CLINICAL EVALUATION OF DEXMEDETOMIDINE-MIDAZOLAM-KETAMINE WITH ATRACURIUM FOR ISOFLURANE ANAESTHESIA IN DOGS

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(15-MVP-001)

THESIS

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DECLARATION

I hereby declare that this thesis entitled **"Clinical evaluation of dexmedetomidine-midazolam-ketamine with atracurium for isoflurane anaesthesia in dogs"** is a bonafide record of research done by me during the course of research and that the thesis has not previously formed the basis for the award of any degree, diploma, fellowship or other similar title, of any other University or Society.

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EXTERNAL EXAMINER

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Introduction

1. INTRODUCTION

General anaesthesia with good muscle relaxation is inevitable for most of the surgical procedures performed in small animal practice. Practitioners perform general anaesthesia, by giving a sedative premedicant followed by an injectable induction agent with or without a benzodiazepine. The anaesthesia is then maintained either with intermittent boli of the induction agent or with an inhalant anaesthetic in oxygen.

When there is a need for more muscle relaxation during the surgical procedure, anaesthesia is deepened either by giving additional doses of the induction agent, or by increasing the concentration of the inhalant anaesthetic, with further doses of the benzodiazepines. But this practice always involves the side effects associated with the increased doses of the anaesthetic drugs.

Additional muscle relaxation, without deepening anaesthesia, could be attained by administering a peripheral acting muscle relaxant like atracurium. Atracurium is a non-depolarising muscle relaxant, and provides skeletal muscle relaxation through its effects at the neuromuscular junction. This drug gets eliminated from the body based on'Hoffmann degradation principle' which is dependent on body temperature and pH. Paralysis of all skeletal muscles, including the respiratory muscles, occurs at clinically used doses necessitating mechanical ventilation. Because of the paralyzing effects of the drug on the respiratory muscles and need of mechanical ventilation, apprehension prevails for the use of atracurium in providing muscle relaxation during general anaesthesia for surgical procedures in small animal practice.

Hence, the present study was undertaken to evaluate the clinico-physiological and haemodynamic effects of atracurium at a lower dose, in dogs induced with dexmedetomidine-midazolam-ketamine combination and maintained with isoflurane anaesthesia for routine surgeries. Once established, the protocol can be efficiently used in surgical procedures requiring marked muscle relaxation.

Review of Literature

2. REVIEW OF LITERATURE

2.1. BALANCED ANAESTHESIA AND ITS IMPORTANCE

Fabio *et al.* (2007) studied medetomidine-midazolam combination as intramuscular premedicant in dogs, followed by anaesthetic induction with propofol and maintenance with isoflurane. Authors reported that the intramuscular administration of medetomidine midazolam combination produced good sedation, muscle relaxation and analgesia.

Barletta *et al.* (2011), evaluated dexmedetomidine and ketamine along with opioids as an intramuscular injectable anaesthetic for castration in dogs reported that there was rapid and smooth induction of anaesthesia which allowed intubation in most cases and maintenance of anaesthesia sufficient for short surgical procedure.

Ahmad *et al.* (2013), in their study on dexmedetomidine with midazolam, ketamine and fentanyl observed that dexmedetomidine when combined with midazolam and ketamine proved to be effective in producing good sedation, muscle relaxation and anaesthesia and found it a safe combination.

2.2. ANAESTHETIC DRUGS

2.2.1. Dexmedetomidine

Lawrence and Lange (1997) in their study comparing effects of a single shot of dexmedetomidine and maintaining anaesthesia under isoflurane against a placebo group could not find any significant variation in the systolic blood pressure between the two groups, but heart rate varied and that the analgesic requirement post-operatively in patients administered dexmedetomidine was far lesser when compared with the placebo group.

Penttilä *et al*. (2004) found that dexmedetomidine when administered through a route that prevents its concentration peaks, produces long lasting effects on parasympathetic efferent neurones.

Santosh *et al.* (2013), in their study reported that dexmedetomidine, due to their high lipophilic property produced rapid onset of sedation and subjected the animal to recumbency.

Blanco *et al*. (2014) in their study of post-operative analgesic effects of different agents found that infusion of dexmedetomidine provided less analgesia when compared with fentanyl and Lidocaine-ketamine-dexmedetomidine drug combinations.

Bisht *et al.* (2016), in a study on the clinicophysiological and haematobiochemical effects of dexmedetomidine-etomidate-sevoflurane anaesthesia in dogs observed that the required dose to induce anaesthesia was significantly lower in animals induced with a higher dexmedetomidine dose of 15µg/kg body weight. The authors also found that there was no significant difference between the groups, in the time taken for the animals to recover from anaesthesia or the time required by the animals to regain sternal recumbency and assume a standing posture unassisted.

Rafee *et al.* (2016), reported in their study on the clinico-physiological and haemodynamic changes during midazolam-ketamine anaesthesia in dogs premedicated with dexmedetomidine with or without pentazocine that induction of anaesthesia with midazolam and ketamine, following premedication with dexmedetomidine produced a rapid and smooth induction of anaesthesia in dogs.

2.2.2. Midazolam

Fujii *et al.* (2001), in their study on the contractile ability of propofol and midazolam concluded that midazolam causes inhibition of contractility of

diaphragm thus producing pronounced respiratory depression compared to that with propofol.

Stegmann *et al.* (2001), in their study in midazolam premedicated dog under isoflurane anaesthesia showed minimal change in blood pressure.

Tamura *et al*. (2002), opined that midazolam, in addition to being a skeletal muscle relaxant was also a drug that prevented the sensation of pain.

Seddighi *et al.* (2011), reported that systemic administration of midazolam during isoflurane anaesthesia reduced the MAC value of isoflurane and a ceiling effect was produced after which there was no change in the MAC of isoflurane probably due to the ceiling effect of midazolam.

2.2.3. Ketamine

Ko *et al.* (2000), in their study on sedative and cardiorespiratory effects of medetomidine, medetomidine-butorphanol and medetomidine- ketamine in dogs, reported that the intensity of respiratory depression increased with an increased dose of ketamine administered during anaesthesia.

Sarrau *et al*. (2007) suggested that ketamine be used for providing pain relief after surgery only as a multimodal analgesic regimen rather than as a sole method.

2.2.4. Isoflurane

Hirshman *et al.* (1977), reported that Isoflurane at clinical doses reduced the ventilatory response during hypoxia and the rising carbon dioxide augmented the depression further.

Gelman *et al.* (1984), found that isoflurane caused minimal hepatic damage as suggested by the clearance of Indol green when compared to that of halothane.

Kastrup *et al.* (2005), in their study on volatile anaesthetic like sevoflurane on neuromuscular blockade found that sevoflurane produced augmentation of neuromuscular blockade produced by atracurium at doses of 0.2 and 0.3 mg/kg body weight.

2.2.5. Atracurium

Meyer *et al.* (1986), found that there is a linear trend to the recovery of an animal from atracurium infusion and occured at a rapid rate. They also proved that whole body hyperthermia can cause a faster elimination of atracurium by Hofmann degradation principle.

Ward *et al.* (1987) described that atracurium was inactivated by a fission mechanism termed Hofmann degradation principle wherein the drug was metabolised into laudanosine and monoquarternary acrylate and monoquarternary acid and alcohol which at their peak concentration did not prove to be detrimental to health even in renal compromised patients.

Clutton *et al.* (1992), opined that shifting from mechanical ventilation to spontaneous ventilation during antagonism from neuromuscular blockade using reversal agents like neostigmine with atropine or glycopyrrolate, cardiac output was affected, which could be avoided by providing controlled hyperventilation so as to suppress the respiratory stimulation at the respiratory centre.

Knutgen *et al.* (1999), observed that the pharmacodynamics of atracurium is inversely related to the septicaemia present in an animal and that larger doses are warranted to produce sufficient neuromuscular stimulation.

2.3. MONITORING OF ANAESTHESIA

2.3.1. Effects on Respiratory system

2.3.1.1. Respiratory rate

Meyer *et al.* (1986), in their study on the determination of continuous rate infusion of atracurium in animals with whole body hyperthermia observed that the last muscles to be relaxed are the intercostal and diaphragm, leading to apnoea.

Stegmann *et al.* (2001), found that midazolam premedication caused respiratory depression with a decrease in PaO_2.

Santhosh *et al.* (2013), observed that the administration of dexmedetomidine-midazolam-ketamine combination in an anaesthetic procedure, significantly reduced the respiratory rate.

Rafee *et al.* (2016), observed in their study on the clinico-physiological and haemodynamic effects of midazolam-ketamine anaesthesia in dogs premedicated with dexmedetomidine with or without pentazocine that, the anaesthetic drug combination produced a significant decrease in the respiratory rate attributed to the combined effect of the drugs

2.3.1.2. End-tidal carbon dioxide ($EtCO_2$) concentration

Nguyen *et al.* (1992) summarised that, dexmedetomidine when combined with isoflurane produced significant depression of the hypercapnic response.

Barletta *et al.* (2011), in their study using dexmedetomidine-ketamine combination, supported with an opioid, found that the end-tidal concentration of carbon dioxide increased due to depression of respiratory muscles, which was easily corrected by supplementing 100% oxygen.

2.3.1.3. Saturation of oxygen in peripheral blood (SpO_2)

Lawrence and Lange (1997), observed in their study in the comparison between dexmedetomidine-isoflurane group with the placebo that the oxygen saturation of the animal remained above 95% and no variations were observed between the groups.

Rafee *et al.* (2016), in their study on the clinico-physiological and haemodynamic effects of midazolam-ketamine anaesthesia in dogs pre-medicated with dexmedetomidine with or without pentazocine, observed that the saturation of oxygen in the peripheral blood was maintained between 90 -97, throughout the anaesthetic period.

2.3.2. Effects on Cardiovascular system

2.3.2.1. Heart rate and function

Hackett *et al.* (1989), in their comparison on the haemodynamic effects of 5 non-depolarising skeletal muscle relaxants, atracurium and pancuronium observed least variations in dynamic parameters of blood on administration of atracurium and pancuronium.

On comparative haemodynamic study between isoflurane and sevoflurane found that, isoflurane at 2 MAC caused an increase in coronary blood flow thus providing adequate oxygenation of the cardiac musculature, Bernard *et al.* (1990).

Fukushima *et al.* (1990), in their study on the cardiovascular effect of atracurium and its metabolite reported that atracurium caused tachycardia, resulting from histamine release.

Barletta *et al.* (2011), reported that bradycardia is produced in dogs induced with dexmedetomidine-ketamine combination along with an opioid, which they suggested that it might have occurred due to the reflex response to the

α2 adrenergic agonist, dexmedetomidine attributed to its biphasic response producing vasoconstriction due to a high blood pressure.

2.3.2.2. Non-invasive Blood pressure

Fukushima *et al.* (1990), in their study on the cardiovascular effect of atracurium and its metabolite reported that atracurium caused hypotension which could be attributed to the release of histamine.

McMurphy *et al.* (2004), in their study on the effect of atracurium on the blood pressure, in isoflurane anaesthetized dogs did not observe any variations.

Uilenreef *et al*. (2008) suggested that one of the benefit of combining dexmedetomidine and isoflurane was dexmedetomidine induced vasoconstriction attenuated by favourable afterload and cardiac work due to the peripheral vasodilatory properties of isoflurane.

2.3.2.3. Electrocardiography

Barletta *et al.* (2011), observed that an anaesthetic combination including dexmedetomidine-ketamine-opioid produced sinus arrhythmias during recovery with a high intensity than that seen during the peri-operative period which could have been due to reduction in sympathetic outflow resulting from absence of surgical stimulation.

2.3.2.4. Blood gases and electrolytes

Sullivan *et al.* (1998), in their study on the respiratory function and extraocular muscle paralysis following administration of pancuronium bromide reported that, rapid and marked acidosis was developed in dogs receiving the neuromuscular blocker in the absence of mechanical or assisted ventilation. They also reported that hypoventilation does not necessarily decreased the partial pressure of oxygen if 100% oxygen is being administered to the dog.

Boscan *et al.* (2005), in their study on the cardiovascular and respiratory effects on ketamine-isoflurane-anaesthetized dogs found that ketamine reduced the partial pressure of carbon dioxide proportionally to the level of ketamine concentrations reached in the blood, thus having a ventilation-improving effect, when compared to isoflurane alone. They also reported that ketamine produced a decrease in the base excess and bicarbonate levels, but well maintained within the normal ranges.

Hofmeister *et al.* (2009), in their study on the effects of graded doses of propofol for anaesthesia induction on cardiovascular parameters and intraocular pressures in normal dogs, reported that an increase in the $PaCO_2$ with a stable base excess, induced by the profound respiratory depression caused by propofol and atracurium, characterized the decrease as respiratory acidosis.

Kumar *et al.* (2016), in their study on the clinicophysiological and haematobiochemical effects of dexmedetomidine along with ketamine in dogs, reported decrease in the serum potassium and sodium, which was attributed to the entry of potassium into the cells due to the action of insulin in conjugation with corticosteroids.

2.3.3. Effects on Body temperature

Boscan *et al.* (2005), reported that administration of ketamine during isoflurane anaesthesia in dogs improved the core body temperature in a linear fashion based on the concentration of ketamine attained during infusion.

Fabio *et al.* (2007), in their study reported that, α2-adrenoceptor agonists due to their biphasic response produced a vasoconstrictive effect initially producing a rise in the body temperature followed by a decrease in the same.

2.3.4. Effects on Neuromuscular conduction

Donati *et al.* (1986), in their study on the potency of pancuronium at the diaphragm and at the *adductor pollicis* muscle in humans, observed that the resistance to neuromuscular blockade is highest at the diaphragm followed by other respiratory muscles and muscles of face.

Adam *et al.* (2001), in their study on cis-atracurium, one of the 10 isomers of atracurium reported that a two nerve muscle unit be used in the monitoring of neuromuscular blockade, because when compared with the facial muscle unit, the distal limb blockade fade later and returns earlier. The authors also reported that the twitches returned as soon as the blockade was reversed using an anticholinesterase and neostigmine, during general anaesthesia.

Kirov *et al.* (2004), in their study on the comparison of neuromuscular blocking effect of cisatracurium and atracurium on the larynx and *adductor pollicis* muscle, found that the estimation of neuromuscular blockade at the larynx is more significant when compared to that at the *adductor pollicis* muscle.

Flores *et al.* (2011), in their study on twitch potentiation measured after atracurium administration observed that in a clinical setting with an aim to reduce the complications arising from residual neuromuscular blockade, the assessment of Train-of-four ratio was preferred.

2.3.5 Effects on ventilatory parameters

Nguyen *et al.* (1992), conducted study on dexmedetomidine with and without isoflurane and found that, dexmedetomidine did not elicit any significant effect on the effect on ventilatory hypoxia in dogs induced with dexmedetomidine and isoflurane. They also found that dexmedetomidine caused a dose dependent decrease on the minimum alveolar concentrations of isoflurane.

Sullivan *et al.* (1998), in their study on the respiratory function and extraocular muscle paralysis following administration of pancuronium bromide adviced the use of mechanical or assisted ventilation in all the animals that received a neuromuscular blocking agent to avoid hypercapnia and subsequent complications.

McMurphy *et al.* (2004), suggested that intermittent positive pressure ventilation be administered to animals recovering from atracurium CRI, even after reappearance of the last twitch, because of the remaining substantial respiratory suppression.

2.3.6 Changes in blood glucose

Bisht *et al.* (2016), in a study on the clinicophysiological and haematobiochemical effects of dexmedetomidine-etomidate-sevoflurane anaesthesia in dogs, observed an increase in the blood glucose, after induction of anaesthesia in dogs using dexmedetomidine and etomidate followed by maintenance with sevoflurane.

Kumar *et al.* (2016), in their study on the clinicophysiological and haematobiochemical effects of dexmedetomidine along with ketamine in dogs, suggested that the increase in the blood glucose levels observed following administration of dexmedetomidine and/or dexmedetomidine and ketamine might have been due to the hypoinsulinemia produced by dexmedetomidine.

2.3.7. Haematological and Serum biochemical changes

Boscan *et al.* (2005), in their study reported that incorporating ketamine in an anaesthetic protocol involving a inhalant anaesthetic mixture like isoflurane

increased the volume of packed red cells, haemoglobin and total protein, which could increase in presence of a noxious stimulation.

Saunders *et al.* (2009), in their study on cardiac troponin and C-reactive protein concentration during anaesthesia, suggested that tissue hypoxia can be indirectly measured by estimating the lactate content in blood.

Kumar *et al.* (2016), reported a non-significant increase in the alanine aminotransferase and aspartate aminotransferase values which returned to the normal ranges in 48 hours, in their study with dexmedetomidine and ketamine. They also reported a transient decrease in the total protein which was suggested to be resulting from haemodilution and an increase in the blood urea nitrogen and creatinine which might have been due to the inhibitory effect on the renal blood flow and resultant reduction in the glomerular filtration rate. Reduction in the haemoglobin, volume of packed red cells and total erythrocyte was also noted in the study, which the authors suggested, might have been due to the pooling of blood in the spleen as a consequence of the effect of administration of dexmedetomidine.

Materials and Methods

3. MATERIALS AND METHODS

The study was carried out in twelve dogs which underwent various surgical procedures, in the Department of Veterinary Surgery and Radiology (Teaching Veterinary Clinical Complex) College of Veterinary and Animal Sciences, Pookode, Wayanad.

3.1 SELECTION OF ANIMALS

Dogs of the age group one to seven years, belonging to both sexes were posted for various surgeries, following overnight fasting, and were randomly allotted to two groups – Group I and Group II, of 6 animals each.

Group I (Control Group)	Group II (Study Group)
Inj. Dexmedetomidine @ 5 µg/kg, Inj. Midazolam @ 0.2 mg/kg, Inj. Ketamine @ 5 mg/kg body weight, was combined in a single syringe and given as intramuscular injection. Anaesthesia was maintained using Isoflurane[d] in 95-99% oxygen for a period of 60 minutes following induction indicated by the abolition of pain reflex. At the end of the procedure, isoflurane vaporizer was cut off and animal was maintained on oxygen alone.	Inj. Dexmedetomidine @ 5 µg/kg, inj. Midazolam @ 0.2 mg/kg, Inj. Ketamine @ 5 mg/kg body weight, was combined in a single syringe and given as intramuscular injection. Anaesthesia was maintained using Isoflurane[d] in 95-99% oxygen for a period of 60 minutes following induction indicated by the abolition of pain reflex. Inj. Atracurium @ 0.1 mg/kg body weight as bolus injection was administered, immediately followed by a continuous rate infusion (CRI) of Atracurium @0.1 mg/kg/hour. At the end of the procedure, isoflurane vaporizer was cut off and animal was maintained on oxygen alone.

3.2 DRUGS USED IN THE ANAESTHETIC STUDY (Plate 1 and 2)

3.2.1 Dexmedetomidine

Dexmedetomidine (Dexmeto®, 100 µg/mL (Miraculus Pharma Pvt. Ltd. (Aesmira), 213, Shivai Dongre Industrial Premises, Andheri Kurla Road, Mumbai, Maharashtra, India) is the dextro enantiomer of medetomidine, the methylated derivative of etomidine.

3.2.2 Midazolam

Midazolam (Mezolam®, 5mg/mL (Neon Medicals, 28 Mahai, Andheri, Mumbai, Maharashtra, India) is an imidazobenzodiazepine, belonging to benzodiazepine class.

3.2.3 Ketamine

Ketamine (Zokent®, 50 mg/mL (Miraculus Pharma Pvt. Ltd. (Aesmira), 213, ShivaiDongre Industrial Premises, Andheri Kurla Road, Mumbai, Maharashtra, India) is an arylcyclohexylamine derivative.

3.2.4 Atracurium

Atracurium (Crimat®, 25 mg/2.5 mL (Miraculus Pharma Pvt. Ltd. (Aesmira), 213, ShivaiDongre Industrial Premises, Andheri Kurla Road, Mumbai, Maharashtra, India)) is a bisquaternary benzylisoquinolinium compound.

3.2.5 Isoflurane

Isoflurane (Sosrane®, Neon Medicals, 28 Mahai, Andheri, Mumbai, Maharashtra, India) is an inhalant anaesthetic.

3.3 INSTRUMENTATION

3.3.1 Multi Parameter Patient Monitor (Plate 3)

BPL Multi Parameter Monitor ULTIMA PRIME of BPL Ltd, Palakkad, Kerala, India, was used for the advanced anaesthetic monitoring of

electrocardiography, heart rate, pulse rate, concentrations of gases and anaesthetics, respiratory rate, saturation of oxygen in peripheral blood and non-invasive blood pressure.

3.3.2 Anaesthesia machine (Plate 3)

Anaesthesia and ventilation was maintained during the surgical procedure using Datex-Ohmeda 9100c anaesthesia workstation, of Datex-Ohmeda, Instrumentarium Corp, Helsinki, Finland.

3.3.3 Blood Gas Analyzer (Plate 4 A)

A Blood gas analyser (epoc® Blood Analysis System, Alere™, No. 404, 4th floor, BPTP Park Centra, NH-8, opp. 32nd milestone, Haryana) was used to estimate the Blood gases and ions, during the procedure.

3.3.4 Neuromuscular stimulator-mapper-locator (Plate 4 B)

A Neuromuscular stimulator cum mapper cum TOF monitor (NSML-100, Inmed Equipments, Pvt. Ltd. 710, Linking Road, Khar, Mumbai, India), was used to monitor Train-of-four parameter, which reflected the degree of muscle relaxation, during this study.

3.3.5 Serum Biochemistry Analyzer

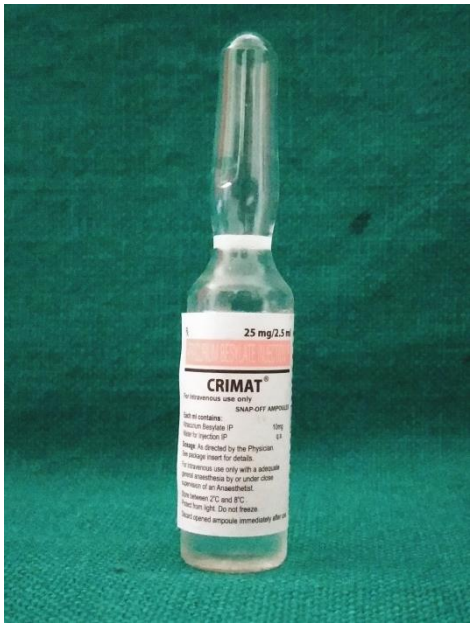
A semi auto serum biochemical analyser – MasterT® of Hospitex Diagnostics, Italy was employed for the serum biochemical analysis in this study.

3.4 MAIN ITEMS OF OBSERVATION

3.4.1 Time Taken for Induction

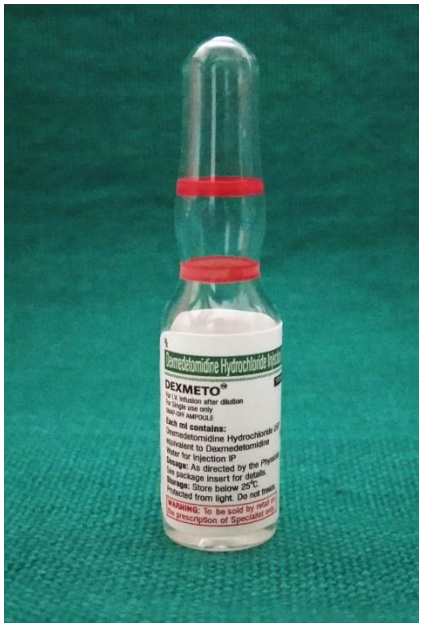
Time taken for induction (in minutes) was estimated from the time of start of injection of Dexmedetomidine-Midazolam-Ketamine combination, to abolishment of cough reflex permitting endotracheal intubation.

Plate 1. Drugs used in the Anaesthetic Protocol



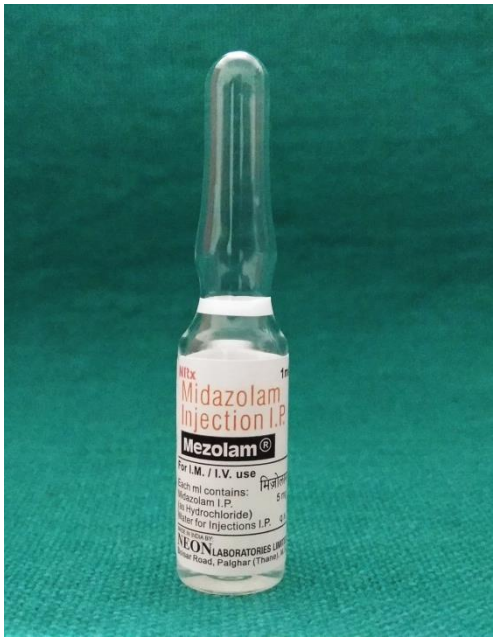
Crimat® 25mg/2.5mL

(Atracurium)

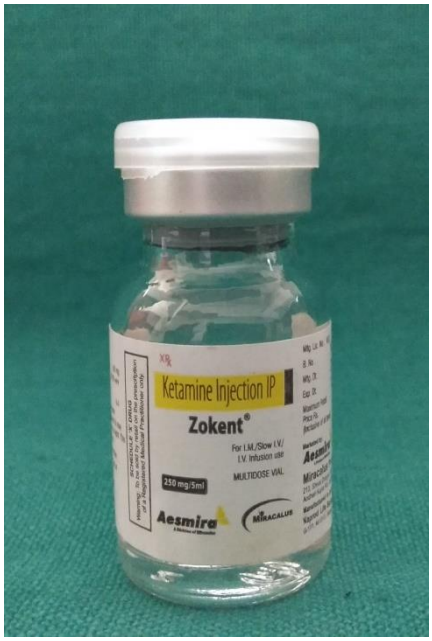


Dexmeto® 100µg/mL

(Dexmedetomidine)



Mezolam® 5mg/mL (Midazolam)

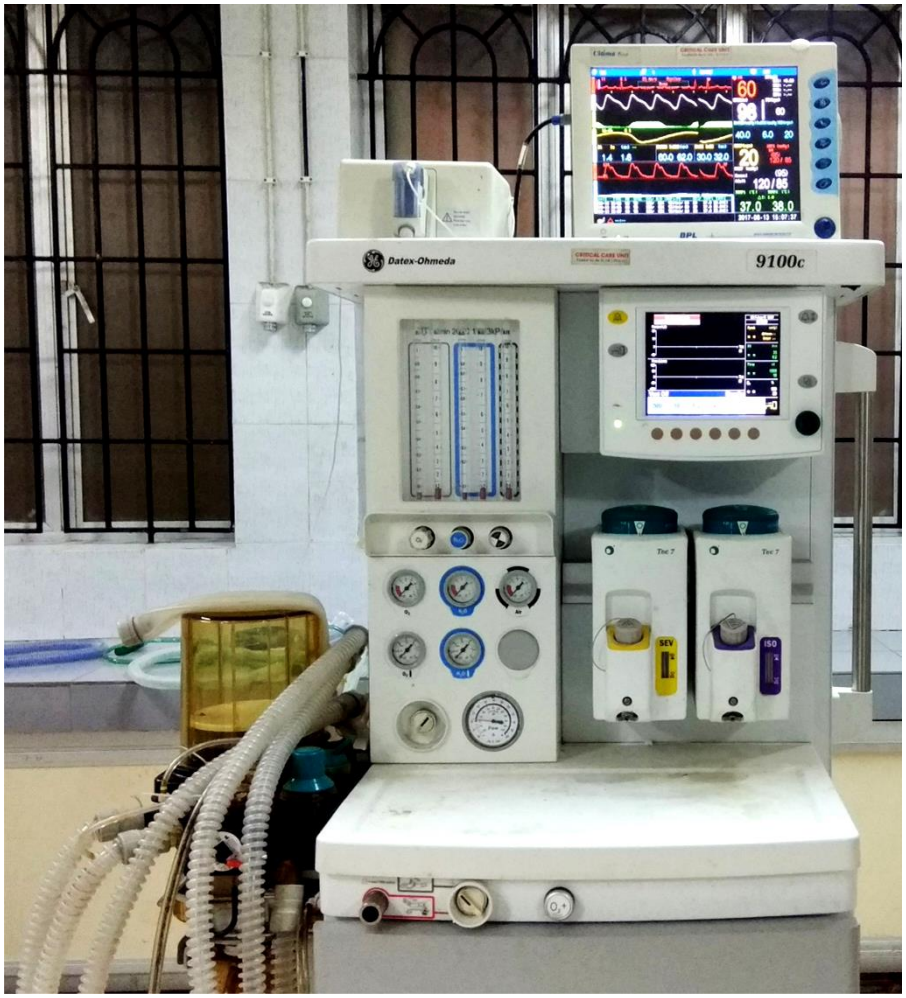


Zokent® 50mg/mL (Ketamine)

Plate 2. Drugs used in the Anaesthetic Protocol

Sosrane® (Isoflurane)

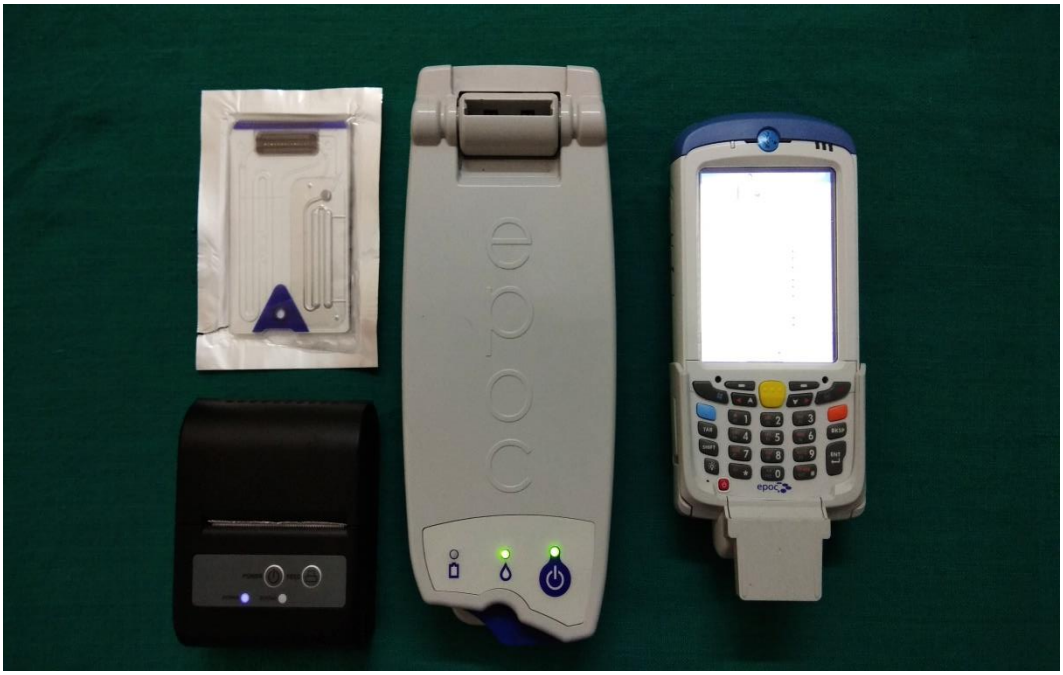
Plate 3. Instrumentation



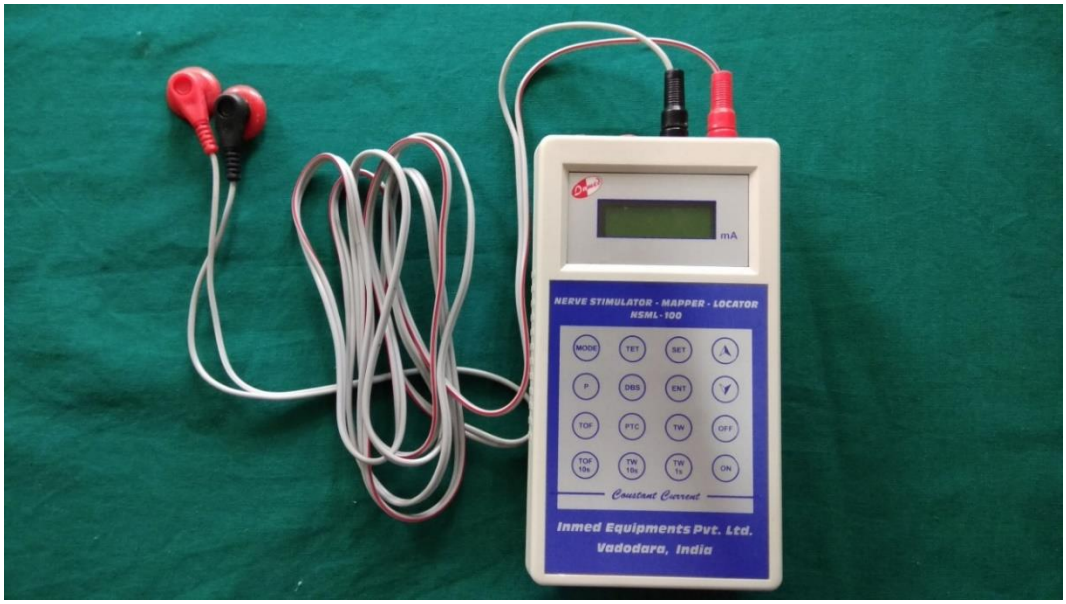
Datex-Ohmeda 9100c Anaesthesia Workstation

and Multi-parameter Patient Monitor

Plate 4. Instrumentation



(A) epoc® Blood Analysis System



(B) Neuromuscular Stimulator-Mapper-Locator Unit

3.4.2 Quality of Induction

Quality of anaesthetic induction was judged based on the sedation, character of induction and ease of intubation.

3.4.3 Time Taken for Recovery

Time taken for recovery (in minutes) was noted as the time period from the stoppage of Isoflurane administration to the rejection of endotracheal tube.

3.4.4 Quality of Recovery

Quality of recovery was judged according to the character of transition from anaesthesia, presence or absence of paddling and vocalisation.

3.4.5 Time Taken to Assume Sternal Recumbency

The time taken for the animal to attain sternal recumbency (in minutes) after termination of isoflurane and continuous rate infusion of atracurium was noted as the time taken to assume sternal recumbency.

3.4.6 Time Taken to Stand up Unassisted

The ability of the animal to stand unassisted for a minimum of 10 seconds, after termination of isoflurane administration (in minutes) was taken as the time to stand.

3.4.7 Physiological Parameters

3.4.7.1 Rectal Temperature

In both the Group I and Group II animals, rectal temperature was noted (in ^{0}C) before induction, after induction and every 10 minutes thereafter throughout the anaesthetic period.

3.4.7.2 Heart rate

Heart rate (beats per minute) was recorded before induction, after induction and every 10 minutes throughout the anaesthetic period.

3.4.7.3 Pulse rate

Pulse rate (pulse per minute) was monitored before induction, after induction and every 10 minutes thereafter till the end of anaesthetic period.

3.4.7.4 Respiratory rate

Respiratory rate (inspirations or expirations per minute) was measured before induction, after induction and continuously monitored using the ventilator and recorded every 10 minutes thereafter, throughout the anaesthetic period.

3.4.7.5 Capillary refill time (CRT)

Capillary refill time was noted (in seconds) before induction, after induction and every 10 minutes thereafter till the end of anaesthetic period.

3.4.7.6 Non- Invasive Blood Pressure Monitoring (NIBP)

Non-invasive blood pressure (mmHg) was measured before induction, after induction and every 10 minutes thereafter till the end of anaesthetic period.

3.4.7.7 Electrocardiogram (ECG)

Electrocardiograhy was recorded before induction, after induction and every 10 minutes thereafter till the end of anaesthetic period.

3.4.7.8 End-tidal Carbondioxide ($EtCO_2$)

End tidal carbon dioxide (mmHg) was measured every 10 minutes following intubation throughout the anaesthetic period.

3.4.7.9 Saturation of Oxygen in Peripheral Blood

Saturation of oxygen in peripheral blood (percent) was monitored in all dogs using a tongue probe, over the multipara patient monitor. The readings were recorded from the time of induction till recovery, at every 10 minutes interval. The readings were recorded in percentage.

3.4.8 Haematology

In Group I, blood samples were collected before induction, immediately after induction and every 30 minutes till end of anaesthetic period. In Group II, blood samples were collected before induction, immediately after induction, after atracurium administration and every 30 minutes thereafter till end of anaesthetic period.

For haematology, whole blood was collected in K_3 EDTA vials and noted for complete blood count (Haemoglobin concentration, Volume of packed red cells, Total erythrocyte count, Total leucocyte count, Differential leucocyte count). Samples were analysed using the auto haematology analyser (eosVet, Exigo Auto Blood Analyzer of Boule Medical AB, Sweden).

3.4.9 Blood Gas Analysis

Arterial blood collected in pre-heparinised syringe before induction, after induction and every 30 minutes till the end of anaesthetic period. Samples were then evaluated for, blood glucose, blood gases (PO_2, PCO_2), pH, bicarbonate, lactate, base excess value and electrolytes (sodium and potassium) using a semi-automatic blood gas analyzer.

3.4.10 Serum Biochemistry

For serum biochemistry, blood was collected before induction and after recovery, in Clot activator tubes. The sera obtained were subjected to analysis using commercially available enzyme reagents and absorbance read against light at specific intensities, using a serum biochemistry analyser.

3.4.10.1 Total Protein

Total protein was estimated by biuret method. A commercial Liquick Cor – TOTAL PROTEIN 60 (PZ Cormay S. A., Wiosenna 22, 05-092, Lomianki, Poland), was used for this procedure, and readings expressed in g/dL.

3.4.10.2 Serum Albumin

Serum albumin was estimated using the commercial Liquick Cor-ALBUMIN 60 (PZ Cormay S. A., Wiosenna 22, 05-092, Lomianki, Poland) and readings obtained were expressed in g/dL.

3.4.10.3 Serum Globulin

Serum globulin was estimated from the difference between total protein and albumin and expressed in g/dL.

3.4.10.4 Total Bilirubin

Total bilirubin was estimated using the commercial BILIRUBIN T&D (Spinreact S.A.U/SPINREACT, S.A. Ctra. Santa Coloma, 7, E-17176, Sant Esteve de Bas (Girona), Espana) and readings obtained expressed in mg/dL.

3.4.10.5 Alanine Aminotransferase

ALT was estimated using the commercial GPT (ALT)–LQ (Spinreact S.A.U/SPINREACT, S.A. Ctra. Santa Coloma, 7, E-17176, Sant Esteve de Bas (Girona), Espana) and readings obtained was expressed in IU/L.

3.4.10.6 Aspartate Aminotransferase

AST was estimated using the commercial GPT (AST)-LQ (Spinreact S.A.U/SPINREACT, S.A. Ctra. Santa Coloma, 7, E-17176, Sant Esteve de Bas (Girona), Espana) and readings obtained was expressed in IU/L.

3.4.10.7 Alkaline Phosphatase

ALP was estimated using the commercial ALP-LQ (Spinreact S.A.U/SPINREACT, S.A. Ctra. Santa Coloma, 7, E-17176, SantEsteve de Bas (Girona), Espana) and readings obtained was expressed in IU/L.

3.4.10.8 Blood Urea Nitrogen (BUN)

BUN was estimated by Enzymatic method with urease and glutamate dehydrogenase. The commercial Urea-LQ (Spinreact S.A.U/SPINREACT, S.A. Ctra. Santa Coloma, 7, E-17176, SantEsteve de Bas (Girona), Espana), was used for this purpose and readings obtained were expressed in mg/dL.

3.4.10.9 Creatinine

Creatinine was estimated by Jaffe's method using the commercial CREATININE-J (Spinreact S.A.U/SPINREACT, S.A. Ctra. Santa Coloma, 7, E-17176, SantEsteve de Bas (Girona), Espana), and readings obtained expressed in mg/dL.

3.5 EVALUATION OF MUSCLE RELAXATION BY NEUROMUSCULAR STIMULATION

Supramaximal current was measured before induction by placing the leads of the neuromuscular monitor over the metacarpals or metatarsals. Train-of-four was estimated before induction, after induction and at every 10 minutes throughout the anaesthetic period in the control and study group.

3.6 STATISTICAL ANALYSIS

The data obtained during the study were subjected to statistical analysis using the statistical software SPSS version 21.0. The value of $p < 0.05$ was considered as significant.

Comparison between two groups for haematological parameters and serum values were done and subjected to Independent Student t-test. Within group values for each parameters were subjected to Repeated Measures ANOVA.

Results

4. RESULTS

The study was carried out in twelve dogs which underwent different surgical procedures in the Department of Veterinary Surgery and Radiology (Teaching Veterinary Clinical Complex), College of Veterinary and Animal Sciences, Pookode. The observations of the study are presented below.

4.1 ANAESTHETIC PARAMETERS

4.1.1 Induction parameters

4.1.1.1 Character and quality of anaesthetic induction

The injectable anaesthetic combination produced profound sedation in all the twelve animals studied. The transition to anaesthesia was calm in all animals, without any paddling. Eyeball rolled ventrally and medially in all animals upon anaesthesia. There was profound relaxation of jaw muscle and laryngeal tone permitting intubation in all animals. The quality of anaesthetic induction was thus judged as excellent in all the animals studied.

The observations on the character and quality of anaesthetic induction in the animals studied are presented in Table 1.

4.1.1.2 Time taken for onset of various anaesthetic signs and induction of anaesthesia

The time taken for induction of anaesthesia in the twelve animals studied, following the injectable anaesthetic combination was 8.16 ± 0.76minutes.

Observations on time taken for induction following the injectable anaesthetic combination are detailed in Table 2.

Table 1. Observations on the character and quality of anaesthetic induction						
	Nausea or Vomiting	Jaw muscle tone	Position of eyeball	Palpebral reflex	Pedal reflex	Laryngeal reflex
Animal 1	Absent	Moderate	Ventrally and medially	Present	Present	Present
Animal 2	Absent	Moderate	Ventrally and medially	Present	Present	Present
Animal 3	Absent	Moderate	Ventrally and medially	Present	Present	Present
Animal 4	Absent	Moderate	Ventrally and medially	Present	Present	Present
Animal 5	Absent	Moderate	Ventrally and medially	Present	Present	Present
Animal 6	Absent	Moderate	Ventrally and medially	Present	Present	Present
Animal 7	Absent	Moderate	Ventrally and medially	Present	Present	Present
Animal 8	Absent	Moderate	Ventrally and medially	Present	Present	Present
Animal 9	Absent	Moderate	Ventrally and medially	Present	Present	Present
Animal 10	Absent	Moderate	Ventrally and medially	Present	Present	Present
Animal 11	Absent	Moderate	Ventrally and medially	Present	Present	Present
Animal 12	Absent	Moderate	Ventrally and medially	Present	Present	Present

Table 2. Time taken for onset of various anaesthetic signs and induction of anaesthesia (minutes)	
Parameter	Mean ± SE (n=12)
Time to first sign (Time to show ataxia)	0.97 ± 0.07
Time to sternal	2.71 ± 0.25
Time to head down	4.36 ± 0.54
Time to assume lateral recumbency	6.21 ± 0.73
Time taken for induction (Time taken from injection of Dexmedetomidine-Midazolam-Ketamine combination to intubation)	8.16 ± 0.76

4.1.2 Recovery parameters

The observations on the recovery parameters in the control (group I) and study (group II) groups, following weaning from anaesthesia, are presented in Table 3.

4.1.2.1 Time taken for recovery

Time taken for recovery in animals of the control group (Group I) was 6.63 ± 1.77 minutes, while it was 5.62 ± 1.66 minutes in the study group (Group II).

There was no significant difference in the time taken for recovery between the control and study group.

4.1.2.2 Time to regain sternal recumbency

Time taken for the animals in the control group (Group I) to regain sternal recumbency after weaning from anaesthesia was 15.35 ± 4.38 minutes, while it was 10.60 ± 3.53 minutes in study group (Group II).

There was no significant difference in the time taken to regain sternal recumbency between the groups.

4.1.2.3 Time to assume standing posture unassisted

Time taken for the animals in the control group (Group I) to assume standing posture unassisted following weaning from anaesthesia was 42.67 ± 9.03 minutes, while it was 47.67 ± 8.25 minutes in the study group (Group II).

The time to assume standing posture unassisted did not vary significantly between the groups.

4.2 PHYSIOLOGICAL PARAMETERS

4.2.1 Rectal Temperature (Table 4, Fig. 1)

The Mean ± SE values for rectal temperature in animals of control group (Group I) before induction, after induction and at 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th}

minute post induction were 38.95 ± 0.21, 39.00 ± 0.26, 38.85 ± 0.16, 38.58 ± 0.23, 38.60 ± 0.29, 38.32 ± 0.17, 38.38 ± 0.25, 38.37 ± 0.28 ºC, respectively.

The Mean ± SE values for rectal temperature in animals of the study group (Group II), before induction, after induction and at 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minutes were 38.40 ± 0.40, 38.05 ± 0.32, 37.60 ± 0.34, 37.35 ± 0.47, 37.47 ± 0.40, 37.47 ± 0.43, 37.55 ± 0.47, 37.53 ± 0.41ºC respectively.

The rectal temperature noted at 10^{th}, 20^{th} and 30^{th} minute post induction in the study group were significantly lower (p value) than those of the control group for their respective observation times.

4.2.2 Heart rate (Table 5, Fig. 2)

The Mean ± SE values for heart rate (beats per minute) in animals of control group (Group I) before induction, after induction and at 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minute post induction were 96.33 ± 5.71, 91.17 ± 5.24, 82.67 ± 8.63, 77.67 ± 8.32, 86.83 ± 5.95, 86.67 ± 7.49, 83.67 ± 8.28, 88.00 ± 2.63 respectively.

The Mean ± SE values for heart rate (beats per minute) in animals of the study group (Group II), before induction, after induction and at 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minutes were 103.67 ± 4.30, 90.50 ± 7.90, 84.50 ± 9.89, 88.00 ± 9.69, 102.00 ± 3.47, 96.67 ± 7.11, 98.50 ± 7.06, 101.00 ± 8.13 respectively.

The heart rate in the study group at any point of observation did not vary significantly when compared to those of the control group.

4.2.3 Pulse rate (Table 6)

The Mean ± SE values for pulse rate (beats per minute) in animals of control group (Group I) before induction, after induction and at 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minute post induction were 96.33 ± 5.71, 91.17 ± 5.24, 82.67 ± 8.63, 77.67 ± 8.32, 86.83 ± 5.95, 86.67 ± 7.49, 83.67 ± 8.28, 88.00 ± 2.63 respectively.

The Mean ± SE values for pulse rate (beats per minute) in animals of the study group (Group II), before induction, after induction and at 10^{th}, 20^{th}, 30^{th}, 40^{th},

50^{th} and 60^{th} minutes were 103.67 ± 4.30, 90.50 ± 7.90, 84.50 ± 9.89, 88.00 ± 9.69, 102.00 ± 3.47, 96.67 ± 7.11, 98.50 ± 7.06, 101.00 ± 8.13 respectively.

The pulse rate in the study group at any point of observation did not vary significantly when compared to those of the control group.

4.2.4 Respiratory rate and depth (Table 7 and 8, Fig. 3)

In the control group (Group I), respiratory rate was found reduced after induction of anaesthesia, and throughout the period of maintenance. Depth of respiration was found satisfactory in all animals throughout the period of observation. The Mean ± SE values for respiratory rate (per minute) in animals of control group (Group I) before induction, after induction and at 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minute post induction were 43.83 ± 4.77, 18.17 ± 2.13, 14.67 ± 1.60, 12.17 ± 2.05, 16.83 ± 1.81, 14.83 ± 2.60, 12.67 ± 0.71, 16.00 ± 0.93 respectively.

In the study group (Group II), the respiratory rate was found reduced after induction of anaesthesia. The rate of respiration later became considerably reduced, and the depth had become very shallow in all animals, following administration of atracurium. Apnoea was noted in one animal at the 20^{th} minute. The respiration was thus assisted manually to peak inspiratory pressure of not more than 20 cmH_2O, for each and every spontaneous breaths in all animals of the study group. The Mean ± SE values for respiratory rate (per minute) recorded in animals of the study group (Group II), before induction, after induction and at 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minutes were 37.00 ± 3.35, 13.33 ± 1.72, 9.17 ± 1.51, 5.67 ± 1.67, 7.00 ± 1.12, 9.83 ± 1.44, 9.33 ± 0.61, 13.00 ± 0.82 respectively.

The respiratory rate noted at 10^{th}, 20^{th} and 30^{th} minute post induction in the study group were significantly lower (p value) when compared to that in the control group for their respective observation times. The depth of respiration in the study group following atracurium was considerably shallow when compared to those of the control group.

4.2.5 Capillary refill time (CRT) (Table 9)

The Mean ± SE values for capillary refill time (seconds) in animals of control group (Group I) before induction, after induction and at 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minute post induction were 1.50 ± 0.22, 1.50 ± 0.22, 1.50 ± 0.22, 1.33 ± 0.21, 1.50 ± 0.22, 1.33 ± 0.21, 1.67 ± 0.21 and 1.67 ± 0.21 respectively.

The Mean ± SE values for capillary refill time (seconds) in animals of control group (Group I) before induction, after induction and at 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minute post induction were 1.67 ± 0.2, 1.50 ± 0.22, 1.67 ± 0.21, 1.83 ± 0.17, 1.50 ± 0.22, 1.67 ± 0.21, 1.50 ± 0.22 and 1.67 ± 0.21 respectively.

The capillary refill time in the study group at any point of observation did not vary significantly when compared to those of the control group.

4.3 NON INVASIVE BLOOD PRESSURE

4.3.1 Systolic blood pressure (Table 10)

The Mean ± SE values for systolic blood pressure (mmHg) in animals of control group (Group I) before induction, after induction and at 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minute post induction were 141.33 ± 3.55, 133.83 ± 3.19, 130.00 ± 0.93, 131.33 ± 6.01, 133.00 ± 2.61, 135.67 ± 2.29, 136.50 ± 4.71, 134.00 ± 2.72 respectively.

The Mean ± SE values for systolic blood pressure (mmHg) in animals of the study group (Group II), before induction, after induction and at 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minutes were 135.50 ± 3.44, 133.67 ± 1.98, 133.33 ± 2.33, 131.33 ± 2.64, 131.17 ± 1.70, 130.83 ± 2.51, 132.17 ± 1.96, 132.83 ± 1.97 respectively.

The systolic blood pressure in the study group at any point of observation did not vary significantly when compared to those of the control group.

4.3.2 Diastolic blood pressure (Table 11)

The Mean ± SE values for diastolic blood pressure (mmHg) in animals of control group (Group I) before induction, after induction and at 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minute post induction were found to be 80.50 ± 3.06, 79.83 ± 1.66, 85 ± 2.46, 80.00 ± 6.29, 81.33 ± 0.95, 82.50 ± 4.53, 86.83 ± 5.69, 82.67 ± 3.55 respectively.

The Mean ± SE values for diastolic blood pressure (mmHg) in animals of the study group(Group II), before induction, after induction and at 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minutes were 78.67 ± 0.21, 82.17 ± 0.98, 80.83 ± 0.91, 81.00 ± 1.29, 81.83 ± 1.01, 80.83 ± 0.60, 79.17 ± 0.79, 82.17 ± 0.94 respectively.

The diastolic blood pressure in the study group at any point of observation did not vary significantly when compared to those of the control group.

4.3.3 Mean blood pressure (Table 12)

The Mean ± SE values for mean blood pressure (mmHg) in animals of control group (Group I) before induction, after induction and at 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minute post induction were 110.17 ± 2.43, 103.67 ± 2.46, 103.83 ± 1.30, 99.83 ± 6.71, 103.33 ± 2.94, 107.33 ± 2.04, 108.50 ± 5.89, 107.83 ± 2.62 respectively.

The Mean ± SE values for mean blood pressure (mmHg) in animals of the study group (Group II), before induction, after induction and at 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minutes were found to be 101.33 ± 3.19, 104.17 ± 2.31, 103.00 ± 2.13, 102.50 ± 3.15, 101.67 ± 2.23, 101.67 ± 2.95, 101.00 ± 2.13, 103.00 ± 2.24 respectively.

The diastolic blood pressure in the study group at any point of observation did not vary significantly when compared to those of the control group.

Table 3. Recovery parameters (minutes)				
Time	Mean ± SE		t-value	p-value
	Group I	Group II		
Time to Recovery	6.63 ± 1.77	5.62 ± 1.66	0.415^{ns}	0.687
Time to regain sternal recumbency	15.35 ± 4.38	10.60 ± 3.53	0.844^{ns}	0.419
Time to assume standing	42.67 ± 9.03	47.67 ± 8.25	0.409^{ns}	0.691
ns – non-significant				

Table 4. Observations on rectal temperature (ºC)				
Time interval (minutes)	Mean ± SE		t-value	p-value
	Group I	Group II		
Before induction	38.95 ± 0.21	38.40 ± 0.40	1.214^{ns}	0.261
After induction	39.00 ± 0.26	38.05 ± 0.32	2.274*	0.046
10^{th} minute	38.85 ± 0.16	37.60 ± 0.34	3.296*	0.013
20^{th} minute	38.58 ± 0.23	37.35 ± 0.47	2.364*	0.049
30^{th} minute	38.60 ± 0.29	37.47 ± 0.40	2.311*	0.043
40^{th} minute	38.32 ± 0.17	37.47 ± 0.43	1.826^{ns}	0.098
50^{th} minute	38.38 ± 0.25	37.55 ± 0.47	1.563^{ns}	0.149
60^{th} minute	38.37 ± 0.28	37.53 ± 0.41	1.677^{ns}	0.124
* Significant at 0.05 level; ns – non-significant				

Table 5. Observations on heart rate (beats per minute)

Time interval	Group I	Group II	t-value	p-value
Before induction	96.33 ± 5.71	103.67 ± 4.30	1.025^{ns}	0.329
After induction	91.17 ± 5.24	90.50 ± 7.89	0.070^{ns}	0.945
10^{th} minute	82.67 ± 8.63	84.50 ± 9.89	0.140^{ns}	0.892
20^{th} minute	77.67 ± 8.32	88.00 ± 9.69	0.809^{ns}	0.437
30^{th} minute	86.83 ± 5.95	102.00 ± 3.47	2.201^{ns}	0.052
40^{th} minute	86.67 ± 7.49	96.67 ± 7.11	0.968^{ns}	0.356
50^{th} minute	83.67 ± 8.28	98.50 ± 7.06	1.363^{ns}	0.203
60^{th} minute	88.00 ± 2.63	101.00 ± 8.13	1.521^{ns}	0.179
F-value (p-value)	1.242^{ns}(0.307)	2.456^{ns}(0.103)		

ns – non-significant

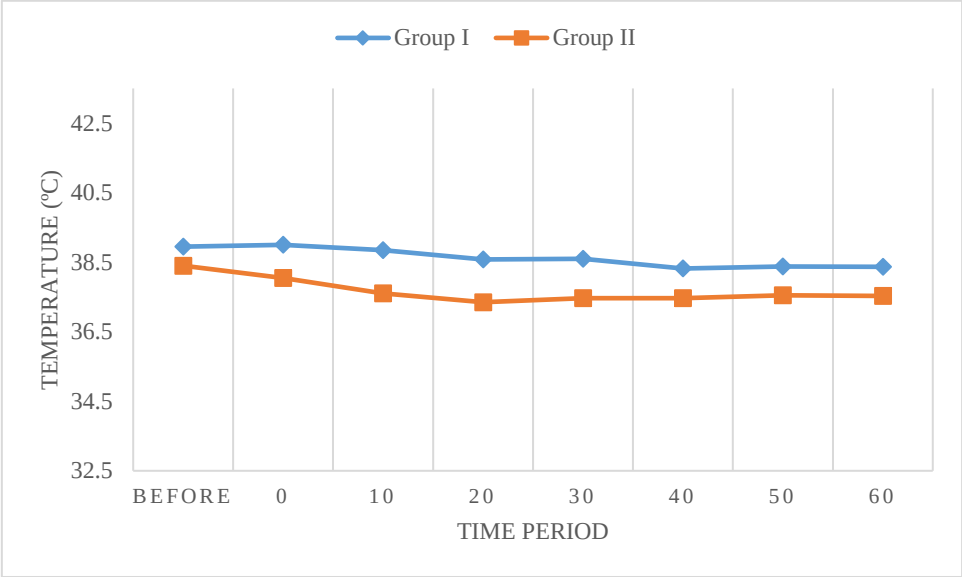


Figure 1. Trend of Rectal Temperature

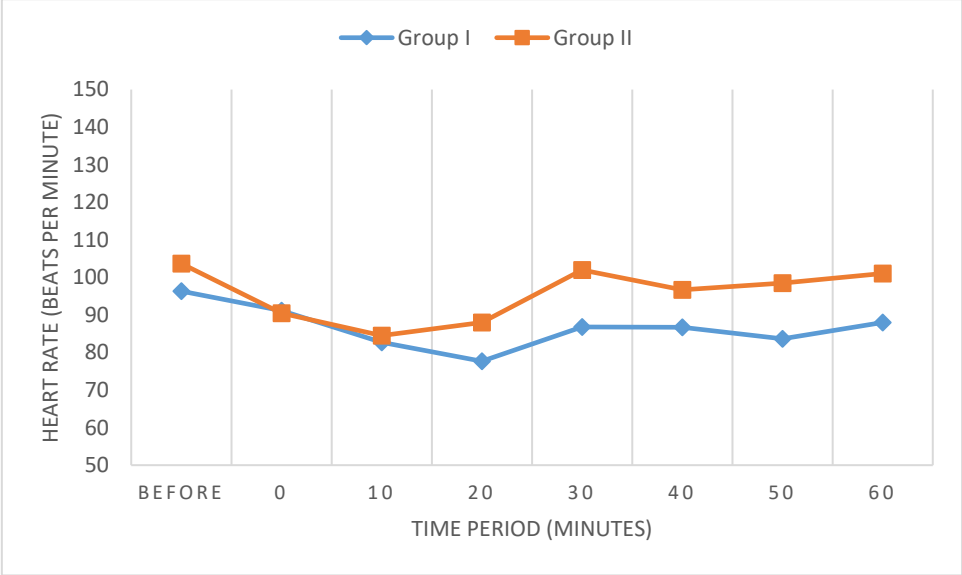


Figure 2. Trend of heart rate

Table 6. Observations on pulse rate (per minute)				
Time interval	Group I	Group II	t-value	p-value
Before induction	96.33 ± 5.71	103.67 ± 4.30	1.025^{ns}	0.329
After induction	91.17 ± 5.24	90.50 ± 7.89	0.070^{ns}	0.945
10^{th} minute	82.67 ± 8.63	84.50 ± 9.89	0.140^{ns}	0.892
20^{th} minute	77.67 ± 8.32	88.00 ± 9.69	0.809^{ns}	0.437
30^{th} minute	86.83 ± 5.95	102.00 ± 3.47	2.201^{ns}	0.052
40^{th} minute	86.67 ± 7.49	96.67 ± 7.11	0.968^{ns}	0.356
50^{th} minute	83.67 ± 8.28	98.50 ± 7.06	1.363^{ns}	0.203
60^{th} minute	88.00 ± 2.63	101.00 ± 8.13	1.521^{ns}	0.179
F-value (p-value)	1.242^{ns}(0.307)	2.456^{ns}(0.103)		
ns – non-significant				

Table 7. Observations on respiratory rate (per minute)				
Time interval	Group I	Group II	t-value	p-value
Before induction	43.83 ± 4.77	37.00 ± 3.35	1.173^{ns}	0.268
After induction	18.17 ± 2.13	13.33 ± 1.72	1.760^{ns}	0.109
10^{th} minute	14.67 ± 1.60	9.17 ± 1.51	2.492*	0.032
20^{th} minute	12.17 ± 2.05	5.67 ± 1.67	2.456*	0.034
30^{th} minute	16.83 ± 1.81	7.00 ± 1.12	4.604**	0.001
40^{th} minute	14.83 ± 2.60	9.83 ± 1.40	1.687^{ns}	0.123
50^{th} minute	12.67 ± 0.71	9.33 ± 0.61	3.536**	0.005
60^{th} minute	16.00 ± 0.93	13.00 ± 0.82	2.423*	0.036
F-value (p-value)	18.79^{**}(<0.001)	35.65^{**}(<0.001)		
* Significant at 0.05 level; ** Significant at 0.01 level; ns – non-significant				

Table 8. Assessment of respiratory depth				
Time interval	Group I	Group II	t-value	p-value
0^{th} minute	426.33 ± 13.49	348.00 ± 152.04	0.516^{ns}	0.617
10^{th} minute	247.00 ± 73.90	393.50 ± 121.24	1.032^{ns}	0.326
20^{th} minute	427.17 ± 50.39	315.83 ± 73.80	1.246^{ns}	0.241
30^{th} minute	402.17 ± 33.51	499.33 ± 98.33	0.935^{ns}	0.385
40^{th} minute	455.17 ± 60.60	347.67 ± 67.88	1.181^{ns}	0.265
50^{th} minute	395.33 ± 25.88	267.00 ± 25.16	3.556**	0.005
60^{th} minute	435.00 ± 12.08	480.50 ± 87.32	0.516^{ns}	0.617
** Significant at 0.01 level; ns – non-significant				

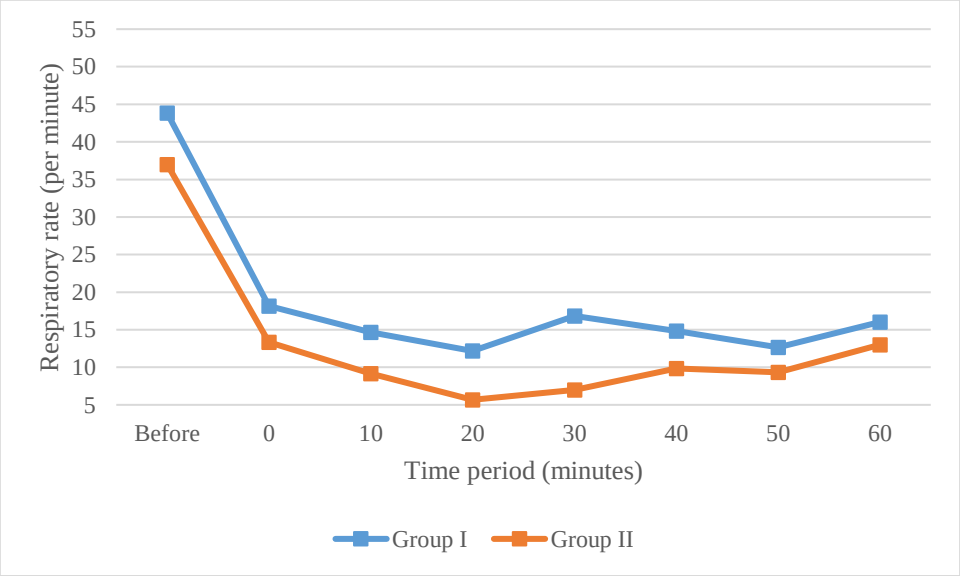


Figure 3. Trend of respiratory rate

Table 9. Observation made on the capillary refill time (seconds)

Parameters	Group I	Group II	t-value	p-value
Before induction	1.50 ± 0.22	1.67 ± 0.21	0.542^{ns}	0.599
After induction	1.50 ± 0.22	1.50 ± 0.22	0^{ns}	1
10^{th} minute	1.50 ± 0.22	1.67 ± 0.21	0.542^{ns}	0.599
20^{th} minute	1.33 ± 0.21	1.83 ± 0.17	1.861^{ns}	0.092
30^{th} minute	1.50 ± 0.22	1.50 ± 0.22	0^{ns}	1
40^{th} minute	1.33 ± 0.21	1.67 ± 0.21	1.118^{ns}	0.29
50^{th} minute	1.67 ± 0.21	1.50 ± 0.22	0.542^{ns}	0.599
60^{th} minute	1.67 ± 0.21	1.67 ± 0.21	0^{ns}	1
F-value (p-value)	1.429^{ns}(0.225)	0.473^{ns}(0.847)		

ns – non-significant

Table 10. Observations on systolic blood pressure (mmHg)				
Time interval	Group I	Group II	t-value	p-value
Before induction	141.33 ± 3.55	135.50 ± 3.44	1.179^{ns}	0.266
After induction	133.83 ± 3.19	133.67 ± 1.98	0.044^{ns}	0.966
10^{th} minute	130.00 ± 0.93	133.33 ± 2.33	1.327^{ns}	0.214
20^{th} minute	131.33 ± 6.01	131.33 ± 2.64	0^{ns}	1
30^{th} minute	133.00 ± 2.60	131.17 ± 1.70	0.589^{ns}	0.569
40^{th} minute	135.67 ± 2.29	130.83 ± 2.52	1.419^{ns}	0.186
50^{th} minute	136.50 ± 4.71	132.17 ± 1.96	0.850^{ns}	0.415
60^{th} minute	134.00 ± 2.72	132.83 ± 1.97	0.347^{ns}	0.736
F-value (p-value)	1.068^{ns}(0.404)	2.40^{ns}(0.115)		
ns – non-significant				

Table 11. Observation made on diastolic blood pressure (mmHg)				
Time interval	Group I	Group II	t-value	p-value
Before induction	80.50 ± 3.06	78.67 ± 0.21	0.597^{ns}	0.576
After induction	79.83 ± 1.66	82.17 ± 0.98	1.209^{ns}	0.254
10^{th} minute	85.00 ± 2.46	80.83 ± 0.91	1.587^{ns}	0.161
20^{th} minute	80.00 ± 6.29	81.00 ± 1.29	0.157^{ns}	0.878
30^{th} minute	81.33 ± 0.95	81.83 ± 1.01	0.359^{ns}	0.727
40^{th} minute	82.50 ± 4.53	80.83 ± 0.60	0.365^{ns}	0.723
50^{th} minute	86.83 ± 5.69	79.17 ± 0.79	1.333^{ns}	0.212
60^{th} minute	82.67 ± 3.55	82.17 ± 0.94	0.136^{ns}	0.894
F-value (p-value)	0.428^{ns}(0.878)	2.279^{ns}(0.131)		
ns – non-significant				

Table 12. Observations made on mean blood pressure (mmHg)				
Time interval	Group I	Group II	t-value	p-value
Before induction	110.17 ± 2.43	101.33 ± 3.19	2.203^{ns}	0.052
After induction	103.67 ± 2.46	104.17 ± 2.31	0.148^{ns}	0.885
10^{th} minute	103.83 ± 1.30	103.00 ± 2.13	0.334^{ns}	0.745
20^{th} minute	99.83 ± 6.71	102.50 ± 3.14	0.360^{ns}	0.727
30^{th} minute	103.33 ± 2.94	101.67 ± 2.23	0.452^{ns}	0.661
40^{th} minute	107.33 ± 2.04	101.67 ± 2.95	1.578^{ns}	0.146
50^{th} minute	108.50 ± 5.89	101.00 ± 2.13	1.197^{ns}	0.259
60^{th} minute	107.83 ± 2.62	103.00 ± 2.24	1.401^{ns}	0.191
F-value (p-value)	0.965^{ns}(0.471)	1.132^{ns}(0.366)		
ns – non-significant				

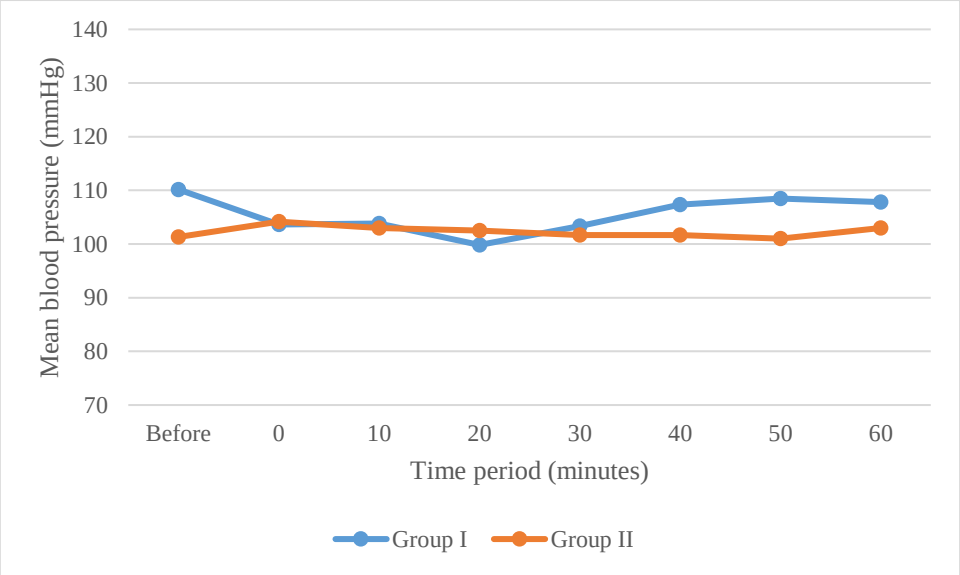


Figure 4. Trend on Mean arterial pressure

4.4 ELECTROCARDIOGRAM (ECG)

In both Group I and Group II, the electrocardiogram revealed a slower heart rates within the normal ranges after induction and throughout the anaesthetic period. Heart rate increased slightly towards the end in case of Group II animals. One animal each in Group I and Group II showed premature ventricular contractions with a depressed ST segment as was displayed in the ECG. The electrocardiograms are represented in Plate 5.

4.5 END TIDAL CARBON DIOXIDE (Table 13)

In the control group (Group I), the end-tidal carbon dioxide concentration ($EtCO_2$) were satisfactory in all animals throughout the periods of observation. The Mean ± SE values for $EtCO_2$ in the animals of control group (Group I) after induction and at 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minute post induction were 38.02 ± 1.47, 39.37 ± 2.61, 38.85 ± 1.92, 39.67 ± 2.16, 38.65 ± 2.09, 35.75 ± 3.51, 39.87 ± 1.53 mmHg respectively.

In the study group (Group II), the end-tidal carbon dioxide concentration increased considerably after administration of atracurium. The respiration was thus assisted manually to peak inspiratory pressure of not more than 20 cmH_2O for each and every spontaneous breaths in all the animals of the study group, to maintain eucapnia. The Mean ± SE values for $EtCO_2$ in the animals of study group after induction and at the 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minutes post induction were 47.45 ± 2.96, 43.88 ± 4.36, 48.17 ± 1.32, 38.95 ± 4.71, 42.47 ± 0.94, 46.13 ± 1.59 and 43.27 ± 1.47 mmHg respectively.

4.6 END TIDAL ISOFLURANE CONCENTRATION (Table 14)

The Mean ± SE values for end-tidal isoflurane concentration in animals of the control group (Group I) during the periods of observation at 10^{th}, 20^{th}, 30^{th}, 40^{th},

50^{th}, 60^{th} minutes were 1.05 ± 0.08, 1.12 ± 0.06, 1.18 ± 0.03, 1.18 ± 0.03, 1.13 ± 0.02 and 1.03 ± 0.02 percentage respectively.

The Mean ± SE value for end-tidal isoflurane concentration in animals of the study group animals at 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minute were 1.10 ± 0.05, 1.07 ± 0.04, 1.05 ± 0.03, 1.03 ± 0.05, 1.03 ± 0.02 and 1 percentage respectively.

End-tidal isoflurane concentration observed in the study group at 30^{th}, 40^{th} and 50^{th} minutes were significantly lesser (p value) when compared to those of the control group for their respective times of observation.

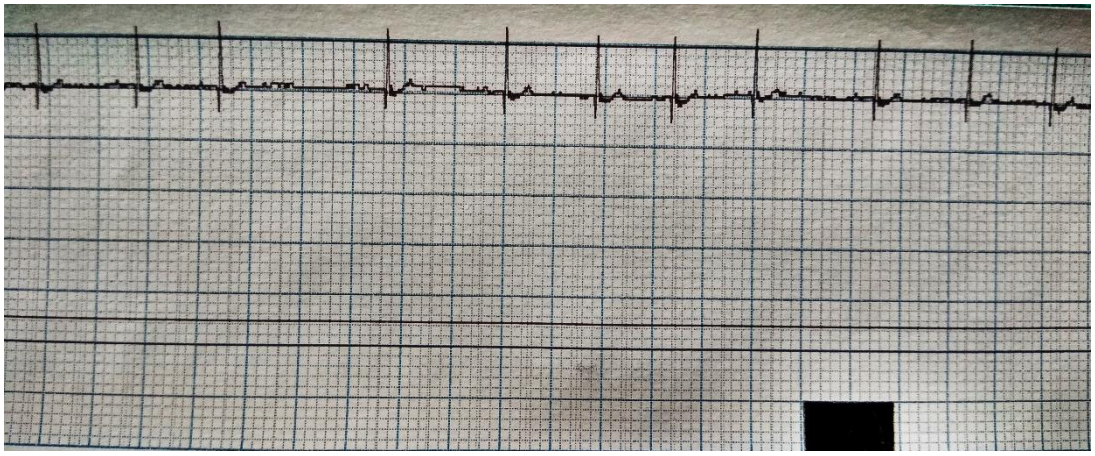
4.7 SATURATION OF OXYGEN IN PERIPHERAL BLOOD (Table 15)

In Group II animals, the Mean ± SE values for saturation pressure of oxygen in peripheral blood after induction and at the 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minutes post induction were 95.33 ± 1.54, 96.17 ± 1.62, 97.00 ± 1.21, 96.67 ± 1.14, 96.17 ± 1.66, 97.50 ± 0.80 and 97.67 ± 0.76 % respectively.

The Mean ± SE values for saturation pressure of oxygen in peripheral blood after induction and at the 10^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minutes post induction were 93.83 ± 2.02, 94.33 ± 1.50, 96.33 ± 1.33, 97.00 ± 0.57, 98.00 ± 0.57, 98.00 ± 0.57 and 97.83 ± 0.48 % respectively.

The saturation pressure of oxygen in peripheral blood in the study group at any point of observation did not vary significantly when compared to those of the control group.

Plate 5. Electrocardiogram



Premature ventricular contractions

Table 13. Observations on end-tidal carbon dioxide concentration (mmHg)

Time interval	Group I	Group II	t-value	p-value
After induction	38.02 ± 1.47	47.45 ± 2.96	2.851*	0.017
10th minute	39.37 ± 2.61	43.88 ± 4.36	0.889^{ns}	0.395
20th minute	38.85 ± 1.92	48.17 ± 1.32	3.999**	0.003
30th minute	39.67 ± 2.16	38.95 ± 4.71	0.138^{ns}	0.893
40th minute	38.65 ± 2.09	42.47 ± 0.94	1.663^{ns}	0.127
50th minute	35.75 ± 3.51	46.13 ± 1.59	2.692*	0.023
60th minute	39.87 ± 1.53	43.27 ± 1.47	1.603^{ns}	0.14
F-value (p-value)	0.630^{ns}(0.705)	1.417^{ns}(0.241)		

ns – non-significant

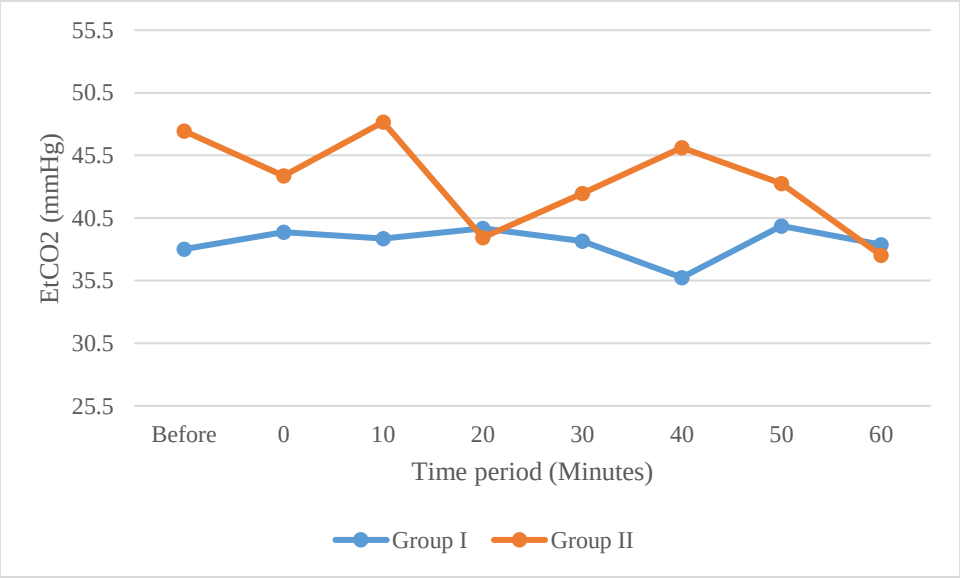


Figure 5. Trend of End-tidal carbon dioxide

Table 14. Observations made on end-tidal isoflurane concentration (%)

Time interval	Group I	Group II	t-value	p-value
10^{th} minute	1.05 ± 0.08	1.10 ± 0.05	0.542^{ns}	0.599
20^{th} minute	1.12 ± 0.06	1.07 ± 0.04	0.643^{ns}	0.535
30^{th} minute	1.18 ± 0.03	1.05 ± 0.03	2.902*	0.016
40^{th} minute	1.18 ± 0.03	1.03 ± 0.05	2.577*	0.028
50^{th} minute	1.13 ± 0.02	1.03 ± 0.02	3.354**	0.007
60^{th} minute	1.03 ± 0.02	1	1.581^{ns}	0.145
F-value (p-value)	2.102^{ns}(0.099)	1.574^{ns}(0.204)		

ns – non-significant

Table 15. Observations on saturation pressure of oxygen in peripheral blood (%)

Time interval	Group I	Group II	t-value	p-value
0^{th} minute	95.33 ± 1.54	93.83 ± 2.02	0.590^{ns}	0.569
10^{th} minute	96.17 ± 1.62	94.33 ± 1.50	0.831^{ns}	0.426
20^{th} minute	97.00 ± 1.21	96.33 ± 1.33	0.370^{ns}	0.719
30^{th} minute	96.67 ± 1.14	97.00 ± 0.57	0.260^{ns}	0.8
40^{th} minute	96.17 ± 1.66	98.00 ± 0.57	1.042^{ns}	0.322
50^{th} minute	97.50 ± 0.80	98.00 ± 0.57	0.504^{ns}	0.625
60^{th} minute	97.67 ± 0.76	97.83 ± 0.48	0.186^{ns}	0.856
F-value (p-value)	1.782^{ns} (0.137)	3.30^{ns} (0.099)		

ns – non-significant

4.8 HAEMATOLOGY

4.8.1 Haemoglobin concentration (Table 16)

The Mean ± SE value for Haemoglobin concentration in the animals of Group I, before induction, after induction and at 30^{th} and 60^{th} minutes were 11.13 ± 0.65, 11.13 ± 0.63, 11.22 ± 0.64 and 11.18 ± 0.62 g/dL respectively.

The Mean ± SE value for Haemoglobin concentration in the animals of Group II, before induction, after induction and at 30^{th} and 60^{th} minutes were 11.23 ± 1.11, 10.47 ± 1.01, 10.98 ± 0.86 and 11.33 ± 0.76 g/dL respectively.

The haemoglobin concentration in the study group at any point of observation did not vary significantly when compared to those of the control group.

4.8.2 Total Erythrocyte Count (Table 17)

The Mean ± SE value for total erythrocyte count in the animals of Group I, before induction, after induction and at 30^{th} and 60^{th} minutes were 5.18 ± 0.26, 5.18 ± 0.26, 5.19 ± 0.26 and 5.18 ± 0.25 millions/mm^3 respectively.

The Mean ± SE value for total erythrocyte count in the animals of Group II, before induction, after induction and at 30^{th} and 60^{th} minutes were 5.54 ± 0.41, 5.54 ± 0.41, 4.70 ± 0.94 and 5.54 ± 0.42 millions/mm^3 respectively.

The total erythrocyte count in the study group at any point of observation did not vary significantly when compared to those of the control group.

4.8.3 Volume of Packed Red Cells (Table 18)

The Mean ± SE value for packed volume of red cells in the animals of Group I, before induction, after induction and at 30^{th} and 60^{th} minutes were 33.50 ± 2.23, 33.50 ± 2.28, 33.33 ± 2.15 and 33.50 ± 2.17 % respectively.

The Mean ± SE value for packed volume of red cells in the animals of Group II, before induction, after induction and at 30^{th} and 60^{th} minutes were 33.50 ± 3.29, 31.33 ± 3.08, 32.95 ± 2.60 and 32.83 ± 2.75 % respectively.

The volume of packed red cells in the study group at any point of observation did not vary significantly when compared to those of the control group.

4.8.4 Total Leucocyte Count (Table 19)

The Mean ± SE value for total leucocyte count in the animals of Group I, before induction, after induction and at 30^{th} and 60^{th} minutes were 8.20 ± 0.13, 8.20 ± 0.12, 8.19 ± 0.13 and 8.19 ± 0.13 thousands/mm^3 respectively.

The Mean ± SE value for total leucocyte count in the animals of Group II, before induction, after induction and at 30^{th} and 60^{th} minutes were 8.17 ± 0.10, 8.18 ± 0.10, 8.17 ± 0.10 and 8.18 ± 0.98 thousands/mm^3 respectively.

The total leucocyte count in the study group at any point of observation did not vary significantly when compared to those of the control group.

4.8.5 Differential Leucocyte Count

4.8.5.1 Neutrophil count (Table 20)

The Mean ± SE value for neutrophil count in the animals of Group I, before induction, after induction and at 30^{th} and 60^{th} minutes were 76.17 ± 1.08, 76.17 ± 1.30, 76.17 ± 1.05 and 75.50 ± 0.56 respectively.

The Mean ± SE value for neutrophil count in the animals of Group II, before induction, after induction and at 30^{th} and 60^{th} minutes were 75.00 ± 0.36, 74.00 ± 0.86, 74.83 ± 1.42 and 74.17 ± 1.35 respectively.

The neutrophil count in the study group at any point of observation did not vary significantly when compared to those of the control group.

4.8.5.2 Lymphocyte count (Table 21)

The Mean ± SE value for lymphocyte count in the animals of Group I, before induction, after induction and at 30^{th} and 60^{th} minutes were 17.83 ± 0.60, 17.17 ± 1.01, 16.67 ± 0.92 and 18.00 ± 0.52 respectively.

The Mean ± SE value for lymphocyte count in the animals of Group II, before induction, after induction and at 30th and 60th minutes were 18.00 ± 0.58, 18.67 ± 0.49, 18.50 ± 0.96 and 19.17 ± 0.91 respectively.

The lymphocyte count in the study group at any point of observation did not vary significantly when compared to those of the control group.

4.8.5.3 Monocyte count (Table 22)

The Mean ± SE value for monocyte count in the animals of Group I, before induction, after induction and at 30th and 60th minutes were 6.00 ± 0.77, 6.67 ± 1.14, 7.17 ± 0.60 and 6.50 ± 0.50 respectively.

The Mean ± SE value for monocyte count in the animals of Group II, before induction, after induction and at 30th and 60th minutes were 7.00 ± 0.52, 7.33 ± 0.92, 6.67 ± 0.56 and 6.67 ± 0.80 respectively.

The monocyte count in the study group at any point of observation did not vary significantly when compared to those of the control group.

4.9 SERUM BIOCHEMISTRY

4.9.1 Aspartate amino transferase (Table 23)

The Mean ± SE value for aspartate amino transferase in the animals of Group I was 18.68 ± 4.72, while that after surgery was 18.68 ± 4.72 IU/L. The Mean ± SE value for aspartate amino transferase in the animals of Group II before surgery was 13.74 ± 0.22, while that after surgery was 13.74 ± 0.22.

There was no significant difference between the two groups ($p>0.05$).

4.9.2 Alanine amino transferase (Table 24)

The Mean ± SE value for alanine amino transferase in the animals of Group I was 42.16 ±8.08, while that after surgery was 42.17 ± 8.08 IU/L. The Mean ± SE

value for alanine amino transferase in the animals of Group II was 28.85 ± 4.08, while that after surgery was 28.77 ± 4.10 IU/L.

There was no significant difference between the two groups (p>0.05).

4.9.3 Alkaline phosphatase (Table 25)

The Mean ± SE value for alkaline phosphatase in the animals of Group I before induction was 67.68 ± 6.04, while that after procedure was 67.54 ± 6.16 IU/L. The Mean ± SE value for alkaline phosphatase in the animals of Group II before procedure was 41.46 ± 13.26, while that after procedure was 46.29 ± 12.09 IU/L.

There was no significant difference between the two groups (p>0.05).

4.9.4 Total Protein (Table 26)

The Mean ± SE value for total protein in the animals of Group I before induction was 6.18 ± 0.16 g/dL, while that after the procedure was 6.19 ± 0.15g/dL. The Mean ± SE value for total protein in the animals of Group II before procedure was 6.66 ± 0.69, while that after procedure was 6.46 ± 0.50 g/dL.

There was no significant difference between the two groups (p>0.05).

4.9.5 Albumin (Table 27)

In The Mean ± SE value for total protein in the animals of Group I before procedure was 2.65 ± 0.04, while that after procedure was 3.16 ± 0.48 g/dL. The Mean ± SE value for total protein in the animals of Group II before procedure was 2.65 ± 0.11, while that after procedure was 2.58 ± 0.07 g/dL.

There was no significant difference between the two groups (p>0.05).

4.9.6 Bilirubin (Table 28)

The Mean ± SE value for bilirubin in the animals of Group I before procedure was 0.15 ± 0.01, while that after procedure was 0.14 ± 0.01mg/dL. The

Mean ± SE value for bilirubin in the animals of Group II before procedure was 0.09 ± 0.02 mg/dL, while that after procedure was 2.58 ± 0.11 mg/dL.

There was no significant difference between the two groups ($p>0.05$).

4.9.7 Blood Urea Nitrogen (Table 29)

The Mean ± SE value for blood urea nitrogen in the animals of Group I before and after the procedure was 12.04 ± 0.42 mg/dL. The Mean ± SE value for blood urea nitrogen in the animals of Group II before procedure was 11.14 ± 0.59 mg/dL, while that after procedure was 11.13 ± 0.59 mg/dL.

There was no significant difference between the two groups ($p>0.05$).

4.9.8 Creatinine (Table 30)

The Mean ± SE value for creatinine in the animals of Group I before and after the procedure was 1.07 ± 0.12 mg/ dL. The Mean ± SE value for creatinine in the animals of Group II before procedure was 0.93 ± 0.09, while that after procedure was 0.92 ± 0.09 mg/dL.

There was no significant difference between the two groups ($p>0.05$).

4.10 BLOOD GLUCOSE (TABLE 31)

The Mean ± SE value for blood glucose in the animals of control group (Group I) before the anaesthetic procedure was 116.00 ± 3.30, while that after procedure was 126.50 ± 2.36 mg/dL. The Mean ± SE value for blood glucose in the animals of the study group (Group II) before the anaesthetic procedure was 109.15 ± 6.34, while that after procedure was 111.98 ± 7.30 mg/dL.

Blood glucose levels in the study group did not vary significantly from those in the control group ($p>0.05$).

Table 16. Assessment of haemoglobin concentration (g/dL)

Time interval	Group I	Group II	t-value	p-value
Before induction	11.13 ± 0.65^{b}	11.23 ± 1.11	0.078^{ns}	0.939
After induction	11.13 ± 0.63^{b}	10.47 ± 1.01	0.558^{ns}	0.6667
30^{th} minute	11.22 ± 0.64^{a}	10.98 ± 0.86	0.218^{ns}	0.832
60^{th} minute	11.18 ± 0.62^{ab}	11.33 ± 0.76	0.152^{ns}	0.882
F-value (p-value)	4.286^{*}(0.023)	1.643^{ns}(0.222)		

Means having different letters as superscript are homogenous within a column (* $p < 0.05$)

Table 17. Observations on total erythrocyte count (10^6/mm^3)

Time interval	Group I	Group II	t-value	p-value
Before induction	5.18 ± 0.26	5.54 ± 0.41	0.735^{ns}	0.479
After induction	5.18 ± 0.26	5.54 ± 0.41	0.748^{ns}	0.472
30^{th} minute	5.19 ± 0.26	4.70 ± 0.94	0.501^{ns}	0.627
60^{th} minute	5.18 ± 0.25	5.54 ± 0.42	0.733^{ns}	0.480
F-value (p-value)	0.348^{ns} (0.619)	1.038^{ns} (0.355)		

ns – non-significant

Table 18. Observations on volume of packed red cells (%)				
Time interval	Group I	Group II	t-value	p-value
Before induction	33.50 ± 2.23	33.50 ± 3.29	0^{ns}	1
After induction	33.50 ± 2.28	31.33 ± 3.08	0.565^{ns}	0.584
30^{th} minute	33.33 ± 2.15	32.95 ± 2.60	0.113^{ns}	0.912
60^{th} minute	33.50 ± 2.17	32.83 ± 2.75	0.190^{ns}	0.853
F-value (p-value)	0.294^{ns} (0.829)	1.642^{ns} (0.222)		
ns – non-significant				

Table 19. Observations on total leucocyte count ($10^3/mm^3$)				
Time interval	Group I	Group II	t-value	p-value
Before induction	8.20 ± 0.13	8.17 ± 0.10	0.184^{ns}	0.858
After induction	8.20 ± 0.12	8.18 ± 0.10	0.174^{ns}	0.865
30^{th} minute	8.19 ± 0.13	8.17 ± 0.10	0.153^{ns}	0.881
60^{th} minute	8.19 ± 0.13	8.18 ± 0.98	0.090^{ns}	0.930
F-value (p-value)	1.442^{ns} (0.270)	0.876^{ns} (0.475)		
ns – non-significant				

Table 20. Observations on the percentage of neutrophils (%)				
Time interval	Group I	Group II	t-value	p-value
Before induction	76.17 ± 1.08	75.00 ± 0.36	1.025^{ns}	0.329
After induction	76.17 ± 1.30	74.00 ± 0.86	1.391^{ns}	0.195
30^{th} minute	76.17 ± 1.05	74.83 ± 1.42	0.755^{ns}	0.468
60^{th} minute	75.50 ± 0.56	74.17 ± 1.35	0.911^{ns}	0.384
F-value (p-value)	0.538^{ns} (0.663)	0.417^{ns} (0.744)		
ns – non-significant				

Table 21. Observations made on the percentage of lymphocytes (%)				
Time interval	Group I	Group II	t-value	p-value
Before induction	17.83 ± 0.60	18.00 ± 0.58	0.200^{ns}	0.845
After induction	17.17 ± 1.01	18.67 ± 0.49	1.330^{ns}	0.213
30^{th} minute	16.67 ± 0.92	18.50 ± 0.96	1.381^{ns}	0.197
60^{th} minute	18.00 ± 0.52	19.17 ± 0.91	1.115^{ns}	0.291
F-value (p-value)	0.882^{ns} (0.473)	0.311^{ns} (0.817)		
ns – non-significant				

Table 22. Observations on the percentage of monocytes (%)				
Time interval	Group I	Group II	t-value	p-value
Before induction	6.00 ± 0.77	7.00 ± 0.52	1.074^{ns}	0.308
After induction	6.67 ± 1.14	7.33 ± 0.92	0.454^{ns}	0.659
30^{th} minute	7.17 ± 0.60	6.67 ± 0.56	0.610^{ns}	0.556
60^{th} minute	6.50 ± 0.50	6.67 ± 0.80	0.176^{ns}	0.864
F-value (p-value)	0.419^{ns} (0.662)	0.505^{ns} (0.685)		
ns – non-significant				

Table 23. Observations on aspartate amino transferase (IU/L)				
Time interval	Group I	Group II	t-value	p-value
Before induction	18.68 ± 4.72	13.74 ± 0.22	1.045^{ns}	0.321
After recovery	18.68 ± 4.72	13.74 ± 0.22	1.045^{ns}	0.321
F-value (p-value)	1.464^{ns} (0.203)	2.301^{ns} (0.070)		
ns – non-significant				

Table 24. Observations on alanine amino transferase (IU/L)				
Time interval	Group I	Group II	t-value	p-value
Before induction	42.16 ± 8.08	28.85 ± 4.08	1.470^{ns}	0.172
After recovery	42.17 ± 8.08	28.77 ± 4.10	1.480^{ns}	0.17
F-value (p-value)	1.164^{ns} (0.297)	0.731^{ns} (0.498)		
ns – non-significant				

Table 25. Observations on alkaline phosphatase (IU/L)				
Time interval	Group I	Group II	t-value	p-value
Before induction	67.68 ± 6.04	41.46 ± 13.26	1.799^{ns}	0.115
After recovery	67.54 ± 6.16	46.29 ± 12.09	1.565^{ns}	0.149
F-value (p-value)	0.734^{ns} (0.496)	0.972^{ns} (0.376)		
ns – non-significant				

Table 26. Observations on total protein (g/dL)				
Time interval	Group I	Group II	t-value	p-value
Before induction	6.18 ± 0.16	6.66 ± 0.69	0.68^{ns}	0.512
After recovery	6.19 ± 0.15	6.46 ± 0.50	0.511^{ns}	0.628
F-value (p-value)	1.000^{ns} (0.363)	1.010^{ns} (0.359)		
ns – non-significant				

Table 27. Observations on albumin (g/dL)				
Time interval	Group I	Group II	t-value	p-value
Before induction	2.65 ± 0.04	2.65 ± 0.11	0.069^{ns}	0.946
After recovery	3.16 ± 0.48	2.58 ± 0.07	1.182^{ns}	0.264
F-value (p-value)	1.008^{ns} (0.360)	1.101^{ns} (0.321)		
ns – non-significant				

Table 28. Observations on bilirubin (mg/dL)				
Time interval	Group I	Group II	t-value	p-value
Before induction	0.15 ± 0.01	0.09 ± 0.02	2.198^{ns}	0.053
After recovery	0.14 ± 0.01	0.09 ± 0.02	2.147^{ns}	0.057
F-value (p-value)	1.000^{ns} (0.363)	1.000^{ns} (0.363)		
ns – non-significant				

Table 29. Observations on blood urea nitrogen (mg/dL)				
Time interval	Group I	Group II	t-value	p-value
Before induction	12.04 ± 0.42	11.14 ± 0.59	1.235^{ns}	0.245
After recovery	12.04 ± 0.42	11.13 ± 0.59	1.251^{ns}	0.240
F-value (p-value)	0^{ns} (1.000)	1.225^{ns} (0.275)		
ns – non-significant				

Table 30. Observations on creatinine (mg/dL)				
Time interval	Group I	Group II	t-value	p-value
Before induction	1.07 ± 0.12	0.93 ± 0.09	0.889^{ns}	0.395
After recovery	1.07 ± 0.12	0.92 ± 0.09	0.914^{ns}	0.382
F-value (p-value)	0.415^{ns} (0.695)	1.581^{ns} (0.175)		
ns – non-significant				

Table 31. Observations on blood glucose (mg/dL)				
Time interval	Group I	Group II	t-value	p-value
Before induction	116.00 ± 3.30	109.15 ± 6.34	0.957^{ns}	0.368
After recovery	126.50 ± 2.36	111.98 ± 7.30	1.892^{ns}	0.107
F-value (p-value)	3.918^{*} (0.011)	2.023^{ns} (0.099)		
* Significant at 0.05 level; ns – non-significant				

4.11 BLOOD GAS AND ELECTROLYTE ANALYSIS

4.11.1 Partial Pressure of Oxygen (Table 32)

The Mean ± SE value for partial pressure of oxygen in the animals of Group I before induction, after induction and at the 30^{th} and 60^{th} minute were 75.68 ± 2.18, 317.12 ± 26.91, 435.77 ± 9.15 and 479.67 ± 1.47 mmHg respectively.

The Mean ± SE value for partial pressure of oxygen in the animals of Group II before induction, after induction and at the 30^{th} and 60^{th} minute were 85.65 ± 6.04, 375.72 ± 59.62, 441.27 ± 17.06 and 442.40 ± 8.35 mmHg respectively.

Significant difference was noted between the groups at the 60^{th} minute ($p<0.01$)

4.11.2 Partial Pressure of Carbon dioxide (Table 33)

The Mean ± SE value for partial pressure of carbon dioxide in the animals of Group I before induction, after induction and at the 30^{th} and 60^{th} minute were 39.02 ± 1.08, 44.15 ± 2.98, 44.17 ± 1.81 and 44.28 ± 1.53 mmHg respectively.

The Mean ± SE value for partial pressure of carbon dioxide in the animals of Group II before induction, after induction and at the 30^{th} and 60^{th} minute were 44.83 ± 3.65, 50.45 ± 2.97, 46.03 ± 4.12 and 48.03 ± 2.39 mmHg respectively.

There was no significant difference between the two groups ($p>0.05$).

4.11.3 pH (Table 34)

The Mean ± SE value for pH in the animals of Group I before induction, after induction and at the 30^{th} and 60^{th} minute were 7.38 ± 0.02, 7.35 ± 0.02, 7.32 ± 0.02 and 7.33 ± 0.02 respectively.

The Mean ± SE value for pH in the animals of Group II before induction, after induction and at the 30^{th} and 60^{th} minute were 7.30 ± 0.02, 6.60 ± 1.09, 7.29 ± 0.01 and 7.27 ± 0.02 respectively.

There was no significant difference between the two groups ($p>0.05$)

4.11.4 Bicarbonate (Table 35)

The Mean ± SE value for bicarbonate in the animals of Group I before induction, after induction and at the 30th and 60th minute were 22.38 ± 1.42, 22.25 ± 1.43, 20.88 ± 1.35 and 21.53 ± 1.38 mEq/L respectively.

The Mean ± SE value for bicarbonate in the animals of Group II before induction, after induction and at the 30th and 60th minute were 20.87 ± 1.30, 22.13 ± 0.75, 21.22 ± 1.53 and 22.23 ± 0.88 mEq/L respectively.

Significant difference was not seen between the two groups ($p>0.05$).

4.11.5 Lactate (Table 36)

The Mean ± SE value for lactate in the animals of Group I before induction, after induction and at the 30th and 60th minute were 1.48 ± 0.23, 1.23 ± 0.20, 1.22 ± 0.18 and 1.16 ± 0.16 mmol/L respectively.

The Mean ± SE value for lactate in the animals of Group II before induction, after induction and at the 30th and 60th minute were 1.42 ± 0.22, 1.28 ± 0.23, 1.60 ± 0.43 and 1.50 ± 0.29 mmol/L respectively.

Difference between the two groups was non-significant ($p>0.05$).

4.11.6 Base excess (Table 37)

The Mean ± SE value for base excess in the animals of Group I before induction, after induction and at the 30th and 60th minute were -1.83 ± 0.96, -1.88 ± 1.08, -2.02 ± 1.11 and -1.7 ± 0.98 mEq/L respectively.

The Mean ± SE value for base excess in the animals of Group II before induction, after induction and at the 30th and 60th minute were -2.78 ± 1.66, -2.12 ± 1.11, -3.28 ± 1.86 and -2.72 ± 1.41 mEq/L respectively.

There was no significant difference between the two groups ($p>0.05$).

Table 32. Observations on the partial pressure of oxygen (mmHg)

Time interval	Group I	Group II	t-value	p-value
Before induction	75.68 ± 2.18	85.65 ± 6.04	1.551^{ns}	0.152
After induction	317.12 ± 26.91	375.72 ± 59.62	0.896^{ns}	0.391
30^{th} minute	435.77 ± 9.15	441.27 ± 17.06	0.284^{ns}	0.782
60^{th} minute	479.67 ± 1.47	442.40 ± 8.35	4.393**	0.001
t-value (p-value)	163.84^{**}(< 0.003)	349.60^{**}(<0.001)		

* Significant at 0.05 level; ** Significant at 0.01 level; ns – non-significant

Table 33. Observations on the partial pressure of carbon dioxide (mmHg)

Time interval	Group I	Group II	t-value	p-value
Before induction	39.02 ± 1.08	44.83 ± 3.65	1.526^{ns}	0.179
After induction	44.15 ± 2.98	50.45 ± 2.97	1.497^{ns}	0.165
30^{th} minute	44.17 ± 1.81	46.03 ± 4.12	0.415^{ns}	0.687
60^{th} minute	44.28 ± 1.53	48.03 ± 2.39	1.321^{ns}	0.216
F-value (p-value)	1.650^{ns} (0.220)	0.818^{ns} (0.504)		

ns – non-significant

Table 34. Observations on pH

Time interval	Group I	Group II	t-value	p-value
Before induction	7.38 ± 0.02	7.30 ± 0.02	2.491^{ns}	0.032
After induction	7.35 ± 0.02	6.60 ± 1.09	0.680^{ns}	0.512
30^{th} minute	7.32 ± 0.02	7.29 ± 0.01	1.067^{ns}	0.311
60^{th} minute	7.33 ± 0.02	7.27 ± 0.02	2.050^{ns}	0.067
F-value (p-value)	2.402^{ns} (0.108)	0.392^{ns} (0.559)		

ns – non-significant

Table 35. Observations on bicarbonate

Time interval	Group I	Group II	t-value	p-value
Before induction	22.38 ± 1.42	20.87 ± 1.30	0.786^{ns}	0.450
After induction	22.25 ± 1.43	22.13 ± 0.75	0.072^{ns}	0.944
30^{th} minute	20.88 ± 1.35	21.22 ± 1.53	0.163^{ns}	0.874
60^{th} minute	21.53 ± 1.38	22.23 ± 0.88	0.427^{ns}	0.679
F-value (p-value)	1.457^{ns} (0.082)	1.464^{ns} (0.264)		

ns – non-significant

Table 36. Observations on lactate (mmol/L)

Time interval	Group I	Group II	t-value	p-value
Before induction	1.48 ± 0.23	1.42 ± 0.22	0.188^{ns}	0.855
After induction	1.23 ± 0.20	1.28 ± 0.23	0.162^{ns}	0.874
30^{th} minute	1.22 ± 0.18	1.60 ± 0.43	0.796^{ns}	0.444
60^{th} minute	1.16 ± 0.16	1.50 ± 0.29	1.033^{ns}	0.339
F-value (p-value)	1.249^{ns} (0.317)	0.618^{ns} (0.546)		

ns – non-significant

Table 37. Observations on the base excess (mmol/L)

Time interval	Group I	Group II	t-value	p-value
Before induction	-1.83 ± 0.96	-2.78 ± 1.66	0.494^{ns}	0.632
After induction	-1.88 ± 1.08	-2.12 ± 1.11	0.151^{ns}	0.883
30^{th} minute	-2.02 ± 1.11	-3.28 ± 1.86	0.584^{ns}	0.572
60^{th} minute	-1.70 ± 0.98	-2.72 ± 1.41	0.592^{ns}	0.567
F-value (p-value)	0.267^{ns} (0.848)	0.863^{ns} (0.413)		

ns – non-significant

4.11.7 Sodium (Table 38)

The Mean ± SE value for sodium in the animals of Group I before induction was 141.50 ± 2.50, while that after surgery was 145.33 ± 2.27 mEq/L. The Mean ± SE value for sodium in the animals of Group I before induction was 138.67 ± 3.15, while that after surgery was 143.50 ± 2.95 mEq/L.

There was no significant difference between the two groups ($p>0.05$).

4.11.8 Potassium (Table 39)

The Mean ± SE value for potassium in the animals of Group I before induction was 3.70 ± 0.19, while that after surgery was 3.67 ± 0.22 mEq/L. The Mean ± SE value for potassium in the animals of Group I before induction was 4.28 ± 0.19, while that after surgery was 4.2 ± 0.22 mEq/L.

There was no significant difference between the two groups ($p>0.05$).

4.12 OBSERVATIONS ON MUSCLE RELAXATION

Animals subjected to study, after administering loading dose of atracurium, 2 twitches disappeared after 5-8 minutes. The number of twitches remained so up to 20^{th} minute of observation. The 3^{rd} and 4^{th} twitches reappeared after 20^{th} minute of observation and remained so throughout the period of anaesthesia.

All four muscle twitches were present in the animals of Group I, after induction and during maintenance of anaesthesia. But the twitches, assessed visually, were not strong as those before administration of the injectable anaesthetic drug combination. There was disappearance of two muscle twitches and central positioning of the eye balls five to eight minutes after administration of atracurium. The third and fourth muscle twitches remained absent up to the 20^{th} minute and the twitches reappeared and remained so throughout the period of anaesthesia.

Table 38. Observations on sodium (mEq/L)				
Time interval	Group I	Group II	t-value	p-value
Before induction	141.5 ± 2.5	138.67 ± 3.15	0.705^{ns}	0.497
After recovery	145.33 ± 2.27	143.5 ± 2.95	0.492^{ns}	0.633
F-value (p-value)	3.557^{*}(0.016)	4.248^{**}(0.008)		
* Significant at 0.05 level; ** Significant at 0.01 level				

Table 39. Observations on potassium (mEq/L)				
Time interval	Group I	Group II	t-value	p-value
Before induction	3.7 ± 0.19	4.28 ± 0.19	2.16^{ns}	0.056
After recovery	3.67 ± 0.22	4.2 ± 0.22	1.70^{ns}	0.12
t-value (p-value)	1.000^{ns}(0.363)	0.955^{ns}(0.383)		
ns – non-significant				

Discussion

5. DISCUSSION

A study was carried out for evaluating the clinico-physiological and haemodynamic effects of atracurium in dogs induced with dexmedetomidine-midazolam-ketamine combination and maintained with isoflurane, for various surgical procedures. The results of the study are discussed below.

5.1 ANAESTHETIC PARAMETERS

5.1.1 Induction parameters

5.1.1.1Character and quality of anaesthetic induction

The quality of anaesthetic induction was excellent in all the animals studied. Therewas profound sedation in all the twelve animals following intramuscular administration of dexmedetomidine-midazolam-ketamine combination. Paddling was not noticed in any of the animals, and the transition to anaesthesia was calm and smooth in all animals. Eyeball rolled ventrally and medially in all animals upon anaesthesia. There was profound relaxation of jaw muscle and laryngeal tone which permitted easy intubation. Barletta *et al.* (2011), in a similar study following intramuscular injection of dexmedetomidine-ketamine-opioid combination found that the induction with the anaesthetic drug combination was rapid and smooth allowing easy intubation. A similar study on dexmedetomidine, midazolam and ketamine, the authors observed that induction of anaesthesia was effective producing good sedation, muscle relaxation and anaesthesia (Ahmad *et al.,* 2013).

5.1.1.2 Time taken for induction

The time taken for induction of anaesthesia in the twelve animals studied, following intramuscular injection of the anaesthetic combination was 8.16 ±0.76 minutes. Rafee *et al.* (2016), in their study with dexmedetomidine, midazolam and ketamine with pentazocine, found a decreased time of induction which can be attributed to the absence of opioid in the combination and the lower dose of

dexmedetomidine selected in this study. In a similar study done by other researchers, using an intramuscular administration of medetomidine-midazolam combination as premedicant got good sedation, muscle relaxation and analgesia and adequate maintenance anaesthesia on isoflurane after induction with propofol (Fabio *et al.*, 2007).

5.1.2 Recovery parameters

5.1.2.1 Time taken for recovery

Animals of the study group took 5.62 ± 1.66 minutes to recover from anaesthesia following weaning, while those in the control group took 6.63 ± 1.77 minutes for recovery. Even though there was slight variation in the times between the groups, it was not significant. From the present findings, it could be assumed that atracurium at the studied doses, did not significantly affect the time taken for recovery following weaning, in dogs maintained on isoflurane after induction with dexmedetomidine-midazolam-ketamine combination. This can be attributed to the employment of Hoffmann elimination principle in weaning of dogs from the neuromuscular blockade caused by atracurium (Meyer *et al.*, 1986). Bisht *et al.* (2016), in their study found a decreased time for recovery from anaesthesia induced by dexmedetomidine-etomidate-sevoflurane which is attributed to the lower dose of dexmedetomidine used in the anaesthetic protocol.

5.1.2.2 Time to regain sternal recumbency

Time taken for the animals in the control group (Group I) to regain sternal recumbency after weaning from anaesthesia was 15.35 ± 4.38 minutes, while it was 10.60 ± 3.53 minutes in study group (Group II). Although there was difference in the time taken for the animals to regain sternal recumbency, it was not significant. From the present findings, it could be assumed that atracurium at the studied doses, did not significantly affect the time to regain sternal recumbency following weaning, in dogs maintained on isoflurane after induction with dexmedetomidine-midazolam-ketamine combination. This can be attributed

to the rapid elimination of atracurium by Hoffmann elimination principle (Meyer *et al.,* 1986). Another study conducted by Bisht *et al.* (2016), also demonstrated a similar reduction in the time taken to regain sternal recumbency.

5.1.2.3 Time to assume standing posture unassisted

Time taken for the animals in the control group (Group I) to assume standing posture unassisted following weaning from anaesthesia was 42.67 ± 9.03 minutes, while it was47.67 ± 8.25 minutes in the study group (Group II).There was no significant difference in the time to assume standing posture between the groups. From the present findings, it could be assumed that atracurium at the studied doses, did not significantly affect the time to assume standing posture following weaning, in dogs maintained on isoflurane after induction with dexmedetomidine-midazolam-ketamine combination. Bisht *et al.* (2016) in their study on dexmedetomidine also observed a reduction in the time taken to assume standing posture unassisted.

5.2 PHYSIOLOGICAL PARAMETERS

5.2.1 Rectal Temperature

Rectal temperature recorded at 10^{th}, 20^{th} and 30^{th} minute post induction in the study group were significantly lower than those of the control group for their respective observation times, although these were within the normal range. The peak action of atracurium and peak of muscle relaxation could be between these observation period, which could have resulted in the lowering of rectal temperature during this period. Fabio *et al.* (2007), in their study observed a decrease in the rectal temperature and suggested that, α2-adrenoceptor agonists due to their biphasic response produced a vasoconstrictive effect initially producing a rise in the rectal temperature followed by a decrease in the same. The maintenance of rectal temperature even during a reduced muscular activity resulting from the administration can also be attributed to the effect of ketamine in

the anaesthetic protocol which maintained the rectal temperature during isoflurane anaesthesia (Boscan *et al.*, 2005).

5.2.2 Heart rate and pulse rate

Heart rate was found reduced in all the animals following induction with the injectable anaesthetic combination and maintenance, but was within the normal range. There was no significant difference in the heart rates between the groups. The reduction in the heart rate noticed after induction of anaesthesia could be attributed to dexmedetomidinedue to a parasympathetic response (Bloor *et al.*, 1992). Since there was no significant difference in heart rates between the study and control groups, it could be assumed that atracurium at the studied doses did not have any significant effect on heart rate in dogs maintained on isoflurane after induction with dexmedetomidine-midazolam-ketamine combination. A study conducted by Hackett *et al.* (1989), reported that atracurium produced the least disturbance in the haemodynamics in the animal administered with atracurium and pancuronium.

5.2.3Respiratory rate and depth

Respiratory rate was found reduced in all the animals following induction with the injectable anaesthetic combination. This could be due to the synergistic action of Dexmedetomidine-midazolam-ketamine (Sabbe *et al.*, 1994, Rafee *et al.*, 2016).In the Group I, the respiratory rate during maintenance of anaesthesia was found reduced, which could be attributed to the simultaneous effects of dexmedetomidine and isoflurane (Rafee *et al.*, 2016), but the depth of respiration was satisfactory. In the Group II, rate of respiration became considerably reduced, and the depth had become very shallow, following administration of atracurium. When compared with the Group I, there was pronounced reduction in the respiratory rate and depth in all animals of the Group II after administration of atracurium. The respiratory rate noted at the 10^{th}, 20^{th} and 30^{th} minutes in the study group were significantly lower when compared to those in the control group for their respective observation times. Spontaneity in the respiration was not

abolished in the animals of the study group except for one which became apnoeic at the 20th minute. The severe reduction in the respiratory rate and depth was insufficient in maintaining eucapnia, which necessitated manual assisted ventilation for every spontaneous breaths in all the animals of the study group. Donati *et al.* (1986), in their study on another neuromuscular blocking drug pancuronium found that the diaphragm was the last to be paralyzed during a neuromuscular blockade, thus retaining very weak respiratory efforts. In the present study, the severe reduction in the rate and depth of respiration following administration of atracurium could be attributed to its neuromuscular blockade it had caused on the intercostal muscles. Meyer *et al.*, (1986), in their study on atracurium, observed that respiratory muscles were the last to be paralysed by neuromuscular blockade. Co-administration of medetomidine together with ketamine produced considerable respiratory depression (Ko *et al.*, 2000)

5.2.4 Capillary refill time

The capillary refill time in the study group did not vary significantly when compared to those of the control group and remained within the normal range throughout the observation period. The findings suggested that atracurium at the studied dose rate preserved the cardiovascular functions well in dogs maintained on isoflurane after induction with dexmedetomidine-midazolam-ketamine combination.

5.3 NON INVASIVE BLOOD PRESSURE

The systolic, diastolic and mean arterial blood pressures in the study group at any point of observation did not vary significantly when compared to those of the control group. The findings suggested that atracurium at the studied dose did not have any significant effect on the blood pressure in dogs maintained on isoflurane after induction with dexmedetomidine-midazolam-ketamine combination. A study on the effect of single shot dexmedetomidine during isoflurane anaesthesia did not show any significant variation in the systolic blood

pressure when compared against a placebo (Lawrence and Lange, 1997). Stegmann *et al.* (2001), in a similar study using midazolam as premedication in dogs under isoflurane anaesthesia observed minimal change in blood pressure. Administration of atracurium in dogs maintained on isoflurane anaesthesia, in a similar study, did not show any variations in the arterial blood pressure (McMurphy *et al.*, 2004).

5.4 ELECTROCARDIOGRAM (ECG)

In both Group I and Group II, the electrocardiogram revealed a low heart rate within the normal range after induction and throughout the anaesthetic period which could be attributed to dexmedetomidine. Heart rate increased slightly towards the end in case of Group II animals. One animal each in Group I and Group II showed premature ventricular contractions with a depressed ST segment as was displayed in the ECG. The observations noticed could be due to the effects of the alpha2 adrenoceptor agonist dexmedetomidine. Barletta *et al.* (2011), in a similar study involving dexmedetomidine-ketamine-opioid observed sinus arrhythmias during recovery with a high intensity than that seen during the peri-operative period and opined that this change could have been due to reduction in sympathetic outflow resulting from absence of surgical stimulation

5.5 END TIDAL CARBON DIOXIDE

In the Group I, the end-tidal carbon dioxide concentration ($EtCO_2$) were satisfactory in all the animals throughout the period of observation. In the Group II however, the end-tidal carbon dioxide concentration increased considerably after administration of atracurium. The respiration was thus assisted manually to peak inspiratory pressure of not more than 20 cmH_2O for each and every spontaneous breaths in all the animals of the study group, to maintain eucapnia. The depth of respiration in all the animals of the study group following atracurium administration was considerably shallow when compared to those of the control

group. This might have been due to the resultant pronounced skeletal muscle relaxant activity of atracurium producing relaxation of respiratory muscle excluding the diaphragm, resulting in a rise in the end-tidal carbon dioxide concentration. In a similar study using dexmedetomidine-ketamine combination, supported with an opioid, a significant increase in the end-tidal concentration of carbon dioxide was observed which was attributed to the depression of respiratory muscles by the drug combination, which was easily corrected by supplementing 100% oxygen (Barletta *et al.*, 2011).

5.6 END TIDAL ISOFLURANE CONCENTRATION

End-tidal isoflurane concentration observed in the study group at 30^{th}, 40^{th} and 50^{th} minutes were significantly lower when compared to those of the control group at the respective times of observation. This significant difference was mainly due to the decreased need of isoflurane concentration, while the animals are on atracurium. As per the studies conducted by other researchers on atracurium, isoflurane augments the action of atracurium. Augmentation of neuromuscular blockade was observed with atracurium in dogs, while maintaining anaesthesia on volatile anaesthetic mixtures (Kastrup *et al.*, 2005).

5.7 SATURATION OF OXYGEN IN PERIPHERAL BLOOD

The saturation of oxygen in peripheral blood in the Group II at any point of observation did not vary significantly when compared to those Group I. This might have been due to the administration of 94-99% of oxygen with assisted manual ventilation in the animals of study group, and adequate oxygenation of blood due to uncompromised cardiovascular function. Rafee *et al.* (2016) in a similar study observed that the saturation of oxygen in peripheral blood remained between 90-97 % in animals induced with midazolam-ketamine following premedication with dexmedetomidine and maintained on isoflurane in 100% oxygen.

5.8 HAEMATOLOGY

Findings on haematological parameters in the present study reveal that there was no significant difference between the study and control groups at any point of observation. This suggest that atracurium at the studied dose rate did not have any significant effect on haematological values in dogs maintained on isoflurane after induction with dexmedetomidine-midazolam-ketamine combination. Contrary to the above findings, a reduction in the haematological values was observed in a similar study by Kumar *et al.* (2016), where they observed a decrease in the values. The difference in observation might have been due to the low dose rate of the drugs used in our study.

5.9 SERUM BIOCHEMISTRY

Serum biochemistry evaluation in the present study revealed that there was no significant difference in aspartate amino transferase, alanine transferase, alkaline phosphatase, total protein, albumin, bilirubin, blood urea nitrogen and creatinine before and after the study in the Group II when compared to those in the control group (Group I). This suggests that atracurium at the studied doses did not significantly affect the serum biochemical values in dogs maintained on isoflurane after induction with dexmedetomidine-midazolam-ketamine combination. Contrary to our findings, in a study on the clinico-physiological and haematobiochemical effects of dexmedetomidine along with ketamine (Kumar *et al.*, 2016), a decrease in the total protein and a transient increase in the serum urea nitrogen and creatinine values were observed. The difference in the findingsof the present study can be attributed to the low dose rate of dexmedetomidine and ketamine used.

5.10 BLOOD GLUCOSE

Blood glucose increased in both control and study groups after the anaesthetic procedure. The increase was within the normal range. The blood glucose values of the study group (Group II) did not vary significantly from that of the control group (Group I). This suggests that atracurium at the studied dose did not significantly affect the blood glucose levels in the dogs maintained on isoflurane after induction with dexmedetomidine-midazolam-ketamine combination. Bisht *et al.* (2016), in their study on dexmedetomidine with etomidate and sevoflurane, observed an increase in the blood glucose, which they reported might have been due to the action of α2-adrenergic agonist, dexmedetomidine reducing the insulin production. A similar study on dexmedetomidine and ketamine also showed an increase in blood glucose after induction (Kumar *et al.,* 2016).

5.11 BLOOD GAS AND ELECTROLYTE ANALYSIS

5.11.1 Partial Pressure of Oxygen

In Group I, there was considerable increase in PaO_2 upon administration of 95-99% concentration of oxygen following induction and during isoflurane maintenance. Similar higher values for the PaO_2 were observed in Group II upon administration of oxygen following induction and subsequent manual assisted ventilation provided after administration of atracurium. The higher values of PaO_2 noticed following induction and during maintenance in Group I could be attributed to the higher concentration of oxygen administered after induction and during maintenance. The findings in the PaO_2 values observed in the Group II at various time intervals suggest that the manual ventilation provided in 100% oxygen, to assist the considerably shallow respiration following atracurium administration, could maintain the partial pressure of oxygen in the arterial blood similar to those in the control group. Sullivan *et al.* (1998), in a similar study using pancuronium bromide to provide neuromuscular blockade under 100%

oxygen in dogs, reported that hypoventilation does not necessarily produce a decrease in partial pressure of oxygen.

5.11.2 Partial Pressure of Carbon dioxide

In the Group I, the partial pressure of carbon dioxide ($PaCO_2$) were satisfactory in all the animals throughout the periods of observation. In the Group II however, the partial pressure of carbon dioxide increased considerably after administration of atracurium. The respiration was thus assisted manually to peak inspiratory pressure of not more than 20 cmH_2O for each and every spontaneous breaths in all the animals of the study group, to maintain eucapnia. The depth of respiration in all the animals of the study group following atracurium administration was considerably shallow when compared to those of the control group. This might have been due to the resultant pronounced skeletal muscle relaxant activity of atracurium producing relaxation of respiratory muscle excluding the diaphragm, resulting in a rise in the partial pressure of carbon dioxide. In a study on the cardiovascular and intraocular pressures in dogs induced with propofol and maintained on atracurium, the $PaCO_2$ values were at a higher value due to the profound depression of respiration (Hofmeister *et al.*, 2009).

5.11.3 pH

The pH values noted were in the normal range,at all points of observation, both in the control (Group I) and study group (Group II). There was no significant difference in the pH values in the study group (Group II) when compared to those in the Group I. The findings on the pH values in the study group suggests that atracurium at the studied dose rate along with manual assisted ventilation couldmaintain the blood pH in normal range similar to those of theanimals in the control group. Hofmeister *et al.* (2009), in their study reported that the respiratory acidosis can result from an elevated $PaCO_2$ with a stable base excess, due to the

respiratory depression that occurs as result of administration of atracurium in animals induced with propofol. The maintenance of normal pH in the present study might have been due to the assisted ventilation provided during the anaesthetic procedure.

5.11.4 Bicarbonate

The bicarbonate values noted were within the normal range, at all the points of observation, both in Group I and Group II. There was no significant difference in the bicarbonate values of the Group II when compared to those in the control group. The findings noted for the bicarbonate values in the Group II suggests that atracurium at the studied dose rate along with manual assisted ventilation could maintain the blood bicarbonate in normal range similar to those of the animals in the Group I. Boscan *et al.* (2005), reported that the bicarbonate levels were within normal range after administration of ketamine in isoflurane anaesthetized dogs.

5.11.5 Lactate

The lactate values noted were within the normal range, at all the points of observation, both in Group I and Group II. There was no significant difference in the lactate values of the Group II when compared to those in the Group I. The above findings of the study suggests that atracurium at the studied dose rate did not have any significant effect on the lactate values. Saunders *et al.* (2009), suggested that tissue hypoxia can be estimated indirectly by the evaluating the lactate content. The normal lactate content in the present study can thus be attributed to the normal oxygenation of tissues.

5.11.6 Base excess

The lactate values noted were within the normal range, at all the points of observation, both in Group I and Group II. There was no significant difference in the bicarbonate values of the Group II when compared to those in the Group I.

The above findings of the study suggests that atracurium at the studied dose rate did not have any significant effect on the base excess values. The base excess values were within the normal range in dogs anaesthetized with ketamine and maintained on isoflurane (Boscan *et al.*, 2005).

5.11.7 Sodium

The levels for sodium increased in both control and study groups after the anaesthetic procedure. Even though there was increase in the sodium levels, it was within the normal range. There was no significant difference in the sodium levels of the Group IIand Group I. This increase in the sodium values after the procedure could be attributed to the infusion of normal saline in all the animals. Kumar *et al.* (2016), in their study in dogs induced with dexmedetomidine and ketamine, observed a decrease in the serum sodium levels.

5.11.8 Potassium

Potassium levels did not show any changes in Group I and Group II and there was no significant difference between the groups. The finding suggests that atracurium at the studied dose rate did not have any significant effect on the potassium levels. Kumar *et al.* (2016), in a similar study, observed a decrease in the serum potassium in dogs induced with dexmedetomidine and ketamine.

5.12 OBSERVATIONS ON MUSCLE RELAXATION

All four muscle twitches were present in the animals of Group I, after induction and during maintenance of anaesthesia. But the twitches, assessed visually, were not as strong as those before administration of the injectable anaesthetic drug combination. The eye ball was positioned ventrally and medially in all animals of Group I, after induction and during maintenance. There was

disappearance of two muscle twitches and central positioning of the eye balls five to eight minutes after administration of atracurium. The eye balls maintained the central position and the third and fourth muscle twitches remained absent up to the 20th minute, after which the eyeballs rolled down and the twitches reappeared and remained so throughout the period of anaesthesia. Flores *et al.* (2011), in a clinical setting, with an aim to reduce the complications arising from residual neuromuscular blockade observed that, the assessment of Train-of-four ratio is preferred. Thus the train-of-four stimulation and its visual assessment can prove useful in monitoring neuromuscular blockade.

Summary

6. SUMMARY

The study was conducted in twelve dogs which underwent various surgical procedures, in the Department of Veterinary Surgery and Radiology, College of Veterinary and Animal Sciences, Pookode, Wayanad. These dogs were randomly allocated into two groups – Group I and Group II, of six animals each.

Animals of Group I were anaesthetised with a drug combination of dexmedetomidine, midazolam and ketamine at the rate of 5 µg/kg, 0.2 mg/kg and 5 mg/kg body weight respectively as a single intramuscular injection. Following endotracheal intubation, isoflurane was administered in oxygen to maintain anaesthesia. In Group II, following induction with the same injectable drug combination and maintenance with isoflurane, a loading dose of atracurium at the dose rate of 0.1 mg/kg body weight was administered intravenously, immediately followed by a continuous rate infusion of atracurium at a dose rate of 0.1 mg/kg/hour. At the end of the procedure, all animals were weaned from anaesthesia by turning off the vaporizer and terminating the continuous rate infusion, and providing oxygen alone until recovery.

The quality of anaesthetic induction, produced by the dexmedetomidine-midazolam-ketamine combination, was excellent in all the animals. There was profound sedation in all the twelve animals following the intramuscular administration of the injectable anaesthetic combination, and the transition to anaesthesia was calm and smooth. Eyeball rolled ventrally and medially. There was profound relaxation of jaw muscle and laryngeal tone which permitted easy intubation.

Respiratory rate reduced in all animals following induction with the injectable anaesthetic combination. The respiratory rate during maintenance of anaesthesia was found reduced in animals of Group I, but the depth of respiration was satisfactory. Administration of atracurium in animals of Group II produced pronounced reduction in the rate and depth of respiration. The severe reduction of respiratory rate and resultant shallow respiration was insufficient in maintaining

eucapnia, which necessitated manual assisted ventilation for every spontaneous breaths.

The rectal temperature following induction and maintenance varied in animals of Group I, but was in the normal range. There was reduction in the rectal temperature in animals of Group II after atracurium administration.

The capillary refill time, heart rate, pulse rate, systolic, diastolic and mean arterial blood pressures remained within the normal range, and did not vary significantly within and between the groups. Occasional ventricular premature contractions were noted on electrocardiogram, in both the groups, after induction and during maintenance of anaesthesia.

All four muscle twitches were present in the animals of Group I, after induction and during maintenance of anaesthesia. But the twitches, assessed visually, were not as strong as those before administration of the injectable anaesthetic drug combination. The eye ball was positioned ventrally and medially in all the animals of Group I, after induction and during maintenance. There was disappearance of two muscle twitches and central positioning of the eye balls five to eight minutes after administration of atracurium. The eye balls maintained the central position and the third and fourth muscle twitches remained absent up to the 20^{th} minute, after which the eyeballs rolled down and the twitches reappeared and remained so throughout the period of anaesthesia.

There were no significant variations in the haematological, serum biochemical, blood gas and electrolyte values in both the groups during the period of observation.

Time taken for recovery, time to regain sternal recumbency and time to assume standing posture unassisted, following weaning from anaesthesia, did not vary significantly in the animals administered with atracurium, when compared to the animals of Group I.

The results of the study were concluded as follows:

1) The anaesthetic combination of dexmedetomidine, midazolam and ketamine at the rate of 5 µg/kg, 0.2 mg/kg and 5 mg/kg body weight respectively given as a single intramuscular injection, produced profound sedation, and uneventful and smooth transition to inhalant anaesthesia.
2) In the anaesthetised dogs, atracurium at the loading dose of 0.1 mg/kg intravenously, immediately followed by continuous rate infusion of 0.1 mg/kg/hr produced significant reduction in the rate and depth of respiration, which could be managed by manual assisted ventilation.
3) Atracurium at the mentioned doses did not have any significant effects on the cardiovascular system in the dogs studied.
4) Administration of atracurium supported with manual assisted ventilation effectively maintained the blood gases and electrolyte values within normal range in the anaesthetised dogs.
5) Pronounced muscle relaxation occurred five to eight minutes after administration of atracurium, and remained so for a period of 12-15 minutes during maintenance, and reduced afterwards.
6) It could be thus concluded that dogs anaesthetised with intramuscular injection of dexmedetomidine-midazolam-ketamine combination and maintained on isoflurane when administered atracurium intravenously followed immediately by a continuous rate infusion, provided profound muscle relaxation without compromising the haemodynamic functions, the marked reduction in the rate and depth of respiration necessitated assisted ventilation.

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CLINICAL EVALUATION OF DEXMEDETOMIDINE-MIDAZOLAM-KETAMINE WITH ATRACURIUM FOR ISOFLURANE ANAESTHESIA IN DOGS

BINU S. JOSELIN

(15-MVP-001)

ABSTRACT

Submitted in partial fulfilment of the requirement for the degree of

MASTER OF VETERINARY SCIENCE

(Veterinary Surgery and Radiology)

2017

Faculty of Veterinary and Animal Sciences

Kerala Veterinary and Animal Sciences University

DEPARTMENT OF VETERINARY SURGERY AND RADIOLOGY

COLLEGE OF VETERINARY AND ANIMAL SCIENCES

POOKOODE, WAYANAD – 673576

KERALA, INDIA

8. ABSTRACT

General anaesthesia with sustained muscle relaxation is inevitable for most of the surgical procedures performed. Additional muscle relaxation, without deepening anaesthesia, could be attained by administering a peripheral acting muscle relaxant like atracurium. Accordingly the study was conducted to find out the clinico-physiological and haemodynamic effects of atracurium on animals induced with dexmedetomidine-midazolam-ketamine combination and maintained on isoflurane for various surgical procedures. The study was conducted in twelve dogs which underwent various surgical procedures, in the Department of Veterinary Surgery and Radiology, College of Veterinary and Animal Sciences, Pookode, Wayanad. These dogs were randomly allocated into two groups – Group I and Group II, of six animals each. Animals of Group I were anaesthetised with a drug combination of dexmedetomidine, midazolam and ketamine at the rate of 5 µg/kg, 0.2 mg/kg and 5 mg/kg body weight respectively as a single intramuscular injection. Following endotracheal intubation, isoflurane was administered in oxygen to maintain anaesthesia. In Group II, following induction with the same injectable drug combination and maintenance with isoflurane, a loading dose of atracurium at the dose rate of 0.1 mg/kg body weight was administered intravenously, immediately followed by a continuous rate infusion of atracurium at a dose rate of 0.1 mg/kg/hour.

The quality of anaesthetic induction, produced by the dexmedetomidine-midazolam-ketamine combination was excellent in all the animals. There was profound sedation in all the twelve animals following the intramuscular administration of the injectable anaesthetic combination, and the transition to anaesthesia was calm and smooth. Eyeball rolled ventrally and medially. There was profound relaxation of jaw muscle and laryngeal tone which permitted easy intubation.

Respiratory rate reduced in all the animals following induction with the injectable anaesthetic combination. Administration of atracurium in the animals of Group II produced pronounced reduction in the rate and depth of respiration which necessitated manual assisted ventilation for every spontaneous breath.

All four muscle twitches were present in the animals of Group I, after induction and during maintenance of anaesthesia. But the twitches, assessed visually, were not as strong as those before administration of the injectable anaesthetic drug combination. The eye ball was positioned ventrally and medially in all the animals of Group I, after induction and during maintenance. There was disappearance of two muscle twitches and central positioning of the eyeballs within five to eight minutes after administration of atracurium. The eyeballs maintained the central position and the third and fourth muscle twitches remained absent up to 20^{th} minute, after which the eyeballs rolled down and the twitches reappeared and remained so throughout the period of anaesthesia.

There were no significant variations in the haematological, serum biochemical, blood gas and electrolyte values in both the groups.

Time taken for recovery, time to regain sternal recumbency and time to assume standing posture unassisted, following weaning from anaesthesia did not vary significantly in the animals administered with atracurium when compared to the animals of Group I.

It could be thus concluded that dogs anaesthetised with intramuscular injection of dexmedetomidine-midazolam-ketamine combination and maintained on isoflurane when administered atracurium intravenously followed immediately by a continuous rate infusion, provided profound muscle relaxation without compromising the haemodynamic functions, but the marked reduction in the rate and depth of respiration necessitated assisted ventilation.

Academic Form No. 19

KERALA VETERINARY AND ANIMAL SCIENCES UNIVERSITY

Faculty of Veterinary and Animal Sciences

PROGRAMME OF RESEARCH WORK OF THESIS FOR MASTERS DEGREE

1. Title of thesis:

Clinical evaluation of dexmedetomidine-midazolam-ketamine with atracurium for isoflurane anaesthesia in dogs

2(a) Title of the departmental/ KVASU research project of which this forms a part:

Nil

(b) Code No. if any, and order by which departmental/ KVASU research project is approved:

Not applicable

3a. Name of student:

Binu S. Joselin

b. Admission Number:

15-MVP-001

4a. Name of Major Advisor (Guide):

Dr. Sooryadas S.

b. Designation:

Assistant Professor
Department of Veterinary Surgery and Radiology,
College of Veterinary and Animal Sciences, Pookode, Lakkidi P.O, Wayanad-673576

5. Objective of the study:

To study the clinico-physiological and haemodynamic effects of atracurium in dogs induced with dexmedetomidine-midazolam-ketamine combination and maintained with isoflurane anaesthesia for routine surgical procedures.

6. Practical/ Scientific utility:

Muscle relaxation is of paramount importance in many of the procedures performed in animals, such as orthopedics, thoracotomy and laparotomy. Many drugs do not produce adequate muscle relaxation for facilitating surgery. Present study is undertaken to evaluate the efficacy of neuromuscular blocking drug namely atracurium as muscle relaxant. Once established, the protocol can be efficiently used in surgical procedures requiring marked muscle relaxation.

7. Important publications on which the study is based:

Jones *et al.* (1992) stated that under conditions of clinical anaesthesia in the presence of halothane, atracurium at a dose of 0.5 mg/kg had a duration of action of 40 minutes. Incremental doses of 0.2 mg/kg were non-cumulative and had a mean duration of action of 17.5 minutes.

Leslie *et al.* (1995) stated that the duration of action of atracurium was prolonged approximately 60 per cent by 3°C of core hypothermia.

Lawrence *et al.* (1997) stated that the administration of the dexmedetomidine had no significant effect on systolic or diastolic blood pressure in humans.

Adams *et al.* (2001) proved that cis-atracurium administered at the dose rate of 0.1 mg/kg intravenously in an anaesthetized dog, produced complete Neuromuscular blockade in 3-8 minutes which persisted for a time period of 15 minutes in one dog and 50 minutes in other after a maintenance dose of 0.1 mg/kg.

Hemmerling *et al.* (2001) concluded that, in comparison to propofol, isoflurane, sevoflurane and desflurane reduce the cumulative dose requirements of cisatracurium to maintain a 90 per cent neuromuscular blockade by 42, 41 and 60 percentages respectively.

Joanna (2005) stated that Dexmedetomidine decreased the whole body O_2 requirements and blood flow to the vital organs remained above levels associated with hypo-perfusion, indicating that cardiac output redistribution induced by dexmedetomidine does not threaten vital tissue.

8. Outline of the technical programme:

A minimum of twelve dogs presented at the Surgery out-patient unit of the Teaching Veterinary Clinical Complex, Pookode, for various surgeries will be selected for the study. They will be randomly divided into groups - Group I and II, of minimum six animals each, and general anaesthesia will be performed as shown below -

Group I	Dexmedetomidine @ 5 µg/kg, Ketamine @ 5 mg/kg and Midazolam @ 0.2 mg/kg, combined in a single syringe and given intramuscular Following anaesthesia, intubation and maintenance using isoflurane
Group II	Dexmedetomidine @ 5 µg/kg, Ketamine @ 5 mg/kg and Midazolam @ 0.2 mg/kg combined in a single syringe and given intramuscular. Following anaesthesia, intubation and maintenance using isoflurane. All animals will be administered bolus injection of atracurium besylate @ 0.1 mg/kg IV followed by continuous rate infusion (CRI) of atracurium besylate @ 0.1 mg/kg/hr IV

Venous blood samples will be collected for routine haematology and serum biochemistry and arterial blood collected for blood gas analysis, before induction, after induction and every 30 minutes thereafter throughout the anaesthetic period.

Physiological parameters will be recorded before induction, after induction and every 10 minutes thereafter throughout the anaesthetic period.

Lead II Electrocardiography will be recorded before induction, after induction and at every 10 minutes thereafter throughout the period of anaesthesia.

Ventilation parameters will be recorded after induction and at every 10 minutes throughout the anaesthetic period.

Liver function test and kidney function test will be estimated before and after surgery

9. Main items of observations to be made:

a. Physiological parameters:

Temperature, Pulse rate, Respiratory rate, Blood pressure (Systolic, Diastolic and Mean arterial pressure) and Capillary refill time.

b. Lead II Electrocardiography

c. Anaesthetic parameters:

Clinical effects of the drugs and their respective times of onset. Time taken for induction, time taken for recovery and quality of anaesthesia. End tidal concentration of isoflurane (EtIso %) required for maintenance of anaesthesia. Complications if any.

d. Ventilation parameters: $EtCO_2$ and SpO_2

e. Haematological parameters:

Haemoglobin concentration, volume of packed red cells, total erythrocyte count, total leucocyte count, differential leucocyte count.

f. Serum biochemistry:

i. Liver function test and kidney function test before and after surgery.

ii. Serum glucose, sodium and potassium.

g. Blood gas analysis:

PaO_2, $PaCO_2$, pH, HCO_3^- base excess and blood lactate.

10. Facilities

(a) Existing:

Facilities existing in the Department of Veterinary Surgery and Radiology and TVCC, Pookode, will be utilized.

(b) Additional facilities required:

Nil

11. Duration of study:

Four Semesters

12. Financial estimate:

Anaesthetics,

Chemical and Reagents	: Rs.	20,000
Contingencies	: Rs.	5,000
Total	**: Rs.**	**25,000**

Signature of Student

Signature of Major Advisor

Place: Pookode

Date:

Name and signature of members of the Advisory Committee

Chairman

Dr. Sooryadas S.

Assistant Professor
Department of Veterinary Surgery and Radiology, College of Veterinary and Animal Sciences, Pookode, Wayanad

Members

Dr. John Martin K. D.

Associate Professor and Head
Department of Veterinary Surgery and Radiology, College of Veterinary and Animal Sciences, Pookode, Wayanad

Dr. Dinesh P.T.

Assistant Professor
Department of Veterinary Surgery and Radiology, College of Veterinary and Animal Sciences, Pookode, Wayanad

Dr. Bipin K.C.

Assistant Professor
Department of Veterinary Epidemiology and Preventive Medicine, College of Veterinary and Animal Sciences, Pookode, Wayanad

APPENDIX- I

References

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APPENDIX- II

(Time frame of study)

Semester I

1. Collection of literature
2. Planning of programme of Research work
3. Preparation of Synopsis

Semester II

1. Collection of literature
2. Procurement of medicines, diagnostic equipments and medicines
3. Starting of research work

Semester III

1. Collection of literature
2. Research work

Semester IV

1. Completion of research work
2. Analysis of result
3. Preparation and submission of thesis

CERTIFICATE

Certified that the research project has been formulated observing the stipulations laid down under the Prevention of Cruelty to Animals Act (Amendment, 1998)

Place: Pookode
Date:

Dr Sooryadas S
Major Advisor

CURRICULUM VITAE

PERSONAL INFORMATION

Name:	Binu S. Joselin
E-Mail:	**binu6989@gmail.com**
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Specialization:	Veterinary Surgery.
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Date and Place of Birth:	6th September 1989 (Kunnathoor, Kerala, India)
Nationality:	Indian
Marital Status:	Unmarried
Present position:	M.V.Sc. Scholar Department of Veterinary Surgery & Radiology College of Veterinary & Animal Sciences, Pookode, Lakkidi, P.O, Wayanad, Kerala-673576, INDIA

UNIVERSITY EDUCATION

Degree	Institution	University/Board	Year	Per cent Marks
B.V.Sc & A.H	College of Veterinary and Animal Sciences, Mannuthy, Thrissur, Kerala	Kerala Veterinary & Animal Sciences University	2007-2015	6.45
AISSCE (12^{th})	Kendriya Vidyalaya, Pattom Thiruvananthapuram	Board of Higher Secondary Examination, Kerala	2005-2007	63%
AISSE (10^{th})	Kendriya Vidyalaya, Pattom Thiruvananthapuram	Board of Secondary Examination, Kerala	2005	74%

Memberships:

1) Indian Veterinary Association
2) Kerala State Veterinary Council
3) Indian Society for Advancement of Canine Practice

Work Experiences:

Six months internship (B.V.Sc & A.H.)

Six months as Veterinary Surgeon, at Special Livestock Breeding Programme,
Iritty Circle, Kannur,
Kerala, India

PAPERS/ POSTERS PRESENTED

Dinesh P. T., **Binu S. Joselin**, Sooryadas S., John Martin K.D. Management of supracondylar femur fracture in a dog by dynamic cross pinning.

Binu S. Joselin, Joju Johns, Kamalesh Kumar K. S., Ellette da Gama Fronia, Vegireddy Ramu. Surgical management of tibiotarsal fracture in a gosling using aluminium wire splints as external coaptation.

Binu S Joselin, Syam K Venugopal, Dinesh P T, Sooryadas S, Reji Varghese, Jinesh Kumar, Joju Johns, Pramod U Menon, Vegireddy Ramu, Kamalesh kumar K S, Maruthi S T, Divya Suresh. Surgical correction of traumatic diaphragmatic hernia in a dog

Binu S. Joselin, Joju Johns, Dinesh P. T., Sooryadas S., Syam K. Venugopal. Surgical excision of harderian gland in a pug