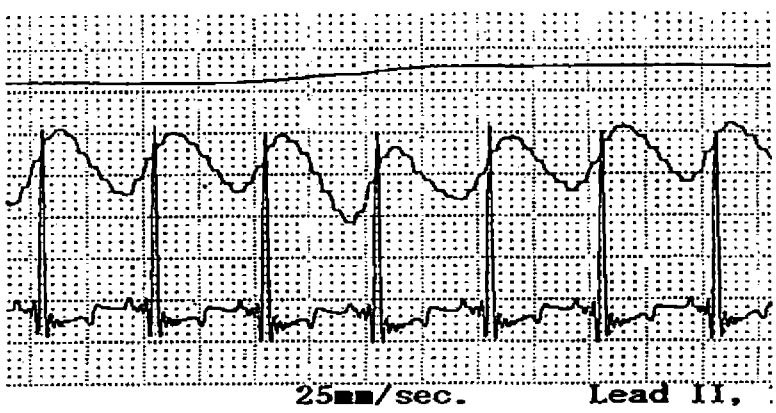


B. Ventricular bigeminy-during ketamine-isoflurane anaesthesia with midazolam premedication in a dog (IV 1)

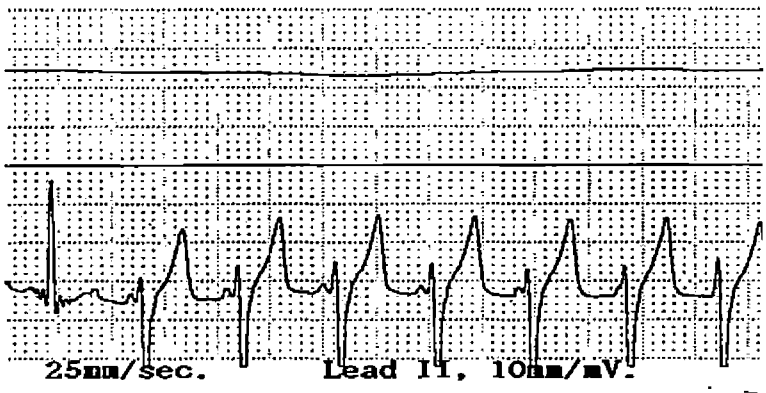


C. Increased R wave amplitude-ketamine-isoflurane anaesthesia with midazolam premedication in a dog (IV 3)

Plate 11



A. ST segment depression during ketamine -isoflurane anaesthesia with midazolam premedication in a dog (IV 5)



B. Ventricular tachycardia-ketamine -isoflurane anaesthesia with midazolam premedication in a dog (IV 2)

Discussion

5. DISCUSSION

The anaesthetic study was conducted in 24 female dogs of different breeds subjected to elective surgical procedures (oopherectomies). They were randomly divided into four groups viz., I, II, III and IV, each consisting of six animals and were numbered serially from 1 to 6.

The dogs were prepared by withholding water for 12 hours and food for 24 hours prior to premedication. Animals of all the groups were administered intramuscularly, glycopyrrolate at the rate of 0.011mg/kg body weight followed by xylazine at the rate of 1.0 mg/kg body weight, at 15 minutes interval. In addition, animals of Group III and IV were also administered intravenously midazolam at the rate of 0.3 mg/kg body weight, 10 minutes after the administration of xylazine.

Fifteen minutes after premedication, to all animals ketamine hydrochloride (10 mg/kg body weight) was administered intramuscularly to induce anaesthesia and to the animals of Group II and IV, isoflurane was also administered for the maintenance of anaesthesia.

5.1 Clinical Observations

5.1.1 Clinical signs: The common clinical signs suggestive of sedation manifested by the dogs following premedication with administration of glycopyrrolate and xylazine were winking of eyes, yawning, inco-ordination of movement, and assumption of sternal recumbency with head down posture. All the dogs were in lateral reccumbency following the administration of midazolam. The other symptoms noticed were vomiting (20), licking (6), urination (4) and defecation (9). These symptoms in dogs following the administration of xylazine had been reported by (Rajankutty, 1996 and Varghese, 2006). Xylazine induced vomiting had also been reported in dogs by Hall (1985). The possible reason for the vomiting can be attributed to the effect of xylazine. According to Moye *et al.*

(1973), emetic action was considered advantageous as it empties the stomach thereby eliminating the possibility of aspiration during surgery and postoperatively.

The induction of both ketamine and ketamine isoflurane anaesthesia with glycopyrrolate-xylazine/glycopyrrolate-xylazine-midazolam premedication were smooth in all the animals. Smooth induction with the supplementation of isoflurane in midazolam-ketamine anaesthesia in cats had also been reported by Faggella and Aronsohn (1993).

In four animals each of Groups I and II, endotracheal intubation could be performed only with resistance, but it was easy in Groups III and IV, in which midazolam was included for premedication. Hellyer *et al.* (1991) also reported rapid intubation as an added advantage of midazolam-ketamine combination in dogs, since it abolished the swallowing reflex.

In the present study, salivation was scanty in all the dogs, evidently due to the prior administration of the anticholinergic, glycopyrrolate. The antisialagogue effect of glycopyrrolate had been reported in dogs (Mirakhur *et al.*, 1978; Preiss and Berguson, 1983; Hall, 1985; Watney *et al.*, 1987 and Tranquilli, 2001). Symptoms like tonoclonic seizures (Haskins *et al.*, 1985 and Wright, 1982) and muscle rigidity (Hall, 1985; Thiruthalinathan *et al.*, 1995 and Thurmon *et al.*, 1996) were encountered following the administration of ketamine. Such symptoms were not observed when ketamine-xylazine combination (Hall, 1985) or ketamine-midazolam combination (Jacobson and Hartsfield, 1993a) was administered. In the present study, induction of anaesthesia was smooth in all the animals may be due to the administration of xylazine/xylazine and midazolam prior to ketamine.

During recovery in a few animals vocalization was noticed, but was absent in those animals premedicated with midazolam. All the animals had an uneventful recovery, though the dogs showed varying degree of dullness, which

lasted for two to six hours and had normal food intake from the next day onwards.

5.1.2 Induction time of anaesthesia: The induction time of anaesthesia was 9.50 ± 0.81, 8.83 ± 0.40, 6.83 ± 0.47 and 6.50 ± 0.43 min in Group I, II, III and IV respectively. The induction time of anaesthesia following the administration of ketamine/ketamine-isoflurane combination was found quicker in dogs premedicated with midazolam combination of glycopyrrolate-xylazine than glycopyrrolate-xylazine, may be due to the added sedative effect of midazolam. Similar findings were also reported by Hellyer *et al.* (1991) when midazolam was combined with ketamine. Rapid induction of anaesthesia in dogs had been reported with isoflurane by Klide (1976) and Ludders (1992) and isoflurane-ketamine combination by Faggella and Aronsohn (1993).

5.1.3 Duration of surgical anaesthesia: The duration of surgical anaesthesia was 31.33 ± 2.97, 45.83 ± 3.74, 37.50 ± 2.14 and 42.33 ± 0.84 min in Group I, II, III and IV respectively. The duration of anaesthesia following ketamine was more or less similar in dogs premedicated with glycopyrrolate-xylazine and with the glycopyrrolate-xylazine-midazolam. With the supplementation of isoflurane, the duration was found further prolonged. Klide (1976) had also reported longer duration of anaesthesia with isoflurane.

5.1.4 Muscle relaxation time: The muscle relaxation time was 41.16 ± 2.14, 49.83 ± 1.83, 41.00 ± 2.31 and 54.66 ± 3.02 min in Group I, II, III and IV respectively. In dogs maintained on isoflurane the muscle relaxation time was more prolonged and further in midazolam premedicated dogs.

5.1.5 Degree of muscle relaxation: The degree of muscle relaxation was poor in four animals and moderate in two animals in Group I, good in Group II and III, and excellent in Group IV. In those animals with poor muscle relaxation, endotracheal intubation could be performed only with resistance. The degree of muscle relaxation during anaesthesia was good in animals premedicated with

midazolam and excellent with isoflurane supplementation. Luna *et al.* (1992) also reported excellent muscle relaxation in horses with midazolam-xylazine combination.

5.1.6 Depth of anaesthesia: The depth of surgical anaesthesia achieved was not satisfactory in all the animals of Group I. Hence to complete the surgical procedure, local infiltration anaesthesia at the laparotomy site using 2% lignocaine hydrochloride was also resorted to. The depth of anaesthesia was satisfactory in Group II, and III, good in Group IV. From the study, it could be inferred that xylazine-ketamine combination at the dose rate of 1 mg/kg and 10 mg/kg respectively may not be always satisfactory for major surgical procedures like laparotomy. The depth of anaesthesia achieved was satisfactory in those animals premedicated with midazolam and good in those maintained on isoflurane. According to Hellyer (1996), unstable patients requiring rapid change in anaesthetic depth, should be anaesthetized with either halothane or isoflurane as both agents are rapidly acting anaesthetics and provide flexibility to change the depth of anaesthesia.

5.1.7 Recovery time: The Recovery time was 71.67 ± 3.07, 74.14 ± 3.75, 108.00 ± 8.47 and 91.50 ± 6.42 min in Group I, II, III and IV respectively. The recovery time was found more prolonged in dogs in which midazolam was included for premedication, may be due to its hypnotic action (Kanto *et al.*, 1982). Amongst the midazolam premedicated animals, those maintained on isoflurane anaesthesia, the recovery was rapid, probably due to the supplementation of oxygen during the recovery period. Rapid recovery in dogs anaesthetized with isoflurane had also been reported by Klide (1976) and Ludders (1992).

5.2 Physiological Observations

5.2.1 Rectal temperature: There was marginal decrease in rectal temperature after premedication and during anaesthesia in all the groups. Decrease in rectal temperature during xylazine-ketamine anaesthesia in dogs (Sharma *et al.*, 1983

and Mohan, 2006) and in sheep (Baniadam *et al.*, 2004), and in horses (Malik and Singh, 2007) during midazolam-xylazine anaesthesia in dogs (Koc *et al.*, 2002) had been reported. The decrease in body temperature during anaesthesia can be attributed to the depressant effect of the drugs on the central nervous system. Peripheral vasodilatation also may be a contributing factor in midazolam premedication (Ramaswamy *et al.*, 1991). Koc *et al.* (2002) opined that the decrease in body temperature during xylazine-midazolam anaesthesia could be due to peripheral vasodilatation, decrease of basal metabolic rate and muscle tone, and depression of thermoregulatory mechanism.

5.2.2 Pulse rate: There was decrease in pulse rate after premedication, during anaesthesia and recovery in all the groups except for a mild increase after premedication in Group I. Hence it could be concluded that in ketamine/ketamine isoflurane anaesthesia midazolam premedication improved the pulse rate during anaesthesia and recovery. A decreased heart rate followed by normal value during recovery in ketamine-midazolam-isoflurane (Jacobson and Hartsfields, 1993b) and xylazine-midazolam anaesthesia (Koc *et al.*, 2002) had been reported. Bishnoi and Saini (2005a) reported nonsignificant changes in pulse rate in calves administered midazolam. Studies carried out in human beings also could not reveal any change in pulse rate with midazolam (Melvin *et al.*, 1982).

5.2.3 Respiration rate: There was decrease in respiration rate following premedication in all the groups. The decrease was significant ($P<0.05$) after premedication and during recovery in Group I and III but in Group II and IV the decrease was not significant. Decrease in respiration rate following the administration of xylazine (Peshin *et al.*, 1980), midazolam (Bishnoi and Saini, 2005a), ketamine (Haskins *et al.*, 1985), xylazine-ketamine (Haskin *et al.*, 1986) and xylazine-midazolam (Koc *et al.*, 2002) had been reported in dogs. Dose related respiratory depression during isoflurane anaesthesia in dogs had also been reported by Galloway *et al.* (2004). But in the present study, it was seen that administration of isoflurane improved the respiration rate during recovery may be

due to the use of reduced concentration of isoflurane and the concurrent administration of oxygen.

5.2.4 Colour of visible mucous membrane: The colour of the visible mucous membrane was pale roseate in all the animals throughout the period of observation, indicating the stability of peripheral circulation.

5.2.5 Oxygen saturation (SPO2) level: There was significant ($P<0.05$) increase in SPO_2 level after premedication in Group I, II, III and during anaesthesia and recovery in Group II and IV. In ketamine-isoflurane anaesthesia, the oxygen saturation was significantly ($P<0.05$) increased during anaesthesia and recovery irrespective of midazolam premedication probably due to the concurrent administration of oxygen during isoflurane maintenance. According to Bishnoi and Saini (2005b) a decrease in SPO_2 level could be evident during hypoventilation. Such a decrease was not observed during the present study and the results revealed that in all the animals the tissue oxygenation status of the peripheral tissues was very good especially during ketamine-isoflurane anaesthesia.

5.2.6 Capillary refill time: The capillary refill time was seen decreased after premedication in Group I and II and increased in Group III and IV. During anaesthesia it was decreased in Group I whereas it was increased in Group III and IV, where midazolam was included for premedication. This increased capillary refill time noticed may be due to the peripheral vasodilatation effect and the loss of muscle tone produced by midazolam (Koc *et al.*, 2002). During recovery, the variations were marginal in Group I and decreased to the near normal value in Group II, III and IV.

5.2.7 Blood coagulation time: There was an increase in coagulation time after premedication and during anaesthesia in all the groups. In Group I and II, the increase was significant ($P<0.05$) but not significant in Group III and IV during anaesthesia. Hence it could be seen that the midazolam premedication with

ketamine and ketamine-isoflurane anaesthesia, the coagulation time can be minimized.

5.2.8 Systolic blood pressure: There was significant increase in systolic blood pressure in Group I and II after premedication, during anaesthesia and recovery whereas in Group III and IV, where midazolam was included, there was significant decrease after premedication, followed by significant increase during anaesthesia. Melvin *et al.* (1982) and Shenoy *et al.* (2002) also observed significant decrease in systolic pressure following the administration of midazolam.

5.2.9 Diastolic blood pressure: There was significant increase in diastolic blood pressure after premedication, during anaesthesia and recovery except in Group I. Whereas in Group III and IV there was no change after premedication, but there was significant increase during anaesthesia and recovery. Hence it is evident that with midazolam premedication the diastolic pressure remained unchanged, but with, subsequent administration of ketamine/ketamine-isoflurane combination it increased significantly.

5.2.10 Mean *arterial blood pressure*: There was significant increase in mean blood pressure after premedication and during anaesthesia with a decreasing trend during recovery in all the groups.

5.3 Electrocardiogram (ECG)

The recording of ECG continuously helped to identify the exact nature of arrhythmias occurred during the period of premedication, anaesthesia and recovery. All the animals showed normal ECG before premedication. Following the administration of glycopyrrolate, the only noticeable change in the ECG was mild to moderate tachycardia, but on administration of xylazine, different arrhythmia were seen including sinoatrial block and sinoatrial arrest. After the administration of ketamine, sinus tachycardia was also noticed. All the abnormalities observed only for a short period of anaesthesia and disappeared

after ketamine administration. The ST segment depression/elevation observed after xylazine midazolam premedication persisted after ketamine administration also. Similar observations were also recorded by Clark et al. (1982).

The supraventricular tachycardia and peaking of T-wave, S-T segment depression elevations are all indicators of myocardial hypoxia (Lang and White, 1976) but in the present study though these abnormalities were seen during the period of premedication and anaesthesia, none of the changes persisted longer and got corrected after a short period.

The ventricular premature contractions occurred continuously may be due to the endogenous catecholamines released during lighter plane of anaesthesia or due to the effect of drugs like xylazine/midazolam or hypoxia. Similar observation also observed by Robertson (1992). In this study, life threatening arrhythmia like ventricular fibrillation was absent.

After premedication sinoatrial block, sinoatrial arrest and sinoarrythmia were observed in animals of all the groups and which were corrected during the period of anaesthesia and recovery. The ventricular tachycardia observed after premedication with xylazine and midazolam were corrected during recovery. The sinus arrythmias observed in all the groups at different intervals were got corrected automatically without any treatment.

The SA blocked observed was seen corrected after isoflurane. This indicates that the isoflurane with oxygen administration corrected this during maintenance.

The changes noticed in ketamine/ketamine-isoflurane anaesthesia with and without midazolam premedication was only sinus arrhythmia which were corrected automatically. The results of the ECG recording indicated that life threatening myocardial abnormalities were absent with these anaesthetic combinations.

5.4 Haematological Parameters

5.4.1 Haemoglobin *concentration*: There was significant ($P<0.05$) decrease in haemoglobin concentration after premedication during anaesthesia and recovery in all the groups. Slight decrease in haemoglobin concentration had been reported in dogs following xylazine administration by Peshin *et al.* (1980) and in horses by Malik and Singh (2007).

***5.4.2 Volume of Packed Red Cells*:** The VPRC was seen decreased after premedication in Group III and IV, increased in Group I and remain as such in group II. During anaesthesia, it was decreased in Group II, III and IV, but in Group I, there was marginal increase. Slight decrease in VPRC had been reported in dogs following the administration of xylazine by Peshin *et al.* (1980).

***5.4.3 Erythrocyte sedimentation rate*:** There was decrease in ESR after premedication during anaesthesia and recovery in all groups except for an increase during anaesthesia in Group III. During anaesthesia, the decrease was more in those animals with midazolam premedication.

***5.4.4 Total leukocyte count*:** The variations in TLC were marginal after premedication and during anaesthesia and recovery in all the groups. Slight decrease in TLC had been reported in dogs following the administration of xylazine by Peshin *et al.*, 1980).

***5.4.5 Neutrophils count*:** The variations were marginal in neutrophil count after premedication and during anaesthesia except for a significant ($P<0.05$) increase after premedication in Group III. There was decrease in Group IV during anaesthesia. Hence it is evident in both ketamine and ketamine-isoflurane anaesthesia with midazolam premedication there was decrease in neutrophil count.

***5.4.6 Lymphocyte count*:** There was marginal variation in lymphocyte count in all the group after premedication and during anaesthesia except in Group IV

where there was increase during anaesthesia. It was seen that in ketamine – isoflurane anaesthesia with midazolam premedication, there was significant ($P<0.05$) increase in lymphocyte count. Decrease in lymphocyte count with subsequent increase in neutrophils count had been reported in dogs following the administration of xylazine by Peshin *et al.* (1980).

5.4.7,8,9 Eosinophil , Monocyte and Basophilic counts: The variations in eosinophil and monocyte count were marginal in all the groups and basophils were not noticed in any of the animals.

5.4.8 Basophil count: Basophils were not noticed in any of the animals.

5.5 Serum Biochemical Parameters

5.5.1 Total protein: There was decrease in total protein content after premedication in Group I, II and III, whereas in Group IV there was marginal increase. But during anaesthesia, there was decrease in all the groups and the decrease was significant ($P<0.05$) in Group I and IV. Bishnoi and Saini (2005 b) had also reported decrease in total protein content following the administration of midazolam in calves.

5.5.2 Creatinine: There was decrease in serum creatinine levels after premedication and during anaesthesia in all the groups indicating normal renal function. Increase in creatinine level following the administration of midazolam and ketamine combination in dogs had been reported by Butola and Singh (2003).

5.5.3 Blood Urea Nitrogen: The BUN level decreased after premedication in Group I, II and III. Whereas in group IV, there was marginal increase. But during anaesthesia, there was decrease in group I, II and IV, whereas in group III, there was significant increase during anaesthesia and recovery. In ketamine-isoflurane anaesthesia without midazolam premedication, there was increase in BUN during anaesthesia. All the changes were within the normal physiological limits and the results indicated that it did not affect the kidney functions much.

Lang and White (1976) reported a rise in blood urea nitrogen during fasting, could be due to decreased renal blood flow or glomerular destruction. The fluctuations in the values noticed in the present study might be due to the preoperative fasting.

5.5.4 Glucose: There was significant increase in glucose concentration after premedication in all groups, but during anaesthesia, though the increase was significant ($P<0.05$) in all the groups, the increase was more in Group III and IV. Significant increase in blood glucose concentration had been reported in dogs following the administration of xylazine (Peshin *et al.*, 1980 and Tiwari *et al.*, 1994) and in springbok following the administration of xylazine-ketamine combination (Jacobson, 1983).

5.5.5 Aspartate amino transferase: There was decrease in AST values after premedication and during anaesthesia in Group I, III and IV, whereas in Group II, there was an increase. Jacobson (1983) had reported nonsignificant change in AST values in springbok in mobilized with xylazine ketamine combination. In ketamine- isoflurane anaesthesia without midazolam premedication. There was increase in AST during anaesthesia.

5.5.6 Alamine amino transferase: There was decrease in ALT values after premedication and during anaesthesia in Group I, III and IV, whereas in Group II, there was an increase. Jacobson (1983) reported significantly higher level of ALT values in springbok immobiliazed with xylazine ketamine combination. In ketamine-isoflurane anaesthesia without midazolam premedication. There was increase in ALT during anaesthesia.

5.5.7 Sodium: There was nonsignificant decrease in serum sodium in Group I, whereas marginal increase in Group II, III and IV after premedication, during anaesthesia and recovery. This effect might be due to the haemodilution in response to vasodilation. Similar findings were also reported in by Malik and Singh (2007).

*5.5.8 **Potassium:*** The variations in serum potassium concentration were marginal after premedication, during anaesthesia and recovery in all the groups. Mild decrease in potassium concentration had been reported in dogs following the administration of xylazine by Peshin *et al.* (1980).

*5.5.9 **Chloride:*** Serum chloride level decreased throughout the period of observation with a significant ($P<0.05$) decrease at 24 h in Group I. The level increased after premedication and anaesthesia and the increase was significant ($P<0.05$) during anaesthesia in Group III and IV. Mild decrease in chloride concentration had been reported in dogs following the administration of xylazine by Peshin *et al.* (1980) and Malik and Singh (2007).

5.6 Arterial Blood Gas Analysis

*5.6.1 **pHa***: During anaesthesia, there was decrease in pHa in Group I and III, whereas it was increased in Group II and maintained in Group IV. Steffey (1996) reported a significant decrease in pHa with isoflurane at all its anaesthetic concentrations. But in the present study, those animals anaesthetized with ketamine irrespective of midazolam premedication, there was decrease in pHa indicating metabolic acidosis. The acidosis might have resulted from inadequate tissue perfusion (Trim and Gilroy, 1985). In ketamine-isoflurane anaesthesia, it was either increased or maintained. Hence clinically it is evident that incorporation of isoflurane for the maintenance of ketamine anaesthesia reduces the chance of metabolic acidosis, there by maintaining adequate perfusion of tissues.

*5.6.2 **Partial Pressure of Oxygen***: There was an increase in $P_a O_2$ during anaesthesia with a decreasing trend during recovery in all the groups. During anaesthesia, the increase was well marked in animals maintained on isoflurane may be due to the concurrent administration of oxygen. From this it is evident that in ketamine anaesthesia the ventilation could be well maintained by incorporating isoflurane with oxygen for maintenance. These types of changes were also observed by Pypendop and Verstegen (1999).

5.6.3 Partial pressure of Carbon dioxide: There was increase in $P_a CO_2$ during anaesthesia in Group I and III with a decrease in trend during recovery. But in Group II and IV, it was maintained with a decrease in trend during recovery. Increase in $P_a CO_2$ following the administration of xylazine-ketamine combination in sheep had been reported by Baniadam *et al.* (2004) and increase in $PaCO_2$ in dogs after the administration of meditomidine midazolam butorphenol was also observed by Pypendop and Verstegen (1999). In the present study it could be seen that there was no change in $P_a CO_2$ in those animals anaesthetized with ketamine-isoflurane combination, irrespective of midazolam premedication.

5.6.4 Bicarbonate: During anaesthesia, there was increase in HCO_3 in Group II where as it was decreased in Group III. The levels were maintained in Group I and IV. According to Bishnoi and Saini (2005b) slight increase in HCO_3 could be helpful for compensating the respiratory acidosis developed during anaesthesia. Respiratory acidosis is compensated by production of bicarbonate (cell buffering) and in acute cases, HCO_3 increases 1 mEq/L for each 10 mmHg increase in $P_a CO_2$, and in chronic cases HCO_3 is increased 3.5 mEq/L for each 10 mm Hg increase in $P_a CO_2$ (Raffe, 1993).

On monitoring the patients included in the present study, it was found that the anaesthetic protocols selected were found satisfactory, safe and did not caused any systemic changes in the body leading to alterations in the functions of cardiovascular, respiratory, renal and central nervous systems. The post operative recovery characteristics are better with midazolam premedication along with glycopyrrolate and xylazine and is an advantage to use in routine surgeries.

5.7 Postanaesthetic Observation

Following recovery, the dogs were with varying degree of dullness which lasted for three to six hours and had the normal food intake from the next day onwards.

Summary

6. SUMMARY

The anaesthetic study was conducted in 24 female dogs of different breeds subjected to elective surgical procedures (oopherectomies). They were randomly divided into four groups viz., I, II, III and IV, each consisting of six animals and were numbered serially from 1 to 6.

Animals of all the groups were administered intramuscularly, glycopyrrolate (0.011mg/kg body weight) followed by xylazine (1.0 mg/kg body weight) at 15 minutes interval. In addition, animals of Group III and IV were also administered intravenously midazolam (0.3 mg/kg body weight) 10 minutes after the administration of xylazine. Fifteen minutes after premedication to all animals ketamine hydrochloride (10 mg/kg body weight) was administered intramuscularly to effect anaesthesia and to the animals of Group II and IV, isoflurane was also administered for the maintenance of anaesthesia.

The common clinical signs manifested by the dogs after premedication with glycopyrrolate and xylazine were winking of eyes, yawning, inco-ordination of movement and assumption of sternal recumbency with head down posture. All the dogs were in lateral reccumbency following the administration of midazolam. The other symptoms noticed were vomiting, licking, urination and defecation. Salivation was scanty in all the dogs and the induction of anaesthesia was smooth in all the animals. In four animals each of Groups I and II, endotracheal intubation could be performed only with resistance, but it was easy in Groups III and IV, in which midazolam was included for premedication.

During recovery in a few animals vocalization was noticed, but was absent in those animals premedicated with midazolam. All the animals had an uneventful recovery, though the dogs showed varying degree of dullness, which lasted for two to six hours and had normal food intake from the next day onwards.

The induction time of anaesthesia was 9.50 ± 0.81, 8.83 ± 0.40, 6.83 ± 0.47 and 6.50 ± 0.43 min in Group I, II, III and IV respectively. The induction time of anaesthesia following the administration of ketamine/ketamine-isoflurane combination was found quicker in dogs premedicated with midazolam combination of glycopyrrolate-xylazine than glycopyrrolate-xylazine.

The duration of surgical anaesthesia was 31.33 ± 2.97, 45.83 ± 3.74, 37.50 ± 2.14 and 42.33 ± 0.84 min in Group I, II, III and IV respectively. The duration of anaesthesia following ketamine was more or less similar in dogs premedicated with glycopyrrolate-xylazine and was further prolonged with the supplementation of isoflurane

The muscle relaxation time was 41.16 ± 2.14, 49.83 ± 1.83, 41.00 ± 2.31 and 54.66 ± 3.02 min in Group I, II, III and IV respectively. In dogs maintained on isoflurane, the muscle relaxation time was prolonged and further in midazolam premedicated dogs.

The degree of muscle relaxation was poor in four animals and moderate in two in Group I, good in Group II and III, and excellent in Group IV. The degree of muscle relaxation during anaesthesia was good in animals premedicated with midazolam and excellent with isoflurane supplementation.

The depth of surgical anaesthesia achieved was not satisfactory in all the animals of Group I. Hence to complete the surgical procedure, local infiltration anaesthesia at the laparotomy site using 2% lignocaine hydrochloride was also resorted to. The depth of anaesthesia was satisfactory in Group II, and III, good in Group IV respectively. From the study, it could be inferred that xylazine-ketamine combination at the dose rate of 1 mg/kg and 10 mg/kg respectively may not be always satisfactory for major surgical procedures like laparotomy. The depth of anaesthesia achieved was satisfactory in those animals premedicated with midazolam and good in those maintained on isoflurane.

The Recovery time was 71.67 ± 3.07, 74.14 ± 3.75, 108.00 ± 8.47 and 91.50 ± 6.42 min in Group I, II, III and IV respectively. The recovery time was found more prolonged in dogs in which midazolam was included for premedication.

Decrease in rectal temperature, pulse rate and respiration rate after premedication and during anaesthesia in all the groups and the colour of mucous membrane was pale roseate throughout the observation. Significant ($p<0.05$) increase in oxygen saturation level was noticed after premedication in Group I, II, III and during anaesthesia and recovery in Group II and IV. It was significantly increased in ketamine-isoflurane, anaesthesia, irrespective of midazolam premedication. Increase in coagulation time was observed after premedication and during anaesthesia in all the groups. There was significant increase in systolic, diastolic and mean blood pressure in all the groups.

Electrocardiogram revealed mild to moderate tachycardia following the administration of glycopyrrolate and sinoatrial block, sinoatrial arrest ST segment depression/elevation, ST coving, increased R amplitude, peaked T wave and ventricular tachycardia following the administration of xylazine. All the abnormalities were observed for a short period of ketamine/ketamine-isoflurane anaesthesia and disappeared during recovery.

Significant ($p<0.05$) decrease in haemoglobin concentration, volume of packed red cells, and erythrocyte sedimentation rate was noticed after premedication, during anaesthesia and recovery in all the groups. The variations in total leukocytes and differential leukocyte counts were marginal.

The variations in total protein, creatinine, blood urea nitrogen, aspartate amino transferase, alamine amino transferase, sodium, potassium and chloride parameters were within he normal physiological limits, but there was significant increase in glucose concentration.

There was decrease in pHa with increase in partial pressure of oxygen, partial pressure of carbon dioxide and variations in bicarbonate levels were observed during anaesthesia.

All the dogs had the normal food intake from the next day onwards.

From the present study, it could be concluded that:

1. Midazolam with glycopyrrolate- xylazine premedication permitted easy endotracheal intubation and adequate sedation leading to lateral recumbency.

2. Midazolam in ketamine/ketamine-isoflurane anaesthesia provided good to excellent muscle relaxation, good depth of anaesthesia and smooth induction and recovery

3. Midazolam with glycopyrrolate-xylazine premedication in ketamine anaesthesia resulted in good muscle relaxation and satisfactory depth of anaesthesia for surgeries of short duration.

4. Midazolam-glycopyrrolate-xylazine premedication in ketamine anaesthesia with isoflurane maintenance resulted excellent muscle relaxation and good depth of anaesthesia for surgeries of prolonged duration.

5. Glycopyrrolate-xylazine premedication with ketamine is not a satisfactory anaesthetic regimen for major surgical procedure like laparotomy.

6. Glycopyrrolate – xylazine premedication with ketamine-isoflurane is a satisfactory anaesthetic regimen for major surgical procedure like laparotomy.

7. Midazolam in combination with glycopyrrolate - xylazine as a pre anaesthetic in ketamine anaesthesia is a suitable and safe injectable anaesthetic regimen for major surgeries of short duration in dogs.

8. Midazolam in combination with glycopyrrolate-xylazine as a pre anaesthetic in ketamine anaesthesia with isoflurane maintenance is a suitable and safe general anaesthetic regimen for major surgeries of prolonged duration in dogs.

References

REFERENCES

Allen, J.L. 1992. Pulse oximetry: every day use in zoological practice. *Vet. Rec.* 130: 354-355.

Baniadam, A., Afsar, F.S. and Fard, Y.A. 2004. The effect of xylazine –ketamine on temperature, heart rate and respiratory rate, arterial blood pressure and blood gases in sheep. *J. Faculty Vet. Med.* 54: 265-270. (Cited in *Vet. Bull.* 2005.75 :1072.

Benjamin, M.M. 1985. *Outline of Veterinary Clinical Pathology.* Third edition. Kalyani Publishers, New Delhi, pp. 60-93.

Bishnoi, P. and Saini, N.S. 2005a. Cardiorespiratory effects of midazolam in calves. *Vet. Pract.* 6: 1-5.

Bishnoi, P. and Saini, N.S. 2005b. Haematobiochemical, blood gas and acid-base status in calves after midazolam sedation. *Vet. Pract.* 6: 99-104.

Butola, V. and Singh, B. 2003. Haematobiochemical effects of midazolam and ketamine anaesthesia in dogs. *Indian J. Vet. Surg.* 24: 44-45

Chauhan, R.S. and Agarwal, D.K. 2006. *Textbook of Veterinary Clinical and Laboratory Diagnosis.* Second edition. Jaypee Brothers, New Delhi, pp. 193-207.

Clark, D.M., Martin, R.A. and Short, C.A. 1982. Cardiopulmonary responses to xylazine/ketamine anaesthesia in the dog. *J. Am. Anim. Hosp. Assoc.* 18: 815-821.

Clutton, R.E., Blissitt, K.J., Bradley, A.A. and Camburn, M.A. 1997. Comparison of three injectable anaesthetic techniques in pigs. *Vet. Rec.* 141: 140-146.

Dunkle, N., Moise, N.S., Kranz, J.S. and Short, C.E. 1986. Cardiac performance in cats after administration of xylazine or xylazine and glycopyrrolate: Echocardiographic evaluations. *Am. J. Vet. Res.* 47: 2212-2216.

Dyson, D.H. and Davies, R.J. 1999. Dose effect and benefits of glycopyrrolate in the treatment of bradycardia in anaesthetized dogs. *Can. Vet. J.* 40: 327-331.

Faggella, A.M. and Aronsohn, M.G. 1993. Anaesthetic techniques for neutering 6 to 14 week old kittens. *J. Am. Vet. Med. Assoc.* 202: 56-62.

Forster, A., Gardaz, J.P., Suter, P.M. and Gemperle, M. 1980a. Midazolam as an induction agent for anaesthesia: A study in volunteers. *Br. J. Anaesth.* 52: 907-910.

Forster, A., Gardaz, J.P., Suter, P.M. and Gemperle, M. 1980b. Respiratory depression by midazolam and diazepam. *Anaesthesiol.* 53: 491-497.

Galloway D.S, Ko, J.F.C, Reaugh, H.F., Mandsagar R.E, Payton, M.E., Inoue, T. and Portillo, E. 2004. Anaesthetic indices of savoflurane and isoflurane in unpremedicated dogs. *J. Am. Vet. Med. Assoc.* 225: 700-704.

Gautam, P.L. and Singh, B. 1998. Blood gas analysis. Effect of storage temperature and delay in estimation. *J. Anaesth. Clin. Pharmacol.* 14: 271-273.

Greene, N.M.1972. Metabolic effect of anaesthetics. In: *Modern Inhalation Anaesthetics.* (ed. Chenoweth, M.B.), Springer–Verlag, New York, p.271.

Gross, M.E., Tranquilli, W.J., Thurmon, J.C. and Benson, G.J. 1992. Yohimbine/ flumazenil antagonism of hemodynamic alternations induced by a combination of midazolam xylazine and butorphanol in dogs. *J. Am. Vet. Med. Assoc.* 201: 1887-1890.

Hall, L.W. 1985. Premedication in canine anaesthesia. *Canine Pract.* 12: 15-21.

Hall, R.I., Schwieger, I.M. and Hug, C.C. 1988. The anaesthetic efficacy of midazolam in the enflurane-anaesthetized dog. *Anaesthesiol.* 68: 862-866.

Haskins, S.C., Farver, T.B. and Patz, J.D. 1985. Ketamine in dogs. *Am. J. Vet. Res.* 46: 1855-1859.

Haskins, S.C., Patz, J.D. and Farver, T.B. 1986. xylazine and xylazine- ketamine in dogs. *Am. J. Vet. Res.* 47: 636-641.

Haskins, S.C.1977 Sampling and storage of blood for pH and blood gas analysis. *J. Am. Vet. Med. Assoc.* 170: 429-433.

Hellyer, P.W. 1996. General anaesthesia for dogs and cats. *Vet. Med.*91: 314-325.

Hellyer, P.W., Freeman, L.C. and Hubbell, J.A.E. 1991. Induction of anaesthesia with diazepam-ketamine and midazolam-ketamine in Greyhounds. *Vet. Surg.* 20: 143-147.

Hsu, W.H., Lu, Z.X. and Hembrough, F.B. 1985. Effect of xylazine on heart rate and arterial blood pressure in conscious dogs, as influenced by atropine 4-aminopyridine, doxapram and yohimbine. *J. Am. Vet. Med. Assoc.* 186: 153-156.

Jacobson, E.R. 1983. Haematological and serum chemical effects of a ketamine/xylazine combination when used for immobilizing springbok. *J. Am. Vet. Med. Assoc.* 183: 1260-1262.

Jacobson, J.D. and Hartsfield, S.M. 1993a. Cardiorespiratory effects of intravenous bolus administration and infusion of ketamine-midazolam in dogs. *Am. J. Vet. Res.* 54: 1710-1714.

Jacobson, J.D. and Hartsfield, S.M. 1993b. Cardiovascular effects of intravenous bolus administration and infusion of ketamine-midazolam in isoflurane anaesthetized dogs. *Am. J. Vet. Res.* 54: 1715-1720.

Jacobson, J.D., Mc Grath, C.J. and Smith, E.P. 1994. Cardiorespiratory effects of induction and maintenance of anaesthesia with ketamine-midazolam combination with and without prior administration of butorphanol or oxymorphine. *Am. J. Vet. Res.* 55: 543-550.

Jones, D.J., Stehling L.C and Zauder, H.L. 1979. Cardiovascular response to Diazepam and Midazolam maleate in the dog. *Anaesthesiol.* 51: 430-434.

Kanto, J., Sjovall, S. and Vrosi, A. 1982. Effect of different kinds of premedication on the induction properties of Midazolam. *Br. J. Anaesth.* 54: 507-511.

Kaur, A. and Singh, S.S. 2004. Clinical effects of midazolam-ketamine and midazolam-thiopentone anaesthesia in bovines. *Indian J. Vet. Surg.* 25: 80-82

Klide, A.M. 1976. Cardiopulmonary effects of enflurane and isoflurane in the dog. *Am. J. Vet. Res.* 37: 127-131.

Klide, A.M., Calderwood, H.W. and Soma, L.R. 1975. Cardiopulmonary effects of xylazine in dogs. *Am. J. Vet. Res.* 36: 931-935.

Ko, J.C.H. and Mc Grath, C.J. 1997. Using xylazine or thiopental to extend xylazine-buorphanol-glycopyrrolate sedation in dogs. *Vet. Med.* 99: 897-902.

Koc, Y., Alkan, F. and Kul, M. 2002. Effects of anaesthetic like combination of midazolam and xylazine on certain clinical parameters in dogs. *Indian Vet. J.* 79: 1281-1284.

Kolata, R.J. and Rawlings, C.A.1983.Cardiopulmonary effects of intravenous xylazine, ketamine and atropine in the dog. *J. Am. Vet. Med. Assoc.* 180: 2196-2198.

Lang, C.M. and White, W.J. 1976. Clinical Laboratory Methods in Physiologic Surgery and Basic Electrocardiography. In: *Animal Physiologic Surgery*. Springer-Verlag, New York, pp. 128-173.

Ludders JW.1992. Advantage and guide lines for using isoflurane. *Vet. Clin. North Am. Small Anim. Pract. 22:* 327-331.

Luna, S.P.L., Massone, F., Castro, G.B., Fantoni, D.T., Hussni, C.A. and Aguiar, A.J.A 1992. A combination of methotrimeparazine, midazolam and guaiphenesin with and without ketamine, in an anaesthetic procedure in horses. *Vet. Rec.* 131: 33-35.

Maddison, J.E., Page, S.W. and Church, D. 2002. *Small Animal Clinical Pharmacology*. W.B Saunders, London, pp.69-100.

Malik, V. and Singh, B. 2007. Clinical and Haematobiochemical studies on ketamine and its combinations with diazepam and xylazine for general anaesthesia in horses. *Indian J. Vet. Surg.* 28: 23-26.

Melvin, M.A., Johnson, B.H., Quasha, A.L. and Eger, E.I. 1982. Induction of anaesthesia with midazolam decreases halothane MAC in humans. *Anaesthesiol.* 57: 238-241.

Millar, R., Eisenksaft, J.B., Jaffe, D.H., Dimich, I., Thys, D.M. and Azers, A. 1980. Comparison of midazolam with thiopental for anaesthesia induction. Effect of innovar premedication. *Anaesthesiol. Rev.* 7: 21-27.

Mirakhur, R.K., Dundee, J.W. and Jones, C.J. 1978. Evaluation of the anticholinergic actions of glycopyrronium bromide. *Br. J. Clin. Pharmacol.* 5: 77-85.

Moens, Y. and Fargetton, X. 1990. A comparative study of medetomidine/ ketamine and xylazine/ketamine anaesthesia in dogs. *Vet. Rec.* 127:567-571.

Mohan, M.R. 2006. Comparative efficacy of xylazine and xylazine-ketamine premedication on propofol anaesthesia for Caesarean section in dogs. M.V.Sc. thesis. Kerala Agricultural University, Thrissur, 76p.

Moye, R.J., Pailet, A. and Smith, M.W. 1973. Clinical use of xylazine in dogs and cats. *Vet. Med.* 68 : 236-241.

Muir, W.W. and Piper, F.S. 1977. Effects of xylazine on indices of myocardial contractility in the dog. *Am. J. Vet. Res.* 38: 931-933.

Mutoh, T., Nishimura, R. and Sasaki, N. 2001. Effects of nitrous oxide on mask induction of anaesthesia with savoflurane or isoflurane in dogs. *Am. J. Vet. Res.* 62: 1727-1733.

Navarro, J.A. and Fiedman, J. R. 1975. A clinical evaluation of xylazine and ketamine for caesarean section in the dog. *Vet. Med. Small Anim. Clin.* : 1075-1079.

Nugent M, Artru A.A and Michenfelder.1982.Cerebral metabolic, vascular and protectiveeffects of midazolam maleate comparison to diazepam. *Anaesthesiol.* 56: 172-176.

Parsania, R.R., Radkod, D.M and Mannari.M.N.1977. Ketalar anaesthesia in dogs. *Indian Vet. J.* 54: 470-474.

Peshin, P.K., Kumar, A. and Singh, H.1980. Cardiovascular,respiratory and haematologic and sedative effects of xylazine in dogs. *Indian J. Vet. Surg.* 1:12-17.

Preiss, D. and Bergnson, P. 1983. Dose-response studies on glycopyrrolate and atropine in conscious cardiac patients. *Br. J. Clin. Pharmacol.* 16: 523-527.

Proakis A.G. and Harris G.B. 1978.Comparitive penetration of glycopyrrolate and atropine across blood brain and placental barrier in anaesthetized dogs. *Anaesthesiol.* 48; 339-344. Cited in: *Am. J. Vet. Res.* 2004, 65: 456-463.

Pypendop, B. and Verstegen, J. 1999. Cardio respiratory effects of a combination of meditomidine, midazolam and butorphanol in dogs. *Am. J. Vet. Res.*60: 1148-1154.

Raffe, R.M.1993. Fluid, electrolyte and acid base therapy in the surgical patients. In: *Text Book of Small Animal Surgery*, Vol.I (eds. Slatter, D.), W.B. Saunders Company, Philadelphia, pp. 11-18.

Rajankutty, K.1996. General anaesthesia in dogs with tiletamine-zolazepam. Ph.D, thesis. Kerala Agricultural University, Thrissur, 130p.

Ramaswamy, V., Balasubramanian, N.N, Gopal, M.S. and David, A. 1991. Studies on efficacy of ketamine hydrochloride as a general anaesthetic in combination with xylazine, diazepam and promazine in canines (quantitative changes). *Indian Vet. J.* 68: 548-551.

Robertson, S.A. and Moon, P.F. 2003. Anaesthetic management for Caesarean section in bitches. *Vet. Med.* 98: 675-694.

Schulman, J. 1981. Induction of anaesthesia in dogs: a viable alternative. *Canine Pract.* 8 : 53-55.

Sharma S.K., Kumar, A. and Singh, H.P.1983. Effects of xylazine on thiopentone sodium induced anaesthesia in dogs. *Indian J. Vet. Surg.* 4:34-40.

Shenoy, S. Kaul, H.L. and Muralidhar, V. 2002. Induction characteristics of midazolam and thiopentone-A comparison. *J. Anaesth. Clin. Pharmacol.* 15: 410.

Short C.E.1987. Anticholinergics. In: *Principles and Practice of Veterinary Anaesthesia.* (ed. Short, C.E.) Williams and Wilkins, Baltimore, USA, pp 8-15.

Snedecor, G.W. and Cochran, W.G. 1985. *Statistical Methods.* Eighth edition. The Iowa State University Press, Ames, 584 p.

Steagall, P.V.M., Neto, F.J.T., Minto, B.W., Campagnol, D. and Correa, M.A. 2006. Evaluation of the isoflurane-sparing effects of lidocaine and fentanyl during surgery in dogs. *J. Am. Vet. Med. Assoc.* 229: 522-527.

Steffey, E.P. 1996. Inhalation anaesthetics. In: *Lumb and Jones' Veterinary Anaesthesia,* (eds. Thurmon, J.C., Tranquilli, W.J, and Benson, G.J.) Third edition. Lea and Febiger, Philadelphia, pp.297-329.

Steffey, E.P. and Howland Jr., D. 1977. Isoflurane potency in dog and cat. *Am. J. Vet. Res.* 38: 1833-1836.

Steffey, E.P. and Howland Jr., D. 1980. Comparison of circulatory and respiratory effects of isoflurane and halothane anaesthesia in horses. *Am. J. Vet. Res.* 41: 831-825.

Steffey, E.P., Pascoe, P.J., Woliner, M.J. and Berryman, E.R. 2000. Effects of xylazine hydrochloride during isoflurane induced anaesthesia in horses. *Am. J. Vet. Res.* 61: 1225-1231.

Stephenson, J.C., Blevins, D.I. and Christie, G.J. 1978. Safety of Rompun/ Ketaset combination in dogs: a two year study. *Vet. Med. Small Anim. Clin.* 73: 303-306.

Thiruthalinathan R., Swaminathan D. and Panneerselvam, 1995. Comparison of ketamine and ketamine-xylazine combination anaesthesia in the wild canines under captivity. *J. Vet. Anim. Sci.* 26: 44-46.

Thurmon, J.C, Tranquilli, W.J, and Benson, G.J. 1996. Injectable anaesthetics. In: *Lumb and Jones' Veterinary Anaesthesia.* (eds. Thurmon, J.C, Tranquilli, W.J, and Benson, G.J.) Third edition. Lea and Febiger, Philadelphia, pp. 210-240.

Tiwari, S.K, Sharda, R. and Yadav, S.K.1994. Clinical and haemato biochemical response to ketamine with diazepam and xylazine premedication in dogs. *Indian Vet. J.* 71: 943-945.

Tranquilli, W.J. 2001. Anaesthesia for Caesarean section in the cat. *Vet. Clin. North. Am. Small Anim. Pract.* 31: 484-486

Tranquilli, W.J., Gross, M.E, Thurmon, J.C, and Benson, G.J. 1990. Evaluation of three midazolam-xylazine mixtures, preliminary trials in dogs. *Vet. Surg.* 19: 168-172.

Trim, C.M. and Gilroy, B.A. 1985. Cardiopulmonary effects of a xylazine and ketamine combination in pigs. *Res. Vet. Sci.* 38: 30-34.

Tyner, C.L., Greene, S.A. and Hartsfield, S.M. 1989. Cardiovascular effects of butorphenol administration in isoflurane –O2 anaesthetized healthy dogs. *Am. J. Vet. Res.* 50: 1340-1342.

Varghese, P. 2006. Clinical evaluation of the comparative efficacy of xylazine and xylazine-ketamine premedication in thiopentone anaesthesia in dogs. M.V.Sc. thesis. Kerala Agricultural University, Thrissur, 71p.

Wagner, A.E. and Bednarski R.M.1992. Use of low-flow and closed-system anaesthesia. *J. Am. Vet. Med. Assoc.* 2000:1005-1010.

Wallner, B.M., Hatch, R.C., Booth N.H., Kitzman, J.V., Clark, J.D. and Brown J. 1982. Complete immobility produced in dogs by xylazine-atropine: Antagonism by 4-aminopyridine and yohimbine. *Am. J. Vet. Res.* 43: 2259-2265.

Watney, G.C.G., Chambers, J.P. and Watkins, S.B. 1987. Anti muscarinic premedication in canine anaesthesia : A comparison of atropine, hyoscine and glycopyrrolate. *J. Small Anim. Pract* .28: 1087-1094.

Whitwam, J.G, Scorr, W.A.C., Kurimoto, S., Orchard, C. and Chakrabarthi, M.K. 1980. Cardiovascular effects of midazolam in the dog. *Br. J. Anaesth* 52:954p.

Wright, M. 1982. Pharmacologic effects of ketamine and its use in veterinary medicine. *J. Am. Vet. Med. Assoc.* 180: 1462-1471.

Yates, W.D. 1973. Clinical use of xylazine-A new drug for old problems. *Vet. Med. Small Anim. Clin.* 68: 483-484.

Zbinden, A.M., Thomson, D.A., Westensknow, D.R., Frei, F. and Maertens, J. 1988. Anaesthetic uptake and elimination: Is there a difference between halothane and isoflurane in the dog. *Br. J. Anaesth.* 60: 395-401.

MIDAZOLAM IN COMBINATION WITH GLYCOPYRROLATE AND XYLAZINE AS A PREANAESTHETIC FOR GENERAL ANAESTHESIA IN DOGS

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ABSTRACT

The anaesthetic study was conducted in 24 female dogs of different breeds subjected to elective surgical procedures (oopherectomies). They were randomly divided into four groups viz., I, II, III and IV, each consisting of six animals and were numbered serially from 1 to 6.

Animals of all the groups were administered intramuscularly, glycopyrrolate (0.011mg/kg body weight) followed by xylazine (1.0 mg/kg body weight) at 15 minutes interval. In addition, animals of Group III and IV were also administered intravenously midazolam (0.3 mg/kg body weight) 10 minutes after the administration of xylazine. Fifteen minutes after premedication to all animals ketamine hydrochloride (10 mg/kg body weight) was administered intramuscularly to effect anaesthesia and to the animals of Group II and IV, isoflurane was also administered for the maintenance of anaesthesia.

The common clinical signs manifested by the dogs after premedication with glycopyrrolate and xylazine were winking of eyes, yawning, inco-ordination of movement and assumption of sternal recumbency with head down posture. All the dogs were in lateral reccumbency following the administration of midazolam. The other symptoms noticed were vomiting, licking, urination and defecation. Salivation was scanty in all the dogs and the induction of anaesthesia was smooth in all the animals. Endotracheal intubation was easy in animals premedicated with midazolam.

During recovery vocalization was not observed in those animals premedicated with midazolam. All the animals had an uneventful recovery, though the dogs showed varying degree of dullness, which lasted for two to six hours. All the dogs had normal food intake from the next day onwards.

The induction time of anaesthesia in ketamine/ketamine-isoflurane combination was quicker in dogs premedicated with combination of glycopyrrolate-xylazine-midazolam than with glycopyrrolate-xylazine. The duration of anaesthesia was more or less similar, but prolonged with the supplementation of isoflurane.

The muscle relaxation time was prolonged with isoflurane maintenance. The degree of muscle relaxation during anaesthesia was good in animals premedicated with midazolam and excellent with isoflurane supplementation. The depth of anaesthesia achieved with a combination of xylazine-ketamine at the dose rate of 1 mg/kg and 10 mg/kg respectively was found not satisfactory for major surgical procedures like laparotomy. But it was satisfactory with midazolam premedication and good with the supplementation of isoflurane. The recovery time was prolonged in dogs in which midazolam was included for premedication.

A marginal decrease in rectal temperature, pulse rate and respiration rate was noticed after premedication and during anaesthesia in all the groups. The colour of mucous membrane was pale roseate throughout the observation. In both ketamine and ketamine –isoflurane anaesthesia, oxygen saturation level and blood coagulation time were increased. Significant increase in systolic, diastolic and mean blood pressures was noticed in all the groups.

Electrocardiogram revealed mild to moderate tachycardia following the administration of glycopyrrolate and sinoatrial block, sinoatrial arrest, ST segment depression/elevation, ST coving, increased R amplitude, peaked T wave and ventricular tachycardia following the administration of xylazine. All the abnormalities were observed for a short period of ketamine/ketamine-isoflurane anaesthesia and disappeared during recovery.

Significant decrease in haemoglobin concentration, volume of packed red cells and erythrocyte sedimentation rate, and marginal variations in total leukocytes and differential leukocyte counts were noticed after premedication, during anaesthesia and recovery in all the groups.

The variations in total protein, creatinine, blood urea nitrogen, aspartate amino transferase, alamine amino transferase, sodium, potassium and chloride parameters were within the normal physiological limits, but the increase in glucose concentration was significant. Arterial blood gas analysis revealed decreased pH with increased partial pressure of oxygen, partial pressure of carbon dioxide and marginal variations in bicarbonate level were observed during anaesthesia. All the dogs had the normal food intake from the next day onwards.