COMPARATIVE STUDY ON THE USE OF DIAZEPAM-KETAMINE AND MIDAZOLAM-KETAMINE AS INDUCTION AGENTS FOR BUTORPHANOL-ACEPROMAZINE-GLYCOPYROLLATE AS PREMEDICANT AND PROPOFOL AS MAINTENANCE IN DOGS

By

PURAM VINAY KUMAR
B.V.Sc & A.H
I.D. No. RVM/2016-53.

THESIS SUBMITTED TO
P.V. NARSIMHA RAO TELANGANA VETERINARY UNIVERSITY
IN PARTIAL FULFILMENT OF THE REQUIREMENTS
FOR THE AWARD OF THE DEGREE OF

MASTER OF VETERINARY SCIENCE

(VETERINARY SURGERY AND RADIOLOGY)

DEPARTMENT OF VETERINARY SURGERY AND RADIOLOGY
COLLEGE OF VETERINARY SCIENCE,
RAJENDRANAGAR, HYDERABAD-500030
OCTOBER - 2019

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CERTIFICATE

Dr. PURAM VINAY KUMAR (ID No. RVM/2016-53) has satisfactorily prosecuted the course of research and the thesis entitled **"COMPARATIVE STUDY ON THE USE OF DIAZEPAM-KETAMINE AND MIDAZOLAM-KETAMINE AS INDUCTION AGENTS FOR BUTORPHANOL-ACEPROMAZINE-GLYCOPYROLLATE AS PREMEDICANT AND PROPOFOL AS MAINTENANCE IN DOGS''** submitted is the result of original research work is of sufficiently high standard to warrant its presentation to the examination. I also certify that the thesis or part thereof has not been previously submitted by him for a degree of any university.

DATE: 03/10/2019

PLACE: HYDERABAD

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CERTIFICATE

This is to certify that the thesis entitled **"COMPARATIVE STUDY ON THE USE OF DIAZEPAM-KETAMINE AND MIDAZOLAM-KETAMINE AS INDUCTION AGENTS FOR BUTORPHANOL-ACEPROMAZINE-GLYCOPYROLLATE AS PREMEDICANT AND PROPOFOL AS MAINTENANCE IN DOGS"** submitted in partial fulfillment of the requirements for the degree of **MASTER OF VETERINARY SCIENCE (VETERINARY SURGERY AND RADIOLOGY)** of **P. V. Narsimha Rao Telangana Veterinary University, Hyderabad,** is a record of the bonafide research work carried out by **Dr. PURAM VINAY KUMAR** under our guidance and supervision. The subject of the thesis has been approved by the student's Advisory Committee.

No part of the thesis has been submitted by the student for any other degree or diploma. The published part has been fully acknowledged. All the assistance and help received during the course of investigation have been duly acknowledged by the author of the thesis.

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(PURAM VINAY KUMAR)

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DECLARATION

I, **PURAM VINAY KUMAR** (ID No. RVM/2016-53), hereby declare that the thesis entitled **"COMPARATIVE STUDY ON THE USE OF DIAZEPAM-KETAMINE AND MIDAZOLAM-KETAMINE AS INDUCTION AGENTS FOR BUTORPHANOL-ACEPROMAZINE-GLYCOPYROLLATE AS PREMEDICANT AND PROPOFOL AS MAINTENANCE IN DOGS"** submitted to P. V. Narsimha Rao Telangana Veterinary University for the degree of MASTER OF VETERINARY SCIENCE in VETERINARY SURGERY AND RADIOLOGY, is a result of original research work done by me. I also declare that the thesis or any part thereof has not been published earlier in any manner.

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ABSTRACT

The present study was carried out on twelve dogs aged between 4 months to 10 years presented for various surgical operations at the Department of Surgery and Radiology, College of Veterinary Science, Rajendranagar, Hyderabad. These dogs were randomly divided into two groups comprising of six animals in each group. All the dogs were uniformly premedicated with Butorphanol, Acepromazine and Glycopyrrolate (BAG) at dose rate of 0.2, 0.04 and 0.01 mg/kg body weight, respectively.

In the dogs of group I, fifteen minutes after premedication, anaesthesia was induced by slow intravenous injection of Diazepam at the rate of 0.28 mg/kg and Ketamine hydrochloride at the rate of 5 mg/kg body weight over a period of 60-90 seconds.

In the dogs of group II, fifteen minutes after premedication, anaesthesia was similarly induced with slow intravenous injection of Midazolam at the rate of 0.28 mg/kg and Ketamine at the rate of 5 mg/kg body weight over a period of 60-90 seconds.

Following induction of anaesthesia in both the groups of dogs, anaesthesia was maintained with intravenous administration of Propofol at the rate of 0.5-2.0 mg/kg body weight. Incremental doses of Propofol were administered "to effect" whenever required during the surgical procedure through the intravenous life line.

The anaesthetic effects like induction of anaesthesia, duration of anaesthesia and recovery time and physiological parameters like rectal temperature, heart rate, respiratory rate, haematological parameters like TEC, Hb, PCV, TLC, DLC, biochemical parameters like AST, ALT, BUN, serum creatinine and electrocardiographic changes were recorded.

The results of the present study indicated that all the dogs showed moderate to profound signs of sedation without any complications. Preanaesthetic combination Butorphanol, Acepromazine and Glycopyrrolate (BAG) nullified side effects of each other and provided excellent analgesic, sedative and antisialogauge effects.

The time to induction and or endotracheal intubation in dogs anaesthetized with Midazolam-Ketamine (group II) was significantly shorter than for those anaesthetized with Diazepam-Ketamine (group I). Induction quality was considered good to fair with Diazepam-Ketamine combination. Induction was good in all the dogs after Midazolam-Ketamine combination.

In the dogs of group I, where Diazepam-Ketamine were used as induction agents, the recovery time was found to be shorter (128.83 ± 2.43 minutes) when compared to the recovery time (205.00 ± 5.97 minutes) resulting from Midazolam-Ketamine (group II). Recovery score was found to be 4 (gradual, smooth, quiet, rapid,

comfortable) in all the dogs of group I, whereas recovery score was 3 (gradual, slow, moderate, restless) in all the dogs induced with Midazolam-Ketamine (group II). This indicated that induction with Diazepam-Ketamine was better than Midazolam-Ketamine as far as the recovery of anaesthesia was concerned.

As far as the physiological parameters were concerned, the results showed that there was a significant decrease in rectal temperatures between the dogs of group I compared to group II at 15 min after premedication, 10, 15, 20, 25, 35, 45 and 60 minutes after induction of anaesthesia. The temperature decreased gradually in both the groups and lowest value of temperature was found at 90 minutes after induction of anaesthesia.

Although the heart rates between the groups were found to differ from each other, they were still well within the normal range and hence were considered in consequential. The respiratory rates also fluctuated within normal physiological limits with a significant difference between the groups at 5, 10, 25 and 35 minutes after induction of anaesthesia. The respiratory rate decreased gradually after premedication and remained low than that recorded prior to premedication in both the groups. The respiratory rate returned to normal as the dogs recovered from anaesthesia. Since these parameters caused no complications and as they returned to normalcy soon, the changes were considered to be clinically acceptable.

Haematological examination revealed that there were no significant differences in the various parameters like TEC, Hb, PCV, TLC and DLC in any of the two groups. This underscored the fact that all the anaesthetic protocols studied were safe and uneventful as far as these observations were concerned.

The results of the present clinical study clearly revealed in all the dogs of the two groups that the various biochemical parameters studied, i.e., AST, ALT, BUN and

serum creatinine remained within normal limits. Hence, this also conclusively proved that the two anaesthetic protocols studied were safe and did not result in any damage to the liver and kidneys during the anaesthetic period.

Electrocardiographic studies in the dogs of both the groups revealed no abnormalities in the sizes of P, QRS or T- waves, no changes in the cardiac axes and no arrhythmias of any kind in any dog of any of the groups.

From the results of the present study, it was concluded that both the anaesthetic protocols produced satisfactory deep surgical anaesthesia in dogs. Butorphanol, Acepromazine and Glycopyrrolate nullified side effects of each other and provided excellent analgesic, sedative and antisialogauge effects to be an effective premedicant combination. Midazolam found to be superior to Diazepam as an induction agent given in combination with Ketamine. Recovery was rapid, smooth and uneventful in Diazepam-Ketamine induction and Propofol maintenance in comparison to Midazolam-Ketamine anaesthesia. None of the anaesthetic combinations produced adverse effects on various physiological, haematological, biochemical and electrocardiographic parameters.

LIST OF ABBREVIATIONS

CNS	Central Nervous System
IV	Intravenous
IM	Intramuscular
SC	Subcutaneous
HCL	Hydrochloride
TIVA	Total intravenous anaesthesia
BAG	Butorphanol, Acepromazine and Glycopyrrolate
ACP	Acepromazine
DK	Diazepam-Ketamine
MK	Midazolam-Ketamine
TEC	Total Erythrocyte Count
TLC	Total Leucocyte Count
Hb	Hemoglobin
PCV	Packed Cell Volume
AST	Serum Aspartate Aminotransferase
ALT	Serum Alanine Aminotransferase
BUN	Blood Urea Nitrogen
C	Serum Creatinine
RT	Rectal Temperature
HR	Heart Rate
RR	Respiratory Rate
EDTA	Ethylenediaminetetraacetic Acid
GABA	Gamma-Aminobutyric Acid
b.wt.	Body Weight
%	Percentage

μL	Microlitre
mg/kg	Milligram/kilogram
mg/kg/min	Milligram/kilogram/minute
mg/dL	Milligram/deciliter
%	Percentage
°F	Degree Fahrenheit
±	Standard Error (SE)
Fig.	Figure
≤	Less than or equal to

CHAPTER- I

INTRODUCTION

The majority of small animal patients are routinely premedicated as part of the anaesthetic protocol, yet the importance of preanaesthetic medication in the whole process of anaesthesia is often forgotten. The choice of drugs will have a major impact on the characteristics of the ensuing general anaesthetic. The appropriate selection of premedicant drugs can significantly contribute to perioperative analgesia, intraoperative cardiovascular stability and quality of recovery (Duke-Novakovski *et al*., 2016).

An ideal general anaesthetic should provide satisfactory duration of anaesthesia with small quantity of drug, excellent muscle relaxation, exert minimum depression on heart and lungs and ensure rapid safe recovery. Since one drug doesn't have all the characteristics expected of a general anaesthetic drug, it is always necessary to administer a combination of two or more drugs as balanced anaesthesia for achieving satisfactory depth of anaesthesia in canine practice. Injectable, intravenous (IV) and intramuscular (IM) anaesthetic drugs can be used to induce immobilization and general anaesthesia. Proper use of preanaesthetic medication (tranquilizers, sedatives, analgesics etc.) is imperative to produce the optimal desired effect with minimal side effects (Muir and Hubbell, 2014).

In the recent years, intravenous anaesthetics are increasingly being used as alternatives to inhalation anesthetic agents. Inhalant anesthetics require an expensive anaesthetic machine and more trained personnel. The intravenous agents carry a lesser

chance of causing cardiovascular and respiratory depression than the inhalation anaesthetics. Total intravenous anaesthesia (TIVA) may be defined as a technique of general anaesthesia in which induction and maintenance of anaesthesia produced with drugs given only by intravenous route and in absence of all inhalation agents including nitrous oxide (Campbell *et al.,* 2003; Dewangan and Tiwari, 2013).

For longer periods of anaesthesia, intravenous anaesthetics may be given by intermittent injections or by continuous infusion. Use of a combination of anaesthetic agents with different mechanisms of action, offers the benefit of using lower doses of individual agents that produce sufficient anaesthesia, while reducing the possibility of risks associated with over dosage (Ibrahim, 2017) thereby rendering it safe.

Towards this end, several induction agents have been used in veterinary anaesthesia. However, Diazepam-Ketamine (Al-Redah, 2011; Ferreira *et al.,* 2015; Yohannes *et al.,* 2018) and Midazolam-Ketamine (Al-Redah, 2011; Abdel-Hady *et al.,* 2017) are some of induction agents employed in canine practice.

Review of literature yielded scanty information and limited reports on Diazepam-Ketamine and Midazolam-Ketamine as induction agents for Butorphanol-Acepromazine-Glycopyrollate (BAG) as premedicant and Propofol as maintenance agent in dogs. Therefore, the present clinical study comparing Diazepam-Ketamine and Midazolam-Ketamine as induction agents preceded by BAG as premedicant was taken up in 12 dogs divided in two groups. Anaesthetic maintenance was carried out in both groups with Propofol.

The objectives of the study were:

1. To study the various anaesthetic parameters in dogs premedicated with BAG (Butorphanol, Acepromazine and Glycopyrrolate), induced with Diazepam-Ketamine versus Midazolam-Ketamine and maintained with Propofol in dogs.

2. To study the physiological, hematological, biochemical and electrocardiographic changes during and after anaesthesia.

3. To evaluate anaesthetic efficacy and safety of the two anaesthetic protocols in dogs.

CHAPTER- II

REVIEW OF LITERATURE

2.1 PREANAESTHETICS

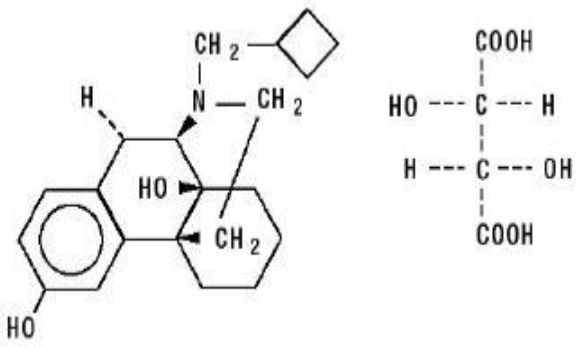
2.1.1 Butorphanol

2.1.1.1 Introduction

Butorphanol is a central-acting analgesic with both narcotic agonist and antagonist properties like μ-receptor antagonist and κ-receptor agonist. It is a morphine derivatives and is chemically 1-N cyclobutyl methyl-6, 10αβ-dihydroxy-1, 2, 3, 9, 10,10α-hexahydro-(4H) 10,4α-imino ethano-phenanthrene tartare. The molecular formula is $C_{21}H_{29}NO_2C_4H_6O$ (Evans *et al.,* 1985; Clarke and Trim, 2014).

Butorphanol tartrate is a synthetic opiate partial agonist and structurally related to morphine but exhibits pharmacologic actions alike other partial agonists such as pentazocine or nalbuphine (Plumb, 2018).

Butorphanol is a synthetic analgesic which is 3 to 5 times potent than morphine (Pircio *et al.,* 1976). It is a widely used and potent analgesic with lower, though still significant, abuse potential than morphine and fentanyl. It is about 50 times less potent than naloxone (Evans *et al.,* 1985).



The injectable product is reported to be compatible with the following IV fluids and drugs: acepromazine, atropine sulfate, glycopyrrolate, chlorpromazine, morphine sulfate, pentazocine lactate, and xylazine. The drug is reportedly incompatible with pentobarbital sodium (Plumb, 2018).

The respiratory depressant effects of butorphanol are less than those of morphine. Respiratory depression appears to reach a "ceiling" beyond which higher doses do not produce an appreciably greater depression. The ceiling effect will also be observed when it is used for its analgesic properties (Roebel *et al*., 1977). It does not produce any significant changes in bile flow, whereas morphine produces a dose-related significant decrease. When injected IM (0.5 mg/kg), butorphanol produce mild sedation in dogs and no changes in blood histamine concentrations (Pircio *etal.,* 1976).

The drug has also been shown to be completely absorbed following IM administration. Following IV doses in horses, the onset of action is approximately 3 minutes with a peak analgesic effect at 15-30 minutes. The duration of action in horses may be up to 4 hours after a single dose (Plumb, 2018). Analgesia should last 45 min to 1.5 h in the dog and more than twice as long in cats (Sawyer and Rech, 1987).

The injection preparation of butorphanol tartrate is available in concentration of 2 mg/ml or 10 mg/ml in a buffered solution (pH 3.5 to 5.5) (Wells, 2008).

2.1.1.2 Mode of action

Butorphanol, like other opioids, exerts its pharmacologic effects by the interaction with the opioid receptors found in the body (Branson *et al.,* 2001; Boothe, 2001).

Most of the actions of morphine-like drugs seem to be mediated through the μ (mu) opioid receptor (Branson *et al.,*2001). There are two subtypes of mu receptors that are responsible for analgesia and sedation: μ (mu) 1-receptors that act above the level of the spinal cord, and μ (mu) 2-receptors that act within the spinal cord. μ (mu) 2-receptors are also thought to be responsible for respiratory depression and suppression of gastrointestinal motility (Branson *et al.,* 2001). The kappa opioid receptor is involved in spinal and supraspinal analgesia, miosis, and sedation. Butorphanol is an opioid agonist-antagonist that exhibits agonist effects at kappa receptor sites, and antagonist effects at mu receptors (Boothe, 2001).

2.1.1.3 Therapeutic effects

Butorphanol is commonly used in veterinary medicine as a preanesthetic and perioperative analgesic agent in cats and dogs (Branson *et al.*, 2001; Boothe, 2001). It is also used as an antitussive, an antiemetic prior to cisplatin treatment, and for the control of post-operative pain in small animals (Boothe, 2001).

In horses, butorphanol is commonly used as an analgesic, and after xylazine, is the next best drug at controlling visceral pain. Butorphanol can also be used to partially reverse the sedative or respiratory depressant effects caused by oxymorphone, a pure opioid agonist (Reisine *et al.*, 1996; Troncy *et al.*, 1996).

Murphy and Hug (1981) found that butorphanol @ 0.1 to 0.3 mg/kg IV reduced enflurane MAC in dogs but higher doses did not further reduce MAC. Butorphanol has been studied extensively given IM, IV, and SC alone following halothane anesthesia (Houghton *et al.,* 1991).

Butorphanol used successfully in patients with hepatic disease despite certain pharmacological consequences (decreased clearance and prolonged half-life) (Gelman, 2008).

2.1.1.4 Side effects

High dose of butorphanol (5 to 30 mg/kg subcutaneously) produce a dose-related diuretic response associated with decreased urinary excretion of antidiuretic hormone (Miller, 1975). Animals with the stomach or esophageal obstruction have a great risk of vomition so opioids are contraindicated in such cases however mixed opioids like butorphanol rarely causes vomiting (Dyson, 2002).

All opiates should be used with caution in patients with hypothyroidism, severe renal insufficiency, and adrenocortical insufficiency and in geriatric or severely debilitated patients. Like other opiates, butorphanol must be used with extreme caution inpatients with head trauma, increased CSF pressure or other CNS dysfunction (e.g., coma) (Plumb, 2018).

Butorphanol is, in general, a very safe drug with a greater margin of safety than morphine. As such, risk of acute overdose or toxicity with butorphanol is low (Troncy *et al.,* 1996). Toxicity studies have indicated the LD_{50} in dogs following oral administration to be greater than 50 mg/kg. Clinical signs of butorphanol intoxication include CNS depression, cardiovascular changes and respiratory depression (Hosgood, 1990).

2.1.2 Acepromazine

2.1.2.1 Introduction

Acepromazine or acetyl promazine, the 2-acetyl derivative of promazine, a phenothiazine compound is one of the most commonly used tranquilizers in veterinary surgery, which acts on the CNS by depressing the brain stem and connections to the cerebral cortex (Dyson, 2002). Its tranquillizing properties make it a common choice of premedicant for anaesthesia in the dog. It has been in veterinary use since the early 1960's.

Phenothiazine derivatives are classed as neuroleptics due to both their tranquillizing effects and their ability to modify psychotic behaviors in humans (Gross, 2001).Acepromazine has been mixed with atropine, buprenorphine, chloral hydrate, ketamine, meperidine, oxymorphone, xylazine and glycopyrrolate. Diazepam have been reported to be physically incompatible with phenothiazine (Plumb, 2018).

2.1.2.2 Mode of action

Acepromazine is a phenothiazine neuroleptic agent. While the exact mechanisms of action are not fully understood, the phenothiazines block post-synaptic dopamine receptors in the CNS and may also inhibit the release and increase the turnover rate of dopamine (Plumb, 2018).So brain stem activity is depressed, as are the connections to the cerebral cortex (Pugh, 1964; Gross, 2001). In the periphery, catecholamine function, most specifically adrenergic function, is blocked by ACP and other phenothiazines. This property elicits most of the cardiovascular side-effects of ACP.

2.1.2.3 Therapeutic effects

Therapeutic effects include changes to the skin of the face, with looser, wrinkled skin over the frontal bones, drooping of the upper eyelid and protrusion of the nictitating membrane, “Voluntary” recumbency follows signs of posterior in-coordination. Dogs become more amenable to handling. These effects to be appear after 3-4hr of drug administration (Pugh, 1964).

Pugh (1964) reported acepromazine as a highly potent and effective preanaesthetic sedative prior to thiopental sodium anaesthesia and it reduces 48.3 % dose of thiopental in canines.

Intramuscular doses used for producing tranquillization in dogs vary from 0.04mg/kg to 1.0mg/kg (Popovic *et al.,* 1972). Lower doses have gained popularity in more recent times, particularly in combination with other drugs. The length of action is dose dependent but can be prolonged. Clinically sedation effect lasts 4–6 hours after doses of 0.02 mg/kg (Clarke and Trim, 2014).

The use of ACP alone decreases anaesthetic requirements both for induction and maintenance such as thiopental and inhalants like halothane (Raiha *et al.,* 1989), with a 0.04mg/kg IM dose decreasing the halothane MAC by 46%.

ACP also acts as an anti-emetic (Valverde *et al.,* 2004), and is effective in raising the threshold for catecholamine-induced ventricular fibrillation in dogs anaesthetized with thiamylal and halothane (Muir *et al.,* 1975).

Geel (1991) evaluated that effect of premedication on the induction dose of propofol was determined in 15 cats and 25 dogs undergoing elective surgical procedures. The induction dose of propofol in dogs younger than 8 years old was 6.9 ±

0.9 mg/kg (n=4) without premedication and 4.3 ± 1.4 mg/kg (n=12) with premedication with acetylpromazine malate.

Lighta *et al.* (1993) stated that acepromazine appears to be more effective than oxymorphone in decreasing anxiety behaviors in dogs.

Fantoni *et al.* (1999) reported the sedative effect of acepromazine in canines and concluded that acepromazine has minimal adverse effects on cardiorespiratory system. Additionally, phenothiazines have varying degrees of anticholinergic, antihistaminic, antispasmodic, and alpha-adrenergic blocking effects. The primary desired effect for the use of acepromazine in veterinary medicine is its tranquilizing action (Plumb, 2018).

Gross (2001) studied the effects of ACP used in combination with various opioids, a combination known as neuroleptanalgesia such opioids include oxymorphone and butorphanol. As acepromizine alone lacks analgesic effect, these combinations provide analgesia and longer duration of action at low level of ACP (Barnhart *et al.*, 2000).

Valverde *et al.* (2004) evaluated effects of acepromazine on the incidence of vomiting associated with opioid administration in 116 dogs (ASA I or II), admitted for elective surgical procedures. The dogs were a mixed population of males and females, pure breeds and mixed breeds, 0.25–13.4 years of age, weighing 1.8–57.7 kg. A prospective clinical trial in which the dogs were randomly assigned to one of three groups. All groups received acepromazine (0.05 mg/kg, IM). Group I received acepromazine 15 minutes prior to opioid administration. Group II received acepromazine in combination with the opioid. Group III received acepromazine 15 minutes after opioid administration. One of three different opioids was administered IM to each dog; morphine sulfate at 0.5 mg/kg, hydromorphone hydrochloride at 0.1 mg/kg, or oxymorphone hydrochloride at 0.075 mg/kg. Dogs receiving acepromazine

before the opioid (group I) had a significantly lower incidence of vomiting (18%) than dogs in groups II (45%) and III (55%). The degree of sedation was significantly lower in the dogs receiving the combination of acepromazine and the opioid (group II) than in dogs receiving the opioid as the first drug (group III). Acepromazine administered 15 minutes before the opioid lowers the incidence of vomiting induced by opioids.

Tobias *et al.* (2006) used acepromazine (i.e., acetylpromazine) maleate in dogs with a history of seizures is reportedly contraindicated because of the risk of decreasing the seizure threshold in these animals. In this retrospective study, acepromazine was administered for tranquilization to 36 dogs with a prior history of seizures and to decrease seizure activity in 11 dogs. No seizures were seen within 16 hours of acepromazine administration in 36 dogs that received the drug for tranquilization during hospitalization. After acepromazine administration, seizures abated for 1.5 to 8 hours (n=6) or did not recur (n=2) in eight of 10 dogs that were actively seizing. Excitement-induced seizure frequency was reduced for 2 months in one dog. Acepromazine (ACP) provides moderate sedation via antidopaminergic effects and animals may require lower dosages of general anesthetics following acepromazine (Posner, 2007).

Khan *et al.* (2007) studied effect of acepromazine as preanaesthetic given @ 0.2 mg/kg b.wt. IV, 10 minutes prior to propofol anaesthesia @ 5 mg/ kg b.wt. in six dogs. Haematological and biochemical parameters were evaluated. A significant increase in haematological parameters, viz., TLC, TEC, Hb and platelet count and a non-significant decrease in PCV were also observed. A significant increase in blood glucose concentration was recorded where as no changes in the other biochemical parameters, i.e., SGPT, SGOT, BUN and serum creatinine was observed. A significant increase in blood glucose concentration was recorded where as no change in the other biochemical parameters, i.e., SGPT, SGOT, BUN and serum creatinine were observed.

According to Senior (2007) in a recent extensive epidemiological study into peri-anaesthetic deaths in small animals in the UK, acepromazine was shown to reduce the risk of death during anaesthesia from cardiovascular causes. There are several possible reasons for the apparent protective effect of ACP on the cardiovascular system. ACP reduces the required amount of volatile agents and may lead to a reduction of myocardial sensitivity to catecholamines and a reduction of baroreflex induced vagal tone. Perhaps most importantly, the peripheral vasodilation caused by ACP, reduces after load on the heart, the resultant decrease in myocardial workload on the heart may be important during anaesthesia. It should be stressed that ACP should still be used with caution in certain cases like brachycephalic breeds, hypotensive/ hypovolaemic and exicted animals.

Pottie *et al.* (2008) studied that premedication with acepromazine decreased the dose requirement and time to induction for dogs induced with propofol, but did not significantly change the time to intubation for inhalant inductions.

Acepromazine has no analgesic properties by itself, and it is frequently given in combination with opioids to produce neuroleptanalgesia, a state characterized by sedation and analgesia (Grimm, *et al.,* 2015).

2.1.2.4 Side effects

Popovic *et al.* (1972) studied the effect of acepromazine and recorded decrease the arterial blood pressure, intermittent bradycardia and decrease in respiratory rate in dogs. Due primarily to its adrenergic antagonist action, ACP causes vasodilation and subsequent hypotension in the dog. Doses of up to 1.1mg/kg intravenously or intramuscularly produced approximately a 15% decrease in MAP over 2hr.

Turner *et al.* (1974) observed tachycardia in dogs, five minutes after administration of acepromazine. Further, they attributed the greater popularity of acepromazine to its higher potency, fewer side effects and rapid onset of action. Intramuscular doses of 0.11mg/kg caused decreases of approximately 20% in mean arterial pressure (MAP).

Stephien *et al.* (1995) observed depression of cardiac function, respiratory rate and mean systolic arterial pressure without any change in heart rate following acepromazine injection. In dogs, acepromazine effects may be individually variable and breed dependent. In geriatric patients, very low doses have been associated with prolonged effects of the drug. Giant breeds and greyhounds may be extremely sensitive to the drug, while terrier breeds are somewhat resistant to its effects. Boxers are reported to very sensitive to the hypotensive and bradycardic effects of acepromazine and should be used cautiously and in small doses in these breed. Atropine is often suggested to be given with acepromazine to help negate its bradycardic effects. A dose dependent decrease in hematocrit is seen within 30 minutes after dosing in the horse and the dog. Besides a lowering of arterial blood pressure in the dog, acepromazine causes an increase in central venous pressure, a vagally induced bradycardia effect and transient sinoatrial arrest (Plumb, 2018).

A combination of acepromazine with butorphanol reflected similar decreases in MAP as a measure of cardiovascular function (Kojima *et al.,* 1999). However, other studies have shown no significant changes in MAP after doses in combination with butorphanol or oxymorphone (Cornick and Hartsfield, 1992). Heart rate may decrease mildly when using ACP (Kojima *et al.*, 1999).

Stephan *et al.* (2003) reported that hydromorphone (0.04-0.08 mg/kg) and acepromazine (0.04 mg/kg) caused significant miosis at 10 and 25 min. following intramuscular administration in clinically healthy dogs.

They are thought to depress portions of the reticular activating system which assists in the control of body temperature, basal metabolic rate, emesis, vasomotor tone, hormonal balance, and alertness (Plumb, 2018).

ACP undergoes extensive liver metabolism and is long acting (6–12 hours) and liver disease/shunting can make for a prolonged recovery. ACP causes mild respiratory depression and inhibits platelet function (decreases platelet aggregation). ACP provides no analgesia, but can potentiate other analgesics (eg, opioids). Acepromazine should be avoided in patients with hypotension, hypovolemia, shock, significant heart disease, liver disease or coagulopathy/platelet disease (Posner, 2007).

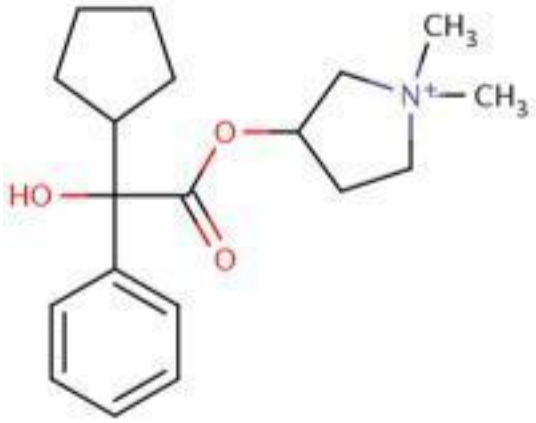
Acepromazine has a slow onset of effect (~20 minutes), but a long duration of action (3–6 hours), therefore prolonged recovery may occur, especially with a hepatic dysfunctional or aged patient. Acepromazine has a vasodilation and antithermoregulation effect, resulting in hypotension and hypothermia (Ko, 2013). Decreased systemic vascular resistance and blood pressure are the main adverse effects of acepromazine usage. Hematologic effects of acepromazine administration include decreased packed cell volume (PCV) and a reduction of platelet aggregation (Grimm *et al.*, 2015).

2.1.3 Glycopyrrolate

2.1.3.1 Introduction

Glycopyrrolate is a synthetic quarternary ammonium anticholinergic compound (Mirakhur and Dundee, 1983). Anticholinergics are used predominantly in veterinary

anesthesia to treat and prevent vagally-induced bradycardia, as well as to reduce excessive salivation during anesthesia (Clarke *et al.*, 1990; Short, 1986).



The antisialagogue effect of these drugs is not a significant advantage, since excessive salivation is not a significant complication in modern day anesthesia of dogs. Unnecessary routine use of anticholinergic drugs is not advised due to the potential production of an excessive tachycardia, associated increase in oxygen demand, and potential for dysarrhythmias (Dyson and James-Davies, 1999).

The following drugs are reportedly physically compatible with glycopyrrolate: atropine sulfate, butorphanol, acepromazine, chlorpromazine HCl, fentanyl, hydromorphone, lidocaine HCl, meperidine HCl, morphine sulfate and oxymorphone HCl. The following drugs are reportedly incompatible with glycopyrrolate: dexamethasone sodium phosphate, diazepam, methyl prednisolone sodium succinate, pentazocine lactate, pentobarbital sodium and thiopental sodium (Plumb, 2018).

2.1.3.2 Mode of action

Like other anticholinergic, glycopyrrolate antagonizes the muscarinic action of acetylcholine by competitively binding to the autonornic effector cell receptors innervated by postganglionic cholinergic nerves (Stoeltling, 1991).

Glycopyrrolate has been found to be more selective in the ratio of ganglion blocking to antimuscarinic activity because of the drugs greater nicotinic activity (Brown, 1990).

In veterinary patients the effects of glycopyrrolate are evident within 1 to 5 minutes after intravenous administration and within 30 to 35 minutes after subcutaneous or intramuscular administration. Following intravenous administration, the vagal blocking effect persists for 2 to 3 hours and the antisialogue effect persists for up to seven hours (Grimm *et al.,* 2015).

2.1.3.3 Therapeutic effects

In dogs, cats and horses, glycopyrrolate was also noted to produce a more stable and gradual increase in heart rate after induction and during maintenance of general anesthesia (Short, 1991; Short *et al.,* 1978).

The antisialogue effect of glycopyrrolate has been shown to be greater than atropine in humans (Mirakhur *et al.,* l983) and dogs (Watney *et al.* 1987).

Glycopyrrolate may be given IM, IV, or SC to dogs at a dose of 0.005 to 0.011 mg/kg of bodyweight (Grimm *et al.,* 2015). In dogs, doses higher than 0.011 mg/kg did not produce greater cardiovascular and antisialogue effects (Short and Miller, 1978). The effective dose of glycopyrrolate has been associated with the size and metabolic rate of the animal (Dyson *et al.,* 1999). Smaller dogs (<10 kg) required higher dosages of glycopyrrolate (0.0 1 mg/kg) to significantly increase HR, versus larger dogs (>10 kg) where in lower dosages (0.005 mg/kg) still significantly increased HR.

Watney *et al*. (1987) evaluated that glycopyrrolate is superior to atropine for the prevention as well as treatment of bradycardia due to it's longer duration of action and fewer fluctuations in HR.

2.1.3.4 Side effects

As an anticholinergic agent, it has among other properties the ability to cause dryness of the mouth and pharynx. It appears to be free from side effects. Glycopyrrolate was associated with fewer complications than atropine and appeared to be equally effective to atropine in preventing bradycardia in various trials in dogs (Short, 1991).

Dyson *et al.* (1999) observed an appreciable increase in blood pressure with glycopyrrolate administration in bradycardic anesthetized horses and dogs. The increase in blood pressure is attributed to an increase in CO secondary to the increase in HR. The vasoconstriction produced with α2-agonists in addition to the improvernent in CO accounts for more drastic increase in blood pressure, which may not be physiologically beneficial in conjunction with other α2-agonist cardiovascular effects.

In dogs, the LD_{50} for glycopyrrolate is reported to be 25 mg/kg IV. Doses of 2 mg/kg IV daily for 5 days per week for 4 weeks demonstrated no signs of toxicity. Because of its quaternary structure, it would be expected that minimal CNS effects would occur after an overdose of glycopyrrolate when compared to atropine (Plumb, 2018).

2.1.4 Combination of Butorphanol and Acepromazine

Dyson and Atilola (1992) administered butorphanol (0.2 mg/kg, maximum 4.5 mg) with acepromazine (0.05 mg/kg) intravenously to dogs undergoing radiological examination of the pelvis and evaluated a lower incidence of temporary excitement and less panting in dogs sedated with butorphanol than with oxymorphone. There were no

significant differences in degree of sedation, response to noise or manipulation, vocalization, defecation, heart rate, reversibility, sedation after reversal.

Bufalari *et al.* (1997) evaluated cardiovascular, pulmonary and anaesthetic-analgesic responses in 18 male and female dogs to determine the effect of the injectable anaesthetic propofol used in conjuction with acepromazine and butorphanol. Significant respiratory depression and decreased arterial blood pressure were seen after propofol induction in dogs receiving butorphanol with or without acepromazine.The anaesthetic duration and recovery times were longer in dogs premedicated with acepromazine - butorphanol.

Kojima *et al.* (1998) studied sedative effects of medetomidine-midazolam, acepromazine-butorphanol and midazolam-butorphanol in dogs with dose rate of medetomidine at 20 μg/kg and midazolam at 0.3 mg/kg (MM), acepromazine at 0.05mg/kg and butorphanol at 0.2 mg/kg (AB) and midazolam at 0.1 mg/kg and butorphanol at 0.2 mg/kg (MB). Six of seven dogs given AB were laterally recumbent within 16 min of the administration of the drugs, and this combination induced relatively deep sedation but only a mild depression of arousal reactions to external stimuli. MB induced mild or moderate sedation with relatively large differences in effects among individuals. The recovery from sedation in each group was smooth and total recovery times were not significantly different.

Mutoh *et al.* (2002) characterized the effects of medetomidine-midazolam, midazolam-butorphanol, or acepromazine-butorphanol as premedicants for mask induction of anesthesia with sevoflurane in dogs. Mask induction with sevoflurane in dogs that received each premedicant resulted in a shorter induction time and milder changes in heart rate, mean arterial blood pressure, cardiac output, and respiratory rate,

compared with mask induction without premedicants. The use of premedicants provides a smoother and better quality mask induction with sevoflurane.

Tobias *et al*. (2004) premedicated the dogs with acepromazine and butorphanol, and a light plane of anesthesia was induced with isoflurane by mask to compare the effects of IV doxapram on glottic size and arytenoid motion in normal dogs and in dogs with laryngeal paralysis. A geater degree of sedation, calmness was noticed in all the dogs administered with butorphanol, acepromazine and glycopyrrolate as preanesthetics (Pramodh and Mohindroo, 2010).

2.1.5 Combination of Butorphanol, Acepromazine and Glycopyrrolate (BAG)

Butorphanol, acepromazine and glycopyrrolate may be mixed together in a multiple dose bottle as follows: combine 4 ml of butorphanol, 0.5 ml of acepromazine (10 mg/ml), 5 ml of glycopyrrolate and balance sterile water or saline to provide a 20 ml mixture of BAG. Atropine may be substituted for glycopyrrolate. This combination should be given as preanaesthetic medication in the cat or dog at a dose of 0.1 ml/kg IM or SC 20 to 30 min prior to induction. For older animals or dogs over 40 kg, only 0.25 ml of acepromazine is used in the mixture (Sawyer, 1982).

Lemke *et al*. (2002) premedicated the dogs with glycopyrrolate, acepromazine, and butorphanol and anesthetized with thiopental; anesthesia was maintained with isoflurane to determine the effects of preoperative administration of ketoprofen on anesthetic requirements and signs of postoperative pain in dogs undergoing electiveovariohysterectomy**.**

Campbell *et al*. (2003) anesthetized the dogs with acepromazine, glycopyrrolate, thiopental and isoflurane to determine frequency and severity of post-anesthetic hypoxemia and hypercarbia in healthy dogs undergoing elective ovariohysterectomy or

castration and butorphanol (n=10) or hydromorphone (n=10) was used for perioperative analgesia.

Yadav *et al.* (2006) used combination of butorphanol, acepromazine and glycopyrrolate as 0.2 mg/kg, 0.1 mg/kg and 0.01 mg/kg body weight, respectively mixed in a single syringe as IM for preanaesthesia 20 minute before induction for static intramedullary interlocking nail for the management of complicated femur fractures in dogs. All dogs were induced with 5% thiopental sodium given to effect and maintained with 2% halothane and oxygen by closed circuit method.

Roon *et al.* (2007) evaluated sedative effect of BAG- butorphanol, acepromazine HCL and glycopyrrolate @ 0.1, 0.1 and 0.01 mg/kg b.wt. respectively as a combination in one syringe and administered IV. Induction was done using diazepam @ 0.5 mg/kg b.wt. and ketamine HCL @ 2 mg/kg b.wt. mixture given IV about 5 min. after premedication with BAG. All animals showed profound sedation without any complications. Physiological (heart rate, respiration rate and rectal temperature) and clinical studies (onset of sedation, duration, onset of recovery, complete recovery time) showed advantage of BAG as a premedication to provide additional postoperative analgesia along with significant reduction in dosage of diazepam-ketamine for induction.

Raghunath and Singh (2008) used combination of butorphanol, acepromazine and glycopyrrolate as 0.2 mg/kg, 0.05 mg/kg and 0.01 mg/kg body weight, respectively for preanaesthesia. Induction of dogs were performed with 5% thiopentone sodium administered IV “till effect” and maintained on 1-2 % halothane with oxygen using Boyle’s apparatus for intramedullary interlocking nailing for management of long bone diaphyseal fractures in dogs.

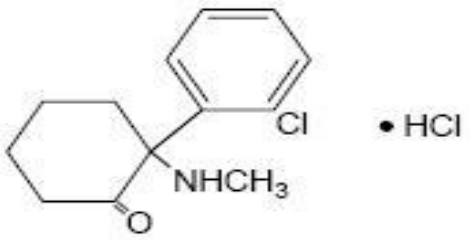
2.2 INDUCTION

2.2.1 Ketamine

2.2.1.1 Introduction

Ketamine is a rapid acting general anesthetic that also has significant analgesic activity and a lack of cardiopulmonary depressant effects (Plumb, 2018). Ketamine is the most commonly used dissociative agent so induces anesthetic stages I & II, but not stage III. Dissociative anaesthesia is a state in which the patients are "dissociated" from the environment, resembling a catatonic state, the eyes remain open and the patient is not unconscious. Muscle relaxation is not present and varying degrees of hypertonus and purposeful movement occur independent of surgical stimulation (Branson, 2001).

The main advantage of ketamine in small animal anaesthesia is that it can be given by either IV or IM routes, and so, is particularly useful for fractious patients, especially cats, where it may be impossible to achieve IV access. The SC route can be used but is slightly less predictable (Flaherty, 2003).



Ketamine may be mixed with sterile water for injection, 5% dextrose, and normal saline for diluent purposes. Ketamine is compatible with xylazine in the same

syringe. Do not mix ketamine with barbiturates in the same syringe or IV bag as precipitation may occur (Plumb, 2018).

Ocular and pharyngeal reflexes are retained, or attenuated less, with ketamine than with other anesthetic agents, which can make traditional monitoring of anesthetic depth using observation of physical signs misleading (Grimm *et al.,* 2015).

Ketamine can be used to induce anesthesia prior to maintenance with a gaseous agent. Alternatively, it can be used to induce and maintain anesthesia for procedures of short-to-moderate duration. Ketamine causes marked muscle rigidity and is rarely administered as the sole agent. It is usually combined with a α2-agonist such as medetomidine or a benzodiazepine such as diazepam or midazolam (Flaherty, 2003).

Ketamine is an extremely versatile agent because it can be administered by IM or IV route without appreciable issue irritation. This is so because the drug is considered to be relatively safe, as it generally causes minimal cardiovascular and respiratory depression. It may actually stimulate cardiovascular function via its sympathomimetic effect (Ajadi *et al.,* 2008).

Ketamine's unique properties, including profound analgesia, stimulation of the sympathetic nervous system, bronchodilation, and minimal respiratory depression, make it an important alternative to the other intravenous anesthetics and a desirable adjunct in many cases (Pardo and Miller, 2018).

2.2.1.2 Mode of action

Unlike other injectable anesthetics, ketamine has no effect at the GABA receptor. Its main effects, i.e. dissociative anesthesia and analgesia, result from an antagonistic action at the NMDA receptor (Pardo and Miller, 2018; Pawson and Forsyth, 2008).

Ketamine pharmacokinetics resembles those of thiopental, being rapid in onset and of short duration. Ketamine is 5 to10 times more lipid soluble than thiopental, ensuring rapid transfer to the CNS and recovery through rapid redistribution. Ultimate clearance of ketamine from the body is dependent on hepatic metabolism (Branson, 2001).

2.2.1.3 Adverse effects

Chamberlain *et al.* (1992) investigated the effect of ketamine on myocardial function. In dogs the drug was infused directly into the left main coronary artery. The concentration chosen was similar to the peak concentration found following a bolus intravenous injection. A mild depression of inotropic state was found which recovered completely after stopping the infusion. No changes in high energy phosphates were found in these hearts after 45–60 minutes of perfusion with ketamine in the perfusion medium. This study confirms that myocardial depression occurs with ketamine but suggests that it is unlikely to be of clinical significance. Depletion of high energy phosphates did not seem to be the cause of the depression.

Ketamine increases cerebral blood flow and thereby raises intracranial pressure. Combination with a benzodiazepine lessens the rise in ICP. Ketamine can induce seizures, especially if used alone in dogs. Sedative premedication reduces the incidence and severity of such side effects. Ketamine has a two-fold effect on the cardiovascular system (Pawson and Forsyth, 2008).

Overall, ketamine appears to produce minimal cardiovascular depression and can be administered to many patients with cardiovascular disease. Transient respiratory depression occurs and hypoxia is possible in the animal breathing room air. The severity of the respiratory depression is dependent on the dose administered and the concurrentadministration of other sedative and anesthetic agents. Ketamine appears to

have no effect on hepatic function. Ketamine appears to have no direct effect on the kidney but anesthetic-induced hypotension can result in compromised renal function. Animals with renal or post renal disease can have a prolonged recovery time. After rapid intravenousinjection transient apnea is occasionally seen, but this is easily managed with a brief period of bag-mask ventilation (Pawson and Forsyth, 2008).

2.2.1.4 Therapeutic effects

Ko *et al.* (2001) observed faster and smoother endotracheal intubation when dogs were given ketamine than when induced with isoflurane. Dogs were given medetomidine (10 µg/kg body weight, intramuscularly) followed in 10 minutes by either ketamine (4 mg/kg body weight, intravenously) or isoflurane mask induction and maintained on isoflurane for 30 minutes. Analgesia was excellent in all groups. Respiratory depression was more profound when dogs were given ketamine. Recovery quality was smooth and similar among all groups. Medetomidine-premedicated dogs could be induced with either ketamine or isoflurane and maintained on 1.3% isoflurane to achieve good analgesia with smooth recovery from anesthesia.

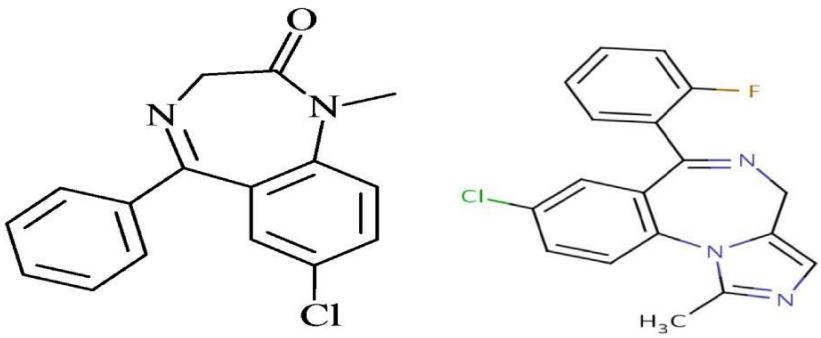
2.2.2 Diazepam and Midazolam

2.2.2.1 Introduction

A variety of benzodiazepines are used in human medicine for their sedative, anxiolytic, spinal cord mediated skeletal muscle relaxant, anticonvulsant and amnestic properties. Although not capable alone of general anesthesia, uses include preanaesthesiaand anesthesia induction and they may be part of a balanced anesthesia regimen (Rall, 1990). Current veterinary use is limited largely to diazepam, midazolam and zolazepam, typically in combination with another agent (e.g., a hypnotic or dissociative like ketamine) for anesthesia or anesthetic induction.

It is very difficult if not impossible to induce anaesthesia with benzodiazepine drugs in fit healthy animals, although they do combine with almost any other central nervous depressant drug to give anaesthesia. It is in combinations with such drugs as opioids that they are generally employed. Certainly, when used for premedication at subanaesthetic doses, they do markedly reduce the dose required of subsequent anaesthetic agents, but when they are used in many combinations their advantage of causing minimal cardiovascular and respiratory effects may be lost (Dundee and Wyant, 1989).

Diazepam is a benzodiazepine central nervous system depressant and anxiolytic. Its main use is in anxiety states and it is an effective sedative. The drug has muscle relaxant properties (Diamantis and Kletzkin, 1966) and has minor effects on the cardiovascular system (Baldessarini, 1980).



Chemical structure of Diazepam and Midazolam

Midazolam, a water-soluble benzodiazepine tranquilizer, has been considered by some veterinary anaesthesiologists to be suitable as a combination anaesthetic agent when administered concurrently with ketamine because of its water solubility and miscibility with ketamine. However, the pharmacokinetics of midazolam has not been extensively described in the dog (Brown *et al.*, 1992).

The use of water-soluble benzodiazepine midazolam is well established in human anaesthesia as a premedicant, anxiolytic and anaesthetic induction agent. Notably, midazolam has been used successfully in patients in intensive care units in hospitals to cause unconsciousness (Aitkenhead *et al.,* 1989; Ronan *et al.,* 1995).

Midazolam is unique in combining properties; high affinity for the benzodiazepine receptor *in vitro* (directly acting compound), basicity of the molecule which makes possible the preparation of water-soluble salts giving very stable, well tolerated purely aqueous injectable solutions and short duration of action due to rapid metabolic inactivation (Gerecke, 1983).

In dogs, midazolam has been shown to act as a mild sedative when administered alone and with a synergistic interaction when given with other drugs, including medetomidine, xylazine, butorphanol, acepromazine and buprenorphine (Itamoto *et al.,* 2000; Kojima *et al.,* 2002; Mutoh *et al.,* 2002; Pypendop *et al.,* 1996; Stegmann and Bester, 2001).

Induction of anaesthesia by intravenous midazolam was successful and enabled safe endotracheal intubation. The dose used depended on the animals' reaction and averaged 0.46 mg/kg, thereby remaining within the recommended therapeutic dosingrange of 0.2 to 0.5 mg/kg. No significant correlation was observed between the dose of midazolam and the dogs' age and body weight. Full recovery of consciousness and motor functions was rapidly achieved in all dogs after using midazolam as an induction (Cwiek *et al.,* 2010).

Diazepam is effective in treating convulsions from a variety of causes (Pieri *et al.,* 1981). In diazepam, solutions for injections contain solvents such as propylene glycol, ethanol, and sodium benzoate in benzoic acid. Intravenous injection may give

rise to thrombophlebitis and this is thought to be due to the solvents rather than to diazepam itself (Clarke and Trim, 2014).

2.2.2.2 Mode of action

The main site of action of diazepam, as with other benzodiazepines, is at the gamma-aminobutyric acid (GABA) receptor (Ortells & Lunt, 1995). GABA is the major inhibitory neurotransmitter in the mammalian central nervous system. Benzodiazepines including diazepam alter GABA binding at the $GABA_A$ receptor in an allosteric fashion but these drugs do not directly activate the receptors, which may account in part for their safety. Therefore the benzodiazepines may be envisaged as potentiating the effects of GABA receptors in the central nervous system (Costa and Guidotti, 1979). Thus, the benzodiazepines potentiate the endogenous control of the central nervous system against hyper-excitation (Sellström, 1992) and inhibit calcium channels (Rampe *et al.*, 1987). It has been suggested that various actions of the benzodiazepines may be mediated by different $GABA_A$ receptor subtypes (Johnston, 1996; Sieghart and Sperk, 2002).

2.2.2.3 Advantages of Midazolam over Diazepam

Midazolam is metabolized in the liver and in man its half-life is considerably shorter than that of diazepam thus it is less cumulative and recovery is more rapid. These properties have led to its being used for IV sedation and induction of anaesthesia (Dundee and Wyant, 1989).

Diazepam is painful when administered IM, and because it also has poor absorption from this site, it should probably be restricted to the intravenous route. It does not cause thrombophlebitis and can be administered intramuscularly. Midazolam is

a water-soluble benzodiazepine, with about twice the potency of diazepam, but a shorter duration of action (Clarke and Trim, 2014).

Diazepam and midazolam are both effective for conscious sedation in patients. Midazolam causes less pain on injection, a significantly greater degree of early sedation and a more rapid return to baseline function (Wright *et al.*, 1993).

Midazolam has been shown to have superior sedative effects (Larsen, 1996) and to be less likely to produce phlebitis and aqueous solution is not painful (Dundee and Wyant, 1989) than diazepam following intravenous administration (Edomwonyi *et al.*, 2001).

Although diazepam may cause a dose-dependent increase in heart rate in sheep (Komar *et al.*, 1991), no changes in heart rate were observed following the administration of midazolam (0.1 mg/kg) in dogs (Fujii and Toyooka, 2001).

2.2.2.4 Diazepam-Ketamine

Pandey *et al.* (1991) used diazepam (3mg/kg) and ketamine (10 mg/kg) to induce anaesthesia for an average duration of 37.00 ± 3.29 minutes in clinical cases. It caused drop in pulse rate, respiratory rate and body temperature. There was a significant increase in total leukocyte count and neutrophil percentage, while lymphocytes were dropped significantly.

Chonde *et al.* (2004) conducted clinical study on fifteen healthy mongrel dogs of either sex, aged 1-2 years and weighting 10-15 kg were randomly divided into 3 groups of 5 animals each. Atropine sulfate was given to the animals of all groups @ 0.04 mg/kg body weight IM prior to start of treatment. In group I, ketamine was administered 7.5 mg/kg body weight intravenously. In group II, atropine premedication as group I was followed, 10 min. later, by administration of medetomidine @ 30 mg/kg

body weight IM and 10 min. later ketamine @ 7.5 mg/kg body weight. In group III, 10 min. after atropine premedication, diazepam was administered @ 2 mg/kg body weight IV. This was followed, 10 min. later, by administration of ketamine @ 7.5 mg/kg body weight IV and concluded that there was no significant difference in the anaesthesia between all groups and revealed that diazepam in combination with ketamine produced anaesthesia of longer duration than ketamine alone.

Fayyaz *et al.* (2009) evaluated and compared the cardiopulmonary effects of induction of anesthesia with isoflurane (ISO), ketamine-diazepam (KD) in hypovolemic dogs and concluded that hypovolemic dogs KD used in their study to induce anesthesia, resulted in less hemodynamic depression compared to isoflurane.

Ferreira *et al.* (2015) studied anaesthetic induction and recovery characteristics of diazepam-ketamine combination with propofol alone were compared in dogs undergoing elective orchidectomy. Thirty-six healthy adult male dogs were used. The dogs were sedated with morphine and acepromazine. Forty minutes later general anaesthesia was induced using a combination of diazepam-ketamine (Group D/K) or propofol (Group P) and maintained with isoflurane and stated that both groups were associated with acceptable quality of induction and recovery from anaesthesia and concluded that propofol had inferior anaesthetic induction characteristics, but superior and quicker recovery from anaesthesia compared with diazepam-ketamine.

Abdel-Hady *et al.* (2017) designed two anaesthetic combinations and compared their effects in Mongrel dogs: combination 'A' consisting of atropine, xylazine, ketamine plus propofol, and combination 'B' consisting of atropine, diazepam, ketamine plus propofol. The onset and duration of anaesthesia induction, the duration of maintenance as well as the period of recovery were recorded and compared for both combinations and concluded that combined administration of

atropine, xylazine, ketamine plus propofol (combination 'A') is considered satisfactory for anaesthesia in dogs with minimal postoperative side effects.

2.2.2.5 Midazolam-Ketamine

Jacobson and Hartsfield (1991) determined the cardiorespiratory effects of IV ketamine (10 mg/kg) and IV midazolam (0.5 mg/kg). Six dogs received ketamine-midazolam (KM) as a bolus (B group) over 30 seconds and six dogs received KM as an infusion (I group) over 15 minutes and stated that in the B group HR was increased significantly at all time intervals. In the I group HR was increased significantly at all time intervals except 45 minutes.

Jacobson and Hartsfield (1993) determined cardiorespiratory effects of IV administered ketamine (10 mg/kg of body weight) and midazolam (0.5 mg/kg) in twelve healthy dogs. Dogs received a ketamine-midazolam combination (K-M) as a bolus over 30 seconds and the other half received the K-M as an infusion over 15 minutes. Induction of anesthesia by use of K-M was good in all dogs. Ketamine-midazolam combination as a bolus or infusion induced minimal cardiorespiratory effects, except for significant ($P < 0.05$) increase in mean heart rate and rate-pressure product. The increase in heart rate was greater in dogs of the infusion group. Mild and transient respiratory depression was observed in dogs of both groups immediately after administration of K-M, but was greater in dogs of the bolus group than in dogs of the infusion group. Duration of action of K-M for chemical restraint was short. Salivation and defecation were observed in a few dogs. Extreme muscular tone was developed in one of the dogs after K-M bolus administration.

Brondani *et al.* (2003) evaluated the effects of ketamine, midazolam and nitrous oxide anesthesia (K-M) in dogs artificially ventilated with 66% nitrous oxide and 33% oxygen or 100% oxygen. Anesthesia was maintained with 5 mg/kg ketamine and 0.25 mg/kg midazolam IV as a bolus injection every 10 minutes after induction. Two groups were studied: N2O and O2. In one group (N2O) 8 dogs were artificially ventilated with 66% nitrous oxide (N2O) and 33% oxygen (O2). In the other group (O2) 8 dogs were artificially ventilated with 100% O2 and stated that K-M injectable anesthesia do not produce cardiovascular depressant effects and hypothermia, promotes quiet induction and satisfactory recovery with salivation and produces adequate analgesia and muscular relaxation to cervical esophagus in dogs. Additional doses of K-M were necessary ($p<0.05$) in the O2 group suggesting that nitrous oxide decreases the dose of K-M in dogs.

Butola and Singh (2003[a]) studied physiological and clinical effects of midazolam and ketamine in dogs concluded that intravenous administration of midazolam-ketamine combination can be utilized for short duration of surgical procedures without adverse effects on cardiopulmonary functions in dogs.

Butola and Singh (2003[b]) studied haemato-biochemical effects of midazolam and ketamine in dogs. Eight clinically healthy dogs aged 2-4 years and weighing 10-25 kg were divided into 2 groups of 4 animals in each. The animals of groups T1 and T2 received midazolam @ 0.3 and 0.5 mg/kg IV, respectively, followed immediately by administration of ketamine HCL (20 mg/ml) by slow IV injection till effect by observing the pedal reflex. The dose of ketamine used in 2 groups of animals was 15.543 ± 1.018 and 12.11 ± 0.879 mg/kg body weight, respectively. The haematological (viz. packed cell volume, haemoglobin, total leucocyte count and differential leukocyte count) and biochemical (blood glucose, SGOT, SGPT and creatinine) parameters were

recorded before and at 10, 20, 30, 60, 120, 1440 (24 hrs) and 2880 (48 hrs) minutes after administration of the drugs. A non-significant decrease in haemoglobine and PCV content was observed in T1 group while in T2 group the decrease was significant ($P < 0.01$) at 20 min. A nonsignificant decrease in TLC observed in both groups. The DLC in the study was fluctuated within the normal physiological limits in all animals. Both groups of animals showed a nonsignificant increase in blood glucose levels. Non significant decrease in value of SGOT and SGPT were recorded in both groups. Non significant increase in value of creatinine was recorded in both groups. So results of the present study did not reveal any deleterious effect on any vital function and organ in the body and drugs regimens can safely used in routine clinical cases of surgery without any risk in dogs.

2.2.2.6 Comparison of Diazepam-Ketamine, Midazolam-Ketamine combinations for induction of anaesthesia

Hellyer *et al.* (1991) studied diazepam-ketamine and midazolam-ketamine anesthesia in greyhounds. Anesthesia was induced with a mixture of diazepam or midazolam (0.28 mg/kg) and ketamine (5.5 mg/kg) and maintained with halothane. Time to intubation with diazepam-ketamine was significantly longer than with midazolam-ketamine. Heart rate and respiratory rate did not vary significantly during anesthesia in either treatment groups. These data suggested that the both diazepam-ketamine and midazolam-ketamine were useful anesthetic combinations in greyhound dogs. In combination with ketamine, midazolam offers little advantage over diazepam.

Riviera and Pires (2002) compared anesthetic induction and recovery quality with S(þ) ketamine in combination with diazepam or midazolam in 10 dogs (ASA 1) admitted for elective surgery. After all clinical examinations, the dogs were separated into two groups (G I and G II). All animals received acepromazine (0.1 mg/kg) and

fentanyl (5 mg/kg) IM, 20 minutes before induction with S(þ) ketamine (6 mg/kg) and diazepam (0.5 mg/kg) IV (G I) or midazolam 0.2 mg/kg (G II) IV. S(þ) ketamine, one of the two enantiomers of racemic ketamine, is a phencyclidine derivative that induces amnesia and analgesia. Its activity is related to blockade of NMDA receptors and some opioid action. All dogs were intubated and then maintained with halothane in oxygen at a vaporizer setting sufficient to maintain surgical anesthesia. Quality of induction, time needed for intubation, heart rate, respiratory rate, SpO2, time to extubation and quality of recoverywere evaluated. Smooth induction and recovery were observed in all animals. The time to intubation was 45 ± 20 (GI) and 25 ± 6 seconds (GII), HR was 122 ± 12 (GI) and 125 ± 7 beats/minute (GII), RR was 17 ± 2 (GI) and 21 ± 3 breaths/minute (GII), SpO2 was 96 ± 2 (GI) and 94 ± 1% (GII), time to extubation was 7 ± 3 (GI) and 4 ± 1 minutes (GII). No statistical differences were found in analyses, although time to intubation was less in GII. The results suggested that both combinations could be used safely for anesthetic induction in healthy dogs. As per literature described above ketamine-diazepam and ketamine-midazolam combinations have been universally established as a balanced anaesthetia in dogs, in which disadvantage of ketamine HCL can be masked by using benzodizepines that produces minimal respiratory and cardiovascular depression with better sedation and skeletal muscle relaxation.

Allison *et al.* (2018) compared quality and safety of general anaesthesia induced using ketamine alone with anaesthesia co-induced using ketamine and midazolam in ponies and concluded ketamine-midazolam co-induction compared to ketamine alone improved quality of induction, ease of intubation and muscle relaxation without impacting recovery quality.

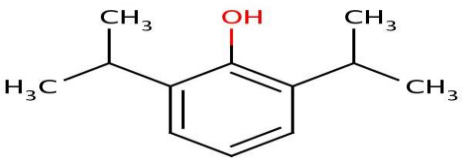
2.2.3 Propofol

2.2.3.1 Introduction

Propofol is an intravenous anaesthetic agent, a derivative of phenol, chemically described as 2, 6-diisopropylphenol. It was first synthesized in the early 1970's. Its reformulation in an emulsion is available containing soybean oil, glycerol, egg lecithin and sodium hydroxide (Reves *et al.,* 1994; Branson, 2001). This emulsion contains no preservative and will support bacterial and fungal growth (Bryson *et al.,* 1995).

Compatibility with other agents has not been well established. Propofol is compatible with the commonly used IV solutions (e.g., LRS, D5W) when injected into a running IV line (Plumb, 2018).

It is a preservative-free product with a neutral pH value, it will support bacterial growth and endotoxin production (Berry *et al*., 1993; Quinn *et al*., 1993; Sosis and Braverman, 1993; Sosis *et al*., 1995; Aydin *et al*., 2002; Joubert *et al*., 2005; Stachan *etal*., 2008) and consequently aseptic conditions must be observed during its handling (Lorenz *et al*., 2002).



2.2.3.2 Mode of action

Propofol is a short acting hypnotic unrelated to other general anesthetic agents. Its mechanism of action is not well understood (Plumb, 2018).

The action of propofol involves a positive modulation of the inhibitory function of the neurotransmitter gama-aminobutyric acid (GABA) through $GABA_A$

receptors.Propofol also inhibits the N- methyl- D- aspartate (NMDA) receptor through modulation of channel gating which may also contribute to its central nervous system effects. Propofol is a nonbarbiturate hypnotic with noncumulative properties has been used for induction and maintenance of anaesthesia in dogs (Duke-Novakovski *et al.,* 2016; Grimm *et al.,* 2015; Pardo and Miller, 2018; Pottie *et al.,* 2008).

Recent results from recombinant human $GABA_A$ receptor experiments and findings from the work exploring the effects at other receptors (e.g., glycine, nicotinic, and muscarinic receptors) are reviewed. Studies showing its antiepileptic and anxiolytic properties are also discussed. Some adverse effects have been reported like signs of pain at injection (less commonly reported in animals than in man), vomiting during recovery, excitation, paddling, muscle twitching and opisthotonous (Davies, 1991; Cullen and Reynoldson, 1993; Smith, *et al*., 1993; Smedile *et al.,* 1996). However, the use of a pre-anaesthetic tranquillizer, sedative or opioid decreases the incidence of these reactions.

2.2.3.3 Therapeutic effects

Propofol induces general anaesthesia when administered by intravenous injection, generally as a single bolus. Early described doses to allow endotracheal intubation in unpremedicated dogs ranged from 5.2 ± 2.6 mg/kg (Weaver and Raptopoulos, 1990) to 6.55 ± 1.7 mg/kg. Premedication with various agents, most commonly acepromazine lowered these doses to 3.6 ± 1.4 and 4.5 ± 1.53 mg/kg respectively (Morgan and Legge, 1989).

Intermittent boluses of propofol can be used to maintain anesthesia following initial bolus induction (Ko, 2013). To prolong anesthesia, small boluses of 0.44–2.2 mg/kg can be given as required or alternatively an infusion of 0.2–0.5 mg/kg/min can be administered (Paddleford, 1999).

Distribution to the CNS is rapid, followed by a slower elimination that relies heavily on metabolism. However, redistribution to tissues such as muscle probably accounts for most of the decrease in plasma concentration required for termination of propofol's hypnotic effects. In mixed breed dogs given a single induction bolus of propofol for endotracheal intubation, recovery to sternal recumbency and to standing occurred at plasma propofol concentrations of 0.753 ± 0.484 and 0.676 ± 0.338 g/ml respectively. Mean plasma concentrations at 60 min post-induction were 0.161 ± 0.059 g/ml in mixed breed dogs, indicating a concentration well below that expected to influence recovery, if anaesthesia was maintained with a gaseous agent (Zoran *et al.*, 1993).

Recovery after a single induction bolus of propofol was judged complete in 18 ± 7 min in unpremedicated dogs and 22 ± 10 min in dogs premedicated with low doses of acepromazine (Watkins *et al.,* 1987). Mixed breed, unpremedicated dogs stood after14.63 ± 3.6 min in another study, whereas greyhounds took 21.7 ± 3.3 min (Zoran *et al.,* 1993).

In dogs, propofol produces rapid, yet smooth and excitement-free anesthesia induction (in 30-60 seconds) when given slowly IV. Sub-anesthetic dosages will produce sedation, restraint and an unawareness of surroundings. Anesthetic dosages produce unconsciousness (Plumb, 2018).

Propofol is metabolized and redistributed by the liver and extrahepatic sites, resulting in an ultrashort duration of action, because of its unique pharmacokineticprofile (including a short context-sensitive half-time in dogs), it may be given by repeated injection or continuous infusion to maintain total IV anesthesia without significantly prolonging recovery.It is metabolized quickly, has a fast onset of action, and has short duration of effect, making it a relatively safe induction agent when

administered correctl.Intermittent boluses of propofol can be used to maintain anesthesia following initial bolus induction (Ko, 2013).

2.2.3.4 Maintenance of anaesthesia with Propofol

Two techniques are used to maintain anaesthesia with an IV agent, namely multiple bolus injections or continuous infusion (Smith and White, 1998[a]). Administering the agent by multiple bolus injections has the advantage of being very simple, but results in the administration of a large total drug dose and slow recovery (Miller, 1994; Smith and White, 1998[b]; Padfield 2000).

Propofol was introduced into clinical practice in 1986 and has been described as being the most suitable drug currently available for TIVA (White, 1988). It has many of the properties of the ideal IV agent, namely rapid onset of action, short duration of clinical effect, high clearance, and minimal tendency for accumulation and minimal side-effects (Morgan, 1983; Miller, 1994).

The cardiovascular depressant effects of propofol have been documented previously and although well tolerated in healthy humans, compromised patients may develop hypotension following administration of a bolus dose. The administration of propofol by infusion is associated with less hypotension when compared with bolus injection (Kneeshaw and Mills, 2000).

Maintenance of anesthesia is usually performed with a propofol infusion ranging from 0.15 to 0.45 mg/kg/minute (Robertson *et al.*, 1992; Vainio, 1991).

Keegan and Greene (1993) studied cardiovascular effects during 2 hours of anesthesia with either a continuous propofol infusion or isoflurane were compared in the same six healthy dogs. Dogs were randomly assigned to be anesthetized with either propofol (5 mg/kg, IV administered over 30 seconds, immediately followed by a

propofol infusion beginning at 0.4 mg/kg/min), or isoflurane (2.0% end-tidal concentration). The propofol infusion was adjusted to maintain a light plane of anesthesia. Dogs anesthetized with propofol had higher values for systemic arterial pressure due to higher systemic vascular resistance. Apnea and cyanosis were observed during induction of anesthesia with propofol. At the end of anesthesia the mean time to extubation for dogs anesthetized with either propofol or isoflurane was 13.5 min and 12.7 min, respectively. A continuous infusion of propofol (0.44 mg/kg/min) provided a light plane of anesthesia.

Recovery after a two hour continuous infusion of propofol was similar to an equivalent period of isoflurane anaesthesia, with extubation in a mean of 13.5 min, compared to 12.7 min after isoflurane (Keegan and Greene, 1993).

Hughes *et al.* (1999) evaluated concomitant propofol and fentanyl infusions as an anesthetic regime, in greyhounds. Dogs were premedicated with acepromazine (0.05 mg/kg) by intramuscular (IM) injection. Forty five minutes later anesthesia was induced with a bolus of propofol (4 mg/kg) by intravenous (IV) injection and a propofol infusion was begun (time = 0). Five minutes after induction of anesthesia, fentanyl (2 mg/kg) and atropine (40 mg/kg) were administered IV and a fentanyl infusion begun. Propofol infusion (0.2 to 0.4 mg/kg/min) lasted for 90 minutes and fentanyl infusion (0.1 to 0.5 mg/kg/min) for 70 minutes. Blood samples were collected for propofol and fentanyl analysis at varying times before, during and after anesthesia. Mean heart rate of all dogs varied from 52 to 140 beats/min during the infusion. During the same time period, mean blood pressure ranged from 69 to 100 mmHg. On clinical assessment, all dogs appeared to be in light surgical anesthesia. Mean times (6 SEM), after termination of the propofol infusion, to return of spontaneous ventilation, extubation, head lift and standing for all dogs were 26 ± 7, 30 ± 7, 59 ± 12, and 105 ± 13 minutes, respectively. Five out of eight

dogs either whined or paddled their forelimbs in recovery. Greyhounds which were not undergoing any surgical stimulation, total intravenous anesthesia maintained with propofol and fentanyl infusions induced satisfactory anesthesia.

Kazuto *et al.* (2004) evaluated anesthetic effects of total intravenous anesthesia with propofol and fentanyls (PF-TIVA) in 100 dogs. Dogs were pre-medicated by intravenous injections (IV) of 0.05 mg/kg propionyl-promazine, 0.25 mg/kg droperidol, and 0.3 mg/kg midazolam or 5μg/kg medetomidine. Surgical anesthesia was induced with propofol, and fenantyl was infused continuously at a rate of 0.2 μg/kg/min following 2 μg/kg bolus IV. The propofol infusion rate was controlled to maintain surgical anesthesia. Requirement infusion rate of propofol infusion was significantly lower in dogs pre-medicated with medetomidine (0.2-0.3 mg/kg/min, $P<0.001$) than in the other animals (0.3-0.4 mg/kg/min). During PF-TIVA, controlled ventilation was necessary in 41 dogs (41%). Body temperature decreased below 36.0 ˚C in 36 dogs (36%). Heart rate was significantly lower in dogs pre-medicated with medetomidine (70-80 bpm, $P<0.001$) than in dogs given some other premedication (80-120 bpm). Moderate, treatable hypotension occurred in 19 dogs (19%). Recovery from PF-TIVA was very quiet and smooth. In conclusion, PF-TIVA was successful in major surgery in dogs.

Tsai *et al.* (2007) clinically compared characteristics of recovery from total intravenous anesthesia (TIVA) with propofol and inhalation anesthesia with isoflurane in 149 client-owned dogs that anesthetized for surgical or diagnostic procedures. In all dogs, anesthesia was induced with an intravenous injection of propofol following premedication with acepromazine or diazepam. As a result, 58 dogs anesthetized with propofol-TIVA showed slower but smoother recovery than 91 dogs anesthetized with isoflurane anesthesia. The dogs stood at 34.5 ± 19.3 and 27.7 ± 17.2 min after propofol-

TIVA and isoflurane anesthesia, respectively. Adverse effects, including hypersalivation, neurologic excitement (paddling, muscle tremor/twitching, opisthotonos) and vomiting/retching, were observed in similar infrequent incidences during the recovery from both anesthetic protocols. Propofol-TIVA is suggested to be an alternative anesthetic protocol for canine practice.

2.2.3.5 Side effects

Keegan and Greene (1993) studied cardiovascular effects during 2 hours of anesthesia with either a continuous propofol infusion or isoflurane were compared in the same six healthy dogs. Dogs were randomly assigned to be anesthetized with either propofol (5 mg/kg, IV administered over 30 seconds, immediately followed by a propofol infusion beginning at 0.4 mg/kg/min), or isoflurane (2.0% end-tidal concentration). Dogs anesthetized with propofol had higher values for systemic arterial pressure due to higher systemic vascular resistance. Dogs anesthetized with isoflurane had higher values for heart rate and mean pulmonary artery pressure. Apnea and cyanosis were observed during induction of anesthesia with propofol. At the end of anesthesia the mean time to extubation for dogs anesthetized with either propofol or isoflurane was 13.5 min and 12.7 min, respectively.

Hall and Chambers (1987) studied the minimum infusion rate of propofol needed to maintain anaesthesia and to compare the quality of the anaesthesia with that produced by halothane/nitrous oxide/oxygen in 40 dogs was premedicated with acepromazine (0·05 mg/kg) and atropine (0·02 mg/kg). In 30 dogs, anaesthesia was induced with propofol and maintained with a continuous infusion and in the other ten dogs anaesthesia was induced with thiopentone and maintained with the inhalation agents. An infusion rate of 0·4 mg/kg/min of propofol produced surgical anaesthesia

indogs breathing oxygen or oxygen-enriched air. Cardiovascular and respiratory effects were similar to those in dogs anaesthetized with halothane/nitrous oxide and with both anaesthetic regimens myocardial oxygen consumption appeared to increase with increasing duration of anaesthesia. A possible familial susceptibility resulting in a more prolonged recovery was revealed and propofol infusion was associated with a 16 per cent incidence of vomiting in the recovery period. It was concluded that in canine anaesthesia the continuous infusion of propofol to maintain anaesthesia in healthy dogs was safe.

The most prominent cardiovascular effect of propofol administration is a decrease in arterial blood pressure, decreases in systemic vascular resistance and cardiac output are also seen. It causes dose- dependent depression of ventilation and postinduction apnea with transient cyanosis occurring regularly. It does not adversely affect hepatic blood flow or glomerular filtration rate in dogs. Like thiopental, it produces muscle relaxation. Occasionally, however, myoclonic movements have been reported in both humans and dogs. These movements resolve spontaneously. Propofol produces neither antinociception nor hyperalgesia (Grimm *et al.,* 2015).

CHAPTER III

MATERIALS AND METHODS

3.1 MATERIALS

The present study was carried out on twelve dogs aged between 4 months to 10 years presented for various surgical operations at the Department of Surgery and Radiology, College of Veterinary Science, Rajendranagar, Hyderabad. The standard procedures and required kits were used for haematological examination and biochemical analysis.

3.2 DESIGN OF STUDY

The twelve dogs that formed the material of the present study were randomly divided into two groups comprising of six dogs in each group. All the dogs were uniformly premedicated with Butorphanol, Acepromazine and Glycopyrollate (BAG). Following premedication, the dogs were anaesthetized and maintained under anaesthesia as follows:

In the six dogs of group I, anaesthesia was induced with intravenous injection of Diazepam-Ketamine and maintained with Propofol administered intravenously during the operative period.

In dogs of group II, anaesthesia was induced by intravenous administration of Midazolam-Ketamine and maintained with Propofol administered intravenously during the surgical procedure. The aneasthetic protocols used in group I and group II in the present study are configured in Table.1. The drugs used in the present study are depicted in Fig 1.

The relative efficacy of the two anaesthetic protocols was compared on the basis of physiological, anaesthetic, haematological, biochemical and electrocardiographic parameters, recorded before induction, during anaesthesia and after recovery.

Table 1: Design of the Clinical Study

S.No	Group	Number of dogs	Age	Sex	Body Wt (kg)	Breed	ET size (mm)	Surgeries Performed	Anaesthetic protocol
1	I	6	2.6yrs	M	30	Labrador	8.5	Aural haematoma	Premedication-BAG Induction-D-K Maintenance-Propofol
			8 yrs	M	30	Labrador	7.5	Bone plating	
			9.6 yrs	M	29	German Shepherd	8.5	Perineal hernia	
			8 yrs	F	25	Doberman	9	Digit amputation	
			3 yrs	F	30	German Shepherd	8.5	Vaginal hyperplasia	
			6.5 yrs	F	20	German Shepherd	6.5	Ovariohysterectomy	
2	II	6	10 yrs	M	20	Non descript	6.5	Perineal hernia	Premedication-BAG Induction-M-K Maintenance-Propofol
			10 yrs	M	10	Non descript	5.5	Castration	
			4 month	M	10	Non descript	5.5	Bone plating	
			10 yrs	F	30	German Shepherd	8.5	Mammary tumor	
			1.3 yrs	F	8.8	Pomerarian	5.5	Ovariohysterectomy	
			5 yrs	M	39	Great Dane	8	Aural haematoma	

BAG: Butorphanol-Acepromazine-Glycopyrrolate; D-K: Diazepam-Ketamine; M-K: Midazolam-Ketamine

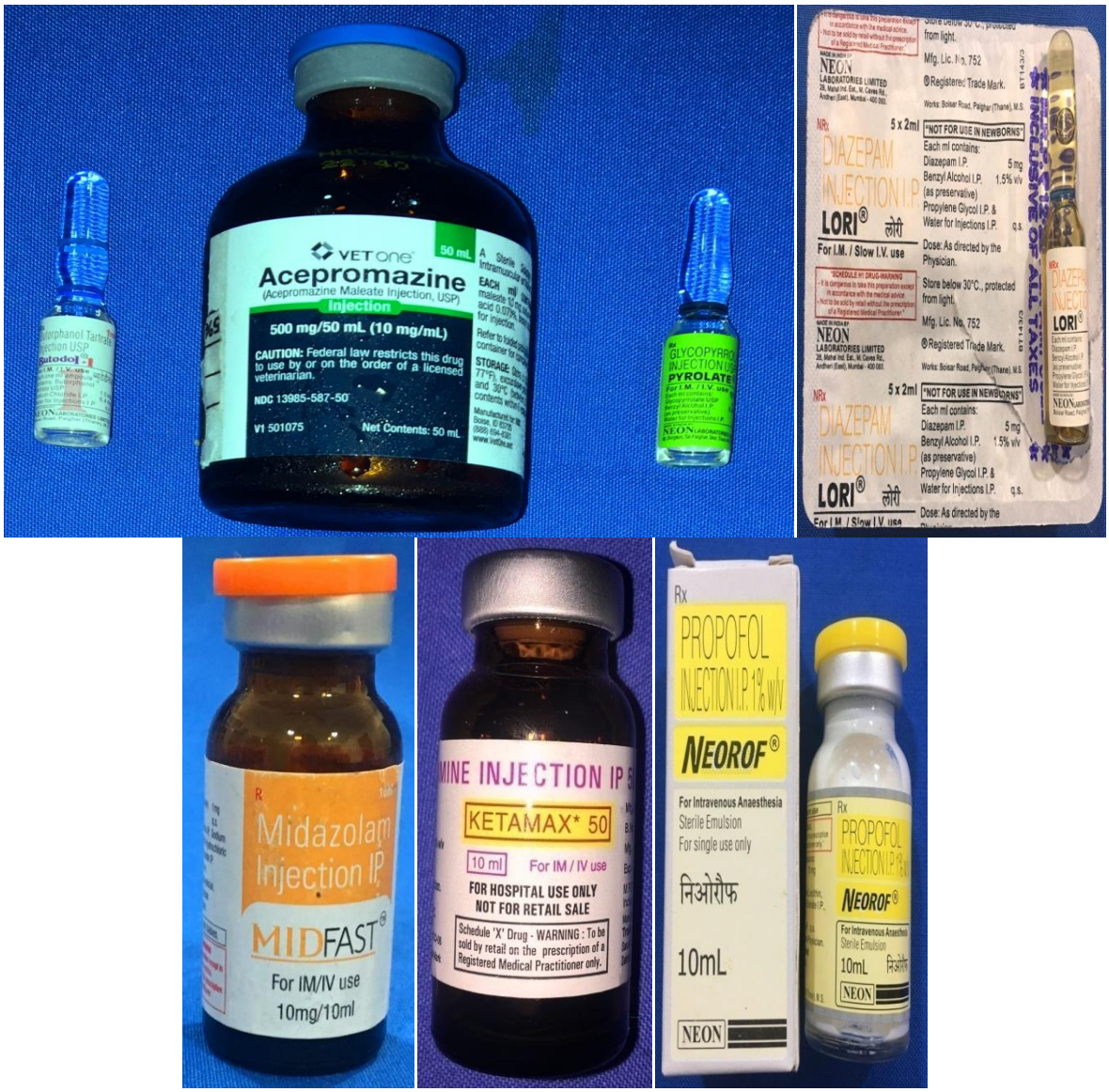


Fig 1 - Drugs used in the present study: Butorphanol, Acepromazine, Glycopyrrolate, Diazepam, Midazolam, Ketamine and Propofol.

3.3 PREANAESTHETIC EVALUATION OF DOGS

3.3.1 Signalment and History of the Patient

Details regarding age, sex and body weight were recorded to determine the dose of the drugs used in the present study. History regarding the vaccination status, diet and incidence of systemic disease etc., was collected to rule out concurrent diseases and the dogs were prepared for anaesthesia after conducting the patient evaluation.

3.3.2 Electrocardiogram (ECG)

Electrocardiogram (ECG) is a recording of the electrical activity generated in the heart that is measured at the body surface. In all the dogs of the two groups, ECG was recorded 10 minutes after premedication, 30 minutes during the depth of anaesthesia and 10 minutes after recovery.

For ECG recording, the dog was placed on the table in right lateral recumbency. The fore limbs and hind limbs were positioned approximately perpendicular to the body and slightly separated from each other by placing gauze bandage rolls so that the limbs were parallel to each other. The skin and electrodes were moistened with ECG jelly and the electrodes were attached. The color coded leads labeled right arm (RA), left arm (LA), right leg (RL) and left leg (LL) were attached to the corresponding limbs of the dog proximal to the olecranon process of ulna (elbow) and at the level of the patellar ligaments (stifle) (Fig.2). The standard six lead electrocardiogram was recorded at 50 mm/sec for a brief period and analyzed (Tilley and Burtnick, 2009).

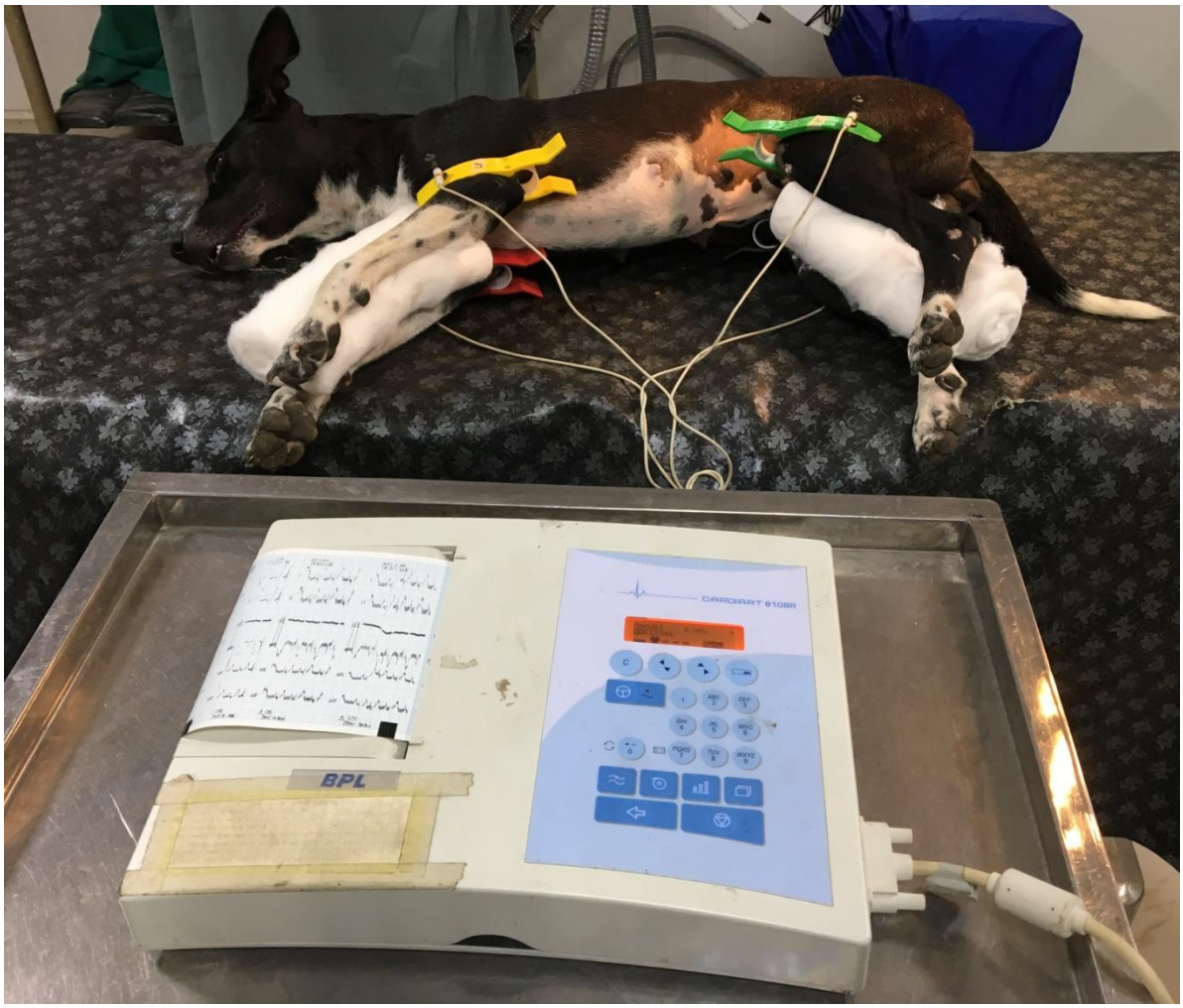


Fig 2: Recording Electrocardiogram (ECG)

3.3.3 Preanaesthetic Preparation of the Dog

Food was withheld for 12 hrs prior to anaesthesia. However, free access to water was allowed to all the dogs for upto two hours before they were anaesthetized. The preanaesthetic and anaesthetic doses for each dog were calculated on the basis of body weight. Five milliliters of blood was collected from cephalic vein for haematological and biochemical studies in all the dogs before premedication. Similarly, physiological parameters such as rectal temperature, heart and respiratory rates per minute were recorded before administration of anaesthetic drugs.

3.3.4 Administration of Preanaesthetic Medications - Butorphanol, Acepromazine and Glycopyrrolate (BAG)

The dogs of the two groups were premedicated with Butorphanol[1], Acepromazine[2] and Glycopyrrolate[3] (BAG) at dose rate of 0.2, 0.04 and 0.01 mg/kg body weight respectively as a combination in one syringe administered intramuscularly. The time taken for the onset of sedation was recorded in minutes. Quality of sedation of preanaesthetic medications was evaluated as recommended by Pottie *et al.,* (2008) in Table 2.

1. Butodol -1, Butorphanol tartrate injection 1mg/ml, Neon laboratories limited, Mumbai, India.
2. Acepromazine, Acepromazine maleate injection USP, 10mg/ml, Acepromazine, Manufactured for: MWI, Boise, ID 83705 (888) 694-8381.
3. Pyrolate, Glycopyrrolate USP, 0.2mg/ml, Neon laboratories limited, Mumbai, India.

Table 2: Criteria for Evaluation of Dogs for Quality of Sedation after Preanaesthesia (Pottie *et al* ., 2008).

Score	QUALITY OF SEDATION
4	Profound- resistance none: Dog is recumbent, can be aroused but not willing to stand and walk. No resistance to being moved or manipulated. Seems barely aware of being manipulated.
3	Moderate- resistance slight: Dog is recumbent when not aroused. Will stand and walk if encouraged. Possibly some resistance when manipulated and moved however only one person required moving and restraining dog.
2	Slight- resistance moderate: Dog obviously more relaxed and calm compared to prior to premedication. Walks easily, not necessarily recumbent when not being aroused. May require two people to manipulate and restrain dog**.**
1	None- resistance profound: Dog is excitable unchanged from prior premedication. Marked force may be required for moving and manipulating the patient.

3.3.5 Intravenous Catheterisation

Each dog had an intravenous catheter placed in the cephalic vein. Either a 22G, 1.00" or a 20G, 1.16" intravenous catheter was used, depending on the size of the dog. Immediately after intravenous catheterisation, a life line with slow infusion of normal saline was started.

3.4 INDUCTION OF ANAESTHESIA

3.4.1 Group I – Induction of Anaesthesia

In the dogs of group I, fifteen minutes after premedication, anaesthesia was induced by slow intravenous injection of Diazepam[4] at the rate of 0.28 mg/kg and Ketamine[5] hydrochloride at the rate of 5 mg/kg body weight over a period of 60-90 seconds.

4. Lori, Diazepam injection I.P, 5mg/ml, Neon laboratories limited, Mumbai, India.
5. Ketamax-50, Ketamine injection, 50mg/ml, TroikaaPharmaceuticals Ltd, India.

3.4.2 Group II – Induction of Anaesthesia

In the dogs of group II, fifteen minutes after premedication, anaesthesia was similarly induced with slow intravenous injection of Midazolam[6] at the rate of 0.28 mg/kg and Ketamine at the rate of 5 mg/kg body weight over a period of 60-90 seconds.

The dogs of the two groups were observed for quality of induction viz., eye ball position, muscle tone, response to opening of the mouth and tongue movement (Jaw relaxation) during endotracheal intubation. Quality of induction was evaluated as recommended by White *et al.* (2001) as presented in Table 3. Endotracheal intubation was carried out with the dogs in sternal recumbency with endotracheal tubes of size mentioned in Table 1. A laryngoscope was used to facilitate intubation.

Table 3: Criteria for Evaluation of Dogs for Quality of Induction (White *et al* ., 2001).

Score	**QUALITY OF INDUCTION**
1	Good: trachea easily intubated, easy transition to unconsciousness
2	Fair: several attempts before successful intubation
3	Poor: trachea difficult to intubate
4	Very poor: paddling, vocalizing, impossible to intubate

6. Midfast, Midazolam injection I.P, 10mg/10ml, Samrath Life Sciences pvt.ltd, India.

3.5 MAINTENANCE OF ANAESTHESIA

Following induction of anaesthesia in both the groups of dogs, anaesthesia was maintained with intravenous administration of Propofol[7] at the rate of 0.5-2.0 mg/kg body weight. Incremental doses of Propofol were administered "to effect" whenever required during the surgical procedure through the intravenous life line.

3.6 ANAESTHETIC PARAMETERS

The relative efficacy of the two protocols was assessed on the basis of the following parameters:

3.6.1 Induction Time

The time interval from administration of anaesthetic agent to the time the dogs allowed intubation was considered as the induction time and was recorded in seconds.

3.6.2 Duration of Surgical Anaesthesia

Surgical plane of anaesthesia was marked as the time of induction to time of extubation.

3.6.3 Recovery Time

The time taken from extubation and return of coughing and swallowing reflexes to walking was considered as recovery time and recorded in minutes (Thurmon *et al.*, 1999). Recovery was evaluated as recommended by Pottie *et al.*, (2008) in Table 4.

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7. Neoprof, Propofol injection, 10mg/ml, Neon laboratories limited, Mumbai, India

Table 4: Criteria for Evaluation of Dogs for Quality of Recovery (Pottie *et al.*, 2008).

Score	QUALITY OF RECOVERY
4	Gradual, smooth, quiet, rapid, comfortable
3	Gradual, slow, moderate, restless
2	Whinning, agitated, some paddling or trembling
1	Vocalization, restless, paddling, urination and/or defecation
0	Unacceptable recovery

3.7 QUALITY OF ANAESTHESIA

The following anaesthetic effects that indicated the quality of anaesthesia were recorded in all the dogs of the two groups.

3.7.1 Assessment of Reflexes

Various reflexes like pedal, palpebral, corneal and laryngotracheal reflexes were recorded 10 minutes after premedication and at 5, 10, 15, 20, 25, 30, 35, 40 and 60 minutes after induction and during the maintenance of anaesthesia. The reflexes were checked and recorded as present (P), moderate (M) or absent (A).

3.7.1.1 Pedal reflex

Pedal reflex was assessed by pinching the interdigital web in the hind limb. Withdrawal of the limb indicated the presence of the pedal reflex.

3.7.1.2 Palpebral reflex

Palpebral reflex was assessed by presence or absence of blinking induced by gently touching the medial canthus and was recorded as present or absent.

3.7.1.3 Corneal reflex

Corneal reflex was assessed by blinking induced by gently touching the cornea with fine strands of cotton wool. Blinking indicated positive response and vice versa. Corneal reflex was recorded as present or absent.

3.7.1.4 Laryngotracheal reflex

Laryngeotracheal reflex was assessed in the dogs by very gently moving the endotracheal tube and observing if this manouvre led to cough. Coughing indicated a positive reflex and it was recorded as present or absent.

3.8 PHYSIOLOGICAL PARAMETERS

The following physiological parameters were recorded prior to premedication, 15 minutes after premedication, 0 (induction), 5, 10, 15, 25, 35, 45, 60 and 90 minutes in all the dogs of the two groups.

3.8.1 Rectal Temperature

Rectal temperature was measured in degrees Fahrenheit (^{0}F) by using a clinical thermometer.

3.8.2 Heart Rate

Heart rate was determined by auscultation and expressed as beats per minute.

3.8.3 Respiratory Rate

Respiratory rate was determined by counting thoracic and abdominal excursions during one minute and expressed as breaths per minute.

3.9 HAEMATOLOGICAL STUDIES

Haematological parameters such as total erythrocyte count in millions/cumm (TEC), hemoglobin in grams per dl (Hb), packed cell volume as per cent (PCV), total leukocyte count in thousands per cumm (TLC) and differential leucocyte count in percentage (DLC) were recorded prior to premedication, 15 minutes after premedication and after 30 and 90 minutes of induction in minutes. The blood samples were analyzed with the aid of automatic whole blood analyzer[8].

3.10 BIOCHEMICAL STUDIES

The following biochemical parameters were estimated from the blood collected prior to premedication, 15 minutes after premedication, and after 30 and 90 minutes of induction.

3. 10.1 Serum Aspartate Aminotransferase (AST)

Serum AST levels were estimated prior to premedication, 15 minutes after premedication, and after 30 and 90 minutes of induction of anaesthesia by modified IFCC[9] method and expressed as units/ml.

3.10.2 Serum Alanine Aminotransferase (ALT)

Serum ALT levels were estimated 15 minutes after premedication, and after 30 and 90 minutes of induction of anaesthesia by DNTP[10] Colorimeter Method and expressed as units/ml.

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8. Humacount, Med Source Ozone, Biomedical, and Pvt.Ltd.,
9. Coral Clinical Systems, Goa.
10. Span Diagnostic Ltd. Surat, Gujarat, India.

3.10.3 Blood Urea Nitrogen (BUN)

Blood Urea Nitrogen (BUN) levels in the dogs of the two groups were estimated prior to premedication, 15 minutes after premedication, and after 30 and 90 minutes of induction of anaesthesia by DAM[11] method and expressed mg/dl.

3.10.4 Serum Creatinine (C)

Serum Creatinine levels were estimated prior to premedication, 15 minutes after premedication, and after 30 and 90 minutes of induction of anaesthesia by alkaline picrate[12] method and expressed mg/dl.

3.11 STATISTICAL ANALYSIS

The means and standard errors of all parameters were computed as per Snedecor and Cochran (1994). The variations in anaesthetic effects, haematological and biochemical parameters between the groups at different time intervals were analysed using independent t-test as described by Snedecor and Cochran (1994).

11. Span Diagnostic Ltd. Surat, Gujarat, India.

CHAPTER IV

RESULTS

4.1 PREANAESTHETIC PREPARATION AND PREMEDICATION

In all the dogs of the two groups, the preanaesthetic procedure of fasting the animal for 12 hours and allowing water free choices upto two hours prior to the administration of preanaesthetic medication proved to be safe since no dog exhibited any symptoms of nausea or vomiting during induction, anaesthetic and recovery periods.

Intramuscular administration of BAG (Butorphanol, Acepromazine and Glycopyrrolate at dose rate of 0.2, 0.04 and 0.01 mg/kg body weight respectively as a combination in one syringe) produced sedation within 4 to 18 minutes with mean sedation time of 12.25 ± 1.29 minutes. The sedation score ranged from 3 to 4 in the 12 dogs. BAG provided moderate (slight resistance) to profound (resistance none) sedation. Among the 12 dogs, sedation was adjudged to be moderate in 10 dogs (83.33 %) and profound in 2 dogs (16.67 %).

4.2 INDUCTION TIME

In group I, anaesthesia was induced by slow intravenous administration of Diazepam at the rate of 0.28 mg/kg and Ketamine hydrochloride at the rate of 5 mg/kg

body weight. The time of induction ranged from 55 seconds to 71 seconds, with a mean induction time of 62.33 ± 1.29 seconds.

In group II, anaesthesia was induced by slow intravenous administration of Midazolam at the rate of 0.28 mg/kg and Ketamine hydrochloride at the rate of 5 mg/kg body weight. The time of induction ranged from 25 seconds to 43 seconds, with a mean induction time of 31.67 ± 1.67 seconds.

Induction score was found to be 1 (good) in four dogs and 2 (fair) in two dogs of group I, whereas, the induction score was 1 (good) in all the dogs of the group II induced with Midazolam-Ketamine.

Statistical analysis revealed that the induction time in the dogs of group I was significantly higher when compared to the dogs of group II. The results of the statistical analysis were presented in table 5 and fig. 3.

Table.5 Induction Time

	Group- I (n=6)	Group-II (n=6)
Induction Time* (In seconds)	62.33[a] ±1.29 (Range 55-71 seconds)	31.67[b] ±1.67 (Range 25-43 seconds)

*-Significant (P≤0.05) - Means with different superscripts differ significantly.

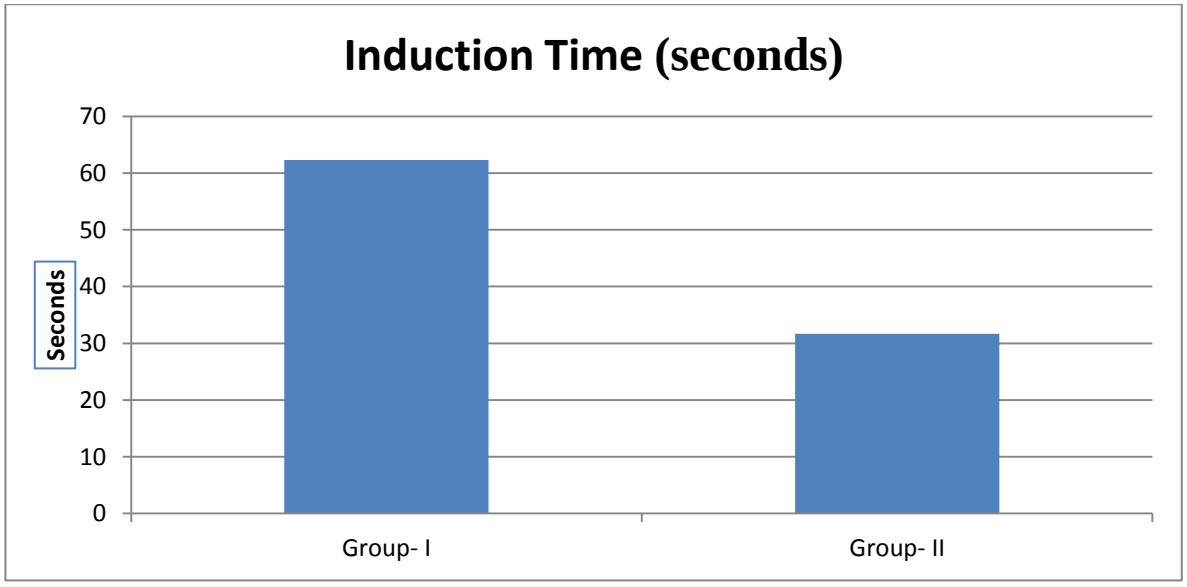


Fig.3 Induction time in groups I and II

4.3 DURATION OF SURGICAL ANAESTHESIA

In the dogs of group I, anaesthesia could be maintained for a period of 38 to 50 minutes, with a mean period of 45.22 ± 1.68 minutes. In the dogs of group II, anaesthesia could be maintained to satisfaction for a period ranging from 55 to 65 minutes, with a mean period of 61.19 ± 1.40 minutes.

Statistical analysis of the data revealed that the maintenance period was significantly higher in the dogs of group II. The results of the statistical analysis and the data are presented in table 6 and fig. 4.

Table.6 Duration of Surgical Anaesthesia in the two groups.

	Group- I	Group-II
Duration Of Surgical Anaesthesia (In Minutes)	45.22^{a}±1.68 (Range 38-50 Minutes)	61.19^{b}±1.40 (Range 55-65 Minutes)

*-Significant (P≤0.05) - Means with different superscripts differ significantly.

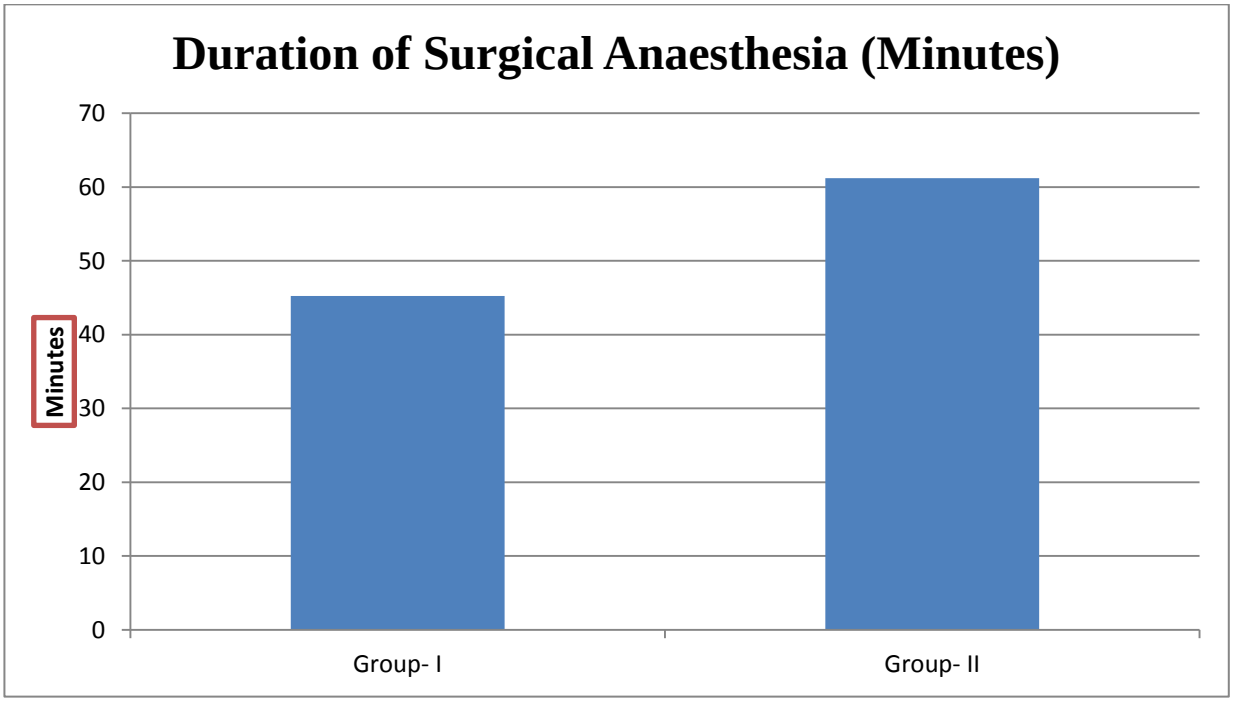


Fig.4 Duration of surgical anaesthesia in groups I and II

4.4 RECOVERY TIME

In the dogs of group I, the anaesthetic recovery time ranged from 120 to 135 minutes, with a mean period of 128.83 ± 2.43 minutes. In the dogs of group II, the anaesthetic recovery time ranged from 186 to 223 minutes, with a mean period of 205.00 ± 5.97 minutes.

The recovery time from anaesthesia was significantly shorter in the dogs of group I when compared to group II. The results of the statistical analysis and the data are presented in table 7 and fig. 5.

The recovery score was 4 (gradual, smooth, quiet, rapid, comfortable) in all the dogs of group I and 3 (gradual, slow, moderate, restless) in all the dogs of group II.

Table.7 RecoveryTime

	Group- I	Group-II
Recovery Time (Minutes)	128.83[a]±2.43 (Range 120-135 Minutes)	205.00[b]±5.97 (Range 186-223 Minutes)

*-Significant (P≤0.05) - Means with different superscripts differ significantly.

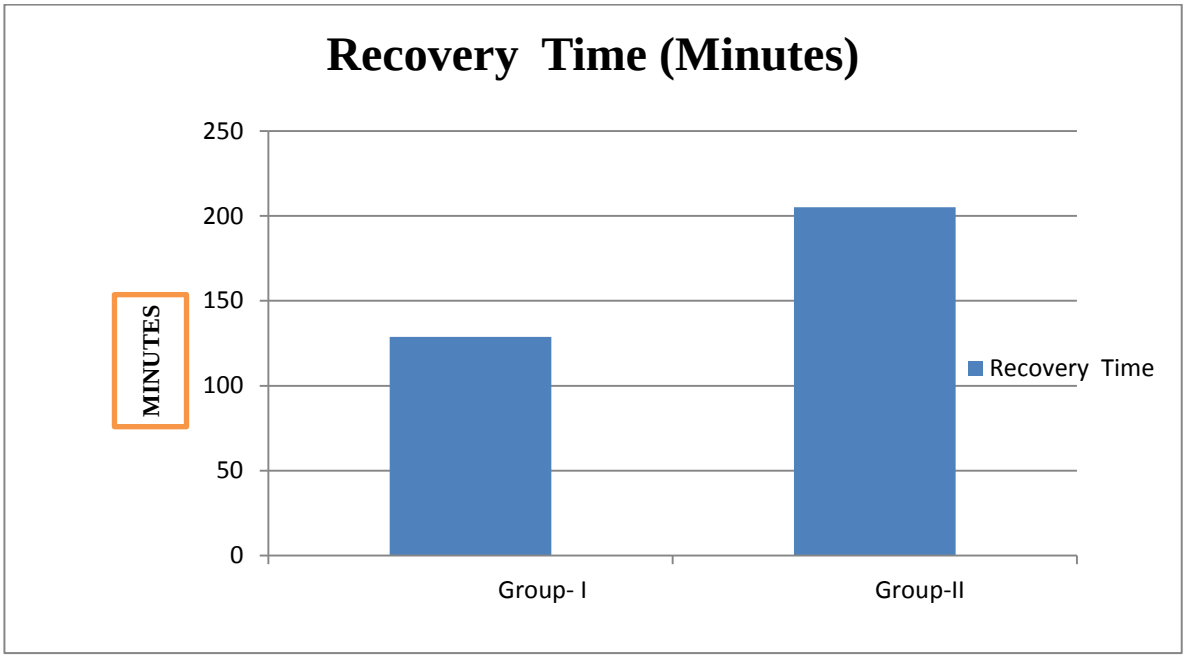


Fig.5 Recovery from anaesthesia in group I and II

4.5 ASSESSMENT OF REFLEXES

Various reflexes like pedal, palpebral, position of eyeball, corneal and laryngotracheal reflexes were recorded before and during anaesthesia in the two anaesthetic protocols studied. The various reflexes checked and recorded as present (P), moderate (M), absent (A), Central (C), Ventromedially Rolled Down (RD).

In the two groups, all the reflexes were brisk to sluggish 10 minutes after premedicaton of anaesthesia. After induction and during the maintenance of anaesthesia, all the reflexes tested were absent. However, after about five minutes of withdrawal of Propofol maintenance in all the dogs of the two groups, the reflexes started reappearing to moderate and then onwards reflexes were fully present. The details regarding the reflexes studied were presented in table 8.

TABLE.8 Assessment of Reflexes

Group	Reflexes	Observation period in minutes									
		0	5	10	15	20	25	30	35	40	60
I(n=6)	Pedal Reflex	P	A	A	A	A	A	A	M	P	P
	Palpebral	P	A	A	A	A	A	A	M	P	P
	Position of Eye Ball	C	RD	RD	RD	RD	RD	RD	RD	C	C
	Corneal Reflex	P	A	A	A	A	A	A	M	P	P
	Laryngeal Reflex	P	A	A	A	A	A	A	M	P	P
II(n=6)	Pedal Reflex	P	A	A	A	A	A	A	A	A	M
	Palpebral	P	A	A	A	A	A	A	A	A	M
	Position Of Eye Ball	C	RD	RD	RD	RD	RD	RD	RD	RD	C
	Corneal Reflex	P	A	A	A	A	A	A	A	A	M
	Laryngotracheal Reflex	P	A	A	A	A	A	A	A	A	M

P-Present; M-Moderate; A- Absent; C- Central; RD-Ventromedially Rolled Down
0-Before Premedication

4.6 PHYSIOLOGICAL PARAMETERS

The physiological parameters were recorded prior to premedication, 15 minutes after premedication, and 0 (induction), 5, 10, 15, 25, 35, 45, 60 and 90 minutes in all the dogs of the two groups. The values are presented in table 9 and fig. 6.

The mean rectal temperature (^{0}F) at prior to premedication, 15minutes after premedication, 0 (induction), 5, 10, 15, 25, 35, 45, 60 and 90 minutes in the dogs of group I were found to be 101.38 ± 0.21, 100.73 ± 0.14, 100.33 ± 0.11, 100.14 ± 0.12, 99.54 ± 0.15, 99.27 ± 0.17, 98.86 ± 0.21, 97.71 ± 0.18, 97.46 ± 0.25, 97.06 ± 0.31, 96.61 ± 0.11 respectively. The corresponding values in the group II were 101.50 ± 0.16, 100.88 ± 0.13, 100.38 ± 0.38, 100.20 ± 0.42, 99.94 ± 0.53, 99.48 ± 0.11, 99.67 ± 0.21, 98.47 ± 0.12, 97.81 ± 0.13, 97.45 ± 0.57, 97.24 ± 0.38, respectively.

The mean heart rate at the intervals mentioned above was found to be 164.33 ± 1.12, 160.67 ± 3.88, 178.50 ± 2.22, 174.55 ± 2.81, 166.63 ± 1.12, 166.84 ± 1.82, 169.33 ± 1.43, 169.73 ± 2.67, 164.45 ± 2.34, 170.26 ± 1.05 and 177.00 ± 1.21 beats per minute respectively in the dogs of group I. The corresponding values in the dogs of group II were 151.08 ± 2.21, 154.15 ± 6.78, 168.64 ± 1.14, 169.31 ± 1.28, 166.44 ± 2.12, 165.59 ± 1.67, 165.92 ± 3.23, 164.60 ± 1.08, and 165.49 ± 1.51, 165.52 ± 0.50 and 162.41 ± 1.60 beats per minute, respectively.

The mean respiratory rates at the said intervals in the dogs of group I were found to be 17.35 ± 1.06, 16.02 ± 1.01, 15.05 ± 2.21, 15.42 ± 0.71, 16.04 ± 0.63, 16.03 ± 0.76, 16.93 ± 1.84, 15.41 ± 1.20, 15.59 ± 0.63, 15.70 ± 0.55 and 16.29 ± 1.12 breaths per minute respectively. The corresponding values in the dogs of group II were found to 18.34 ± 2.02, 16.33 ± 1.03, 16.09 ± 2.23, 15.65 ± 1.01, 15.63 ± 0.82, 16.93 ± 2.01, 15.65 ± 1.96, 15.66 ± 1.21, 16.05 ± 1.04, 17.33 ± 0.52 and 17.02 ± 1.92 breaths per minute, respectively.

Statistical analysis of the data of rectal temperature revealed that there was a significant difference in rectal temperatures between the dogs of group I as compared to group II at 15 min after premedication, 10, 15, 20, 25, 35, 45 and 60 minutes after induction of anaesthesia. The temperature decreased gradually in both the groups and lowest value of temperature was found at 90 minutes after induction of anaesthesia. The values are presented in table 9 and fig. 6.

In dogs of both the groups, the heart rates fluctuated within normal physiological limits with a significant difference between the groups I and II at 0, 5, 10, 25, 60 and 90 minutes after induction of anaesthesia. The heart rate was increased gradually after premedication and remained high than that recorded prior to premedication in both the groups upto 90 minutes after induction of anaesthesia. The results of the statistical analysis are presented in table 9.

The respiratory rates were also fluctuated within normal physiological limits with a significant difference between the groups I and II at 5, 10, 25 and 35 minutes after induction of anaesthesia. The respiratory rate was decreased gradually after premedication and remained low than that recorded prior to premedication in both the groups upto 90 minutes after induction of anaesthesia. The results of the statistical analysis are presented in table 9.

Table.9 Mean values of physiological parameters in dogs

Group	Time Intervals		Temperature (^{0}F)	Heart Rate (beats/min)	Respiratory Rate (breaths/min)
I (n=6)	**Prior to Premedication**		101.38±0.21	164.33±1.12	17.35± 1.06
	After Premedication	**15 min**	100.73^a±0.14	160.67± 3.88	16.02± 1.01
	After Diazepam-Ketamine Induction	**0 min**	100.33± 0.11	178.50 ^{a}± 2.22	15.05± 2.21
		5 min	100.14± 0.12	174.55 ^{a} ± 2.81	15.42 ^{a} ±0.71
		10min	99.54^a±0.15	166.63 ^{a} ± 1.12	16.04 ^{a} ±0.63
		15 min	99.27^a± 0.17	166.84± 1.82	16.03±0.76
		25 min	98.86^a±0.21	169.33 ^{a} ± 1.43	16.93 ^{a}± 1.84
		35 min	97.71^a± 0.18	169.73± 2.67	15.41 ^{a} ± 1.20
		45 min	97.46^a ±0.25	164.45± 2.34	15.59± 0.63
		60 min	97.06 ^{a}± 0.31	170.26 ^{a} ± 1.05	15.70±0.55
		90min	96.61±0.11	177.00 ^{a} ± 1.21	16.29± 1.12
II (n=6)	**Prior to Premedication**		101.50±0.16	151.08± 2.21	18.34± 2.02
	After Premedication	**15 min**	100.88^b± 0.13	154.15±6.78	16.33± 1.03
	After Midazolam-Ketamine Induction	**0 min**	100.38 ± 0.38	168.64 ^{b} ± 1.14	16.09± 2.23
		5 min	100.20 ±0.42	169.31 ^{b}± 1.28	15.65 ^{b} ± 1.01
		10 min	99.94^b± 0.53	166.44^b± 2.12	15.63 ^{b} ± 0.82
		15 min	99.48^b ± 0.11	165.59± 1.67	16.93± 2.01
		25 min	99.67^b± 0.21	165.92 ^{b} ± 3.23	15.65 ^{b} ± 1.96
		35 min	98.47^b ± 0.12	164.60± 1.08	15.66 ^{b} ± 1.21
		45 min	97.81^b± 0.13	165.49± 1.51	16.05± 1.04
		60 min	97.45^b± 0.57	165.52 ^{b} ± 0.50	17.33±0.52
		90 min	97.24± 0.38	162.41 ^{b}± 1.60	17.02± 1.92

*-Significant (P≤0.05%) - Means with different superscripts differ significantly.

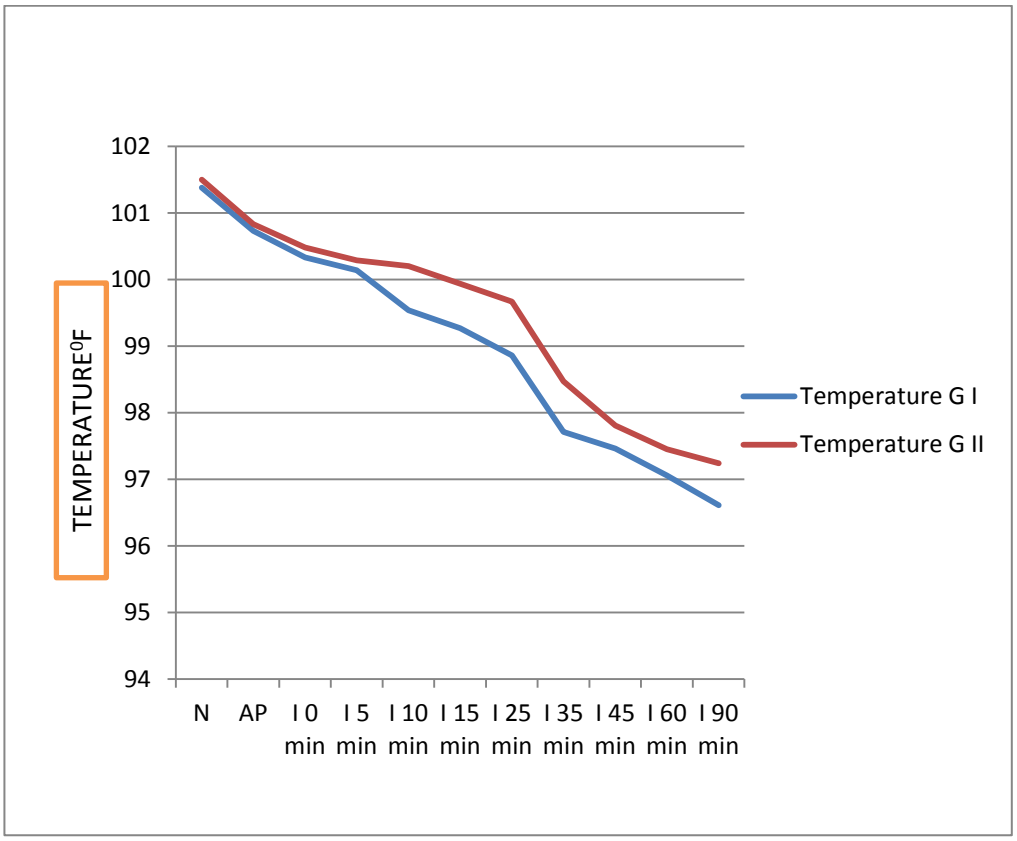


Fig.6 Variation of Rectal Temperature (^{0}F) between groups I and II

4.7 HAEMATOLOGICAL OBSERVATIONS

Haematological parameters such as total erythrocyte count (TEC) in millions/cumm, hemoglobin (Hb) in grams per dl, packed cell volume (PCV) as percent, total leukocyte count (TLC) in thousands per cumm and differential leucocyte count in percentage (DLC) were recorded prior to premedication, 15 minutes after premedication and after 30 and 90 minutes of induction.

4.7.1 Total Erythrocyte Count (TEC)

The mean total erythrocyte count (TEC) values prior to premedication, 15 minutes after premedication and after 30 and 90 minutes of induction in the dogs of group I were recorded to be 6.68 ± 0.07, 5.59 ± 0.05, 5.34 ± 0.11 and 5.19 ± 0.10, where as in the dogs of group II, the values were found to be 6.78 ± 0.13, 5.58 ± 0.07, 5.31 ± 0.14 and 5.13 ± 0.15 millions per cumm respectively.

Statistical analysis revealed that the total erythrocyte count followed non-significant difference between the dogs of both the groups prior to premedication, 15 minutes after premedication and after 30 and 90 minutes of induction and TEC decreased gradually in both the groups and are presented in table 10.

4.7.2 Haemoglobin (Hb)

The mean haemoglobin (Hb) levels in the dogs of group I were recorded to be 12.18 ± 0.11, 9.65 ± 0.13, 9.20 ± 0.17 and 9.13 ± 0.12 while in the dogs of group II the Hb levels were found to be 13.3 ± 0.10, 9.97 ± 0.11, 9.50 ± 0.11 and 9.28 ± 0.14 g/dl respectively.

Statistical analysis revealed that the haemoglobin levels followed non-significant difference between the dogs of both the groups prior to premedication, 15

minutes after premedication and after 30 and 90 minutes of induction and haemoglobin levels decreased gradually in both the groups and the details are presented in table 10.

4.7.3 Packed Cell Volume (PCV)

The mean packed cell volume (PCV) levels in the dogs of group I and group II were recorded to be 44.36 ± 0.76, 39.22 ± 0.22, 37.89 ± 0.21 and 35.25 ± 0.21%; 47.25 ± 0.58, 40.84 ± 1.52, 37.03 ± 0.14, 36.51 ± 0.31% respectively.

Statistical analysis revealed that the packed cell volume (PCV) levels followed non-significant difference between the dogs of the both the groups prior to premedication, 15 minutes after premedication as well as after 30 and 90 minutes of induction and PCV decreased gradually in both the groups. Details are presented in table 10.

4.7.4 Total Leucocyte Count (TLC)

The mean total leukocyte count (TLC) values prior to premedication, 15 minutes after premedication and after 30 and 90 minutes of induction in the dogs of group I were recorded to be 6.85 ± 0.04, 6.61 ± 0.09, 6.60 ± 0.07 and 6.55 ± 0.05 while in the dogs of group II similar values were recorded to be 6.83 ± 0.15, 6.25 ± 0.10, 6.16 ± 0.09 and 6.11 ± 0.14 thousands per cumm respectively.

Statistical analysis revealed that the total leucocyte Count (TLC) followed non-significant difference between the dogs of both the groups prior to premedication, 15 minutes after premedication and after 30 and 90 minutes of induction and TLC decreased gradually in both the groups and are presented in table 10.

4.7.5 Differential Leucocyte Count (DLC)

The mean neutrophil (N) count in the dogs of group I was recorded to be 65.50 ± 0.62, 70.37 ± 0.88, 72.21 ± 0.63 and 74.18 ± 0.57% and in the dogs of group II, these values were found to be 66.06 ± 0.39, 70.66 ± 0.17, 71.20 ± 1.37 and 73.35 ± 0.92% respectively.

Statistical analysis revealed that there was a non-significant difference at various intervals in neutrophil count between the group I and group II and neutrophil count increased gradually in both the groups and are presented in table 10.

The mean lymphocyte (L) count in the dogs of group I were recorded to be 33.19 ± 0.63, 27.37 ± 0.28, 26.93 ± 0.52 and 28.01 ± 0.37. In the dogs of group II, these values were found to be 32.04 ± 0.30, 26.93 ± 1.08, 26.10 ± 0.62 and 27.72 ± 0.74% respectively.

Statistical analysis revealed that there was a non-significant difference at various intervals in lymphocyte count between the group I and group II and lymphocyte count decreased gradually in both the groups and are presented in table 10.

The mean monocyte (M) count in the dogs of group I were recorded to be 0.98 ± 0.11, 0.92 ± 0.12, 0.83 ± 0.16 and 0.74 ± 0.14% and in group II, 0.95 ± 0.22, 0.91 ± 0.16, 0.88 ± 0.22 and 0.74 ± 0.21% respectively.

Statistical analysis revealed that there was a non-significant difference at various intervals in monocyte count between the group I and group II and the monocyte count decreased gradually in both the groups and are presented in table 10.

The mean eosinophil (E) count in the dogs of group I were recorded to be 0.82 ± 0.12, 0.93 ± 0.11, 0.83 ± 0.13 and 0.85 ± 0.17 and in group II, 0.87 ± 0.11, 0.93 ± 0.14, 0.88 ± 0.17 and 0.94 ± 0.12% respectively.

Statistical analysis revealed the differences among the intervals and between the groups to be non-significant and at 90 minute interval, there was a significant difference in the value of eosinophil between group I and group II and are presented in table 10.

Table.10 Mean values of haematological parameters in dogs anaesthetized with Diazepam-Ketamine and Propofol (Group-I;n=6); Midazolam-Ketamine and Propofol (Group-II;n=6)

Group	Time Intervals		TEC (10^6/cmm)	Hb (g/dl)	PCV (%)	TLC (10^3/cmm)
I	Prior to Premedication		6.68±0.07	12.18±0.11	44.36±0.76	6.85±0.04
	After Premedication	15 min	5.59±0.05	9.65 ± 0.13	39.22±0.22	6.61±0.09
	After Diazepam-Ketamine Induction	30 min	5.34±0.11	9.20 ± 0.17	37.89±0.11	6.60±0.07
		90 min	5.19±0.10	9.13 ± 0.12	35.25± 0.21	6.55±0.05
II	Prior to Premedication		6.78±0.13	13.33±0.10	47.25±0.58	6.83± 0.15
	After Premedication	15 min	5.58±0.07	9.97 ± 0.11	40.84±1.52	6.25±0.10
	After Midazolam-Ketamine Induction	30 min	5.31±0.14	9.50 ± 0.11	37.03±0.14	6.16±0.09
		90 min	5.13±0.15	9.28 ± 0.14	36.51± 0.31	6.11± 0.14

Group	Time Intervals		Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)
I	Prior to Premedication		65.50± 0.62	33.19±0.63	0.98± 0.11	0.82±0.12
	After Premedication	15 min	70.37± 0.88	27.37±0.28	0.92± 0.12	0.93±0.11
	After Diazepam-Ketamine Induction	30 min	72.21± 0.63	26.93± 0.52	0.83± 0.16	0.83±0.13
		90 min	74.18± 0.57	28.01 ±0.37	0.74±0.14	0.85^{a}±0.17
II	Prior to Premedication		66.06±0.39	32.04±0.30	0.95±0.22	0.87± 0.11
	After Premedication	15 min	70.66± 0.17	26.93±1.08	0.91±0.16	0.93±0.14
	After Midazolam-Ketamine Induction	30 min	71.20± 1.37	26.10± 0.62	0.88±0.22	0.88±0.17
		90 min	73.35± 0.92	27.72± 0.74	0.74±0.21	0.94^{b} ±0.12

*-Significant (P≤0.05) - Means with different superscripts differ significantly.

4.8 BIOCHEMICAL STUDIES

The biochemical observations were studied prior to premedication, 15 minutes after premedication and after 30 and 90 minutes of induction.

4.8.1 Serum Aspertate Amino Transferase (AST)

The mean serum AST levels in the dogs of group I were recorded to be 28.86 ± 0.49, 24.50 ± 0.22, 23.22 ± 0.41 and 22.33 ± 0.61 IU/L while in the group II, the values were recorded to be 29.13 ± 0.72, 24.19 ± 0.20, 23.25 ± 0.71 and 22.33 ± 0.42 IU/L, respectively.

Statistical analysis revealed that there was a significant increase in AST levels of group I compared to group II at 15 minutes after premedication and then gradually non-significantly increased upto 90 minutes after induction in both the groups. The values are presented in table 11.

4.8.2 Serum Alanine Amino Transferase (ALT)

The mean serum ALT levels in the dogs of group I were recorded to be 19.40 ± 0.11, 16.53 ± 0.55, 15.56 ± 0.21 and 14.28 ± 0.54 IU/L and in the group II, similar values were recorded to be 16.53 ± 0.65, 15.77 ± 0.40, 14.46 ± 0.71 and 13.41 ± 0.13 IU/L respectively.

Statistical analysis revealed that there was a non-significant difference at various intervals in ALT levels of group I and group II and the ALT decreased gradually in both the groups and are presented in table 11.

4.8.3 Blood Urea Nitrogen (BUN)

The mean BUN levels in the group I were recorded to be 8.51 ± 0.11, 11.32 ± 0.43, 12.24 ± 0.71 and 14.51 ± 0.79 mg/dl. In the dogs of group II, the BUN values were found to be 8.80 ± 0.44, 11.63 ± 0.61, 12.54 ± 0.66 and 14.90 ± 0.74 mg/dl respectively.

Statistical analysis revealed that there was a non-significant difference at various intervals in BUN levels of group I and group II and the BUN levels increased gradually in both the groups. Significant difference observed at 30 minute interval between the groups and are presented in table 11.

4.8.4 Serum Creatinine (C)

The mean serum creatinine levels in group I were recorded to be 0.52 ± 0.06, 0.88 ± 0.05, 1.42 ± 0.13 and 1.41 ± 0.10 mg/dl. On the other hand, in the dogs of group II, the concerned values were found to be 0.53 ± 0.02, 1.27 ± 0.03, 1.73 ± 0.01 and 1.85 ± 0.08 mg/dl respectively.

Statistical analysis revealed that there was a non-significant difference at various intervals in serum creatinine levels of group I and group II and the serum creatinine levels increased gradually in both the groups. Significant difference observed at 30 minute interval between the groups and are presented in table 11.

Table.11 Mean values of biochemical parameters in dogs anaesthetized with Diazepam-Ketamine and Propofol(Group-I; n=6); Midazolam-Ketamine and Propofol (Group-II; n=6)

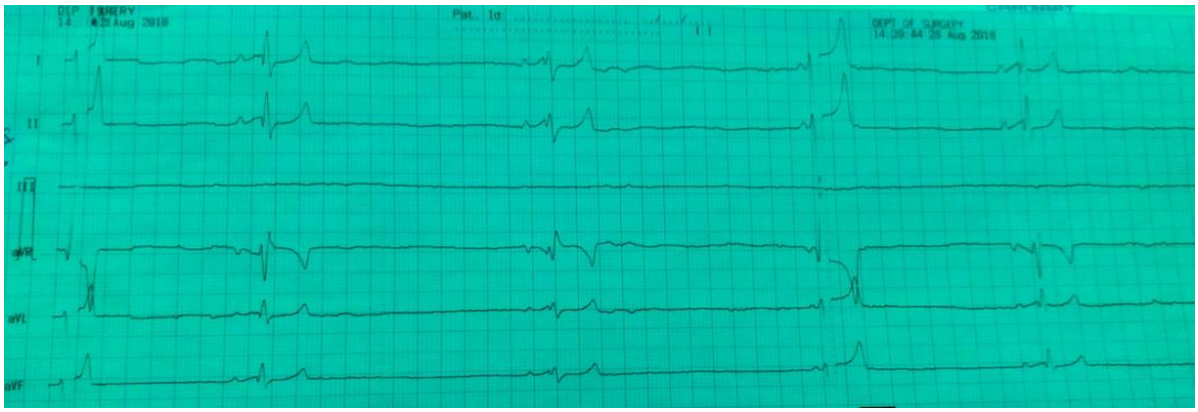
Group	Time Intervals		AST (IU/L)	ALT (IU/L)	BUN (mg/dl)	C (mg/dl)
I	Prior to Premedication		28.86±0.49	19.40± 0.11	8.51± 0.11	0.52± 0.06
	After Premedication	15 min	24.50^{a}±0.22	16.53± 0.15	11.32± 0.43	0.88± 0.05
	After Diazepam-Ketamine Induction	30 min	23.22± 0.41	15.56± 0.21	12.24^{a}± 0.71	1.42^{a}±0.13
		90 min	22.33±0.61	14.28±0.54	14.51± 0.79	1.41±0.10
II	Prior to Premedication		29.13± 0.72	16.53± 0.65	8.80± 0.44	0.53±0.02
	After Premedication	15 min	24.19^{b}±0.20	15.77±0.40	11.63± 0.61	1.27± 0.03
	After Midazolam-Ketamine Induction	30 min	23.25± 0.71	14.46± 0.71	12.54^{b}± 0.66	1.73^{b}±0.01
		90 min	22.33±0.42	13.41±0.13	14.90± 0.74	1.85±0.08

*-Significant (P≤0.05%) - Means with different superscripts differ significantly.

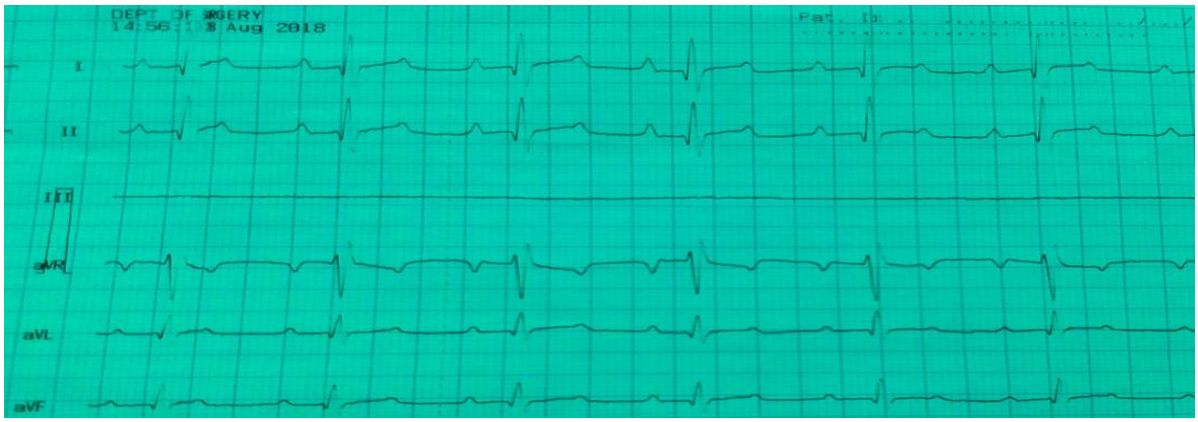
4.9 ELECTROCARDIOGRAPHY

Electrocardiography in the dogs of two groups revealed no abnormalities in the sizes of P, QRS or T waves. No changes in the cardiac axis were recorded. No arrhythmias of any kind wave recorded in any animals of any group. Representative ECG recordings obtained 10 minutes after premedication, 30 minutes during the depth of anaesthesia and 10 minutes after recovery for each of the two groups are presented in fig.7 and fig. 8.

After Premedication



During Surgical Anaesthesia



After Recovery

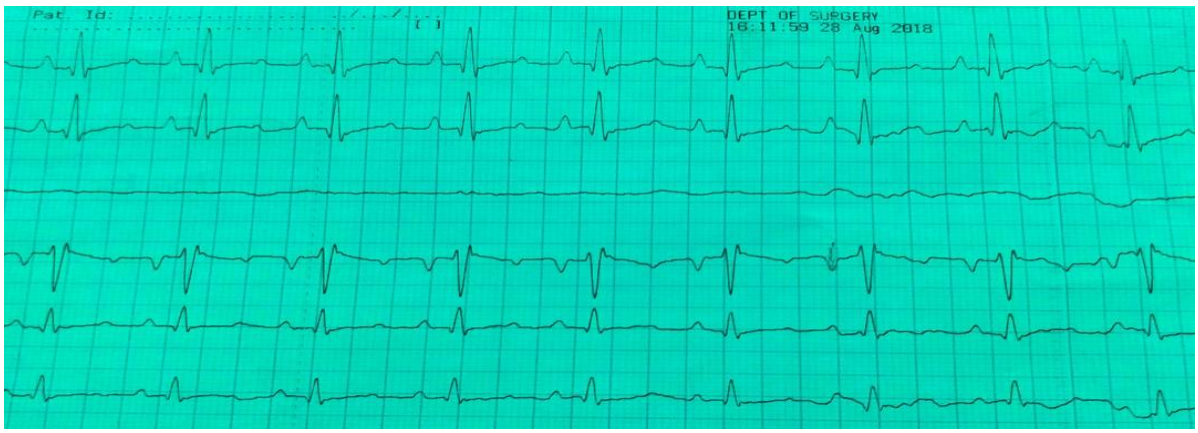
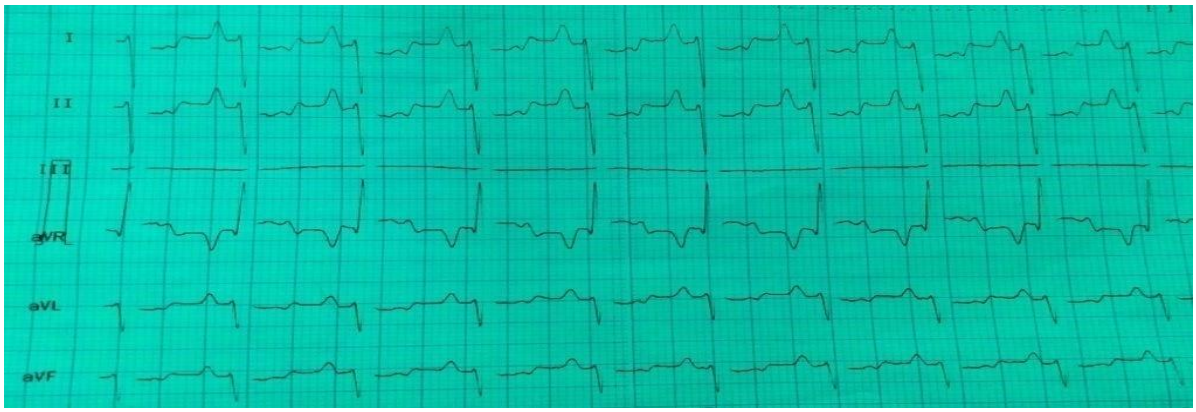
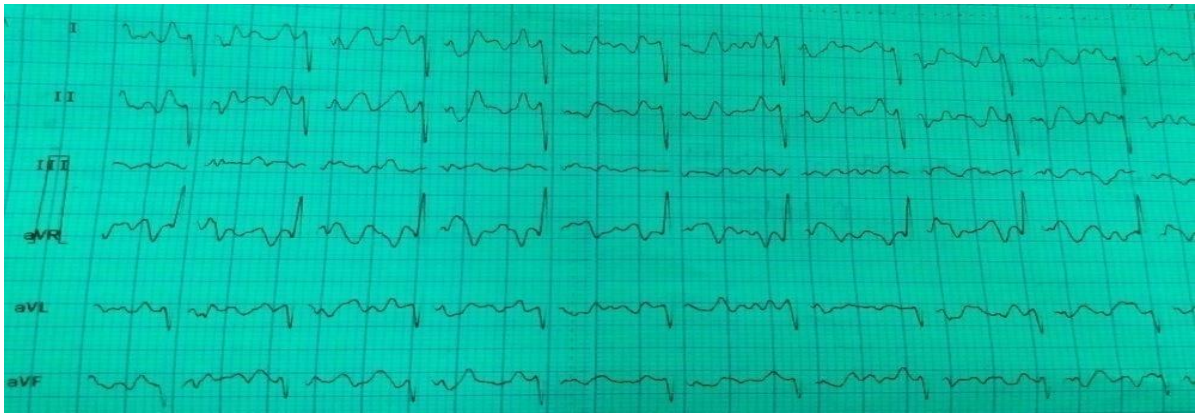


Fig.7 Electrocardiogram 10 minutes after premedication, 30 minutes during the depth of anaesthesia and 10 minutes after recovery – Group I – Diazepam-Ketamine inducton and Propofol maintenance.

After Premedication



During Surgical Anaesthesia



After Recovery

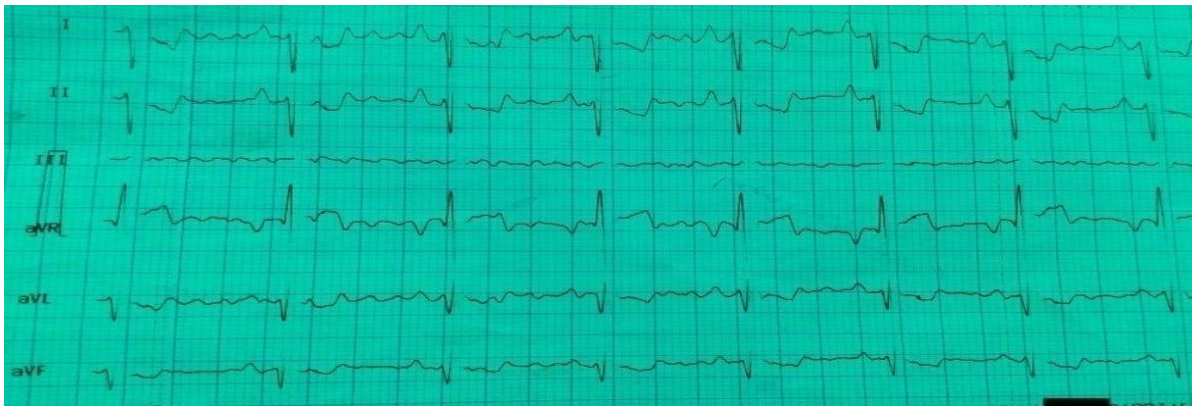


Fig.8 Electrocardiogram 10 minutes after premedication, 30 minutes during the depth of anaesthesia and 10 minutes after recovery – Group II – Midazolam-Ketamine inducton and Propofol maintenance.

CHAPTER V

DISCUSSION

Advances in the field of anaesthesiology have made several surgical operations possible and safer in both human and animal surgical patients. The induction of anaesthesia does not only involves rendering the animal unconscious, but is also closely associated with maintenance of several vital parameters within the normal range during the anaesthetic duration (Paddleford, 1999). Several anaesthetic protocols and procedures have been developed and are in use in both veterinary and human anaesthesia.

Total intravenous anaesthesia (TIVA) is associated with its own side effects and complications (Clarke and Trim, 2014). Similarly, the use of only inhalation anaesthesia in animals is also not always possible owing to the temperament of the animals (Thurmon *et al*., 1999). Therefore, several different combinations of anaesthetics have come into use in human and animal anaesthesiology. The use of balanced anaesthesia (Anagnostou, 2011; Thurmon *et al*., 1999; Grimm *et al*., 2015), total intravenous anaesthesia (Clarke and Trim, 2014), intravenous anaesthetic induction followed by maintenance with inhalation anaesthetics (Altug *et al*., 2009; Yarsan *et al.,* 2010) have all become the routinely used protocols. In spite of such rapid advances in the field of anaesthesiology, no anaesthetic combination can be described as "ideal". Hence, there is

need to use different combinations to enhance safety of the patient since anaesthesia related complications and deaths are the major cause of concern during surgical operations.

The present study was taken up in 12 dogs to compare the suitability and safety of the use of anaesthetic induction agents, i.e., diazepam-ketamine (i/v) and midazolam-ketamine (i/v) with BAG (Butorphanol, Acepromazine, Glycopyrrolate) i/m as preanesthetic agents and intravenous administration of propofol for maintenance.

5.1 PREANAESTHETIC PREPARATION AND PREMEDICATION

The results of the present study indicated that the preanaesthetic preparation of the patients in the two groups and the premedication procedures adopted were satisfactory, since no complications were encountered in any animal. The sedation score ranged from 3 to 4. BAG provided moderate (slight resistance) to profound (resistance none) sedation. Among the 12 dogs, 10 dogs (83.33 %) had moderate sedation and only 2 dogs (16.67 %) indicated the signs of profound sedation. Roon *et al.* (2007) reported that acetylpromazine provided profound sedation while the same drug was reported to have produced moderate sedation (Posner, 2007) without any complications via antidopaminergic effects. Pircio *et al.* (1976) reported that butorphanol also produced mild sedation in dogs, when injected IM at 0.5 mg/kg. Singh *et al.* (2013) also reported mild to profound sedation after butorphanol-acepromazine-glycopyrrolate administration in dogs. Ranpariya *et al.* (2013) stated that butorphanol-acepromazine-glycopyrrolate combination provided moderate to profound sedation.

No side effect or complication was seen during this study. In their works, vomition was recorded with butorphanol administration (Dyson, 2002), while Stephan *et al.* (2003) observed miosis following administration of acepromazine and glycopyrrolate as a single preanaesthetic agent in dogs. In the present study, it was

considered possible that the combination of three drugs, viz., butorphanol, acepromazine and glycopyrrolate nullified side effects of one another. A greater degree of sedation and calmness was observed in all dogs premedicated with butorphanol, acepromazine and glycopyrrolate in the study carried out by Pramodh and Mohindroo (2010).

5.2 INDUCTION OF ANAESTHESIA

In the present study, the time to induction and or endotracheal intubation in dogs anaesthetized with midazolam-ketamine was significantly shorter than for those anaesthetized with diazepam-ketamine. Similar observation was made by Hellyer *et al.* (1991).

Induction score was found to be 1 (good) in four dogs and 2 (fair) in two dogs of group I whereas induction score was 1 (good) in all the dogs induced with midazolam-ketamine (group II). The quality of induction was adjudged to be fair to good with diazepam-ketamine induction and this observation was in accordance with the findings of White *et al.* (2001).

Hellyer *et al.* (1991) and Ranpariya *et al.* (2013) also stated that good, smooth and satisfactory induction was observed after ketamine-midazolam administration. However, in their studies, the same combination was noted to have resulted in stable maintenance with isoflurane during orthopaedic procedures in all the dogs. Ferreira *et al*. (2015) also reported that diazepam-ketamine produced good quality of induction as indicated by calm transition and no paddling following their studies.

5.3 MAINTENANCE OF ANAESTHESIA

In the present study, anaesthesia was maintained with intravenous administration of propofol by giving intermittent boluses at the dose rate of 0.5-2.0 mg/kg body weight

and incremental doses were administered whenever needed during surgical procedure through intravenous route "to effect" in both the groups of dogs.

In the dogs of group I, anaesthesia could be maintained for a period of 38 to 50 minutes and in group II, anaesthesia could be maintained to satisfaction for a period ranging from 55 to 65 minutes. If the intermittent bolus technique is used, the dose is administered when needed "to effect". Paddleford (1999) reported that anaesthetic maintenance by intravenous administration of bolus doses of propofol required doses ranging from 0.44-2.2 mg/kg body weight .

The results of the present study indicated that the maintenance of anaesthesia in the two groups with propofol was satisfactory. This observation was in accordance with the report of Caines *et al.* (2014), who also stated that propofol was easy to use for maintenance of anaesthesia in dogs.

5.4 RECOVERY FROM ANAESTHESIA

In the dogs of group I where diazepam-ketamine were used as induction agents, the recovery time was found to be shorter (128.83 ± 2.43 minutes) when compared to the recovery time of (205.00 ± 5.97 minutes) resulting from midazolam-ketamine (group II). Recovery score was found to be 4 (gradual, smooth, quiet, rapid, comfortable) in all the dogs of group I whereas recovery score was 3 (gradual, slow, moderate, restless) in all the dogs induced with midazolam-ketamine (group II). This indicated that induction with diazepam-ketamine was better than midazolam-ketamine as far as the recovery of anaesthesia was concerned.

Bufalari *et al.* (1997) reported long anaesthetic duration and recovery times in dogs premedicated with acepromazine-butorphanol. Recoveries tended to be better with diazepam-ketamine than with midazolam-ketamine, perhaps because of the longer

elimination time of diazepam (7.6 hours) than midazolam (1.1 hours) as reported by Hellyer *et al.* (1991). Emergence excitement was commonly observed. Haskins *et al.*, (1985) reported that hyperthermia from increased muscular activity and metabolic activity frequently occurred in non-premedicated dogs waking up from ketamine induction. However, this was not observed in any of the dogs of the present study as animals were under effect of acepromazine. Smooth recovery seen in all the dogs premedicated with butorphanol, acepromazine and glycopyrrolate during the present study. Pramodh and Mohindroo (2010) and Ranpariya *et al.* (2013) also made similar observations.

5.5 REFLEXES

In the two groups, all the reflexes were graded to be brisk to sluggish until 10 minutes after premedicaton. After induction and during the maintenance of anaesthesia, all the reflexes tested for were absent. However, after about five minutes of withdrawal of propofol maintenance in all the dogs of the two groups, the reflexes started reappearing. The reflexes were initially sluggish and turned to moderate and then onwards reflexes were fully present. Similar observations were made by Paddleford (1999). Along with these reflexes, the eye balls that were found to be rotated ventromedially in all the dogs of the two groups by 15 minutes after induction with diazepam-ketamine, remained unchanged throughout the anaesthetic period (Abdel-Hady *et al.*, 2017).

Yohannes *et al.* (2018) assessed different body reflexes such as palpebral, corneal and pedal reflexes during anaesthesia and stated that these reflexes are lost at mean 12.2 ± 2.12 minutes, 12.2 ± 2.12 minutes and 12.15 ± 2.21 after diazepam-ketamine induction respectively and remained unchanged throughout the anaesthesia.

5.6 PHYSIOLOGICAL PARAMETERS

The results showed there was a significant decrease in rectal temperatures between the dogs of group I compared to group II at 15 minutes after premedication and at 10, 15, 20, 25, 35, 45 and 60 minutes after induction of anaesthesia. The temperature decreased gradually in both the groups and the lowest rectal temperatures was recorded at 90 minutes after induction of anaesthesia. Chonde *et al.* (2004) also recorded a non-significant reduction of rectal temperature in dogs that were induced with diazepam and ketamine anaesthesia. Butola and Singh (2003[a]) also made similar observations regarding a non-significant fall in rectal temperature after midazolam and ketamine anaesthesia in dogs. The decrease in rectal temperature was attributed to inhibition of skeletal muscle movement, reduction in metabolic rate and depression of the thermoregulatory centre (Jadon and Kumar, 1994).

In dogs of both the groups the heart rates fluctuated within normal physiological limits with a significant difference between the groups at 0, 5, 10, 25, 60 and 90 minutes after induction of anaesthesia. The heart rate was found to have increased after premedication and remained higher than that recorded prior to premedication. This was observed in both the groups of dogs upto 90 minutes after induction of anaesthesia. Although the heart rates between the groups were found to differ from each other, they were still well within the normal range and hence were considered in consequential. Fayyaz *et al.,* (2009) also described similar trend of increased heart rate in ketamine-diazepam compared to isoflurane when used as maintenance agent. Jacobson and Hartsfield (1991), Butola and Singh (2003[a]) also reported significantly increased heart rate at all time intervals where ketamine-midazolam were used as induction agents. Henao-Guerrero and Ricco (2014) also stated that there was significant increased in heart rate 5 minutes after induction of anaesthesia with diazepam-ketamine.

The respiratory rates also fluctuated within normal physiological limits with a significant difference between the groups at 5, 10, 25 and 35 minutes after induction of anaesthesia in the present study. Respiratory rate was found to have decreased gradually after premedication and remained lower than that recorded prior to premedication. Similar observations were made in respect of respiratory rate in both the groups upto 90 minutes after induction of anaesthesia in accordance with Aithal *et al.* (2013) during midazolam-ketamine anaesthesia.

Popovic *et al.* (1972) and Stephien *et al.* (1995) also recorded similar effects of decrease in respiratory rate in dogs after acepromazine premedication. Reduction in respiratory rate (RR) was also observed in midazolam-ketamine groups which were in accordance with the findings of Butola and Singh (2003[a]). Hellyer *et al.* (1991) reported a non-significant decrease in the respiratory rate during diazepam-ketamine and midazolam-ketamine anaesthesia.

5.7 HAEMATOLOGICAL OBSERVATIONS

Results of the present clinical study revealed a non-signficant difference between the two groups with regards to total erythrocyte count (TEC) during all the intervals tested. Within the two groups, however, the gradual and mild decrease in the TEC counts observed at various time intervals, i.e., prior to premedication, 15 minutes after premedication and after 30 and 90 minutes of induction was considered clinically inconsequential, since the counts remained within normal range. (Grimm *et al*., 2015) stated that the decrease in TEC counts during anaesthesia could be due to sequestration of blood cells in spleen and lungs during anaesthesia.

The Haemoglobin levels also showed a similar trend of reduction in haemoglobin levels at the different intervals tested in both the groups of dogs in present clinical study. Haemoglobin acts as a vehicle to carry and supply oxygen to tissues. The major pathological effect of low haemoglobin level is its threat to the transport of oxygen imposed by the diminution in the oxygen carrying capacity. Bhatia *et al.* (1979) stated that general anaesthesia induces vasodilation causing haemodilution and that affected the haemoglobin levels. It was reported that the decrease in haemoglobin might also be due to increase in CO_2 concentration during anaesthesia. Since increase or decrease in the value of haemoglobin depends on the size and number of circulating erythrocytes (Weiss and Wardrop, 2010), the decrease in haemoglobin concentration during anaesthesia in the present study was assumed to be due to decrease in total erythrocyte count. Decrease in haemoglobin levels was also reported during propofol (Gill *et al.*, 1996 and Kale *et al.*, 2006) and ketamine-midazolam anaesthesia (Butola and Singh, 2003[a]).

The results of the present cinical study showed that packed cell volume (PCV) levels fell mildly and gradually during the time intervals in both the groups of dogs. Despite reduction in PCV levels, they were observed to be well within the normal PCV range indicating that the changes were clinically inconsequent in all the dogs of the two groups. Decrease in mean PCV was recorded in dogs under the influence of a diazepam by Robertson *et al.* (1992). Butola and Singh (2003[a]) reported non-significant decrease in PCV under midazolam-ketamine anaesthesia in dogs.

Total Leucocyte Count (TLC) showed non-significant differences between the dogs of both the groups prior to premedication and at 15 minutes after premedication and at 30 and 90 minutes following induction. Butola and Singh (2003[a]) also made

similar observations. Weiss and Wardrop (2010) and Oyama *et al.* (1970) attributed the slight and statistically non-significant decrease in TLC during anaesthesia to adrenocortical stimulation and subsequent effect of glucocorticoids on circulating neutrophils and lymphocytes. Yohannes *et al.* (2018) also made similar observations following their anesthetic studies using diazepam-ketamine anaesthesia in dogs.

The changes in the differential leucocyte counts in the present study were found to be very minimal and negligible and the changes were within normal range in all the dogs of the two groups. Hence, the changes observed were concluded to be of no consequence in the two groups. Similar observations were also reported by Pandey *et al.* (1991) and Butola and Singh (2003[a]).

5.8 BIOCHEMICAL STUDIES

Statistical analysis of the liver enzyme levels observed in the dogs of the present clinical study showed that the fluctuations in the AST and ALT values in both the groups of dogs at different intervals were well within the normal range. This indicated that the doses of the drugs used in the present study in both the groups of dogs did not cause any hepatic damage. Similar observations were made by Butola and Singh (2003[a]) and Jadon *et al.* (2007).

The results of the present study showed a gradual increase in BUN and serum creatinine levels in both the groups. The fluctuations in all the dogs of the two groups were found to be within normal range. BUN and serum creatinine values are indicators of renal function. Jones *et al.* (1981) attributed the changes of these parameters to preanaesthetic fasting or anaesthesia induced mild depression of kidney function. Similar observations were made by Alexaki-Tsivanidou (1970), Kumar and Thurmon (1977), Pathak *et al.* (1982) and Singhal *et al.* (1983) during different anaesthetic

procedures. The change in the serum creatinine values were reported to be related to kidney function. A marginal increase in the values was considered possible whenever there was decreased renal flow and consequent decrease in glomerular filtration rate. Robertson *et al.* (1992) reported that this might happen due to altered haemodynamics, especially during anaesthesia. Similarly, Butola and Singh (2003[a]) reported a non-significant increase in value of creatinine during midazolam-ketamine anaesthesia in dogs.

5.9 ELECTROCARDIOGRAPHIC STUDIES

Electrocardiographic studies in all the twelve dogs of the two groups revealed no abnormalities in the sizes of P, QRS or T- waves, no changes in the cardiac axis and no arrhythmias of any kind in any dog of the two groups. The heart rates recorded in the electrocardiograms compared favourably with the manual stethoscope monitored readings, emphasizing the fact that none of the anaesthetic protocols tested in the present study led to any untoward changes in the functioning of the heart. Similar observations were also made by Paddleford (1999) and the same found at variance with the findings of Gunay *et al*. (2004), Choi *et al.* (2011) and Rafee *et al.* (2016).

5.10 CONCLUSION

The following conclusions were drawn from the results of the present clinical study:

1. Both the anaesthetic protocols tested in the present study provided satisfactory deep surgical anaesthesia in dogs.
2. Use of Butorphanol, Acepromazine and Glycopyrrolate (BAG) 15 minutes prior to induction proved to be an effective premedicant combination.
3. Butorphanol, Acepromazine and Glycopyrrolate nullified side effects of each other and provided excellent analgesic, sedative and antisialogauge effects.
4. Midazolam was found to be superior to Diazepam as an induction agent given in combination with Ketamine.
5. Recovery was rapid, smooth and uneventful in Diazepam-Ketamine induction and Propofol maintenance in comparison to Midazolam-Ketamine induction and Propofol maintenance.
6. None of the anaesthetic combinations produced adverse effects on various physiological, haematological, biochemical and electrocardiographic parameters.

CHAPTER VI

SUMMARY

With refinement in the day to day clinical surgery being performed in pet animals, the demands for better and safer anaesthetic protocols are increasing. Injectable balanced anaesthesia for today's veterinarians is the order of the day.

The present study was carried out on twelve clinical cases of dogs aged between 4 months to 10 years presented for various surgical operations. The dogs were randomly divided into two groups of six each. All the dogs were uniformly premedicated intramuscularly with Butorphanol, Acepromazine and Glycopyrrolate (BAG) at dose rate of 0.2, 0.04 and 0.01mg/kg body weight, respectively. Standard procedures were followed for haematological and biochemical analysis.

In the dogs of group I, fifteen minutes after premedication, anaesthesia was induced by slow intravenous injection of Diazepam at the rate of 0.28 mg/kg and Ketamine hydrochloride at the rate of 5 mg/kg body weight over a period of 60-90 seconds.

In the dogs of group II, fifteen minutes after premedication, anaesthesia was similarly induced with slow intravenous injection of Midazolam at the rate of 0.28 mg/kg and Ketamine at the rate of 5 mg/kg body weight over a period of 60-90 seconds.

Following induction of anaesthesia in both the groups of dogs, it was maintained with intravenous administration of Propofol at the rate of 0.5-2.0 mg/kg body weight. Incremental doses of Propofol were administered “to effect” whenever required during the surgical procedure through the intravenous life line.

Onset of sedative effect of preanaesthesia and anaesthetic effects like induction of anaesthesia, duration of anaesthesia, recovery time and physiological parameters like rectal temperature, heart rate, respiratory rate were studied prior to premedication, 15 minutes after premedication, 0 (induction), 5, 10, 15, 25, 35, 45, 60 and 90 minutes in all the dogs of the two groups. Haematological parameters like TEC, Hb, PCV, TLC and DLC and biochemical parameters like AST, ALT, BUN and serum creatinine were recorded prior to premedication, 15 minutes after premedication and after 30 and 90 minutes of induction. Electrocardiographic changes were recorded, 10 minutes after premedication, 30 minutes during anaesthesia and 10 minutes after recovery.

No complications were reported in any cases premedicated with BAG in entire study. Onset of sedation after giving BAG was found to be 4 to 18 minutes. The score of sedation quality ranged from 3 to 4. BAG provided moderate (slight resistance) to profound (resistance none) sedation. BAG nullified side effects of each other and provided excellent analgesic, sedative and antisialogauge effects.

In the present study the induction time in Diazepam-Ketamine (Group I) was found to be 55 to 71 seconds with a mean induction time of 62.33 ± 1.29 seconds while Midazolam-Ketamine (Group II) took 25 to 43 seconds with a mean induction time of 31.67 ± 1.67 seconds. The time to induction in dogs anaesthetized with Midazolam-Ketamine was significantly shorter than for those anaesthetized with Diazepam-Ketamine. Not a single side effect was recorded during or after induction in any case that received Diazepam-Ketamine or Midazolam-Ketamine as induction combination.

Induction quality was considered good to fair with Diazepam-Ketamine combination. Induction was good in all the dogs after administration of Midazolam-Ketamine combination.

The results indicated that the maintenance of anaesthesia in the two groups with Propofol were satisfactory. The anaesthetic protocols produced satisfactory and safe deep surgical anaesthesia in both the groups of dogs.

In the present study, in the dogs of group I where Diazepam-Ketamine were used as induction agents, the recovery time was found to be shorter (128.83 ± 2.43 minutes) when compared to the recovery time of (205.00 ± 5.97 minutes) Midazolam-Ketamine (group II). Recovery score was found to be 4 (gradual, smooth, quiet, rapid, comfortable) in all the dogs of group I, whereas recovery score was 3 (gradual, slow, moderate, restless) in all the dogs induced with Midazolam-Ketamine (group II). This indicated that induction with Diazepam-Ketamine was better than Midazolam-Ketamine as far as the recovery of anaesthesia was concerned.

As far as the physiological parameters were concerned, the results showed that there was a significant decrease in rectal temperatures between the dogs of group I compared to group II at 15min after premedication, 10, 15, 20, 25, 35, 45 and 60 minutes after induction of anaesthesia. The temperature decreased gradually in both the groups and lowest value of temperature was found at 90 minutes after induction of anaesthesia.

Although the heart rates between the groups were found to differ from each other, they were still well within the normal range and hence were considered in consequential. The respiratory rates were also fluctuated within normal physiological limits with a significant difference between the groups at 5, 10, 25 and 35 minutes after induction of anaesthesia. The respiratory rate was decreased gradually after

premedication and remained low than that recorded prior to premedication in both the groups. The respiratory rate returned to normal as the dogs recovered from anaesthesia. Since these parameters caused no complications and since they returned to normalcy soon, the changes were considered to be clinically acceptable.

In the two groups, all the reflexes were brisk to sluggish 10 minutes after premedicaton of anaesthesia. After induction and during the maintenance of anaesthesia, all the reflexes tested were absent. However, after about five minutes of withdrawal of propofol maintenance in all the dogs of the two groups, the reflexes started reappearing to moderate and then onwards reflexes were fully present.

Haematological examination revealed that there were no significant differences in the various parameters like TEC, Hb, PCV and TLC in any of the two groups. However in DLC, there were no significant differences in neutrophil count, lymphocyte count and monocyte count except eosinophil count which showed significant difference at 90 min interval between group I and group II. This underscored the fact that all the anaesthetic protocols studied were safe and uneventful as far as these observations were concerned.

The results of the present clinical study clearly revealed in all the dogs of the two groups that the various biochemical parameters studied, i.e., AST, ALT, BUN and serum creatinine remained within normal limits. Hence, this also conclusively proved that the two anaesthetic protocols studied were safe and did not result in any damage to the heart, liver and kidneys during the anaesthetic period.

Electrocardiographic studies in the dogs of both the groups revealed no abnormalities in the sizes of P, QRS or T- waves, no changes in the cardiac axes and no arrhythmias of any kind in any dog of any of the groups.

The following conclusions were drawn from the results of the present clinical study:

1. Both the anaesthetic protocols tested in the present study provided satisfactory deep surgical anaesthesia in dogs.
2. Use of Butorphanol, Acepromazine and Glycopyrrolate (BAG) 15 minutes prior to induction proved to be an effective premedicant combination.
3. Butorphanol, Acepromazine and Glycopyrrolate nullified side effects of each other and provided excellent analgesic, sedative and antisialogauge effects.
4. Midazolam was found to be superior to Diazepam as an induction agent given in combination with Ketamine.
5. Recovery was rapid, smooth and uneventful in Diazepam-Ketamine induction and Propofol maintenance in comparison to Midazolam-Ketamine induction and Propofol maintenance.
6. None of the anaesthetic combinations produced adverse effects on various physiological, haematological, biochemical and electrocardiographic parameters.

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