STUDIES ON PHYSIOLOGICAL, HAEMATOBIOCHEMICAL AND CLINICAL EFFECTS OF ETOMIDATE, PROPOFOL, KETAMINE AND SEVOFLURANE ANAESTHESIA IN DEXMEDETOMIDINE PREMEDICATED DOGS

Thesis
Submitted to the

G.B Pant University of Agriculture & Technology, Pantnagar-263 145 (U.S. Nagar), Uttarakhand, India

By

Devender Singh Bisth

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF

Doctor of Philosophy
(Veterinary Surgery and Radiology)

JANUARY, 2017
Words are ineffable to express my profound gratitude and sincere regards to my esteemed advisor Dr. Narendra Singh Jadon, Professor & Head, Department of Veterinary Surgery & Radiology, and Chairman of my Advisory Committee, for his inspiring guidance, unconditional cooperation, constructive suggestions and constant support throughout the course of this study and preparation of manuscript.

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I will be failing in my duty if I don’t express my sympathy to all those dogs (Rocky, Toffee, Baalu, Blacky, Jelly, Molu, Piku and Laalu to name a few) who took
the stress of anaesthesia and surgery upon themselves for the sake of advancement of science and knowledge.

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Pantnagar
January, 2017

(Devender Singh Bisth)
Author
CERTIFICATE

This is to certify that the thesis entitled "Studies on physiological, haematobiochemical and clinical effects of etomidate, propofol, ketamine and sevoflurane anaesthesia in dexmedetomidine premedicated dogs" submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy with major in Veterinary Surgery and Radiology and minor in Veterinary Gynaecology and Obstetrics of the College of Post Graduate Studies, G.B. Pant University of Agriculture and Technology, Pantnagar, is a record of bona fide research carried out by Mr. Devender Singh Bisth, Id. No. 44333 under my supervision and no part of the thesis has been submitted for any other degree or diploma.

The assistance and help received during the course of this investigation have been duly acknowledged.

Pantnagar
January, 2017

(Narendra Singh Jadon)
Chairman
Advisory Committee
CERTIFICATE

We, the undersigned, members of the Advisory Committee of Mr. Devender Singh Bisth, Id. No. 44333, a candidate for the degree of Doctor of Philosophy with major in Veterinary Surgery and Radiology and minor in Veterinary Gynaecology and Obstetrics, agree that the thesis entitled "Studies on physiological, haematobiochemical and clinical effects of etomidate, propofol, ketamine and sevoflurane anaesthesia in dexmedetomidine premedicated dogs" may be submitted in partial fulfillment of the requirements for the degree.

(Narendra Singh Jadon)
Chairman
Advisory Committee

(G.K. Singh)  (Mahesh Kumar)
Member  Member

(H.P. Gupta)  (A.K. Das)
Member  Member

Head of the Department
(Ex-Officio Member)
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<tr>
<td>&gt;</td>
<td>greater than</td>
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<tr>
<td>&lt;</td>
<td>less than</td>
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<tr>
<td>µg</td>
<td>microgram</td>
</tr>
<tr>
<td>ACTH</td>
<td>adreno cortico trophic hormone</td>
</tr>
<tr>
<td>ALB/Alb</td>
<td>Albumin</td>
</tr>
<tr>
<td>ALP</td>
<td>alkaline phosphatise</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine amino transferase</td>
</tr>
<tr>
<td>ASA</td>
<td>American society of anaesthesiologists</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate amino transferase</td>
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<tr>
<td>AV</td>
<td>atrio-ventricular</td>
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<tr>
<td>b. wt.</td>
<td>body weight</td>
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<td>BIS</td>
<td>bispectral index</td>
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<tr>
<td>BT</td>
<td>body temperature</td>
</tr>
<tr>
<td>BUN</td>
<td>blood urea nitrogen</td>
</tr>
<tr>
<td>CK</td>
<td>creatine kinase</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>CO₂</td>
<td>carbon dioxide</td>
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<tr>
<td>CRI</td>
<td>constant rate infusion</td>
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<tr>
<td>D</td>
<td>Dextrorotatory</td>
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<td>DBP</td>
<td>diastolic blood pressure</td>
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<td>DLC</td>
<td>differential leucocyte count</td>
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<td>ECG</td>
<td>Electrocardiography</td>
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<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
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<td><em>et al.</em></td>
<td>et. alii/alia (with other people)</td>
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ETCO₂  end tidal carbon dioxide
Fig.  Figure
GABA  gama amino butyric acid
GIT  gastrointestinal tract
GLB/Glb  Globulin
Hb  Haemoglobin
HPLC  high performance liquid chromatography
HR  heart rate
hr/hrs  hour/hours
i.e.  that is
ICU  intensive care unit
IL-6  interleukin-6
KET-DEX  ketamine-dexmedetomidine
Kg/kg  kilogram
L  levorotatory
MAC  minimum alveolar concentration
MAP  mean arterial pressure
MCH  mean corpuscular haemoglobin
MCHC  mean corpuscular haemoglobin concentration
MCV  mean corpuscular volume
mg  milligram
Min./min.  minute
N  neutrophil
ng  nanogram
NSAID  non steroidal anti-inflammatory drug
PaCO₂  arterial partial pressure of carbon dioxide
PaO₂  arterial partial pressure of oxygen
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<td>partial pressure of carbon dioxide</td>
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<td>packed cell volume</td>
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<td>pulse rate</td>
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<td>red blood cell</td>
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<td>RR</td>
<td>respiration rate</td>
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<td>s/sec.</td>
<td>second</td>
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<td>Sevoflurane</td>
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<td>total glycerides</td>
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<td>TIVA</td>
<td>total intravenous anaesthesia</td>
</tr>
<tr>
<td>TLC</td>
<td>total leucocyte count</td>
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<td>TP</td>
<td>total protein</td>
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<td>TVCC</td>
<td>Teaching Veterinary Clinical Complex</td>
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<td>Viz.</td>
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Introduction
In veterinary science anaesthesia is an integral part of surgery. Any major surgical process is to be accompanied by absolute unconsciousness, analgesia and immobility which would not be possible without a strong and reliable anaesthetic support with minimum alterations in the physiological parameters of various body systems. Anaesthesia means loss of sensation of a part or whole of the body, with or without loss of consciousness. General anaesthesia is a drug induced unconsciousness characterized by controlled and reversible depression of CNS and perception. Role of anaesthesiologist and evaluation of anaesthetic effect is more important in veterinary field as compared to the human patients due to the inability of animal to explain the experience of anaesthesia after recovery.

The term Anaesthesia was first coined by Dr Oliver Wendell Holmes on Nov 21, 1846 to describe a mental state produced as a result of inhalation of ether vapours. The word Anaesthesia originates from the Greek word “anaisthæsia” which means absence of sensation. It is a relatively new clinical discipline but has its origin many centuries before present times. In India the great sage Susruta (called father of surgery) performed operations around 500BC under the influence of opium, wine and Indian Hemp. In Bhoj Prabandh the use of “Sammohini” for induction and “Sanjivani” for recovery from anaesthesia has been described. A cranial operation was performed on Raja Bhoj in 527 AD. In 300 BC Bian Que used general anaesthesia for surgery. In the western world, the modern journey of the discipline can be assumed to have started after the preparation of Nitrous oxide in 1773 by Joseph Priestley and description of its properties by Humphry Davy in 1800. After these two discoveries, many anecdotes and important events helped to establish a firm foundation of the modern discipline of anaesthesia in the west. From then onwards the science and art of anaesthesia spread gradually to the whole world and today we see it in a highly advanced state.

Apart from being a very useful science, anaesthesia is also a double edged weapon since inadequate and inefficient handling of the procedures and drugs can yield very undesirable results, sometimes (though rarely) causing mortality. Therefore
anaesthesia has also been described as a journey towards death and back. This dictates that (at least ideally), anaesthesia should provide only the desirable characteristics like unconsciousness, analgesia, amnesia and muscle relaxation and should spare the important body systems (cardiovascular and respiratory with others) from any serious toxic, deleterious and depressive effects of the drugs. Therefore anaesthesiologists have always been in the perpetual search of the safest and best anaesthetic regime(s). In balanced anaesthesia, anaesthesia is delivered by using small amounts of more than one drug instead of using large amount of one drug. In this method the doses of individual drugs are reduced, the desired clinical end points of anaesthesia are reached and the side effects of each drug are reduced to a great extent. Balanced anaesthesia takes advantage of the phenomenon of drug interactions viz. *additivity*, *infra-additivity* and *synergy*. However, these interactions of the anaesthetic drugs can also produce undesirable end points such as profound respiratory depression as with concomitant use of midazolam and fentanyl. At the same time there are only few records available which document the net benefit or risk

In order to achieve drug synergism for benefit of the animal, many different advantages of classes of drugs have been taken by the anaesthesiologists, such as anticholinergics, sedative-hypnotics, benzodiazepines, narcotics, barbiturates, non-barbiturates, dissociatives, steroids, volatile liquids and anaesthetic gases. Taking a cue from the phenomenon of drug synergism the present study was designed with an anticholinergic, an α-2 agonist, a non-barbiturate induction agent and a gaseous maintenance agent.

Preadministration of atropine, an anticholinergic agent is extremely important as it reduces salivary secretions when aspiration may lead to respiratory embarrassment. It attenuates physiological response to the parasympatholytic neuronal impulses. It prevents the slowing of heart rate due to vagal stimulation, increases the cardiac output and arterial blood pressure remains unchanged or increases slightly in normal animals.

Thiopentone has been used very frequently in the veterinary field as a general anaesthetic agent, however, its side effects specially over the cardio-pulmonary system restricts its use in weak and debilitated animals. Use of thiopentone is also not
advocated for the inexperienced anaesthetist owing to the complications that may be encountered during the induction and maintenance and thus, there is a need for the safer drug or drug combination that can be used even in high risk animals requiring clinical surgery.

The present study has, therefore, been undertaken to elucidate the clinico-physiological and hemato-biochemical effects of $\alpha$-2 agonist drug dexmedetomidine with etomidate, propofol and ketamine induced anaesthesia and its maintenance with inhalation anaesthetic agent sevoflurane with the following objectives:-

1. To assess the anaesthetic effect of dexmedetomidine with injectable induction agents etomidate, propofol and ketamine.

2. To assess the anaesthetic effect of dexmedetomidine over the MAC of sevoflurane as gaseous maintenance agent in etomidate, propofol and ketamine induced dogs.

3. To study the clinico-physiological and haemato-biochemical effect of various anaesthetic combinations.

4. To assess the clinical efficacy of various anaesthetic combinations in dogs.
Review of Literature
2.1 HISTORY OF ANAESTHESIA AND DRUG INTERACTION STUDIES:-

Aanta et al. (1990) have evaluated the effects of dexmedetomidine on clinical, haemodynamic, haematobiochemical and thiopentone requirements in women treated for dilatation and curettage of uterus. Dexmedetomidine did not cause significant haemodynamic changes or side effects. It reduced the thiopentone requirements to 70% of their original values and provided a better quality recovery.

Ilkiw (1999) has studied balanced anaesthesia in dogs and cats. He gave the opinion that in balanced anaesthesia small quantities of more than one drug are used so that the undesirable effects of large quantities of one or two drugs do not create any undesirable clinical effect. Further he stated that in animal anaesthesia inhalation agents are used for maintenance whereas balanced anaesthesia is not usually resorted to. Inhalation agents causing increased cardiopulmonary depression with increasing dose has been documented by him.

Harris et al. (2006) have carried out a study to find out the interaction between propofol and sevoflurane by using Dixon’s up and down method. The patients were tested for loss of consciousness and abolition of response to surgical pain. Propofol at 5.4µg/ml (plasma concentration) and sevoflurane at 0.86% abolished the response to surgical incision. A bispectral index value of 70 was the threshold point to distinguish responders and non responders to auditory stimulus elicited to test consciousness. It was concluded that propofol and sevoflurane interact in an additive manner which suggests a common site of action.

Hendrickx et al. (2008) have reviewed the drug interactions which cause hypnosis and sedation. It was found that most of the interactions were synergistic, whereas, some drugs behave in a different manner e.g. ketamine, which interacts additively or antagonistically with few drugs. Inhalation agents showed synergy (with IV anaesthetic), additivity and sometimes infra-additivity (e.g. nitrous oxide and isoflurane, interact antagonistically). It was concluded that apart from the above facts no two inhalation agents interacted in a synergistic manner with each other.
Ahmad et al. (2013) have compared the clinico-physiological and haemodynamic parameters of dexmedetomidine alone or with its combination with midazolam, fentanyl and ketamine. It was opined that the use of more than one drug is better than the use of a single drug for sedation. Opting for this methodology affords the advantage of the phenomenon of synergy which results in sedation and recovery of good quality. Doses of individual drugs are also reduced in this phenomenon and the side effects are minimum. It was found that dexmedetomidine provides moderate sedation, which can be enhanced when midazolam or fentanyl is also used concomitantly. If ketamine is added in this combination then complete anaesthesia is achieved with lesser heart and lung depression. It was concluded that dexmedetomidine was safe to use with the above mentioned drugs for clinical use.

Shah et al. (2014) have highlighted many important events of the history of anaesthesia in the Indian, western, Chinese and Arabic world. Susuruta used opium, wine and Indian hemp for surgery in 500 BC in India. “Bhoj Prabandha” mentioned the use of “Sammohini” for induction and “Sanjivani” for recovery from anaesthesia. Time from the pre Christian era to the present has been covered. Important developments like the ether frolics, anaesthesia in dentistry and ancient cranial surgery in India have been included in the paper. The development of various professional societies of anaesthesia, and the beginning of important journal like Anaesthesia and Analgesia are duly covered.

2.2 ANAESTHETIC COMPLICATIONS:-

Goldstein and Keats (1970) have examined “the risk of anaesthesia” and opined that in a true sense the anaesthetic risk occurs during the period starting from the induction to the beginning of the incision, otherwise the anaesthetic risk is confounded with the surgical risk and a second set of persons and procedures. Estimates of risk of anesthesia have been derived from study of large samples, and these estimates range widely. When applied to individual patients, risk estimates have been so inaccurate as to be of little more value than intuitive.

Dyson et al. (1998) have studied morbidity and mortality occurring in the administration of anaesthesia in small animals. The data showed that 0.11% of 8,087 dogs and 0.1% of 8,702 cats died after anaesthesia whereas 2.1% dogs and 1.3% cats...
had faced a complication during the anaesthetic period. Different odd ratios associated with various factors have been calculated by the authors. The study will be helpful for practitioners to manage the small animal practices worldwide.

Arbous et al. (2001) have conducted a study to recognise the anaesthetic factors in people who either died or went into coma after surgery. The causes of these deaths were analysed to nail either anaesthesia or other factors. Anaesthetic factors and improper postoperative care were assessed to be the causes of these deaths.

Bille et al. (2012) has studied the risk due to anaesthetic drugs for canines (dog) and felines (cat). A number of factors like correlation between anaesthetic death and ASA status, species, age, type of operation, anaesthetic drugs used and epidural use of morphine and bupivacaine were considered. A death rate of 1.35% was found. Death rate of animals with low ASA score was low while the death rate of animals with higher ASA score was higher. It was recommended that a good patient evaluation and patient stabilisation before surgery were key factors to obtain a favourable outcome from surgery and anaesthesia.

Gil and Redondo (2013) have studied canine postoperative deaths and recognised the causes responsible for it. Death occurring for upto 24 hours after the operation was called anaesthetic death. Analysis of the data showed that higher ASA score was positively correlated with mortality. In their study 1.29% dogs died after surgery. The outcome of surgery could be gauged from the ASA category of the inbound surgical patient. Drugs like opioid or non opioid analgesics when used after the operation and presurgical stabilisation of the patient helped to improve the survival rate.

Ellis et al. (2014) have studied the anaesthesia related cardiac arrests in people. Cardiac arrests were classified to be either “anaesthesia attributable” or “anaesthesia contributory”. Anaesthesia-attributable cardiac arrests were those cases in which anaesthesia was determined to be the primary cause of cardiac arrest. Anaesthesia-contributory cardiac arrests were those cases where anaesthesia was determined to have contributed to the cardiac arrest. It was found that in fourteen (0.6 per 10000 anaesthesia) cardiac arrests anaesthesia could be implicated as a cause, whereas in twenty three (1.1 per 10000 anaesthesia) deaths anaesthesia was considered to be one
of the many causes of death. Each cause is further analysed and it was concluded that from among 160 cardiac arrests, 37 were caused by anaesthesia related causes.

2.3 MINIMUM ALVEOLAR CONCENTRATION (MAC) STUDIES OTHER THAN SEVOFLURANE

Eger et al. (1965) has opined that all inhalation anaesthetics can be compared with each other by the yardstick of minimum alveolar concentration. It was observed that minimum alveolar concentration required to prevent gross movement to any painful stimulus remained unaltered in dogs subjected to halothane use. When the intensity of the stimulus was increased the minimum alveolar concentration increased to the range of two times but beyond that an increasing intensity of painful stimulus did not cause an increase in the minimum alveolar concentration. Again when a stimulus of fixed intensity was applied to different dogs the minimum alveolar concentration remained the same in all the dogs. The minimum alveolar concentration remained unaltered by an increased blood pressure, increased blood carbondioxide, duration of anaesthesia or a decreased carbon dioxide level in blood or a little decrease in blood oxygen saturation. Blood loss or metabolic acidosis decreased minimum alveolar concentration by 10-20% and severe hypoxia decreased minimum alveolar concentration by 25 to 50%.

Quasha et al. (1980) have reviewed the method of measurement and applications of MAC of inhalant anaesthetic gases. It was opined that minimum alveolar concentration is a method to measure the potency of anaesthetic gases. Minimum alveolar concentration had become widely accepted as method of measuring the potency of anaesthetic gases because it relies on the abolition of response to painful stimuli of surgery. The method of minimum alveolar concentration applies to all inhalant agents and it has a great degree of reproducibility. Many pharmacological and physiological entities affect minimum alveolar concentration. It was concluded that minimum alveolar concentration is the sole criterion to gauge the potency and safety of inhalant anaesthetics.

Aranake et al. (2003) have opined that since 1965 after many years of its introduction in the field of anaesthesia, minimum alveolar concentration still remains the criterion to judge the potency of anaesthetic liquids and gases. It was emphasized that the seat of action of volatile agents to suppress movement lies in the spinal cord whereas the
memory loss and sleep are affected by the brain. It was further discussed that the concentration required for memory loss and unconsciousness is lower than that required for prevention of response to painful stimuli of surgery. Apart from minimum alveolar concentration “measurement of real time anaesthetic concentration” is another method of measuring the anaesthetic concentration in blood, which is a reliable, inexpensive and available. It was concluded that despite certain limitations, minimum alveolar concentration remains the most common method of measurement of anaesthetic potency and that any alternative method of measurement of anesthetic depth will have to prove its superiority in order to supersede minimum alveolar concentration.

Sonner et al. (2003) have studied the various mechanisms by which inhalant anaesthetics produce immobility (minimum alveolar anaesthetic concentration- MAC) by actions on the spinal cord. It was opined that many indicators are available which suggest that GABA, acetylcholine, potassium, 5-hydroxytryptamine-3, opioids and α2-adrenergic drugs may not be involved in the mechanisms to produce MAC while glycine, N-methyl-d-aspartate (NMDA) and sodium may be involved in the mechanism to produce MAC by the inhalant anaesthetics.

Valverde et al. (2003) have compared 3 types of noxious stimuli (applied to different body parts of anesthetized dogs and rabbits) for determination of the minimum alveolar concentration of inhalation anaesthetics. Dogs were anesthetized with isoflurane and halothane and rabbits with isoflurane. The minimum alveolar concentration was determined by skin incision, clamping of the tail and paws and electric current (only in dogs). It was found that electrical current and clamping showed similar minimum alveolar concentration values whereas skin incision showed lower values of minimum alveolar concentrations and that minimum alveolar concentration values were different with different stimuli in different species.

Valverde et al. (2004) have studied the minimum alveolar concentration reducing effects of lidocaine used at low (50 μg kg⁻¹ min⁻¹) and high (200 μg kg⁻¹ min⁻¹) dose CRI in dogs anaesthetized with isoflurane. The minimum alveolar concentration was reduced from 1.34% to 1.09% by the low doses and to 0.76% by the high dose CRI. Hence it was concluded from their study that lidocaine reduces the minimum alveolar concentration of isoflurane in proportion to its dose used as CRI without affecting the heart rate and blood pressure to greater extent.
Pascoe et al. (2006) have measured the minimum alveolar concentration of isoflurane in dogs who were subjected to three dose rates of dexmedetomidine constant rate infusions. Minimum alveolar concentration reduced at 0.5 and 3µg/kg/hr but not at 100µg/kg/hr. It was concluded in the study that since dexmedetomidine decreased the isoflurane requirement, it might be worth using in a situation where analgesia and a diminished response to stressful stimuli are warranted.

Eger et al. (2008) have carried out a study in rats and found that there is no synergistic interaction between the volatile anaesthetics. It was assumed that any two specific volatile anaesthetics with different potencies on their receptors can act in a synergistic manner. The interactions of minimum alveolar concentration for 11 pairs of anesthetic drugs were studied. It was found that these drugs interacted in additive manner only. The pair of nitrous oxide and isoflurane interacted in an antagonistic manner. Therefore it was concluded that there is only one site of action of the inhaled anaesthetics.

Ebner et al. (2013) have studied whether the minimum alveolar concentration (MAC) of isoflurane is affected by use of dexmedetomidine (D), morphine-lidocaine-ketamine (MLK), and dexmedetomidine-morphine-lidocaine-ketamine (DMLK) in dogs. Bispectral index (BIS) was used as a measure of depth of anaesthesia. It was found that D, MLK, and DMLK decreased the minimum alveolar concentration of isoflurane by 30%, 55%, and 90%, respectively. Hence it was concluded that infusion of dexmedetomidine, MLK, or DMLK reduced the minimum alveolar concentration of isoflurane in dogs.

GutierrezBlanco et al. (2013) have evaluated the isoflurane sparing effects of IV fentanyl (FENT), lidocaine (LIDO), ketamine (KET), dexmedetomidine (D), or lidocaine-ketamine-dexmedetomidine (LKD) in dogs. Cardiopulmonary parameters and end tidal isoflurane were measured. It was concluded that that FENT and LKD had greater dose sparing effect than LIDO, KET or CONTROL.

2.4 ATROPINE

Nunn and Bergman (1964) have reported that administration of atropine causes slight increase in minute volume, bronchial muscles are relaxed and the bronchial secretions are reduced with an increase in the anatomical and physiological dead space.
Muir (1978) has opined that the rhythms of the cardiac cycle can be disturbed by the use of atropine in animals.

Kantelip et al. (1985) have performed atrial pacing in the heart of awake dogs using atropine and hyoscine methobromide. It was found in the study that lower doses (of both the drugs) decrease the heart rate and AV conduction. The heart rate and AV conduction were accelerated at higher dose of both the drugs. The effects of the two drugs were similar and comparable.

Watney et al. (1987) have opined that the anticholinergic drugs were of common use in canine anaesthesia to prevent bradycardia and secretions. Atropine, hyoscine and glycopyrrolate were compared in the study in which thiopentone was used to induce anaesthesia which was maintained by halothane-oxygen-nitrous oxide. In the study all the tested drugs reduced salivation. Atropine and hyoscine caused the heart rate to first increase and then decrease, however glycopyrrrolate did not cause any rise or fall of the pulse or heart rate but maintained a steady heart rate. It was concluded that glycopyrrolate is the ideal anticholinergic drug for use in anaesthesia.

Muir and Hubbell (1989) have reported that the anticholinergics (atropine, glycopyrrolate and scopolamine) are competitive antagonists of acetylcholine primarily used to prevent salivary secretions and bradycardia of vagal origin. Larger doses can cause stimulation of brain centres leading to restlessness, disorientation and delirium. These drugs reduce the glandular secretions of gastro intestinal tract (GIT), respiratory tract and the oral and nasal caravities. The gastric pH is increased and intestinal motility is decreased which might cause colic in horses.

Jadon et al. (1995) have evaluated the haematobiochemical effects of detomidine and ketamine anaesthesia in dogs using atropine sulphate as an anticholinergic drug. Satisfactory anaesthesia was produced to carry out the clinical procedures in the animals. Total leucocyte count, total erythrocyte count, packed cell volume, haemoglobin, clotting time, plasma protein, albumin, glucose, blood urea nitrogen and creatinine were measured.

Reibold et al. (1995) have reported that atropine is a plant derived alkaloid having parasympatholytic activity. It stimulates the medulla and higher cerebral centres, causes mydriasis by paralyzing the ciliary body, inhibits oral, nasal and
bronchial secretions, decreases airway resistance by dilating the bronchioles, increases heart rate and decreases gastric secretions, smooth muscle tone and the peristalsis.

**Hendrix and Robinson (1997)** have described that atropine causes a dose dependent tachycardia. The mean dose to cause tachycardia has been described to be 0.04mg/kg iv in dogs.

**Tiwari et al. (1998)** have carried out medetomidine-ketamine anesthesia in atropinized dogs. The anaesthetic effects were reversed with the use of atipamezole. Various clinical and haematological parameters were studied and operations like gastrotomy, enterotomy, enterectomy, urethrotomy, cystotomy and ovariohysterectomy were performed under this anaesthesia.

**Kandpal and Kumar (1998)** have observed satisfactory anaesthesia with the use of atropine-ketamine, atropine-diazepam-ketamine and atropine-detomidine-ketamine in bovine calves. Clinical, physiological and haematological parameters along with ECG were recorded in the study.

**Adams (2001)** has reported that Atropine is a prototype muscarinic receptor blocking alkaloid. It is derived from the plant *Atropa belladonna* (deadly nightshade) which belongs to the solonaceae family. The alkaloids derived from *Atropa belladonna* are atropine, scopolamine and some other less important ones. Atropine is a racemic mixture of *d* (dextrorotatory) hyoscyamine and *l* (levorotatory) hyoscyamine. Atropine acts by binding to the muscarinic receptors of the effector cells and thus makes them unavailable to the binding by acetyl choline. Thus the physiological effects of parasympathetic nerve impulses are attenuated. Atropine is a routine drug to be used as an adjunct to general anaesthesia, particularly the inhalant anaesthetics. Its principal function is to reduce the salivary and airway secretions. These actions are greatly helpful in maintenance of a patent airway. Atropine has varied types of effects on the various body systems. In the cardiovascular system it increases the heart rate and cardiac output but not the blood pressure. The secretions of the gastrointestinal tract are inhibited very efficiently as also the salivary secretions. The airway secretions are inhibited and the bronchiolar diameter is increased. It causes mydriasis and hampers the drainage of anterior chamber. In the urinary system it relaxes the smooth muscles and thus retains urine but may be beneficial in uretral/renal colic.
Brock (2001) has opined on the use of atropine in small animal practices. He has opined that the prophylactic use of atropine was far superior to any disadvantage associated with its use because atropine was a least toxic drug that could cause a life threatening complication. It was recommended that when specialist anaesthetists are available the drug be given only when required and after other causes of bradycardia have been ruled out (e.g. too deep anaesthesia or hypoventilation).

Hall et al. (2001) has described that anticholinergic agents are widely used in anaesthesia to block the muscarinic effects of acetylcholine and to hamper the nerve transmission at the parasympathetic postganglionic nerve endings. Its principal uses are to reduce salivary and bronchial secretions, blocking of the vagus nerve impulses and inhibit the effects of drugs that stimulate the parasympathetic nervous system. However the use of anticholinergic was not recommended in ruminants as it would make the saliva more viscous and would rather cause respiratory obstruction. Use of anticholinergics is particularly useful with the alpha-2 agonists which cause vagal-mediated bradycardia. Atropine disappears very rapidly from the blood in dogs. Atropine does not affect whole of the body with equal intensity so that its effects are more obvious on the heart and salivary glands. Urinary bladder and intestines are affected to a lesser degree. Therefore heart rate increases but the blood pressure remains unchanged. Atropine causes mydriasis so that the animals can have difficulty in judging the distance and such animals must be approached cautiously. As atropine reduces the muscle tone in the gastrointestinal tract there is a possibility of post-anaesthetic colic in horses.

Emami et al. (2007) have conducted a study to compare the clinical and physiological effects of romifidine and xylazine in dogs administered with atropine sulphate. ECG and analgesia were measured and response to skin incision and suturing were used as indicators of anaesthesia. Satisfactory anaesthesia was produced in all the groups in the study and bradyarrhythmia produced after the administration of romifidine/xylazine was corrected by the administration of ketamine.

Hughes (2008) has opined that the anticholinergic drugs (Atropine and others) should not be used in geriatric dogs and cats since they already have an elevated resting heart rate. Any anaesthetic regime, with which the anaesthetist is familiar, was
considered safe and if newer drugs were to be used, they should be tried in advance in healthy subjects. Low doses of acepromazine or benzodiazepines were considered safer for older dogs and cats.

**Vesal et al. (2011)** have evaluated the effects of acepromazine-xylazine with and without atropine sulphate in dogs. The dogs administered with atropine showed elevated heart rates. No dog administered with atropine showed first degree heart block whereas a self correcting arrhythmia was found in all the dogs.

**Liptak et al. (2014)** have compared the effects of atropine-medetomidinediazepam (AMD) and atropine-xylazine-diazepam (AXD) in dogs maintained with propofol-fentanyl. Among these two combinations AXD was found to be better for premedication due to lesser degree of cardiovascular and hemodynamic suppression.

**Khurana et al. (2014)** have evaluated clinical and biochemical parameters in dogs using atropine-butorphanol-diazepam-propofol-halothane and atropine-butorphanol-acepromazine-propofol-halothane. It was observed that haemoglobin, total erythrocye count, packed cell volume and aspartate amino transferase decreased whereas other biochemical parameters (blood urea nitrogen, creatinine, sodium, potassium) did not show significant changes. ECG was overall normal and authors did not attach significance to the changes of time and voltage parameters in the ECG recordings. It was concluded that the tested drugs (atropine, diazepam, butorphanol, propofol, halothane, acepromazine) were safe to produce anaesthesia in dogs.

**Lerche (2015)** has opined that anticholinergics are commonly used in veterinary anaesthesia to treat or prevent bradycardia, decrease airway and salivary secretions, dilate the pupil, decrease the vagal reflexes and to reduce the effects of parasympathomimetic drugs. Atropine is used to prevent bradycardia during anaesthesia. It is historically used in the cardiopulmonary-cerebral resuscitation.

**Saikia et al. (2016)** have used total intravenous anaesthesia using atropine-xylazine-propofol, atropine-xylazine-ketamine and atropine-xylazine-ketofol. Human patients were administered atropine for its anticholinergic actions (reduced salivation and bronchial secretionds, blockage of impulses on the vagus nerve). It was concluded that the combinations mentioned provided a suitable alternative to the gaseous anaesthesia but the importance of premedicants and analgesics should not be overlooked.
2.5 DEXMEDETOMIDINE

2.5.1 CLINICOPHYSIOLOGICAL STUDIES

Vickery et al. (1988) have studied the anaesthetic-sparing and hemodynamic effects medetomidine in dogs. Minimum alveolar concentration of halothane and base haemodynamic functions were determined, after it DL, D or L-medetomidine at 1, 3, and 10µg/kg was administered by infusion. After the injection of medetomidine minimum alveolar concentration of halothane and hemodynamic variables were again measured. Minimum alveolar concentration of halothane decreased in a direct proportion to the dose of medetomidine so that at the highest medetomidine dose the minimum alveolar concentration remained 0.1%. Only D and not the L isomer had any effect in reducing the minimum alveolar concentration. In the study it was found that medetomidine reduced the minimum alveolar concentration to an extent which has been unparalleled so far. It was recommended to carry out further studies to examine if medetomidine can act as an anaesthetic supplement.

Aanta et al. (1990) have evaluated the effects of dexmedetomidine on clinical, haemodynamic, haematobiochemical and thiopentone requirements in women treated for dilatation and curettage of uterus. Dexmedetomidine did not cause significant hemodynamic changes or side effects. It reduced the thiopentone requirements to 70% of their original values and provided a better quality recovery.

Aho et al. (1992) have studied the use of dexmedetornidine alongwith thiopental, fentanyl and nitrous oxide for maintaining anaesthesia. Use of dexmedetomidine reduced the isoflurane requirement by >90% and as a result heart rate did not increase in response to attempts at tracheal intubation.

Bloor et al. (1992) have studied the haemodynamic and sedative effects of dexmedetomidine (DMED) in dogs. DMED administration reduced isoflurane anaesthetic requirements to 89% at half an hour and to 50% at the end of four hours post injection. One minute after the injection arterial pressure recorded a peak. Arterial pressure remained high during whole of the study period. When arterial pressure was increased, the heart rate and cardiac output decreased whereas systemic vascular resistance and left ventricular end diastolic pressure increased.
Ko et al. (1994) have evaluated the effects of etomidate in medetomidine premedicated dogs. It was found that SA and AV blocks appeared on the ECG but vanished within 8 minutes. Apnea was not encountered and analgesia was of good quality. Respiration decreased without any effect on haemodynamic function. It was concluded that atropine-medetomidine-etomidate was a good and safe combination for dogs.

Salmenpera et al. (1994) have studied the effects of dexmedetomidine (Dex)-fentanyl in dogs. Both the drugs produced a reduction in the minimum alveolar concentration of isoflurane in proportion to their doses used. The reduction of minimum alveolar concentration thus obtained was more which could be explained by only an additive interaction. Dex caused an increase in the blood pressure and decreased the cardiac output which was not affected by the use of fentanyl which further decreased the blood pressure.

Ko et al. (2000a) have studied the effects of medetomidine alone or with butorphanol and ketamine in dog. All dogs except one, placed themselves in lateral recumbency within six minutes after injection of the drug. Endotracheal intubation was more difficult in dogs given medetomidine alone than in other groups. Responses to analgesic tests were similar in all groups. The PaCO2 and the arterial pH was lower in the medetomidine group as compared to other groups. It showed that it was better to use medetomidine in a combination (with butorphanol or ketamine), rather than alone for a good clinical sedation.

Kuusela et al. (2000) have studied the clinico-physiological effects of medetomidine (MED), dexmedetomidine (DEX) and levomedetomidine (LEVO) given intravenously in dogs, at prefixed dose rates. Clinical, haemodynamic, respiratory and blood gas parameters were evaluated. In the study dexmedetomidine was found to be more potent than medetomidine or levomedetomidine, though levomedetomidine cleared more rapidly from the circulation and had negligible effects on cardiopulmonary and clinical parameters.

Kuusela et al. (2001b) have studied the various effects of levomedetomidine and dexmedetomidine in dogs. It was found that levomedetomidine did not cause any observable clinical effects, however it’s higher doses enhanced bradycardia and
reduced the sedative and analgesic effects of dexmedetomidine. It was concluded that
dexmedetomidine has better cardiovascular effects as compared to medetomidine. It
was recommended for further studies to establish the clinical effects of
levomedetomidine.

Kuusela et al. (2001a) have compared intravenous medetomidine and
dexmedetomidine as premedication drugs in dogs. Sedation and analgesia were scored
before induction. End-tidal isoflurane concentration, heart rate, and arterial blood
pressures and gases were measured. The choice of dose rate and not the drug affected
the quality of sedation and analgesia. It was concluded that dexmedetomidine and
medetomidine were equally effective for sedation in animals.

Kuusela et al. (2003) have studied propofol and propofol-isoflurane anaesthesia
in dogs premedicated with dexmedetomidine. Cardiac, blood gases, haemodynamic,
recovery and stress indicator variables were recorded. Heart rate decreased and
recovery time was longer in propofol group. It was concluded that propofol-isoflurane
anaesthesia was more useful than propofol alone because of milder degree of
respiratory depression and faster recovery with the former.

Sinclair (2003) has reviewed the clinicophysiological effects of medetomidine
in small animal practice. It is the most potent sedative of α-2 class of drugs and
produces sedation and pain relief in proportion to the dose used. It caused dose
reduction of anaesthetics, increase in intraocular pressure and urine output, decrease in
body temperature, intestinal motility and vomition along with reduced respiratory and
cardiac functions. It was recommended that the use of anticholinergic with
medetomidine has not been thoroughly investigated and approved. Atipamezole has
been recommended as the reversal agent to be used in serious depression of heart and
lungs.

Kuusela (2004) has studied the clinical effects and pharmacokinetics of
medetomidine, dexmedetomidine and levomedetomidine in dogs. Dexmedetomidine
and medetomidine were equally effective as sedatives whereas levomedetomidine was
not at all a sedative. It was rapidly metabolized and eliminated and partially inhibited
the effects of dexmedetomidine and medetomidine. A dose of 2 µg/kg of
dexmedetomidine caused stable cardiovascular effects when used as premedicant
before propofol/isoflurane anaesthesia. Dexmedetomidine also caused little depression of respiration.

Lemke (2004) have reviewed the use of selective alpha-2 agonists and antagonists in small animals. An opinion was given that alpha-2 agonists give reliable sedation, analgesia and muscle relaxation in dogs and cats, aid in the reduction of requirement of the anaesthetic drugs and augment the analgesia afforded by the opioids and other drugs. These properties of the alpha-2 agonists can be harnessed to administer a balanced anaesthesia to animals.

Lerche et al. (2004) have studied the effect of medetomidine on respiratory rate (RR), tidal volume (VT), minute volume (VM) and central respiratory neuromuscular drive. Increase in FiCO$_2$ (fractional inspired CO$_2$) increased RR, VT, and VM. Administration of medetomidine significantly decreased RR and VM. Hence it was concluded that use of dexmedetomidine should be done with extreme care in dogs whose nervous and respiratory systems have been compromised.

Gomez-Villamandos et al. (2005) have conducted trials using propofol, medetomidine, romifidine and sevoflurane for administration of general anaesthesia in beagle dogs. RR, HR, MAP, SBP, DBP and body temperature fell in all the groups after administration of the anaesthetic drugs. It was concluded that the combination of medetomidine, romifidine and sevoflurane is good for inducing and maintaining general anaesthesia in dogs.

Gómez-Villamandos et al. (2006) have compared dexmedetomidine and medetomidine as premedicants in dogs induced with propofol and maintained with desflurane. Though heart rate and respiratory rate decreased, cardiorespiratory parameters, desflurane requirements and recovery time followed a similar pattern in all the drug combinations. Etomidate and desflurane was different among all the combinations tried. It was concluded that the dexmedetomidine, propofol and desflurane were suitable for induction and maintenance of general anaesthesia in dogs.

Lin et al. (2008) have performed a study to evaluate the effects of 24 hr dexmedetomidine CRI associated with propofol or isoflurane. The CRI caused clinical signs as expected of an alpha-2 agonist drug but with minimum suppression of respiratory system. Therefore it was concluded that dexmedetomidine was efficacious to use with the above two drugs for anaesthesia.
Uilenreef et al. (2008) have studied the effects of three rates of dexmedetomidine (Dmed) at constant rate infusion (CRI) in surgical clinical cases of dogs. Arterial blood pressure remained within physiological limits however heart rate was inversely proportional to the dose of dexmedetomidine used. Dexmedetomidine CRI was found to be a reliable and valuable adjunct to isoflurane anaesthesia in maintaining surgical anaesthesia in healthy dogs. Use of dexmedetomidine was characterized by sufficient tissue perfusion and reduced isoflurane requirement. Atipamezole provided a smooth recovery.

Marcilla et al. (2010) have evaluated the effects of two different constant rate infusions (CRI) of dexmedetomidine in ponies. As a result of use of dexmedetomidine the heart rate, cardiac output and oxygen delivery decreased with other parameters studied. It was concluded that there were not remarkable differences between the clinical effects shown by the two dose rates studied.

Shukry and Miller (2010) have reviewed the use and applications of dexmedetomidine which was introduced two decades ago to facilitate intubation. From that time onwards it has been used in other category of patients also. Dexmedetomidine had been used in a variety of soft tissue, dental, neuro, cardiac, ophthalmic, paediatric and vascular surgery. Its doses ranged from 0.5 to 5µg/kg (loading) to 0.2 to 10µg/kg/h (infusion). It has been used along with other sedatives and local anaesthetics. Ketamine was used with dexmedetomidine to negate bradycardia. Dexmedetomidine was found very useful in any procedure where a patient requires spontaneous breathing.

Barletta et al. (2011) have evaluated the efficacy and cardiorespiratory effects of dexmedetomidine and ketamine with opioids (butorphanol, buprenorphine and hydromorphone) in male dogs undergoing neutering. Satisfactory anaesthesia was provided by all drug combinations studied. HR decreased, MABP first increased and then decreased and RR was in physiological limits It was concluded that DKBup (dexmedetomidine-ketamine-buprenorphine) was the best combination among the above drugs. Atipamezole hastened the recovery and least side effects were seen in all the groups.

Bell et al. (2011) have compared sedation in dogs as obtained by a combination of dexmedetomidine, buprenorphine and acepromazine. Heart rate decreased whereas
mean arterial blood pressure increased with the use of dexmedetomidine. It was found that a combination of dexmedetomidine and buprenorphine did not have an edge over acepromazine. The doses of dexmedetomidine studied showed clinical effects as expected.

Lee (2011) has opined that dexmedetomidine causes reduction in blood pressure, heart rate and plasma catecholamines in proportion to its dose used. In one case dexmedetomidine caused a pulseless electrical activity in heart of an elderly person. Rapid use of dexmedetomidine can cause hypertension and bradycardia or tachycardia. Therefore it should be given over 10 minutes as an infusion. It was advised to carry out further studies on the use of dexmedetomidine with other drugs and also in people of different sex and race. Hence till date dexmedetomidine has not been approved for use in children in Korea.

Oostrom et al. (2011) carried out a study in dogs to investigate the physiological effects of dexmedetomidine given by a constant rate infusion. Pain relief needed a higher blood level of dexmedetomidine than required for sedation. Higher doses of dexmedetomidine did not deepen the sedation but increased the length of time in sedated animals.

Sudheesh and Harsoor (2011) have opined that dexmedetomidine has become one of the frequently used anaesthetic drugs due to its haemodynamic, sedative, anxiolytic, analgesic, neuroprotective and anaesthetic sparing effects. It is also said to induce minimal respiratory depression alongwith cardioprotective, neuroprotective and renoprotective actions. If all of the above effects of dexmedetomidine are true to a greater or lesser degree then it becomes very useful for a large variety of procedures and anaesthetic techniques. As it is a highly selective α-2 agonist, the side effects arising out of α-1 receptor engagement is greatly reduced. It has been shown in dogs that it causes a dose dependent reduction of isoflurane MAC after epidural administration. Having observed all the above properties of dexmedetomidine the authors have forecasted that for a long time to come, dexmedetomidine will stay in the arena of anaesthetic drugs.

Thakur et al. (2011) have experimented with spiti ponies for the use of detomidine–butorphanol-guaifenesin-ketamine anaesthetic combination. Anaesthesia was
achieved within 3 minutes after the injection of ketamine. Alanine amino tranferase, total protein and glucose showed increased values without any deleterious result. Other biochemical values did not change outside the physiological results. It was concluded that the tested drugs were safe to induce total intravenous anaesthesia (TIVA) in equines in field conditions where monitoring facilities are almost always not available.

Yacout et al. (2012) have found in their study that dexmedetomidine caused a decrease in HR, MAP, cortisol and glucose levels either intraoperatively or post operatively. It also reduced the post operative rise of inflammatory cytokine (IL6) and the pain score.

Ahmad et al. (2013) have tested dexmedetomidine alone and in combination with midazolam, fentanyl and ketamine. It was opined by them that in order to achieve sedation a combination of drugs is better than any single drug due to the phenomenon of synergism which reduces the dose of individual drugs. In the study HR and RR decreased, MAP first increased and then decreased, pedal and palpebral reflexes had the greatest score in the group in which all the drugs of the protocol were used. It was concluded that dexmedetomidine can be used alone or in a satisfactory combination of the above drugs to achieve sedation or complete anaesthesia as desired.

Congdon et al. (2013) have studied the effects of dexmedetomidine on cardiovascular, respiratory and acid base balance in dogs which were induced with propofol and maintained on isoflurane. The heart rate, mean arterial pressure, systolic arterial pressure and diastolic arterial pressure remained non significant, plasma glucose increased whereas body temperature and respiratory rate did not wander far from baseline values.

Mousa and Alsobky (2013) have studied the efficacy of intravenous propofol, dexmedetomidine+fentanyl (dex-fenta) and sevoflurane for anaesthesia in people. Dexmedetomidine and propofol were found to be superior to sevoflurane. The haemodynamics and clinical parameters of the drug combinations used were compared. In all the groups haemodynamic variables showed a downward trend whereas in dex-fenta group the respiratory variables were on the higher platter.

Cardoso et al. (2014) have studied the clinico-physiological parameters of dexmedetomidine with methadone, morphine and tramadol in experimental dogs. The
studied parameters (heart rate, respiratory rate rectal temperature) showed similar (and downward) trend in all the treatments. Methadone and morphine showed a deeper sedation when used alone with dexmedetomidine. Use of a tramadol and dexmedetomidine together did not score very well over the use of dexmedetomidine alone.

Jena et al. (2014) have evaluated and compared the clinico-physiological, haemodynamic and haematobiochemical effects in response to different total intravenous anaesthesia techniques using xylazine, dexmedetomidine and propofol in dogs. Pedal and palpebral reflex scores and heart rate increased with the use of the anaesthetic combinations. Haemoglobin, packed cell volume, neutrophil, eosinophil, glucose, blood urea nitrogen and creatinine increased in the study. All combinations studied provided good anaesthesia. The authors did not conclude in favour of any combination and opined that both combinations were satisfactory for clinical anaesthesia.

Sharma et al. (2014) have compared the effects of atropine-xylazine and atropine-dexmedetomidine as premedicants for general anaesthesia in dogs. The dogs were divided in two groups which received either of the two treatments viz. atropine-butorphanol-xylazine-ketamine (BXK) or atropine-butorphanol-dexmedetomidine-ketamine (BDK) and both maintained on halothane. Pedal and palpebral reflexes attained high scores with halothane and remained at this level in the study. Haemoglobin, packed cell volume, total erythrocyte count, glucose, blood urea nitrogen, creatinine, alanine amino transferase and aspartate amino transferase did not change in the BDK group in which dexmedetomidine was used. It was concluded that all recovery times were significantly less with BDK group along with a better quality of recovery.

2.5.2 HAEMODYNAMIC STUDIES

Flacke et al. (1993) have studied the haemodynamic effects of dexmedetomidine in the anesthetized dog. Dexmedetomidine shows its effects even in the autonomically denervated dogs. Several haemodynamic and haematobiochemical parameters were recorded. Heart rate decreased and systemic vascular resistance increased in proportion to the dose of dexmedetomidine. The haemodynamic parameters were reversed with atipamezole.
Pypendop and Verstegen (1998) have studied the haemodynamic effects of medetomidine in normal dogs. In their study various haemodynamic parameters were recorded. It was found that medetomidine depressed these variables in proportion to the dose administered. To harvest optimal benefit it was recommended that medetomidine can be used by a constant rate infusion.

Gertler et al. (2001) observed that the uses of alpha-2 agonist drugs have increased many fold since their discovery. Dexmedetomidine- a drug of this category, has been ascribed having the property of anaesthetic sparing and haemodynamic stability. It can be beneficial in ischemia. Patients treated with dexmedetomidine suffered some degree of hypotension which had to be corrected medicinally. It gives good quality sedation. It was recommended that it should be given as a constant rate infusion and not as a bolus.

Kuusela et al. (2001b) have studied the various effects of levomedetomidine and dexmedetomidine in dogs. It was found that levomedetomidine did not cause any observable clinical effects, however it’s higher doses enhanced bradycardia and reduced the sedative and analgesic effects of dexmedetomidine. It was concluded that dexmedetomidine has better cardiovascular effects as compared to medetomidine. Further studies were recommended to establish the clinical effects of levomedetomidine.

Kuusela et al. (2003) have studied propofol and propofol-isoflurane anaesthesia in dogs premedicated with dexmedetomidine. Cardiac, blood gases, haemodynamic, recovery and stress indicator variables were recorded. Heart rate decreased and recovery time was longer in the propofol group. It was concluded that propofol-isoflurane anaesthesia was more useful than propofol alone because of milder degree of respiratory depression and faster recovery with the former.

Lin et al. (2008) have performed a study to evaluate the effects of 24 hr dexmedetomidine constant rate infusion (CRI) associated with propofol or isoflurane. The CRI caused clinical signs as expected of an alpha-2 agonist drug but with minimum suppression of respiratory system. Therefore it was concluded that dexametomidine was efficacious to use with the above two drugs for anaesthesia.

Carter et al. (2010) have studied the haemodynamic parameters associated with a medetomidine CRI in dogs. Sevoflurane was used as the anaesthetic. After recovery
the CRI of medetomidine at the rate of 1, 2 or 3 µg kg\(^{-1}\) hour\(^{-1}\) over a one hour period was started. Systolic, mean, and diastolic arterial pressure, heart rate (HR), cardiac output, stroke volume, stroke index (SI), cardiac index (CI), total peripheral resistance (TPR), and total peripheral resistance index (TPRI) were measured/calculated. It was concluded from the study that medetomidine produces important changes in many of the parameters studied and that even low doses of medetomidine can induce clinically important suppression of vital parameters and therefore great care should be exercised while using it.

**Congdon et al. (2013)** have studied the effects of dexmedetomidine on cardiovascular, respiratory and acid base balance in dogs which were induced with propofol and maintained on isoflurane. Hemodynamic parameters and acid base balance of the dogs did not show any deviation from their own baseline values at any time point during the study.

**Mousa and Alsobky (2013)** have studied the efficacy intravenous dexmedetomidine and fentanyl (dex-fenta), and compared it with sevoflurane anaesthesia. In the study the heart rate and mean arterial pressure increased whereas the respiratory rate increased after initiation of the anaesthetic protocol. The haemodynamics and clinical parameters of the drug combinations were compared. In all the groups haemodynamic variables showed a downward trend whereas in dex-fenta group the respiratory variables were on the higher platter.

**Carmona et al. (2014)** have studied the various effects of two CRIs of dexmedetomidine (dex) in dogs. In the study HR decreased while SAP and DAP increased. Higher dose of dex produced a deeper anaesthesia. The cardiac index was reduced in all groups under study. It was recommended to use oxygen with the administration of dexmedetomidine. Dexmedetomidine provided a good quality recovery.

### 2.5.3 HEAMATO BIOCHEMICAL STUDIES

**Maze et al. (1991)** have studied the effect of dexmedetomidine on adrenal steroid synthesis because the imidazole compounds could produce inhibition of the steroid synthesis. This can affect the morbidity and mortality in the subjects. The effect of dexmedetomidine was tested at \(10^{-8}\) to \(10^{-3}\) M in rat adrenal cells. It was noted that
the steroid biosynthesis is inhibited by dexmedetomidine only in high concentrations and at the doses used clinically for anaesthesia significant suppression of steroid synthesis is not anticipated.

Jadon et al. (1995) have evaluated the haematobiochemical effects of detomidine and ketamine anaesthesia in dogs. It was found that total leucocyte count increased whereas there was a non significant effect on total erythrocyte count, packed cell volume, haemoglobin and clotting time. Plasma protein and albumin decreased whereas glucose, blood urea nitrogen and creatinine increased in the study.

Kuusela et al. (2003) have studied propofol and propofol-isoflurane anaesthesia in dogs. Cardiac, blood gases, hemodynamic, recovery and stress indicator variables were recorded. There was a decrease in heart rate, blood pressure and adrenaline levels. It was concluded that propofol-isoflurane anaesthesia was more useful than propofol alone because of milder degree of respiratory depression and faster recovery with the former.

Ambrisco et al. (2005) have experimented with ketamine, butorphanol, fentanyl and medetomidine and recorded the neurohumoral metabolic responses elicited by these drugs in dogs. Ketamine, fentanyl and butorphanol elevated the epinephrine, cortisol and glucose levels which resembles the clinical picture of stress. Medetomidine reduced these changes to a great exchange but did not prevent elevation of glucose levels. It was recommended that a combination of drugs as medetomidine-butorphanol or medetomidine-ketamine should be used for sedation to harness the benefit of a stable neurohumoral profile.

Ahmad et al. (2012) have evaluated stress response in dogs using dexmedetomidine, midazolam, fentanyl and ketamine. It was found that neutrophils and glucose increased whereas insulin and cortisol decreased in the blood. It was concluded that dexmedetomidine and the drugs tested could reduce the stress response elicited in surgery and anaesthetic periods. Therefore the tested drugs were safe to use for the purpose of sedation, surgery or anaesthesia.

Restitutti et al. (2012) have studied various plasma biochemical parameters while using dexmedetomidine and MK-467 in dogs. Dexmedetomidine (DEX) increased plasma glucose and reduced plasma insulin while non esterified fatty acid
decreased. This reduction was of very long duration with dexmedetomidine. Plasma lactate concentrations increased with DEX. Plasma cortisol level was not affected by any drug. MK-467 caused a cessation of all the biochemical changes thus far observed.

**Riha et al. (2012)** have opined that inhalational anesthetics had shown cardioprotective effects in myocardial ischemia-reperfusion injury. It was noted that the assumed superiority of inhalation anaesthetics over injectable anaesthetics had been questioned. Ketamine was treated at par with sufentanil, as it had shown some anti-inflammatory actions. Further it was re-emphasised that dexmedetomidine had shown myocardial protective effects. In their study, the influence of ketamine-dexmedetomidine based anaesthesia on the release of cardiac biomarkers was compared with that of sevoflurane sufentanil-based anesthesia in cardiac surgery patients. Among the SEVO and KET-DEX groups, the latter group showed lesser cardiac troponin I and myocardial fraction of creatine kinase (CK-MB).

**Yacout et al. (2012)** have found in their study that dexmedetomidine caused a decrease in heart rate, mean arterial pressure, cortisol and glucose levels either intraoperatively or postoperatively. It also reduced the post operative rise of inflammatory cytokine (IL6) and the pain score.

**Guedes and Rude (2013)** have evaluated the effects of dexmedetomidine in healthy dogs and dogs with insulinoma who underwent the required surgical procedures. It was found that in both the groups of dogs plasma insulin level decreased and glucose level increased during the surgery. Therefore it was concluded that dexmedetomidine suppresses the insulin secretion in dogs.

**Umar and Adam (2013)** have evaluated the effects of ketamine-medetomidine on the parameters like packed cell volume, haemoglobin, total erythrocyte count, total leucocyte count, differential leucocyte count, creatinine, blood urea nitrogen and alanine amino transferase in dogs. The results showed decreases in packed cell volume, erythrocyte count, haemoglobin, neutrophils and lymphocytes. Leucocytes and creatinine increased whereas blood urea nitrogen, alanine amino transferase, monocytes and eosinophils did not differ with base values. All the above changes in the values of clinical and biochemical parameters did not affect the outcome of the experiment in any adverse manner and the recovery was satisfactory from the clinical point of view.
Akbar et al. (2014) have studied the effects of medetomidine on clinical and blood parameters in dogs. Body temperature, pulse, respiration rate and blood pressure decreased after medetomidine injection. Alanine amino transferase and aspartate amino transferase values were dependent on the dose used (decreasing with increasing dose). Haemoglobin and erythrocyte sedimentation rate decreased whereas total and differential leucocyte count showed non significant changes. It was concluded that detomidine was a potent drug that can be used safely to cause sedation in dogs.

Kumar et al. (2014) have studied the clinical-physiological, blood biochemical and haemodynamic parameters in uraemic goats subjected to anaesthesia with propofol, dexmedetomidine and ketamine. It was found that propofol-dexmedetomidine were effective at lower doses than dexmedetomidine-ketamine. Mean arterial pressure decreased in both the groups, heart rate decreased but improved after ketamine administration. In their study packed cell volume, haemoglobin, total erythrocyte count decreased, blood urea nitrogen and glucose increased and creatinine fluctuated. It was concluded that both the drug combinations were suitable for producing TIVA however, ketamine provided better haemodynamic stability and propofol gave better muscle relaxation.

Wang et al. (2014) have conducted a study to compare the effects of variable doses of dexmedetomidine on the stress response in people. It was found that the stress response was far less in people receiving low and high doses of dexmedetomidine and it was supported by the lower serum cortisol, glucose, MAP and HR values at designated time intervals. It also reduced the sevoflurane requirement and occurrence of dysphoria, and did not prolong the recovery and extubation times.

Mazumdar et al. (2015) have studied the effects of dexmedetomidine on blood biochemical parameters dogs. Two dose rates of dexmedetomidine viz. 20 and 40 µg/kg body weight were compared. It was found that packed cell volume, haemoglobin, total erythrocyte count, total leucocyte count, alkaline phosphatase and total protein decreased whereas blood urea nitrogen, creatinine and cortisol increased in the studied animals. Based on the observations of the various parameters the dose rate of 20 µg/kg body weight was recommended over the dose rate of 40 µg/kg body weight.

Rafee et al. (2015b) have conducted a study and measured the biochemical changes occurring in dogs subjected to ovariohysterectomy. It was found that
haemoglobin and total leucocyte count decreased whereas glucose increased in the dogs. Packed cell volume, creatinine, insulin, cortisol and neutrophils showed non significant changes. It was concluded that dexmedetomidine obtunds the stress response of the surgical patients and hence cortisol and neutrophils did not increase to a greater extent.

Harsoor et al. (2016) have evaluated the effects of dexmedetomodine on clinical and biochemical parameters in humans. Glucose level and sevoflurane requirements were reduced due to dexmedetomidine whereas heart rate and mean arterial pressure reduced in the perioperative period. Sedation and pain score were also better with dexmedetomidine. It was concluded that dexmedetomidine causes a blunting of stress response.

2.5.4 MAC (MINIMUM ALVEOLAR CONCENTRATION) STUDIES

Aanta et al. (1997) have studied the effects of dexmedetomidine on the MAC of isoflurane in women. Dexmedetomidine was infused at two plasma target concentrations of 0.3 and 0.6ng/ml and it was found that at higher doses of dexmedetomidine the MAC of isoflurane was reduced by 47% in women undergoing abdominal hysterectomy.

Pascoe et al. (2006) have experimented with the changes in MAC of isoflurane when used with dexmedetomidine. It was found that 0.5 and 3.0 µg decreased the MAC while 0.1µg did not affect it. Heart rate decreased with increasing doses of dexmedetomidine while blood pressure increased. With increasing dexmedetomidine dose rate the heart slowed down. It was concluded that dexmedetomidine decreases the isoflurane MAC and also provides some analgesia with attenuation of the stress response.

Ebner et al. (2013) have determined the effect of dexmedetomidine, morphine, lidocaine and ketamine (D, M, L, K) on isoflurane minimum alveolar concentration (MAC) in canines. Haemodynamic parameters were also recorded which showed variation with the drug combinations. It was found that D, MLK and DMLK reduced MAC of isoflurane by 30%, 55%, and 90%, in that order. Hence DMLK afforded a greatest reduction in MAC of isoflurane in the dogs tested.

Gutierrez-Blanco et al. (2013) have experimented with the effects of fentanyl, lidocaine, ketamine and dexmedetomidine on the anaesthetic requirement of isoflurane.
It was found that fentanyl and lidocaine-ketamine-dexmedetomidine reduced the MAC of isoflurane more than that reduced by lidocaine or ketamine. Lowering of heart rate was a disadvantage with the use of fentanyl.

**Moran-Munoz et al. (2014)** have studied whether lidocaine or dexmedetomidine can affect the MAC of sevoflurane, either alone or in combination with each other, in dogs. The authors found that lidocaine, dexmedetomidine and their combination reduced the MAC of sevoflurane by 26.1±9.0%, 43.7±11.8% and 54.4±9.8% respectively. Therefore it was concluded that the MAC of sevoflurane was drastically reduced by the use of CRI of lidocaine and dexmedetomidine.

**Pascoe (2015)** have studied the cardiopulmonary effects of dexmedetomidine in dogs. Dexmedetomidine-isoflurane was compared with isoflurane alone. It was noted that conspicuous differences in the two treatments existed with respect to their effects on haemodynamic parameters. It was concluded that dexmedetomidine caused a reduction in the MAC of isoflurane at the dose rates of 0.5-3.0µg/kg/hr, therefore low (and not high) doses were found useful in anaesthesia.

### 2.6. ETOMIDATE

#### 2.6.1 CLINICO-PHYSIOLOGICAL STUDIES

**Gooding and Corssen (1976)** have reported that etomidate produced hypnosis in one arm-to-brain circulation and that the plasma concentration of its metabolites was maximum after seven minutes of administration. Cardiovascular, respiratory and any other body systems were not affected and there were no signs of any other side effect. Pain on injection site and myclonus were reported by them as major untoward incidents while using etomidate.

**Kissin et al. (1983)** have evaluated the powers of etomidate and thiopental to decrease the myometrial contractility in papillary muscles of dog. It was found that both the drugs studied decreased the contractility of heart muscle but in equianesthetic doses etomidate has a far less depressing effect (inotropic effect) on the cardiac muscles.

**Muir and Mason (1989)** have studied the side effects of etomidate in experimental as well as clinical cases of dogs. It was found that etomidate causes
excitement, myoclonus, vomiting, pain on injection and apnea in these dogs. These side effects were reduced to a minimum or negligible magnitude when drugs like diazepam, morphine or acepromazine were used as a premedicants.

Ko et al. (1994) have evaluated the haemodynamic and clinical properties of etomidate on dogs which were premedicated with medetomidine. It was found that S-A and A-V blocks were experienced but disappeared within 8 minutes, apnoea was not encountered in the experiment and analgesia was very good and lasted for the whole duration of the experiment. The haemodynamic variables were least affected though respiration was depressed. It was concluded that atropine-medetomidine-etomidate was a satisfactory anaesthetic regime for dogs.

Mazerolles et al. (1996) have investigated the effects of pentobarbital and etomidate on systolic blood pressure (SBP) and heart rate (HR) in dogs. The results showed that pentobarbital decreases the activity of the two components of the autonomic nervous system whereas etomidate induces only minimal changes in these components.

Sokolove et al. (2000) have studied the effects of etomidate given to pediatric patients with respect to the adrenal gland depression and a decreased blood pressure. It was found that in the 100 children under the age of 10 years whose cases were studied, no one developed adrenal insufficiency or a clinically significant blood pressure drop. It was recommended for further studies regarding the safety of etomidate in children.

Sprung et al. (2000) have studied the contractility of human heart muscle as affected by etomidate. As the dose of etomidate increased the heart muscles developed less and less tension. All the negative inotropic effects were reversed by the application of β-adrenergic drugs. Therefore it was concluded from there study that the above effects are seen at dose rates which are greater than the doses routinely applied in clinical cases, and hence this phenomenon would not be a hinderance to the use of etomidate in clinical cases despite the patients having myocardial insufficiencies.

Rothermel (2003) has opined that sedation in pediatric patients was a necessary and difficult job. He studied etomidate and propofol for this purpose and noted that etomidate was a sedative hypnotic drug without any analgesic property. It had a rapid onset of action, short duration of action, and minimal haemodynamic effects. Etomidate

Review of Literature..................
had been shown to be safe for this purpose. Propofol also had a rapid onset and short duration of action and had been in use in children for long. It was concluded that though some studies have shown propofol to be suitable for paediatric use but the many side effects assoaciated with it viz. apnea, hypoxia and hypotension might act in its disfavour.

**Sarkar et al. (2005)** have carried out cardiac procedures in children using etomidate and observed that etomidate causes no significant alterations in cadiac or respiratory variables. It was for recommended further studies to establish that etomidate is safe to use in children with cardiac anomalies other than those studied.

**Kamp and Kress (2007)** have expressed their concern on the fact that etomidate is associated with increased mortality with or without the use of corticosteroids in severely ill patients. But it has been emphasized that no other agent provides the haemodynamic stability as required in these patients in the ICU. It was proposed that in this condition, use of an opioid (fentanyl), a topical local anaesthetic or no agent at all can be considered for future considerations. It was recommended further studies for establishing the use of etomodate.

**Vinclair et al. (2008)** have studied the length of time for which adrenal suppression is affected by a single dose of etomidate. It was found that adrenal suppression is effective for and within a period of 48 hrs post injection, after which cortisol levels return to original values. It was further advocated that supplemental use of steroids can be considered for and within the 48 hr period immediately following the etomidate injection.

**Forman (2011)** has reviewed the clinical and molecular pharmacologic features of etomidate. It was opined that etomidate has the most favourable therapeutic index. A very different property of etomidate from other anaesthetics is the inhibition of adrenal gland steroid synthesis which has been associated with increased mortality in very sick peopole. It binds to the GABA\textsubscript{A} receptors in brain to produce hypnosis. Based on an advanced understanding of the molecular structure of etomidate and its binding sites, it has become possible to evolve less toxic derivatives of etomidate (e.g. “Methoxy carbonyl etomidate” and “carboetomidate”) for future development and use.

**Cherfan et al. (2012)** have evaluated the pros and cons of using etomidate in critically ill patients. Taking note of the views of both sides of scientists (favouring and
opposing the use of etomidate in these patients), a conclusion was drawn that as long as the safety of etomidate is not established beyond doubt with respect to the danger of mortality, other drugs should be given preference for use in critically ill patients.

**Legrand and Plaud (2013)** have compared the effects of etomidate with a metaphor in physics viz. “the butterfly effect”. This effect states that a small difference in the state of a physical system can cause a major effect on the state of the system at some later stage. Some studies were mentioned which have associated etomidate with increased mortality while other studies have not found an association between mortality and etomidate. It was emphasized that a causal relationship between adrenal insufficiency and mortality had remained “speculative”. Therefore it was recommended that so long as results of more controlled studies from many sources are not available, other drugs esp. propofol or ketamine should be used in place of etomidate (wherever feasible clinically) so that the population is not exposed to some minor differences which may prove to be a major negative factor in a longer run (butterfly effect).

**Erdoes et al. (2014)** have opined that etomidate has found wide application in patients with haemodynamic instabilities. Presently it has become debatable whether or not to use etomidate due to its association with high mortality. This mortality is thought to arise from the adrenal gland depression after use of etomidate. It was recommended to carry out more studies to establish the safety of using etomidate and to find its alternatives.

### 2.6.2 HAEMODYNAMIC STUDIES

**Brussel et al. (1989)** have observed that of the two drugs (etomidate and propofol), propofol caused a reduction in heart rate, systolic blood pressure, diastolic blood pressure, cardiac output and systemic vascular resistance. Etomidate caused least changes in the haemodynamic parameters. It was concluded that propofol has inherently negative inotropic effects.

**De Hert et al. (1990)** have experimented with heart fragment of dog inflicted with ischemia and the effect of anaesthetic drugs thiopental, etomidate, and propofol on it. All drugs caused a decrease of end-diastolic length (hence a decrease in ventricular filling) in proportion to their own doses used. Thiopentone caused a systolic shortening (proportional to own dose), propofol caused systolic shortening identically in ischemic...
and non ischemic segments whereas etomidate did not alter the systolic or diastolic length. Hence etomidate was assumed to have a haemodynamic stabilising effect.

**Fanton et al. (2000)** have conducted experiment in rhesus monkeys to compare the cardiovascular effects of etomidate and propofol. It was found that in their study that MAP, HR and myocardial contractility were decreased with both the drugs. The other parameters like left ventricular diastolic pressure, cardiac output, stroke volume and total peripheral resistance did not change significantly. It was concluded that from the study that both the drugs cause notable alterations in haemodynamic parameters in monkeys.

**Perk et al. (2002)** have evaluated the effects of etomidate and alfentanil on various blood parameters. It was found that total leucocyte count, alanine amino transferase, aspartate amino transferase, haemoglobin, total protein and blood urea nitrogen did not show remarkable changes whereas total erythrocyte count, packed cell volume and glucose increased as a result of the use of these two drugs.

**Medeiros et al. (2004)** have studied the effects of diazepam, midazolam, propofol and etomidate on cardiac contractility and coronary blood flow. It was found that all the drugs reduced myocardial contractility and coronary blood flow. Further it was found that variations in one variable did not correlate well with variations in the other variable in rats.

**Sams et al. (2008)** have compared the effects of propofol and etomidate in dogs. It was found that propofol caused a decrease in SAP and MAP compared to etomidate which maintained arterial blood pressure near the normal range. Etomidate was associated with longer and poor quality recovery. Therefore propofol was found more suitable for smooth rapid recovery whereas etomidate was superior if anaesthesia with minimal cardiovascular effects was desired.

**Rodriguez et al. (2012)** have compared the cardiopulmonary parameters after induction of anaesthesia with alfaxalone and etomidate in dogs. Alfaxalone caused significant tachycardia and increase in cardiac index, and statistically (but not clinically) significant decreases in arterial pressure and systemic vascular resistance index. Etomidate caused no statistically significant cardiovascular changes. Alfaxalone gave a better quality recovery. Both these drugs caused hypoxia, warranting oxygen supplementation.
Masoudifar and Beheshtian (2013) have compared the propofol and etomidate with respect to tracheal intubation and larygoscopy. The haemodynamic variables were compared and it was found that systolic, diastolic and mean arterial blood pressure showed more changes in propofol group. There were no significant differences in the heart rate, SpO\textsubscript{2}, tachycardia or bradycardia in the two groups (etomidate and propofol). It was advocated to use etomidate for general anaesthesia if there would not be any contraindications to its use in those clinical conditions (where it would be intended to be used).

Das et al. (2015) have compared etomidate, propofol and thiopentone in relation to their hemodynamic effects in laparoscopic surgery. It was found that etomidate did not cause significant changes in heart rate, systolic, diastolic and mean arterial blood pressure in the human patients after induction of anaesthesia, propofol caused first a fall and then a gain in the values of above mentioned parameters whereas thiopentone yielded fluctuating values of these parameters. The values of the parameters returned to their base values first in etomidate, then in propofol and at last in case of thiopentone. The authors concluded that etomidate behaved like an ideal anaesthetic.

Kaushal et al. (2015) have evaluated effects of etomidate and propofol in cardiac patients. It was noted that SBP, DBP and MAP decreased whereas cortisol and glucose increased in the patients undergoing coronary bypass surgery.

Shivanna et al. (2015) have studied the haemodynamic effects of propofol and etomidate in human cardiac surgery with special reference to induction and intubation. It was found in the study that propofol causes significant reductions in cardiac contractility, arterial blood pressure and afterload. Etomidate was found to be less efficient in alleviating the stress response.

Desai et al. (2016) have compared the suitability of etomidate and propofol for cardioversion in human patients. The patients treated with propofol showed decreased SBP, DBP and MAP, hypotension and longer recovery period. Etomidate treated patients suffered more with myoclonus. Etomidate was recommended over propofol for cardioversion in human patients due to the above characteristics.
2.6.3 HAEMATO-BIOCHEMICAL STUDIES

**Famewo et al. (1979)** have evaluated the values of glucose, sodium and potassium in humans in whom etomidate or suxamethonium were used. It was found that values of glucose increased after etomidate and suxamethonium use, however the increase was much greater for suxamethonium. Sodium and potassium did not show remarkable changes after the use of any of the two anaesthetics.

**Fragen et al. (1984)** have examined the surgical stress in women who received etomidate or thiopental during laparotomy. It was observed that the women receiving etomidate had lower blood levels of cortisol and aldosterone than the women receiving thiopental. Since levels of both cortisol and aldosterone were lowered, it was concluded that etomidate must be suppressing early steroidogenesis in order to inflict such an effect.

**DeCoster et al. (1987)** have evaluated the effects of etomidate and its fluoro analogue, R8110, in dogs. Dogs were given tetracosactide, half an hour after the administration of the above drugs. Cortisol response to tetracosactide was almost fully depressed by etomidate and R8110. It was reported that the inhibitory effect of R8110 on adrenal gland was far less than etomidate.

**Preziosi and Vacca (1988)** have studied the effects of etomidate on secretion of various hormones. It was noted that the (+) isomer was more active than the (±) and the (-) isomer. Advice was given against the use of etomidate for long term sedation/anaesthesia. It was found that high levels of etomidate may inhibit testosterone synthesis, estradiol levels are unaffected, with increased levels of GH (growth hormone) and ACTH and decreased prolactin in rats but not in humans.

**Absalom et al. (1999)** have compared the effects of etomidate and thiopentone on adrenal gland function in a clinical trial with people. A blood sample was collected before anaesthesia to measure cortisol concentration. Exactly one day after the anaesthesia, adrenocorticotrophic hormone stimulation test was performed. All the groups did not show similar values of baseline, pre-ACTH and post-ACTH cortisol. The etomidate group showed a poor response to the ACTH stimulation. The clinical significance of these findings was not clear but it was concluded that etomidate suppresses the cortisol synthesis by adrenal gland.
Perk et al. (2002) have evaluated the effects of etomidate and alfentanil on various blood parameters. It was found that total leucocyte count, alanine amino transferase, aspartate amino transferase, haemoglobin, total protein and blood urea nitrogen did not show remarkable changes whereas total erythrocyte count, packed cell volume and glucose increased as a result of the use of these two drugs.

Brinker et al. (2007) have compared the values of cortisol, ACTH and 11-deoxycortisol in children who were administered etomidate. It was seen that these children developed lower levels of cortisol and 11-deoxycortisol and higher levels of ACTH upto 24 hr post injection. About 88% children died after receiving etomidate. Hence it was concluded that etomidate can cause higher mortality in the recipients.

Cuthberton et al. (2009) have tested whether use of etomidate and mortality are correlated. This question arises out of the fact that etomidate is known to suppress body’s response to corticotrophin. It was concluded that etomidate was associated with an increased mortality rate in patients and extreme caution in the use of etomidate was recommended.

Jabre et al. (2009) have compared the effects of etomidate and ketamine for use in emergency situations in critically ill patients for intubation, because use of etomidate is associated with adrenal insufficiency and increased mortality. It was observed in the study that more patients receiving etomidate had suffered adrenal insufficiency than the patients receiving ketamine. It was concluded that ketamine should be considered as an alternative to etomidate for the severely sick patients.

Hohl et al. (2010) have studied the effect of a dose of etomidate on cortisol level and mortality. The patients administered etomidate had lower cortisol levels than those who did not receive cortisol. It was found that no conclusive evidence is associated with higher mortality rates and administration of etomidate and hence it was suggested to use other induction agents till reliable studies are available that can suggest the efficacy of etomidate on mortality.

Albert et al. (2011) have evaluated the effect of etomidate on the adrenal gland in the critically ill patients. It was observed that despite being a preferred anaesthetic for rapid intubation in patients, etomidate is known to cause cessation of cortisol production and adrenal insufficiency. The effects of etomidate with other anaesthetics
to probe mortality and adrenal insufficiency were compared. It was concluded that there is an increased risk of mortality and adrenal insufficiency with the use of etomidate in critically ill patients.

Sumer et al. (2012) have reported on the biochemical and hematologic parameters in patients treated with etomidate and propofol. It was reported that levels of cortisol decreased in the patients administered with etomidate compared to the propofol group, insulin and glucose levels increased whereas the level of TLC showed a non significant change.

Wagner et al. (2014) have studied the relationship between etomidate used and results of heart surgery in human patients. It was opined that it is unknown whether use of etomidate would affect the results of surgery or not, because etomidate is known to suppress the adrenal gland function. In the study no factor was found that would preclude the use of etomidate as an induction agent.

Kaushal et al. (2015) have evaluated effects of etomidate and propofol in cardiac patients. It was noted that SBP, DBP and MAP decreased whereas cortisol and glucose increased in the patients undergoing coronary bypass surgery.

Qin et al. (2016) have provided the clinical values of heart rate, mean arterial pressure, bispectral index (HR, MAP, BIS), cortisol and aldosterone in dogs which got a continuous infusion of etomidate for maintenance of anaesthesia. It was reported that cortisol and aldosterone decreased whereas HR, MAP and BIS did not show remarkable changes in their values.

2.7 PROPOFOL

2.7.1 CLINICOPHYSIOLOGICAL STUDIES

Ebert et al. (1992) have opined that propofol causes hypotension on induction of anaesthesia. It was observed the neural causes behind this and found out that etomidate does not alter/afffect the autonomic nervous system whereas propofol inhibits the sympathetic nervous system and deranges the baroreflex regulatory mechanism.

Thurmon et al. (1994) have evaluated the effects of propofol in dogs previously treated with medetomidine. It was found that SA and AV blockade appeared and disappeared within 10 minutes of starting of experiment. Apnea was not
encountered and analgesia was of good quality. All the dogs experienced good quality recovery. It was concluded that atropine-medetomidine-propofol was a satisfactory anaesthetic combination for the use in dogs.

Wilder–Smith et al. (1995) have studied analgesia as produced by the injections of propofol and thiopentone in dogs. It was found that the threshold of thermal pain was not lowered by any of the two drugs, therefore it cannot be expected that the two drugs would be causing hyperalgesia in clinical cases utilising (their) usual working doses of thiopentone or propofol.

Reid and Nolan (1996) have evaluated the pharmacokinetics of propofol (5mg/kg i.v.) as an induction agent in geriatric dogs. It was found that propofol was slowly cleared from body and also caused apnoea. It was recommended that propofol should be used in lower doses in geriatric dogs.

Sprung et al. (2001) have determined the direct effects of propofol on the contractility of human nonfailing and failing atrial and ventricular muscles. It was concluded in the study that propofol (at concentrations greater than those used clinically) has negative inotropic effect on human heart muscles. The negative inotropic effect of propofol is caused by lesser uptake of Ca\(^{2+}\) into the sarcoplasmic reticulum but, it is offset by an increased sensitivity of SR to activator Ca\(^{2+}\) when propofol is used in the clinical settings at the usual doses to induce anaesthesia.

Kuusela et al. (2003) have studied propofol and propofol-isoflurane anaesthesia in dogs premedicated with dexmedetomidine. Cardiac, blood gases, haemodynamic, recovery and stress indicator variables were recorded. HR decreased, recovery time was longer when propofol was used. It was concluded that propofol-isoflurane anaesthesia was more useful than propofol alone because of milder degree of respiratory depression and faster recovery with the former.

Rothermel (2003) has opined that procedural sedation for paediatric patients was a necessary but difficult job. He studied etomidate and propofol for this purpose and noted that etomidate had no analgesic properties but had a rapid onset of action, short duration of action and least hemodynamic effects. Etomidate was considered safe for the above purpose. Similarly propofol also had rapid onset and short duration of action and had been in use for surgery in the ICU. It was observed that though propofol
had been shown to be safe for use in children but its side effects (apnea, hypoxia and hypotension) might cause it to be not favoured.

**Musk et al. (2005)** have evaluated the suitability of four target controlled infusion rates of propofol in dogs. Cardiac and respiratory parameters were noted and BP reduced in all the groups. It was concluded that a concentration of 3.5µg/ml of propofol in plasma was the most suitable with regard to induction of anaesthesia and the impact on cardiopulmonary parameters. Blood pressure decreased in all the treatments.

**Kale et al. (2006)** have studied the clinico-physiological parameters resulting from use of lipid-free propofol in dogs. Propofol alone gave a poorer quality of anaesthesia whereas propofol-diazepam and propofol-triflupromazine gave better quality anaesthesia compared to propofol alone respectively. Of the parameters studied heart rate increased whereas rectal temperature and respiration rate decreased after administration of anaesthesia.

**Intelisano et al. (2008)** have opined that propofol and ketamine provide a good anaesthesia for use in animals. Anaesthesia produced by two combinations viz. propofol-racemic ketamine (PRK) and propofol-S-ketamine (PSK) were compared. Haemodynamic, metabolic and ventilatory parameters were measured in the experiment at preset time points. In both groups, heart rate increased and all other parameters viz. systemic blood pressure, cardiac output, cardiac index, systolic index, respiratory rate were reduced. Due to these observations artificial respiration was instituted in all cases.

**Sams et al. (2008)** have compared the effects of propofol and etomidate in dogs. It was found that propofol caused a decrease in systolic and mean arterial pressure as compared to etomidate which maintained arterial blood pressure near the normal range. Etomidate was associated with longer and poor quality recovery. Therefore propofol was found more suitable for smooth rapid recovery whereas etomidate was superior if anaesthesia with minimal cardiovascular effects was desired.

**Sharma and Bhardwaj (2010)** have experimented with propofol, xylazine and midazolam in dogs. In group I propofol, in group II propofol and xylazine and in group III propofol and midazolam were used. Clinico-physiological, haematobiochemical parameters and side effects were noted. Respiratory rate, rectal temperature,
haemoglobin, packed cell volume, total erythrocyte count, blood urea nitrogen and creatinine decreased whereas heart rate increased in the study. Haematobiochemical parameters did not show any remarkable variations. Apnoea, vomiting, urination, paddling, ophisthotonus and salivation were observed during anaesthesia. It was concluded that xylazine-propofol anaesthesia was the best of the three regimens tested due to rapid onset, longer duration and minimum side effects.

Sooryadas et al. (2011) have presented an electrocardiographic study after using propofol and xylazine in dogs. Tachycardia, bradycardia, wandering pace maker, ventricular pre-excitation, atrial premature contraction, ST coving, biphasic T waves and peaked T waves were the chief ECG changes observed in the anaesthetized dogs.

Jiménez et al. (2012) have evaluated the recovery quality in dogs which were anaesthetized with alfaxalone or propofol. The dogs were sedated with methadone and anaesthetized with alfaxalone or propofol. It was found that the sex, behaviour or duration of anaesthesia did not have an impact on the scores of sedation. The dogs heavily sedated showed a better recovery than the dogs which were poorly sedated in the preoperative period. The quality of recovery was better with propofol than alfaxalone, which showed poor recoveries. Therefore it was recommended that heavy sedation and propofol (not alfaxalone) will give better recoveries in clinical settings.

Keates and Whittem (2012) have studied respiratory patterns after injection of alfaxalone or propofol in dogs. Dogs were administered the drugs in multiples of 1, 2, 5, 10 or 20 of the standard doses. Occurrence of apnoea was specifically noted. It was found that a 5X dose of alfaxalone and a 2X dose of propofol caused apnoea, hence it was concluded that there were more chances of developing apnoea with propofol than with alfaxalone when anaesthesia was induced with these two drugs. The study showed the depressing effect of propofol on respiration.

Kushwaha et al. (2012) have evaluated midazolam and propofol as anaesthetics in dogs. Induction, recovery, clinicophysiological, haematobiochemical and haemodynamic parameters were recorded. It was concluded that midazolam and local anaesthetics were good for minor surgery whereas propofol and midazolam together could achieve balanced anaesthesia.

Review of Literature............

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Review of Literature............
Alkattan and Helal (2013) have examined the effects of ketamine-xylazine and propofol-isoflurane anaesthesia on clinicophysiological and blood gas parameters in dogs. High doses of xylazine (5mg/kg i.v.) and ketmine (15mg/kg i.m.) were used in the study. The anesthesia produced with propofol-isoflurane was adjudged to be the best because of rapid onset, short duration and smooth recovery. It was concluded that it could be used for laparoscopy in dogs with high risk scores.

Costa et al. (2013) have opined that the oxidative status of cells can be affected by circulating anaesthetics in blood which can further cause immune suppression. The study was conducted with propofol and it was found that red blood cells, hematocrit, haemoglobin, leukocyte count decreased whereas platelets, neutrophil, eosinophil, basophil and monocytes did not show significant changes. Hence it was recommended that since propofol causes a reduction in cell count, it should be used with caution in immune compromised patients.

Güzel et al. (2013) have studied the haemodynamic and clinical effects of propofol, diazepam and alfentanil in older dogs. The dose rates employed were propofol 6 mg/kg (i.v), diazepam 0.5 mg/kg (i.v.) and alfentanil 40 µg/kg (i.v.). It was concluded from their study that, in the older dogs propofol was preferable to diazepam-alfentanil since it gave reliable haemodynamic and respiratory data.

Mousa and Alsobky (2013) have studied the efficacy of intravenous propofol, dexmedetomidine+fentanyl and sevoflurane for anaesthesia in humans. Dexmedetomidine and propofol were found to be superior to the sevoflurane. The haemodynamics and clinical parameters of the drug combinations used were compared. In all the groups haemodynamic variables showed a downward trend whereas in dexmedetomidine-fentanyl group the respiratory variables were on the higher platter.

Sanchez et al. (2013) have experimented with midazolam and propofol in dogs by altering the temporal sequence in which the two drugs were administered. Heart rate, respiration rate, blood pressure, ETCO\textsubscript{2} and SpO\textsubscript{2} were recorded. In both the cases (midazolam or propofol before each other) propofol requirement reduced compared to the control group, though a greater reduction was achieved when propofol was administered before midazolam.
Bayan and Konwar (2014) have evaluated anaesthesia produced by a mixture of ketamine and propofol in 1:1 ratio (ketofol) in dogs. The quality of sedation and analgesia were satisfactory in all the animals. The heart rate, respiratory rate, rectal temperature and blood pressure remained within the normal physiological limit. It was concluded in the study that ketofol is safe for induction without any serious adverse affect on the normal physiological function.

Hopkins et al. (2014) have described the concomitant use of midazolam and propofol in dog. This combination of drug was helpful in reducing the dose required to induce anaesthesia with propofol. It was observed that midazolam caused a decrease in systemic arterial pressure. This decrease in the blood pressure was not found to be very significant clinically and hence was considered acceptable.

Jena et al. (2014) have evaluated and compared the clinico-physiological, hemodynamic and hematobiochemical effects in response to different total intravenous anaesthesia using xylazine, dexmedetomidine and propofol in dogs. All combinations studied provided good anaesthesia. Therefore both the drug combinations were found satisfactory for clinical anaesthesia in dogs.

Khurana et al. (2014) have evaluated clinical and biochemical parameters in dogs using propofol. It was observed that haemoglobin and AST decreased whereas other biochemical parameters (creatinine, sodium, potassium) did not show significant changes. ECG was overall normal and authors did not attach significance to the changes of time and voltage parameters in the ECG recordings obtained. It was concluded that the tested drugs (diazepam, butorphanol, propofol, halothane, acepromazine) were safe to produce anaesthesia in dogs.

Kleine et al. (2014) have reported the factors responsible for the time to extubation in dogs. Induction with propofol had a shorter time to extubation, while premedication with acepromazine increased it. Similarly higher body weight, decreased body temperature and increased length of anaesthesia increased the time to extubation. The above mentioned factors if controlled well by the anaesthetist can give a shorter time to extubation and hence a better and shorter recovery.

Taboada and Leece (2014) have compared the clinico-physiological parameters in dogs that were treated with propofol or a mixture of propofol and
ketamine (ketofol). Induction mixture volume was lower for ketofol than propofol. It was concluded that from the study that ketofol causes a higher pulse rate and mean arterial pressure than propofol and decreases the respiratory rate. Induction and intubation were better with ketofol than propofol.

2.7.2 HAEMODYNAMIC STUDIES

Brussel et al. (1989) have observed in their experiment that of the two drugs etomidate and propofol, propofol caused a reduction in heart rate, systolic blood pressure, diastolic blood pressure, cardiac output and systemic vascular resistance. Etomidate caused least changes in the haemodynamic parameters. It was concluded that propofol has inherently negative inotropic effects.

Fanton et al. (2000) have conducted experiment in rhesus monkeys to compare the cardiovascular effects of etomidate and propofol. It was found that mean arterial pressure, heart rate and myocardial contractility decreased with both the drugs. The other parameters like left ventricular diastolic pressure, cardiac output, stroke volume and total peripheral resistance did not change significantly. It was concluded that both the drugs cause notable alterations in haemodynamic parameters in monkeys.

Lerche et al. (2000) have studied the anaesthetic effects of propofol and propofol-ketamine in dogs premedicated with acepromazine and pethidine. Various clinicophysiological and cardiorespiratory parameters were monitored. Increased heart rate with lower systolic blood pressure was observed in propofol-ketamine group. Apnoea occurred more frequently with propofol-ketamine. Muscle twitching and recovery times had a similar picture. The authors found both that both the groups were similar in clinical effects.

Kehl et al. (2002) have studied the effects of propofol anaesthesia on the function of left atrium in dogs. Aortic, LA (left atrial) and left ventricular (LV) pressures (micro manometers) and LA volume (epicardial orthogonal sonomicrometers) were measured. Propofol decreased heart rate, mean arterial pressure and the maximal rate of increase of LV pressure. It was observed that propofol’s effects on the function of heart were complex and it depressed LA myocardial contractility but this depression was also compensated by propofol.
Medeiros et al. (2004) have studied, in rat hearts the effects of diazepam, midazolam, propofol and etomidate on cardiac contractility and coronary blood flow. It was found that all the drugs reduced myocardial contractility and coronary blood flow. Further it was found that variations in one variable did not correlate well with variations in the other variable.

Paula et al. (2010) have studied the clinical effects of propofol and etomidate on intracranial parameters in dogs. Intracranial pressure, temperature, perfusion pressure, BT and MAP were noted along with heart rate (HR). None of the parameters showed a deviation from their normal values. Etomidate caused lowering of the body and intracranial temperatures. It was concluded that perfusion of brain and regulatory mechanisms were not affected by a continuous perfusion of the above mentioned two drugs.

Kushwaha et al. (2012) have evaluated midazolam and propofol as anaesthetics in dogs. Different induction, recovery, clinicophysiological, haematobiochemical and haemodynamic parameters were recorded. Heart rate first increased and then decreased, it regained the original values by 24 hrs. It was concluded that midazolam was a good tranquilizer for concomitant use with local analgesics and that propofol and midazolam could provide balanced anaesthesia in dogs.

Mannarino et al. (2012) have studied the haemodynamic effects and bispectral index in dogs anaesthetized with propofol, lidocaine and ketamine combinations. All the haemodynamic parameters studied decreased and only the systemic vascular resistance index increased in the drug combinations tested. It was found that only lidocaine-ketamine reduced the infusion rate of propofol but no drugs tested could reduce the depression of cardiovascular system accompanying the use of propofol.

Suarez et al. (2012) have compared the clinico-physiological and blood gas parameters in dogs anaesthetized with alfaxalone and propofol. Both the drugs provided adequate and smooth induction, maintenance and recovery. Propofol reduced the RR while HR, SAP, DAP and MAP were increased in the study. Propofol at 5.8mg/kg i.v. (bolus) and 0.3mg/kg/min. CRI were found satisfactorily in the experiment. It was found that hypoventilation occurred during the course of study therefore it was recommended to take adequate respiratory measures while using any of the two above mentioned drugs.
Masoudifar and Behshtian et al. (2013) have compared propofol and etomidate with respect to tracheal intubation and laryngoscopy. The haemodynamic variables were compared and it was found that SBP, DBP and MAP showed more changes in propofol group. There were no significant differences in the HR, O₂Sat, tachycardia or bradycardia in the two groups (etomidate and propofol). Etomidate was advocated for general anaesthesia if there were not any contraindications to its use in the clinical conditions.

Riccó and Guerrero (2014) have studied the haemodynamic parameters after endotracheal intubation in dogs using propofol, propofol-ketamine and ketamine-diazepam. Haemodynamic parameters viz. heart rate, systolic, diastolic and mean arterial blood pressure, cardiac index, stroke volume index, and systemic vascular resistance were observed. The studied parameters did not show significant changes between the groups. In all groups, arterial blood pressures decreased at different time intervals whereas systolic arterial pressure increased in all groups at 30 seconds. Other parameters did not show remarkable changes in any of the groups. Only ketamine-diazepam (and not propofol or propofol-ketamine) caused an elevated blood pressure in response to endotracheal intubation. It was concluded that propofol or ketamine-propofol will be better to use in dogs suffering from an elevated blood pressure.

Das et al. (2015) have compared etomidate, propofol and thiopentone with respect to their hemodynamic effects in laparoscopic surgery. It was found that etomidate did not cause significant changes in haemodynamic variables in the human patients after induction of anaesthesia, propofol caused first a fall and then a gain in the values of above mentioned parameters whereas thiopentone yielded fluctuating values of these parameters. The values of the parameters returned to their base values first in etomidate, then in propofol and at last in case of thiopentone. On the basis of the above parameters it was concluded that etomidate behaved like an ideal anaesthetic.

Shivanna et al. (2015) have studied the haemodynamic effects of propofol and etomidate in human cardiac surgery with special reference to induction and intubation. It was found that propofol causes significant reductions in cardiac contractility, arterial blood pressure and afterload. Etomidate was found to be less efficient in alleviating the stress response.
Desai et al. (2016) have compared the suitability of etomidate and propofol for cardioversion in human patients. The patients treated with propofol showed decreased SBP, DBP and MAP, hypotension was more prevalent and showed longer recovery period. Etomidate treated patients suffered more with myoclonus. Etomidate was recommended over propofol for cardioversion in people due to the above characteristics.

2.7.3 HAEMATOBIOCHEMICAL STUDIES

Yagmurdur et al. (2004) have observed the effects of propofol, etomidate and thiopentone on the values of biochemical parameters in human patients. It was found that ALT and AST levels decreased at 24 hrs whereas the MDA (malondialdehyde) were decreased with propofol.

Kushwaha et al. (2012) have evaluated midazolam and propofol as anaesthetics in dogs. Different induction, recovery, clinicophysiological, haematobiochemical and haemodynamic parameters were recorded. Serum creatinine first increased and then decreased whereas serum glucose values first increased and then returned to normal in 24 hrs. It was concluded that midazolam was a good tranquilizer for concomitant use with local analgesics and that propofol and midazolam could provide balanced anaesthesia in dogs.

Jiang et al. (2014) have calculated the values of insulin, glucagon, T₃ and T₄ in dogs anaesthetized with propofol and emulsified isoflurane. It was found that (compared to the isoflurane group) insulin, glucose, T₃ and T₄ increased in the propofol group along with decreased glucagon.

Khurana et al. (2014) have evaluated clinical and biochemical parameters in dogs using propofol. It was observed that haemoglobin and AST decreased whereas other biochemical parameters (creatinine, sodium, potassium) did not show significant changes. ECG was overall normal and authors did not attach significance to the changes of time and voltage parameters in the ECG recordings obtained. It was concluded that the tested drugs (diazepam, butorphanol, propofol, halothane, acepromazine) were safe to produce anaesthesia in dogs.

Kumar et al. (2014) have studied the clinical-physiological, blood biochemical and haemodynamic parameters in uraemic goats subjected to anaesthesia with propofol,
dexmedetomidine and ketamine. It was found that propofol-dexmedetomidine were effective at lower doses than dexmedetomidine-ketamine. Mean arterial pressure decreased in both the groups and heart rate decreased but improved after ketamine administration. In the study haemoglobin, packed cell volume and total leucocyte count decreased. Blood urea nitrogen and glucose increased and creatinine fluctuated. It was concluded that both the drug combinations were suitable for producing TIVA however, ketamine provided better haemodynamic stability and propofol gave better muscle relaxation.

Anandmay et al. (2016) have evaluated the biochemical effects of propofol and buprenorphine in dogs. It was found that the values of Hb, PCV, TEC and AST decreased whereas glucose and ALT increased. The values of TP, ALP, creatinine, and BUN showed non significant changes.

2.8 KETAMINE

2.8.1 CLINICOPHYSIOLOGICAL STUDIES

Schwartz and Horwitz (1975) have studied the effects of ketamine on the physiological response of heart. Ketamine when injected alone caused an increase in the heart rate, however heart rate was not altered after administration of propanolol and atropine. Ketamine did not exert any effect on the systemic vascular resistance. It was concluded in the study that ketamine increases the sympathetic discharge and reduces the vagal discharge to the heart and in the absence of sympathetic and vagal influence ketamine depresses the contractility of heart.

Waxman et al. (1980) have studied the heart and lung function of severely ill patients as affected by a single dose of ketamine used for induction. It was found that ketamine decreased the performance of cardiovascular and respiratory systems. It was assumed that preoperative stress can be a reason for this response to ketamine, and recommended that ketamine should be used with great caution in severely ill patients as long as results of other studies are available regarding its use in these patients.

Huyghens and Buylaert (1990) have reported that ketamine should not be used as a sole anaesthetic in dogs. It should be used only in combination with other anaesthetics e.g. ketamine combined with an inhalation anaesthetic or an injectable one.
Deleforge et al. (1991) have studied the clinical effects of two enantiomers of ketamine (KTM) viz. dextro-ketamine (D-KTM or S (+) KTM and laevo-ketamine (L-KTM or R (-) KTM. It was noted time to unconsciousness, analgesia, muscle relaxation, heart rate, convulsions and salivation during the study at prefixed time points. Metabolites of racemic ketamine or D or L ketamine were analysed by HPLC. It was found that D ketamine was three times as potent as the L ketamine. It was recommended that the benefit of using D ketamine has only a small therapeutic advantage which would be is offset by its high cost.

Cheng et al. (1996a) have tested the airway smooth muscles (ASM) relaxing effect of ketamine, propofol and midazolam in dogs. At $10^{-6}$M no drug showed a relaxing effect. About 18% relaxation was seen with ketamine at $10^{-5}$M plasma concentration, on distal ASM but not on the proximal ASM. At $10^{-5}$M propofol and midazolam did not show any relaxing effects. At $10^{-4}$M concentration of all the drugs tested, the distal muscles were more sensitive than the proximal muscles. It was concluded that all the three drugs tested had smooth muscle relaxing effects on ASM, which was more pronounced at the distal muscles than at the proximal muscles. This effect was more likely to be encountered with ketamine at clinical doses.

Iida et al. (1997) have opined that in humans, ketamine can provide analgesia when given intra-thecally/spinally. Intraspinal evoked potentials were used by them to find out the validity of this effect in dogs. Results of their study augmented the fact that ketamine blocks conduction in the neurons. Hence it was concluded that the blockade of conduction by ketamine can be a reason for the pain relief afforded by use of ketamine.

Ko et al. (2000a) have studied the effects of medetomidine alone or with butorphanol and ketamine in dog. All the dogs except one placed themselves in lateral recumbency within six minutes after injection of the drug. Endotracheal intubation was more difficult in dogs given medetomidine alone than in other groups. Responses to analgesic tests were similar in all groups. The PaCO2 was higher and the arterial pH and PaO2 lower in the medetomidine group compared to other groups. It was better to use medetomidine in a combination (with butorphanol or ketamine), rather than alone for a good clinical sedation.
Ikeda et al. (2001) have opined in their study that redistribution of heat from core of body towards periphery causes hypothermia during anaesthesia. Anaesthetic drugs cause arteriolar and venous dilation as the tonic vasoconstriction (thermoregulatory) of arteriovenous shunts is inhibited centrally, which cause this redistribution. It was noted that ketamine increases arteriolar resistance and propofol induces venodilation. Ketamine did not cause vasodilation but propofol rapidly induced vasodilation. Body core temperature in ketamine treated patients remained higher than that of the patients treated with propofol. The study indicated that vasoconstriction during anesthesia reduces the extent to which body temperature can fall.

Wagner et al. (2002) have evaluated the analgesic and behaviour modifying potential of low doses of ketamine in surgical cases of dogs. Glycopyrrolate, morphine, propofol, and isoflurane were used in the anaesthetic protocol. Pain was assessed in the dogs at prefixed time intervals by the authors and also by the aid of owners in the post operative period. It was found that those dogs who received low doses of ketamine experienced lesser pain and were more active on day 3 post operation than the dogs which did not receive ketamine. Hence it was concluded that low doses of ketamine can potentiate analgesia and comfort in the post operative period.

Boscan et al. (2005) have studied the cardiorespiratory effects of ketamine in dogs anaesthetized with isoflurane. The dogs were anaesthetized with 1.25MAC isoflurane and ketamine injected to achieve preset target plasma concentrations of 0, 0.5, 1, 2, 5, 8, and 11 µg/mL. Various cardiopulmonary and clinico-physiological parameters were noted. Body temperature increased in proportion to dose and PCV, Hb and TP increased in the study. It was observed that ketamine at the dose rate of 2-3mg/kg will give a balanced anaesthesia with isoflurane however at higher doses side effects like myoclonus, salivation and dysphoria were observed. Therefore it was recommended that the smaller doses should be used.

Neils et al. (2007) have studied the effects of ketamine hydrochloride anaesthesia in Nigerian dogs. Dogs were given low (11mg/kg) and high (33mg/kg) doses of the drug. Induction time was 2minutes (s/c route) and 1 minute (im route), duration of anaesthesia was shorter for low dose and longer for high dose. Salivation when present was controlled by atropine. Some animals showed limb rigidity.
Abolition of pharyngeal, pedal, spinal and blink reflexes was reported. Defecation and vomition were observed after injection in recovery phase. Rectal temperatures of the dogs slightly decreased. In this study it was concluded that ketamine was useful to tame dogs of fractious nature.

**Duque et al. (2008)** have studied the potencies of ketamine and S(+) ketamine in dogs. The doses were found to be 9.82±3.02 mg/kg and 7.76±2.17mg/kg for ketamine and S(+) ketamine respectively. S(+) ketamine was found to be two times as potent as the racemic ketamine and four times more potent than R(-) ketamine. The complete recovery time was 41 minutes, time to ambulation 26.4 minutes and time to first attempt to rise was 18.2 minutes with a dose rate of 6mg/kg of racemic ketamine.

**Intelisano et al. (2008)** have opined that propofol and ketamine provide a good anaesthesia in animals. Anaesthesia produced by two combinations viz. propofol-racemic ketamine (PRK) and propofol-S-ketamine (PSK) was compared. Haemodynamic, metabolic and ventilatory parameters were measured in the experiment at preset time points. In both groups, heart rate increased and all other parameters viz. systolic blood pressure, cardiac output, cardiac index, systolic index, respiratory rate were reduced. Due to these observations artificial respiration was instituted in all cases.

**Bergadano et al. (2009)** have investigated the pain relieving action of low-dose constant-rate-infusion (CRI) of ketamine in dogs. Withdrawal reflexes of digital plantar nerve were recorded from the biceps femoris muscle. Ketamine did not affect the nociceptive withdrawal reflex thresholds. As a result of the study the use of ketamine CRI as an analgesic was not recommend for dogs.

**Barletta et al. (2011)** have evaluated the efficacy and cardiorespiratory effects of dexmedetomidine and ketamine with opioids (butorphanol, buprenorphine and hydromorphone) in male dogs undergoing neutering. The BT decreased initially and then came to near normal values, HR decreased, MAP first increased and then decreased whereas RR did not show significant changes in the study. Satisfactory anaesthesia was provided by all drug combinations studied. It was concluded that DKBup (dexmedetomidine-ketamine-buprenorphine) was the best combination among the above drugs. Atipamezole hastened the recovery and least side effects were seen in any group.
Bhardwaj et al. (2011) have compared the effects of evaluated the role of ketamine given epidurally (and compared with lignocaine and pethidine), in mitigating the stress response in dogs undergoing orthopaedic surgery. It was measured the plasma cortisol concentration as an indicator of stress response. It was found in the study that among the drugs compared, epidurally administered ketamine was the foremost to attenuate the stress response and pethidine and lignocaine followed in that order.

Alkattan and Helal (2013) have examined the effects of ketamine-xylazine and propofol-isoflurane anaesthesia on clinicophysiological and blood gas parameters in dogs. In the study higher doses of xylazine (5mg/kg i.v.) and ketamine (15mg/kg i.m.) have been used. The anesthesia produced with propofol-isoflurane was adjudged to be the best because of rapid onset, short duration and smooth recovery. It was concluded that it could be used for laparoscopy in dogs with high risk scores.

Ko et al. (2013) have studied the effects of ketamine on the cardiopulmonary parameters of dexmedetomidine-buprenorphine and the reversal of their effects with atipamezole in dogs. Haemodynamic data were collected in the conscious dogs and sedated dogs. It was concluded from the study that ketamine kept the HR elevated, delayed the sinus arrhythmias and reduced the stroke volume and cardiac output.

Bayan and Konwar (2014) have evaluated anaesthesia produced by a mixture of ketamine and propofol in 1:1 ratio (ketofol) in dogs. The quality of sedation and analgesia were satisfactory in all the animals. The heart rate, respiratory rate, rectal temperature and blood pressure remained within the normal physiological limits. It was concluded in the study that ketofol is safe for induction without any serious adverse affect on the normal physiological functions.

Peterson et al. (2014) have used acepromazine, butorphanol and meloxicam, or carprofen as preanaesthetics and tiletamine/zolazepam or ketamine/diazepam as anaesthetics to anaesthetize the dogs for removal of heart worms. With this anaesthetic protocol no perioperative complication were observed since a cardiovascular sparing effect could be achieved with ketamine or tiletamine. It was found that the anaesthetic protocol used was adequate for sterilising and rehabilitating the shelter dogs.

Taboada and Leece (2014) have compared the clinico-physiological parameters in dogs that were treated with propofol or a mixture of propofol and
ketamine (ketofol). Induction was achieved with lesser amount of drug when ketofol was used as compared to propofol alone. It was concluded from the study that ketofol causes a higher PR and MAP than propofol along with a decrease in the respiratory rate. Induction and intubation were better with ketofol than propofol.

Abubakar et al. (2015) have evaluated the effects of epidural ketamine and ketamine-xylazine on analgesia, physiological and haematological parameters in dogs. There was complete analgesia caudal to the thoracic region in both the groups. The onset of analgesia in ketamine group was of shorter duration than the ketamine-xylazine group. The ketamine-xylazine group also experienced a longer duration of analgesia than the ketamine group. HR and RR increased in all groups for short durations. It was concluded that epidural ketamine-xylazine produces analgesia of caudal thorax and the cardiopulmonary and haematological parameters are minimally affected by the two drugs.

Gutierrez-Blanco et al. (2015) have evaluated the post ovariohysterectomy analgesic effects of CRI of fentanyl, lidocaine, ketamine, dexmedetomidine and the combination of lidocaine-ketamine-dexmedetomidine in dogs. It was found that lidocaine-ketamine-dexmedetomidine and fentanyl provided adequate level of post-operative analgesia whereas lidocaine, ketamine and dexmedetomidine did not provide a satisfactory post-operative analgesia in dogs subjected to ovariohysterectomy.

Bornkamp et al. (2016) have evaluated the effect of benzodiazepine-ketamine or benzodiazepine-propofol on the body temperature of dogs being spayed. It was found that dogs administered with benzodiazepine-propofol developed a greater degree of hypothermia than the dogs administered with benzodiazepine-ketamine. These dogs also required a longer period of time to regain their normal body temperature. It was recommended that the dogs subjected to the latter combination of drugs should be provided with adequate measures to control the forthcoming hypothermia during surgical intervention.

Mazzeffi et al. (2016) have reviewed the effects of ketamine in cardiac surgery patients. It was opined that ketamine provides analgesia, hypnosis and amnesia without causing significant cardiovascular depression. It caused tachycardia and could minimise the inflammatory response. Despite the above mentioned properties further
studies were recommended to replace propofol or dexmedetomidine in the ICU settings.

2.8.2 HAEMODYNAMIC AND HEMATO BIOCHEMICAL STUDIES

Schwartz and Horwitz (1975) have studied the effects of ketamine on the physiological response of heart. Ketamine when injected alone caused an increase in the heart rate, however heart rate did not alter after the administration of propanolol and atropine. Ketamine did not exert any effect on the systemic vascular resistance. It was concluded that ketamine increases the sympathetic discharge and reduces the vagal discharge to the heart and in the absence of sympathetic and vagal influence ketamine depresses the contractility of heart.

Jadon et al. (1995) have reported the haematobiochemical effects of detomidine and ketamine anaesthesia in dogs. There was an increase in TLC, glucose, BUN and creatinine level alongwith decrease in plasma protein and albumin. A non significant effect on TEC, PCV, Hb and clotting time was also observed.

Lerche et al. (2000) have studied the anaesthetic effects of propofol and propofol-ketamine in dogs premedicated with acepromazine and pethidine. Various clinicophysiological and cardiorespiratory parameters were monitored. Heart rate was higher and systolic blood pressure lower in propofol-ketamine group than the other group. Apnoea occurred more frequently with propofol-ketamine. Muscle twitching and recovery times had a similar picture in both the groups. The authors found both the groups similar in clinical effects.

Butola and Singh (2003) have studied the haematological and biochemical effects of ketamine with midazolam premedication in dogs. Blood glucose, SGOT, SGPT, creatinine, sodium, potassium and chloride contents were estimated. The values of the parameters obtained during the experiment did not wander far from their normal values. Therefore it was concluded that ketamine–midazolam anaesthesia did not cause any lasting negative effects on any of the body systems.

Ambrisko et al. (2005) have experimented with ketamine, butorphanol, fentanyl and medetomidine and recorded the neurohumoral metabolic responses elicited by these drugs in dogs. Ketamine, fentanyl and butorphanol elevated the epinephrine, cortisol and glucose levels which resembles the clinical picture of stress.
Medetomidine reduced these changes to a greater extent but did not prevent elevation of glucose levels. It was recommended that a combination of drugs as medetomidine-butorphanol or medtomidine-ketamine can be used for sedation to harness the benefit of a stable neurohumoral profile.

Fraga et al. (2006) have compared ketamine and etomidate with respect to induction after treatment of haemorrhagic shock in dogs. The dogs were first bled and then volume was restored by the use of normal or hypertonic saline. Then anaesthesia was induced with ketamine or etomidate. It was concluded that both the drugs were capable of maintaining hemodynamic stability in the dogs treated with volume restoration.

Kiliç (2008) has evaluated the values of temperature, Hb, PCV, TEC, glucose, creatinine and ALT in calves subjected to detomodinie-midazolam-ketamine anaesthesia. The body temperature, haemoglobin, PCV, and RBC registered a decline whereas glucose, creatinine, and ALT increased significantly. All the altered values of parameters became normal by 24 hr. Muscle relaxation was good and no complications were recorded.

Ahmad et al. (2012) have evaluated stress response in dogs using dexmedetomodine, midazolam, fentanyl and ketamine. There was an increase in neutrophils and glucose levels alongwith decrease in insulin and cortisol. It was concluded that dexmedetomidine and the drugs tested could reduce the stress response elicited in surgery and anaesthetic periods. Therefore the tested drugs were safe to use for the purpose of sedation, surgery or anaesthesia.

Amin et al. (2012) have carried out a study to examin biochemical effects of anaesthesia in donkeys. Romifidine, midazolam and ketamine were used as anaesthetic drugs. The values of AST, ALT, ALP and serum glucose were estimated at predetermined time intervals. Changes were observed in AST level however no significant changes were observed in ALT and ALP.

Mannarino et al. (2012) have studied the haemodynamic effects and bispectral index in dogs anaesthetized with propofol, lidocaine and ketamine combinations. All the haemodynamic parameters studied decreased and only the systemic vascular resistance index increased in the drug combinations used. It was found that only
Lidocaine-ketamine reduced the infusion rate of propofol but no drugs tested could reduce the depression of cardiovascular system accompanying the use of propofol.

**Yayla et al. (2012)** have studied the effects (clinical, biochemical and haemodynamic) of ketamine in dogs operated for ovariohysterectomy. The parameters have shown significant variations in PR, RR, SBP, DBP, glucose, BUN and AST. It was concluded that intrathecal ketamine could serve as an alternative to the traditional methods employed for ovariohysterectomy.

**Çamkerten et al. (2013)** have studied haematological and biochemical parameters in ketamine anaesthetized dogs. It was found that Hb, TLC, TEC, PCV, BUN, creatinine, ALT, AST, ALB, ALP, GLB and cholesterol showed non significant change in their values. Only glucose and CK increased alongwith decrease in TP and TG.

**Umar and Adam (2013)** have evaluated the effects of ketamine-medetomidine on the parameters like PCV, Hb, TEC, TLC, DLC, creatinine, BUN and ALT in dogs. The results showed decreases in PCV, RBC, haemoglobin, neutrophils and lymphocytes alongwith an increase in WBC and creatinine, BUN, ALT, monocytes and eosinophils did not differ with base values. All the above changes in the values of clinical and biochemical parameters did not affect the outcome of the experiment in any adverse manner and the recovery was satisfactory from the clinical point of view.

**Khan et al. (2014)** have tested the effects of xylazine, diazepam and ketamine on the blood glucose levels in dogs and found that all the three drugs elevate the blood glucose level. It was concluded that these drugs should be used with care in dogs suffering from stress and increased blood glucose levels.

**Kumar et al. (2014)** have studied the clinico-physiological, blood biochemical and haemodynamic parameters in uraemic goats subjected to anaesthesia with propofol, dexmedetomidine and ketamine. It was found that propofol-dexmedetomidine were effective at lower doses than dexmedetomidine-ketamine. Mean arterial pressure decreased in both the groupswhereas HR decreased but improved after ketamine administration. Haemoglobin, PCV and TLC decreased and BUN and glucose increased whereas creatinine levels fluctuated. It was concluded that both the drug combinations were suitable for producing TIVA however, ketamine provided better haemodynamic stability and propofol gave better muscle relaxation.
Kumar et al. (2014a) have carried out evaluation of ketamine with midazolam in buffalo calves. Clinical parameters (RT, HR, RR), blood glucose, ALT, AST, BUN, creatinine, TP, albumin, Hb, PCV and some electrolytes were recorded. Haemoglobin and PCV decreased whereas glucose and AST showed non-significant increase in their values. All other biochemical parameters remained within normal limits. It was concluded that the midazolam-ketamine was a satisfactory anaesthetic combination for use in buffalo calves which affected the clinical and biochemical parameters to a minimum extent.

Riccó and Guerrero (2014) have studied the haemodynamic parameters after endotracheal intubation in dogs using propofol, propofol-ketamine and ketamine-diazepam. Haemodynamic parameters viz. heart rate, systolic, diastolic and mean arterial blood pressure, cardiac index, stroke volume index, and systemic vascular resistance were studied. The studied parameters did not show significant differences between the groups. In all the groups, arterial blood pressures decreased at different time points whereas systolic arterial pressure increased in all groups at 30 seconds. Other parameters did not show remarkable changes in any of the groups. Only ketamine-diazepam (and not propofol or propofol-ketamine) caused an elevated blood pressure in response to endotracheal intubation. It was concluded that propofol or ketamine-propofol will be better to use in dogs suffering from an elevated blood pressure.

Rafee et al. (2015a) have tested the clinical implications of using dexmedetomidine and ketamine with and without butorphanol in dogs induced with midazolam. It was found that the drug combinations tested caused a decrease in RR and RT; and a decrease after initial increase in HR, SBP, DBP and MAP. Additional use of butorphanol did not improve/change the clinical outcome.

2.8.3 MAC STUDIES

Muir et al. (2003) have studied whether morphine (M), lidocaine (L) and ketamine (K) can affect the end tidal and MAC of isoflurane when given as constant rate infusions. The depth of anaesthesia was measured by the use of bispectral index (BIS). The mean MAC of isoflurane was found to be 1.38% which was reduced by 48, 29, 25, and 45% by morphine, lidocaine, ketamine, and MLK respectively. It was
concluded that the ketamine, morphine and lidocaine individually and in combination reduce the MAC of isoflurane and the BIS score is a reliable method to gauge the depth of anaesthesia.

**Solano et al. (2006)** have studied the MAC reducing effects of ketamine in dogs. It was found that with increasing plasma concentrations of ketamine the MAC of isoflurane also decreased in parallel with it so that a highest reduction of 95% could be achieved in the MAC of isoflurane. It was concluded that ketamine (barring its high doses) can provide a balanced anaesthesia to dogs, and that at high doses side effects (salivation, mydriasis, and regurgitation etc.) can be encountered.

**Wilson et al. (2008)** have studied the manner in which the MAC of sevoflurane in dogs is affected by lidocaine (L) and ketamine (K), alone or in combination with each other. By using electric current as a noxious stimulus, MAC of sevoflurane was determined before starting the infusions of lidocaine or ketamine. Lidocaine and ketamine reduced the MAC by 39.6% and 44.7% respectively whereas their combination achieved an MAC reduction of 62.8%.

**Aguado et al. (2011a)** have studied the effects of ketamine and remifentanil on the MAC of sevoflurane in rats. The rats were given ketamine and remifentanil alone and in combination with each other. Both the drugs reduced the MAC of sevoflurane. It was reported a subadditive effect in the reduction of MAC by these two drugs. Maximum MAC reductions were 41% (ketamine at 80mg/kg), 30% (remifentanil at 240µg/kg/hr) and 62% (ketamine 80mg/kg and remifentanil 240µg/kg/hr).

**Aguado et al. (2011b)** have reported the effects of lidocaine (L), ketamine (K), morphine (M) and fentanyl (F) on the MAC of isoflurane (MACISO) which was judged by the Dixon’s up and down method, in dogs. A skin incision was used as the noxious stimulus. MACISO was 0.70 % in the control group, 0.30% in the MLK group (45% MAC reduction) and 0.00 % in the FLK group (97% MAC reduction). It was concluded that the maximum reduction in the MAC was achieved with FLK which was more than the MLK group.

**Cerejo et al. (2013)** have evaluated the effect of a CRI of analgesic or anaesthetic drugs on the anaesthesia with isoflurane. The isoflurane consumption reduced by 15.7% and 21.05% in dogs administered with fentanyl and fentanyl-
lidocaine-ketamine respectively. It was concluded that the method of administering the drugs by CRI is a valid, safe and non-toxic component of balanced anaesthetic technique in dogs.

Gianotti et al. (2014) have evaluated the influence of prior determination of baseline MAC of isoflurane on the effect of ketamine on MAC in dogs. Baseline MAC was determined and was found to decrease with ketamine CRI. When ketamine was stopped the MAC of isoflurane increased. Hence the sparing effects of ketamine on isoflurane MAC were demonstrated.

2.9 SEVOFLURANE

2.9.1 MAC STUDIES

Kazama and Ikeda (1988) have determined the anaesthetic requirements for sevoflurane, isoflurane and halothane in dogs. The MACs were 2.36%, 1.39% and 0.89% for sevoflurane, isoflurane and halothane. The ratio of alveolar concentration/inspired concentration was 0.75, 0.6 and 0.25 for the above gases in that order. It was concluded that sevoflurane gives a smooth induction free of involuntary movements or ptyalism.

Katoh and Ikeda (1998) have opined that fentanyl produces only slight reduction in the MAC of sevoflurane. Patients were subjected to plasma concentrations of fentanyl at 0, 1, 1.5, 3, 6, 10 and 14ng/ml. The plasma concentration of 3ng/ml produced 59% reduction in MAC (abolishment of response to skin incision) and 24% reduction in the MACawake (loss of consciousness).

Haitjema and Cullen (2001) have reported on various aspects of using sevoflurane in canine patients undergoing surgeries. It was reported that Sevoflurane is expensive and less potent than halothane or isoflurane and thus has a higher MAC (2.0% to 2.3%). Rapid induction and recovery were the major advantages of using sevoflurane.

Docquier et al. (2003) have observed whether MAC of a gas anaesthetic can be used to gauge the analgesic potency of drugs like clonidine and sufentanil. Tail clamping and paw withdrawal to pressure and heat were used as noxious stimuli. It was concluded that the results obtained were due to the interaction of the gas anaesthetic...
and the drug and cannot be taken to be the antinociceptive effect of the drugs alone. Therefore MAC would not serve to replace the classic methods of gauging analgesic potency of drugs.

Valverde et al. (2003) have compared three types of noxious stimuli (applied to different body parts of anesthetized dogs and rabbits) for determination of the minimum alveolar concentration (MAC) of inhalation anaesthetics. Dogs were anesthetized with isoflurane and halothane and rabbits with isoflurane. The MAC was determined by skin incision, clamping of the tail and paws and electric current (only in dogs). It was found that electrical current and clamping showed similar MAC values whereas skin incision showed lower values of MACs. The MAC values were different with different stimuli in different species.

Duke et al. (2006) have studied the effects of nitrous oxide on requirements of halothane, isoflurane and sevoflurane for surgical anaesthesia. It was found that use of nitrous oxide with oxygen reduces the requirements of the above mentioned three anaesthetic gases by 12.4%, 37.1% and 21.4% in that order. With a highest reduction in requirement of isoflurane, there was an increase in blood pressure.

Hofmeister et al. (2008) have studied the induction and MAC characteristics of isoflurane and sevoflurane. MAC\textsubscript{awake} in relation to MAC was examined. It was found that induction and intubation could be achieved in a shorter time with sevoflurane as compared to isoflurane. The MAC\textsubscript{awake} for dogs was higher than the corresponding values in humans for both the drugs. Further studies were recommended to validate the results of the study.

Wilson et al. (2008) have studied the manner in which the MAC of sevoflurane in dogs is affected by lidocaine (L) and ketamine (K), alone or in combination with each other. By using electric current as a noxious stimulus, MAC of sevoflurane was determined before starting the infusions of lidocaine or ketamine. Lidocaine and ketamine reduced the MAC by 39.6% and 44.7% respectively whereas their combination achieved an MAC reduction of 62.8%.

Yamashita et al. (2008) have studied the anaesthetic sparing effects of carprofen, meloxicam and butorphanol. Sevoflurane was used both as the induction and maintenance agent in the experiment. Tail clamp method was used for determining the
MAC of sevoflurane. The dogs were treated with the NSAID about one hour before the 
anaesthesia. The MACs obtained were: carprofen alone 2.10%, meloxicam alone 2.06%,
and sevoflurane alone (control) 2.39%; butorphanol 2.12%, carprofen-butorphanol 1.78%
and meloxicam-butorphanol 1.66%. Hence it was showed that NSAIDs, when used prior
to anaesthesia can significantly reduce the MAC of sevoflurane.

Matsubara et al. (2009) have studied the haemodynamic and MAC sparing
effects of lidocaine in dogs. MAC of the anaesthetic was determined by tail clamp
method. Plasma lidocaine concentration was measured along with heart rate and blood
pressure. It was found that lidocaine reduced the MAC of sevoflurane in proportion to
its dose without major alterations of the heart rate however at higher doses vomition
was a concern.

Seddigi et al. (2009) have studied the manner in which MAC of sevoflurane
is affected by tramadol administered by constant rate infusion. Induction was done by
face mask. After 45 minutes of induction the MAC was determined and tramadol
infusion started. The MAC was determined again after 45 minutes of infusion. It
decreased by 26 ± 8% and 36 ± 12% respectively for the lower and higher doses of
tramadol infusion (constant rate infusion). It was concluded that the MAC reductions
were not in proportion to the doses studied.

Yamashita et al. (2009) have conducted an experiment to find out how the
effects of age on the MAC of sevoflurane in dogs. The MAC of sevoflurane in young
as well as older dogs was determined by the tail clamp method. Younger dogs had
MAC value of 2.25% whereas the older dogs had MAC value of 1.86%. Hence it was
concluded that age of the subject affects the MAC of sevoflurane to a great extent.

Rezende et al. (2011) have studied the MAC of sevoflurane as it is affected by
lidocaine administration (intravenous constant rate infusion). Xylazine, ketamine, and
diazepam were used to induce anaesthesia which was maintained with sevoflurane.
Lidocaine caused an approximate drop in the MAC of sevoflurane by 27%. It was
concluded that this property of lidocaine could be harnessed to achieve balanced
anaesthesia in horses, however further studies with lidocaine and sevoflurane have been
recommended.
Alvillar et al. (2012) have tested the MAC of sevoflurane by tail clamp method and the manner in which it is affected by maropitant in dogs. First the MAC was determined only for sevoflurane alone (without any additional drug), second time with use of maropitant and the third time with epidural use of maropitant. A reduction of 16% was achieved by the intravenous administration of maropitant whereas epidurally given maropitant had no effect on the MAC of sevoflurane.

Yamashita et al. (2012) have studied the MAC of sevoflurane required for abolition of response to a noxious stimulus and for diminishing the adrenergic response in dogs by using electric current (applied to gingival mucus membrane) as a stimulus. MAC for noxious stimulus was 2.1% whereas it was 3.33% for diminishing the adrenergic response. The study showed that when movement to surgical stimuli is not present, the adrenergic response is still present.

Itami et al. (2013) have studied the effects of intravenous tramadol on minimum alveolar concentration (MAC) of sevoflurane in Dogs. The MAC was reduced by 22.3 ± 12.2% with intravenous tramadol. Haemodynamic parameters did not change much between the groups. Hence it was concluded that tramadol causes major reduction in the MAC of sevoflurane in dogs.

Moran-Munoz et al. (2014) have studied whether lidocaine or dexmedetomidine can affect the MAC of sevoflurane, either alone or in combination with each other in dogs. It was found that lidocaine, dexmedetomidine and their combination reduced the MAC of sevoflurane by 26.1 ± 9.0%, 43.7 ± 11.8% and 54.4 ± 9.8% respectively. Therefore it was concluded that the MAC of sevoflurane was drastically reduced by the use of CRI of lidocaine and dexmedetomidine.

2.9.2 CLINICO-PHYSIOLOGICAL STUDIES

Mutoh et al. (1995a) have studied the effects of rapid induction (at 2.5 MAC) by inhalant gases on heart and lung functions in dogs. The blood-gas solubility was ascertained to be the reason for differences in the clinico-physiological parameters. In a decreasing order sevoflurane, isoflurane and halothane achieved smooth-rapid inductions. The haemodynamic parameters studied (heart rate, cardiac output and rate-pressure product) showed increase in their values in sevoflurane and isoflurane.
anaesthesia. Therefore it was concluded that sevoflurane (followed by isoflurane) was best for rapid inhalation induction.

**Mutoh et al. (1995b)** have tested rapid inhalation induction with isoflurane and sevoflurane in dogs at 5.0% vaporiser settings. Induction, loss of reflexes and movement time with isoflurane were shorter than those with sevoflurane. Intubation was easier and movements were fewer with isoflurane. Movements increased as the body weight increased. Therefore it was concluded that in dogs with small or medium body weights, inhalant induction was safe to carry out with isoflurane.

**Sloan et al. (1996)** have opined that due to its nonpungent odour and low blood-gas solubility coefficient, sevoflurane might be an ideal drug for single-breath inhaled induction of anesthesia. Induction times were similar for sevoflurane and isoflurane. During induction, heart rate increased with both sevoflurane and isoflurane. The increase with isoflurane was greater than with sevoflurane. Times to eye opening for sevoflurane did not differ significantly from those for isoflurane. During recovery patients who received sevoflurane had higher pain scores than those who received isoflurane. Hence it was concluded that sevoflurane is more suitable than isoflurane for single-breath induction, because it produces a smoother induction.

**Mutoh et al. (1998)** have studied the effects of halothane, enflurane, isoflurane, and sevoflurane on vagal capsaicin (CAPS)-sensitive C-fibers in dogs. The CAPS-sensitive C-fibers were significantly stimulated by all volatile anaesthetics with a significantly greater response to halothane than with sevoflurane. A significant increase in respiratory frequency ($f_R$) and a significant decrease in tidal volume ($V_T$) were observed with halothane and isoflurane, and a significant increase in $f_R$ was observed with sevoflurane. In contrast, a significant decrease in $f_R$ was induced by enflurane. The tachypnea induced by halothane, isoflurane, and sevoflurane was significantly reduced or no longer observed after perineural CAPS-treatment or bilateral vagotomy, whereas the slowing of respiration observed with enflurane was not affected by either of these treatments. These results suggest that vagal C-fibers play an important role in the reflex tachypnea that occurs with halothane, isoflurane, and sevoflurane.

**Mutoh et al. (1999)** have compared the effects of halothane, isoflurane and sevoflurane on the physiological responses arising out of the stimulation of laryngeal
receptors in dogs. Inspiratory and expiratory phases were either increased or decreased with the application of anaesthetic gases to an isolated larynx. When halothane decreased both the phases of respiration and isoflurane only the expiration phase, sevoflurane did not affect any of the two phases. The observations of the study strongly support the use of sevoflurane for induction of anaesthesia.

Mutoh et al. (2001a) have studied the respiratory reflexes in spontaneously breathing anaesthetized dogs in response to nasal application of sevoflurane (Sevo) and isoflurane (Iso) with and without nasal administration of lidocaine. Sevoflurane and isoflurane caused an immediate dose-dependent increase in expiratory time and decrease in expired volume per unit of time, decrease in respiratory minute ventilation and increase in end-tidal PCO$_2$. These reflexes were abolished after lidocaine nebulisation into the upper airway. It was concluded that isoflurane induced a greater reflex inhibition of breathing than sevoflurane when the anaesthetics are inhaled into the upper airway at clinical concentrations.

Mutoh et al. (2001b) have studied the effects of anaesthetic gases as applied to the nasal passages of dogs. Expiration time increased with an attendant decrease in volume expired per unit time which was proportional to the doses of anaesthetic used. This phenomenon was observed with halothane, isoflurane and sevoflurane. Sevoflurane had the least effect among the three gases. The above mentioned reflex responses could be kept at bay to greater extent by application of lidocaine to the nasal passages. It was concluded that these reflexes could modify the induction of anaesthesia with sevoflurane, isoflurane or halothane.

Galloway et al. (2004) have compared sevoflurane and isoflurane by calculation of their anaesthetic indices (anaesthetic index = apneic concentration/MAC). For sevoflurane it was 3.45 and for isoflurane 2.61. Sevoflurane or isoflurane anaesthesia did not give rise to important haemodynamic or respiratory parameter alterations. Cardiovascular depression with both the drugs was identical but respiratory depression was less severe with sevoflurane.

Harris et al. (2006) have carried out a study to find out the interaction between propofol and sevoflurane by using Dixon’s up and down method. The patients were tested for loss of consciousness and abolition of response to surgical pain. Propofol at
5.4µg/ml plus sevoflurane 0.86% abolished the response to surgical incision. A Bispectral Index value of 70 was the threshold point to distinguish responders and non responders to auditory stimulus (elicited to test consciousness). It was concluded from the study that propofol and sevoflurane interact in an additive manner which suggests a common site of action.

Wilson et al. (2006) have evaluated whether maintenance of anaesthesia with halothane or sevoflurane is associated with a lower incidence of gastro-oesophageal reflux (GER) than with the use of isoflurane in dogs during orthopaedic surgery. Dogs were anaesthetized with halothane, isoflurane, or sevoflurane to maintain anaesthesia. GER was defined as an oesophageal pH < 4 or > 7.5. It was concluded from the study that the risk of developing GER was equal with any one of the three inhalant gases used in the experiment.

Sakata et al. (2007) have conducted the test with desflurane and sevoflurane. It was found that recovery times were reduced by 52% and 64% for sevoflurane and desflurane respectively while using hypercapnia and hyperventilation. It was concluded from the study that concurrent hyperventilation (to rapidly remove the anesthetic from the lungs) and (rebreathing to induce hypercapnia) can significantly shorten recovery times and produce the same proportionate decrease for anesthetics that differ in solubility.

Lopez et al. (2009) have studied the quality of recovery in relation to the anaesthetic gas concentration of desflurane, isoflurane and sevoflurane in dogs. Recovery time was shortest with desflurane, intermediate with sevoflurane and longest with isoflurane. Recovery quality and blood gas concentrations were indifferent among the three groups. It was concluded that desflurane had the shortest time to recovery of about 12 minutes, sevoflurane with a recovery time of about 19 minutes was intermediate. Short recovery time was adjudged to be a clinically desirable trait which came very handy with the outdoor procedures and with procedures requiring short recoveries.

Itamoto et al. (2010) have conducted a study to investigate whether the action of non-depolarizing neuromuscular blocking agent vecuronium is potentiated by the concomitant use of halothane, isoflurane and sevoflurane. Anaesthesia was induced with propofol (7mg/kg bolus) and maintained with 1.2 and 1.8 MAC of each inhalant.
anaesthetic (halothane, isoflurane and sevoflurane). Vecuronium was used at 0.1mg/kg. It was concluded that the effect of vecuronium was potentiated by all the anaesthetics therefore a safe anaesthesia could be achieved.

Singh et al. (2010) have conducted a study in canine abdominal patients (with foreign bodies in the GIT) to evaluate an appropriate anaesthetic combination of sevoflurane or isoflurane. The efficacy of anaesthetics was measured by clinicophysiological and haematobiochemical parameters measured at predesignated time intervals. The changes in the values of various parameters were less conspicuous in the sevoflurane group than in the isoflurane group. The values of HR and TEC decreased while those of Hb, PCV, TLC, RR, RT, TP and Alb increased non-significantly in the study. Sevoflurane was recommended to be combined with thiopentone for use in canine abdominal patients as this combination did not affect the heart and lung functions adversely.

Basha and Ranganath (2012) have studied the clinicophysiological and biochemical effects of isoflurane and sevoflurane anaesthesia in dogs. Rectal temperature and respiratory rate decreased while pulse, heart rate, ALT, total plasma proteins, blood glucose, serum creatinine and BUN increased in the study. The study revealed that the parameters studied did not show remarkable changes from their base values.

Vettorato et al. (2012) have compared the effects of isoflurane and sevoflurane in lambs subjected to spinal surgery. Clinico-physiological parameters alongwith time to reunion with ewe were recorded. It was concluded that both the drugs were adequate for anaesthesia of lambs however sevoflurane had an added advantage due to the rapid recovery.

Shimamura et al. (2014) have studied the number and function (adhesion, phagocytosis and the oxidative burst) of neutrophils in dogs subjected to a haemodialysis procedure of three hours duration and anaesthetized with sevoflurane. It was concluded from the study that there was a reduction in the number and phagocytic capacity of neutrophils in dogs subjected to haemodialysis.

2.9.3 HAEMODYNAMIC STUDIES

Mutoh et al. (2002) have studied the effect of premedication on sevoflurane anaesthesia (delivered by mask induction) in dogs. Medetomidine, midazolam,
butorphanol and acepromazine were used in combination with each other as premedicants and the effects noted on clinical and cardiopulmonary parameters. The premedication resulted in shorter induction and mild effects on the cardiac parameters (HR decreased while MAP first increased and then decreased to normal values). It was concluded that a better quality induction with sevoflurane is achieved after premedication.

Pypendop and Ilkiv (2004) have studied several haemodynamic and respiratory parameters in cats subjected to sevoflurane anaesthesia. BT, Hb, TP, RR and MAP decreased (in a dose dependent manner) whereas HR and SAP increased. It was concluded that sevoflurane depresses the cardiac parameters in proportion to the doses used, though a ceiling effect was observed in this context which must be further studied; however the depression of respiratory parameters was less than that observed in other species.

Neto et al. (2007) have studied the effects of halothane, isoflurane and sevoflurane on heart and lung functions in cases of large haemorrhages in dogs. Heart rate, mean arterial pressure and mean pulmonary arterial pressures were measured before and after inducing a haemorrhage. It was concluded that though in normal dogs isoflurane and sevoflurane showed similar response, however in case of blood loss isoflurane showed hemodynamic stability better than other two gases. Therefore it was opined that this fact could be utilized in cases of blood loss patients to achieve better cardiac functions in them.

Mousa and Alsobky (2013) have studied the efficacy intravenous dexametomidine and fentanyl, and compared it with sevoflurane anaesthesia. The haemodynamics and clinical parameters of the drug combinations used were compared. In all the groups haemodynamic variables showed a downward trend whereas in dexametomidine-fentanyl group the respiratory variables were on the higher platter.

2.9.4 HAEMATOBIOCHEMICAL STUDIES

Eger et al. (1997) have studied the nephrotoxicity inflicted by sevoflurane and desflurane in human patients. It was opined that at present sevoflurane is recommended to be delivered by a gas flow rate of 2 L / min or more due to the reports that sevoflurane produces “Compound A” by reaction with carbon dioxide in CO₂.
absorbers. The urine of the volunteers was analysed for evidence of renal injury and serum creatinine and blood urea nitrogen were measured. Desflurane, unlike sevoflurane, did not cause kidney damage. Sevoflurane caused injury to the glomerulus, the proximal tubule and the distal tubule and liver (increased ALT values).

Singh et al. (2010) have conducted a study in canine abdominal patients (with foreign bodies in the GIT) to evaluate an appropriate anaesthetic combination of sevoflurane or isoflurane. The efficacy of anaesthetics was measured by clinicophysiological and haematobiochemical parameters measured at predesigned time points. The changes in the values of various parameters were less conspicuous in the sevoflurane group than in the isoflurane group. The values of HR and TEC decreased while those of Hb, PCV, TLC, RR, RT, N, TP and Alb increased non-significantly in the study. Sevoflurane was recommended to be combined with thiopentone for use in canine abdominal patients as this combination did not affect the heart and lung functions adversely.

Basha and Ranganath (2012) have studied the clinicophysiological and biochemical effects of isoflurane and sevoflurane in dogs. The parameters studied were rectal temperature, respiratory rate, pulse rate, heart rate, ALT, total plasma proteins, blood glucose, serum creatinine, PaCO₂, PaO₂ and arterial blood pH. The study revealed that the parameters studied did not show remarkable changes from their base values.

Zlateva and Aminkov (2014) have performed ovariohysterectomy on cats and compared the values of ACTH, insulin, cortisol, glucose and adrenaline between two groups of the experiment. It was found that in the group anaesthetised with propofol the values of glucose and insulin increased whereas ACTH, cortisol and adrenaline experienced a decrease in their values.
Materials and Methods
Chapter 3  MATERIALS AND METHODS

PLACE OF WORK

The study was conducted in the Department of Veterinary Surgery and Radiology, College of Veterinary and Animal Sciences, Gobind Ballabh Pant University of Agriculture and Technology, Pantnagar, Distt. Udham Singh Nagar-263145, Uttarakhand, during the months of January 2016 to June 2016.

INSTITUTIONAL ANIMAL ETHICS COMMITTEE APPROVAL:

Approval for conducting the study on clinical cases requiring anaesthesia for various purpose/procedures was obtained vide letter no. IAEC/VSR/CVASC-232 dated 05.12 2015 from the Institutional Animal Ethics Committee of College of Veterinary and Animal Sciences, GBPUAT Pantnagar.

ANIMALS

The study was conducted in 36 adult dogs of either sex (required surgical intervention/anaesthesia) presented to the TVCC Pantnagar for treatment during the above mentioned period. The dogs were dewormed with albendazole at the dose rate of 10mg/kg orally. Clinical status of the animals was judged by recording the rectal temperature (°C), heart rate (beats per minute) and respiration rate (breaths per minute). They were admitted for one day before the surgery. The dogs were kept off feed for 12 hours and off water for 6 hours before the commencement of the surgery.

DESIGN OF THE STUDY

The 36 dogs were randomly divided into three groups viz. Groups A, B and C of twelve dogs each. Each group was further divided in two subgroups i.e. A-1, A-2; B-1, B-2; and C-1 and C-2; having six dogs each.

In the present study atropine sulphate, dexmedetomidine, etomidate, ketamine, propofol and sevoflurane were used as the preanaesthetic and maintenance agents. In all the groups anticholinergic agent atropine sulphate was administered at the dose rate of 0.04mg/kg s/c. Five minutes after the administration of atropine sulphate,
Dexmedetomidine was administered at the dose rate of 10µg/kg IV as a preanaesthetic agent in the groups A1, B1 and C1 and at the dose rate of 15 µg/kg IV in the groups A-2, B-2 and C-2. Ten minutes after the administration of dexmedetomidine, different induction agents were administered to the animals of the three groups i.e. Etomidate for group A, Propofol for group B and Ketamine for group C at various dosage and routes as shown below in the table.

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Group</th>
<th>Subgroup</th>
<th>Preanaesthesia</th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anticholinergic</td>
<td>Sedative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>A</td>
<td>A-1</td>
<td>Atropine sulphate 0.04mg/kg s/c</td>
<td>Dexmedetomidine 10µg/kg iv</td>
<td>Etomidate 1.66mg/kg iv</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>A-2</td>
<td>Atropine sulphate 0.04mg/kg s/c</td>
<td>Dexmedetomidine 15µg/kg iv</td>
<td>Etomidate 1.58mg/kg iv</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>B-1</td>
<td>Atropine sulphate 0.04mg/kg s/c</td>
<td>Dexmedetomidine 10µg/kg iv</td>
<td>Propofol 2.46mg/kg iv</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>B-2</td>
<td>Atropine sulphate 0.04mg/kg s/c</td>
<td>Dexmedetomidine 15µg/kg iv</td>
<td>Propofol 2.45mg/kg iv</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>C-1</td>
<td>Atropine sulphate 0.04mg/kg s/c</td>
<td>Dexmedetomidine 10µg/kg iv</td>
<td>Ketamine 7.70mg/kg iv</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>C-2</td>
<td>Atropine sulphate 0.04mg/kg s/c</td>
<td>Dexmedetomidine 15µg/kg iv</td>
<td>Ketamine 7.60mg/kg iv</td>
</tr>
</tbody>
</table>

After induction, maintenance of anaesthesia was done with Sevoflurane at 2.2% (as described by Mahidol and Thengchaisri, 2015) and its minimum alveolar concentration (MAC) was determined by the tail clamp method (Mahidol and Thengchaisri, 2015) in order to assess the effect of varying doses of dexmedetomidine on its MAC.
The animals were first weighed and then placed on the surgical table in the sitting posture (sternal recumbency). The skin over the cephalic vein of the right forelimb (for placing of the scalp vein set and IV line) and over the right recurrent tarsal vein (for repeated collection of blood samples at the preset time intervals) were prepared for aseptic injection, likewise the skin over the point of both elbows and over the patella was clipped for placement of ECG electrodes. An intravenous line was instituted in the cephalic vein of right forelimb already clipped and prepared aseptically. Drugs were delivered via a 20 or 22 gauge commercially available scalp vein set and an intravenous set connected to an NSS bottle of 500ml capacity.

Atropine sulphate was injected at the prescribed dose rate by s/c route in all the dogs. Dexmedetomidine (DEX) was administered IV at the pre decided dose rate of 10 or 15µg/kg in all the animals of subgroups of groups A, B and C (as shown in the table), 5 minutes after administration of atropine.

After 10 minutes of DEX administration, Etomidate was administered in the animals of Group A, Propofol in the animals of Group B and Ketamine in the animals of Group C (all by IV route at the respective dose rates as shown in the table above) slowly to effect in order to just achieve endotracheal intubation by depressing the epiglottis with a Macintosh type laryngoscope blade. Endotracheal tubes no. 5, 6 or 7 were used depending upon the size and body weight of the animal and the cuff was inflated to achieve an airtight seal for patency of the airway and preventing any leakage/loss of inhaled/exhaled air and anaesthetic gas mixture.

Having intubated the dogs, the endotracheal tube was connected to the anaesthesia machine (open circuit) after about 10 minutes of induction. Oxygen was delivered at the rate of 2L/min. Sevoflurane was delivered by monitoring the vaporizer setting and observing the response of the dog to a noxious stimulus. MAC of the sevoflurane was determined by the tail clamp method.

The effect of anaesthetic combinations was assessed by determining the various clinico-physiological (Induction time, duration of anaesthesia, muscle relaxation, pedal reflex, palpebral reflex, recovery time, sternal recumbency time, standing time,
complete recovery time, required doses of induction agents, sevoflurane MAC reductions, body temperature, heart rate, respiration rate, blood pressure, capillary refill time, haemoglobin oxygen saturation (SpO₂) and electrocardiography), haematological (haemoglobin, total erythrocyte count, erythrocyte sedimentation rate, total leucocyte count, differential leucocyte count, packed cell volume and erythrocytic indices (MCV, MCH, MCHC) and biochemical (serum glucose, serum insulin, serum cortisol, total protein, serum albumin, serum urea nitrogen, serum creatinine, alanine amino transferase and aspartate amino transferase) parameters.

Blood sampling was done at 0 minutes (base line value), 30 minutes, 1 hour, 6 hour and 24 hours post-induction for the determination of various haematological and biochemical parameters.

**Clinical studies:** To assess the clinical efficacy of different anaesthetic regimes used in the study various surgical operations viz. laparotomy, ovariohysterectomy, cystotomy, and splenectomy were performed under these anaesthetic combinations.

### 3.1 CLINICAL PARAMETERS

#### 3.1.1 Induction time

The time elapsed from administration of etomidate, propofol or ketamine in respective groups to the induction of anaesthesia (adjudged by the loss of pedal reflex) was called as induction time and was recorded in seconds.

#### 3.1.2 Duration of anaesthesia

The time elapsed from the induction of anaesthesia to the first spontaneous movement of any body part by the animal (after detachment of sevoflurane) was called as duration of anaesthesia and was recorded in minutes.

#### 3.1.3 Muscle Relaxation

Muscle relaxation was judged on the musculature of abdomen, legs and jaws at various time intervals as for analgesia. It involved judging the ease with which the jaws could be opened, the limbs could be flexed without much resistance and the flaccidity of the abdominal muscles. It was recorded on a scale of 1 to 4 as given below.
1 No muscle relaxation  Tightly closed jaws, stiff limbs resisting any attempt to flex and tight abdominal muscles.

2 Mild relaxation  Moderate resistance to opening of the jaws and flexing of the limbs, mild flaccidity of the abdominal muscles.

3 Moderate relaxation  Mild resistance to opening of the jaws and flexing of the limbs, moderate flaccidity of the abdominal muscles.

4 Excellent relaxation  No resistance to opening of the jaws and flexing of the limbs, completely flaccid abdominal muscles.

3.1.4 Reflexes

Degree of abolition of pedal reflex and palpebral reflex was recorded at various intervals in all the groups. The response to stimuli in the reflexes was recorded on a scale of 1 to 4 as shown below.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Excellent response to stimulus</td>
</tr>
<tr>
<td>2</td>
<td>Moderate response to stimulus</td>
</tr>
<tr>
<td>3</td>
<td>Mild response to stimulus</td>
</tr>
<tr>
<td>4</td>
<td>Completely abolished response</td>
</tr>
</tbody>
</table>

3.1.5 Recovery time

The time from discontinuation of sevoflurane to the first spontaneous movement of any body part by the dogs was called as the recovery time. It was recorded in minutes.

3.1.6 Sternal recumbency time

The time from discontinuation of sevoflurane administration to regaining of sternal recumbency by the dogs was recorded as the sternal recumbency time. It was recorded in minutes.
3.1.7 Standing time

The time from discontinuation of sevoflurane administration to regaining of standing position by the dog was recorded as the standing time. It was recorded in minutes.

3.1.8 Complete recovery time

The time from discontinuation of sevoflurane to walking of the dog without any ataxia was called as complete recovery time and was recorded in minutes.

3.1.9 Required doses of different drugs (induction agents)

The required doses of propofol, etomidate and ketamine (mg/kg) were calculated after completion of each trial.

3.1.10 Percent reduction in the MAC of sevoflurane

The percent reduction in the MAC of sevoflurane in each animal was observed by the tail clamp method. The average of the highest MAC with positive response to the tail clamp response and the lowest MAC with negative tail clamp response was taken as the MAC for a particular measurement.

3.2 Physiological parameters

3.2.1 Rectal temperature

Rectal temperature (°C) was monitored by the veterinary patient monitor (model no. MMED 8000-CV, Beijing Choice Electronic Technology Co. Ltd., Beijing, China) at different time intervals. Its values were expressed in °C.

3.2.2 Heart rate

Heart rate (beats per minute) was monitored by the veterinary patient monitor (model no. MMED 8000-CV, Beijing Choice Electronic Technology Co. Ltd., Beijing, China) at different time intervals. Its values were expressed in beats per minute.

3.2.3 Respiration rate

Respiratory rate (breaths per minute) was monitored by the veterinary patient monitor (model no. MMED 8000-CV, Beijing Choice Electronic Technology Co. Ltd.,
Beijing, China) at different time intervals. Its values were expressed in breaths per minute.

3.2.4 Blood pressure/ Non invasive blood pressure (NIBP)

Systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were monitored by the veterinary patient monitor (model no. MMED 8000-CV, Beijing Choice Electronic Technology Co. Ltd., Beijing, China), a non invasive blood pressure monitor, at different time intervals. Its values were expressed in mmHg.

3.2.5 Capillary refill time

Capillary refill time (seconds) was monitored by pressing the gingival mucosa digitally. Its values were expressed in seconds.

3.2.6 Haemoglobin oxygen saturation (SpO₂)

Haemoglobin oxygen saturation was monitored by the pulse oximeter using the veterinary patient monitor (model no. MMED 8000-CV, Beijing Choice Electronic Technology Co. Ltd., Beijing, China) at various time intervals. Its value was expressed in percent (%).

3.2.7 Electrocardiography (ECG)

Electrocardiograph was recorded by veterinary ECG machine (model Cardivet, Mediglo systems Chandigarh, India) using the Lead II at different time intervals.

3.3 Haematological parameters

Determination haemato-biochemical parameters was carried out by collecting 5ml. of blood from the recurrent tarsal vein of each dog at 0, 0.5, 1, 6 and 24 hrs (post anaesthesia) and was kept in anti-coagulated vials and plain vials respectively. Haematology was done on whole blood while biochemical study was done after harvesting the serum.

3.3.1 Haemoglobin (Hb)

Haemoglobin was measured as per the Acid hematin method of Sahli and described by Jain (1986). It was expressed in g/dl of blood.
3.3.2 Total erythrocyte count (TEC)

Total erythrocyte count was measured by Neubauer’s hemocytometer as described by Jain (1986) using Hayem’s fluid and values were expressed in millions/microlitre of blood (10^6/µl).

3.3.3 Erythrocyte sedimentation rate (ESR)

Erythrocyte sedimentation rate was measured by Wintrobe Haematocrit method as described by Jain (1986) and its values were expressed in millimetre per hour (mm/hr).

3.3.4 Total leucocyte count (TLC)

Total leucocyte count was measured by the Neubauer’s hemocytometer as described by Jain (1986) and its values expressed in thousand (cells) per microlitre of blood (×10^3/µl).

3.3.5 Differential leucocyte count (DLC)

Differential leucocyte count was calculated by staining a thin smear blood film made over a clean grease free glass slide and stained with Giemsa Stain (Jain 1986). The cells were counted manually by the battlement method under high power light microscope. The values were expressed in percent (%) for the individual cell type.

3.3.6 Packed cell volume (PCV)

Packed cell volume was measured by “Wintrobe Hematocrit” method as described by Jain (1986) and its values were expressed in percent (%).

3.3.7 Erythrocytic indices

The erythrocyte indices viz. mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) were calculated from the values of Hb, TEC and PCV as described by Jain (1986) as shown below.

i. Mean corpuscular volume (MCV).

MCV was calculated as per the given formula:

\[
MCV \text{ (fl) } = \frac{PCV}{TEC} \times 10.
\]
ii. Mean corpuscular haemoglobin (MCH).

MCH was calculated as per the given formula:

\[
\text{MCH (pg)} = \left[ \frac{\text{Hb}}{\text{TEC}} \right] \times 10.
\]

iii. Mean corpuscular haemoglobin concentration (MCHC)

MCHC was calculated as per the given formula:

\[
\text{MCHC (\%)} = \left[ \frac{\text{Hb}}{\text{PCV}} \right] \times 100.
\]

3.4 **Biochemical parameters**

3.4.1 **Serum Glucose**

Estimation of serum glucose was done by the GOD-POD method as described by Kaplan (1984), utilising the commercial test kit- [AUTOSPAN®, (ARKRAY Healthcare Pvt. Ltd, Surat, India)]. Its values were expressed in mg/dl of serum.

3.4.2 **Serum Insulin**

Serum insulin was estimated using commercial insulin ELISA kit (“Insulin ELISA”, from CALBIOTECH Inc. 10461 Austin Dr, Spring Valley, CA, 91978 USA) as per the method described by Ashby and Frier (1981) and Dhahir et al. (1992). Its values were expressed in µIU/ml of serum.

3.4.3 **Serum Cortisol**

Serum cortisol was estimated using the commercial cortisol estimation kit “Cortisol ELISA”, (from CALBIOTECH Inc., 10461 Austin Dr, Spring Valley, CA, 91978, USA) by the method as described by Demer (2008). Its values were expressed in ng/ml of serum.

3.4.4 **Total Protein**

Total Protein was estimated using the commercial kits (Autospan®) supplied by ARKRAY Healthcare Pvt. Ltd, Surat, India as per the Biuret method as described by Doumas et al. (1981). Its values were expressed in g/dl of serum.
3.4.5 Serum Albumin

Serum Albumin was estimated using the commercial kits available [LIQUIXX ALBUMIN (ALB), from Transasia Bio-Medicals Ltd. Solan, (HP) India] which as per the method of Doumas and Biggs (1972). Its values were expressed in g/dl of serum.

3.4.6 Serum Urea Nitrogen

Serum urea nitrogen and was estimated using the commercial kits ERBA from Transasia Bio-Medicals Ltd. Solan, (HP) India, as per the method given by Talke and Schubert (1965). Its values were expressed in mg/dl of serum.

3.4.7 Serum Creatinine

Serum creatinine was estimated using the commercial kits [ERBA from Transasia Bio-Medicals Ltd. Solan, (HP) India] as per the method of Jaffe (1886). It's values were expressed in mg/dl of serum.

3.4.8 Alanine Amino Trasferase (ALT)

Alanine amino transferase was estimated by using the commercial ALT test kit [AUTOSPAN®, supplied by ARKRAY Healthcare Pvt. Ltd, Surat, India] as per the Method of Schumann et al. (2002a). Its values were expressed in IU/L.

3.4.9 Aspartate Amino Transferase (AST)

Aspartate aminotransferase was estimated by using the commercial AST test kit (AUTOSPAN®) supplied by ARKRAY Healthcare Pvt. Ltd, Surat, India as per the method described by Schumann et al (2002b). Its values were expressed in IU/L of serum.

Statistical Analysis: Data obtained was analysed by one way ANOVA as per the standard procedure described by Snedecor and Cochran (1994).
Plate 1: Measurement of NIBP from the middle coccygeal artery.

Plate 2: Measurement of different parameters using the multiple parameter monitor.
Plate 3: Probes of the multiple parameter monitor and anaesthesia machine attached to the anaesthetized animal.

Plate 4: Animal attached to anaesthesia machine for anaesthesia/operation.
Results and Discussion
In the present study dexmedetomidine has been used as a premedicant in the animals of all the groups as per the protocol shown earlier, at two different dose rates (low and high) i.e. at 10µg/kg body weight (low) and 15µg/kg body weight (high). The minimum possible doses of the induction agents (etomidate, propofol and ketamine) were administered to achieve the induction of anaesthesia just sufficient for the facilitation of endotracheal intubation in order to assess the effects of the two varying doses of dexmedetomidine (low and high) on the various parameters observed in the study.

4.1 Clinical Observations

4.1.1 Induction Time

Mean±SE values of induction time in various groups of animals premedicated with dexmedetomidine at the dose rate of 10µg/kg (A1, B1 and C1) and 15µg/kg (A2, B2 and C2) are given in Table 4.1 and depicted in Fig 4.1. The mean values of induction time were 167.83±7.45, 125.11±11.33, 179.00±23.05, 108.00±7.73, 60.83±8.76 and 55.33±5.70 seconds in groups A1, A2, B1, B2, C1 and C2 respectively. The induction time was significantly (P<0.05) lower in the animals of group A2 as compared to the animals of group A1. Induction time was significantly (P<0.05) lower in the animals of group B2 (108±7.73 seconds) as compared to the animals of group B1 (179±23.05 seconds). There was a non-significant (P<0.05) difference in the induction time in the animals of group C1 (60.83±8.76 seconds) as compared to the animals of group C2 (55.33±5.70 seconds) though the induction time was numerically lower in the animals of group C2 as compared to the animals of group C1. Among the animals subjected to the administration of dexmedetomidine at the dose rate of 10µg/kg induction time was lowest in the group C1, followed by the animals of group A1 and B1. Similarly among the animals subjected to the administration of dexmedetomidine at the dose rate of 15µg/kg, the values of induction time was lowest in the animals of group C2, followed by group A2 and group B2.
Induction time of 6.4±2.30 minutes after administration of atropine-detomidine-ketamine has been reported by Jadon et al. (1995) in dogs premedicated with atropine and diazepam. Induction time of 3.0±0.69 minutes in dogs administered with atropine-detomidine-ketamine was also reported by Kandpal and Kumar (1998). Adetunji et al. (2002) have reported an induction time of 1.4±0.2 minutes and 1.2±0.2 minutes in dogs premedicated with atropine-xylazine and administered with propofol as repeat bolus or continuous infusion respectively. The high lipid solubility of propofol was thought to be the reason for rapid induction of anaesthesia in Nigerian dogs (Kanto and Gepts 1989). Induction time of 1 minute was reported by Neils et al. (2007) in Nigerian dogs administered with ketamine at a dose rate of 11mg/kg i.m. which was ascribed to the rapid absorption of cyclohexamines. Alkattan and Helal (2013) recorded an induction time of 2.78±0.33 minutes in dogs administered xylazine-ketamine and 0.92±0.14 minute in dogs induced with propofol only. The rapid induction with propofol was due to the high lipid solubility and rapid blood-brain equilibrium obtained after administration of propofol (Schrouff et al., 2011). An induction time (sedation) varying inversely with the dose of dexmedetomidine was reported by Akbar et al. (2014) in dogs administered with dexmedetomidine alone. The observations of the present study confirm to the findings of the above mentioned studies, since the induction time noted in various groups of animals were shorter in the animals of groups A2, B2 and C2 (administered with dexmedetomidine at the dose rate of 15µg/kg) as compared to the animals of groups A1, B1 and C1 (administered with dexmedetomidine at the dose rate of 10µg/kg). Rafee et al. (2015a) have noted induction time of 4.75±2.92 vs. 5.00±3.12 minutes in dogs administered with atropine-dexmedetomidine-butorphanol-midazolam-ketamine and atropine-dexmedetomidine-midazolam-ketamine respectively. Ferreira et al. (2015) have reported that induction time was shorter in dogs administered with dexmedetomidine-ketamine vis-à-vis those administered with propofol alone. The present study is in agreement with the studies mentioned above which have also reported decrease in induction time with the use of dexmedetomidine in various animals.

4.1.2 Duration of Anaesthesia.

Mean±SE values of duration of anaesthesia in various groups of animals premedicated with dexmedetomidine at the dose rate of 10µg/kg (groups A1, B1 and
C1) and 15µg/kg (groups A2, B2 and C2) are given in Table 4.2 and depicted in Fig. 4.2. The duration of anaesthesia was 70±7.45 minutes in the animals of group A1 and 82.5±11.33 minutes in the animals of group A2. In the animals of group B1 and B2 the values of duration of anaesthesia stood at 70±23.05 and 85±7.73 minutes. In the animals of group C1 and C2 the duration of anaesthesia was 82.5±8.76 and 97.5±5.70 minutes. The duration of anaesthesia was higher in the groups administered with dexmedetomidine at the dose rate of 15µg/kg body weight (A2, B2 and C2) as compared to the animals in which dexmedetomidine was administered at the dose rate of 10µg/kg body weight (A1, B1 and C1). This was due to the reason that dexmedetomidine had caused dose dependent sedation in the dogs administered with a higher dose rate and therefore the MAC had to be tested for a more number of times in order to measure the percentage reduction of MAC with the particular dose schedule of dexmedetomidine in the group as compared to the animals administered with a lower dose rate and shallower sedation.

Bufalari et al. (1997) have reported a longer duration of anaesthesia with the administration of acepromazine and butorphanol as premedicants in dogs anaesthetized with propofol. Pypendop et al. (1998) have found that the duration of sedation was dose dependent with the use of detomidine. The dose dependent sedation can safely be assumed to affect the duration of anaesthesia in the animals administered with varying doses of dexmedetomidine. A longer duration of anaesthesia has also been reported by Kandpal and Kumar (1998) in dogs administered with atropine-detomidine–ketamine vis-a-vis atropine-diazepam-ketamine. The findings in group C2 of the present study is in agreement with the findings of Bufalari et al. (1997) and Kandpal and Kumar (1998), where longest duration of anaesthesia was observed. Khattri et al. (2013) have also recorded duration of anaesthesia of 55 minutes with dexmedetomidine-propofol in uraemic buffalo calves. Incremental doses of medetomidine are recorded to have imparted increasingly longer duration of recumbency to dogs (Akbar et al. 2014). Akbar et al. (2015) have reported long duration of anaesthesia in cats administered with medetomidine and medetomidine-ketamine. Similarly Rafee et al. (2015a) have recorded longer duration of anaesthesia with atropine-dexmedetomidine-midazolam-ketamine as compared to atropine-dexmedetomidine-butorphanol-midazolam-ketamine in dogs. The findings of the present study are in agreement with the studies mentioned.
above which have reported longer duration of anaesthesia with increased doses of dexmedetomidine in various species of animals.

4.1.3 Muscle Relaxation

The Median±SD values of muscle relaxation in the animals of various groups administered with dexmedetomidine at the dose rate of 10µg/kg body weight (A1, B1 and C1) or 15µg/kg body weight (A2, B2 and C2) are given in Table 4.3 and depicted in Fig. 4.3. The muscle relaxation score in the animals of group A1 and A2 was 1.00±0.00 at 5 minutes time interval and it gradually increased at 10 minutes interval to the score of 3.00±0.18. It further increased to the score of 4.00±0.18 at 15 minutes and thereafter it remained at the level of 4.00±0.00 up to 60 minutes time interval. At 75 minutes interval it was 2.00±0.00 in the animals of group A1 and 4.00±0.00 in the animals of group A2. The score decreased to 1.00±0.00 at 90 minutes interval in the animals of both the groups. In the animals of group B1 the muscle relaxation score was 1.00±0.00 at 5 minutes interval, 3.00±0.18 at 10 minutes interval and 4.00±0.18 at 15 minutes interval. It remained at the level of 4.00±0.00 from 20 minutes to 60 minutes interval. It decreased to 1.50±0.18 at 75 minutes and to 1.00±0.00 at 90 minutes interval. In the animals of group B2 the score was 1.00±0.00 at 5 minutes and 3.00±0.28 at 10 minutes interval. It increased to 4.00±0.23 at 15 minutes and thereafter remained at the level of 4.00±0.00 from 20 minutes to 75 minutes interval before decreasing to 2.00±0.21 at 90 minutes interval. In the animals of group C1 and C2 the muscle relaxation was at the level of 1.00±0.00 and 3.00±0.00 at 5 and 10 minutes respectively. It gained value of 4.00±0.00 at 15 minutes interval and remained at same level up to 75 minutes. It decreased to the level of 3.00±0.0 in the animals of group C1 and remained at the level of 4.00±0.0 in the animals of group C2, at 90 minutes interval. The above observations indicate that adequate muscle relaxation was obtained with the use of dexmedetomidine at the dose rate of 10µg/kg or 15µg/kg in the animals of various groups.

Jadon et al. (1995) have recorded good muscle relaxation in dogs administered with atropine-detomidine-ketamine which lasted for about 42minutes. Desirable level of muscle relaxation was also observed by Tiwari et al. (1998) in dogs administered with medetomidine-ketamine. Sinclair (2003) has reviewed the muscle relaxation
properties of dexmedetomidine and these have been ascribed to the inhibition at interneuron level of spinal cord. Nagore et al. (2012) have recorded adequate muscle relaxation (which increased with passage of time) with dexmedetomidine in cats. Ahmad et al. (2013) have demonstrated that the muscle relaxation obtained with dexmedetomidine was moderate and it increased further with the combination of midazolam due to the synergistic interaction of the drugs (Lemke, 2007; Ahmad et al., 2013). Santosh et al. (2013) have recorded better muscle relaxation in dogs lasting for 90 minutes, when dexmedetomidine was combined with midazolam-fentanyl-ketamine. Similarly Khattri et al. (2013) have also reported excellent muscle relaxation with the combined use of dexmedetomidine-butorphanol-propofol which lasted for the entire study period and was attributed to the synergistic effect of the drugs used in the study. Ninu et al. (2015) have reported good muscle relaxation in buffalo calves administered with glycopyrrolate-acepromazine-xylazine-ketamine/thiopentone for diaphragmatic herniorrhaphy.

4.1.4 Pedal Reflex

The Median±SD values of pedal reflex in the animals of various groups administered with dexmedetomidine at the dose rate of 10µg/kg body weight (A1, B1 and C1) or 15µg/kg body weight (A2, B2 and C2) are given in Table 4.4 and depicted in Fig. 4.4. The median pedal reflex score of the animals in group A1 was 1.00±0.00 at 5 minutes and 1.00±0.23 at 10 minutes interval followed by 2.00±0.00 at 15 minutes time interval. It increased to the level of 4.00±0.00 at 20 minutes interval and remained at this level up to 60 minutes interval. The score decreased to the level of 3.00±0.00 and 1.00±0.00 at 75 and 90 minutes interval respectively. In the animals of group A2 the score of pedal reflex was 1.00±0.00 at 5 minutes interval, 2.00±0.23 at 10 minutes interval and 2.00±0.00 at 15 minutes interval. It increased to the level of 4.00±0.00 at 20 minutes and remained at this level up to 75 minutes. The score decreased to 1.00±0.00 at 90 minutes interval. In the animals of group B1 the pedal reflex score was 1.00±0.00 at 5 minutes interval and 2.00±0.00 at 10 and 15 minutes interval. It increased to 4.00±0.00 at 20 minutes interval and remained at this level up to 60 minutes interval. The score decreased to 3.00±0.00 at 75 minutes interval and to 1.00±0.00 at 90 minutes interval. In the animals of group B2 the pedal reflex score was 1.00±0.00 at 5 minutes interval and 2.00±0.00 at 10 and 15 minutes interval. It
increased to 4.00±0.00 at 20 minutes interval and remained at this level up to 75 minutes interval. The score decreased to 1.00±0.00 at 90 minutes interval. In the animals of group C1 and C2 the pedal reflex score was 1.00±0.00 at 5 minutes interval and 2±0.00 at 10 and 15 minutes interval. It increased to the level of 4±0.00 at 20 minutes interval and remained at this level up to 75 minutes interval. It decreased to the level of 3.00±0.00 in the group C1 whereas it remained at level of 4±00.00 in the animals of group C2 at 90 minutes interval.

Tiwari et al. (1998) have reported that the pedal reflexes remained intact during anaesthesia of dogs with medetomidine-ketamine however in the present study the pedal reflexes were totally abolished after the administration of dexmedetomidine and the various anaesthetic induction agents (etomidate, propofol and ketamine) in various groups, to this extent the present study did not confirm with the findings of Tiwari et al. (1998), however Singh et al. (2010) have reported complete loss of pedal reflex during the anaesthesia period in dogs anaesthetized with atropine-diazepam-thiopentone-isoflurane/sevoflurane. Present study is in accordance with the study of Singh et al. (2010) as the pedal reflexes were totally lost in our study. Ahmad et al. (2013) have also reported complete loss of pedal reflex in dogs anaesthetized with dexmedetomidine-midazolam-fentanyl–ketamine. Santosh et al. (2012) and Santosh et al. (2013) have also reported total loss of the pedal reflex in dogs administered with dexmedetomidine-midazolam-fentanyl–ketamine. Jena et al. (2014) and Sharma et al. (2014) have also recorded complete loss of pedal reflex in dogs anaesthetized with xylazine/detomidine–propofol and atropine-dexmedetomidine-butorphanol-ketamine-halothane. The loss was ascribed to the high potency of dexmedetomidine at the alpha-2 receptors (Scheinin et al. 1989, Jena et al. 2014) and thereby meaning that the stage of surgical anaesthesia was achieved (Surbhi et al. 2010, Jena et al. 2014) while Sharma et al. (2014) attributed the loss of reflex to analgesia produced by the stimulation of central presynaptic alpha-2 adrenoceptors which inhibited the release of nor-epinephrine (Hsu, 1981; Sharma et al., 2014).

4.1.5 Palpebral Reflex

The Median±SD values of Palpebral reflex in the animals of various groups administered with dexmedetomidine at the dose rate of 10µg/kg body weight (A1, B1
and C1) or 15µg/kg body weight (A2, B2 and C2) are given in Table 4.5 and depicted in Fig. 4.5. The median palpebral reflex score of the dogs in groups A1 and A2 was 1.00±0.00 at 5 minutes interval and 2.00±0.00 at 10 and 15 minutes interval. It increased to the level of 4.00±0.00 at 20 minutes interval and remained at this level up to 60 minutes interval in the animals of group A1 and up to 75 minutes interval in the animals of group A2. It decreased to the level of 3.00±0.00 in the animals of group A1 at 75 minutes and decreased to the level of 1.00±0.00 in the animals of both the groups at 90 minutes interval. In the animals of group B1 and B2 the palpebral reflex score was 1.00±0.00 and 2.00±0.00 at 5 and 10 minutes interval and 2.00±0.23 and 2.00±0.00 at 15 minutes interval respectively. It increased to the level of 4.00±0.00 at 20 minutes interval and remained at this level up to 60 minutes in the animals of group B1 and up to 75 minutes in the animals of group B2. The score decreased to 3.00±0.00 and 1.00±0.00 at 75 and 90 minutes in the animals of group B1 whereas it decreased to 1.00±0.00 at 90 minutes interval in the animals of group B2. The palpebral reflex score in the animals of group C1 was 1.00±0.00 at 5 minutes and 2.00±0.00 at 10 and 15 minutes interval. It was 2.00±0.23 at 20 minutes interval and increased to 2.50±0.24 at 30 minutes interval. It decreased to the level of 2.00±0.23 at 45 minutes interval and remained at this level throughout the remaining period of the study. In the animals of group C2 the palpebral reflex score was 1.00±0.00 at 5 minutes interval which increased to the level of 2.00±0.00 from 10 to 20 minutes interval. It increased further to the level of 3.00±0.00 at 30 minutes interval. Thereafter it decreased to 2.50±0.24 at 45 minutes interval. It became 3.00±0.23 at 60 minutes, 3.00±0.18 at 75 minutes and 3.00±0.23 at 90 minutes interval.

**Tiwari et al. (1998)** have reported that the palpebral reflex was depressed but remained intact during anaesthesia of dogs with medetomidine-ketamine. In the present study the palpebral reflex was totally abolished after the administration of anaesthetic induction agents etomidate and propofol but not with ketamine, therefore to this extent the present study is in agreement with the findings of **Tiwari et al. (1998)**, however **Singh et al. (2010)** have reported complete loss of palpebral reflexes during the anaesthesia period in dogs anaesthetized with atropine-diazepam-thiopentone-isoflurane/sevoflurane. **Ahmad et al. (2013)** have reported greater suppression of palpebral reflex in dogs administered with dexmedetomidine-midazolam-fentanyl or
dexmedetomidine-midazolam-fentanyl-ketamine as compared to those administered with dexmedetomidine alone. This could have been due to the synergistic effect of the drugs administered along with dexmedetomidine. Further the present study confirms the findings of Khattri et al. (2013) who have reported that the palpebral reflexes was mildly depressed with the administration of sedatives (at 5 and 10 minutes) but totally lost after induction of anaesthesia in buffalo calves anaesthetized with dexmedetomidine-butorphanol-propofol, albeit it was more depressed in the group administered with dexmedetomidine-butorphanol-propofol as compared to the group administered only with dexmedetomidine-propofol. Santosh et al. (2013) have recorded a more consistent palpebral reflex in the dogs anaesthetized with dexmedetomidine-midazolam-fentanyl-ketamine, though in other groups (using dexmedetomidine at higher and lower doses) the palpebral reflex score was reduced at the higher doses probably due to arousal and vigilance resulting from activation of $\alpha_1$ adrenoceptor (Puumala et al., 1997). It was also observed in the present study that the palpebral reflex did not increase with increased dose of dexmedetomidine probably due to the same reason as given by Puumala et al. (1997). Jena et al. (2014) and Sharma et al. (2014) have also recorded complete loss of palpebral reflex in dogs anaesthetized with xylazine/detomidine-propofol and atropine-dexmedetomidine-butorphanol-ketamine-halothane. The loss was ascribed to the high specificity of dexmedetomidine at the alpha-2 receptors (Scheinin, 1989; Jena, 2014). The affinity of xylazine or dexmedetomidine to produce excellent sedation (loss of palpebral reflex) has been proved by the studies of Selmi et al. (2003) and Sharma et al. (2014). The present study (with the administration of respective anaesthetic protocols in various groups of animals), is in agreement with the studies mentioned above which recorded complete abolition of the palpebral reflex (and hence excellent sedation). Tiwari et al. (1998) have also recorded that the palpebral reflex was not abolished completely with the use of medetomidine-ketamine in dogs as was also found in the present study (with the administration of dexmedetomidine-ketamine in group C1 and C2).

4.1.6 Recovery Time

The Mean±SE values of recovery time of the animals in various groups administered with dexmedetomidine at the dose rate of 10µg/kg body weight (A1, B1 and C1) or 15µg/kg body weight (A2, B2 and C2) are given in Table 4.6 and depicted

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in Fig. 4.6. The recovery time (in minutes) of animals in group A1, A2, B1, B2, C1 and C2 was 4.97±1.37, 5.30±0.64, 3.17±0.64, 6.48±0.38, 8.15±1.26 and 10.75±2.12 minutes respectively. The recovery time was non-significantly higher in the animals of group A2 as compared to that of animals of group A1. The recovery time of animals of group B2 was significantly (P<0.05) higher than those of group B1. In the animals of group C1 the mean recovery time was non-significantly lower than that of animals of group C2. Recovery time was lowest in the animals (administered with dexmedetomidine at the dose rate of 10µg/kg body weight) of group B1 followed by the animals of group A1 and C1. The recovery time was lowest in the animals (administered with dexmedetomidine at the dose rate of 15µg/kg body weight) of group B2 followed by animals of group A2 and C2.

Bufalari et al. (1997) have reported that the recovery time increased with acepromazine or butorphanol premedication in dogs anaesthetized with propofol. The recovery time in the dogs anaesthetized with propofol was found to be shorter than that of dogs anaesthetized with etomidate (Sams et al., 2008). Santosh et al. (2012) have also reported that the recovery time increased as the dose of dexmedetomidine increased in the dogs anaesthetized with dexmedetomidine-midazolam-ketamine. Alkattan and Helal (2013) have recorded prolonged recovery times in animals anaesthetized with xylazine-ketamine as compared to those anaesthetized with propofol-halothane. Prolonged recovery time was also noticed in the animals of group C1 and C2 in the present study where dexmedetomidine and ketamine seem to have prolonged the recovery period. Prolongation of recovery time with increasing doses of dexmedetomidine has also been reported by Santosh et al. (2013) in dogs administered with different dose of dexmedetomidine in combination with midazolam, ketamine and fentanyl. Similarly prolongation of recovery time has also been reported by Kumar et al. (2014) and Akbar et al. (2015) in goats and cats which were anaesthetized with dexmedetomidine-propofol/dexmedetomidine-ketamine and medetomidine-ketamine respectively. In the present study the recovery time increased with increase in dose of dexmedetomidine (10µg/kg body weight or 15 µg/kg body weight) used for preanaesthesia in combination with etomidate, propofol and ketamine.
4.1.7 Sternal Recumbency Time

The Mean±SE values of sternal recumbency time of the animals in various groups administered with dexmedetomidine at the dose rate of 10µg/kg body weight (A1, B1 and C1) or 15µg/kg body weight (A2, B2 and C2) are given in Table 4.7 and depicted in Fig. 4.7. The sternal recumbency times (in minutes) in the animals of groups A1, A2, B1, B2, C1 and C2 were 8.52±0.90, 11.60±3.47, 7.61±0.87, 8.31±0.78, 11.12±1.8 and 15.40±2.16 minutes respectively. The mean sternal recumbency time in the animals of group A2 was non-significantly higher than that of the animals of group A1. The sternal recumbency time in the animals in group B2 was also non-significantly higher than the animals of group B1 administered with dexmedetomidine at the dose rate of 15µg/kg body weight and 10µg/kg body weight respectively. The sternal recumbency time in the animals of group C2 was significantly (P<0.05) higher than that of the animals of group C1 administered with dexmedetomidine at the dose rate of 15µg/kg body weight and 10µg/kg body weight respectively. The animals of group B1 had the shortest sternal recumbency time (7.61±0.87 minutes) among the animals administered with dexmedetomidine at the dose rate of 10µg/kg body weight followed by A1 (8.52±0.9 minute) and C1 (11.12±1.8 minutes). The animals of group B2 had the shortest sternal recumbency time (8.31±0.78 minutes) among the animals administered with dexmedetomidine at the dose rate of 15µg/kg body weight followed by A2 (11.60±3.47 minutes) and C2 (15.40±2.16 minutes).

Longer sternal recumbency time with etomidate as compared to propofol has been reported by Sams et al. (2008) in dogs and in the present study the same has been observed as dexmedetomidine in combination with etomidate must have caused the longer sternal recumbency time. Malik et al. (2011) have recorded shorter sternal recumbency time with dexmedetomidine as compared to midazolam in buffaloes. The sternal recumbency time in the present study increased with increase in the dose of dexmedetomidine which confirms the findings of Santosh et al. (2012) in dogs and Selmi et al. (2003) in cats. Longest sternal recumbency time observed in the animals of group C, especially in the group C2 administered with dexmedetomidine (at the dose rate of 15µg/kg body weight) and ketamine in the present study confirms the findings of Kumar et al. (2014).
4.1.8 Standing Time

The Mean±SE values of standing time in minutes of the animals in various groups of animals administered with dexmedetomidine at the dose rate of 10µg/kg body weight (A1, B1 and C1) or 15µg/kg body weight (A2, B2 and C2) are given in Table 4.8 and depicted in Fig. 4.8. The standing time in the animals of group A1 (13.07±3.70 minutes) was shorter than the standing time in the animals of group A2 (14.65±1.61 minutes). The standing time in the animals of group B1 (11.00±0.89 minutes) was significantly (P<0.05) lower than the standing time in the animals of group B2 (13.00±2.79 minutes) respectively. The standing time in the animals of group C1 (15.71±2.10 minutes) was significantly (P<0.05) lower than the animals in group C2 (19.29±2.56 minutes). In the present study the shortest standing time was shown by the animals of group B1 (11.00±0.89) while the animals of group C2 showed the longest (19.29±2.56) standing time.

Sams et al. (2008) have reported that the standing time noted with etomidate were significantly longer than those noted with the use of propofol in dogs. Similar findings have been observed in the present study. Singh et al. (2013) have reported that the standing times were similar in animals administered with dexmedetomidine or medetomidine however the standing time increased in animals subjected to premedication with medetomidine/dexmedetomidine as compared to the another group in which dexmedetomidine/medetomidine were not used as premedicants. The findings of the present study are in agreement with the observations of Santosh et al. (2013) who have reported that higher dose of dexmedetomidine with ketamine vis-a-vis a lower dose of dexmedetomidine with ketamine caused the standing times to increase and decrease in proportion to the dose rate of dexmedetomidine.

4.1.9 Complete Recovery Time

The Mean±SE values of complete recovery time (in minutes) in the animals of various groups administered with dexmedetomidine at the dose rate of 10µg/kg body weight (A1, B1 and C1) or 15µg/kg body weight (A2, B2 and C2) are given in Table 4.9 and depicted in Fig. 4.9. The complete recovery time in the animals of group A1, A2, B1, B2, C1 and C2 was 20.00±2.77 minutes, 21.67±2.88 minutes, 14.00±0.94 minutes, 24.16±4.71 minutes, 20.53±2.34 minutes and 25.52±3.14 minutes.
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respectively. The complete recovery time of group A2 was non-significantly (P<0.05) higher than the complete recovery time of group A1. The complete recovery time in the animals of group B2 was significantly (P<0.05) higher than the complete recovery time in the animals of group B1. The complete recovery time in the animals of group C2 was non-significantly (P<0.05) higher than the complete recovery time of the animals of group C1. It was observed that an increased dose of dexmedetomidine in the animals of groups B2 (administered with dexmedetomidine at the dose rate of 15µg/kg body weight) had caused a longer complete recovery time than the animals of group B1 (administered with dexmedetomidine at the dose rate of 10µg/kg body weight) however an increased dose of dexmedetomidine in the animals of groups A2 and C2 (administered with dexmedetomidine at the dose rate of 15µg/kg body weight) had caused only a non-significantly longer complete recovery time than the animals of group A1 and C1 (administered with dexmedetomidine at the dose rate of 10µg/kg body weight).

Tiwari et al. (1998) have reported complete recovery time of 94.14±6.18 minutes in dogs anaesthetized with medetomidine-ketamine. A longer complete recovery time with the use of etomidate observed in the present study confirms the findings of Sams et al. (2008) in dogs anaesthetized with midazolam-propofol (18.1 minutes) or midazolam-etomidate (48.8 minutes). The findings reported by Santosh et al. (2012) and Santosh et al. (2013) were similar to the findings of the present study wherein an increase in the dose of dexmedetomidine resulted in an increase in the complete recovery time in dogs anaesthetized with dexmedetomidine (at low and higher dose) with midazolam-ketamine and fentanyl. Lu et al. (2014) have reported non-significant change in the complete recovery time in dogs anaesthetized with tiletamine-zolazepam-xylazine (78.47±8.55 minutes) and tiletamine-zolazepam-xylazine-tramadol-atipamezole (98.33±7.54 minutes).

4.1.9 Required Doses of Different Drugs

The Mean±SE values of required doses of different drugs (induction agents) in various groups of animals administered with etomidate (group A1 and A2), propofol (group B1 and B2) and ketamine (group C1 and C2) along with dexmedetomidine at the dose rate of 10µg/kg body weight (A1, B1 and C1) or 15µg/kg body weight (A2,
Results and Discussion

The induction dose of etomidate in group A1 and A2 was 1.66±0.11mg/kg and 1.58±0.19mg/kg respectively. In the animals of group B1 and B2 the corresponding doses of propofol were 2.46±0.19mg/kg and 2.45±0.20mg/kg whereas in the animals of group C1 and C2 the mean required dose rate of ketamine were 7.70±0.17 mg/kg and 7.60±0.20mg/kg respectively.

Bufalari et al. (1997) have observed satisfactory anaesthesia with reduced dose of propofol (3.3mg/kg) along with acepromazine and butorphanol in dogs. Glass (1998) has also mentioned the reduction in the requirements of isoflurane, desflurane, sevoflurane and propofol after interaction with fentanyl, sufentanil, alfentanil and remifentanil. Kuusela et al. (2001a) have observed a significant effect of the dose level of premedicant (irrespective of the drug used) on the dose of propofol required to induce anaesthesia in dogs premedicated with medetomidine or dexmedetomidine. It is evident from the studies mentioned above that the interaction of anaesthetic drugs brings a reduction in the doses of anaesthetic drugs. Santosh et al. (2012) have reported that at a higher dose of dexmedetomidine (10µg/kg vs 20µg/kg) the requirement of ketamine as an induction agent is reduced. Santosh et al. (2013) have reported a marginal decrease in the induction dose of ketamine in dogs premedicated with two doses of dexmedetomidine (10µg/kg and 20µg/kg). Sen et al. (2013) have also reported 48% and 61% reduction in requirement of propofol for induction and maintenance respectively in human patients premedicated with dexmedetomidine vis-a-vis saline placebo. In the present study the induction doses of etomidate, propofol and ketamine were reduced after premedication with increased doses of dexmedetomidine (15µg/kg) which confirms the findings of the earlier authors.

4.1.10 Sevoflurane MAC Reduction (%)

The Mean±SE values of the sevoflurane MAC reductions (%) observed in various groups of animals induced with etomidate (group A1 and A2), propofol (group B1 and B2) and ketamine (group C1 and C2) and premedicated with dexmedetomidine at the dose rate of 10µg/kg body weight (groups A1, B1 and C1) or 15µg/kg body weight (groups A2, B2 and C2) are given in Table 4.11 and depicted in Fig. 4.11. The reduction in the MAC of sevoflurane was significantly (P<0.05) higher in the group A2.
(21.18±1.66%) as compared to that of group A1 (13.60±0.17%). The MAC reduction obtained was significantly (P<0.05) higher in group B2 (22.70±0.20%) as compared to the group B1 (13.6±0.08%). Following the similar trend the MAC reduction value in group C2 was significantly (P<0.05) higher (30.28±1.66%) than the MAC reduction obtained in group C1 (21.18±1.66%). It is evident that the increase in dose of dexmedetomidine has caused reduction in the MAC of sevoflurane required to maintain anaesthesia.

Drug interactions are known to occur in clinical pharmacology for some time. Vickery et al. (1988) have documented the interaction of dexmedetomidine to be synergistic resulting in reduction of the MAC of halothane in dogs. Eger (1989) has mentioned the phenomenon of additivity of drug actions regarding the MAC of Enflurane in rats. Segal et al. (1989) have documented the interaction of dexmedetomidine to be synergistic and causing a reduction of the MAC of halothane in rats. Aho et al. (1992) demonstrated that infusion of dexmedetomidine reduced the requirements of isoflurane by >90% in women undergoing abdominal hysterectomy, this could have been due to the alpha-2 agonists causing increased K⁺ efflux and diminished neuronal excitability. Drug synergism between dexmedetomidine and fentanyl to reduce the MAC of enflurane has also been reported by Salmenpera et al. (1994) in dogs where increasing doses of fentanyl resulted in decreased MAC levels of enflurane that could not be explained by a simple additive interaction. Similarly with the infusion of dexmedetomidine, Aanta et al. (1997) and Katoh et al. (1998) have recorded about 50% reduction in MAC of isoflurane and app. 59% reduction in the MAC of sevoflurane, in women (undergoing abdominal hysterectomy) and people (in that order) respectively. This could have been due to the alpha-2 agonists causing increased K⁺ efflux and diminished neuronal excitability (Aanta et al. 1997). Glass (1998) has also reported the reduction in the requirements of isoflurane, desflurane, sevoflurane and propofol after interaction with fentanyl, sufentanil, alfentanil and remifentanil. Reduction in the MAC of inhaled anaesthetics has been recorded in dogs by Muir et al. (2003), Solano et al. (2006) and Wilson et al. (2008). Ebner et al. (2013) and Gutierrez-Blanco et al. (2013) have reported reduction in MACs of isoflurane in dogs administered with dexmedetomidine, morphine, lidocaine, ketamine and fentanyl, ketamine, lidocaine and dexmedetomidine respectively. The reduction in
the MAC of sevoflurane in various groups of animals observed in the present study is in agreement with the observations of Moran-Munoz et al. (2014) who have reported that the MAC of sevoflurane was reduced by app. 55% by the administration of lidocaine-dexmedetomidine.

4.2 Physiological Parameters

4.2.1 Rectal Temperature

The mean±SE values of rectal temperature in various groups of animals premedicated with dexmedetomidine at the dose rate of 10µg/kg (A1, B1 and C1) and 15µg/kg (A2, B2 and C2) are given in Table 4.12 and depicted in Fig 4.12. The mean rectal temperature in the animals of all the groups showed gradual decline in its values at different time intervals and then rose to gain the base level values at 24 hours interval. In the animals of group A1 the mean rectal temperature decreased significantly (P<0.05) at 30 minutes. It further decreased significantly (P<0.01) at 45 to 75 minutes time interval. Thereafter it showed slight increase in its values at 90 minutes to 3 hrs, however these were still significantly (P<0.05) lower as compared to the base values. Rectal temperature reached near base values at 24 hrs in the animals of group A1. The animals of group A2 showed a significant (P<0.01) decrease at 30 minutes to 3 hours interval followed by an increase in its value at 6 hours. However at 6 hours interval it value was significantly (P<0.05) lower before reaching near the base value at 24 hours. Decrease in rectal temperature was more pronounced for a longer period in the animals of group A2 as compared to the animals of group A1. Values of rectal temperature remained significantly (P<0.05) lower than the preanaesthetic values from 30 minutes to 6 hour interval in both the groups. In group B1 the rectal temperature registered a gradual and non-significant (P<0.05) decrease at 15 minutes interval, however its values decreased significantly (P<0.01) from 30 minutes to 6 hours interval but gained the base level at 24 hours interval. In group B2 the rectal temperature after registering a gradual and significant (P<0.01) fall up to 60 minutes (the lowest value was registered at 60 minutes interval) started rising at 75 minutes interval and attained values near the base level at 24 hours interval. In the animals of group C1 the temperature followed a significant (P<0.01) decrease in its values from base line to 60 minutes, thereafter a gradual increase in its level was observed and its level have reached to the near base...
level values at 6 hours interval. It was significantly (P<0.01) lower at 15 minutes to 3 hours as compared to the 0 hour values whereas in group C2 the rectal temperature after falling gradually from the base line to 60 minutes had attained the value of the base line at 24 hours time interval.

Decrease in rectal temperature as observed in the present study can be a result of the reduced heat production consequent to decreased muscle activity or by action of the drug on the hypothalamus (Virtanen 1989), or by the thermoregulatory centre being affected by central alpha-2 adrenoceptors (Sabbe et al., 1994). It has been reported by Pypendop et al. (1998) that by the administration of medetomidine rectal temperature remains at a lower level up to 2hr after the administration of the drug. Kuusela et al. (2001b), Sinclair et al. (2003) and Lemke et al. (2004) have also recorded that the rectal temperature decreases with the administration of dexmedetomidine. Kale et al. (2006) have reported that the reduction in the rectal temperature with the use of propofol could have been due to the decreased metabolic rate and peripheral circulation. Granholm et al. (2007) have reported that the rectal temperature remained below the baseline values for more than 180 minutes after the administration of medetomidine and dexmedetomodine in dogs. Nagore et al. (2012) have reported significant decrease in rectal temperature of cats after administration of dexmedetomaline at the dose rate of 20µg/kg. The findings in the present study are in accordance with the findings of most of the studies indicating decrease in body temperature after the administration of dexmedetomidine as a premedicant along with other induction agents (Granholm et al. 2007, Santosh et al. 2013, Rafee et al. 2015a).

4.2.2 Heart Rate (HR)

The Mean±SE values of heart rate in various groups of animals premedicated with dexmedetomidine at the dose rate of 10µg/kg (A1, B1 and C1) and 15µg/kg (A2, B2 and C2) are given in Table 4.13 and depicted in Fig. 4.13. The mean HR in the all the groups showed gradual decline in its values at different time intervals and then rose to gain the base level values except in the groups C1 and C2 in which the HR showed a decline only at 15 minutes and thereafter it showed significant (P<0.01) gain in values which has reached near baseline at 24 hours interval. In the animals of group A1 the
mean HR was significantly (P<0.01) lower at 15 to 90 minutes interval as compared to base values. In the animals of group A2 it was also significantly (P<0.01) lower at 15 minutes to 3 hours interval as compared to the base values. In the both the groups lowest HR was recorded at 75 minutes interval, thereafter it increased gradually and reached near the base level value at 24 hour interval. In group B1 the HR registered a gradual and significant (P<0.01) decrease from the base level at 15 minutes to 90 minutes interval, thereafter it gradually increased to attain values near the base level at 3 hours. In group B2 the HR after registering a gradual and significant (P<0.01) fall at 15 to 75 minutes started rising at 90 minutes interval and attained values near the base level at 6 hours interval. Its level was significantly (P<0.05) lower at 15 minutes to 90 minutes interval as compared to the base values. In the animals of group C1 the HR followed a significant (P<0.01) decrease in its values from base line only at 15 minutes interval and thereafter increased significantly (P<0.01) from 30 to 90 minutes interval and attained the base level values at 3 hours interval whereas in group C2 the HR decreased significantly (P<0.01) from base line to 15 minutes and thereafter a significant (P<0.01) increase in its values at 30 to 90 minutes interval was observed and its level has reached near base level values at 3 hours interval.

The increase in heart rate after the administration of ketamine in group C may be due to direct stimulatory effect of ketamine on the sympathetic outflow may have been the cause for this (Slogoff and Allen 1974, Waxman et al., 1980). In a study conducted by Pypendop et al. (1998) heart rate remained at a low level for up to 120 minutes after the administration of medetomidine. The decrease in heart rate and other cardiovascular parameters were proportional to the dose rates of medetomidine used in the study, being lower for low doses (1-2µg/kg) and higher for the high doses. In the present study similar results were obtained with lower and higher doses of dexmedetomidine. Kuusela et al. (2001b) have compared the clinical and cardiovascular parameters in dogs which were administered with low and high doses of levomedetomidine. Dexmedetomidine was added to the protocol to compare the effects of the two drugs. All the dogs in which dexmedetomidine was administered experienced a decrease in the heart rate though the high doses of levomedetomidine also caused a decrease in heart rate (but without any sedation or analgesia). Alpha-2 agonist action of medetomidine was thought to be the reason for a drop in the heart
rate. Gertler et al. (2001) have reported a maximum reduction of 18% in the value of heart rate with the use of dexmedetomidine and clonidine in human patients. Sinclair (2003) has observed that there can be a diminished sympathetic tone and increased systemic vascular resistance which leads to the negative cardiovascular effects of alpha-2 agonist drugs like xylazine and dexmedetomidine. Granholm et al. (2007) have found that medetomidine and dexmedetomidine were equivalent in their clinical effects and the heart rate remained below its base level values for more than 180 minutes. This could have been due to the central effects of alpha-2 adrenoceptors (Sabbe et al. 1994). Increase in the heart rate in dogs has also been reported by Rafee et al. (2015a) in dogs anaesthetized with dexmedetomidine-midazolam-ketamine. Similar findings have been observed in the present study.

4.2.3 Respiration Rate

The Mean±SE values of the respiration rate in the animals of various groups premedicated with dexmedetomidine at the dose rate of 10µg/kg (A1, B1 and C1) and 15µg/kg (A2, B2 and C2) are given in Table 4.14 and depicted in Fig. 4.14. In the animals of group A1 there was a gradual and significant (P<0.01) decrease in the respiration rate from 15 minutes to 90 minutes interval. The respiration rate was at the base level value at 3 hours interval. The lowest value of respiratory rate was recorded at 60 minutes interval. In the animals of group A2 a significant (P<0.01) reduction in the respiration rate was recorded at 15 minutes to 90 minutes interval. The lowest values were recorded at 45 minutes in the animals of group A2. In the animals of group B1 the respiration rate significantly (P<0.01) decreased at 15 minutes to 75 minutes whereas in the animals of group B2 the respiratory rate significantly (P<0.01) decreased at 15 minutes to 90 minutes interval. The least values were recorded at 60 minutes in the animals of group B1 and at 45 minutes in group B2. In the animals of group C1 and C2 the respiratory rate showed significant (P<0.01) decrease in its values at 15 minutes to 90 minutes interval. The lowest values recorded were at 75 minutes interval in both the groups.

There was a decrease in respiration rate after the administration of dexmedetomidine in the present study which confirms the findings of Gertler et al. (2001) who have reported that respiration rate was lower in the patients treated with
dexmedetomidine. Kuusela et al. (2001a) have reported significant decrease in the respiratory rate in animals after the administration of dexmedetomidine or medetomidine at the dose rates ranging from 2-40µg/kg body weight. Sinclair (2003) has reported that respiratory rate decreased after the administration of dexmedetomidine due to the CNS depression accompanying the alpha-2 agonists. Gomez-Villamandos (2005) have compared the effects of romifidine and detomidine in propofol-sevoflurane anaesthesia in dogs and found that respiration rate depressed for more than one hour with the administration of medetomidine. Kushiro et al. (2005) have reported that respiratory rate decreased after the administration of anaesthetic protocol involving midazolam-ketamine-medetomidine-sevoflurane for the whole duration of the anaesthetic period, this could have been due to the stimulation of prejunctional alpha-2 receptors present in the sympathetic nervous system. Granholm et al. (2007) have also reported that respiratory rate decreased for more than 180 minutes in dogs which were administered dexmedetomidine and medetomidine and subsequently reversed with atipamezole.

4.2.4 Blood Pressure

4.2.4.1 Systolic blood pressure

The Mean±SE values of systolic blood pressure in various groups of animals premedicated with dexmedetomidine at the dose rate of 10µg/kg (A1, B1 and C1) and 15µg/kg (A2, B2 and C2) are given in Table 4.15 and depicted in Fig. 4.15. In the animals of group A1 the values of systolic blood pressure showed an initial significant (P<0.01) rise in its values at 15 minutes time interval. After initial rise it gradually and significantly (P<0.01) decreased at 30 minutes to 90 minutes interval as compared to the base level values. At 3 hour interval the value of systolic blood pressure had regained its base level value. In the animals of group A2 the systolic blood pressure showed a similar significant (P<0.01) rise in its value at 15 minutes and thereafter it decreased significantly (P<0.01) at 30 minutes to 90 minutes interval. The systolic blood pressure gained its base level value at 3 hour interval. The systolic blood pressure in the animals of group B1 and B2 also showed an initial significant (P<0.01) increase at 15 minutes interval after which it decreased significantly (P<0.01) at 30 minutes to 90 minutes interval and at 3 hour interval it had gained the level equal to the base
values. In the animals of group C1 and C2 the systolic blood pressure showed a significant (P<0.01) increase in its values at 15 minutes to 75 minutes interval and became near normal at 3 hour interval. The systolic blood pressure values in the group C1 significantly (P<0.01) decreased at 6 hours and 24 hours whereas it were significantly (P<0.01) decreased only at 6 hours in group C2.

Gomez-Villamandos et al. (2005) have reported that the systolic blood pressure values decreased after registering an initial increase after the administration of medetomidine in dogs however the initial rise in systolic blood pressure (after administration of romifidine) was not measured because of late recordings. It was considered to be the typical findings associated with the alpha-2 agonists. Ko et al. (2013) have reported that the systolic blood pressure registered an elevation in the level of its values after the administration of ketamine in dogs premedicated with dexmedetomidine and buprenorphine, this could have been due to ketamine induced stimulatory effect on the sympathetic nervous system. Akbar et al. (2014) have reported that the systolic blood pressure showed a decrease in the level of its values after an initial rise in its values. The findings of the present study also have similar trends in the behavior of systolic blood pressure after the administration of dexmedetomidine. Jena et al. (2014) have reported that after the administration of xylazine-propofol or dexmedetomidine-propofol the systolic blood pressure values decreased in dogs at five minutes and then increased at 10-15 minutes before decreasing finally up to 60 minutes. This pattern could have been due to the stimulation of peripheral alpha_{2B} receptors. Rafee et al. (2015a) have also reported the increase in systolic blood pressure (in dogs administered with atropine-dexmedetomidine-butorphanol-midazolam-ketamine) initially followed by a decrease in its values possibly due to the effect of atropine which increased the systolic blood pressure and later on when dexmedetomidine was metabolized the systolic blood pressure values showed a decrease.

4.2.4.2 Diastolic blood pressure

The Mean±SE values of diastolic blood pressure in animals of various groups premedicated with dexmedetomidine at the dose rate of 10µg/kg (A1, B1 and C1) and 15µg/kg (A2, B2 and C2) are shown in Table 4.16 and depicted in Fig. 4.16. The
values of diastolic blood pressure in the animals of groups A1 has significant (P<0.01) rise in its values at 15 minutes time interval. After initial rise in its values, it significantly (P<0.01) decreased at 30 minutes to 90 minutes interval. At 24 hour interval the value of diastolic blood pressure was slightly lower than the base level value. In the animals of group A2 the diastolic blood pressure showed a similar significant (P<0.01) rise in its value at 15 minutes and thereafter it decreased significantly (P<0.01) at 30 minutes to 90 minutes interval. The diastolic blood pressure gained its near base level value at 3 hour interval. The diastolic blood pressure in the animals of group B1 and B2 also showed an initial significant (P<0.01) increase at 15 minutes interval thereafter which it decreased significantly (P<0.01) at 30 minutes to 90 minutes interval. It had gained the level near to the base values at 3 hour interval in group B1 and at 6 hour interval in group B2. In the animals of group C1 and C2 the diastolic blood pressure showed a significant (P<0.01) increase (as compared to the base level values) in its values at 15 minutes to 45 minutes interval. Thereafter at all the other time intervals the diastolic blood pressure was maintained near the base level in both the groups throughout the period of study.

The decrease in the level of diastolic blood pressure observed in the present study might have been due to the stimulation of peripheral alha-2 receptors (Pypendop et al., 1998). Sinclair (2003) has also reported that alpha-2 agonist drugs particularly medetomidine causes an elevation of blood pressure before influencing it negatively over time. Gomez-Villamandos et al. (2005) have reported that alpha-2 agonist drugs romifidine and medetomidine first causes an initial elevation in diastolic blood pressure before causing a drop in the values of diastolic blood pressure. Lee (2011) has reported that dexmedetomidine causes a dose dependent drop in the values of blood pressure. Bell et al. (2011) have found that the diastolic blood pressure reduced non-significantly in dogs subjected to the administration of buprenorphine and dexmedetomidine. Akbar et al. (2014) have also reported that the diastolic blood pressure remained consistently low during the period of observation in dogs sedated with medetomidine at different dose rates ranging from 15 to 60µg/kg body weight. Jena et al. (2014) have reported on the use of alpha-2 agonist xylazine and dexmedetomidine with propofol in dogs and found that the values of diastolic blood pressure showed a decrease after an initial increase in its level. This could have been due to the effect of atropine and the
stimulation of peripheral alpha$_{2B}$ receptors. *Rafee et al. (2015a)* have observed that the diastolic blood pressure declined after an initial rise in its values in dogs administered with atropine-dexmedetomidine-butorphanol-midazolam-ketamine anaesthesia. This could have been due to metabolism of dexmedetomidine and stimulation of alpha-2A receptors and inhibition of noradrenaline in the autonomic nervous system.

### 4.2.4.3 Mean Arterial Pressure

The Mean±SE values of mean arterial pressure of animals various groups premedicated with dexmedetomidine at the dose rate of 10µg/kg (A1, B1 and C1) and 15µg/kg (A2, B2 and C2) are given in Table 4.17 and depicted in Fig. 4.17. In the animals of groups A1, the mean arterial pressure showed an initial and significant (P<0.01) increase at 15 minutes time interval. Thereafter this initial rise it gradually decreased and significantly (P<0.01) lower values (as compared to the base level values) were recorded at 30 minutes to 90 minutes interval. At 3 hour interval the value of mean arterial pressure had regained its base level value. In the animals of group A2 the mean arterial pressure showed a similar significant (P<0.01) increase at 15 minutes and thereafter it declined significantly (P<0.01) at 30 minutes to 90 minutes interval. The mean arterial pressure gained its base level value at 3 hour interval. The mean arterial pressure in the animals of group B1 and B2 also showed an initial significant (P<0.01) increase at 15 minutes interval thereafter it decreased significantly (P<0.01) at 30 minutes to 90 minutes interval and at 3 hour interval it had gained the level equal to the base values. In the animals of group C1 the mean arterial pressure showed a significant (P<0.01) increase at 15 minutes to 45 minutes and thereafter it significantly (P<0.05) decreased at 60 to 75 minutes interval. It was near base level value at 90 minutes in this group. Thereafter the mean arterial pressure values were maintained near the base level throughout the remaining period of the study. In the animals of group C2 the mean arterial pressure significantly (P<0.01) increased at 15 minutes to 60 minutes interval and thereafter it decreased to the near base level at 75 minutes to 24 hours interval.

*Pypendop et al. (1998)* have also reported that the mean arterial pressure decreased in dogs after medetomidine administration. It could have been due to the stimulation of central and peripheral receptors at low and high doses respectively. *Bell*
et al. (2011) reported that both the systolic and diastolic blood pressures decreased in dogs after the administration of dexmedetomidine. Santosh et al. (2013) have reported that in dogs anaesthetized with midazolam-dexmedetomidine-ketamine, the mean arterial pressure values first increased and then decreased with the passage of time but remained within the normal physiological range. Raffee et al. (2015a) have reported that the values of mean arterial pressure decreased after an initial increase till 120 minutes of time interval in dogs (anaesthetized with atropine-dexmedetomidine-midazolam-ketamine).

### 4.2.5 Capillary Refill Time

The capillary refill time in all the animals at various time intervals recorded, was always less than 2 seconds. Cyanosis or pallor of the mucus membranes was not seen at any time interval noted in animals of any group included in the study.

Capillary refill time is an aid to adjudge the tissue perfusion along with the colour of the mucus membranes and the blood pressure. Tissue perfusion is assumed to be compromised if the mucus membrane (gum) colour is pale instead of pink and the capillary refill time is more than 1.5 seconds (Hall et al., 2001). It also provides information on the state of homeostasis and should be less than 1.5 to 2.0 seconds (Hubbell 2006, Reibold 2007). A capillary refill time of less than 2 seconds was observed in the present study confirms the findings of Girard et al. (2010) in dogs administered intravenous medetomidine or butorphanol (alone or in combination). The capillary refill time observed in the present study did not show any significant changes throughout the study period and hence the findings are in accordance with the above mentioned studies.

### 4.2.6 Haemoglobin Oxygen Saturation (Pulse Oximetry-SpO₂)

The Mean±SE values of haemoglobin oxygen saturation (SpO₂) of animals of various groups premedicated with dexmedetomidine at the dose rate of 10µg/kg (A1, B1 and C1) and 15µg/kg (A2, B2 and C2) are shown in Table 4.18 and depicted in Fig. 4.18. In the animals of groups A1, the SpO₂ was significantly (P<0.05) lower at 15 minutes as compared to the baseline values, thereafter it further decreased significantly (P<0.01) at 30 minutes interval. It increased non-significantly thereafter at 1 and 3
hours interval followed by a significant (P<0.05) decrease at 6 hours before reaching the base value at 24 hours. In the group A2 it showed significant (P<0.01) decrease at 15 and 30 minutes and then it increased non-significantly at 1 and 3 hours however its value decreased significantly (P<0.05) at 6 hours interval. The SpO\(_2\) in the animals of group B1 showed significant (P<0.01) decrease in its values at 15 minutes, 30 minutes and 6 hours and also significant (P<0.05) decrease at 1 hour interval. In the animals of group B2 it showed significantly (P<0.05) low values at 15 minutes which further decreased significantly (P<0.01) at 30 minutes followed by increase at 1 hour to 24 hour interval. In the animals of group C1 the SpO\(_2\) showed an increase at 15 minutes interval followed by a decrease at 30 minutes interval, thereafter which it increased from 1 to 24 hour. In the animals of group C2 it was significantly (P<0.05) lower at 15 minutes which further decreased at 30 minutes to 1 hour interval, thereafter it increased and equalized the near base value at 24 hours interval. The haemoglobin oxygen saturation in the animals of all the groups was consistently maintained above 95% and cyanosis of the mucus membranes was not seen at any time interval in the all groups of animals.

*Uilenreef et al.* (2008) have reported non-significant (P>0.05) change in the values of SpO\(_2\) in dogs anaesthetized with dexmedetomidine-buprenorphine-propofol-isoflurane. No significant change was found at different time intervals between different groups. *Santosh et al.* (2012) have observed that the SpO\(_2\) values differed significantly at 30 and 45 minutes, and 105 minutes in dogs anaesthetized with dexmedetomodine-midazolam-ketamine and dexmedetomodine-midazolam-fentanyl-ketamine respectively. *Singh et al.* (2013) have reported that the SpO\(_2\) values were significantly lower in animals treated with fentanyl-dexmedetomidine-thiopentone. This could have been due to a decrease in respiratory rate in the animals administered with dexmedetomidine as premedicant. *Santosh et al.* (2013) have reported that the SpO\(_2\) values decreased at some time points up to 45 minutes time interval in dogs anaesthetized with midazolam-dexmedetomidine-ketamine or midazolam-dexmedetomidine-fentanyl-ketamine. Decrease in SpO\(_2\) was observed at higher doses of dexmedetomidine which could have been due to vasoconstriction caused by dexmedetomidine.
4.2.7 Electocardiography (ECG)

The electrocardiographic changes observed in the animals of various groups are shown in Fig. 4.19. In the animals of group A1 increased P-R and Q-T interval and inverted T waves were observed at 30 minutes interval. In the animals of group A2 sinus arrhythmia was observed at 30 minutes interval. In the animals of group B1 biphasic and inverted T wave at 15 minutes interval were observed whereas in the group B2 bradyarrhythmia was observed at 30 minutes. The arrhythmia had disappeared at 60 minutes. In the animals of group C1 elevated T waves were observed at 30 minutes interval whereas in the animals of group C2 biphasic T waves were observed at 30 minutes. In the animals of all the groups the morphology of the sinus complex was inconspicuous at 0, 3, 6 and 24 hours interval.

Ko et al. (1994) have administered atropine-medetomidine-etomidate to dogs and observed that bradycardia and SA and AV blocks occurred within two minutes of the administration of these drugs, however the blocks disappeared within 8 minutes of the administration the drugs. Amarpal et al. (2002) have recorded bradycardia, increased Q-T interval, biphasic T wave, inverted T wave, increased amplitude of T wave, sinus dysrhythmia, increased P-R interval and second degree A-V blocks in goats administered with spinal romifidine. Bradycardia and increased Q-T interval could have been due to a slow speed of depolarization of the ventricles and the inverted T wave could have been a result of hypoxia of the ventricles (Tilley 1985), whereas the sinus dysrhythmia and second degree A-V block could be due to vagal stimulation observed with the use of romifidine. Kuusela et al. (2002) while experimenting with dexmedetomidine in dogs found that the second degree A-V blocks were observed after the administration of dexmedetomidine when the bradycardia was most prominent and bradycardia and A-V block were the most common finding with the use of alpha-2 agonists in dogs. Kinjavdekar et al. (2006) have reported the incidence of bradycardia, increased PR and QT interval, increased amplitude of T-wave, sinus dysrhythmia, biphasic and inverted T wave and second degree A-V blocks in goats administered with romifidine and lidocaine. Arrhythmia and second degree A-V block has also been recorded by Emami et al. (2007) in dogs administered with atropine-romifidine-ketamine and atropine-xylazine-ketamine. Ahmad et al. (2012) have recorded that the P wave amplitude decreased in dogs administered with dexmedetomidine as the
amplitude directly correlated to the heart rate. The Q-T interval increased in a reverse relation to the heart rate.

4.3 Haematological Parameters

4.3.1 Haemoglobin

The Mean±SE values of haemoglobin of animals in various groups premedicated with dexmedetomidine at the dose rate of 10µg/kg (A1, B1 and C1) and 15µg/kg (A2, B2 and C2) are given in Table 4.20 and depicted in Fig. 4.20. The values of haemoglobin in the animals of group A1 showed significant decrease (P<0.01) in its values at 30 minutes to 6 hours interval. The animals of group A2 showed non-significantly (P<0.05) decreased values throughout the period of the study. Lowest values were recorded at 6 hr and 1 hr interval in the groups A1 and A2 respectively. In group B1 the haemoglobin showed a significant (P<0.05) decrease at 1 hr and 6 hr interval. The animals of group B2 showed significant (P<0.05) decrease in haemoglobin level at 6 hours only. The animals of group C1 showed non-significant changes in values of haemoglobin over the entire period of study whereas the animals of group C2 showed significant (P<0.05) decrease in haemoglobin values at 6 hours time interval. In all the animals of group A, B and C the haemoglobin values returned near to their base level at 24h interval.

A decrease in the haemoglobin level observed in the present study confirms the findings of Jadon et al. (1995) who observed a non significant decrease in the values of Hb in detomidine-ketamine anaesthetized dogs. The decrease observed in the study could have been due to pooling of blood in the storage organ (spleen) as a result of decrease in sympathetic tone by dexmedetomidine (Kilic 2004, Pawde 2000). Mazumdar et al. (2015) have reported decrease in the values of haemoglobin in dogs administered with dexmedetomidine at 20 and 40µg/kg body weight. The decrease in haemoglobin level might be due to the pooling of blood in spleen of the dogs due to reduced sympathetic impulses (Skarda and Muir 1996).

4.3.2 Total Erythrocyte Count (TEC)

The Mean±SE values of total erythrocyte count (TEC) of animals in various groups premedicated with dexmedetomidine at the dose rate of 10µg/kg (A1, B1 and
C1) and 15µg/kg (A2, B2 and C2) are given in Table 4.21 and depicted in Fig. 4.21. The values of TEC in the animals of group A1 and A2 showed non-significant decrease 30 minutes to 6 hours time intervals. In the animals of group B1 the TEC values showed significant (P<0.05) decrease at 30 minutes. It further decreased significantly (P<0.01) at 1 hours and 6 hours before reaching the baseline value at 24 hrs. In the animals of group B2 the values of TEC recorded non-significant(P>0.05) decline at 30 minutes and 1 hour interval which has regained the base level values at 6 hours interval. In the animals of group C1 the TEC values were significantly (P<0.05) lower at 1 hours interval whereas in the animals of group C2 TEC values recorded a non-significant (P<0.05) decrease in its values at 30 minutes to 6 hour interval. The values of TEC had reached to near normal level by 24 hours in all the groups of animals.

Fazio et al. (2015) have reported non-significant decrease in TEC values in dogs and cats which were anaesthetized with acepromazine-zloazepam-dexmedetomidine-tramadol and medetomidine-fentanyl-propofol respectively. Zlateva and Marinov (2015) have found that the TEC values decreased throughout the study period in cats anaesthetized with xylazine-ketamine-isoflurane, acepromazine-propofol-isoflurane or aepromazine-meloxicam-propofol-isoflurane. The variation in the value of this parameter was thought to be due to the direct effect of drug and the decreased release of catecholamines, it was in accordance with the studies of Wilson et al. (2004) and Zlateva and Marinov (2015). Transient decrease in values of TEC in dogs treated with epidural ketamine alone or with xylazine has been reported by Abdul et al. (2015). It may be due to rapid systemic absorption of ketamine/xylazine from the epidural site which caused a shift in the body fluid from extravascular to the intravascular compartment in order to maintain the cardiac output (Mion and Villevieille 2013). Mazumdar et al. (2015) while studying the effects of dexmedetomidine (alone) given to dogs at 20 and 40 µg/kg body weight found decreased level of TEC which could be due to the result of splenic pooling of the RBCs.

4.3.3 Erythrocyte Sedimentation Rate (ESR)

The Mean±SE values of erythrocyte sedimentation rate (ESR) of animals in various groups premedicated with dexmedetomidine at the dose rate of 10µg/kg (A1,
B1 and C1) and 15µg/kg (A2, B2 and C2) are given in Table 4.22 and depicted in Fig. 4.22. The ESR, in animals of group A1 showed a significant (P<0.01) increase in its value at 1 hr interval whereas in the group A2 it recorded a significant (P<0.05) increase at 30 minutes time interval. It further increased significantly (P<0.01) at 1 hr to 6 hr time interval. In the animals of groups B1 and B2 the values of ESR recorded a significant (P<0.01) increase in its values at 1 hours interval. In the animals of group C1 the ESR recorded a significant (P<0.01) increase at 1 to 6 hours interval whereas in the animals of group C2 it recorded a significant (P<0.05) increase in its values at 1 hr to 6 hr time interval. Hence it was observed that the ESR recorded a rise in its values in all the groups of animals which regained the base level values at 24 hours.

The increase in ESR level may be due to the stress during the analgesic period and due to an increase in ACTH or due to the effect of subcortical pathways involved in the ACTH regulation (Steyn 1969). Ajadi et al. (2013) have reported an increase in the level of ESR up to three days after arthroscopy surgery in dogs administered with atropine-xylazine-diazepam-ketamine anaesthesia. It was thought to be an indicator of inflammation in the dogs operated for arthroplasty. A non-significant decrease in ESR was reported by Akbar et al. (2014) in dogs administered with medetomidine at different dose rates. Akbar et al. (2015) have reported non-significant increase in ESR in cats administered with medetomidine-ketamine or medetomidine alone.

4.3.4 Total Leucocyte Count (TLC)

The Mean±SE values of total leucocyte count (TLC) of animals in various groups premedicated with dexmedetomidine at the dose rate of 10µg/kg (A1, B1 and C1) and 15µg/kg (A2, B2 and C2) are given in Table 4.23 and depicted in Fig. 4.23. The level of TLC decreased gradually and significantly (P<0.01) in the animals of group A1 and A2 up to 1 hour interval. In group B1 it was significantly (P<0.01) lower at 30 minutes to 1 hour interval whereas in the animals of group B2 it was significantly (P<0.01) lower at 1hr and 6 hr time interval as compared to control. In the animals of group C1 the values of TLC were significantly (P<0.01) lower at 1 hr time interval. The values of TLC were significantly (P<0.01) lower at 1 hr and 6 hr interval in the animals of group C2. The values of TLC, after recording an initial decline returned near to the base level values by 24 hour in all the animals of different groups.
Inter compartmental shift of fluid and the pooling of cells in spleen could explain the observations made in the study. **Jena et al. (2014)** have studied the effects of detomidine-propofol in dogs and found that the values of TLC first increased and then decreased at the end of surgery. This could be explained by polling of cells in the spleen and other reservoirs due to decreased sympathetic tone (**Soliman et al., 1965**). **Akbar et al. (2014)** have reported that the TLC values did not show any significant changes in dogs administered with dexmedetomidine alone. The increased dose levels of dexmedetomidine results in higher order of TLC. This was not observed in the present study possibly due to the administration of induction/maintenance agents as per the anaesthetic protocol. **Kumar et al. (2014)** have recorded a decrease in the values of TLC throughout the period of study which was explained by pooling of cells in spleen due to reduced sympathetic activity in the goats.

### 4.3.5 Differential Leucocyte Count (DLC)

#### 4.3.5.1 Neutrophils

The Mean±SE values of neutrophils of animals in various groups premedicated with dexmedetomidine at the dose rate of 10µg/kg (A1, B1 and C1) and 15µg/kg (A2, B2 and C2) are given in Table 4.24 and depicted in Fig. 4.24. The values of neutrophils in the animals of group A1 recorded significant (P<0.01) increase in its values at 6 hr interval. Whereas in the animals of group A2 its values showed a non-significant (P<0.01) increase till 6 hr time interval, thereafter it decreased non-significantly to reach near the base value at 24 hours interval. The animals of group B1 showed a non-significant (P<0.01) increase in neutrophil values whereas in the animals of group B2 its value were significantly (P<0.05) higher at 1 hr time interval as compared to the 0 hour values. Animals of groups C1 showed significant (P<0.05) increase in the value of neutrophils at 6 hr time interval. In the group C2 the neutrophils recorded non-significant (P<0.01) increase in its values till 1 hr interval and then declined non-significantly to reach near base value by 24 hours. The values of neutrophils had regained their base level by 24h interval in all the groups of animals.

Increase in neutrophil level was thought to be the stress in the animals included in the present study (**Ameerjan 1993, Tiwari et al., 1999**). However **Singh et al. (2010)** have reported a non-significant change in the values of neutrophils in canine
patients administered with atropine-diazepam-thiopentone-sevoflurane/isoflurane. Costa et al. (2013) have reported that the values of neutrophils did not show any significant changes in their level in dogs administered propofol and tramadol, probably due to propofol granting stability to the number of neutrophils. Umar and Adam (2013) have reported that the neutrophils increased in dogs administered medetomidine-ketamine during the entire study period however the values remained in the normal physiological range for dogs. Jena et al. (2014) have observed an increase in neutrophil count due to the stress borne by the dogs during the anaesthetic period. Rafee et al. (2015b) have attributed the non-significant changes in the neutrophil numbers due to dexametomidine which obtunds the neuroendocrine response in animals. Increase in number of neutrophils has also been reported by Akbar et al. (2015) and Canpolat et al. (2016) however Abdul et al. (2015) have reported a significant decrease in the number of neutrophils. The present study agrees with the findings of above mentioned studies which have also documented an increase in neutrophil numbers in various groups of animals administered with an alpha-2 agonist drug with other induction agents.

4.3.5.2 Lymphocytes.

The Mean±SE values of lymphocytes in animals of various groups premedicated with dexametomidine at the dose rate of 10µg/kg (A1, B1 and C1) and 15µg/kg (A2, B2 and C2) are given in Table 4.25 and depicted in Fig. 4.25. The mean values of lymphocytes decreased gradually and significantly (P<0.01) at 1 hr and 6 hr interval in the animals of group A1. In the animals of group A2 its value was significantly (P<0.05) low at 30 minutes. It further decreased significantly (P<0.01) at 1 hr time interval in these animals. In the animals of group B1 it showed only non-significant (P<0.01) decrease in its values at different time intervals however its values were significantly (P<0.01) low at 30 minutes and 1 hr in the animals of group B2. The animals of group C1 showed significantly (P<0.01) decreased values of lymphocytes at 30 minutes and the group C2 recorded significantly (P<0.01) low values at 30 minute and 1 hr interval. In the animals of all the groups the level of lymphocyte returned to the near base levels at 24h interval.

The decrease in the lymphocyte count observed in the present study may be due to the suppressive effects of detomidine on the immune system of body possibly due to
increased cortisol concentrations following detomidine administration \citep{Wood1992, Khan2003}. \textit{Ajadi et al.} \citeyearpar{2013} have observed an increase in the values of lymphocytes 3 days after surgery when the number of neutrophils had decreased in dogs operated for arthroplasty under atropine-xylazine-diazepam-ketamine anaesthesia. \textit{Costa et al.} \citeyearpar{2013} have observed that the values of lymphocytes did not show any significant changes in their level in dogs administered propofol and tramadol. The increased levels of norepinepherine might have caused the reduction in the lymphocyte numbers. \textit{Umar and Adam} \citeyearpar{2013} have also observed that the lymphocytes decreased in dogs administered medetomidine-ketamine during the entire study period however the values remained in the normal physiological range in dogs. \textit{Akbar et al.} \citeyearpar{2015} have reported a non-significant increase in number of lymphocytes in cats administered with medetomidine alone or in combination with ketamine whereas \textit{Abdul et al.} \citeyearpar{2015} and \textit{Canpolat et al.} \citeyearpar{2016} have reported a significant decrease in the number of lymphocytes which could be due to the stress borne by the animal during the study period.

4.3.5.3 Monocytes

The Mean±SE values of monocytes of animals in various groups of animals premedicated with dexmedetomidine at the dose rate of 10µg/kg (A1, B1 and C1) and 15µg/kg (A2, B2 and C2) are given in Table 4.26 and depicted in Fig. 4.26. The values of monocytes showed significant (P<0.05) decrease at 6 hr interval in group A1 whereas its values were significantly (P<0.01) high at 30 minute, 1 hr and 6 hr time interval in the animals of group A2. In the animals of group B1 its values were significantly (P<0.01) low at 30 minute, 1 hr and 6 hr whereas its values were significantly (P<0.01) low at 1 hr in the animals of group B2. In the animals of group C1 the values of monocytes showed non-significant (P<0.05) changes whereas in the animals of group C2 significantly (P<0.05) high values were observed at 6 hr time interval.

\textit{Singh et al.} \citeyearpar{2010} have reported a non-significant fluctuating change in the values of monocytes in dogs administered with atropine-diazepam-thiopentone and sevoflurane or isoflurane which might have been due to least adverse effects of sevoflurane or isoflurane. \textit{Costa et al.} \citeyearpar{2013} have reported that the values of
monocytes did not show any significant changes in their level in dogs administered propofol and tramadol because propofol promoted stability in the number of the cells. A significant decrease in the values of DLC has also been reported by Akbar et al. (2014) who administered medetomidine as a solo drug in dogs. Abdul et al. (2015) have attributed a significant decrease in the level of granulocytes to the stress involved in the procedure.

4.3.5.4 Eosinophils

The Mean±SE values of eosinophils in various groups of animals premedicated with dexmedetomidine at the dose rate of 10µg/kg (A1, B1 and C1) and 15µg/kg (A2, B2 and C2) are given in Table 4.27 and depicted in Fig. 4.27. The values of eosinophils in the animals of group A1 showed significant (P<0.01) decrease in its values at 30 minute. In the animals of group A2 it was non-significant (P<0.01) changes in its values over the entire period of study. In the animals of group B1 the eosinophils showed non-significant (P<0.01) increase in its values at 1 hr time interval. In the animals of group B2 eosinophils recorded non-significant (P<0.01) change in its values over the entire study period. The values of eosinophils recorded in the animals of group C1 were significantly (P<0.05) high at 6 hr interval whereas in the animals of group C2 its values were significantly (P<0.05) high at 1 hr and 6 hr interval. It was observed that the level of eosinophils showed an irregularly decreasing or increasing pattern in its values in the animals of all the groups and remained within normal physiological range throughout the period of study in all the groups of animals.

Slight changes in the eosinophil level observed in the present study may be due to the suppressive effects of detomidine on the immune system of the animals possibly due to increased cortisol concentrations following detomidine administration. Singh et al. (2010) have also reported a non-significant fluctuating change in the values of eosinophils in dogs administered with atropine-diazepam-thiopentone and sevoflurane or isoflurane. Costa et al. (2013) have reported that the values of eosinophils did not show any significant changes in their level in dogs administered propofol and tramadol because propofol promoted a stability in the number of the cells. A significant decrease in the value of DLC has also been reported by Akbar et al. (2014) with the administration of medetomidine alone in dogs. Akbar et al. (2015) have also reported
that the values of eosinophils increased significantly in cats administered with medetomidine alone or in combination with ketamine.

4.3.6 Packed Cell Volume (PCV)

The Mean±SE values packed cell volume of (PCV) in various groups of animals premedicated with dexmedetomidine at the dose rate of 10µg/kg (A1, B1 and C1) and 15µg/kg (A2, B2 and C2) are given in Table 4.28 and depicted in Fig. 4.28. The mean PCV values of the animals in group A1 showed a gradual and significant (P<0.05) decrease in its values at 30 minute and 1 hour time interval. The values of PCV in the animals of group A2 was significantly (P<0.05) lower at 30 minute and 24 hour interval as compared to 0 hr value. In the groups B1 and B2 the PCV showed non-significant (P<0.01) decrease in its values at all the time intervals but reached near the base values at 24 hr interval. Animals of group C1 showed non-significant (P<0.01) decrease in PCV values which reached near the base level values at 24 hr interval, however in the animals of group C2 significantly (P<0.05) decreased level of PCV was observed at 30 minute interval.

The decrease in PCV observed in the present study could have been due to pooling of blood in the storage organ spleen as a result of decrease in sympathetic tone by dexmedetomidine (Pawde 2000, Kiliç 2004). Singh et al. (2010) have also found reduction in the values of PCV till 2 hr interval in dogs administered with atropine-diazepam-thiopentone and sevoflurane or isoflurane. Abdul et al. (2015) and Mazumdar et al. (2015) have also reported decrease in the values of PCV in dogs administered epidural ketamine-xylazine and dexmedetomidine alone.

4.3.7 Erthrocytic Indices.

4.3.7.1 Mean Corpuscular Volume (MCV)

The Mean±SE values of mean corpuscular volume (MCV) in various groups of animals premedicated with dexmedetomidine at the dose rate of 10µg/kg (A1, B1 and C1) and 15µg/kg (A2, B2 and C2) are given in Table 4.29 and depicted in Fig. 4.29. The MCV of the animals in various groups of animals showed a non significant (P<0.01) decrease in its values throughout the period of the present study. In group A1 and A2 the minimum level was observed at 1 hr time interval, in group B1 at 1 hr and
in group B2 at 6 hr time interval. The lowest levels were recorded at 6 hr and 1 hr in groups C1 and C2 respectively. Thereafter the level of MCV started increasing and had attained the base at 24 hour in all the groups of animals.

Peighambarzadeh et al. (2014), Abdul et al. (2015), Ahmed et al. (2015) and Fazio et al. (2015) and have observed non-significant changes in MCV of Lori-Bakhtiar sheep, dogs, camel (minimum changes in CBC) and cats respectively, subjected to the administration of ketamine and xylazine, whereas Canpolat et al. (2016) have reported a non-significant change in the MCV of goats injected with ketamine-medetomidine. Apart from the above studies only Al-Sobayil et al. (2016) have reported a significant (P<0.05) increase in level of MCV in camels treated with xylazine-ketamine which could have been due to splenic compromise during and stress involved in the procedure. The present study is in agreement with the above mentioned studies which included non-significant changes in the value of MCV in different animals anesthetized with different anaesthetics.

4.3.7.2 Mean Corpuscular Haemoglobin (MCH)

The Mean±SE values of mean corpuscular haemoglobin (MCH) in various groups of animals anaesthetized with dexmedetomidine at the dose rate of 10µg/kg body weight (A1, B1 and C1) or 15µg/kg body weight (A2, B2 and C2) are given in Table 4.30 and depicted in Fig. 4.30. The values of MCH of the animals in various groups showed a non significant (P>0.01) decrease in its values over the entire period of study. In the animals of group A1 and A2 the MCH level decreased non-significantly (P>0.01) at 30 minute and 1 hr time interval followed by non-significant (P>0.01) increase near to the base values at 24h interval. In the animals of groups B1 and B2 the MCH decreased non-significantly (P>0.01) at 1 and 6 hr respectively before reaching near base value at 24 hours interval. In the animals of group C1 and C2 groups the level of MCH first increased gradually at 30 minutes and 1 hour interval and then it decreased gradually and non-significantly (P>0.01) at 6 hr interval and attained the value equivalent to the base level at 24h interval.

Canpolat et al. (2016) have reported a non-significant change in the MCH in goats injected with ketamine-medetomidine. Apart from the above study only Al-Sobayil et al. (2016) have reported a significant increase in level of MCH in camels
treated with xylazine-ketamine which could have been due to splenic compromise and stress involved in the procedure. The present study is in agreement with the studies mentioned above which comprised of non-significant changes in the value of MCH in different groups of animals anesthetized with different combinations of the drugs used in this study.

4.3.7.3 Mean Corpuscular Haemoglobin Concentration (MCHC)

The Mean±SE values of mean corpuscular haemoglobin concentration (MCHC) in the animals of various groups anaesthetized with dexmedetomidine at the dose rate of 10µg/kg body weight (A1, B1 and C1) or 15µg/kg body weight (A2, B2 and C2) are given in Table 4.31 and depicted in Fig. 4.31. The changes in MCHC values in the animals of different groups were non-significant (P<0.01) throughout the period of this study. Mean corpuscular haemoglobin concentration values in the animals of group A1 and A2 fluctuated non-significantly. Similarly the animals of groups B1 and B2 showed gradual and non-significant decrease in its values up to 6 hr interval and equated the base level values at 24 hr. In group C1 and C2 the values of MCHC showed non-significant decrease at 6 hr and 1 hr interval respectively and its values has reached to near normal at 24 hours interval.

Non significant changes in the values of MCHC have been reported by Casas-Diaz et al. (2011) who have reported a decline in the level of MCHC in Iberian ibex anaesthetized with xylazine-ketamine which was thought not to be associated with pre capture handling and the drugs administered. Umar and Adam (2013) and Umar and Wakil (2013) have reported that there were non-significant changes in the value of MCHC in dog and Sahel goats respectively, anaesthetized with ketamine and medetomidine in both the studies. The present study is in agreement with the studies mentioned above which comprised of non-significant changes in the values of MCHC in different species of animals anaesthetized with the respective drugs.

4.4 Biochemical Parameters

4.4.1 Serum Glucose

The Mean±SE values of serum glucose levels in animals of various groups anaesthetized with dexmedetomidine at the dose rate of 10µg/kg body weight (A1, B1
and C1) or 15µg/kg body weight (A2, B2 and C2) are given in Table 4.32 and depicted in Fig. 4.32. The serum glucose level in the animals of group A1 and A2 showed a gradual and significant (P<0.01) increase in its values at 30 minutes to 6 hr time interval and fell back to the base level values at 24 hour interval. The glucose levels in groups B1 and B2 were significantly (P<0.01) higher at 30 minutes to 6 hr time interval. Similarly in the animals of group C1 and C2 the glucose levels were significantly (P<0.01) higher at 30 minutes to 6 hr time interval as compared to the 0 hour values. The glucose levels of all the animals in various groups returned near to the base level values at 24 hour time interval.

The increased level of glucose observed in this study may be attributed to either insulin suppression by alpha-2 agonists or to increased glucose production in the liver (Feldberg and Symonds 1986). Hyperglycaemia in dogs after medetomidine-ketamine anaesthesia should be considered to be an important side effect of medetomidine. Ambrisko et al. (2005). Singh et al. (2010) have also reported increase in glucose level in dogs anaesthetized with atropine-diazepam-thiopentone-sevoflurane/isoflurane and the increase was attributed to anoxia (liver glycogen is unstable in anoxic condition and is converted to glucose) during anaesthesia or due to glucocorticoids released during anaesthesia. Ahmad et al. (2012) have attributed the rise in glucose levels in dogs administered dexmedetomidine to the inhibition of insulin secretion from pancreas by the activity of the drug on alpha-2 receptors of the beta cells. Similarly Restituti et al. (2012) attributed the rise in glucose level of dogs administered dexmedetomidine to suppressed insulin release from pancreatic beta cells by the stimulation of α2A receptors of beta cells. Harsoor et al. (2016) have opined that dexmedetomidine caused stable blood glucose levels as compared to the placebo group in the study and hence it was assumed that it obtunded the metabolic stress response in major surgeries in humans.

4.4.2 Serum Insulin

The Mean±SE values of serum insulin levels in animals of various groups administered with dexmedetomidine at the dose rate of 10µg/kg body weight (A1, B1 and C1) or 15µg/kg body weight (A2, B2 and C2) are given in Table 4.33 and depicted in Fig. 4.33. The insulin level in the animals of group A1 showed a significant (P<0.01) decrease at 1 and 6 hr interval. The animals of group A2 showed a gradual and
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Significant (P<0.05) decrease its values at 30 minutes which was followed by a further significant (P<0.01) decrease at 1 and 6 hr interval. In the animals of group B1, B2, C1 and C2 the level of insulin decreased gradually and significantly (P<0.05) at 30 minute which further decreased significantly (P<0.01) at 1 hr and 6 hr intervals. The lowest level of insulin were recorded at the interval of 6 hrs in all the groups of animals. The insulin level regained the value equivalent to the base level at 24 hours time interval in all the groups of animals.

The decrease in insulin level observed in the present study could be explained by the action of alpha-2 adrenergic drug causing suppression of insulin release from pancreatic beta cells by the stimulation of alpha-2 receptors of beta cells (Hsu and Hummel 1981) and by the stress response to anaesthesia causing elevation of cortisol which acts opposite of insulin in the body (Djik et al., 2003). Ambrisko et al. (2005) have reported that hypoinsulinaemia in dogs after medetomidine-ketamine anaesthesia should be considered to be an important side effect of medetomidine. Ahmad et al. (2012) have attributed the decrease in insulin level in dogs administered dexmedetomidine due to the inhibition of insulin secretion from pancreas by the activity of the drug on alpha-2 receptors of the beta cells. Similarly Restituti et al. (2012) have assigned the cause of diminished insulin levels in dogs administered with dexmedetomidine due to the suppressed insulin release from pancreatic beta cells by the stimulation of α2A receptors of beta cells.

4.4.3 Serum Cortisol

The Mean±SE values of serum cortisol levels in animals of various groups administered with dexmedetomidine at the dose rate of 10µg/kg body weight (A1, B1 and C1) or 15µg/kg body weight (A2, B2 and C2) are given in Table 4.34 and depicted in Fig. 4.34. The serum cortisol levels in the animals of groups A1 and A2 showed gradual and significant (P<0.01) decrease in its values at 30 minutes to 24 hr interval. The level of cortisol was slightly lower even at 24 hr interval in both the groups. In the animals of group B1 and B2 the level of cortisol showed a gradual and significant (P<0.01) increase at 1 hr and 6 hr interval as compared to the base value. Its level had equalized the base level at 24hr interval. Similarly in the animals of group C1 and C2 the cortisol level showed a gradual and significant (P<0.01) increase at 1 hr and 6 hr
intervals. The cortisol level had returned to the base level values at 24 hours in all groups of animals.

De Coster et al. (1987, 1988) have reported that the plasma concentration of cortisol decreased significantly (P<0.05) by the administration of etomidate and its analogue R-8110, because etomidate inhibits the enzyme 11β-hydroxylase in the adrenal gland. Similarly Frangen et al. (1984), Bloomfield and Noble (2006), Brinker et al. (2007), Forman (2011) and Ge et al. (2013) have reported the incidence of adrenal insufficiency resulting in decreased plasma cortisol levels after administration of etomidate. It was recorded that detomidine exerts no effect (Raekallio et al. 1991) and slightly negative effect (Carroll et al., 1997) on the plasma cortisol concentrations in horses and ponies respectively. Alpha-2 agonists are known to reduce the stress response to surgery in dogs (Ko et al., 2000). Djik et al. (2003) while studying the effects of detomidine in horses found that detomidine causes decrease in the plasma cortisol which increases after the antagonism of detomidine. These observations are in agreement with earlier studies mentioned above, which showed that the adrenal gland suppression caused by etomidate results in lower plasma cortisol concentrations up to 12 hours (Annane et al. 2002, 2003), up to 24 hours (Lipinen-Friedman 2007, Sprung 2008) and up to 72 hours (Annane 2005). Alterations (increase) in the level of cortisol immediately after administration of anaesthesia or surgery has also been recorded by Bhardwaj et al. (2011) in dogs which could be due to stimulation of HPA (hypothalamo-pituitary-adrenal) axis, effects of restraining or blood collection. Ahmad et al. (2012) found a non-significant (P<0.05) decrease in the level of cortisol in a study involving application of dexmedetomidine alone and in combination with midazolam, fentanyl and ketamine in dogs. In the present study the decrease in the level of cortisol in group A1 and A2 is assumed to be due to the negative impact of etomidate on the synthesis of cortisol by the adrenal gland (Bloomfield and Noble 2006, Brinker et al. 2007, Forman 2011 and Ge et al. 2013). In the animals of group B1 and B2, the non-significant effect of dexmedetomidine and propofol on cortisol levels was probably the reason for the elevated levels of cortisol. Van Hemelrijk et al. (1995), Zhang et al. (2000) and Du et al. (2015) have recorded that propofol does not inhibit the elevation of cortisol levels in surgical, anaesthesia and anaesthesia cases respectively. The elevated levels of cortisol in group B1 and B2 is in agreement with these studies.
Elevated levels of cortisol in group C1 and C2 as a result of dexmedetomidine and ketamine are in agreement with the findings of Ambrisko et al. (2005) who have recorded increase in cortisol level in dogs administered with ketamine alone, the effect may be due to the blockade of reuptake of norepinepherine at the presynaptic membrane of adrenergic neurons resulting in high level of norepinepherine in the blood circulation.

4.4.4 Total Protein

The Mean±SE of the values of total protein levels in animals of various groups administered with dexmedetomidine at the dose rate of 10µg/kg body weight (A1, B1 and C1) or 15µg/kg body weight (A2, B2 and C2) are given in Table 4.35 and depicted in Fig. 4.35. The mean values of total protein showed a significant (P<0.05) decrease in the animals of group A1 at 6 hr interval however in the animals of group A2 a non-significant decrease in its values was recorded at various time intervals which had equalized the base level at 24 hours. In the animals of group B1 the total protein values showed significant (P<0.05) decrease at 1 hr interval which further decreased significantly (P<0.01) at 6 hr interval. At 24 hour interval it had reached the baseline values. In the animals of group B2 the level of total protein decreased significantly (P<0.05) only at 6 hr interval. In the animals of groups C1 the total protein level decreased significantly (P<0.05) at 6 hr whereas in the animals of group C2 it was significantly (P<0.05) lower at 1 to 6 hr intervals. The total protein values had reached near the base line at 24 hour in both the groups of animals.

Pascoe et al. (2006) have also reported non-significant changes in values of total protein in dogs subjected to three different CRIs of dexmedetomidine. Singh et al. (2010) and Kalim et al. (2011) have recorded non-significant decrease in total protein values in dogs and buffalo calves respectively, anaesthetized with atropine-diazepam-thiopentone-isoflurane/sevoflurane and epidural bupivacaine-medetomidine in that order. Similarly non-significant changes in the values of total protein have also been recorded by Çamkerten et al. (2013) in Greyhound dogs administered with ketamine-xylazine. The observations in the present study are in agreement with the studies mentioned above which comprised of non-significant changes in the values of total protein in different groups with different anaesthetic combinations.
4.4.5 Serum Albumin

The Mean±SE values of serum albumin levels in animals of various groups administered with dexmedetomidine at the dose rate of 10µg/kg body weight (A1, B1 and C1) or 15µg/kg body weight (A2, B2 and C2) are given in Table 4.36 and depicted in Fig. 4.36. The albumin level in the animals of Group A1 and A2 showed a gradual but significant (P<0.01) decrease in its values at 1 and 6 hour intervals as compared to 0 hour values. The level of albumin in the animals of group B1 was significantly (P<0.01) lower at 1 hour as compared to the 0 hour values and in the animals of group B2 albumin level was significantly (P<0.01) lower at 1 hour and 6 hours (P<0.05) intervals. In the animals of group C1 a significant (P<0.05) decrease in values of albumin was recorded at 30 minute which further decreased significantly (P<0.01) at 1 hr to 6 hours interval. Animals of group C2 showed decrease in the value of albumin which was significant (P<0.05) at 6 hour interval. Albumin level had reached near or equal to the base level values at 24 hours interval in all groups of animals.

Jadon et al. (1995) have recorded a decrease in the albumin level at 6 to 24h after administration of detomidine and ketamine in dogs which was assumed to be due to haemodilution. Aithal et al. (2001) have reported a significant decrease in albumin levels in the goats administered with intrathecal romifidine-ketamine. Reduction of albumin levels has also been reported by Singh et al. (2010) and Fararh et al. (2011) in dogs and buffalo calves anaesthetized with atropine-diazepam-thiopentone-isoflurane/sevoflurane and xylazine-butorphanol-ketamine respectively. Similarly Çamkerten et al. (2013) have also described decrease in albumin levels in Greyhound dogs administered with xylazine-ketamine.

4.4.6 Serum Urea Nitrogen

The Mean±SE values of serum urea nitrogen levels in animals of various groups administered with dexmedetomidine at the dose rate of 10µg/kg body weight (A1, B1 and C1) or 15µg/kg body weight (A2, B2 and C2) are given in Table 4.37 and depicted in Fig. 4.37. The serum urea nitrogen levels in the animals of group A1 increased significantly (P<0.01) at 1 hour interval whereas it showed non-significant (P<0.01) increase in its values in the animals of group A2. In the animals of group B1 the serum urea nitrogen levels increased significantly (P<0.05) at 1 hour time.
intervals whereas it increased significantly (P<0.01) at 1 hour and 6 hr interval in the animals of group B2. In the animals of group C1 serum urea nitrogen levels increased significantly (P<0.01) at 30 minutes to 6 hour interval whereas it showed non-significant increase in the group C2. Its level had reached near normal by 24 hours in all the groups of animals.

Jadon et al. (1995) have recorded increase in the level of serum urea nitrogen in dogs anaesthetized with detomidine-ketamine which was assigned to the renal, pre-renal and post renal changes. Non-significant changes in blood urea nitrogen have been reported by Aithal et al. (2001) in goats administered intrathecal romifidine or romifidine-ketamine. Administration of single drug(s) medetomidine in dogs, medetomidine in cats and dexmedetomidine in dogs causing non-significant changes in blood urea nitrogen levels has been recorded by Akbar et al. (2014), Akbar et al. (2015) and Mazumdar et al. (2015).

4.4.7 Serum Creatinine

The Mean±SE values of serum creatinine levels in animals of various groups administered with dexmedetomidine at the dose rate of 10µg/kg body weight (A1, B1 and C1) or 15µg/kg body weight (A2, B2 and C2) are given in Table 4.38 and depicted in Fig. 4.38. The serum creatinine level in the animals of group A1 increased significantly (P<0.01) at 1 hr and 6 hr interval. The serum creatinine in the animals of group A2 showed a significant (P<0.01) rise in its values at 1 hour time interval. In the animals of group B1 the serum creatinine significantly (P<0.05) increased at 1 hr and 6 hr (P<0.05) interval. In the animals of group B2 serum creatinine recorded significantly (P<0.01) higher levels at 30 minutes and 1 hr interval. The serum creatinine levels increased significantly (P<0.01) at 1 hr in the animals of group C1 whereas it increased significantly (P<0.01) at 30 minutes to 6 hr interval in the animals of group C2. In the present study the serum creatinine levels reached near the base values at 24 hours interval.

Jadon et al. (1995) have recorded non-significant increase in the level of serum creatinine in dogs administered with detomidine-ketamine which could have been due to impairment of renal function. Non-significant increase in the creatinine level in dogs administered with medetomidine-ketamine has also been reported by Umar and Adam.
These changes observed in the present study could have been due to transient suppression of renal function (Khan et al. 2003) and temporarily reduced blood flow to kidney (Umar and Adam 2013). Similarly non-significant changes in the creatinine levels in dogs administered with medetomidine alone, dexmedetomidine basal anaesthesia and dexmedetomidine alone have also been recorded by Akbar et al. (2014), Rafee et al. (2015b) and Mazumdar et al. (2015) respectively which may be due to increased level of ADH and decreased renal perfusion.

4.4.8 Alanine Amino Transferase (ALT)

The Mean±SE values of serum alanine amino transferase (ALT) in animals of various groups administered with dexmedetomidine at the dose rate of 10µg/kg body weight (A1, B1 and C1) or 15µg/kg body weight (A2, B2 and C2) are given in Table 4.39 and depicted in Fig. 4.39. The ALT level of animals in groups A1 showed gradual and significant (P<0.05) increase in its values at 1 hr and 6 hr interval whereas in the animals of group A2 it was significantly higher (P<0.01) at 1 hr interval as compared to 0 hour values. In the animals of groups B1, B2, C1 and C2 the level of serum ALT increased significantly (P<0.01) at 1 hr time interval. Maximum level of ALT was recorded at 1 hour interval and reached to near normal by 24 hours interval in all the groups of animals.

The increased level of ALT observed in this study was accounted to the oxidative transformation of the drugs in liver resulting in increased permeability of plasma membrane of hepatocytes to the enzymes. However Çamkerten et al. (2013), Umar and Adam (2013) and Kumar et al. (2014b) have observed that the level of ALT increased non-significantly in Greyhounds, dogs and buffalo calves anaesthetized with xylazine-ketamine, medetomidine-ketamine and midazolam-ketamine respectively. Akbar et al. (2014), Khurana et al. (2014) and Sharma et al. (2014) have also recorded non-significant decrease in the ALT levels of dogs which were administered with medetomidine, atropine-butorphanol-acepromazine-propofol and dexmedetomidine premedication. Changes in ALT values within physiological limits observed in the present study are indicative of least deleterious effects of different combinations of drugs (used in the study) on liver.
4.4.9 Aspartate Amino Transferase (AST)

The Mean±SE values of serum aspartate amino transferase (AST) in animals of various groups administered with dexmedetomidine at the dose rate of 10µg/kg body weight (A1, B1 and C1) or 15µg/kg body weight (A2, B2 and C2) are given in Table 4.40 and depicted in Fig. 4.40. It was observed that the AST levels showed a gradual increase in its value over time and then regained the near base level values at 24 hours interval. The AST levels in the animals of group A1 increased significantly (P<0.01) at 1 hr interval. In the animals of group A2 the AST levels increased significantly (P<0.05) at 30 minutes to 6 hr interval. In the animals of group B1 the AST levels increased significantly (P<0.01) at 1 hr and 6 hr (P<0.05) interval. In the animals of group B2 AST levels increased significantly (P<0.01) at 1 hr interval. In the group C1 and C2 the AST levels increased significantly (P<0.01) at 1 hr intervals. Its level has reached to near base level by 24 hrs.

The changes in the AST levels observed in the present study may be due to changes in the cell membrane permeability of liver or muscle tissues due to the hypoxia created as a consequence of respiratory depression caused by alpha-2 agonist (Kalim 2011). However Çamkerten (2013), Kumar (2014b) and Sharma et al. (2014) have reported that the level of AST decreased non-significantly in Greyhounds, buffalo calves and dogs administered with xylazine-ketamine, midazolam-ketamine and xylazine-dexmedetomidine premedication, respectively. Akbar et al. (2014) and Khurana et al. (2014) have recorded non-significant decrease in the AST levels of dogs administered with medetomidine and atropine-butorphanol-acepromazine-propofol respectively. Similarly Anandmay et al. (2016) have also recorded non-significant increase in AST levels in dogs anaesthetized with atropine-propofol. The findings of the present study are in agreement with the studies of Sharma et al. (2014).

4.5 Clinical studies

Surgical operations viz. laparotomy, gastrotomy, cystotomy, enterotomy, ovariohysterectomy and splenectomy were performed in the animals of group A, B and C under the effect of various anaesthetic combinations. Surgical anaesthesia was induced with etomidate, propofol and ketamine in the animals of groups A, B and C respectively after premedication with atropine and dexmedetomidine. The anaesthesia
was maintained with sevoflurane in all the groups of animals. The duration of anaesthesia was 70.00±7.45 minutes, 82.50±11.33 minutes, 70.00±23.05 minutes, 85.00±7.73 minutes, 82.50±8.76 minutes and 97.50±5.70 minutes in the animals of groups A1, A2, B1, B2, C1 and C2 respectively. Surgical anaesthesia was well maintained without any complications in various groups of animals however the level of anaesthesia was comparatively better in the animals of group A2, B2 and C2 as compared to the animals of groups A1, B1 and C1. The recovery was smooth and uncomplicated in all the animals.

The anaesthesia was adjudged to be good and well maintained with sevoflurane in all the groups of animals and thereby permitted successful accomplishment of surgical operations. No significant difference in heart rate and respiration rate was observed in the animals undergoing surgery as compared to those which were not put to surgical stress. Hypothermia was recorded in all the animals subjected to anaesthesia alone and the surgical operations. The decrease was relatively more in the animals undergoing surgery particularly abdominal surgery. It may be due to heat dissipation from the exposed abdominal organs (Dripps et al., 1972). Duration of anaesthesia and recovery period was slightly prolonged in animals of the surgical group. The significant increase in the duration of anaesthesia in the animals of groups A2, B2 and C2 was due to the fact that more anaesthesia was required in these animals to complete the surgical procedures. Shivering during recovery period observed in two animals is a quite common phenomenon and may be due to prolonged vasodilation in contrast with cold surroundings, otherwise recovery was smooth, uncomplicated and uneventful in all the cases.
TABLE 4.1: Mean±SE Induction times (seconds) in various groups of animals treated with their respective anaesthetic protocols.

<table>
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<tr>
<th>GROUPS</th>
<th>A</th>
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<th>B</th>
<th>B2</th>
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<th>C2</th>
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<tr>
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</table>

* Significant at 5% level of significance, (P<0.05)

Fig. 4.1 : Induction time of animals in various groups anaesthetized with their respective protocols
TABLE 4.2: Mean±SE Duration of anaesthesia (minutes), in various groups of animals treated with their respective anaesthetic protocols.

<table>
<thead>
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<th>B1</th>
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<th>C1</th>
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<td>82.5±11.33**</td>
<td>70.00±23.05</td>
<td>85.00±7.73**</td>
<td>82.5±8.76</td>
<td>97.5±5.70**</td>
</tr>
</tbody>
</table>

** Significant at 1% level of significance, (P<0.01)

Fig. 4.2: Duration of anaesthesia in animals of various groups anaesthetized with their respective protocols.
Table 4.3: Median±SD score of muscle relaxation in animals of different groups anaesthetized with respective anaesthetic protocols.

<table>
<thead>
<tr>
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<th>30</th>
<th>45</th>
<th>60</th>
<th>75</th>
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</tr>
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Fig. 4.3: Muscle relaxation (median score) of dogs in various groups anaesthetized with respective anaesthetic protocols.
Table 4.4: Median±SD score of Pedal reflex in animals of different groups anaesthetized with respective anaesthetic protocols.

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Fig. 4.4: Pedal reflex (median score) of dogs in various groups anaesthetized with respective anaesthetic protocols.
Table 4.5: Median±SD score of Palpebral reflex in animals of different groups anaesthetized with respective anaesthetic protocols.

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Fig. 4.5: Palpebral reflex (median score) of dogs in various groups anaesthetized with respective anaesthetic protocols.
TABLE 4.6: Mean±SE Recovery time (minutes) in various groups of animals treated with their respective anaesthetic protocols.

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<td>RECOVERY TIME</td>
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* Significant at 5% level of significance, (P<0.05)

Fig. 4.6 : Recovery time in animals of various groups anaesthetized with their respective anaesthetic protocols.
TABLE 4.7: Mean±SE Sternal recumbency time (minutes) in various groups of animals treated with their respective anaesthetic protocols.

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* Significant at 5% level of significance, (P<0.05)

Fig. 4.7: Sternal recumbency time of animals in various groups anaesthetized with their respective...
TABLE 4.8: Mean±SE Standing time (minutes) in various groups of animals treated with their respective anaesthetic protocols.

<table>
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<td></td>
</tr>
<tr>
<td>B2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>C2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Significant at 5% level of significance, (P<0.05)

Fig. 4.8: Standing time of animals in various groups anaesthetized with their respective anaesthetic protocols.
**TABLE 4.9:** Mean±SE complete recovery time (minutes) in various groups of animals treated with their respective anaesthetic protocols.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>C</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A1</td>
<td>A2</td>
<td>B1</td>
<td>B2</td>
<td>C1</td>
</tr>
<tr>
<td>COMPLETE RECOVERY TIME</td>
<td>20.00±2.77</td>
<td>21.67±2.88</td>
<td>14.00±0.94</td>
<td>24.16±4.71*</td>
<td>20.53±2.34</td>
</tr>
</tbody>
</table>

* Significant at 5% level of significance, (P<0.05)

**Fig. 4.9:** Complete recovery time of animals in various groups anaesthetized with their respective anaesthetic protocols.
Table 4.10: Mean±SE of required doses of induction agents in various groups of animals treated with their respective anaesthetic protocols.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>ETOMIDATE</th>
<th>PROPOFOL</th>
<th>KETAMINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>A1</td>
<td>A2</td>
<td>B1</td>
</tr>
<tr>
<td>Dose (total)</td>
<td>1.66±0.11</td>
<td>1.58±0.19</td>
<td>2.46±0.19</td>
</tr>
</tbody>
</table>

* Significant at 5% level of significance, (P<0.05)

Fig. 4.10: Mean dose rates of induction agents in animals of various groups induced with their respective induction agents.
Table 4.11: Mean ±SE of percentage reductions in the MAC of Sevoflurane obtained in different groups of animals treated with their respective anaesthetic protocols.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>A1</th>
<th>A2</th>
<th>B1</th>
<th>B2</th>
<th>C1</th>
<th>C2</th>
</tr>
</thead>
<tbody>
<tr>
<td>% reduction in MAC</td>
<td>13.60±0.17</td>
<td>21.18±1.66*</td>
<td>13.60±0.08</td>
<td>22.70±0.20*</td>
<td>21.18±1.66</td>
<td>30.28±1.66*</td>
</tr>
</tbody>
</table>

* Significant at 5% level of significance, (P<0.05)

Fig. 4.11: Percentage reduction in the MAC of Sevoflurane in animals of various groups anaesthetized with their respective anaesthetic protocols.
Table 4.12: MEAN±SE rectal temperature (°C), in various groups of animals treated with their respective anaesthetic protocols.

<table>
<thead>
<tr>
<th>Group</th>
<th>0Min.</th>
<th>15 Min.</th>
<th>30 Min.</th>
<th>45 Min.</th>
<th>60 Min.</th>
<th>75 Min.</th>
<th>90 Min.</th>
<th>3h</th>
<th>6h</th>
<th>24h</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>38.20±0.19</td>
<td>38.00±0.20</td>
<td>37.60±0.45*</td>
<td>36.96±0.69**</td>
<td>37.17±0.83**</td>
<td>37.12±0.30**</td>
<td>37.40±0.37*</td>
<td>37.81±0.32*</td>
<td>37.87±0.16*</td>
<td>38.15±0.20</td>
</tr>
<tr>
<td>A2</td>
<td>38.33±0.36</td>
<td>38.11±0.70</td>
<td>37.83±0.27**</td>
<td>37.09±0.29**</td>
<td>37.12±0.30**</td>
<td>37.15±0.53**</td>
<td>37.34±0.45**</td>
<td>37.69±0.44**</td>
<td>38.04±0.35*</td>
<td>38.29±0.56</td>
</tr>
<tr>
<td>B1</td>
<td>38.63±0.41</td>
<td>38.40±0.55</td>
<td>38.07±0.55**</td>
<td>37.34±0.39**</td>
<td>37.44±0.40**</td>
<td>37.55±0.40**</td>
<td>38.05±0.39**</td>
<td>38.21±0.24**</td>
<td>38.23±0.28**</td>
<td>38.66±0.17</td>
</tr>
<tr>
<td>B2</td>
<td>38.70±0.27</td>
<td>37.96±0.55**</td>
<td>37.90±0.59**</td>
<td>37.58±0.23**</td>
<td>37.45±0.42**</td>
<td>37.50±0.58**</td>
<td>38.05±0.34**</td>
<td>38.11±0.26**</td>
<td>38.26±0.37**</td>
<td>38.76±0.30</td>
</tr>
<tr>
<td>C1</td>
<td>38.31±0.38</td>
<td>37.83±0.47**</td>
<td>37.57±0.54**</td>
<td>37.30±0.21**</td>
<td>37.22±0.30**</td>
<td>37.44±0.53**</td>
<td>37.61±0.55**</td>
<td>37.88±0.11**</td>
<td>38.03±0.14*</td>
<td>38.40±0.22</td>
</tr>
<tr>
<td>C2</td>
<td>38.29±0.18</td>
<td>38.16±0.16</td>
<td>38.05±0.12</td>
<td>37.55±0.21**</td>
<td>37.11±0.15**</td>
<td>37.38±0.22**</td>
<td>37.77±0.22**</td>
<td>38.00±0.22*</td>
<td>38.07±0.34</td>
<td>38.09±0.31</td>
</tr>
</tbody>
</table>

** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Fig. 4.12: Rectal Temperature of animals in various groups anaesthetized with their respective anaesthetic protocols.
Table 4.13: MEAN±SE heart rate (beats per minute) in various groups of animals treated with their respective anaesthetic protocols.

<table>
<thead>
<tr>
<th>Group</th>
<th>TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0Min.</td>
</tr>
<tr>
<td>A1</td>
<td>80.67 ±4.32</td>
</tr>
<tr>
<td>A2</td>
<td>78.83 ±00.9</td>
</tr>
<tr>
<td>B1</td>
<td>82.17 ±21.10</td>
</tr>
<tr>
<td>B2</td>
<td>84.67 ±0.97</td>
</tr>
<tr>
<td>C1</td>
<td>78.83 ±1.43</td>
</tr>
<tr>
<td>C2</td>
<td>75.50 ±1.22</td>
</tr>
</tbody>
</table>

** Significant at 1% level of significance, (P<0.01).  * Significant at 5% level of significance, (P<0.05)
Heart Rate

Fig. 4.13: Heart rate of animals in various groups anaesthetized with their respective anaesthetic protocols.
Table 4.14: MEAN±SE Respiration rate (breaths per minute) in various groups of animals treated with their respective anaesthetic protocols.

<table>
<thead>
<tr>
<th>Group</th>
<th>TIME</th>
<th>0Min.</th>
<th>15 Min.</th>
<th>30 Min.</th>
<th>45 Min.</th>
<th>60 Min.</th>
<th>75 Min.</th>
<th>90 Min.</th>
<th>3h</th>
<th>6h</th>
<th>24h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>17.67</td>
<td>14.33</td>
<td>14.50</td>
<td>14.00</td>
<td>13.50</td>
<td>14.33</td>
<td>15.00</td>
<td>17.00</td>
<td>16.00</td>
<td>16.50</td>
<td>±1.7</td>
</tr>
<tr>
<td></td>
<td>±1.19**</td>
<td>±1.57**</td>
<td>±2.06**</td>
<td>±1.19**</td>
<td>±2.12**</td>
<td>±1.05**</td>
<td>±2.12**</td>
<td>±1.05**</td>
<td>±2.06</td>
<td>±2.13</td>
<td>±1.7</td>
</tr>
<tr>
<td>A2</td>
<td>18.33</td>
<td>14.00</td>
<td>13.50</td>
<td>13.17</td>
<td>14.50</td>
<td>14.30</td>
<td>15.79</td>
<td>17.50</td>
<td>17.00</td>
<td>17.00</td>
<td>±0.46</td>
</tr>
<tr>
<td></td>
<td>±0.46</td>
<td>±0.88**</td>
<td>±1.99**</td>
<td>±1.00**</td>
<td>±1.76**</td>
<td>±0.88**</td>
<td>±2.49**</td>
<td>±1.20</td>
<td>±0.85</td>
<td>±1.40</td>
<td>±0.46</td>
</tr>
<tr>
<td>B1</td>
<td>18.17</td>
<td>15.33</td>
<td>14.13</td>
<td>13.50</td>
<td>14.20</td>
<td>15.00</td>
<td>16.83</td>
<td>19.17</td>
<td>17.17</td>
<td>16.50</td>
<td>±0.77</td>
</tr>
<tr>
<td></td>
<td>±0.77</td>
<td>±1.83**</td>
<td>±3.29**</td>
<td>±1.67**</td>
<td>±1.04**</td>
<td>±0.83**</td>
<td>±1.07</td>
<td>±1.28</td>
<td>±1.97</td>
<td>±0.97</td>
<td>±0.77</td>
</tr>
<tr>
<td>B2</td>
<td>18.50</td>
<td>14.17</td>
<td>15.00</td>
<td>12.50</td>
<td>13.00</td>
<td>14.00</td>
<td>15.83</td>
<td>17.20</td>
<td>19.67</td>
<td>18.83</td>
<td>±3.23</td>
</tr>
<tr>
<td></td>
<td>±3.23</td>
<td>±2.22**</td>
<td>±0.49**</td>
<td>±0.88**</td>
<td>±0.97**</td>
<td>±0.77**</td>
<td>±0.46**</td>
<td>±0.49</td>
<td>±0.73</td>
<td>±1.40</td>
<td>±3.23</td>
</tr>
<tr>
<td>C1</td>
<td>18.00</td>
<td>12.67</td>
<td>13.67</td>
<td>14.00</td>
<td>13.50</td>
<td>12.50</td>
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<td>17.20</td>
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</tr>
<tr>
<td></td>
<td>±0.49</td>
<td>±0.67**</td>
<td>±0.37**</td>
<td>±0.52**</td>
<td>±1.53**</td>
<td>±1.23**</td>
<td>±1.05**</td>
<td>±1.01</td>
<td>±0.61</td>
<td>±1.31</td>
<td>±0.49</td>
</tr>
<tr>
<td>C2</td>
<td>17.67</td>
<td>12.33</td>
<td>13.00</td>
<td>14.33</td>
<td>14.80</td>
<td>13.00</td>
<td>13.50</td>
<td>18.00</td>
<td>17.00</td>
<td>18.67</td>
<td>±1.01</td>
</tr>
<tr>
<td></td>
<td>±1.01</td>
<td>±0.37**</td>
<td>±0.83**</td>
<td>±0.62**</td>
<td>±0.96**</td>
<td>±0.97**</td>
<td>±0.85</td>
<td>±0.75</td>
<td>±0.75</td>
<td>±0.88</td>
<td>±1.01</td>
</tr>
</tbody>
</table>

** Significant at 1% level of significance, (P<0.01).  * Significant at 5% level of significance, (P<0.05)
Fig. 4.14: Respiration rate of animals in various groups anaesthetized with their respective anaesthetic protocols.
Table 4.15: MEAN±SE systolic blood pressure (mmHg) in various groups of animals treated with their respective anaesthetic protocols.

<table>
<thead>
<tr>
<th>Group</th>
<th>TIME</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0Min.</td>
<td>15 Min.</td>
<td>30 Min.</td>
<td>45 Min.</td>
<td>60 Min.</td>
<td>75 Min.</td>
<td>90 Min.</td>
<td>3h</td>
<td>6h</td>
</tr>
<tr>
<td>A1</td>
<td>143.67 ±7.44</td>
<td>170.50 ±7.71**</td>
<td>120.33 ±10.83**</td>
<td>115.67 ±7.96**</td>
<td>110.33 ±4.24**</td>
<td>115.00 ±3.65**</td>
<td>112.67 ±3.92</td>
<td>143.33 ±3.92</td>
<td>140.33 ±3.65</td>
</tr>
<tr>
<td>A2</td>
<td>142.17 ±3.85</td>
<td>175.17 ±12.28**</td>
<td>118.67 ±6.73**</td>
<td>117.83 ±5.10**</td>
<td>115.50 ±6.80**</td>
<td>114.00 ±5.10**</td>
<td>110.17 ±1.68**</td>
<td>143.33 ±2.31</td>
<td>145.83 ±2.20</td>
</tr>
<tr>
<td>B1</td>
<td>138.50 ±7.69</td>
<td>170.83 ±14.40**</td>
<td>115.17 ±11.22**</td>
<td>110.50 ±12.30**</td>
<td>102.33 ±10.32**</td>
<td>105.67 ±5.42**</td>
<td>107.00 ±2.45**</td>
<td>136.17 ±3.29</td>
<td>130.53 ±6.11</td>
</tr>
<tr>
<td>B2</td>
<td>140.33 ±1.15</td>
<td>175.00 ±1.67**</td>
<td>117.83 ±1.68*8</td>
<td>115.50 ±3.08**</td>
<td>104.17 ±4.78**</td>
<td>104.67 ±2.71**</td>
<td>102.50 ±3.67**</td>
<td>140.33 ±3.06</td>
<td>134.67 ±1.83</td>
</tr>
<tr>
<td>C1</td>
<td>140.17 ±1.91</td>
<td>175.67 ±3.71**</td>
<td>190.83 ±4.36**</td>
<td>185.67 ±1.64**</td>
<td>160.83 ±5.55**</td>
<td>155.83 ±5.55**</td>
<td>145.00 ±3.46**</td>
<td>142.50 ±5.05</td>
<td>128.33 ±5.60**</td>
</tr>
<tr>
<td>C2</td>
<td>145.00 ±2.90</td>
<td>170.67 ±2.23**</td>
<td>188.33 ±2.71**</td>
<td>186.33 ±2.31**</td>
<td>165.67 ±4.83**</td>
<td>160.67 ±6.43**</td>
<td>140.83 ±4.78**</td>
<td>140.50 ±2.74</td>
<td>132.50 ±3.67**</td>
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</tbody>
</table>

** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Fig. 4.15: Systolic Blood Pressure of animals in various groups anaesthetized with their respective anaesthetic protocols.
<table>
<thead>
<tr>
<th>Group</th>
<th>TIME</th>
<th>0Min.</th>
<th>15 Min.</th>
<th>30 Min.</th>
<th>45 Min.</th>
<th>60 Min.</th>
<th>75 Min.</th>
<th>90 Min.</th>
<th>3h</th>
<th>6h</th>
<th>24h</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td></td>
<td>98.33±11.46</td>
<td>110.00±11.22**</td>
<td>85.83±8.08**</td>
<td>80.17±4.56**</td>
<td>82.17±8.77**</td>
<td>75.50±8.22**</td>
<td>70.00±6.93**</td>
<td>91.83±2.20</td>
<td>91.47±1.68</td>
<td>92.00±3.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95.00±4.00</td>
<td>115.83±14.45**</td>
<td>85.67±4.40**</td>
<td>80.00±6.79**</td>
<td>80.50±9.52**</td>
<td>70.67±4.40**</td>
<td>65.00±1.41**</td>
<td>90.83±4.10</td>
<td>96.67±3.37</td>
<td>92.50±3.39</td>
</tr>
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<td>90.00±17.65</td>
<td>120.83±17.01**</td>
<td>80.33±7.75**</td>
<td>70.33±11.13**</td>
<td>68.50±10.06**</td>
<td>62.50±5.05**</td>
<td>65.50±6.75**</td>
<td>90.17±4.98</td>
<td>89.17±2.20</td>
<td>87.33±5.34</td>
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<tr>
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<td>92.33±2.31</td>
<td>125.67±2.31**</td>
<td>78.00±2.97**</td>
<td>71.83±5.62**</td>
<td>70.50±5.05**</td>
<td>65.50±3.67**</td>
<td>65.00±2.00**</td>
<td>87.50±1.87</td>
<td>90.67±2.71</td>
<td>85.50±4.64</td>
</tr>
<tr>
<td>B1</td>
<td></td>
<td>95.00±4.69</td>
<td>115.00±6.60**</td>
<td>120.50±7.48**</td>
<td>125.00±4.72**</td>
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<td>95.17±3.74</td>
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<td>97.50±4.47</td>
<td>96.67±4.86</td>
<td>95.50±1.83</td>
</tr>
<tr>
<td>B2</td>
<td></td>
<td>95.33±2.71</td>
<td>115.83±3.92**</td>
<td>118.50±2.35**</td>
<td>121.33±1.83**</td>
<td>100.50±5.96</td>
<td>94.00±3.45</td>
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<td>98.50±3.39</td>
<td>95.00±5.03</td>
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</tr>
</tbody>
</table>

** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Fig. 4.16: Diastolic Blood Pressure of animals in various groups anaesthetized with their respective anaesthetic protocols.
Table 4.17: MEAN±SE mean arterial pressure (mmHg) in various groups of animals treated with their respective anaesthetic protocols.

<table>
<thead>
<tr>
<th>Group</th>
<th>0Min.</th>
<th>15 Min.</th>
<th>30 Min.</th>
<th>45 Min.</th>
<th>60 Min.</th>
<th>75 Min.</th>
<th>90 Min.</th>
<th>3h</th>
<th>6h</th>
<th>24h</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>112.48±10.63</td>
<td>128.13±9.92**</td>
<td>96.66±8.85**</td>
<td>91.28±4.72**</td>
<td>91.20±8.42**</td>
<td>89.32±6.66**</td>
<td>84.37±6.26**</td>
<td>109.38±2.93</td>
<td>107.20±2.20</td>
<td>109.20±3.76</td>
</tr>
<tr>
<td>A2</td>
<td>110.18±10.88</td>
<td>137.23±13.68**</td>
<td>95.20±3.89**</td>
<td>92.30±5.52**</td>
<td>92.00±8.42**</td>
<td>86.33±4.46**</td>
<td>80.37±0.87**</td>
<td>107.97±2.79</td>
<td>113.05±2.69</td>
<td>106.90±2.14</td>
</tr>
<tr>
<td>B1</td>
<td>106.82±12.02</td>
<td>140.60±14.82**</td>
<td>90.48±7.21**</td>
<td>84.52±11.14**</td>
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<td>102.85±2.72</td>
<td>104.97±6.07</td>
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<td>B2</td>
<td>108.62±1.63</td>
<td>142.40±1.94**</td>
<td>91.00±2.38**</td>
<td>86.22±3.17**</td>
<td>80.39±4.50**</td>
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** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Fig. 4.17: Mean arterial pressure of animals in various groups anaesthetized with their respective anaesthetic protocols.
Table 4.18: MEAN±SE Haemoglobin oxygen saturation (SpO₂) (%) in various groups of animals treated with their respective anaesthetic protocols.

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<td>± 0.00</td>
<td>± 0.85*</td>
<td>± 0.52**</td>
<td>± 0.55</td>
<td>± 0.83</td>
<td>± 0.54*</td>
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<td>± 0.18</td>
<td>± 0.46**</td>
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<td>± 0.66</td>
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<td>± 0.73</td>
<td>± 0.54**</td>
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<td>± 0.34**</td>
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<td>±0.18</td>
<td>±0.40</td>
<td>± 0.75</td>
<td>± 0.54</td>
<td>± 0.44</td>
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<td>±0 0.00</td>
<td>± 0.59*</td>
<td>±0.37**</td>
<td>± 0.62**</td>
<td>± 0.66</td>
<td>± 0.63</td>
<td>± 0.44</td>
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** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Fig. 4.18: Haemoglobin oxygen saturation (SpO₂) of animals in various groups anaesthetized with their respective anaesthetic protocols.
Fig. 4.19(a) Inverted T. Wave, increased P-R interval, increased Q-T interval in group A-1, (b) sinus dysrhythmia group A-2, (c) biphasic T-wave group B-1, (d) bradycardia in group B-2, (e) elevated T. Wave group C-1,
Table 4.20: MEAN±SE haemoglobin (g/dl) in various groups of animals treated with their respective anaesthetic protocols.

<table>
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<tr>
<td>A1</td>
<td>14.07 ±1.25</td>
<td>13.20 ±0.64**</td>
<td>13.07 ±0.96**</td>
<td>12.89 ±0.69**</td>
<td>13.87 ±1.14</td>
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<td>A2</td>
<td>12.70 ±0.33</td>
<td>12.57 ±0.58</td>
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<td>12.47 ±0.53</td>
<td>12.60±0.34</td>
</tr>
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<td>B1</td>
<td>12.37 ±0.30</td>
<td>12.23 ±0.32</td>
<td>11.60 ±0.42*</td>
<td>11.63 ±0.42*</td>
<td>12.70 ±0.34</td>
</tr>
<tr>
<td>B2</td>
<td>12.40 ±0.48</td>
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<td>12.22 ±0.60</td>
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<td>12.30 ± 0.67</td>
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<tr>
<td>C1</td>
<td>13.07 ±0.43</td>
<td>12.77 ±0.61</td>
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<td>12.50 ±0.39</td>
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<td>12.07 ±0.46</td>
<td>11.60 ±0.38*</td>
<td>12.10 ±0.37</td>
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** Significant at 1% level of significance, (P<0.01).  * Significant at 5% level of significance, (P<0.05)
Fig. 4.20: Haemoglobin of animals in various groups anaesthetized with their respective anaesthetic protocols.
Table 4.21: MEAN ±SE, total erythrocyte count ($10^6 /\mu l$) in various groups of animals treated with their respective anaesthetic protocols.

<table>
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<tr>
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<tr>
<td>A1</td>
<td>6.10 ±0.26</td>
<td>6.02 ±0.30</td>
<td>5.97 ±0.16</td>
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<td>A2</td>
<td>5.98 ±0.16</td>
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<td>5.88 ±0.25</td>
<td>5.95 ±0.25</td>
</tr>
<tr>
<td>B1</td>
<td>5.85 ±0.18</td>
<td>5.62 ±0.14*</td>
<td>5.47 ±0.20**</td>
<td>5.50 ±0.07**</td>
<td>5.80 ±0.14</td>
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<tr>
<td>B2</td>
<td>5.87 ±0.12</td>
<td>5.73 ±0.21</td>
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<td>5.70 ±0.32</td>
<td>5.90 ±0.23</td>
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<tr>
<td>C1</td>
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<td>5.87 ±0.30</td>
<td>5.72 ±0.17</td>
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** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Fig. 4.21: Total Erythrocyte Count of animals in various groups anaesthetized with their respective anaesthetic protocols.
Table 4.22: MEAN ±SE, erythrocyte sedimentation rate (mm/hr)) in various groups of animals treated with their respective anaesthetic protocols.

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<tr>
<td>A1</td>
<td>2.33 ±0.23</td>
<td>2.67 ±0.23</td>
<td>3.00 ±0.28**</td>
<td>2.67 ±0.46</td>
<td>2.30 ±0.18</td>
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<td>3.10 ±0.44**</td>
<td>2.83 ±0.34**</td>
<td>2.33 ±0.37</td>
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<tr>
<td>B1</td>
<td>2.50 ±0.24</td>
<td>2.67 ±0.46</td>
<td>3.10 ±0.34**</td>
<td>2.90 ±0.37</td>
<td>2.40 ±0.37</td>
</tr>
<tr>
<td>B2</td>
<td>2.33 ±0.23</td>
<td>2.50 ±0.23</td>
<td>3.00 ±0.40**</td>
<td>2.67 ±0.46</td>
<td>2.40 ±0.72</td>
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<tr>
<td>C1</td>
<td>2.17 ±0.18</td>
<td>2.40 ±0.28</td>
<td>2.90 ±0.23**</td>
<td>2.83 ±0.34**</td>
<td>2.17 ±0.18</td>
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<tr>
<td>C2</td>
<td>2.33 ±0.23</td>
<td>2.60 ±0.28</td>
<td>3.00 ±0.37**</td>
<td>2.83 ±0.44*</td>
<td>2.50 ±0.37</td>
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** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Fig. 4.22: Erythrocyte sedimentation rate of animals in various groups anaesthetized with their respective anaesthetic protocols.
Table 4.23: Mean±SE, Total leucocyte count (10$^3$/µl) in various groups of animals treated with their respective anaesthetic protocols.

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<tr>
<td>A1</td>
<td>6.48 ±0.27</td>
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<td>5.88 ±0.25**</td>
<td>6.21 ±0.2</td>
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<td>6.08 ±0.18**</td>
<td>6.50±0.05</td>
<td>6.70 ±0.29</td>
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<tr>
<td>B1</td>
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<td>6.00 ±0.28**</td>
<td>5.90 ±0.16**</td>
<td>6.38 ±0.30</td>
<td>6.38 ±0.14</td>
</tr>
<tr>
<td>B2</td>
<td>5.99 ±0.38</td>
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<td>5.50 ±0.37**</td>
<td>5.49 ±0.24**</td>
<td>5.80 ±0.46</td>
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<td>6.30±0.13**</td>
<td>6.37±0.29**</td>
<td>6.78±0.18</td>
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** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Total Leucocyte Count (TLC)

Fig. 4.23: Total leucocyte count of animals in various groups anaesthetized with their respective anaesthetic protocols.
TABLE 4.24: Mean±SE, neutrophils (%) in various groups of animals treated with their respective anaesthetic protocols.

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<td>A1</td>
<td>71.60 ±1.54</td>
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<td>74.50 ±0.47*</td>
<td>73.17 ±0.52</td>
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<tr>
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** Significant at 1% level of significance, (P<0.01).  * Significant at 5% level of significance, (P<0.05)
Fig. 4.24: Neutrophil counts of animals in various groups anaesthetized with their respective anaesthetic protocols.
TABLE 4.25: MEAN ±SE lymphocytes (%), in various groups of animals treated with their respective anaesthetic protocols.

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<td>24.17 ±0.44</td>
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<td>22.13 ±0.54**</td>
<td>24.27 ±1.01</td>
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<tr>
<td>B2</td>
<td>24.83 ±2.07</td>
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<td>23.00 ±1.23**</td>
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<td>23.50 ±0.57</td>
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** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Fig. 4.25: Lymphocyte count of animals in various groups anaesthetized with their respective anaesthetic protocols.
**TABLE 4.26: MEAN±SE monocytes (%) in various groups of animals treated with their respective anaesthetic protocols.**

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<td>A1</td>
<td>2.00 ±0.28</td>
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<td>1.95 ±0.52</td>
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</tr>
<tr>
<td>A2</td>
<td>1.17 ±0.18</td>
<td>1.83 ±0.18**</td>
<td>2.07 ±0.34**</td>
<td>1.66 ±0.44**</td>
<td>1.23 ±0.44</td>
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</tr>
<tr>
<td>B1</td>
<td>2.17 ±0.34</td>
<td>1.50 ±0.24**</td>
<td>1.33 ±0.23**</td>
<td>1.50 ±0.24**</td>
<td>1.87 ±0.18</td>
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</tr>
<tr>
<td>B2</td>
<td>1.67 ±0.37</td>
<td>1.50 ±0.24</td>
<td>2.17 ±0.23**</td>
<td>1.67 ±0.37</td>
<td>1.83 ±0.18</td>
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</tr>
<tr>
<td>C1</td>
<td>1.50 ±0.37</td>
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<td>1.67 ±0.23</td>
<td>2.00 ±0.28*</td>
<td>1.73 ±0.23</td>
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** ** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Fig. 4.26: Monocyte counts of animals in various groups anaesthetized with their respective anaesthetic protocols.
TABLE 4.27: MEAN ±SE eosinophils (%), in various groups of animals treated with their respective anaesthetic protocols.

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<td>A1</td>
<td>1.73 ±0.40</td>
<td>1.27 ±0.34**</td>
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<tr>
<td>A2</td>
<td>1.33 ±0.46</td>
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<td>1.60 ±0.28</td>
<td>1.20 ±0.37</td>
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</tr>
<tr>
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<td>1.33 ±0.23</td>
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<td>1.57 ±0.23</td>
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<td>1.38 ±0.34</td>
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<td>B2</td>
<td>1.17 ±0.18</td>
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<td>1.33 ±0.37</td>
<td>1.33 ±0.23</td>
</tr>
<tr>
<td>C1</td>
<td>1.17 ±0.18</td>
<td>1.33 ±0.23</td>
<td>1.00 ±0.23</td>
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<td>1.10 ±0.40</td>
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<td>C2</td>
<td>1.33 ±0.46</td>
<td>1.33 ±0.23</td>
<td>1.67 ±0.37*</td>
<td>1.67 ±0.37*</td>
<td>1.20 ±0.18</td>
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</tbody>
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** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Fig. 4.27: Eosinophil counts of animals in various groups anaesthetized with their respective anaesthetic protocols.
TABLE 4.28: MEAN±SE packed cell volume (%) in various groups of animals treated with their respective anaesthetic protocols.

<table>
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<tr>
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<td>A1</td>
<td>41.33 ±3.33</td>
<td>39.33 ±2.15*</td>
<td>39.29 ±3.15*</td>
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<td>39.87 ±1.60</td>
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<td>38.13 ±2.18</td>
<td>40.20 ±1.91</td>
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<td>37.53 ±1.18</td>
</tr>
<tr>
<td>B1</td>
<td>37.50 ±1.12</td>
<td>36.00 ±0.94</td>
<td>36.83 ±1.07</td>
<td>37.33 ±0.61</td>
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<td>37.83 ±0.82</td>
</tr>
<tr>
<td>B2</td>
<td>38.33 ±1.12</td>
<td>37.00 ±1.83</td>
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<td>37.50 ±2.17</td>
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<td>38.83 ±1.59</td>
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\* Significant at 5% level of significance, (P<0.05)

** Significant at 1% level of significance, (P<0.01)
Fig. 4.28: Packed cell volume of animals in various groups anaesthetized with their respective anaesthetic protocols.
TABLE 4.29: MEAN±SE mean corpuscular volume (fL) in various groups of animals treated with their respective anaesthetic protocols.

<table>
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<td>0.5h</td>
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<td>24h</td>
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<td>A1</td>
<td>66.42±3.41</td>
<td>65.80±2.75</td>
<td>65.26±2.01</td>
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<td>66.95±3.32</td>
</tr>
<tr>
<td>B1</td>
<td>68.18±1.07</td>
<td>65.97±1.20</td>
<td>65.53±2.44</td>
<td>66.87±2.27</td>
<td>65.87±1.68</td>
</tr>
<tr>
<td>B2</td>
<td>65.29±1.59</td>
<td>64.91±2.27</td>
<td>64.86±4.00</td>
<td>64.55±2.91</td>
<td>65.81±1.75</td>
</tr>
<tr>
<td>C1</td>
<td>68.50±2.02</td>
<td>69.80±1.78</td>
<td>69.00±2.09</td>
<td>66.33±2.74</td>
<td>67.50±1.49</td>
</tr>
<tr>
<td>C2</td>
<td>68.00±2.92</td>
<td>66.73±1.17</td>
<td>66.72±3.17</td>
<td>68.10±2.39</td>
<td>65.50±2.36</td>
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</table>

** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Fig. 4.29: Mean corpuscular volume of animals
**TABLE 4.30:** MEAN ±SE mean corpuscular haemoglobin (pg) in various groups of animals treated with their respective anaesthetic protocols.

<table>
<thead>
<tr>
<th>Group</th>
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<td>24</td>
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<td>A1</td>
<td>23.06 ±1.03</td>
<td>22.05 ±0.71</td>
<td>21.98 ±0.62</td>
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<td>21.05 ±0.67</td>
<td>20.98 ±0.62</td>
<td>21.40 ±0.72</td>
<td>21.60 ±1.12</td>
</tr>
<tr>
<td>B1</td>
<td>21.40 ±0.33</td>
<td>21.30 ±0.64</td>
<td>20.57 ±0.68</td>
<td>21.14 ±0.55</td>
<td>21.30 ±0.38</td>
</tr>
<tr>
<td>B2</td>
<td>21.10 ±1.19</td>
<td>21.00 ±0.64</td>
<td>21.12 ±0.93</td>
<td>20.27 ±0.68</td>
<td>20.40 ±0.30</td>
</tr>
<tr>
<td>C1</td>
<td>21.70 ±1.15</td>
<td>22.20 ±0.51</td>
<td>22.04 ±0.80</td>
<td>20.90 ±0.99</td>
<td>21.30 ±1.32</td>
</tr>
<tr>
<td>C2</td>
<td>21.00 ±0.63</td>
<td>21.25 ±0.66</td>
<td>21.56 ±1.00</td>
<td>20.35 ±0.65</td>
<td>20.72 ±0.55</td>
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</tbody>
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**Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)**
Fig. 4.30: Mean corpuscular haemoglobin of animals in various groups anaesthetized with their respective anaesthetic protocols.
TABLE 4.31: MEAN ±SE Mean corpuscular haemoglobin concentration (%) in various groups of animals treated with their respective anaesthetic protocols.

<table>
<thead>
<tr>
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<td>24h</td>
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<tr>
<td>A1</td>
<td>34.04±0.77</td>
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<td>32.20±0.61</td>
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<td>32.40±0.17</td>
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<td>32.10±1.05</td>
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<tr>
<td>B2</td>
<td>32.20±1.25</td>
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<td>31.85±1.57</td>
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<td>30.65±0.45</td>
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** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Fig. 4.31: Mean corpuscular haemoglobin concentration of animals in various groups anaesthetized with their respective anaesthetic protocols.
TABLE 4.32: MEAN±SE serum glucose (mg/dL) in various groups of animals treated with their respective anaesthetic protocols.

<table>
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<td>75.67±4.07</td>
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<td>81.33±2.31</td>
<td>91.83±2.61**</td>
<td>108.17±3.75**</td>
<td>100.00±3.70**</td>
<td>84.50±2.35</td>
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<td>B1</td>
<td>75.00±5.29</td>
<td>89.33±6.73**</td>
<td>98.33±9.24**</td>
<td>112.50±6.60**</td>
<td>80.00±5.23</td>
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<td>B2</td>
<td>74.17±5.18</td>
<td>90.50±6.75**</td>
<td>103.83±7.93**</td>
<td>114.17±3.29**</td>
<td>78.50±5.05**</td>
</tr>
<tr>
<td>C1</td>
<td>90.83±0.91</td>
<td>100.00±2.45**</td>
<td>112.50±2.74**</td>
<td>105.50±1.22**</td>
<td>88.33±2.71</td>
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<tr>
<td>C2</td>
<td>86.67±3.36</td>
<td>95.00±4.00**</td>
<td>107.50±3.94**</td>
<td>100.17±3.29**</td>
<td>88.33±1.83</td>
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** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Fig. 32: Serum glucose concentration of dogs in various groups of animals anaesthetized with their respective anaesthetic protocols.
TABLE 4.33: Mean±SE serum insulin (µU/ml) in various groups of animals treated with their respective anaesthetic protocols.

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<td>A1</td>
<td>13.63±0.96</td>
<td>12.60±0.67</td>
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<td>9.67±0.37**</td>
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<td>13.87±1.08</td>
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<td>11.45±1.16**</td>
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<td>B2</td>
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<td>12.50±1.04*</td>
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<td>10.83±0.72**</td>
<td>12.53±1.28</td>
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<tr>
<td>C1</td>
<td>14.03±1.05</td>
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<td>11.00±1.20**</td>
<td>12.83±1.53</td>
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** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Fig. 4.33: Serum insulin concentration in animals of various groups anaesthetized with their respective anaesthetic protocols.
Table 4.34: Mean±SE serum cortisol (µg/dl) in various groups of animals treated with their respective anaesthetic protocols.

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<td>2.35±0.41</td>
<td>2.00±0.38**</td>
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<td>0.93±0.23**</td>
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<td>3.25±0.25**</td>
<td>3.30±0.22**</td>
<td>2.90±0.20</td>
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<tr>
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<td>2.87±0.04</td>
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<td>2.84±0.05</td>
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<tr>
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<td>3.60±0.09**</td>
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** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Fig. 4.34: Serum cortisol concentration of animals in various groups anaesthetized with their respective anaesthetic protocols.
**TABLE 4.35**: Mean±SE total protein (g/dL) in various groups of animals treated with their respective anaesthetic protocols.

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<td>24h</td>
</tr>
<tr>
<td>A1</td>
<td>6.22±0.24</td>
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<td>5.93±0.24*</td>
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<td>6.17±0.14</td>
<td>6.18±0.14</td>
<td>6.25±0.13</td>
</tr>
<tr>
<td>B1</td>
<td>6.27±0.31</td>
<td>6.10±0.29</td>
<td>6.02±0.31*</td>
<td>5.87±0.29**</td>
<td>6.25±0.20</td>
</tr>
<tr>
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** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)**
Fig. 4.35: Total protein of animals in various groups anaesthetized with their respective anaesthetic protocols.
TABLE 4.36: Mean±SE serum albumin (g/dL) in various groups of animals treated with their respective anaesthetic protocols.

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<tbody>
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<td></td>
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<td>2.77±0.13**</td>
<td>2.95±0.13</td>
</tr>
<tr>
<td>A2</td>
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<td>3.10±0.06</td>
<td>2.98±0.08</td>
<td>2.92±0.09**</td>
<td>2.90±0.08**</td>
<td>3.05±0.08</td>
</tr>
<tr>
<td>B1</td>
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<td>3.12±0.13</td>
<td>3.00±0.11</td>
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<td>3.05±0.05</td>
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<tr>
<td>B2</td>
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<td>3.02±0.15</td>
<td>2.90±0.15</td>
<td>2.83±0.15**</td>
<td>2.88±0.16*</td>
<td>2.98±0.16</td>
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<tr>
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<tr>
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<td>2.95±0.06</td>
<td>2.87±0.10</td>
<td>2.85±0.10</td>
<td>2.80±0.14*</td>
<td>2.84±0.14</td>
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</tbody>
</table>

** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Fig. 4.36: Serum albumin of animals in various groups anaesthetized with their respective anaesthetic protocols.
TABLE 4.37: Mean±SE serum urea nitrogen (mg/dL) in various groups of animals treated with their respective anaesthetic protocols.

<table>
<thead>
<tr>
<th>Group</th>
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<tr>
<td>A1</td>
<td>20.00±0.28</td>
<td>22.67±2.31</td>
<td>24.67±3.37**</td>
<td>21.67±5.85</td>
<td>22.60±1.91</td>
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<tr>
<td>A2</td>
<td>24.00±1.41</td>
<td>25.33±2.31</td>
<td>26.00±2.00</td>
<td>23.83±2.61</td>
<td>25.33±2.63</td>
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<tr>
<td>B1</td>
<td>22.50±1.22</td>
<td>24.33±2.93</td>
<td>25.50±4.81*</td>
<td>24.00±1.77</td>
<td>24.10±1.67</td>
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<tr>
<td>B2</td>
<td>19.50±1.76</td>
<td>21.50±1.83</td>
<td>23.67±3.98**</td>
<td>22.10±3.01**</td>
<td>21.50±2.45</td>
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<tr>
<td>C1</td>
<td>19.50±2.13</td>
<td>22.10±2.42**</td>
<td>24.83±1.37**</td>
<td>23.83±2.61**</td>
<td>20.67±1.08</td>
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<td>C2</td>
<td>25.83±1.53</td>
<td>26.00±1.47</td>
<td>27.83±1.94</td>
<td>26.83±1.51</td>
<td>25.67±0.97</td>
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** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
**SERUM UREA NITROGEN**

Fig. 4.37: Serum urea nitrogen of animals in various groups anaesthetized with their respective anaesthetic protocols.
TABLE 4.38: Mean±SE serum creatinine (mg/dL) in various groups of animals treated with their respective anaesthetic protocols.

<table>
<thead>
<tr>
<th>Group</th>
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</tr>
<tr>
<td>A1</td>
<td>0.72±0.07</td>
<td>0.80±0.09</td>
<td>0.95±0.15**</td>
<td>0.89±0.18**</td>
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<tr>
<td>A2</td>
<td>0.75±0.07</td>
<td>0.80±0.12</td>
<td>1.00±0.13**</td>
<td>0.70±0.07</td>
<td>0.78±0.08</td>
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<tr>
<td>B1</td>
<td>0.75±0.04</td>
<td>0.85±0.11</td>
<td>0.92±0.18**</td>
<td>0.89±0.04*</td>
<td>0.69±0.04</td>
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<tr>
<td>B2</td>
<td>0.73±0.07</td>
<td>0.89±0.08**</td>
<td>0.93±0.09**</td>
<td>0.82±0.03</td>
<td>0.68±0.04</td>
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<tr>
<td>C1</td>
<td>0.70±0.07</td>
<td>0.80±0.10</td>
<td>0.90±0.11**</td>
<td>0.75±0.07</td>
<td>0.70±0.07</td>
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<tr>
<td>C2</td>
<td>0.68±0.06</td>
<td>0.90±0.08**</td>
<td>1.00±0.25**</td>
<td>0.87±0.19**</td>
<td>0.76±0.07</td>
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** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Fig. 4.38: Serum creatinine levels of animals in various groups anaesthetized with their respective anaesthetic protocols.
TABLE 4.39: Mean±SE serum alanine amino transferase (U/L) in various groups of animals treated with their respective anaesthetic protocols.

<table>
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<tr>
<td>A1</td>
<td>27.67±0.97</td>
<td>28.33±1.87</td>
<td>32.00±1.39**</td>
<td>30.83±3.29*</td>
<td>26.33±2.03</td>
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<tr>
<td>A2</td>
<td>31.00±2.86</td>
<td>31.17±2.29</td>
<td>35.00±3.64**</td>
<td>32.33±3.86</td>
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<td>36.50±4.04**</td>
<td>33.50±1.76</td>
<td>32.83±1.48</td>
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<td>39.50±3.29**</td>
<td>35.50±3.39</td>
<td>33.17±1.91</td>
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<tr>
<td>C1</td>
<td>32.50±2.74</td>
<td>34.17±2.83</td>
<td>36.17±3.10**</td>
<td>33.50±2.35</td>
<td>31.83±2.01</td>
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<tr>
<td>C2</td>
<td>30.50±2.45</td>
<td>32.17±2.32</td>
<td>35.17±3.04**</td>
<td>32.00±3.52</td>
<td>30.67±1.51</td>
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** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Fig. 4.39: Alanine amino transferase levels of animals in various groups anaesthetized with their respective anaesthetic protocols.
TABLE 4.40: Mean±SE aspartate amino transferase (U/L), in various groups of animals treated with their respective anaesthetic protocols.

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<tr>
<td>A1</td>
<td>24.50±3.03</td>
<td>25.00±2.06</td>
<td>28.60±2.06**</td>
<td>26.60±2.50</td>
<td>23.50±1.41</td>
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<tr>
<td>A2</td>
<td>22.67±3.33</td>
<td>26.67±2.63*</td>
<td>28.00±2.62**</td>
<td>26.00±3.29*</td>
<td>24.83±2.46</td>
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<td>B1</td>
<td>22.00±4.69</td>
<td>25.67±2.71</td>
<td>28.67±1.67**</td>
<td>25.33±2.71*</td>
<td>24.67±2.71</td>
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<tr>
<td>B2</td>
<td>24.83±2.11</td>
<td>26.00±2.68</td>
<td>29.17±1.93**</td>
<td>25.60±2.48</td>
<td>24.33±1.83</td>
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<tr>
<td>C1</td>
<td>23.67±4.33</td>
<td>26.67±3.33</td>
<td>29.80±2.71**</td>
<td>26.63±2.61</td>
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<td>29.00±1.43**</td>
<td>24.00±2.76</td>
<td>24.83±1.75</td>
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** Significant at 1% level of significance, (P<0.01). * Significant at 5% level of significance, (P<0.05)
Fig. 4.40: Aspartate amino transferase in animals of different groups anaesthetized with respective protocols
Plate 5(a): Initiation of operation on the anaesthetized animal.

Plate 5(b): Initiation of operation on the anaesthetized animal.
Plate 6: Ovariohysterectomy in a case of pyometra.

Plate 7: Abdominal incision closed in the same animal as in Fig. (6).
Plate 8: Semiautomatic biochemical analyzer for analysis of biochemical parameter.

Plate 9: Plate showing result of insulin ELISA.
Plate 10: Plate showing result of cortisol ELISA.
Summary and Conclusions
Summary and Conclusions

Chapter 5

SUMMARY AND CONCLUSIONS

The present study was conducted in the Department of Veterinary Surgery and Radiology, College of Veterinary and Animal Sciences, Gobind Ballabh Pant University of Agriculture and Technology, Pantnagar, Distt. Udham Singh Nagar-263145, Uttarakhand, during the months of January 2016 to June 2016. Approval of the Institutional Animal Ethics Committee of the College of Veterinary and Animal Sciences, GBPUAT Pantnagar was taken for conducting the study with its letter no. IAEC/VSR/CVASc-232 dated 05.12.2015.

The study was carried out in 36 adult dogs of various breeds and of either sex presented for various clinical procedures in the TVCC Pantnagar. The dogs weighed between 10 and 15 kg and were divided randomly into three groups of twelve dogs each viz. A, B and C. Each group was further subdivided into two subgroups (1 and 2) and comprised of six dogs each. Hence there were six subgroups viz. A1, A2, B1, B2, C1 and C2. Clinical status of the animals was adjudged by recording the rectal temperature (°C), pulse (beats per minute) and respiration (breaths per minute). They were admitted one day before the surgery. The dogs were kept off feed for 12 hours and off water for 6 hours before the administration of anaesthetic agents.

All the dogs were subjected to the administration of atropine sulphate at the dose rate of 0.04 mg/kg S/C before the administration of induction and maintenance agents. Five minutes after the administration of atropine sulphate, injection dexmedetomidine was administered i.v. at two different dose rates (10 µg/kg and 15 µg/kg) as shown below, through an intravenous line in the cephalic vein of the forelimb. All future injections were administered through this line. Ten minutes after the administration of dexmedetomidine the animals were induced with etomidate, propofol or ketamine as per the respective anaesthetic protocols of the group. The induction agents were used at the minimum total dose possible, just enough to achieve endotracheal intubation and the doses of induction agents (required to achieve endotracheal intubation) were noted. After ten minutes of endotracheal intubation the maintenance of anaesthesia was started with sevoflurane in oxygen in all groups at the
rate of 2.2% of inhaled concentration constituting 1 MAC of sevoflurane. An equilibrium period of fifteen minutes was allowed before proceeding with the measurements of MAC of sevoflurane in various groups. The MAC of sevoflurane was measured in all the animals by the tail clamp method and the reduction in the MAC percentage of sevoflurane was also measured for individual animal. The average of the ‘lowest MAC with negative tail clamp response’ and the ‘highest MAC with positive tail clamp response’ was taken as the MAC for any particular measurement. The anaesthetic agents were administered as per the details given in the animals of various groups.

**Group A1**: Atropine sulphate (0.04 mg/kg s/c)-dexmedetomidine (10µg/kg i.v.)-etomidate (1.66±0.11 mg/kg i.v.) and sevoflurane.

**Group A2**: Atropine sulphate (0.04mg/kg s/c)-dexmedetomidine (15µg/kg i.v.)-etomidate (1.58±0.19 mg/kg i.v.3mg/kg i.v.) and sevoflurane.

**Group B1**: Atropine sulphate (0.04mg/kg s/c)-dexmedetomidine (10µg/kg i.v.)-propofol (2.46±0.19 mg/kg i.v.4mg/kg i.v.) and sevoflurane.

**Group B2**: Atropine sulphate (0.04mg/kg s/c)-dexmedetomidine (15µg/kg i.v.)-propofol (2.45±0.20 mg/kg i.v.4mg/kg i.v.) and sevoflurane.

**Group C1**: Atropine sulphate (0.04mg/kg s/c)-dexmedetomidine (10µg/kg i.v.)-ketamine (7.70±0.17 mg/kg i.v.5mg/kg i.v.) and sevoflurane.

**Group C2**: Atropine sulphate (0.04mg/kg s/c)-dexmedetomidine (15µg/kg i.v.)-ketamine (7.60±0.20 mg/kg i.v.5mg/kg i.v.) and sevoflurane.

Efficacy of the anaesthetic combinations was assessed by determining following parameters. Various parameters measured in the study were as follows.

**Clinical parameters**: induction time, duration of anaesthesia, muscle relaxation, pedal reflex, palpebral reflex, recovery time, sternal recumbency time, standing time, complete recovery time, required doses of drugs (induction agents) and MAC of sevoflurane.

**Physiological parameters**: heart rate, respiratory rate, rectal temperature, blood pressure (systolic, diastolic and mean), capillary refill time, haemoglobin oxygen saturation (SpO₂) and electrocardiography.
**Haematological parameters:** Haemoglobin, total erythrocyte count, erythrocyte sedimentation rate, total leucocyte count, differential leucocyte count, packed cell volume, erythrocytic indices (MCV, MCH, MCHC).

**Biochemical parameters:** serum glucose, serum insulin, serum cortisol, total protein, serum albumin, serum urea nitrogen, serum creatinine, alanine amino transferase and aspartate amino transferase.

Blood samples were collected for the determination of various haematological-biochemical parameters at 0, 0.5, 1, 6 and 24 hours time intervals. Serum was obtained and preserved for analysis. Haematology was done immediately after collection of blood and biochemical parameters were determined within 3 days of collection of samples.

The mean values of induction time was 167.83±7.45 seconds, 125.11±11.33 seconds, 179.00±23.05 seconds, 108.00±7.73 seconds, 60.83±8.76 seconds and 55.33±5.70 seconds in the animals of groups A1, A2, B1, B2, C1 and C2 respectively. It was observed that an increase in the dose of dexmedetomidine from 10 µg/kg body weight to 15 µg/kg body weight had caused a reduction in the induction time of animals in all the groups of animals. Duration of anaesthesia was 70±7.45 and 82.5±11.33 minutes in the animals of group A1 and A2 respectively. In the animals of group B1 and B2 duration of anaesthesia was 70.00±23.05 and 85.00±7.73 minutes respectively. In the animals of group C1 and C2 the duration of anaesthesia was 82.50±8.76 and 97.50±5.70 minutes respectively. The duration of anaesthesia in the present study was dependent on the responses of the animals to the tail clamp. Animals which did not respond to the tail clamp at any particular MAC of sevoflurane were subjected to further administration of sevoflurane and the animals responding positively to the tail clamp were not subjected to further administration of sevoflurane.

The median score of muscle relaxation in the animals of all groups increased gradually after the administration of premedication with dexmedetomidine and after induction of anaesthesia adequate muscle relaxation was obtained. Therefore all anaesthetic combinations tested in the study were able to provide adequate muscle relaxation including the animals administered with ketamine. The median pedal reflex and palpebral reflex score of all the animals gradually increased after administration of...
dexmedetomidine at 5 minutes interval. It was seen that the pedal reflex and palpebral reflex were totally lost after administration of the induction agents in all the groups except the palpebral reflex in group C where it was not lost completely at any time interval during the period of the study.

The recovery time in the animals in group A1, A2, B1, B2, C1 and C2 was 4.97±1.37 minutes, 5.30±0.64 minutes, 3.17±0.64 minutes, 6.48±0.38 minutes, 8.15±1.26 minutes and 10.75±2.12 minutes respectively. It was observed that an increase in the dose of dexmedetomidine caused an increase in the recovery time of animals of all the groups used in the study. The Sternal recumbency time in the animals of groups A1, A2, B1, B2, C1 and C2 were 8.52±0.90 minutes, 11.60±3.47 minutes, 7.61±0.87 minutes, 8.31±0.78 minutes, 11.12±1.8 minutes and 15.40±2.16 minutes respectively. The sternal recumbency time, increased significantly (P<0.01) in the groups A2, B2 and C2 administered with higher doses of dexmedetomidine (15µg/kg) as compared to the animals of group A1, B1 and C1 respectively which were subjected to the administration of dexmedetomidine at the dose rate of 10µg/kg body weight.

The standing time in the animals of group A1, A2, B1, B2, C1 and C2 was 13.07±3.70 minutes, 14.65±1.61 minutes, 11.00±0.89 minutes, 13.00±2.79 minutes, 15.71±2.10 minutes and 19.29±2.56 minutes respectively. The standing time increased significantly (P<0.01) in the groups A2, B2 and C2 administered with higher doses of dexmedetomidine (15µg/kg) as compared to the animals of group A1, B1 and C1 respectively. The complete recovery time in the animals of groups A1, A2, B1, B2, C1 and C2 were 20.00±2.77 minutes, 21.67±2.88 minutes, 14.00±0.94 minutes, 24.16±4.71 minutes, 20.53±2.34 minutes and 25.52±3.14 minutes respectively. The complete recovery time increased significantly (P<0.01) in the groups A2, B2 and C2 administered with higher doses of dexmedetomidine (15µg/kg) as compared to the animals of group A1, B1 and C1 respectively which were subjected to the administration of dexmedetomidine at the dose rate of 10µg/kg body weight.

The requirement of induction agents etomidate, propofol and ketamine was higher in the animals of group A1 (etomidate 1.66±0.11mg/kg), B1 (propofol 2.46±0.19mg/kg) and C1 (ketamine 7.70±0.17mg/kg) subjected to the administration of dexmedetomidine at the dose rate of 10g/kg body weight as compared to the animals of
groups A2 (etomidate 1.58±0.19mg/kg), B2 (propofol 2.45±0.20mg/kg) and C2 (ketamine 7.60±0.20mg/kg). The reductions in the MAC (%) of sevoflurane in the various groups of animals was 13.60±0.17 (A1), 21.18±1.66 (A2), 13.60±0.08 (B1), 22.70±0.20 (B2), 21.18±1.66 (C1) and 30.28±1.66 (C2). The reductions in the MAC of sevoflurane obtained in the groups A2, B2 and C2 administered with higher doses of dexmedetomidine (15µg/kg) was significantly higher (P<0.05) than the percentage reductions obtained in the groups A1, B1 and C1 administered with lower doses of dexmedetomidine (10µg/kg). The animals in the group C2 administered with dexmedetomidine at the dose rate of 15µg/kg body weight and induced with ketamine showed the greatest reduction of MAC of sevoflurane (30.28±1.66%).

There was a significant (P<0.01) decrease in the rectal temperature up to 45 minutes interval in all the groups of animals and thereafter its level had returned to near normal at or after 6 hours interval in all the groups of animals. A significant (P<0.01) decrease in the heart rate was observed up to 75 to 90 minutes after the administration of various combinations of drugs as compared to 0 hour values. Its level had reached near normal by 6 hours time interval in all the groups of animals. A significant (P<0.01) decrease in the respiratory rate heart rate was observed at 60 to 75 minutes after the administration of various combinations of drugs as compared to 0 hour values. Its level had reached near normal by 3 hours time interval in all the groups of animals.

Systolic, diastolic and mean arterial pressures showed a significant (P<0.01) reduction in its values at 60 and 75 minutes in the animals of groups A and B subjected to the administration of etomidate and propofol however no significant reduction was observed in these parameters subjected to the administration of ketamine in the animals of group C. The systolic, diastolic and mean arterial pressures soon returned to the base values at 3 hours interval in the animals of all the groups.

The capillary refill time was less than 2 seconds in all the animals of various groups at different time intervals. Hence cyanosis or pallor of the mucus membranes was not seen at any time interval in any of the groups of animals. Haemoglobin oxygen saturation (SpO2) was consistently higher than 95% at all the time intervals in all the groups of animals and cyanosis or pallor of the mucus membranes was not seen at any time interval in any group included in the study. No significant difference in SpO2 level
was observed in the animals of group A, B and C at different time intervals. ECG changes observed in the animals of group A1 were increased P-R and Q-T interval and inverted T waves, in the animals of group A2 sinus arrhythmia, in the animals of group B1 biphasic and inverted T wave, in the group B2 bradyarrhythmia, in the animals of group C1 elevated T waves whereas in the animals of group C2 biphasic T waves were observed.

Haemoglobin, total leucocyte count, total erythrocyte count showed significant (P<0.01) decrease in their values at 1 or 6 hours interval in all the animals of group A, B and C. Their level had returned to the baseline at 24 hours interval in all the groups of animals. Erythrocyte sedimentation rate showed a non-significant increase at 1 hour in the animals of groups A,B and C and its level had returned to the baseline values at 24 hours interval in all the groups of animals. Differential leucocyte count viz. neutrophils showed a non-significant increase at 6 hours interval whereas lymphocytes showed a significant (P<0.01) decrease at 1 and 6 hours interval. Their values had returned to baseline at 24 hours interval. Monocytes showed non-significant reduction whereas eosinophils showed significant increase at 1 or 6 hours interval which gained their base values at 24 hours in all the groups of animals.

The packed cell volume of the animals in group A1 was significantly (P<0.01) lower at 1 hour interval while in other groups its level was lower at 30 minutes time interval. Its level had returned to near the baseline values at 6 hours interval. The erythrocytic indices showed non-significant (P<0.01) decrease in their values at different time intervals viz. MCV at 1 and 6 hrs, MCH at 1 hour and MCHC at 6 hour time interval. Their values have returned to the baseline by 24 hours interval in the animals of all the groups. No significant difference was observed in the level of erythrocytic indices in the animals of group A, B and C at respective time intervals throughout the period of the study.

Serum glucose values increased significantly (P<0.01) at 1hr and 6 hr in the animals of all the groups. Its peak value was observed at 6 hours intervals. Glucose level had returned back near to the base line by 24 hours in all the groups of animals. There was no significant (P<0.05) difference in glucose level in the animals of group A, B and C at respective time intervals throughout the period of study. A significant
(P<0.01) decrease in serum insulin was observed up to 6 hours interval in all the animals of groups A, B and C and it has returned to near base values at 24 hours interval. No significant difference was observed in its level at respective time intervals in all the animals of groups A, B, and C throughout the period of study.

A significant (P<0.01) decrease in serum cortisol level was observed up to 24 hours interval in group A. In group B and C a significant (P<0.01) increase in cortisol level was observed at 1 and 6 hours. Cortisol value has returned to near base level at 24 hours interval in group B and C. No significant (P<0.01) difference was observed in its values at respective time intervals in groups B and C however in group A the values were significantly low at respective time intervals as compared to group B and C. A significant (P<0.05) decrease in total protein level was observed at 6 hours interval in all the groups except in the group A2. Its values returned to near base level at 24 hours interval. No significant (P<0.01) difference was observed in its values at respective time intervals in all the animals of groups A, B, and C throughout the period of study. A significant (P<0.01) decrease in serum albumin was observed at 1 hour interval in all the animals of groups A, B and C and it has returned to near base values at 24 hours interval. No significant difference was observed in its values at respective time intervals in all the animals of groups A, B, and C throughout the period of study.

Serum urea nitrogen showed a significant (P<0.01) increase in its level at 1 hours interval in all the groups of animals. No significant difference was observed in its values at respective time intervals in all the animals of groups A, B and C throughout the period of study. Its level has returned to near base level at 24 hours interval in the all groups of animals. Serum creatinine showed a significant (P<0.01) increase in its level at 1 and 6 hours interval. No significant difference (P<0.01) was observed in its values at respective time intervals in all the animals of groups A, B and C throughout the period of study. ALT and AST values showed a significant (P<0.01) increase in its level at 1 hours interval in all the groups of animals. No significant (P<0.01) difference was observed in its values at respective time intervals in all the animals of groups A, B and C throughout the period of study. Their levels have returned to near base values at 24 hours interval in the all groups of animals.

*Summary and Conclusions*.........
The anaesthesia was adjudged to be good and well maintained under the effect of various anaesthetic combinations (maintained with sevoflurane) in all the groups of animals and thereby permitted successful accomplishment of surgical operations viz. laparotomy, gastrotomy, cystotomy, enterotomy, ovariohysterectomy and splenectomy in the animals of group A, B and C. Surgical anaesthesia was maintained without any complications in various groups of animals however the level of anaesthesia was comparatively better in the animals of group A2, B2 and C2 as compared to the animals of groups A1, B1 and C1. No significant difference in heart rate and respiration rate was observed in the animals undergoing surgery as compared to those which were not put to surgical stress. Hypothermia was recorded in all the animals subjected to anaesthesia alone and the surgical operations. The decrease was relatively more in the animals undergoing surgery particularly abdominal surgery. It may be due to heat dissipation from the exposed abdominal organs. Duration of anaesthesia and recovery period was slightly prolonged in animals of the surgical group. The significant increase in the duration of anaesthesia in the animals of groups A2, B2 and C2 was due to the fact that more anaesthesia was required in these animals to complete the surgical procedures. Recovery was smooth, uncomplicated and uneventful in all the cases.

On the basis of the parameters observed in this study it was concluded that The administration of higher doses (15µg/kg) of highly selective alpha-2 agonist drug dexmedetomidine causes an increase in the recovery time, sternal recumbency time, standing time and complete recovery time as compared to its lower doses (10µg/kg) along with decrease in the induction time and required doses of anaesthetic induction agents (etomidate, propofol and ketamine). It imparts a smooth induction and recovery to the animals without any undesirable side effects. Dexmedetomidine causes significant reduction in the MAC of sevoflurane and the reduction was proportional to the dose of dexmedetomidine used. Transient changes within physiological limits were observed in the haematological and biochemical parameters which reached to the base levels by 24 hrs. The most efficacious and safe anaesthetic combination was atropine sulphate (0.04mg/kg s/c)-dexmedetomidine (15 µg/kg i.v.)-ketamine (7.60±0.20mg/kg i.v.)-sevoflurane in group C2 which showed 30.28±1.66% reduction in the MAC of sevoflurane followed by atropine sulphate (0.04mg/kg s/c)-dexmedetomidine (15 µg/kg iv)-propofol (2.45±0.20mg/kg i.v.)-sevoflurane in group B2 with 22.70±0.20% reduction in the MAC of sevoflurane.
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ABSTRACT

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Thirty six adult dogs (requiring various clinical procedures) used in this study were divided randomly into six subgroups (A1, A2, B1, B2, C1 and C2). All the dogs were subjected to the administration atropine sulphate at the dose rate of 0.04mg/kg s/c followed by dexmedetomidine given as preanesthetic at the dose rate of 10 µg/kg iv in groups A1, B1 and C1 and at the dose rate of 15 µg/kg iv in groups A2, B2 and C2. The animals of group A1 and A2 were induced with etomidate at the dose rate of 1.66±0.11mg/kg iv and 1.58±0.19mg/kg iv, animals of group B1 and B2 with propofol at the dose rate of 2.46±0.19mg/kg iv and 2.45±0.20mg/kg iv whereas the animals of group C1 and C2 were induced with ketamine at the dose rate of 7.70±0.17 iv and 7.60±0.20 mg/kg iv respectively. Anaesthesia was maintained in all the groups of animals with sevoflurane. The minimum alveolar concentration (MAC) of sevoflurane was determined in all the animals by the tail clamp method. The level of anaesthesia was determined by observing various clinical (Induction time, duration of anaesthesia, muscle relaxation, pedal reflex, palpebral reflex, recovery time, sternal recumbency time, standing time, complete recovery time, required doses of different drugs and sevoflurane MAC reductions (%), physiological (rectal temperature, heart rate, respiration rate, blood pressure, capillary refill time, haemoglobin oxygen saturation-SpO2, electrocardiography), haematological (haemoglobin, total erythrocyte count, erythrocyte sedimentation rate, total leucocyte count, differential leucocyte count, packed cell volume, erythrocytic indices MCV, MCH, MCHC and biochemical (serum glucose, serum insulin, serum cortisol, total protein, serum albumin, serum urea nitrogen, serum creatinine, alanine amino transferase and aspartate amino transferase) parameters.

The mean values of induction time were decreased in the groups receiving a higher dose of dexmedetomidine (10µg/kg vs. 15µg/kg). The duration of anaesthesia in the present study was dependent on the responses of the animals to the tail clamp. All anaesthetic combinations tested in the study were able to provide adequate muscle relaxation. The pedal reflex and palpebral reflex were totally lost after administration of the induction agents in all the groups barring the palpebral reflex in group C. The recovery time, sternal recumbency time, standing time and complete recovery time were increased in the groups administered with higher dose of dexmedetomidine as compared to the groups receiving lower dose of dexmedetomidine. An increase in the dose of dexmedetomidine resulted in a decrease in the required dose rate of induction agents (etomidate, propofol and ketamine) and the MAC of sevoflurane. The rectal temperature, heart rate and respiration rate showed significant decrease at various time intervals and reached to the base level values by 24 hours post anaesthesia. The systolic, diastolic and mean arterial pressures showed significant decrease in its values in the groups A and B but not in the group C, and returned to their base values by 3 hours post anaesthesia. In all the groups of animals the capillary refill time (CRT) and haemoglobin oxygen saturation (SpO2) were always less than 2 seconds and more than 95% respectively. ECG changes observed in the animals of group A1 were increased P-R and Q-T interval and inverted T waves, in the animals of group A2 sinus arrhythmia, in the animals of group B1 biphasic and inverted T wave, in the group B2 bradyarrhythmia, in the animals of group C1 elevated T waves whereas in the animals of group C2 biphasic T waves were observed. The haemoglobin, TLC and TEC values of the animals in various groups showed significant decrease in its values whereas the ESR showed a non-significant increase. No significant changes were observed in differential leucocyte count and erythrocytic indices. Serum glucose level increased significantly along with decrease in serum insulin levels. Serum cortisol level showed a significant decrease in its values in group A and a significant increase in groups B and C. Decrease in total protein and albumin level along with slight increase in urea nitrogen, creatinine, ALT and AST levels was observed in all the groups of animals. Clinical efficacy of the anaesthetic combinations was determined by performing various surgical operations. On the basis of above mentioned parameters it was concluded that the anaesthetic combinations used in the study have least deleterious effects on the different body systems. The most efficacious anaesthetic combination was atropine sulphate (0.04mg/kg im)-dexmedetomidine (15 µg/kg iv)-ketamine (5mg/kg iv)-sevoflurane (group C2) which caused a 30.28% reduction in MAC of sevoflurane.
इस अनुच्छेद में प्रयुक्त शब्दों को (किसी भी शब्दों के अर्थ की उपलब्धि के लिए) प्रतिविद्या के रूप में उपलब्ध कराता है।