"Comparative study on Constant Rate Infusion (CRI) with Ketamine/Propofol/Ketofol anaesthesia for elective ovariectomy (OVE) in Dogs."

THESIS

BY

Dr. AGYEY PUSP

(BVC/VM-0007/2018-19)

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In partial fulfillment of the requirements

FOR THE DEGREE OF

MASTER OF VETERINARY SCIENCE

IN

VETERINARY SURGERY AND RADIOLOGY

2021

Dedicated to...
My Beloved Parents
And
Brother

DEPARTMENT OF VETERINARY SURGERY AND RADIOLOGY

Bihar Veterinary College, Patna-800014
(Bihar Animal Sciences University, Patna, Bihar)

CERTIFICATE-I

This is to certify that the thesis entitled ***"Comparative study on Constant Rate Infusion (CRI) with Ketamine/Propofol/Ketofol anaesthesia for elective ovariectomy (OVE) in Dogs."***

submitted in partial fulfillment of the requirement for the award of the degree of **Master of Veterinary Science in the discipline of Veterinary Surgery and Radiology** of faculty of Post-Graduate Studies, Bihar Animal Sciences University, Patna, Bihar is the bonafide research carried out by **Dr. Agyey Pusp** son/~~daughter~~ of Sh. Ramdev Rajak under my supervision and that no part of this thesis has been submitted for any other degree or diploma.

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

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CERTIFICATE- II

This is to certify that the thesis entitled ***"Comparative study on Constant Rate Infusion (CRI) with Ketamine/Propofol/Ketofol anaesthesia for elective ovariectomy (OVE) in Dogs."***

Submitted by **Dr. Agyey Pusp,** Registration No. – **BVC/VM -0007//2018-19,** son/~~daughter~~ of Sh. Ramdev Rajak to Bihar Animal Sciences University, Patna, Bihar in partial fulfillment of the requirement for the degree of **Master of Veterinary Science in the discipline of Veterinary Surgery and Radiology** has been approved by the advisory committee after an oral examination of the student in collaboration with an external examiner.

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Place: - Bihar Veterinary College, Patna

Date: - ***(Agyey Pusp)***

Place: - **(अज्ञेय पुष्प)**

CONTENTS

Abbreviations

%	Per cent
/	Per
@	at the rate
<	Less than
=	Equal to
>	Greater than
±	Plus or minus
°F	Fahrenheit
µL	Microliter
µM	micromole
B.wt	Body weight
CNS	Central nervous system
CRT	Complete recovery time
CVP	Central venous pressure
DAP	Diastolic arterial pressure
DLC	Differential leukocyte count
et al	And others
Fig.	Figure
g/dl	Gram per deciliter
g/L	Gram per litre
GABA	Gamma Amino butyric acid
Hb	Haemoglobin
HR	Heart rate
IM	Intramuscular

IV	Intravenous
L/L	Litre per litre
MAP	Mean arterial pressure
mg/kg	Milligram per kilogram
Min	minute
Mm Hg	Millimeter of mercury
mmol/L	Millimole per litre
µg/kg	Microgram per kilogram
µIU	Micro international units
µmol	Micromole
NIBP	Non invasive blood pressure (monitor)
nmol	Nanomole
PCV	Packed cell volume
pmol/L	Picomole per litre
RBC	Red blood corpuscle
RR	Respiration rate
RT	Racal temperature
SAP	Systolic arterial pressure
SE	Standard error
Sec	Second
SRT	Sternal recumbency time
ST	Standing recovery time
TLC	Total leukocyte count
U/L	Unit per litre
WBC	White blood corpuscle

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Introduction

"If you believe in living a respectable life, you believe in self-help which is the best help"

1 INTRODUCTION

Anaesthesia and analgesia are interlinked and autonomic parameters like change in respiratory and cardiovascular responses are indicators of the depth of anaesthesia or anti-nociception (Gruenewald and Ilies, 2013). The purpose of anaesthesia is to produce a convenient, safe, effective analgesia, sedation, and reversible unconsciousness of the animals, so that surgical intervention may be conducted with minimum stress, discomfort, pain, and toxic side effects to the patients (Thurmon *et al*., 1996 and William *et al.,* 2007). Ideal balanced anesthesia helps in rapid and smooth induction, adequate hypnosis, and analgesia for surgical interventions. Pre-anesthetic medications are used to minimize stress, cardiopulmonary depression, and the deleterious effect associated with parental and inhalation anesthetics (Habib *et al*., 2002). Generally, in animals during minor or major surgery a combination of an anticholinergic, sedative and the tranquilizing agent is used as pre-anesthetic agents. For these purposes, pre-anaesthetic generally used is atropine, diazepam, butorphanol, and acepromazine (Mahmud *et al.,* 2014). These drugs help in overcoming the stress of the animals during examination, maintaining the depth of anesthesia, perioperative analgesia, reducing the amount of any single anesthetic agents, increasing margins of safety, and smooth recovery.

An anticholinergic agent is most commonly used as a pre-anesthetic agent in combination with xylazine, acepromazine, and diazepam to minimize or prevent vagal effects. The anticholinergic agent also reduces potential muscles spasm, gastrointestinal motility, and respiratory secretions as well as decrease tear production during anesthesia (Kovaļčukaand Birģele, 2011). The administration of pre-anaesthetic agents in combination with general anesthetics is provided better hemodynamic stability because of a lower dose of general anesthetics for induction and maintenance of anaesthesia (Ilkiw *et al.,* 1994). Butorphanol is a synthetic opioid with agonist-antagonist properties. It is a potent opioid analgesic for managing acute nociceptive pain like injury, peri-operative and post-operative pain, visceral and chronic pain (Ahsam *et al.,* 2020). The analgesic potency of butorphanol is 3-5 times that of morphine. In dogs, butorphanol causes minimal cardiopulmonary depression (Cornick and Hartsfield, 1992).

In veterinary anesthesiology, xylazine was used in the last sixties in domestic and pet animals. It is an alpha-2 adrenoceptors agonist drug that is widely used to provide dose-dependent sedation, analgesia, and muscle relaxation. It is usually used in combination with ketamine during anesthetic applications (Ozkan *et al.,* 2010).

Administration of ketamine alone increases heart rate and means arterial pressure. It can cause undesired effects such as muscular hypertonicity, myoclonus, and convulsions. To minimize these unwanted effects, ketamine is generally administered in combination with other drugs like benzodiazepines and alpha-2 agonists (Ozkan *et al*., 2010 and Dzikiti *et al*., 2007). At present time depending on the species, age, breed, and physical condition of animals, the drug is commonly used in combination with benzodiazepines tranquilizers, and alpha-2-adrenergic agents (Mahmud *et al*., 2014). The objective of constant rate infusion (CRI) is to achieve a constant plasma concentration of drugs in the body. This state can be achieved by the administration of a constant rate of ketamine or propofol. CRI prevents the sudden peaks and valleys associated with intermittent I/V boluses and I/M injection and also maintains a stable plane of anaesthesia superiorly to boluses (Pablo, 2011).

Propofol is a water-insoluble hypnotic alkyl phenol. It is formulated in a lipid emulsion containing extracts of soya and egg protein (Kastner, *et al* 2015). It is considered to be a suitable drug for the induction and maintenance of anaesthesia by CRI (Musk *et al.,* 2005). The advantages of propofol include rapid onset of action with smooth induction and recovery. Constant rate infusion of propofol minimizes delays in recovery and causes less cardiopulmonary depression than the repeat bolus infusion (Njoku, 2015). On the flip view propofol as total intravenous anaesthesia (TIVA) in dogs is associated with dose-dependent hypotension due to reductions in both myocardial contractility and systemic vascular resistance (Nagashima *et al*., 2000).

Ketamine and propofol have an additive effect when administered together (Hui *et al.,* 1995). The combination of ketamine with propofol nullifies deleterious effects on one another and maintains haemodynamic ability (Kennedy and Smith, 2015). Single syringe administration of ketamine and propofol as ketofol admixtures was effective and safe for painful procedures in procedural sedation and analgesia (Willman and Andolfatto, 2007).

Combination of glycopyrrolate, butorphanol, xylazine as premedication, and induction with propofol, and maintenance with ketamine, propofol, and propofol mixtures

(Ketofol 1:1) as CRI would have the ability to maintain better hemodynamic and also reduce the dose of general anaesthesia for maintenance. There are very few reports regarding ketamine, propofol, and ketofol using CRI in dogs along with that appropriate premedication (Intelisano *et al*., 2008). This technique once gets standardized; it may transfer to field veterinarians for elective ovariectomy under a routine animal birth control programme (ABC) for safe handling of canines. Therefore, the present study was designed to evaluate balance anaesthesia for ovariectomy with the following objectives.

OBJECTIVES:

1. **To evaluate the clinco-physiological effect of Ketamine, Propofol, and Ketofol as a CRI anaesthesia in dogs**.
2. **To study the haemodynamic and haemato-biochemical changes with Ketamine, Propofol, and Ketofol as CRI anaesthesia in dogs.**

****

Review Of Literature

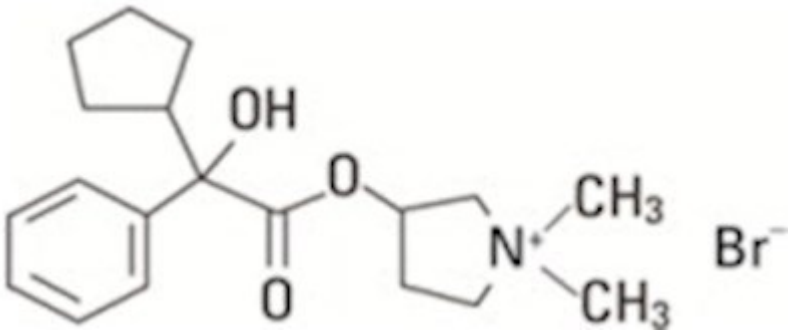
"Get good counsel before you begin

When you have decided out promptly"

2 REVIEW OF LITERTURE

In the canine, intramuscular injection is the preferred route for administration of pre-anesthetic agents to attain sedation, as minimal restraint required for IM injection. Besides, cardiovascular responses are attenuated when anticholinergic and α-2-agonists are administered in combination and the adverse actions of any single drug of pre-anesthetic or anaesthetics agents may be diminished due to the lower doses required (Lin *et al*., 1994). Intravenous anesthetic drugs are usually first administered as a large bolus to fill the volume of distribution of the central compartment, which is then followed by continuous lower dosages to maintain effective drug plasma concentrations for the duration of anesthetic procedure (Beths, 2008).

2.1 Glycopyrrolate:

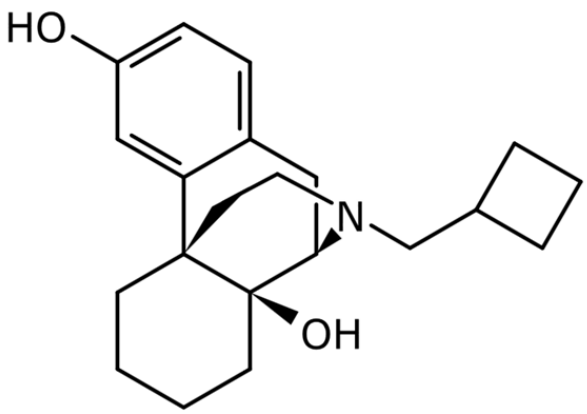


(Glycopyrronium bromide)

The molecular formula is $C_{19}H_{28}BrNO_3$and chemical formula of glycopyrrolate 3-[2-Cyclopentyl (hydroxy) phenylacetoxy]-1, 1-dimethylpyrrolidinium bromide. Glycopyrronium bromide is a medication of the muscarinic anticholinergic group. The injectable form of glycopyrrolate is also used to reduce saliva, nasal, lung, and stomach secretions and to help control heart rate during surgery. It does not cross the blood-brain barrier and consequently has few to no central effects. Anticholinergic agents such as atropine and glycopyrrolate are primarily used to decrease vagal tone due to opioids or traction on the uterus or to support fetal heart rate. Glycopyrrolate blocks the cholinergic muscarinic receptors, stopping muscarinic effects of acetylcholine mainly in parasympathetic postganglionic fibers (Islami *et*

al., 2009). The choice depends on the desire for placental transfer since atropine crosses the placental barrier but glycopyrrolate does not. Glycopyrrolate has potent muscle relaxant and anticonvulsant properties. It uses in a wide range of animal-like wild, domestic animals, and birds. Glycopyrrolate will mitigate the increased vagal tone caused by agonist opioids and prevent maternal bradycardia and possible hypotension. It also increases gastric pH and may decrease the severity of chemical pneumonitis should regurgitation and aspiration occur in the dam (Raffe, 2015). Fetal bradycardia (< 150 beats/min) indicates fetal distress and is one of the prime indicators for emergency CS (Smith, 2012). It is important to optimize maternal oxygenation, cardiac output, and blood pressure, and ensure good ventilation for the puppies after delivery.

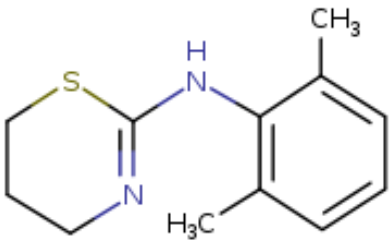
2.2 Butorphanol:



The molecular formula is C21H29NO2C4H6O6 and the chemical formula of butorphanol is 17-cyclobutylmethyl-3, 14-dihydroxy morphinan. Butorphanol is a morphine an-type synthetic agonist–antagonist opioid analgesic developed by Bristol-Myers. Butorphanol is available as the tartrate salt in injectable, tablet, and intranasal spray formulations. Butorphanol is a mixed synthetic agonist-antagonist opioid analgesic commonly used in both humans and veterinary (Gourdon, 2008). It is 3 to 5 times more potent than morphine. Butorphanol is used widely and potent analgesic with lower, abuse potential than morphine and fentanyl (Evans *et al*., 1985). Theoretically, it offers an advantage over traditional opiates such as morphine and meperidine in the treatment of moderate pain. Butorphanol has been used as a preoperative sedative and analgesic, as a supplement to balanced anesthesia, and for suppression of postanaesthesia shaking. Other recognized uses include obstetric analgesia during labor and relief of moderate postpartum

pain. In addition, butorphanol has been used effectively for conscious sedation. Its lack of euphoric effects may be useful in emergency medicine for clinical populations prone to drug-seeking behavior. Butorphanol has been used more recently for epidural analgesia or intravenous patient-controlled analgesia when allergies to opiates exist. Since butorphanol is not a controlled substance, its use can reduce administrative liability for abuse and can lower the number of distribution records associated with schedule II narcotics. Kalpravidh *et al.,* (1984) reported that when it is administered by bolus injection, butorphanol provides a moderate degree of somatic analgesia and a slightly greater degree of visceral analgesia in the horse. However, it also causes a degree in gastrointestinal tract motility. It induces mild sedation and a decrease in arterial blood pressure, and arterial oxygen tension in dogs. Muir and Robertson (1985) have been reported that butorphanol ameliorates signs of superficial and visceral pain in the horse when administered as a bolus IV injection but is effective for only 30 to 90 minutes. Butorphanol is one of the most widely used analgesics and anesthetic adjuvants in veterinary medicine. Butorphanol is used for the management of post-operative pain in minor and major surgical procedures. Butorphanol has been used widely in the management of post-operative pain and capable of relieving intense pain. Receptor specificity of butorphanol has been used to limit respiratory depression, gastrointestinal side effects, and reduced risk of dependency. The analgesic activity of butorphanol is dose-related. Butorphanol has been used as a preoperative sedative and analgesic, as a supplement to balanced anaesthesia, and for suppression of post-anaesthesia shacking (Vogel sang and Hayes, 1991). Pfeffer *et al.,* (1980) reported that butorphanol is rapidly absorbed after IM administration to dogs, with a mean $t^{1/2}$of absorption in 0.11 hour and maximum plasma concentration evident at 0.7 ± 0.3 hours after administration. Elimination is relatively rapid (t1/2=1.53±0.24hr). Intramuscular butorphanol can be used effectively and safely for post-operative pain relief for minor to moderate lower abdominal and pelvic surgeries in humans (Tantry *et al*., 2010). Butorphanol produces a mild lowering of heart rate and minimum cardiovascular effects (Garcia-Pereira *et al.,* 2007). Combination of butorphanol and α-2-agonist synergistic produces reliable and uniform sedation in dogs (Amarpal *et al.,* 1998). The addition of butorphanol for basal anaesthesia reduced the amount of ketamine required for maintenance and better sedation (Rafee *et al.,* 2015). Butorphanol is biotransformed and cleared in hepatic tissue by hydroxylation, dealkylation, and conjugation (Kumari *et al.,* 2017). Butorphanol and alpha-2 adrenoceptor agonist combination provide potential and uniform sedation in dogs and cats, although a significant decrease in heart and respiratory rates are observed (Muir *et al*., 1999; Bartram *et al*., 1994; Ko *et al*., 1996)

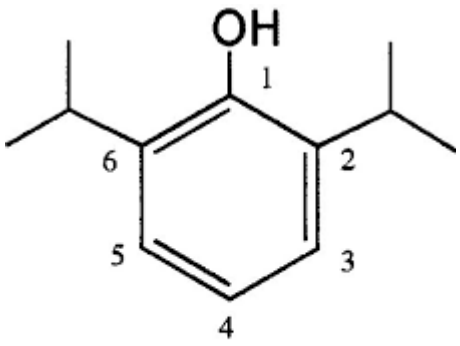
2.3 Xylazine:



Xylazine

The molecular formula is C12H16N2S and the chemical formula N-(2, 6-Dimethylphenyl)-5, 6-dihydro-4H-1, 3-thiazine-2-amine. Xylazine is often used as a sedative, muscle relaxant, and analgesic. It is frequently used in the treatment of tetanus. Xylazine is very similar to drugs such as phenothiazine, tricyclic antidepressants, and clonidine. As an anesthetic, it is typically used in conjunction with ketamine. Xylazine is an analogue of clonidine and an agonist at the alpha-2 class of adrenergic receptor. It is used for sedation, anesthesia, muscle relaxation, and analgesia in animals such as horses, cattle, and other non-human mammals. Veterinarians also use xylazine as an emetic, especially in cats. Its sedative and analgesic activity is related to central nervous system depression. It is muscle-relaxant effect is based on inhibition of the intraneural transmission of impulses in the central nervous system. The principal pharmacological activities develop within 10 to 15 minutes after intramuscular injection, and within 3 to 5 minutes following intravenous administration in horses. Due to the high lipophilic nature of xylazine, it directly stimulates central alpha-2 receptors as well as peripheral α-adrenoceptors in a variety of tissue. As an agonist, xylazine leads to a decrease in the neurotransmission of norepinephrine and dopamine in the central nervous system. It does so by mimicking norepinephrine in binding to presynaptic surface auto-receptors, which leads to feedback inhibition of norepinephrine.

2.4 Propofol:



2,6-Diisopropylphenol
(propofol)

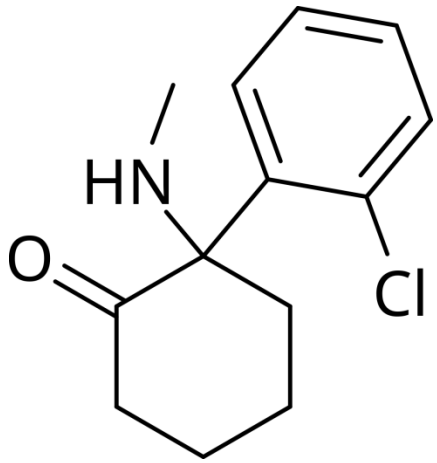
Propofol is a unique non-barbiturate, non-steroid, short-acting non-water-soluble hypnotic general intravenous anaesthetic agent (Kastner, 2007 and Hofmeister *et al*., 2008). The empirical formula of propofol is C12H18O (2,6-diisopropyl phenol) a substitute of phenol derivatives developed as an intravenous agent which produced anaesthesia characterized by rapid onset, short duration, lack of cumulation on repeated administration. The current standard emulsion formulation in propofol (standard propofol emulsion) includes soybean oil (10%), egg yolk lecithin (1.2%), and glycerol (2.25%) (Feng *et al*., 2017).

Propofol has a short half-life and rapid metabolism, including extra-hepatic metabolism, but it can cause cardiopulmonary depression depending on the dose and rate of administration. Propofol followed by isoflurane has puppy survival rates equivalent to epidural anesthesia and is associated with a positive effect on neonatal survival at 7 days (Moon *et al.,* 2000). Propofol has similar fetal mortality rates to mask induction with isoflurane, but it allows IV induction and rapid control and protection of the airway (Moon *et al*., 2000, Moon-Massat and Erb, 2002). It is considered to be a suitable drug for the maintenance of anesthesia by continuous rate infusion (Musk *et al.,* 2005). Propofol TIVA provides a slower but smoother recovery compared with propofol-induced, isoflurane maintained anaesthesia in dogs (Tsai *et al*., 2007). Technically, where a drug is administered continuously but with changes being made to the dose, it is termed as a variable rate infusion (VRI), however the term CRI is usually applied to both situations. When CRIs are used to reduce inhalational anaesthetic agent requirement, it is known as partial intravenous anaesthesia (PIVA). Whereas CRI is used alone to provide anaesthesia, it is termed total intravenous anaesthesia (TIVA) (Duke, 2013). Adverse effects of propofol are pain on injection, respiratory depression and

excitation. Reid and Nolan (1996) suggested that when propofol was used for the maintenance of general anaesthesia in dogs lower doses were required for older dogs. Continuous rate of infusion of propofol in dogs maintains cerebral perfusion and auto regulation (Paula *et al*., 2010). Pharmacodynamically, the interaction between propofol and the opioids is generally found to be synergistic (Vuyk, 1997). Propofol is rapidly cleared by hepatic and along with, extrahepatic metabolism, but mainly metabolized by glucuronide conjugation in the liver (Kanto and Gepts, 1989).

The anaesthetic duration of propofol could be enhanced when used in combination with ketamine hydrochloride (Van Natta and Rex, 2006). The drug has been previously used in equines and produced rapid onset of action, short duration of anaesthesia induction, and prompt recovery. Studies of combined propofol and alpha 2-agonist as xylazine or detomidine (Branson and Gross, 1994) or benzodiazepine (Guit *et al.,* 1991) or ketamine (Minoru *et al.,* 2004) showed an additive anaesthetic effect. Premedication with either xylazine or detomidine improved the quality of anaesthesia produced by a single bolus of propofol (Mathews *et al.,* 1999).

2.5 Ketamine:



The molecular formula is C13H16ClNO and the chemical formula of ketamine is (RS)-2-(2-Chlorophenyl)-2-(methylamino) cyclohexanone.

Ketamine is a chiral compound derivative of arylcyclohexylamine (Kruger, 1998). It has two isomers i.e. S and R ketamine, in which S-ketamine is more potent analgesic than R-ketamine (Ryder *et al*., 1978).

Ketamine is a dissociative anaesthetic and produces very effective analgesia (White *et al.,* 1985; Clarke and Trim, 2013). and widely used for anesthesia and analgesia by veterinary

professionals. Because it is the anaesthetic that is safe and well tested in the full range of species from children to humans and in veterinary from laboratory animals to large and small domestic animals and wild and zoo animals as well as birds and reptiles (Stephen, 2015). Ketamine produces the depression effect via NMDA receptor blocking (Daley *et al.,* 2012) at the thalamocortical, limbic systems and depression of nuclei in the reticular activating system (Posner and Burns, 2009).

Ketamine is similar to other hypnotics in that its effects are modulated to a large degree by blocking excitatory neurotransmission in the brain. However, unlike many general anesthetics, which work on GABA receptors, ketamine is an antagonist at the *N*-methyl-D-aspartate (i.e., NMDA) glutamate receptor, which possesses most of the analgesic, amnestic, and neuroprotective effect (Meyer and Fish, 2008). Ketamine is known to produce a unique state known as dissociative anesthesia which causes the patient to appear conscious but unable to respond to stimuli. Also, the administration of ketamine may be associated with adverse psychological effects, especially when not co-administered with benzodiazepines. Ketamine is extensively redistributed, metabolized by CYP450 in the liver, and eliminated by the kidney. Pharmaco-kinetically, ketamine has short distribution (Kohrs and Durieux, 1998). Nor ketamine, the primary metabolite of ketamine, is one third to one fifth as potent as the parent molecule and may be involved in the prolonged analgesic actions of this drug (Kohrs and Durieux, 1998). A side from its hypnotic effects, ketamine is capable of producing a great degree of amnesia and analgesia.

Ketamine is a unique agent in that it has the ability to increase heart rate, mean arterial pressure, and plasma catecholamines via changes in sympathetic stimulation. As a result of these effects, ketamine is sometimes used in patients with depressed cardiovascular function. Ketamine can be problematic in patients with ischemic disease because the sympathetic adrenergic stimulation may increase myocardial oxygen demands beyond the capacity of coronary blood flow. Ketamine also may increase pulmonary vascular resistance, and it provides a greater degree of broncho dilation than most intravenous anesthetics making its use beneficial in patients with asthma (Kohrs and Durieux, 1998). Ketamine is known to increase cerebral blood flow and cerebral oxygen consumption; therefore, this drug is used with caution in patients with elevated intracranial pressure.

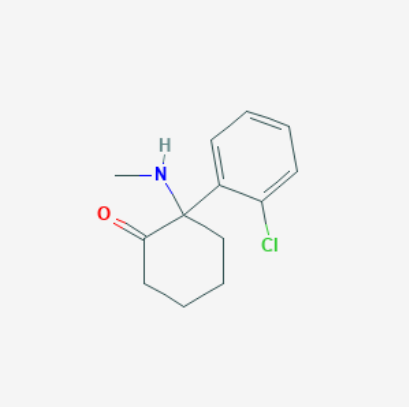
Ketamine acts as a non- competitive antagonist at NMDA-R and binds to it at the phencyclidine site (Hirota and Lambert, 1996). Ketamine specifically binds to the dizocilpine site of NMDA (Roth *et al*., 2013). Ketamine is poor in visceral analgesia. However, it can be

used in combination with xylazine or diazepam to provide good visceral analgesia in case of abdominal surgery (including ovariohysterectomy) and thoracic surgery. Ketamine CRI producing desirable analgesia with anaesthetic effects (Wright, 1982).

Ketamine stimulates the cardiorespiratory system. A direct effect increases cardiac output, arterial blood pressure, heart rate, and central venous pressure. It also has bronchodilator property (Goyal and Agrawal, 2013). Ketamine is also a commonly used agent and In addition to its amnesic and analgesic properties, ketamine increases heart rate and blood pressure by activating the sympathetic nervous system (Arora, 2003). It was observed that a combination of ketamine and propofol reduced consumption of propofol and opioids and ensured better hemodynamic and respiratory stability in patients Morse *et al.,* 2003)

Pain is an unpleasant sensory or emotional experience most commonly associated with potential tissue damage. The sensation of pain is a consequence of the activation of specialized receptors and neurological pathways after such pain stimuli (Mathews A, 2000). However, the use of ketamine alone has two disadvantages: (1) poor muscle relaxation, tachycardia, catalepsy, and muscle tone is often increased (Hall *et al.,*1991), and (2) it produces short-term anaesthesia which is not optimal for long surgical operations (Seliskar *et al*., 2007). But these unwanted effects are reduced by conjunction use of propofol, benzodiazepines, acepromazine, or α2-agonists (Waelbers *et al*., 2009). Therefore, it would be ideal to use ketamine in combination with some additives that help to overcome these limitations and minimize the adverse effects. Diazepam is a typical anti-convulsion's benzodiazepine derivative (Hall *et al.,*1991). It can produce muscle relaxation with minimal side effects (Clarke and Trim, 2013). Moreover, there is a different breed of dogs that requires proper anesthetic medicament combination. Hence, determining the effects of the ketamine in combination with other sedative agents may help to come out with the safest combination for surgical procedures in a local breed of dogs. During surgical producers time taking more than 60 minutes, ketamine with propofol combination better than ketamine and benzodiazepines (Waelbers *et al*., 2009). Ketamine may thus be a useful adjunct to propofol for anaesthetizing dogs (Lerche *et al.,* 2000). Nor-Ketamine is a metabolite of ketamine, which is also having similar pharmacological action to ketamine (Pypendop and Ilkiw, 2005). Cardiovascular parameters during ketamine-based TIVA, a significantly higher heart rate was reported in a group of dogs receiving ketamine as compared to a group of dogs receiving propofol (Hellebrekers *et al*., 1998).

2.6 Ketofol:



The molecular formula is C25H34ClNO2 and chemical formula of ketofol 2-(2-chlorophenyl)-2-(methylamino) cyclohexan-1-one; 2, 6-di (propan-2-yl) phenol

Ketamine and propofol, these two completely different anesthetics compensate each other's deficits due to their opposing physiological effects when administered together. The combination of ketamine and propofol mixed together in a single syringe is a neologism coined refers to ketofol. These two drugs are pharmacologically compatible (Donnelly *et al.,* 2008).In a single syringe infusion of a mixture of ketamine and propofol for sedation and analgesia studied in healthy volunteers (Morse *et al*., 2003) and in emergency clinical patients (Da Silva *et al*., 2011). The combination of these drugs, opposing haemodynamic and respiratory effects of each drug may enhance the utility, increasing both safety and efficacy and allowing a reduction in the dose of propofol required to achieve sedation (Daabiss *et al.,* 2009).

Ketofol administration offered effective sedation for spinal anaesthesia for gynaecologic, ophthalmologic, and cardiovascular procedures in all age groups. The main advantage of this drug combination over alone propofol administration is the opposing hemodynamic and respiratory effects of each drug that enhance safety and efficacy and decrease the dose of propofol required for induction (Daabiss *et al*., 2009).

Ketamine and propofol as TIVA resulted in haemodynamically stable anaesthesia in humans (St Pierre *et al.,* 2002). The mixture of ketamine and propofol has opposing influences on blood pressure (BP), heart rate (HR), and systemic vascular resistance (SVR). And also ketamine supplementing a propofol infusion has been shown to preserve respiratory function and as well as upper airway control (EI Metainy and Saber, 2016). Ketofol in veterinary anaesthesia became popular due to studies in feline patients, notably the use of

ketofol infusion for ovariectomy in cats (Ravasio *et al*., 2012). And pharmacokinetics of constant rate infusion of ketofol in cats (Zonca *et al*., 2012). In dogs, the decrease in heart rate was minimum at anaesthetic induction when co-administration of ketamine and propofol than propofol was given alone (Lerche *et al*., 2000). Ketofol use in dogs was associated with higher pulse rate (PR) and mean arterial pressure(MAP) and superior quality of tracheal intubation and induction of anaesthesia, compared with the use of propofol alone, however, respiratory rate was lower when ketofol was administered (Martinez-Taboada and Leece, 2014). Ketofol 1:1 ratio reduces dose requirement of propofol required for orotracheal intubation and a 50% for maintenance of TIVA in non-premedicated healthy dogs. Whereas Ketofol ratios 1:1 and 2:1 producing smooth induction and maintain better haemodynamic stability compared with propofol and ketamine in atropine, alpha-2 agonist premedicated canine orthopedic patients (Sharma, 2016). Induction and maintenance of TIVA with a 1:1 combination of ketamine and propofol resulted in significantly higher HR and attenuated some of the declines in MAP, but with respiratory depression resulting in hypoxemia and hypercapnia at some time points when dogs breathed room air (Kennedy and Smith, 2015).

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Materials & Methods

"Educating the mind without educating the heart is no education at all."

3 MATERIALS & METHODS

The present clinical study was carried out on 18 clinical cases of female dogs irrespective of age and weight presented for routine surgery i.e. ovariectomy operation at the Department of Surgery and Radiology, Bihar Veterinary College, Patna. All dogs were randomly divided into three groups of six animals in each. The standard procedures required kit were used for haemato-biochemical analysis. The research work was done in Teaching Veterinary Clinical Complex, Department of Veterinary Surgery and Radiology, BASU., Patna -8000014 (BIHAR), India.

3.1 Anamnesis

The experiment was conducted in the Department of Veterinary Surgery and Radiology, BVC Patna. All experimental animals were examined with Ultrasonography for any reproductive abnormality. The bitches presented for elective ovariectomy were selected for this study after obtaining written consent from the respective owners.

3.2 Design of the clinical study

The study was conducted on 18 female dogs and these animals were randomly divided into three experimental groups, each group containing six animals. The groups were designated as Group I, Group II, and Group III on the basis of the induction and maintenance agent. The animals of different groups were administered the following drugs for induction and maintenance of anaesthesia for elective ovariectomy.

3.3 Pre-operative Preparation:

The animals were subjected to preoperative checkups comprising physiological, haemato-biochemical, and haemodynamic parameters. The animals were kept off-fed for a minimum of 12 hours prior to the trial of anaesthesia.

3.4 Premedication and technique of drug administration

After preparation of the animal, blood was withdrawn at 0 min from the cephalic vein, and glycopyrrolate[1]was given @ 0.01mg/kg b.wt intramuscularly at right lumbar epaxial muscles followed by inj. butorphanol[2] @ 0.2 mg/kg b.wt and xylazine[3] @ 1mg/kg b.wt were injected intramuscularly after 5 minutes at left lumbar epaxial muscles by using different syringes.

After premedication animal was placed on the operation table and canulate with 20 gauges (according to need) intravenous catheter and attached with normal saline infusion. After 10 minutes of butorphanol, animals were induced (till effect) with propofol, and immediately just after induction animals were intubated and constant rate infusion of ketamine[4], propofol[5], and ketofol 1:1 started along with normal saline @ 10ml/kg/hr by microinfusion set and infusion of anaesthesia was stopped at last skin suture. The animals were kept in a normal environment throughout the study period.

Table no. 1: Anesthetic drug combination used in dogs of different groups.

Group	No. of Animals	Pre-medication	Induction(I/V)	Maintenance(CRI)
Group I	6	Glycopyrrolate @ 0.01mg/kg b.wt I/M + Butorphanol @ 0.2mg/kg b.wt I/M +Xylazine @ 1mg/kg b.wt I/M	As per requirement with propofol	Ketamine @ 300µg/kg/min
Group II	6	Glycopyrrolate @ 0.01mg/kg b.wt I/M + Butorphanol @ 0.2mg/kg b.wt I/M +Xylazine @ 1mg/kg b.wt I/M	As per requirement with propofol	Propofol @300µg/kg/min
Group III	6	Glycopyrrolate @ 0.01mg/kg b.wt I/M + Butorphanol @ 0.2mg/kg b.wt I/M +Xylazine @ 1mg/kg b.wt I/M	As per requirement with propofol	Ketofol 1:1ratio@300µg/kg/min valume(1ml : 5ml)

IM: Intramuscular route, IV: Intravenous route, CRI: Constant rate infusion

1. Glycopyrrolate: Pyrolate; Neon Laboratories, Palghar, Thane, India.
2. Butorphanol: Butodol; Neon laboratories, Palghar, Thane, India.
3. Xylazine: Xylaxin; Indian Immunological Limited, Telangana.India
4. Ketamine: Ketmin 50; Themis Medicare Limited, Uttarakhand, India.
5. Propofol: Nirfol 1%; Aculife healthcare private limited, Ahmedabad, Gujarat, India.
6. Ketofol1:1; Mixture prepared in a single syringe from commercial ketamine, propofol, and normal saline by BASU, Patna, India (preparation procedure in appendix)

3.5. OBSERVATIONS

3.5.1Clinical parameters:

The clinical parameters such as different reflexes, induction time, duration of anesthesia, duration of recovery, and quality of recovery along with sternal recumbency time were recorded during this study.

3.5.1.1 Reflexes:

Abolition of the palpebral, pedal and corneal reflex was recorded at different intervals in the animals of different groups. In all animals, the plane of analgesia was assessed by observing the response to various painful stimuli. Presence or absences of reflexes were recorded before premedication, 10 minutes after pre-medication, 15, 30, and 60 minutes during maintenance of anaesthesia, and after recovery (120 minutes).

3.5.1.2 Palpebral reflex:

Palpebral reflexes were tested by observing blinking responses when an eyelid is touched gently with fingers or forceps. The response to palpebral reflex was taken as the measure of the depth of sedation and recorded at 0 minutes before administration of the drug and after 10-minute of premedication and 15, 30, and 60 minutes during maintenance and after recovery (120 minutes). The reflexes was graded on a 1 to 4 scoring scales as:

1 : Intact and strong reflex (quick blink)

2 : Intact but weak reflex (slow response)

3 : Very weak reflex (very slow and occasional

4 : Abolished reflex

3.5.1.3 Pedal reflex:

The presence or absence of pedal reflex was recorded by pinching the interdigital webbing of the front and hind limbs approximately for one second with mosquito hemostat forceps. The response to pedal reflex was taken as a measure of the depth of analgesia and it was recorded before premedication, 10 minutes after pre-medication, 15, 30, and 60 minutes during maintenance and after recovery (120 minutes). The reflexes was graded on a 1 to 4 scoring scales as:

1 : Intact and strong reflex (strong withdrawal)

2 : Intact but weak reflex (animal responding slowly)

3 : Intact but very light reflex (slow and occasional response)

4 : Reflex abolished completely

3.5.1.4 Corneal reflex:

It was assessed by blinking induced by gently touching the cornea with wet cotton or a drop of normal saline over the cornea and graded as 1 to 4 scales.

1 : Intact and strong reflex

2 : Intact but weak reflex

3 : Very weak reflex

4 : Abolished reflex

3.5.1.5 Duration of Surgical Anaesthesia:

The duration of surgical anaesthesia was calculated as the time interval between the time of disappearance of pedal reflex and the time of the return of pedal reflex (Narayanan *et al.,* 2011).

3.5.1.6 Duration of Recovery:

Recovery time was calculated as the time interval between the stoppage of infusion of anaesthetic agent and the return of pedal (Narayanan *et al.,* 2011).

3.5.1.7 Sternal recumbency time (SRT):

The time from the end of the administration of constant rate infusion to the spontaneous and the regaining of sternal recumbency (minutes).

3.5.2 Physiological parameters:

The physiological parameters such as rectal temperature (°F), heart rate (beats per minute), and respiratory rate (breaths per minute) were recorded just before premedication, 10 minutes after pre-medication, 15, 30, and 60minutes during maintenance of anaesthesia and after recovery (120 minutes).

3.5.2.1 Heart rate

The heart rate was measured with the help of multi parameters monitor.

3.5.2.2 Respiratory rate

The respiratory rate was determined by visual observation of the thoracic motion per minute (Lemke *et al.,* 2002).

3.5.2.3Rectal temperature

The rectal temperature was measured using a clinical thermometer.

3.5.2.4 Cardiovascular Parameters

The cuff of the NIBP monitor will be tied around the forearm for monitoring systolic and diastolic blood pressures. The following variables were taken recorded before

administration of the drug (0 min) and 10 minutes after pre-medication, and 15, 30, and 60 minutes during surgery and after recovery (120min).

(i) Systolic Arterial blood pressure (SAP) in millimeter(s) of mercury

(ii) Diastolic Arterial blood pressure (DAP) in millimeter(s) of mercury

(iii)Mean Arterial blood pressure (MAP) in millimeter(s) of mercury

3.5.3. Hematological observation:

A total of 5ml blood (Heparin tubes) was collected aseptically from the saphenous vein of each patient before premedication, right 10 minutes after pre-medication, and 15minute, 30, and 60 minutes during surgery and after recovery. Immediately after collection, the blood samples were transferred in a dry, clean and sterile test tube containing ethylene-diamine-tetra-acetic acid (EDTA) as an anticoagulant. It was used within 2 hr. after collection to determine Hemoglobin (Hb), PCV, TEC, and TLC using standard procedures.

3.5.3.1 Haemoglobin (Hb)

Haemoglobin was estimated as per the method of Schalm (1988) using sahle's haemoglobinometer method. The value was expressed in g/L.

3.5.3.2 Packed cell volume (PCV)

The PVC (L/L) was estimated by using the micro haematocrit method as per the method suggested by Schalm (1988).

3.5.3.3 Total Erythrocyte count (TEC)

Erythrocyte count was estimated by using Haemaology analyzer and values were expressed in $x10^{12}/L$

3.5.3.4 Total leukocyte count (TLC)

The TLC was estimated by haemocytometer with improved Neubaur's counting chamber. The values were expressed in $x\ 10^{9}/L$.

3.5.4 Biochemical observation:

3 ml of blood (out of 5 ml) was collected aseptically from a saphenous vein in a sterile vial without anticoagulant from each experimental animal before premedication, 10 minutes after pre-medication, and 15, 30, and 60 minutes during surgery and after recovery (120 minutes). The samples were centrifuged @ 3000 rpm for 15 min. to collect the serum. Serum was used for the estimation of biochemical parameters. The biochemical analysis was included glucose (mg/dl); blood urea nitrogen (BUN mg/dl); creatinine (mg/dl); aspartate aminotransferase (AST-IU/L).

3.5.4.1Blood urea nitrogen (BUN mg/dl):

The BUN was determined by the method of Netelson (1961) using Diacetyl Monoxime (DAM) and the value was expressed in mmol/L.

3.5.4.2 Blood glucose:

Blood glucose estimated by the O' toluidine method as directed by Cooper and MacDaniel (1970) and the value expressed in mmol/L.

3.5.4.3 Creatinine:

Creatinine was estimated by the alkaline picture method (Levinson and McFate, 1969) and the values were expressed in μmol/L.

3.5.4.4 Serum Aspartate Amino Transferase (AST)

AST was estimated by the Auto analyzer. The values of AST were expressed in IU/L

3.5.4.5 Oxidative Stress:

Serum samples were also is used for the estimation of lipid peroxidation (LPO) as per Stock and Dormandy, (1971) at 0 minute and 120 minute and also SOD as per McCord, and Edeas (2005).

Statistical Analysis:

All the collected data were statistically analyzed using SPSS software version 23. Mean ± SE was determined by the descriptive statistics method. Single Factor Analysis of variance (ANOVA), Duncan's multiple range test (DMRT) was used to compare the mean at different time intervals amongst the different groups and compare the mean values at different intervals with their respective base values in each group (Snedecor and Cochran 1994).

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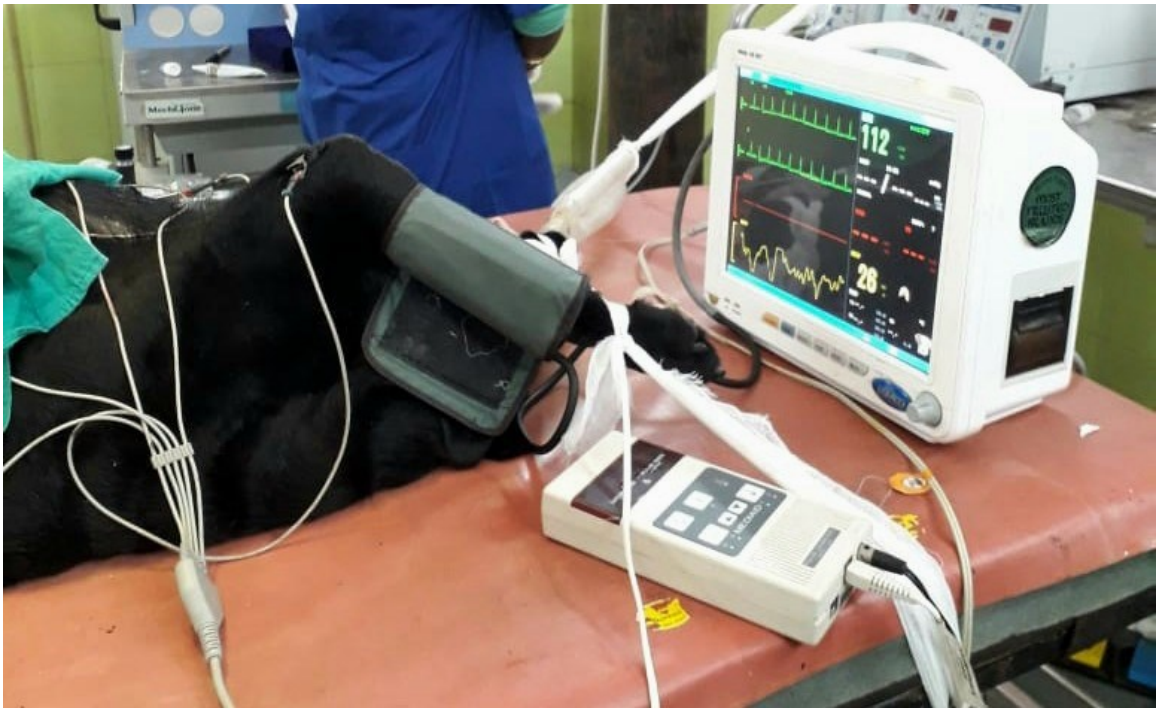

Fig 1: Before the start of CRI, monitoring, and recording of various parameters.

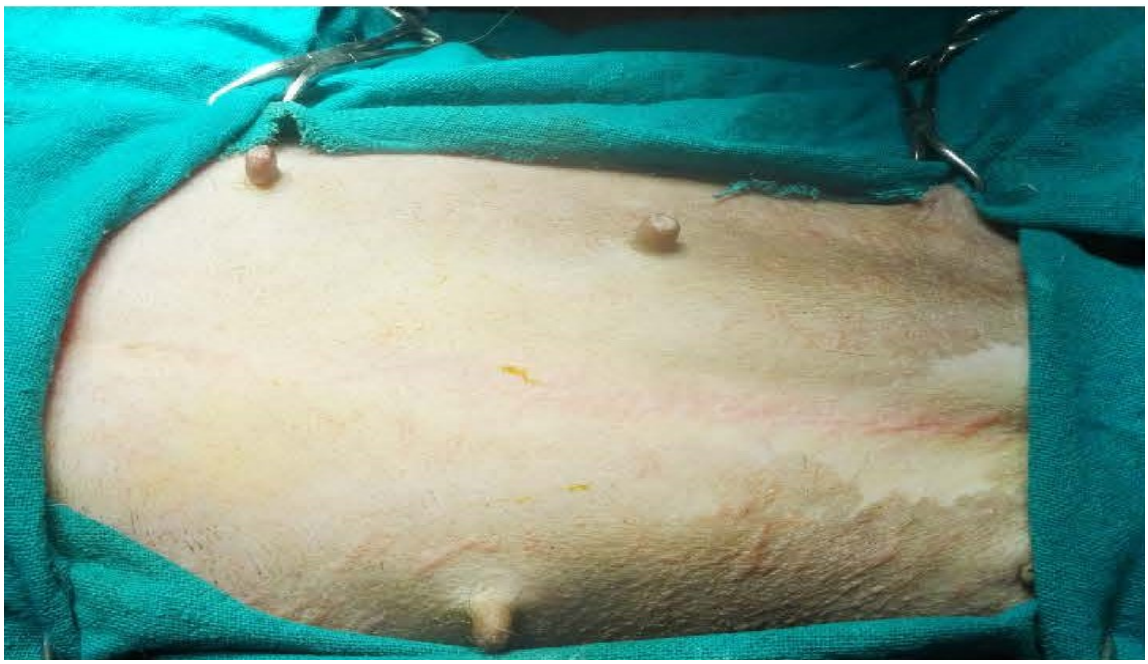

Fig 2: Animal is a dorsoventral or supine position clamped by a sterile drape.

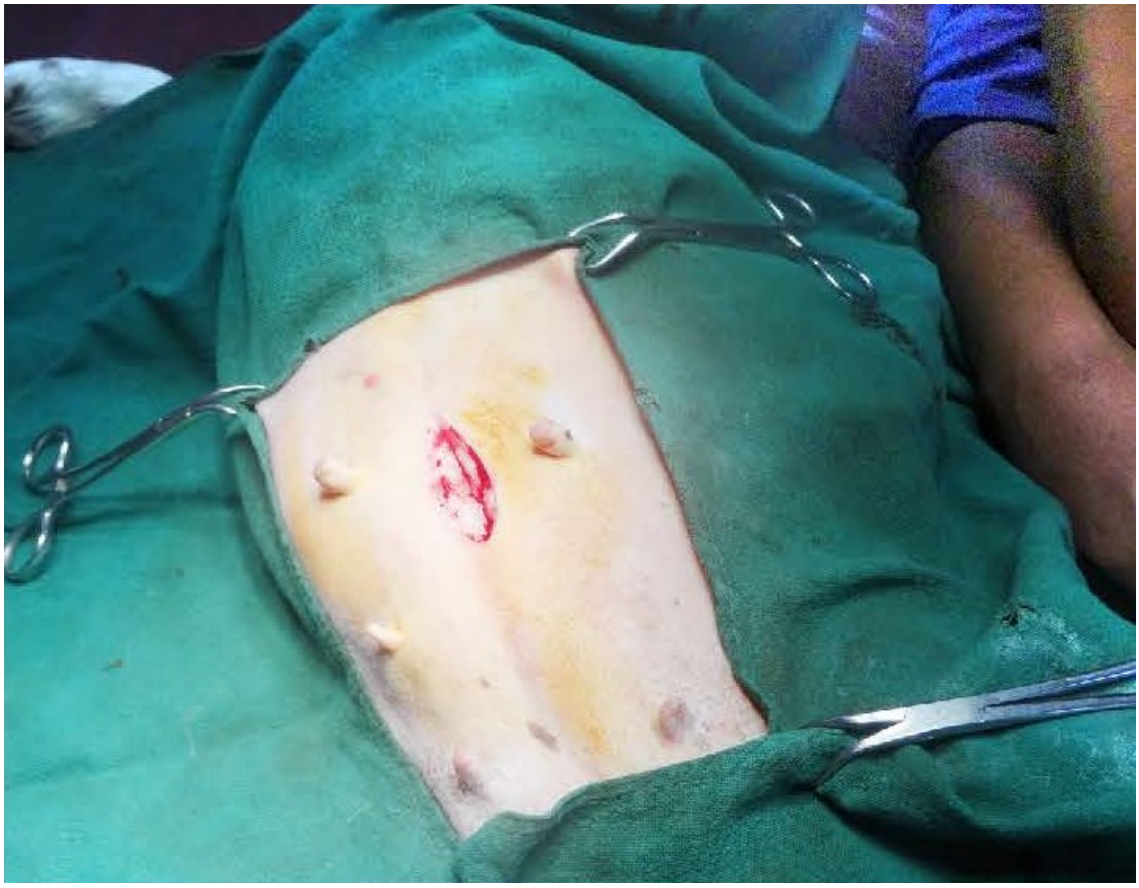

Fig 3: Skin incision on linea alba for ovariectomy

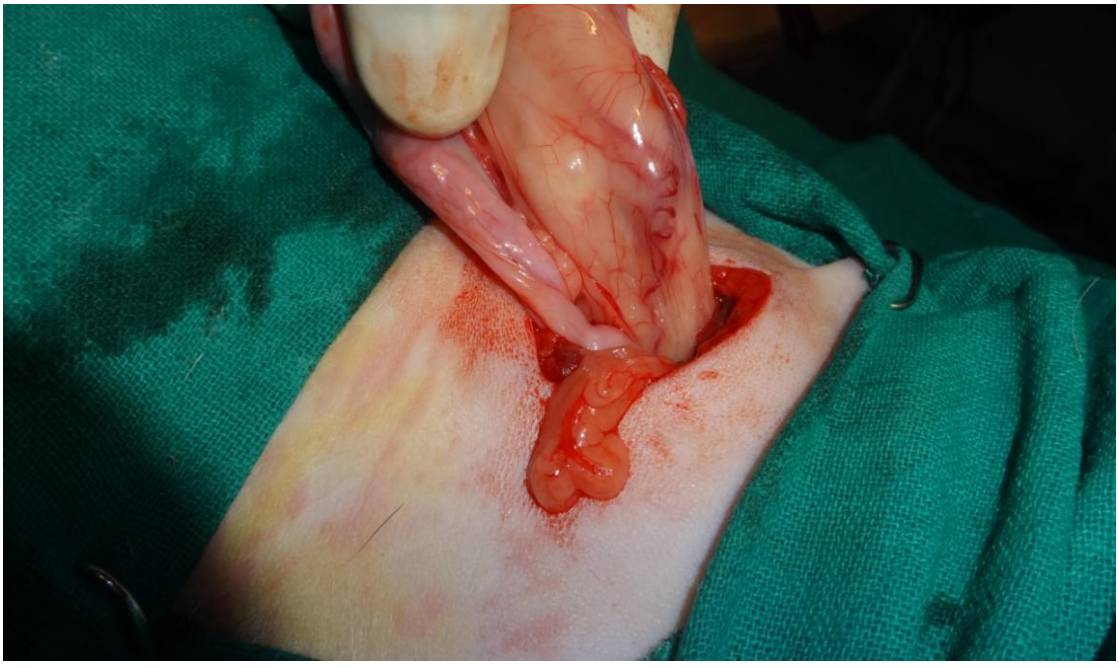

Fig 4: Blood supply in ovary visualized in open surgery

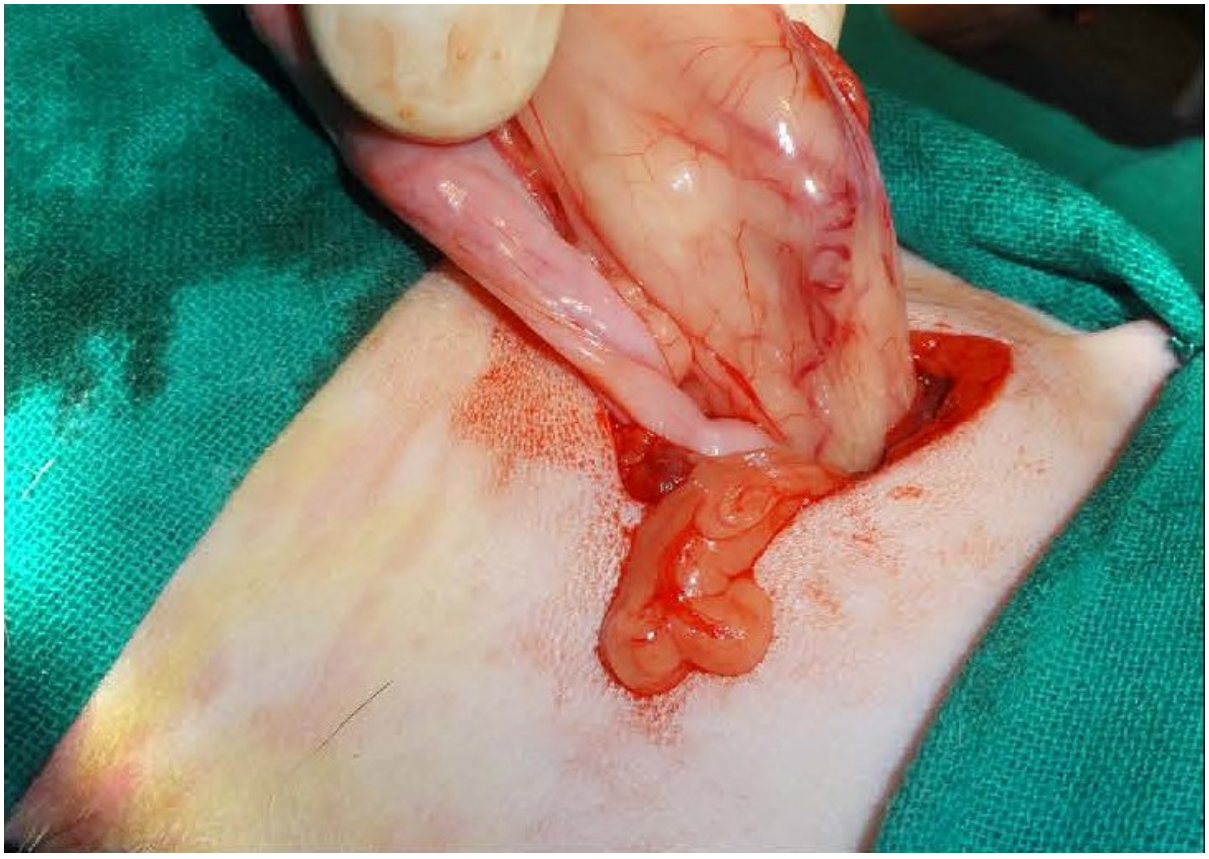

Fig 5: Position of Ovary

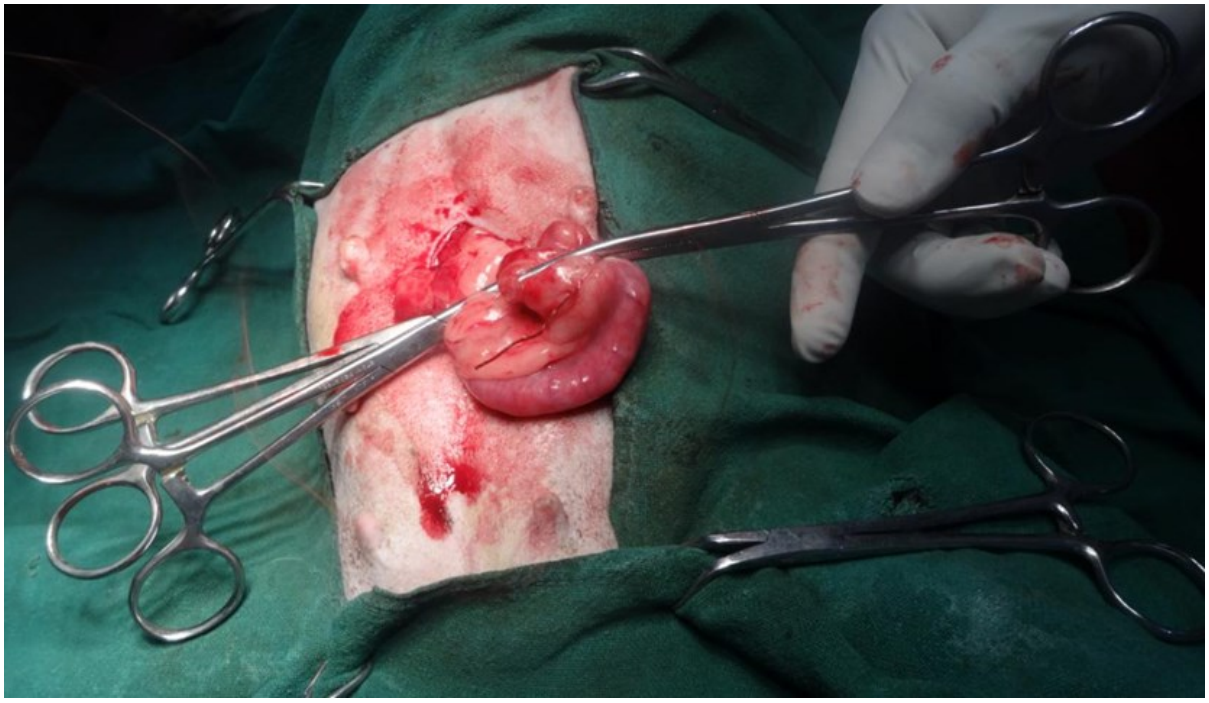

Fig.6 Procedure of ovariectomy

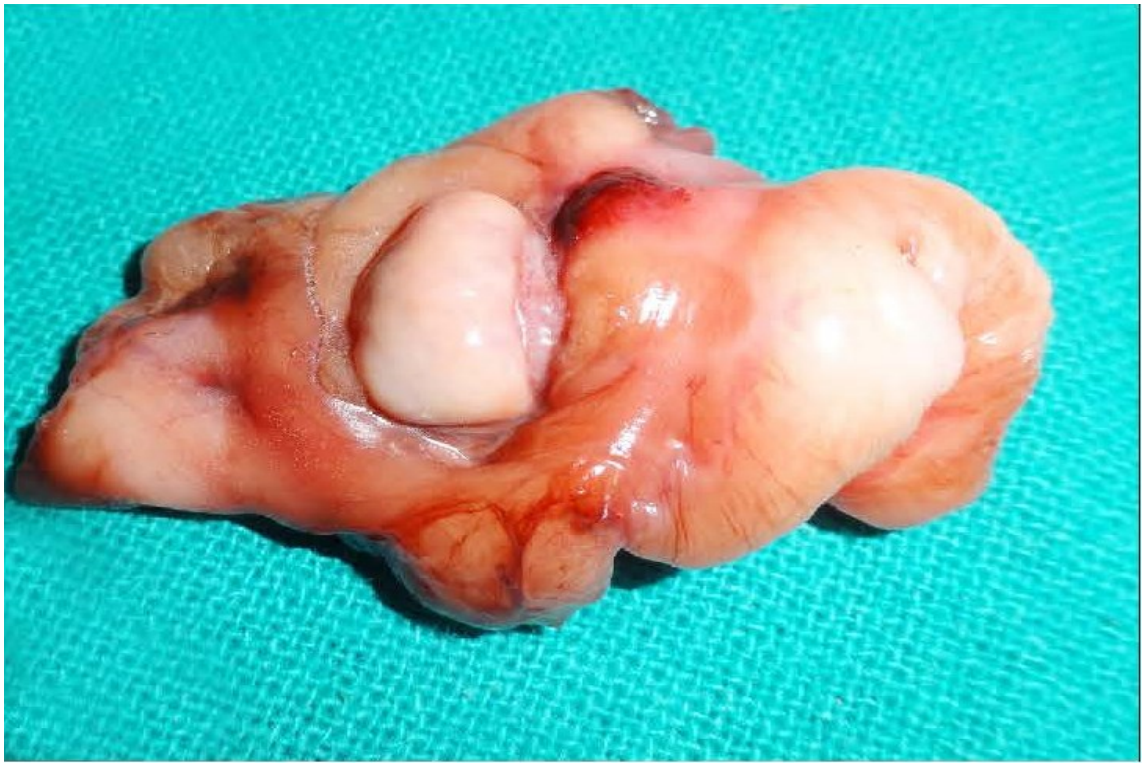

Fig 7a: Surgically excised ovary one

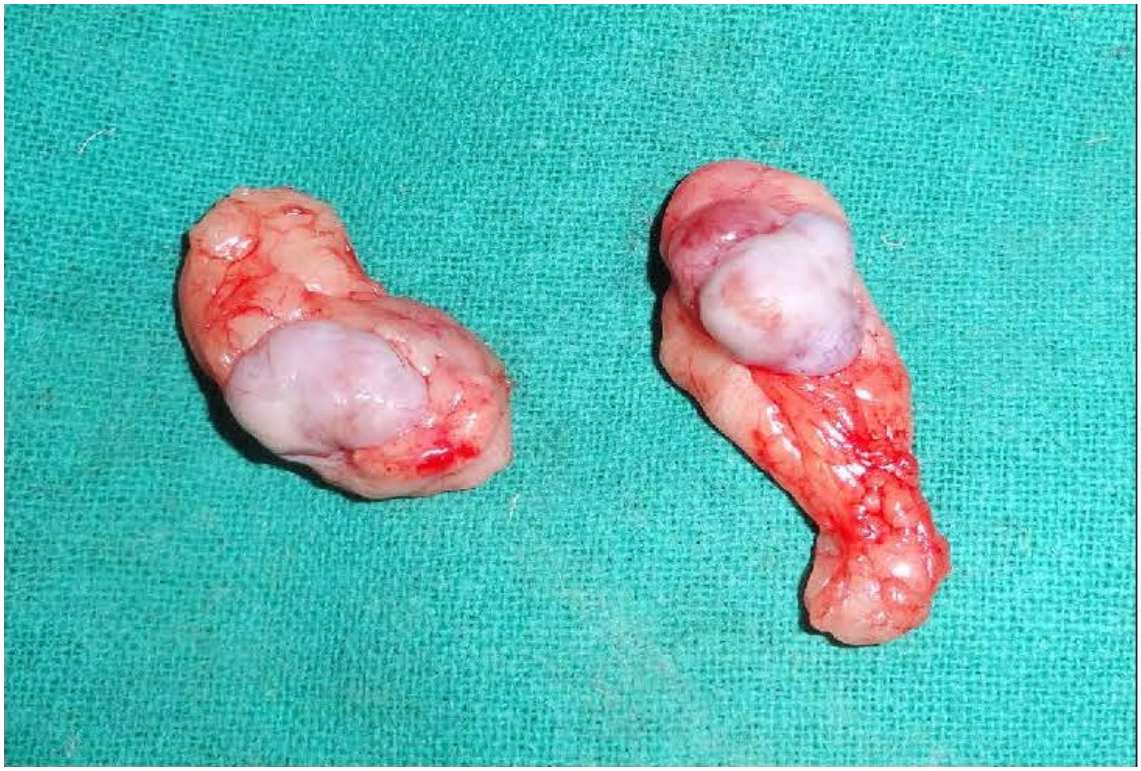

Fig 7b: Surgically excised both ovaries

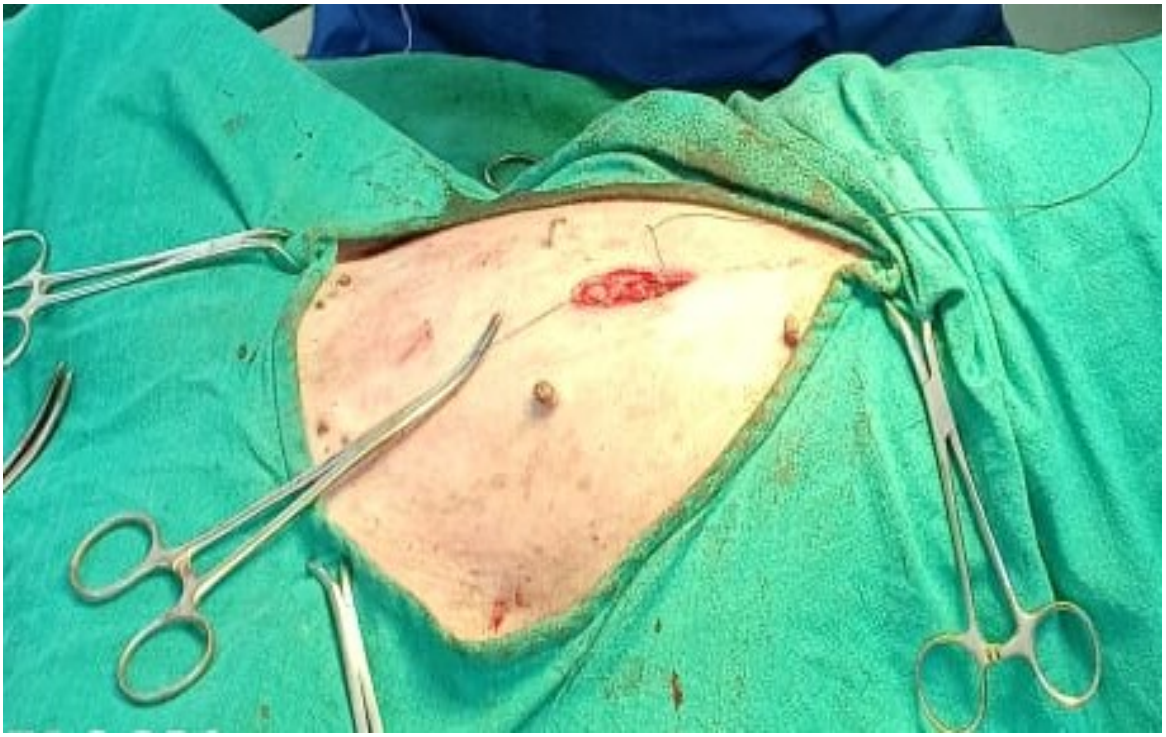

Fig 8a: Suture line post-surgery

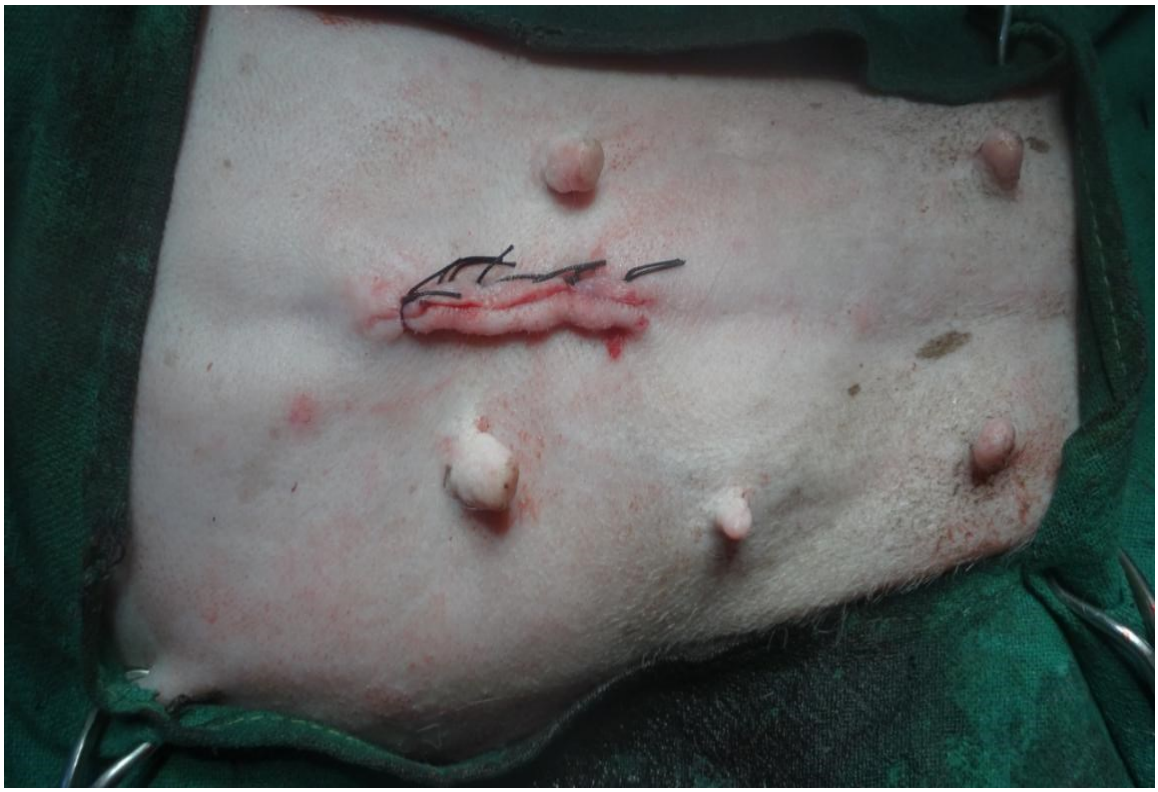

Fig 8b: Suture line post-surgery completed

Results

"The past cannot be changed

the future is yet in your power"

4 RESULTS

4.1 Clinical observations

4.1.1Palpebral reflex:

Mean ± SE values of palpebral reflex recorded in all the three groups at various time intervals are shown in table 2 and figure 9.

In the animals of all three groups, an increase in palpebral reflex was recorded after pre-medication and reaches a maximum depth of sedation after induction. Maximum sedation is maintained during the maintenance of anaesthesia.

Comparison among the groups revealed that there was no significant ($p>0.05$) difference between the different groups in the palpebral reflex score at various time intervals.

4.1.2 Pedal reflex:

Mean ± SE values of pedal reflex recorded in all the three groups at various time intervals are shown in table 3 and figure 10.

In the animals of all three groups, an increase in pedal reflex was recorded after pre-medication and reach at a maximum depth of analgesia after induction. Maximum analgesia is maintained during the maintenance of anaesthesia.

Comparison among the groups revealed that there was no significant ($p>0.05$) difference between the different groups in the pedal reflex score at various time intervals.

4.1.3 Corneal reflex:

Mean ± SE values of corneal reflex recorded in all the three groups at various time intervals are shown in table 4 and figure 11.

In the animals of all three groups, an increased corneal reflex was recorded after pre-medication and reaches a maximum after induction. Maximum score maintained during the maintenance of anaesthesia.

Comparison among the groups revealed that there was no significant ($p>0.05$) difference between the different groups in the corneal reflex score at various time intervals.

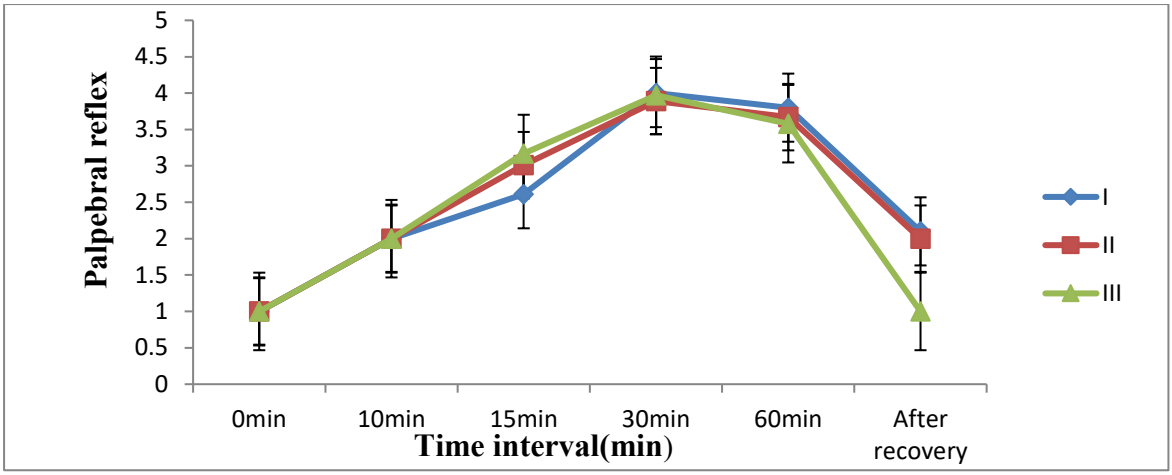

Fig. 9: Mean ± SE values of palpebral reflex in the animals of different groups.

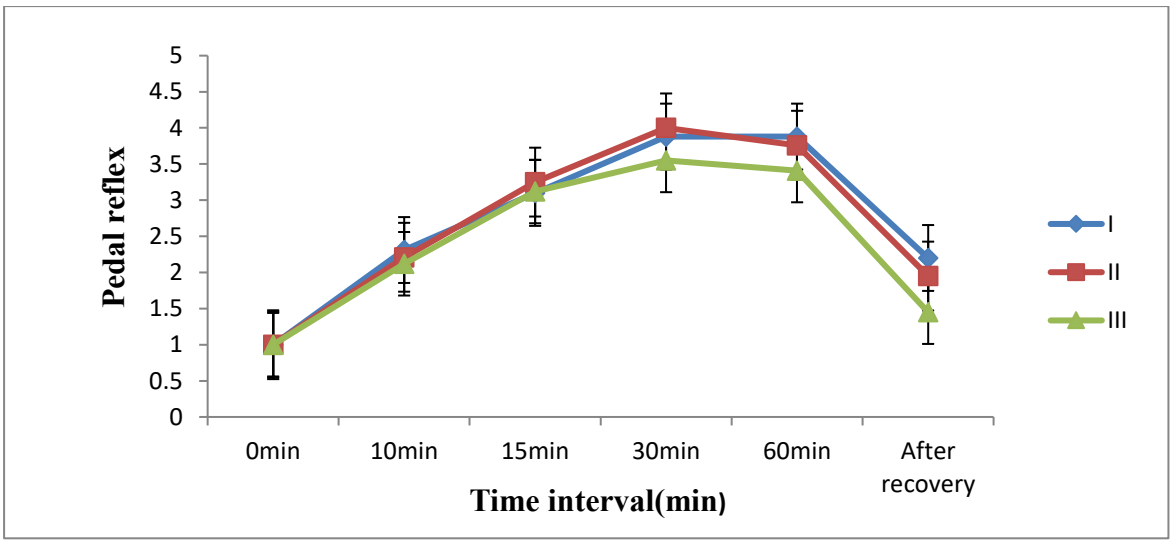

Fig. 10: Mean ± SE values of pedal reflex in the animals of different groups.

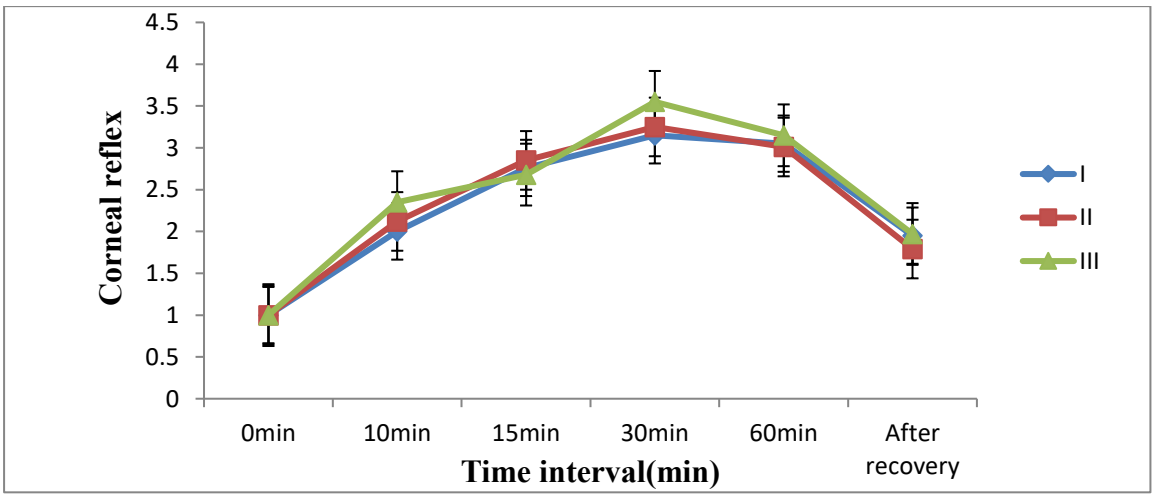

Fig. 11: Mean ± SE values of corneal reflex in the animals of different groups.

4.1.4 Duration of Anaesthesia

Mean± SE duration of anaesthesia (min) in the animals of different groups at various time intervals is shown in table 5 and figure 12 .

The mean values of duration of anaesthesia in groups I, II, and III were 75.5±2.04min, 73.83±2.53 min, and 77.17±1.64 min respectively.

Comparison among the groups showed that duration of anaesthesia among group changed non-significantly ($p>0.05$)

4.1.5 Duration of surgery

Mean ± SE Duration of surgery (min) in the animals of different groups at various time intervals are shown in table 6 and figure 13.

The mean values of duration of surgery in groups I, II, and III were 58.67±1.56 min, 59.00±0.84 min, and 57.00±1.60 min respectively.

Comparison among the groups showed that the duration of surgery changed non-significantly ($P>0.05$)

4.1.6 Recovery time

Mean ± SE Recovery time (min) in the animals of different groups at various time intervals are shown in table 7 and figure 14.

The mean values of Recovery time in groups I, II, and III were 47.17±0.94 min, 25.00±1.33 min, and 46.83±0.60 min respectively.

Comparison among the groups showed that recovery time in group II significantly ($p<0.05$) lower in comparison to groups I and III. Comparison among groups also showed that recovery time in group III non-significantly lower in comparison to groups I.

4.1.7 Sternal recumbency time

Mean ± Sternal recumbency time (min) in the animals of different groups at various time intervals are shown in table 8 and figure 15.

The mean values of sternal recumbency time in groups I, II, and III were 61.17±1.81min, 36.17±1.33min, and 58.67±1.05min respectively.

Comparison among the groups showed that sternal recumbency time in group II significantly ($p<0.05$) lower in comparison to groups I and III. Comparison among groups also showed that sternal recumbency time in group III was non-significantly lower in comparison to groups

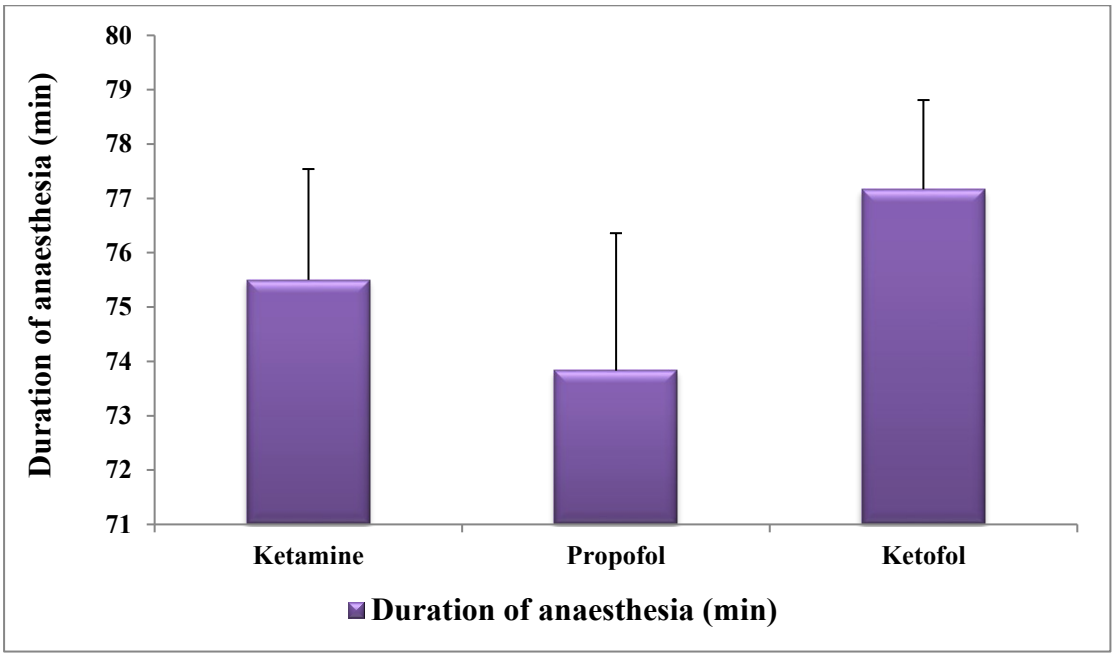

Fig. 12: Mean ± SE values of duration of anaesthesia in animals of different groups.

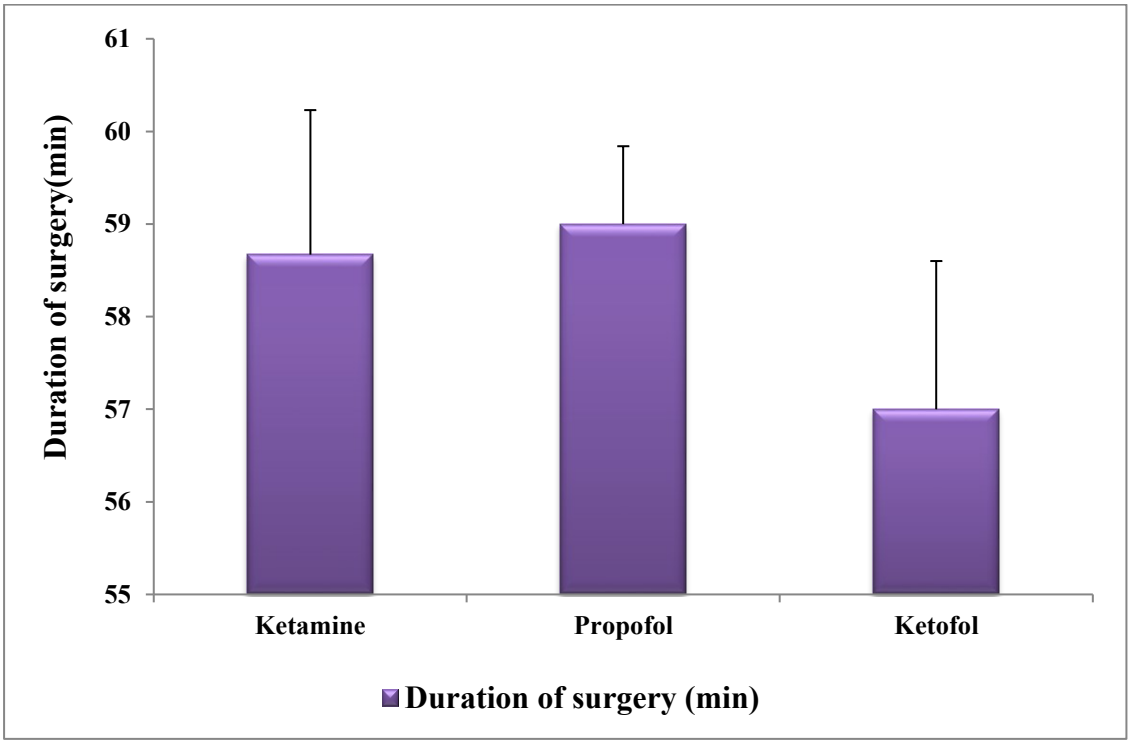

Fig. 13: Mean ± SE values of duration of surgery in animals of different groups.

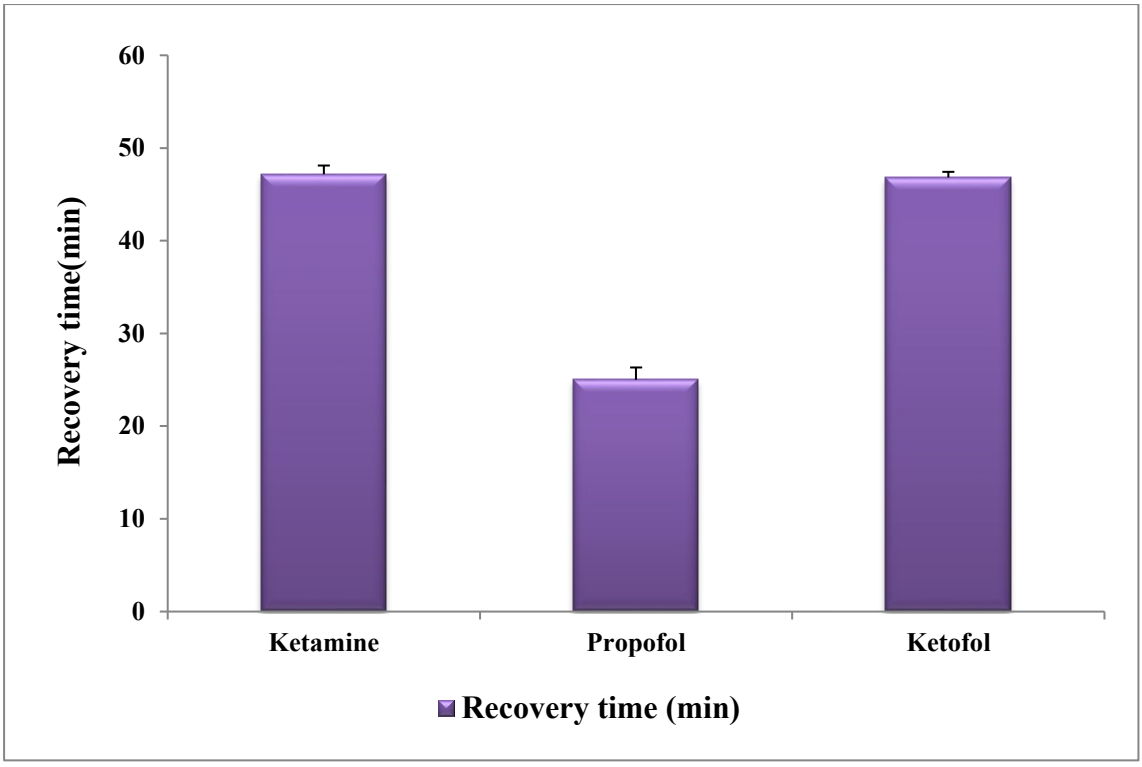

Fig. 14: Mean ± SE values of recovery time in animals of different groups.

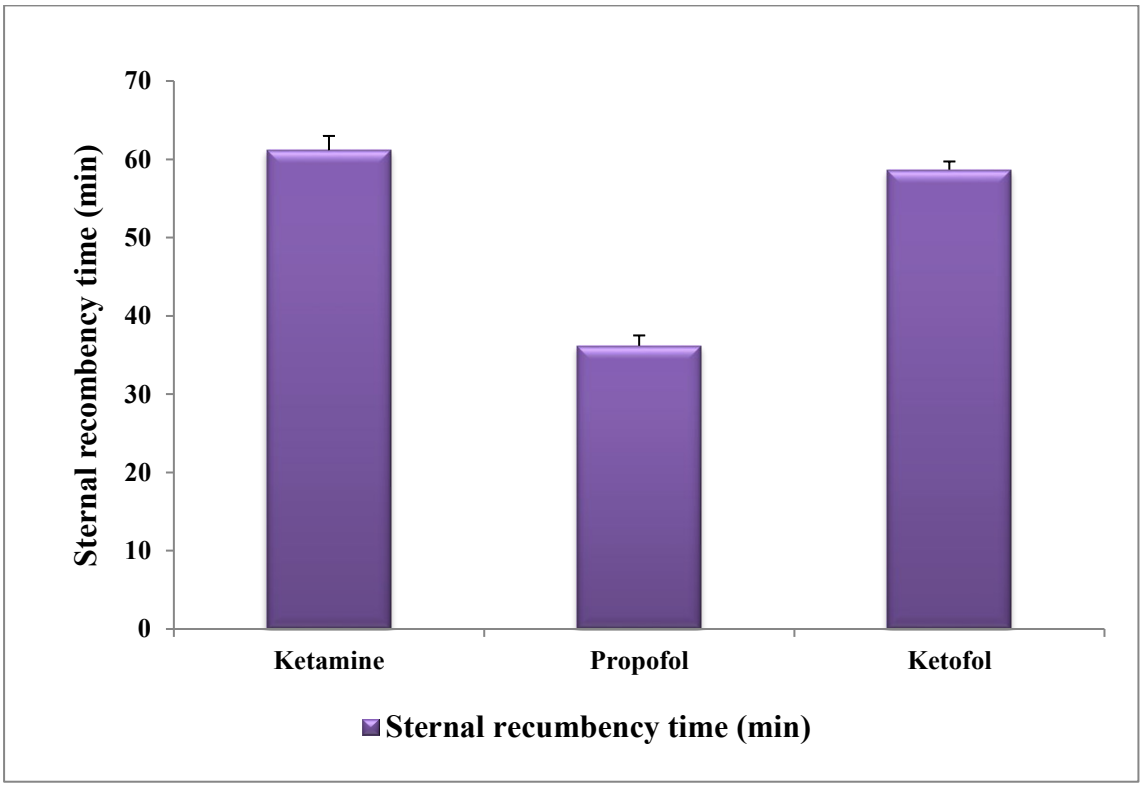

Fig. 15: Mean ± SE values of sternal recumbency time in animals of different groups.

4.2 Physiological Observations

4.2.1 Heart rate (HR)

Mean ± SE values of heart rate (beat/min) were recorded) in the animals of different groups at various time intervals are shown in table 9 and figure 16.

Value of heart rate significantly ($P<0.05$) increased after pre-medication in all three groups in comparisons to respective base values after that decreased but remained non-significantly ($P>0.05$) higher in group I and III, however it become non-significantly lower in group II during maintenance of anaesthesia in comparison to respective base values.

Comparison between the groups showed that heart rate non-significantly ($p<0.05$) change at various intervals of time during the observation period.

4.2.2 Respiratory rate (RR)

Mean ± SE values of respiratory rate (breaths/minute) were recorded) in the animals of different groups at various time intervals are shown in table 10 and figure 17.

The values of respiratory rate in all three groups decreased at different intervals during the observation period in comparison to the baseline values. All three groups showed that respiratory rate value decreased significantly ($p<.05$) after pre-medication and remained significantly lower throughout the observation period. Comparison within groups also showed that respiratory rate in group I was significantly lower at 15 minutes, whereas non-significantly lower at 30 and 60 minutes during maintenance of anaesthesia in comparison to after pre-medication. However, in groups, II and III respiratory rates were non-significantly lower during maintenance of anaesthesia in comparison to after pre-medication.

Comparison between the groups showed that respiratory rate non-significantly ($p>0.05$) change at various intervals of time during the observation period.

4.2.3 Rectal temperature (RT)

Mean ± SE values of rectal temperature (^{0}F) recorded in the animals of different groups at various time intervals are shown in table 11 and figure 18.

The values of rectal temperature in all three groups showed a decrease at different intervals during the observation period in comparison to the baseline values. Groups I showed that rectal temperature gradually decreases after pre-medication and becomes significantly ($p<.05$) lower at 15minute during maintenance of anaesthesia and remained significantly lower up to recovery. However, group II showed rectal temperature gradually decreased after pre-medication and become significantly ($p<0.05$) lower at 30 minutes during maintenance of

anaesthesia, after that remained significantly lower up to recovery in comparison to the respective base values. Similar to group I, group III also showed that rectal temperature becomes significantly lower at 15 minutes during the observation period and then remained significantly lower up to recovery.

Comparison between the groups showed that rectal temperature non-significantly ($p>0.05$) change at various intervals of time except at 15 minutes during the observation period. At 15 minutes during the observation period, rectal temperature was significantly lowered in group III in comparison to group II, whereas non-significantly was lower in comparison to the group I.

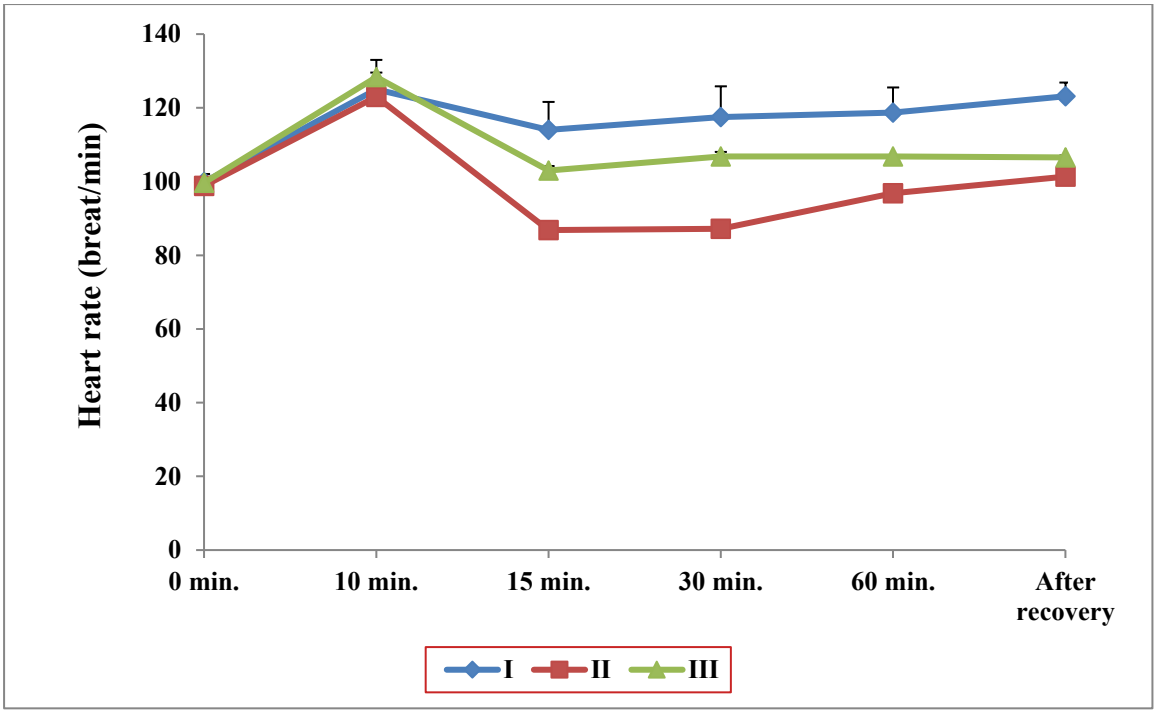

Fig. 16: Mean ± SE values of heart rate (breat/min) of different groups at various time intervals.

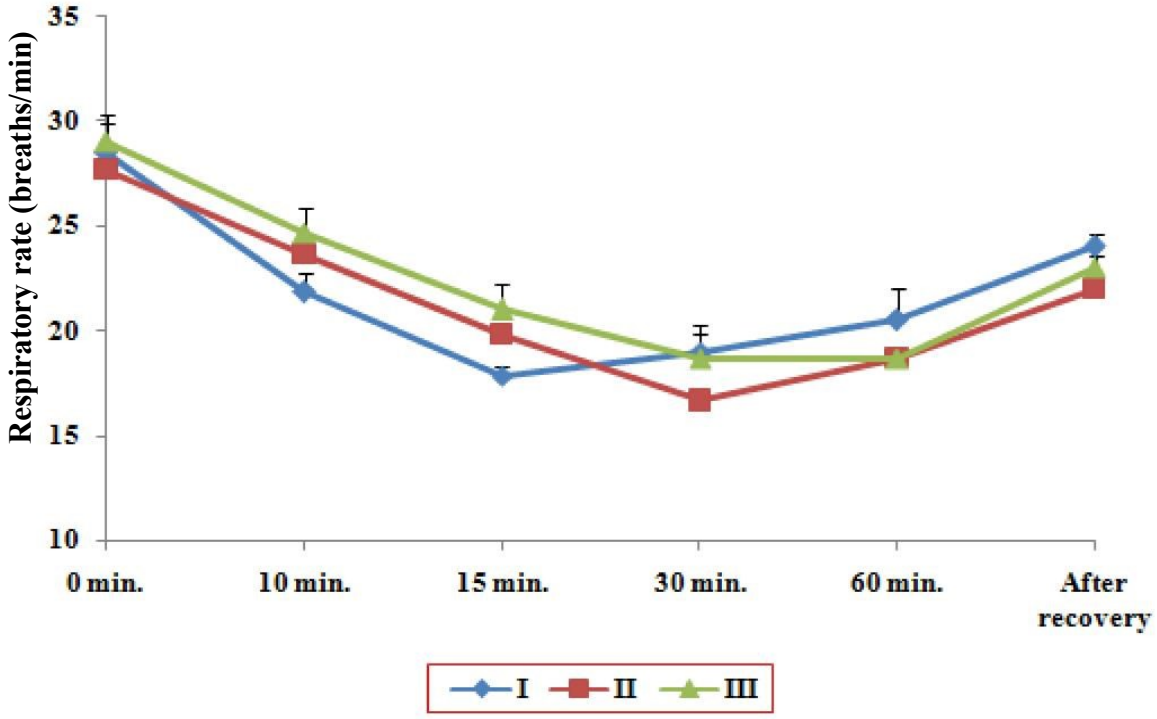

Fig. 17: Mean ± SE values of respiratory rate (breaths/minute) in different groups at various time intervals.

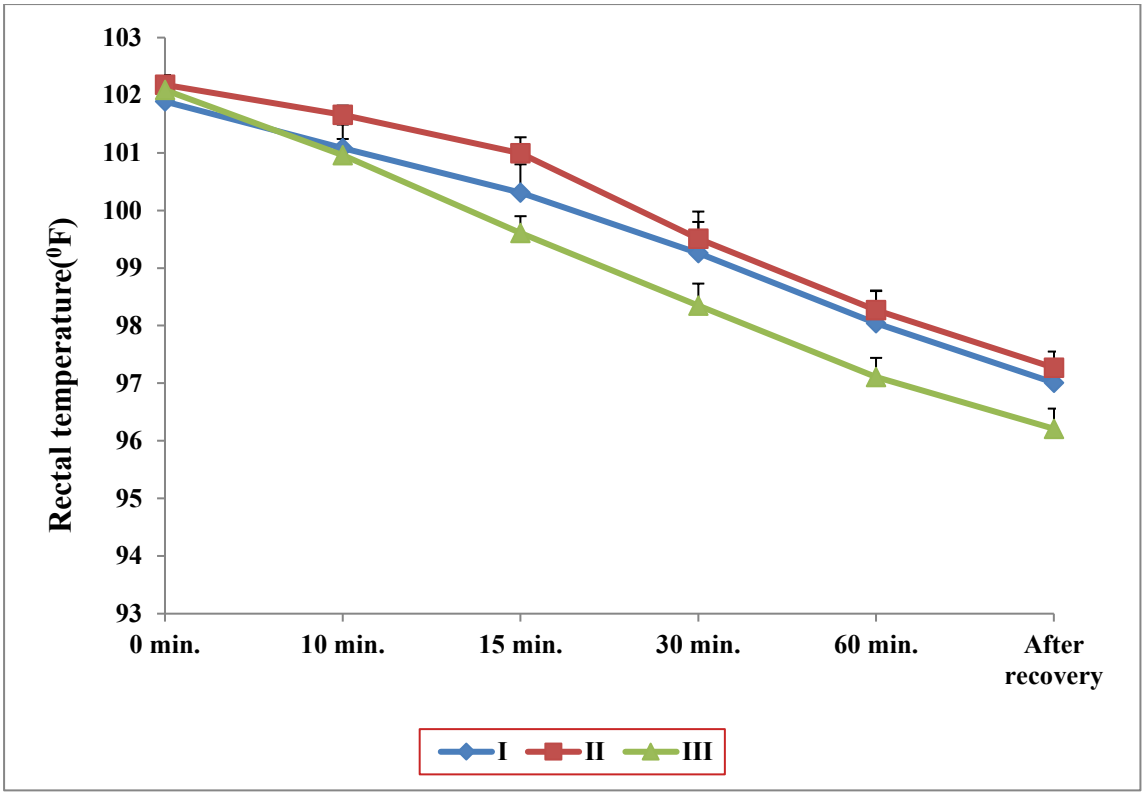

Fig. 18: Mean ± SE values of rectal temperature time in animals of different groups

4.3 Cardiovascular Parameters:

4.3.1Systolic arterial pressure (SAP)

Mean ± SE values of systolic arterial pressure (mm Hg) were recorded) in the animals of different groups at various time intervals are shown in table 12 and figure 19.

The value of systolic arterial pressure increased significantly ($P<0.05$) after pre-medication in all three groups in comparison to respective base values. Comparison within groups showed that SAP non-significantly decreased at 15 minutes and then gradually increased up to maintenance of anaesthesia in group I and III, whereas in group II, SAP gradually decrease from 15 minutes to the entire period of maintenance of anaesthesia in comparison to after pre-medication.

Comparison between the groups showed that systolic arterial pressure non-significantly ($p<0.05$) change from pre-medication to 15 minutes during maintenance of anaesthesia. At 30 minutes and 60 minutes during maintenance, anaesthesia SAP was significantly ($P<0.05$) lower in group II in comparison to groups I and III. Comparison among the groups also showed that at 30 minutes and 60 minutes during maintenance anaesthesia SAP was non-significantly ($P>0.05$) lower in group III in comparison to the group I.

4.3.2 Diastolic arterial pressure (DAP)

Mean ± SE values of diastolic arterial pressure (mm Hg) were recorded) in the animals of different groups at various time intervals are shown in table 13 and figure 20.

Value of diastolic arterial pressure increased significantly ($P<0.05$) after pre-medication in groups I and II, whereas non-significantly ($p>0.05$) in group III in comparisons to respective base values. Comparison within showed that DAP non-significantly decreased at 15 minutes and then gradually increased up to maintenance of anaesthesia in group I and III, whereas in group II, DAP gradually decrease from 15 minutes to the entire period of maintenance of anaesthesia.

Comparison between the groups showed that DAP non-significantly ($p<0.05$) change from pre-medication to 15 minutes during maintenance of anaesthesia. At 30 minutes and 60 minutes during maintenance anaesthesia DAP was significantly ($P<0.05$) lower in group II in comparison to groups I and III. Comparison among the groups also showed that at 30 minutes and 60 minutes during maintenance anaesthesia DAP was non-significantly ($P>0.05$) lower in group III in comparison to group I.

4.3.3 Mean arterial pressure (MAP)

Mean ± SE values of mean arterial pressure (mm Hg) were recorded) in the animals of different groups at various time intervals are shown in table 14 and figure 21.

Value of mean arterial pressure increased significantly ($P<0.05$) after pre-medication in groups II whereas non-significantly ($p>0.05$) in groups I and III in comparisons to respective base values. Comparison within showed that MAP non-significantly decreased at 15 minutes and then gradually increased up to maintenance of anaesthesia in group I and III, whereas in group II, MAP gradually decrease from 15 minutes to the entire period of maintenance of anaesthesia.

Comparison between the groups showed that mean arterial pressure non-significantly ($p<0.05$) change after pre-medication with each-other. From 15 minutes to 60 minutes during maintenance anaesthesia MAP was significantly ($P<0.05$) lower in group II in comparison to groups I and III. Comparison among the groups also showed that from 30 minutes to 60 minutes during maintenance anaesthesia MAP was non-significantly ($P>0.05$) lower in group III in comparison to a group I.

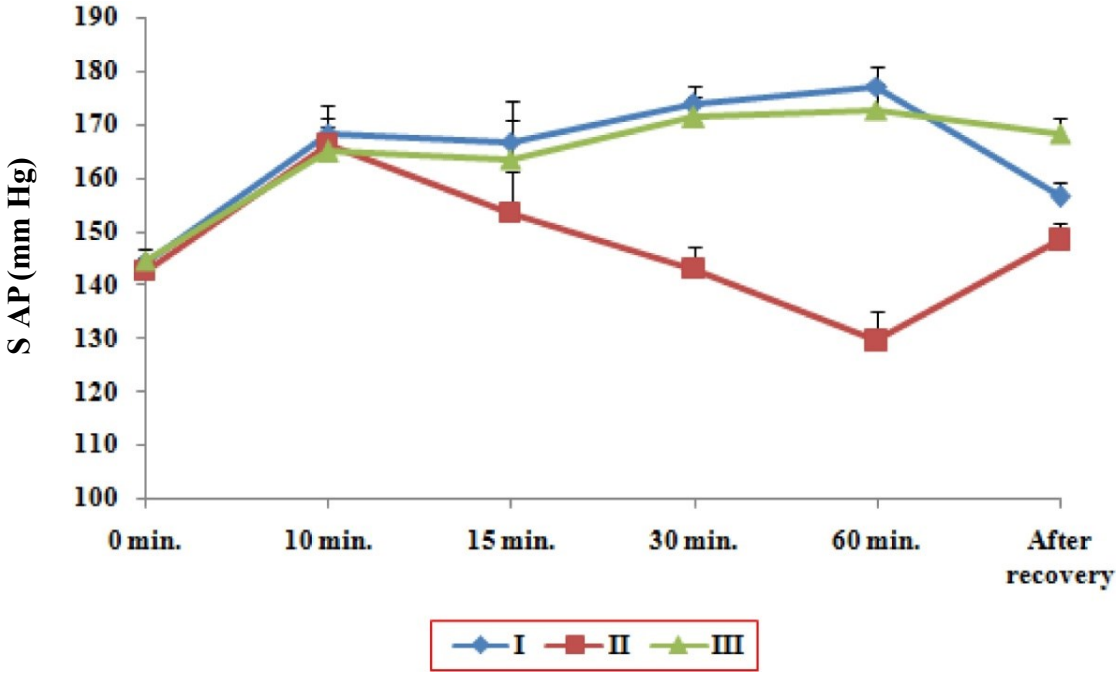

Fig. 19: Mean ± SE values of systolic arterial pressure of different groups at various time intervals.

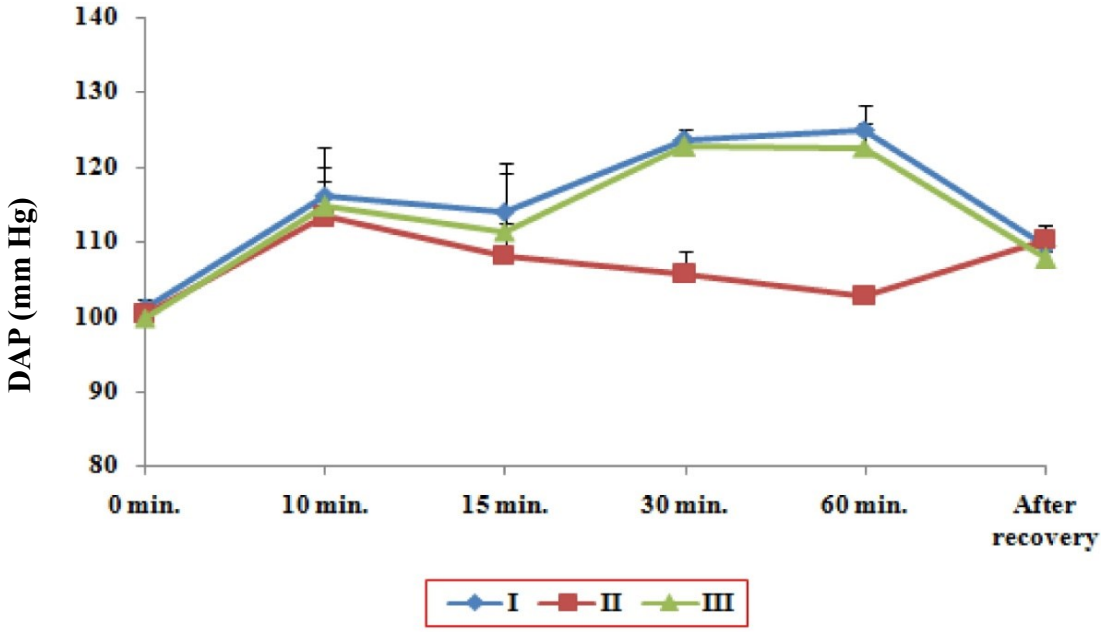

Fig. 20: Mean ± SE values of diastolic arterial in of different groups at various time intervals.

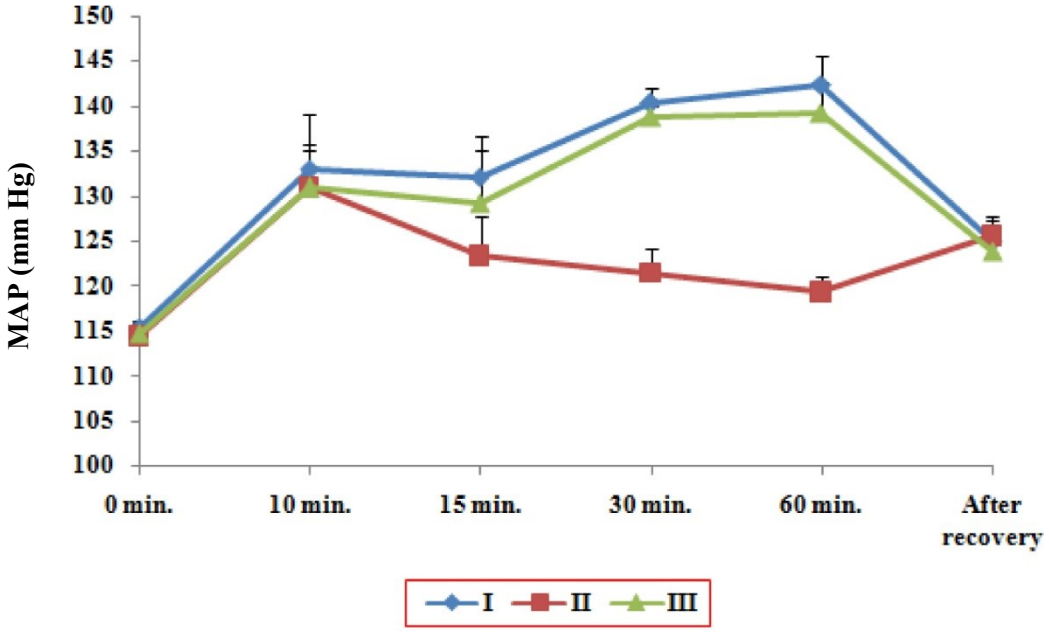

Fig. 21: Mean ± SE values of mean arterial pressure in of different groups at various time intervals.

4.4 Haematological observations:

4.4.1 Hemoglobin (Hb):

Mean ± SE values of hemoglobin (g/dL) recorded) in the animals of different groups at various time intervals are shown in table 15 and figure 22.

The values of haemoglobin in all groups changed non-significantly ($p>0.05$) at various time intervals in comparison to respective base values during the observation period. However, haemoglobin values decreased non-significantly after pre-medication and remained non-significantly lower at various intervals in comparison to respective base values during observation periods except at recovery in group II.

Comparison between the groups showed that haemoglobin non-significantly ($p>0.05$) changes at various intervals of time during the observation period.

4.4.2 Packed Cell Volume (PCV)

Mean ± SE values of packed cell volume (L/L) in different groups at various time intervals are shown in table 16 and figure 23.

The values of packed cell volume in all groups changed non-significantly ($p>0.05$) at various time intervals in comparison to respective base values during the observation period. However, PCV values decreased non-significantly after pre-medication and remained non-significantly higher at various intervals in comparison to respective base values during observation periods except at recovery in group II.

Comparison between the groups showed that PCV non-significantly ($p>0.05$) change at various intervals of time during the observation period.

4.4.3 Total Erythrocyte Count (TEC)

Mean ± SE values of erythrocyte count ($x10^{12}$/L) in different groups at various time intervals are shown in table 17 and figure 24.

The values of TEC in all groups changed non-significantly ($p>0.05$) at various time intervals in comparison to respective base values during the observation period. However, TEC values decreased non-significantly after pre-medication and remained non-significantly lower at various intervals in comparison to respective base values during observation periods except at recovery in group II.

Comparison between the groups showed that TEC non-significantly ($p>0.05$) change at various intervals of time during the observation period.

4.4.4 Total Leukocyte Count (TLC)

Mean ± SE values of total leukocyte count ($x10^9$/L) in different groups at various time intervals have been shown in table 18 and figure 25.

The values of TLC in all groups changed non-significantly ($p>0.05$) at various time intervals in comparison to respective base values during the observation period. However, change in TLC did not show a definite pattern.

Comparison between the groups also showed that TLC non-significantly ($p>0.05$) change at various intervals of time during the observation period.

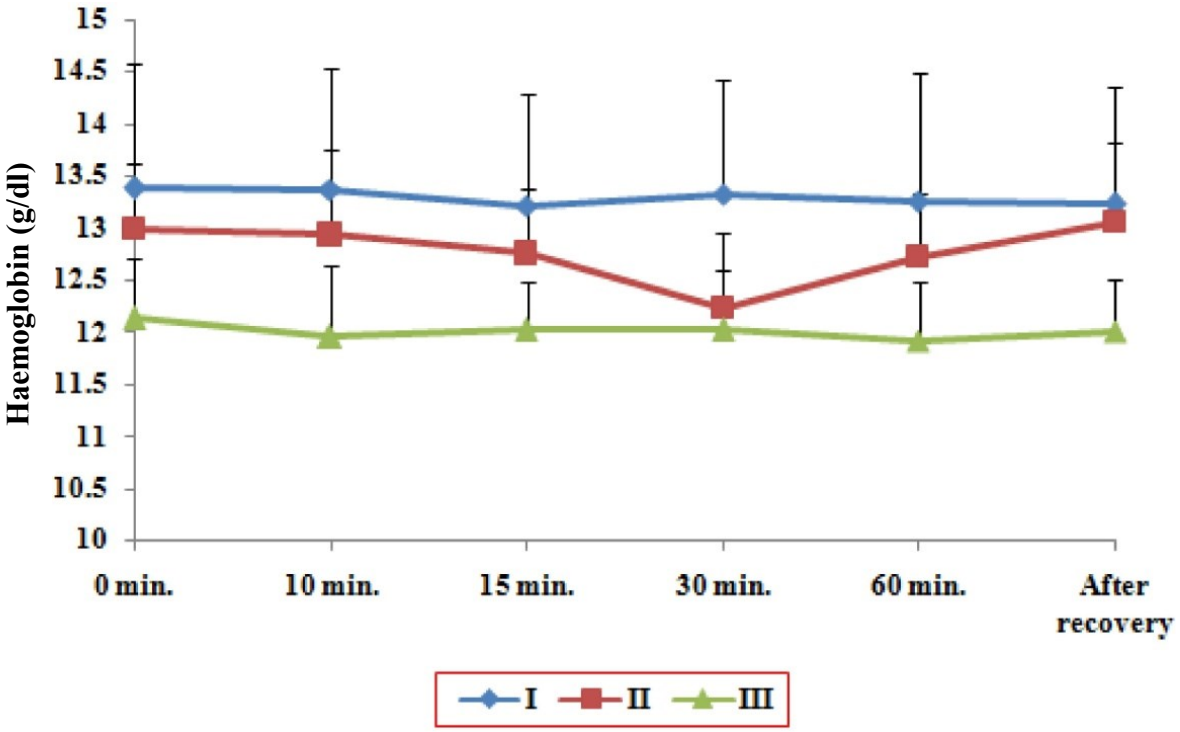

Fig. 22: Mean ± SE values of haemoglobin of different groups at various time intervals.

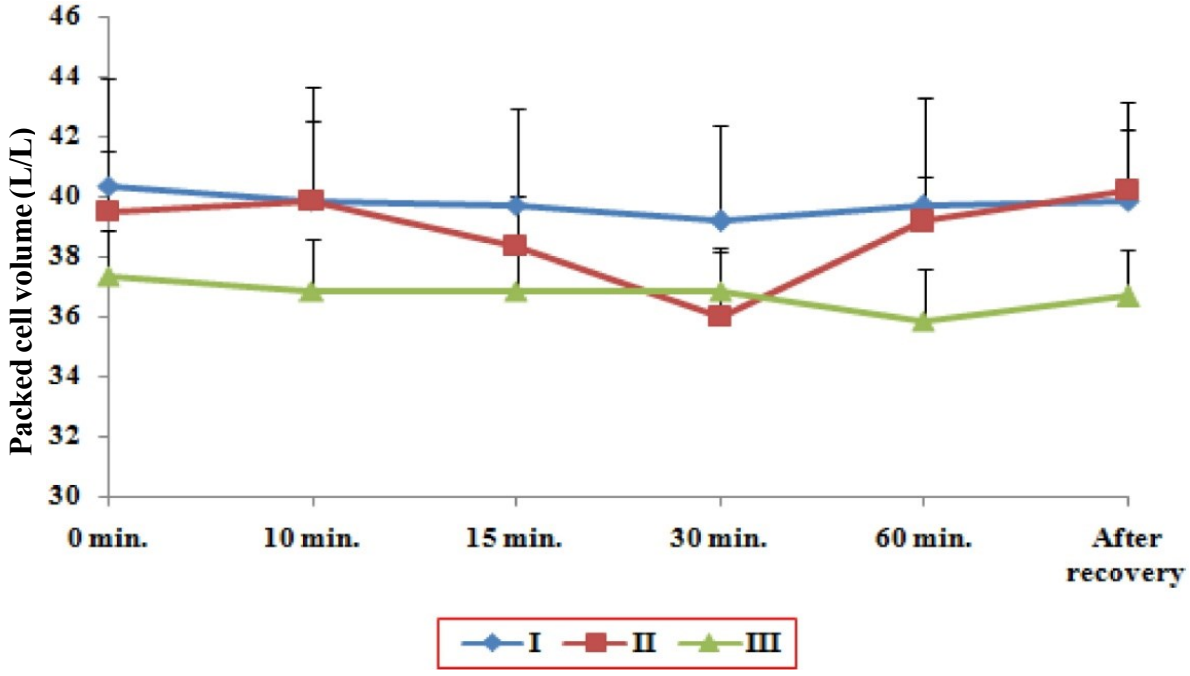

Fig. 23: Mean ± SE values of packed cell volume in different groups at various time intervals.

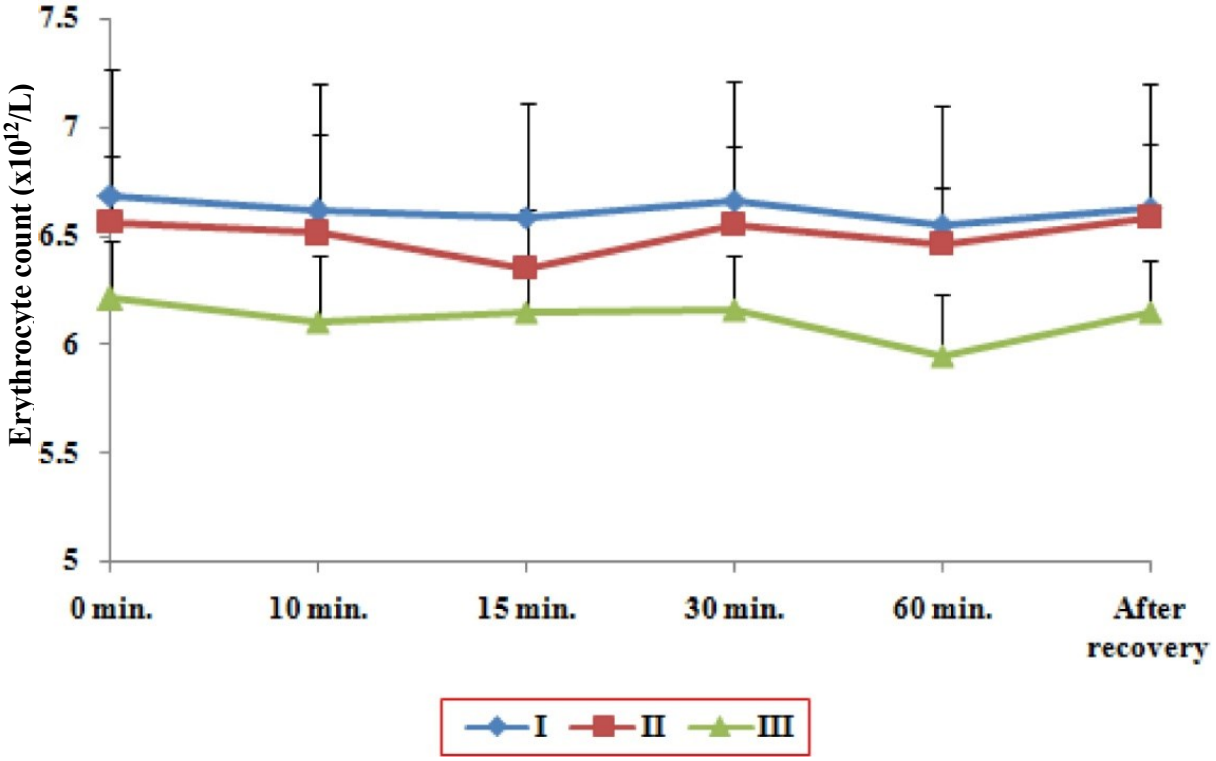

Fig. 24: Mean ± SE values of erythrocyte count in different groups at various time intervals.

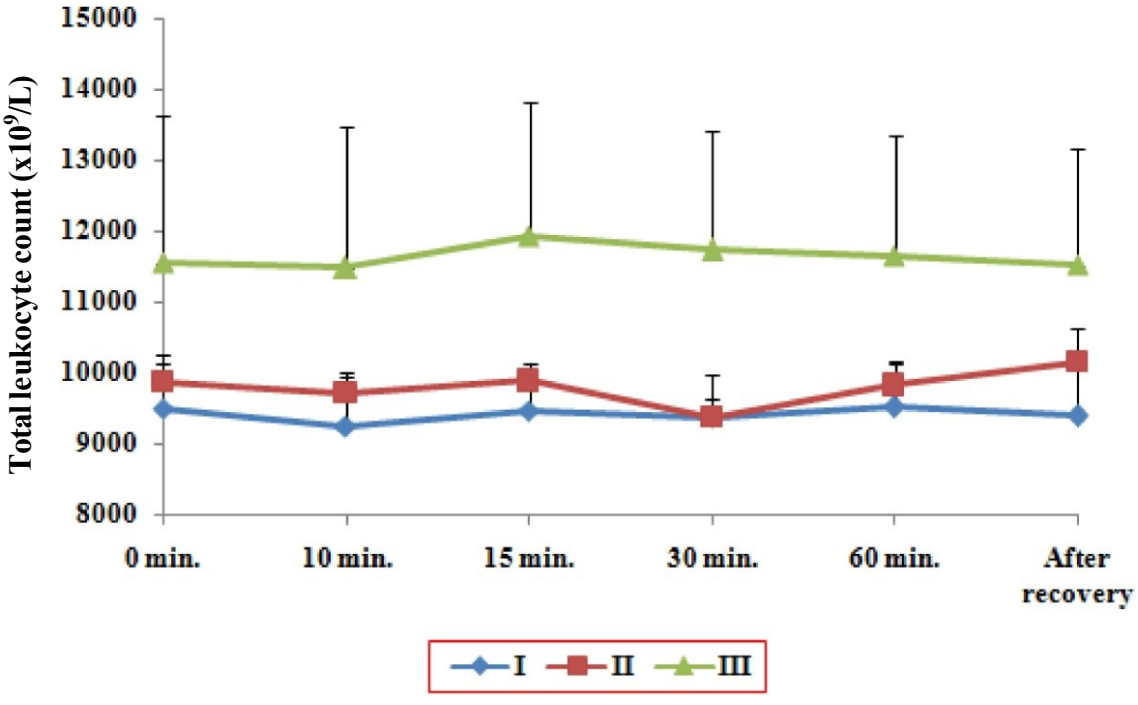

Fig 25: Mean ± SE values of total leukocyte count (x10^9/L) in different groups.

4.5 Biochemical observations:

4.5.1 Blood Urea Nitrogen

Mean ±SE values of blood urea nitrogen (BUN) (mg/dL) recorded in the animals of different groups at various time intervals are shown in table 19 and figure 26.

The values of blood urea nitrogen changed non-significantly ($p>0.05$) at various time intervals from respective base values during the observation period in all three groups. However, blood urea nitrogen (BUN) values in all groups declined non-significantly after pre-medication and remained non-significantly lower at various intervals of time in comparison to respective base values during observation periods.

Comparison between the groups showed that BUN non-significantly ($p>0.05$) change at various intervals of time.

4.5.2 Creatinine

Mean ± SE values of serum creatinine (mg/dL) were recorded) in the animals of different groups at various time intervals are shown in table 20 and figure 27.

The values of serum creatinine in all groups changed non-significantly ($p>0.05$) at various time intervals in comparison to respective base values during the observation period. However, serum creatinine values declined non-significantly after pre-medication and remained non-significantly lower at various intervals in comparison to respective base values during observation periods except at recovery in group I.

Comparison between the groups showed that serum creatinine non-significantly ($p>0.05$) change at various intervals of time during the observation period.

4.5.3 Blood Glucose

Mean ± SE values of serum glucose (mg/dL) were recorded) in the animals of different groups at various time intervals are shown in table 21and figure 28.

The values of serum glucose in all three groups increased at different intervals during the observation period in comparison to the respective baseline values. Groups I and II showed that serum glucose value gradually increases significantly ($p>0.05$) after pre-medication and become significantly higher at the time of recovery. However, group III showed serum glucose increase non-significantly after pre-medication and remained non-significantly higher throughout the observation period in comparison to the respective base values. Comparison between the groups showed that serum glucose non-significantly ($p>0.05$) changes at various intervals of time during the observation period.

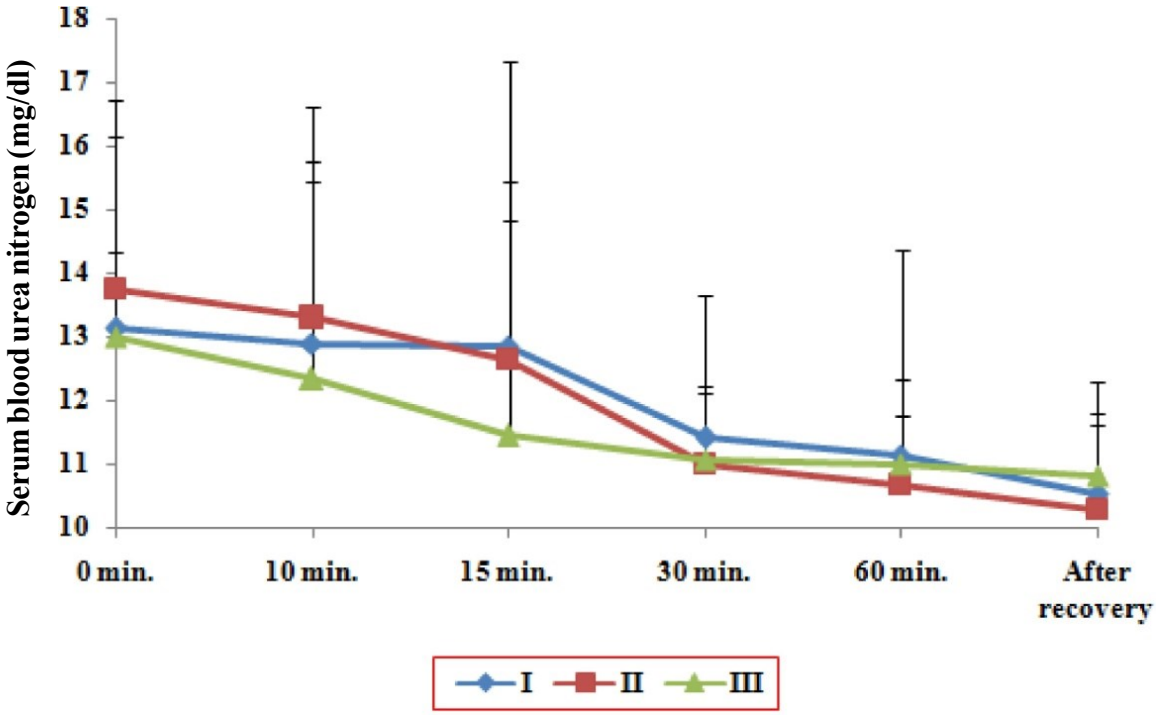

Fig. 26: Mean ± SE values of blood urea nitrogen in different groups at various time intervals.

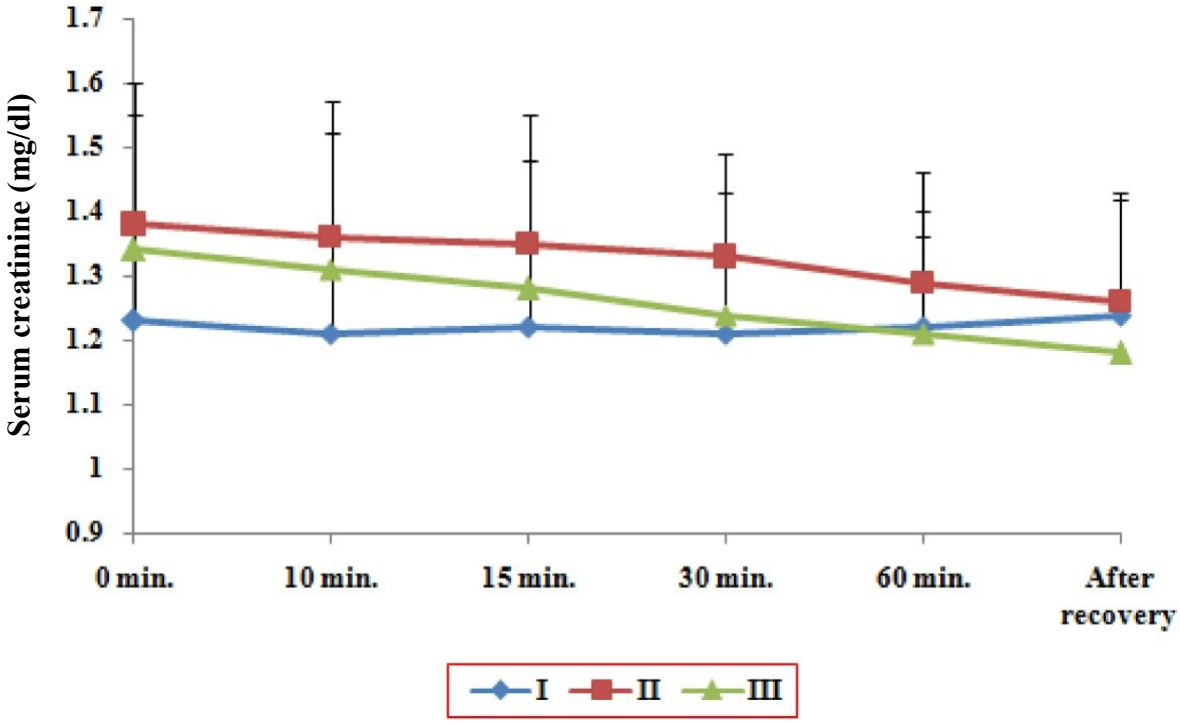

Fig. 27: Mean ± SE values of serum creatinine in different groups at various time intervals

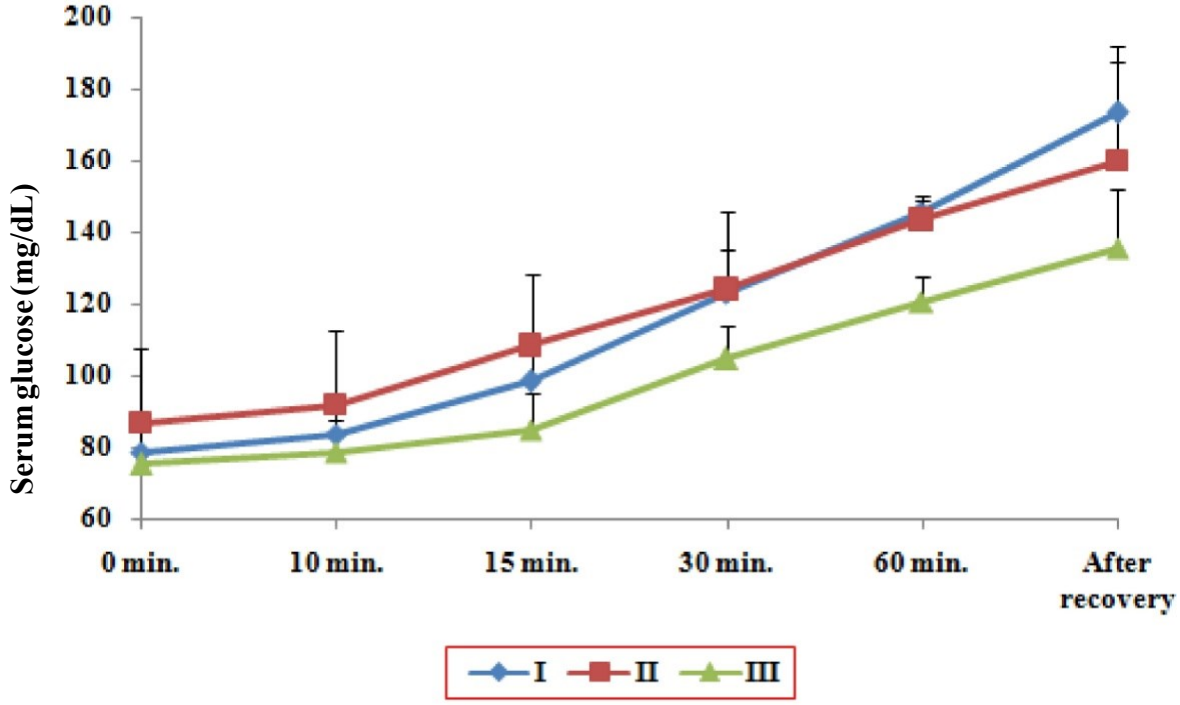

Fig. 28: Mean ± SE values of serum glucose in different groups at various time intervals.

4.5.4Asparte Aminotransferase (AST/SGOT)

Mean ± SE values of aspartate aminotransferase (IU/L) were recorded) in the animals of different groups at various time intervals are shown in table 22 and figure 29.

The values of aspirate amino-transferase in all groups changed non-significantly ($p>0.05$) at various time intervals in comparison to respective base values during the observation period. Values of AST increased non-significantly after pre-medication in groups I and II in comparison to respective base values; however, in group III decreased non-significantly after pre-medication in comparison to base values. Comparison within groups also showed that values of AST in group III remained non-significantly lower during the entire observation period in comparison to the base values; however in groups I and II, a definite pattern of change was not observed at different intervals during the observation period.

Comparison between the groups showed that AST non-significantly ($p>0.05$) change at various intervals of time during the observation period.

4.5.5 Lipid Peroxidation (LPO)

Mean ± SE values of lipid peroxidation (mmol/L) recorded in the animals of different groups at various time intervals are shown in table 23 and figure 30.

The values of lipid peroxidation in all groups changed non-significantly ($p>0.05$) at recovery in comparison to respective base values during the observation period. Values of lipid peroxidation increased non-significantly after recovery in all three groups.

Comparison among the groups revealed no significant ($p>0.05$) difference in lipid peroxidation at level different time intervals.

4.5.6 Superoxide dismutase (SOD)

Mean ± SE values of Superoxide dismutase (U/ml) were recorded in the animals of different groups at various time intervals are shown in table 24 and figure 31.

The values of Superoxide dismutase in all groups changed non-significantly ($p>0.05$) at recovery in comparison to respective base values during the observation period. However, values of Superoxide dismutase increased non-significantly after recovery in all three groups.

Comparison among the groups revealed no significant ($p>0.05$) difference Superoxide dismutase at level different time intervals.

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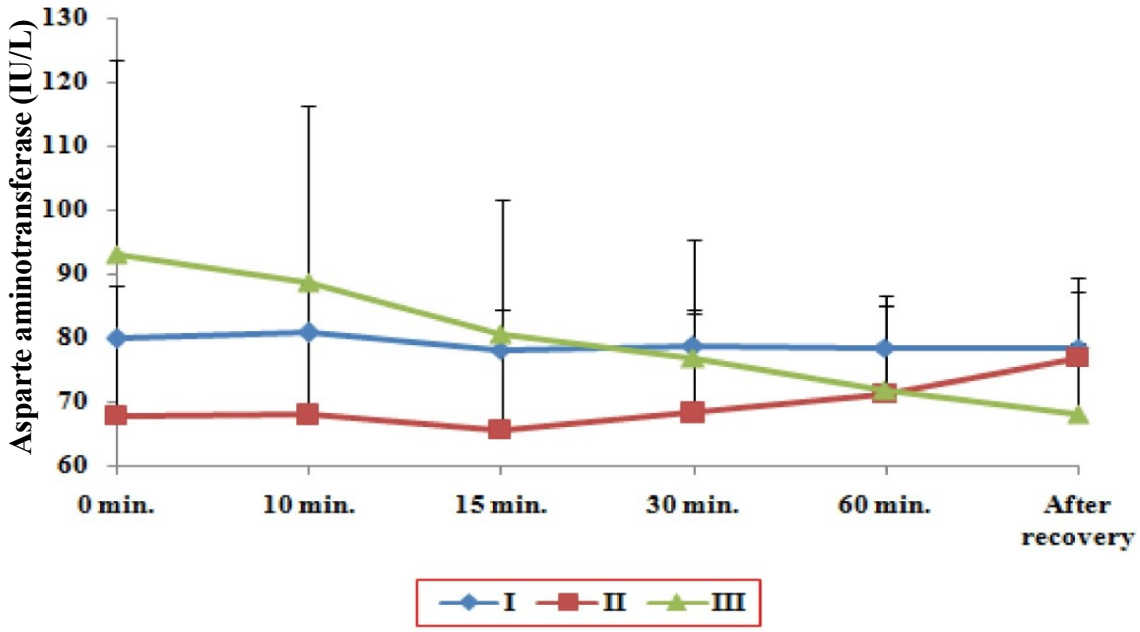

Fig. 29: Mean ± SE values of aspartate aminotransferase in different groups at various time intervals.

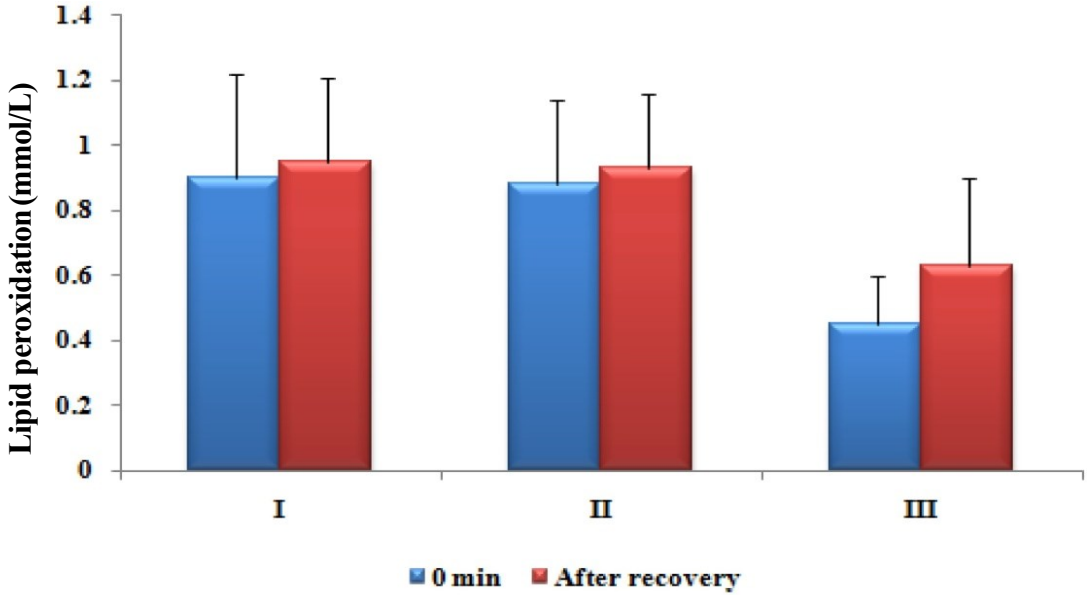

Fig. 30: Mean ± SE values of lipid peroxidation in different groups at various time intervals.

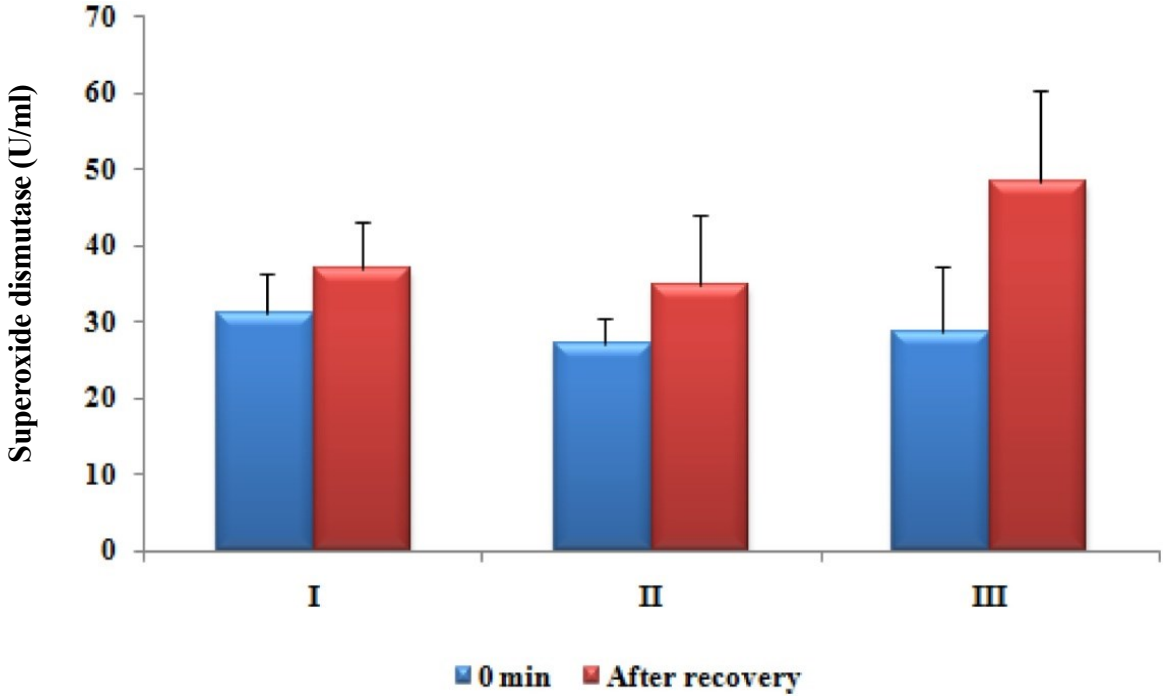

Fig. 31: Mean ± SE values of superoxide dismutase in different groups at various time intervals.

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Discussion

"Education is the most powerful weapon which you can use to change the world"

5 DISCUSSION

The study was designed to investigate the anesthetic effects of CRI ketamine, propofol, and ketofol in canine premedicated with glycopyrrolate, butorphanol, and xylazine for the elective ovariectomy. The study was conducted on 18 healthy female dogs divided into three groups randomly, containing six animals in each group. The groups were designated as group-I, group-II, and group-III on the basis of the induction and maintenance of anaesthesia. Glycopyrrolate was given @ 0.01mg/kg b.wt intramuscularly at right lumbar epaxial muscles, after 5 minutes of that butorphanol @ 0.2 mg/kg b.wt and flowed by xylazine 1 mg/kg b.wt intramuscularly at left lumbar epaxial muscles with use of different syringes. After that animal was placed on the operation table and canulated with a 20 gauge intravenous catheter attached with normal saline infusion. After 15 minutes of premedication, the animal was induced (till effect) with propofol, and immediately just after induction, anaesthesia was maintained with constant rate infusion of ketamine, propofol, and ketofol1:1 combination via surgical maintenance fluid (Normal saline @ 10 ml/kg/hr.) in group I, II, and III respectively until the last skin suture closure. The evaluation and comparison were done on the basis of clinic-physiological and haemato-biochemical, haemodynamic parameters.

Clinical observations

Pedal reflex

The pedal reflex is a useful guide to the depth of analgesia and anaesthesia in dogs. The pedal reflex remained intact after the administration of glycopyrrolate. Pedal reflex an automatic action that is performed without conscious thought as a response to a stimulus in which the limb is flexed in response to painful stimulation of the digits or interdigital region. This reflex is lost as the transition from light to medium surgical anaesthesia occurs. The pedal reflex scores increased after the administration of glycopyrrolate and butorphanol in all the groups. In all groups at induction and during maintenance of anaesthesia, the pedal reflex score was maximum. Alpha2-agonists produce analgesia by stimulating receptors at various sites in the pain pathway within the brain and spinal cord (Stenberg, 2006). Electrophysiological studies have indicated that pre-and postsynaptic inhibitory mechanisms are responsible for the antinociceptive action of alpha2 -adrenoceptor agonists (Yaksh., *et al* 1985). Alpha2 and opiate receptors are found in similar regions of the brain and even on

some of the same neurons. The binding of either alpha2-agonists or μ-opioid agonists to those receptors results in activation of the same signal transduction systems (membrane-associated G proteins), which induces a chain of events that open potassium channels in the neuronal membrane. Activation of potassium channels in the postsynaptic neuron leads to hyperpolarization of the cell, which ultimately makes the cell unresponsive to excitatory input and effectively severs the pain pathway. Consequently, the alpha2-agonists and μ-opioid agonists produce analgesia by similar mechanisms. The alpha2-adrenergic agonists are widely used in injectable sedative analgesic combinations because of their potent sedative, muscle relaxant, analgesic, and anxiolytic effects. They induce dose-dependent sedation and analgesia in dogs. Synergistic sedative and analgesic activity between alpha2-agonists and opioid agonist-antagonist has been reported in horses (Corletto *et al*., 2005; Hofmeister *et al*., 2008; Malik and Singh, 2008), dogs (Amarpal *et al*., 1998a), pigs (Sakaguchi *et al*., 1995) and ruminants (Faulkner *et al*., 1992; Levine *et al*.,1992; Ahmad, 2009; Malik *et al*., 2011; Singh, 2011).

Propofol has no intrinsic analgesic potency (Hall and Clarke, 1991), necessitating the concurrent administration of an analgesic agent or opiates (Langley and Heel, 1988). Anaesthesia with propofol has been successfully induced after pre-medication with alpha2-agonists and butorphanol in dogs (Thurmon *et al*., 1996; Kim and Jang, 1999).

Palpebral reflex

Palpebral reflex is stimulated by tapping the skin at the medial canthus of the eye or by running the finger along the eyelashes. The reflex disappears in light to the medium plane of surgical anaesthesia in small animals (Tranquilli *et al.,* 2007). Slow response in palpebral reflex was observed after the administration of glycopyrrolate and butorphanol at 15 min of observation (Gupta, 2010). In our study during CRI maintenance of anaesthesia in a group, I throughout the observation period from induction to termination of anaesthesia very slow and occasional palpebral reflex observed due to the effect of ketamine (Wright, 1982). A similar finding was also reported by Ibrahim, (2017) in CRI ketamine. In ketofol 1:1 showing absence of palpebral reflex till CRI termination, further, it was similar to ketamine CRI.

Corneal reflex

It is checked by a gentle touch of the cornea which induced to blinking response. Generally, loss of corneal reflex is noticed after the abolition of the palpebral reflex. As per

Tranquilli *et al.,* (2007) the corneal reflex varies in different species. The corneal reflex became moderate after the administration of glycopyrrolate and butorphanol in all three groups. The reflex was abolished completely in all the animals after the induction of anaesthesia with propofol.

Duration of surgery

Duration of ovariectomy in groups I, II, and III was 58.67±1.56 min, 59.00±0.84 min, and 57.00±1.60 min respectively. Comparison between the groups showed a non-significant difference in duration of surgery. Almost similar duration of surgery in all groups could be attributed to the same team of surgeons performing surgery on similar types of animals.

Duration of anaesthesia

The mean values of duration of anaesthesia in groups I, II, and III was 75.5±2.04min, 73.83±2.53 min, and 77.17±1.64 min respectively. The difference between the duration of surgery and the duration of anaesthesia could be due to the time taken by the animals in gaining pedal reflex after end of anaesthesia.

Recovery time

Recovery time was recorded as the time when the pedal reflex reappeared. In the animals of group, I (ketamine), group II (propofol), and group III (ketofol 1:1) the mean recovery time was 47.17±0.94 min, 25.00±1.33 min, and 46.83±0.60 min respectively. Since a decrease in hepatic blood flow would be expected to decrease the clearance of ketamine during anaesthesia and sedative effect along with glycopyrrolate and butorphanol combination (Schwieger *et al.,* 1991). There is a virtual lack of any cumulative effect of propofol caused rapid recovery after its administration for induction and CRI maintenance (Adetunji *et al*., 2002). In the present study, propofol provided rapid induction of anaesthesia, as well as smooth rapid recovery after its administration. Furthermore, the rapid redistribution and metabolism of the drug also explain the rapid, smooth recovery from propofol anaesthesia. Rapid and smooth recovery recorded in the present study was following that reported in the earlier studies in dogs (Mathews *et al*., 2004; Ajadi *et al.,* 2007; Seliskar *et al.,* 2007 and Surbhi, 2008). On the flip side ketofol 1:1, shows that similar recovery time like ketamine may be attributed to the high dose of ketamine cumulative effect with propofol.

Sternal recumbency time

Sternal recumbency time in groups I, II, and III was 61.17±1.81min, 36.17±1.33min, and 58.67±1.05min respectively. Comparison among the groups showed that sternal recumbency time in group II significantly ($p<0.05$) lower in comparison to groups I and III. The increase of sternal recumbency time in ketamine maybe because of ketamine and its metabolites (Kaka and Hayton, 1980).

Physiological Observations:

Rectal temperature

The values of rectal temperature in all the three groups showed a decrease at different intervals during the observation period in comparison of the baseline values, which was significant ($p<0.05$) at 15minutes in group I and group III, However group II showed rectal temperature gradually decreased and become significantly ($p<0.05$) lower at 30 minutes during maintenance of anaesthesia. Comparison between the groups showed that rectal temperature non-significantly ($p>0.05$) change at various intervals of time except at 15 minutes during the observation period.

Hypothermia has been observed following the use of xylazine in cats (Ponder and Clarke, 1980), sheep (Aminkov and Hubenon, 1995), dogs (Surbhi, 2008), and goats (Kinjavdekar *et al.,* 2000). Ahmad (2011) also reported a decreased RT after dexmedetomidine administration or its combination with midazolam in dogs.

The mean rectal temperature dropped significantly in all the groups following propofol infusion which might be due to a decrease in metabolic rate, inhibition of muscle tone, depression of peripheral circulation, vasodilatation, and depression of the thermoregulatory mechanism (Ponder and Clarke, 1980; Weaver and Raptopoulos, 1990; Ilkiw *et al*., 1992; Muir and Gadawski, 2002). One or a combination of these mechanisms might have caused hypothermia by alpha2-agonists, propofol, and ketamine in the present study.

Respiratory rate

The values of respiratory rate in all three groups decreased at different intervals during the observation period in comparison to the baseline values. All three groups showed that respiratory rate value decreased significantly ($p<.05$) after pre-medication and remained significantly lower throughout the observation period. Comparison between the groups

showed that respiratory rate non-significantly ($p>0.05$) change at various intervals of time during the observation period.

The findings of this study were in accordance to Silva *et al.* (2010) who observed the significant drop in respiratory rate ($p<0.05$) after administration of alpha-2 agonist as a pre-anaesthetic to the propofol anaesthesia in dogs. Respiratory depression associated with alpha-2 adrenergic agonists might be secondary to the central nervous system depression produced by alpha-2 adrenoceptors simulation (Sinclair, 2003) or due to direct depression of the respiratory center in the brain (Kumar and Thurman, 1979). Butorphanol, like other opioids, is known to depress respiration in a dose-related manner by acting on μ receptors. It causes mild lowering of respiratory rate and respiratory depression was observed in dogs (Trim, 1983; Greene *et al.,* 1990; Carpenter *et al.,* 2005).

There is a non-significant difference among the groups. The appropriate premedication and better CRI dose may be the possible reason. Although non-significant, ketofol and ketamine group having a higher respiratory rate than propofol group animals, because ketamine may preserve respiratory tone alone as well as a combination with propofol while administering in CRI.

Heart rate

Value of heart rate significantly ($P<0.05$) increased after pre-medication in all three groups in comparisons to respective base values after that decreased but remained non-significantly ($P>0.05$) higher in group I and III, however it become non-significantly lower in group II during maintenance of anaesthesia in comparison to respective base values. Comparison between the groups showed that heart rate non-significantly ($p>0.05$) change at various intervals of time during the observation period.

The heart rate increased after pre-medication in all three groups. An initial rise in heart rate may be attributed to the vagolytic action of an anticholinergic agent. In accordance with the present study, Raffe *et al*. (2015) observed that heart rate increase after pre-medication with atropine, butorphanol, and alpha-2 agonist combination and reached the highest level at 15-minute intervals. A non-significant decline in heart rate was observed in group II induction. The non-significant decrease in heart rate after induction in group 2 could be attributed to the typical hemodynamic response of alpha 2 agonists mediated by the baroreflex and due to a decrease in sympathetic activity. Silva *et al.* (2010) reported similar findings and summarized that the intensity of cardiovascular manifestation after administration of dexmedetomidine depends on the dose, route of administration, and

combination of drugs. However, heart rate remained within the normal physiological limit in all three groups. It might be a combined effect of anticholinergic, alpha-2 agonist, propofol, ketamine, and ketofol.

Cardiovascular Parameters:

Value of blood pressure increased significantly ($P<0.05$) after pre-medication in all three groups in comparison to respective base values. Comparison within groups showed that blood pressure non-significantly decreased at 15 minutes and then gradually increased up to maintenance of anaesthesia in group I and III, whereas in group II, blood pressure gradually decreases from 15 minutes to the entire period of maintenance of anaesthesia in comparison to after pre-medication. Comparison between the groups showed that blood pressure non-significantly ($p<0.05$) change from pre-medication to 15 minutes during maintenance of anaesthesia.

Anticholinergics are capable of causing hypertension (Alibhai *et al*., 1996). Transient initial hypertension of variable duration after administration of alpha-2 agonists was also due to the stimulation of peripheral alpha-2B agonist receptors (Docherty and McGrath, 1980; Link *et al.,* 1996). A biphasic response i.e. transient hypertension followed by prolonged hypotension has been considered a classic response after systemic administration of alpha2-agonists. This biphasic response of blood pressure after administration of alpha2-agonists was not observed in the present study. The stimulation of post-synaptic alpha1- and alpha2-adrenoceptors in vascular smooth muscles (sympathomimetic action) results in initial hypertension. Alpha2-agonists have also been reported to cause a depressive cardiovascular effect with bradycardia, a fall in cardiac output, and a rise in systemic vascular resistance (Pypendop and Verstegen, 1998). A CRI ketamine via sympathetic stimulation also leading to increases in myocardial contractility and systemic vascular resistance which in turn increases systolic arterial blood pressure (Furuya *et al.*, 2001).

Hypertension produced by alpha2-agonists was in accordance with the earlier studies in dogs (Vainio *et al*., 1989; Vainio and Palmu, 1989 and Ahmad, 2009), medetomidine in ponies, and sheep (Bryant *et al.*, 1996). A significant increase in systolic blood pressure was also observed in horses after administration of xylazine-butorphanol combination (Robertson and Muir, 1983). In a similar study, a decrease in arterial pressure after medetomidine butorphanol administration (Ahmad, 2009) was reported and alpha2-agonists with fentanyl administration (Singh, 2011) in buffalo calves.

Comparison between the groups showed that systolic arterial pressure non-significantly ($p>0.05$) change from pre-medication to 15 minutes during maintenance of anaesthesia. At 30 minutes and 60 minutes during maintenance anaesthesia SAP was significantly ($P<0.05$) lower in group II, CRI maintenance of propofol may be a reason because propofol causes vasodilation in comparison to groups I and III. According to the present study, Cima *et al*. (2016) reported that ketofol (1:1) group produces high MAP than the propofol group during the entire period of maintenance of anaesthesia. This corroborates the ketamine inhibits the depressing effects on the cardiovascular system caused by the use of propofol (Mair *et al*., 2009).

Biochemical observations:

Blood Urea Nitrogen

The values of blood urea nitrogen changed non-significantly ($p>0.05$) at various time intervals from respective base values during the observation period in all three groups. Comparison between the groups showed that BUN non-significantly ($p>0.05$) change at various intervals of time.

This finding was supported by Kumar and Thurmon, (1983) in goat after xylazine administration, in dogs (Khan *et al.,* 2006). In the present study, the decrease in BUN in all groups might be due to the continuous infusion of intravenous fluids thus maintaining normal kidney functions. However, Jena *et al.* (2014) recorded a non-significant increase in BUN after premedicated with dexmedetomidine and anaesthetized with propofol.

Creatinine

In the present study serum, creatinine levels decreased non-significantly ($p>0.05$) in all groups at various time intervals in comparison to respective base values during the observation period. Comparison between the groups showed that serum creatinine non-significantly ($p>0.05$) change at various intervals of time during the observation period.

In accordance with to present study, Fang *et al*. (2013) reported a non-significant change in serum creatinine after administration of alpha-2 agonists. However, Singh (2011) observed a significant decrease in the plasma creatinine in animals after administration of alpha2-agonists in combination with fentanyl maintained with isoflurane. Story *et al*. (2001) also found similar changes during the study of the effect of isoflurane, sevoflurane, and propofol values in humans. Alpha-2 agonist preserves blood supply to vital organs like the brain, heart liver, and kidney at the expense of organs like skin and pancreas and this distribution is not affected by the type of anaesthesia. This effect of alpha-2 agonist and

continuous intravenous fluid infusion might have been responsible for adequate renal blood flow and enough glomerular filtration rates to maintain plasma urea nitrogen and creatinine values near the baseline. However, Kushwaha *et al.* (2012) and Jena *et al.* (2014) reported an increase in serum creatinine values between ten minutes to sixty minutes after pre-medication.

Blood Glucose

The value of blood glucose level in the animals of all the three groups was increased non-significant during the observation period in comparison of the respective baseline values.

The present study was also supported by Hikasa *et al.* (2000) that reported a non-significant increase in blood glucose value during sevoflurane and isoflurane anaesthesia in healthy sheep. The cause of hyperglycaemia may be attributed to the α-2 adrenergic inhibit the release of insulin from the beta-pancreatic cells and increases glucose production in the liver (Brockman, 1981; Gasthuys *et al.,* 1987). The high rise of glucose value during the observation period in comparison of the respective baseline values also due to decreased membrane transport of glucose decreased utilization of glucose, impaired insulin activity, and increased adrenocortical hormone concentrations in the blood plasma in dogs (Burton *et al*., 1997). During the observation period of anaesthesia all body muscles relaxed causes lower utilization of glucose at tissue level might also be attributed to hyperglycaemia (Agrawal *et al.,* 1983). Hyperglycemia may also be attributed to the traumatic stress or increased muscular activity and sympathetic stimulation caused by restraining the animals resulting in increased secretion of adrenocortical hormones (Mirakhur *et al*., 1984).

However, Kushwaha *et al.* (2012) in dogs and Bayan *et al.* (2002) in cats observed a significant increase in serum glucose levels during propofol anaesthesia. On the basis of present observations, it could be stated that propofol aggravates hyperglycemic effect of an alpha-2 agonist. The findings of this study are in general agreement with that of Kumar *et al.* (2013), Jena *et al.* (2014), and Brockman (1981).

Asparte Aminotransferase (AST/SGOT)

The values of aspirate aminotransferase in all groups changed non-significantly ($p>0.05$) at various time intervals in comparison to respective base values during the observation period. Comparison between the groups showed that AST non-significantly ($p>0.05$) change at various intervals of time during the observation period.

A non-significant transient increase in SGOT values during sedation and anaesthesia in the present study could be due to rapid distribution and clearance of propofol by hepatic

and extra-hepatic sites (Branson and Gross, 1994). The slight alteration in hepatic values indicates minimum or no effect of propofol on the liver and other body tissues (Bayan *et al.,* 2002). Akbar *et al.* (2014) reported the decrease in enzyme concentration twenty minutes post administration of medetomidine and also reported that the SGOT enzyme response was anaesthetic dose dependant.

Lipid Peroxidation (LPO) and Superoxide dismutase (SOD)

The values of lipid peroxidation and superoxide dismutase in all groups changed non-significantly ($p>0.05$) at recovery in comparison to respective base values during the observation period. However, values of lipid peroxidation and superoxide dismutase increased non-significantly after recovery in all three groups. Comparison among the groups revealed no significant ($p>0.05$) difference in lipid peroxidation and superoxide dismutase at level different time intervals.

Oxidative stress in the body presents an imbalance between the productions of reactive oxygen species (ROS) and the ability of the antioxidant defense mechanisms to detoxify the reactive intermediates. The greater the oxidative stress, the more severe the resulting cellular damage during surgery may cause poor outcomes in patients (Sies. 1997), and the minimization of oxidative stress is therefore very important.

Lipids are one of the most susceptible substrates to free radical damage and biomarkers of lipid peroxidation are considered the best indicators of oxidative stress (Georgieva, 2005). Malondialdehyde (MDA) is one of the several low-molecular-weight end-products formed during the radical-induced decomposition of polyunsaturated fatty acid (Janero, 1990). MDA readily reacts with thiobarbituric acid producing a red pigment that can be easily measured by a spectrophotometer in the form of thiobarbituric acid reactive substance (TBARS) (Janero, 1990). At the post-treatment point of time, group III (0.63 ± 0.27) was observed to be non-significantly lower MDA value among group II and group I respectively. Although higher value in group II (0.78 ± 0.23) observed than group I (0.75 ± 0.26). The values with the groups were non-significantly lower from the base value within the respective period of time. The lowest value of MDA in group III in the present study pointed towards less oxidative injuries in animals.

On the post-treatment the SOD value in group I and group II non-significantly lower than group III. Group II also differ non-significantly from group I. Through group II did not

show any significant difference from group I, albeit a higher value in group III (48.80±11.9) was recorded as compared to group I (37.15±5.9) and group II (34.73±9.5) respectively. The SOD values on post-treatment also non-significantly higher within the respective groups as compared to pre-treatment point of time SOD catalyzes the dismutation of superoxide to hydrogen peroxide (H_20_2) and it is considered the first defense against pro-oxidants (Halliwell and Chirico. 1993). It is a natural antioxidant enzyme against free reactive oxygen radicals, the highest value of SOD in group III followed by the group I. The suggestive of least stress in group II animals as there might be less formation of free radicals and less number of SOD needed to counterbalance the free radicals and more surplus enzymes remain balance in the system. In dairy goats, SOD activity is decreased during the postpartum period probably as a consequence of lower peroxide generation as testified by the decrease in reactive oxygen metabolites (ROM) concentrations (Celi, 2010).

Haematological observations:

Hemoglobin (Hb) and Packed Cell Volume (PCV)

The values of haemoglobin and packed cell volume in all groups were changed non-significantly ($p>0.05$) at various time intervals in comparison to respective base values during the entire observation period. However, haemoglobin and PCV values decreased non-significantly after pre-medication and remained non-significantly lower at various intervals in comparison to respective base values during observation periods except at recovery in group II.

Comparison between the groups showed that haemoglobin and PCV non-significantly ($p>0.05$) change at various intervals of time during the observation period.

The decrease in haemoglobin and PCV levels might be due to shifting of fluids from the extravascular compartment to the intravascular compartment in order to maintain the cardiac output in the animals (Wagner *et al.,* 1991) or due to haemo-dilution in response to fluid therapy (Skarda *et al.,* 1991). In a study, alpha-2 agonists and opioids were reported to decrease Hb and PCV levels in dogs (Amarpal *et al.,* 1998). In addition, butorphanol produces kappa mediated diuretic effect which may be a possible reason (Leander *et al.,* 1987 and Horan and Ho, 1989). The non-significant decrease in PCV at 30 min can be attributed to the effect of propofol induction (Wilson *et al.,* 2004).

Total Erythrocyte Count (TEC)

The values of TEC in all groups changed non-significantly ($p>0.05$) at various time intervals in comparison to respective base values during the observation period. Comparison between the groups showed that TEC non-significantly ($p>0.05$) change at various intervals of time during the observation period.

The decrease in the TLC values could be probably due to the pooling of circulating erythrocytes in the spleen or other reservoirs secondary to the decreased sympathetic stimulation (Kinjavdekar *et al.* 2000). A similar finding was noted by Kushwaha *et al.* (2012) in midazolam propofol Combination in dogs

Total Leukocyte Count (TLC)

The values of TLC in all groups changed non-significantly ($p>0.05$) at various time intervals in comparison to respective base values during the observation period. However, changes in TLC did not show a definite pattern. Comparison between the groups also showed that PCV non-significantly ($p>0.05$) change at various intervals of time during the observation period.

The findings of this study were in accordance with Jena *et al.* (2014) who reported a decrease in TLC upon administration of alpha-2 followed by propofol anaesthesia. The decrease in TLC might be due to enhanced peripheral blood level of adrenaline or nor-adrenaline which suppresses the proliferative response of peripheral blood leucocytes or due to increased plasma volume during anaesthesia on account of vasodilatation resulting in vascular pooling (Venugopalan *et al.*2002) or due to sequestration of blood cells in spleen and lungs (Best and Taylor (1996) and Komar *et al.* (2003). David *et al.* (1993) and Khan *et al.* (2006) reported a decrease in TLC following administration of propofol alone. Similar findings were reported by Kim J.W and I.H. Jang (1999), Ozaydin *et al.* (2001), Jagtap (2003), Bayan *et al.* (2002), and Jain (2004) in dogs. In contrast, Sharma and Bhardwaj (2010) reported increased TLC count which is augmented by Akbar *et al.* (2014) with increasing alteration in TLC upon administration of medetomidine in dogs.

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Summary

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Conclusion

"Education is the milk of tigers who

Will drink he can't stay without roaring"

6 SUMMARY AND CONCLUSION

The present clinical study was carried out on 18 clinical cases of female dogs irrespective of age and weight presented for routine surgery i.e. ovariectomy operation at the Department of Surgery and Radiology, Bihar Veterinary College, Patna to evaluate and compare the tolerability of CRI ketamine, propofol, and ketofol. The study was conducted on 18 female dogs and these animals were randomly divided into three experimental groups, each group containing six animals. The groups were designated as Group I, Group II, and Group III on the basis of the induction and maintenance agent. The animals of different groups were administered the following drugs for induction and maintenance of anaesthesia for elective ovariectomy.

All animals were pre-medicated with glycopyrrolate @ 0.01mg/kg b.wt intramuscularly followed by inj. butorphanol 0.2 mg/kg b.wt and xylazine 1mg/kg b.wt intramuscularly after 5 minutes by using different syringes. After 10 minutes of xylazine, animals were induced (till effect) with propofol, and immediately just after induction animals were maintained with constant rate infusion of ketamine, propofol, and ketofol 1:1 along with normal saline @ 10 ml/kg/hr.

During the present study various physiological, haematological, biochemical, and haemodyamic evaluations were carried out to evaluate the CRI ketamine, propofol, and ketofol in anaesthetic regimen. Sedation score and depth of analgesia were recorded and evaluated in all groups. Similarly, recovery time, sterna recumbency time, duration of surgery, and anaesthesia were also evaluated and recorded in all canines of each group. Different physiological and haemodynamic parameters like heart rate, respiratory rate, rectal temperature, diastolic blood pressure, systolic blood pressure, mean arterial pressure, haemoglobin, were recorded. Haematological parameters like haemoglobin, PCV, TLC, and DLC and biochemical parameters like serum urea nitrogen, serum glucose, serum creatinine were estimated before premedication, 10 minutes after pre-medication, 15, 30, and 60 minutes during maintenance of anaesthesia, and after recovery.

On clinical parameters, the mean values of Recovery time in groups I, II, and III were 47.17±0.94 min, 25.00±1.33 min, and 46.83±0.60 min respectively. The mean values of sternal recumbency time in groups I, II, and III were 61.17±1.81min, 36.17±1.33min, and 58.67±1.05min respectively. The mean values of duration of surgery in groups I, II, and III were 58.67±1.56

min, 59.00±0.84 min, and 57.00±1.60 min respectively and The mean values of duration of anaesthesia in groups I, II, and III were 75.5±2.04min, 73.83±2.53 min, and 77.17±1.64 min respectively.

Physiological parameters showed that the values of rectal temperature in all three groups showed a decrease at different intervals during the observation period in comparison of the baseline values.The values of respiratory rate in all three groups decreased at different intervals during an observation period in comparison to the baseline values. All three groups showed that respiratory rate value decreased significantly ($p<.05$) after pre-medication and remained significantly lower throughout the observation period. Value of heart rate significantly ($P<0.05$) increased after pre-medication in all three groups in comparisons to respective base values after that decreased but remained non-significantly ($P>0.05$) higher in group I and III, however it become non-significantly lower in group II during maintenance of anaesthesia in comparison to respective base values.

Cardiovascular parameters showed that the value of systolic arterial pressure increased significantly ($P<0.05$) after pre-medication in all three groups in comparisons to respective base values. Value of diastolic arterial pressure increased significantly ($P<0.05$) after pre-medication in groups I and II, whereas non-significantly ($p>0.05$) in group III in comparisons to respective base values. Value of mean arterial pressure increased significantly ($P<0.05$) after pre-medication in groups II whereas non-significantly ($p>0.05$) in groups I and III in comparisons to respective base values

Haemato-biochemical parameters showed that the values of haemoglobin and packed cell volume in all groups were changed non-significantly ($p>0.05$) at various time intervals in comparison to respective base values during the entire observation period. However, haemoglobin and PCV values decreased non-significantly after pre-medication and remained non-significantly lower at various intervals in comparison to respective base values during observation periods except at recovery in group II. The values of TLC in the all groups changed non-significantly ($p>0.05$) at various time intervals in comparison to respective base values during the observation period. However, changes in TLC did not show a definite pattern, and values of TEC in all groups changed non-significantly ($p>0.05$) at various time intervals in comparison to respective base values during the observation period. However, TEC values decreased non-significantly after pre-medication and remained non-significantly lower at various intervals in comparison to respective base values during observation periods except at recovery in group II.

Conclusions:

On the basis of the study the following conclusions can be drawn:

- Proper sedation, analgesia, and muscle relaxation were observed in animals of all groups
- Recovery time in the dogs of groups II was significantly lower as compared to group I and III
- Haemodynamic stability was comparatively better in group II in respect to groups I and III
- Respiratory rate and rectal temperature significantly decreased but remain within the normal range in all the groups.
- Clinco-physiological, haemodynamic and haemato-biochemical observation revealed that pre-medication with glycopyrrolate, butorphanol, and xylazine followed induction with propofol and maintenance with CRI propofol was better in comparison to other groups in the present study.

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Mini Abstract

"Life always offers you a second chance.
Its called tomorrow"

7 MINI ABSTRACT

The study was designed to investigate the anaesthetic effects of glycopyrrolate-butorphanol-xylazine premedicated using CRI of ketamine, propofol, and ketofol, to compare using ketofol in the ratio of 1:1 to study the suitability of using ketamine-propofol and ketofol for the elective ovariectomy in dogs. The study was conducted on 18 healthy female dogs divided into three groups, randomly, containing six animals in each group. The group was designated as group I, group II, and group III on the basis of the induction and maintenance agent. Glycopyrrolate was given @ 0.01mg/kg b.wt intramuscularly at right lumbar epaxial muscles followed by inj. butorphanol 0.2 mg/kg b.wt and xylazine 1mg/kg b.wt were injected intramuscularly after 5 minutes at left lumbar epaxial muscles by using different syringes. Immediately after animal was placed on the operation table and canulated with a 20 gauge intravenous catheter attached with normal saline infusion. After 10 minutes of xylazine, butorphanol, animals were induced (till effect), and immediately after induction the animals were maintained with ketamine, propofol, ketofol 1:1 volume ratio (ketamine and propofol) and propofol combination in Group I, Group II, and Group III, respectively. Immediately just after induction animals were intubated and constant rate infusion of ketamine, propofol ketofol 1:1 was started via surgical maintenance fluid normal saline @ 10 ml/kg/hr.by the microinfusion set and ended at last skin suture closed. The evaluation and comparison were done on the basis of clinic-physiological, haemato- biochemical, and haemodynamic parameters.

In all the group's various reflexes were recorded and evaluated using score systems at baseline (0 min) before premedication, 10 minutes after pre-medication, 15, 30, and 60 minutes during maintenance of anaesthesia, and 120min (after recovery). These reflexes included palpebral reflex, pedal reflex, and corneal reflex. Induction time, Duration of surgery, duration of anaesthesia (min), recovery time (min), and Sternal recumbency time (min), was also recorded.

Physiological observations like HR, RR, and RT were recorded before premedication, 10 minutes after pre-medication, 15, 30, and 60 minutes during maintenance of anaesthesia, and 120min (after recovery). Haemato-biochemical parameters namely Hb, PCV, TEC, TLC,

blood urea nitrogen, serum creatinine, and blood glucose, were measured before premedication, 10 minutes after pre-medication, 15, 30, and 60 minutes during maintenance of anaesthesia, and 120min (after recovery)of the study. Haemodynamic studies of SAP, DAP, and MAP were performed before premedication, 10 minutes after pre-medication, 15, 30, and 60 minutes during maintenance of anaesthesia, and 120 min of the study.

In all groups, the palpebral reflex was mild at 15 min in all the groups. The reflex was abolished completely at 30 min in group I, from 30 min to up to 60 min in group II and group III. Recovery time, sternal recumbency time, standing time, and duration of surgery did not reveal any significant difference among the groups. However, group II animals attained early recovery followed by group III and group I. Recovery was smooth and uneventful in group II followed by group III than other groups. Similarly, group II attained early standing than other groups. Group II had the shortest duration of anaesthesia (73.83±2.53 min) and group I (75.5±2.04min) had the longest duration of anaesthesia. Group III (77.17±1.64 min).

In general overall increase in heart rates was noticed at 10 min, after administration of pre-medication in all three groups. In the group from 10 min to 15 min heart rate decreased. Further from 15 min to 60 min, the heart rate was non-significant fluctuation up and down in group I, group II and group III. However, values were within an acceptable range. The respiratory rate decreased in all groups at all intervals from base values. Group III maintained a higher respiratory tone than other groups. However, there was a non-significant difference in respiratory rate. Rectal temperature decreased in all the groups, in which group I and group II had a significant decrease in temperature at 15 min.

In group I, group II, and group III there were no significant changes in haematological observations. All the values were within an acceptable range.

Blood urea nitrogen and plasma creatinine were recorded within the normal physiological limits in all groups. The gradual decrease in blood urea nitrogen from 10 min up to recovery but no significant difference was recorded at any time interval as compared to the baseline value. Similarly, in all groups,a non-significant marginal decrease of serum creatinine at 10 min. Blood glucose remained non-significantly higher than the baseline value at all the intervals in all groups. Group, I was showing high MAP than other groups, whereas group II had the lowest MAP than others.

Conclusions:

Based on the study the following conclusions can be drawn:

- Proper sedation, analgesia, and muscle relaxation were observed in animals of all groups
- Recovery time in the dogs of groups II was significantly lower as compared to group I and III
- Haemodynamic stability was comparatively better in group II in respect to groups I and III
- Respiratory rate and rectal temperature significantly decreased but remain within the normal range in all the groups.
- Clinco-physiological, haemodynamic and haemato-biochemical observation revealed that pre-medication with glycopyrrolate, butorphanol, and xylazine followed induction with propofol and maintenance with CRI propofol was better in comparison to other groups in the present study.

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"The roots of education are bitter but the fruit is sweet."

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Appendix

"There are to educations once should teach us how to make a living and the other how to live"

9 APPENDIX

Preparation of ketofol 1:1 ration mixture

2 ml of ketamine + 8 ml of normal saline : Each 1 ml contains 10 mg of ketamine

(10 ml contains 100 mg)

10 ml of propofol : Each 1 ml contains 10 mg of propofol

(10 ml contains 100 mg)

Dose calculation of Ketamine and Propofol:

For, Ketamine @ 300µg/kg/min = 300µg/kgX60hr =18000µg/kg/hr

For 1kg b.wt. =18mg/kg/hr =18/50=0.36ml/kg/hr

For, Propofol @ 300µg/kg/min = 300µg/kgX60hr =18000µg/kg/hr

For 1kg b.wt. =18mg/kg/hr =18/10=1.8ml/kg/hr

Commercial ketamine: each ml contains 50 mg

Commercial propofol: each ml contains 10 mg

1. Ketamin: Ketmin 50; Themis Medicare Limited, Uttarakhand, India.
2. Propofol : Nirfol 1%; Aculife healthcare private limited, Ahmedabad, Gujarat, India.
3. Normal Saline : NS : Infutec Healthcare Limited, Indore, Madhya Pradesh, India.

Table

"Summing of results provide further leads to prosperity"

Table 2: Mean ± SE values of palpebral reflex recorded in all the three groups at various time intervals.

Group	0min	10min	15min	30min	60min	After recovery
I	1±0	2±0	2.61±0.01	4±0	3.8±0.02	2.1±0.01
II	1±0	2±0	3.01±0.02	3.89±0.06	3.67±0.03	2±0
III	1±0	2±0	3.17±0.01	3.97±0.02	3.58±0.01	1±0

Table 3: Mean ± SE values of pedal reflex recorded in all the three groups at various time intervals.

Group	0min	10min	15min	30min	60min	After recovery
I	1±0	2.31±0.01	3.1±0.02	3.88±0.01	3.88±0.02	2.2±0.01
II	1±0	2.21±0.14	3.25±0.02	4±0	3.76±0.03	1.95±0.01
III	1±0	2.12±0.12	3.12±0.01	3.55±0.02	3.41±0.01	1.45±0.01

Table 4: Mean ± SE corneal reflex recorded in the animals of different groups.

Group	0min	10min	15min	30min	60min	120min
I	1±0	2.00±0.21	2.76±0.16	3.15±0.01	3.05±0.02	1.95±0.12
II	1±0	2.12±0.16	2.85±0.15	3.25±0.12	3.01±0.13	1.79±0.11
III	1±0	2.35±0.12	2.68±0.16	3.55±0.01	3.15±0.16	1.97±0.22

Table 5: Mean± SE duration of anaesthesia (min) in canines of all the three groups.

GROUP	Duration of anaesthesia(min.)
I	75.5±2.04
II	73.83±2.53
III	77.17±1.64

The value did not differ significantly ($p>0.05$) within and among the groups.

Table 6: Mean ± SE duration of surgery (min) in canines of all the three groups

GROUP	Duration of surgery(min.)
I	58.67±1.56
II	59.00±0.84
III	57.00±1.60

One value (Mean±SE) did not differ significantly ($p>0.05$) among the groups.

Table 7: Mean ± SE recovery time (min) in canines of all the three groups

GROUP	Recovery time(min.)
I	47.17 ± 0.94^{b}
II	25.00 ± 1.33^{a}
III	46.83 ± 0.60^{b}

The means with a different case superscript differ significantly ($p<0.05$).

Table 8: Mean ± SE sternal recumbency time (min) in canines of all the three groups

GROUP	Sternal recumbency time(min.)
I	$61.17\pm1.81_{b}$
II	$36.17\pm1.33_{a}$
III	$58.67\pm1.05_{b}$

The means with a different case superscript differ significantly ($p<0.05$).

Table 9: Mean ± SE values of heart rate (beat/minute) recorded in all the three groups at various time intervals.

GROUP	0min.	10 min.	15 min.	30 min.	60 min.	After Recovery
I	$99.83\pm2.21^{A}{}_{a}$	125.00 ± 8.00^{B}	$114.00\pm7.60^{AB}{}_{b}$	$117.50\pm8.33^{AB}{}_{b}$	$118.67\pm6.85^{AB}{}_{b}$	$123.17\pm3.68^{B}{}_{b}$
II	$98.83\pm2.18^{A}{}_{a}$	123.00 ± 2.10^{B}	$86.83\pm1.58^{A}{}_{a}$	$87.17\pm1.96^{A}{}_{a}$	$96.83\pm1.78^{A}{}_{a}$	$101.33\pm1.38^{A}{}_{a}$
III	$99.67\pm1.56^{A}{}_{a}$	128.33 ± 1.36^{B}	$103.00\pm7.19^{A}{}_{a}$	$106.83\pm7.53^{A}{}_{b}$	$106.83\pm8.28^{A}{}_{ab}$	$106.50\pm6.70^{A}{}_{ab}$

The means with a different upper case superscript in a row differ significantly and the means with a different lower case superscript in a column differ significantly ($p<0.05$).

Table 10: Mean ± SE values of respiratory rate (breaths/minute) recorded in all the three groups at various time intervals.

GROUP	0min.	10 min.	15 min.	30 min.	60 min.	After Recovery
I	28.50 ± 1.41^{C}	21.83 ± 0.91^{B}	17.83 ± 0.48^{A}	19.00 ± 1.29^{AB}	20.50 ± 1.57^{ABD}	24.00 ± 0.58^{D}
II	27.67 ± 1.12^{B}	23.67 ± 0.84^{A}	19.83 ± 0.48^{A}	16.67 ± 0.49^{AC}	18.67 ± 0.42^{AC}	22.00 ± 0.52^{A}
III	29.00 ± 1.32^{C}	24.67 ± 1.23^{AB}	21.00 ± 1.21^{A}	18.67 ± 1.20^{AD}	$18.67\pm0.21A^{D}$	23.00 ± 0.58^{A}

The means with a different upper case superscript in a row differ significantly and the means with no lower case superscript in a column differ significantly ($p<0.05$).

Table 11: Mean ± SE values of rectal temperature (^{0}F) recorded in all the three groups at various time intervals.

GROUP	0min.	10 min.	15 min.	30 min.	60 min.	After Recovery
I	101.89 ± 0.28^{A}	101.08 ± 0.41^{AB}	$100.31\pm0.49^{BC}{}_{ab}$	99.26 ± 0.54^{C}	98.04 ± 0.56^{D}	97.01 ± 0.33^{D}
II	102.18 ± 0.17^{A}	101.66 ± 0.16^{A}	$100.99\pm0.28^{AB}{}_{b}$	99.51 ± 0.47^{BC}	$98.27\pm0.34C^{D}$	97.27 ± 0.28^{D}
III	102.09 ± 0.19^{A}	100.96 ± 0.28^{AB}	$99.61\pm0.29^{BC}{}_{a}$	98.35 ± 0.38^{C}	97.11 ± 0.33^{D}	96.21 ± 0.35^{D}

The means with a different upper case superscript in a row differ significantly and the means with a different lower case superscript in a column differ significantly ($p<0.05$).

Table 12: Mean ± SE values of systolic arterial pressure (mm Hg) recorded in all the three groups at various time intervals.

GROUP	0min.	10 min	15 min	30 min	60 min	After Recovery
I	144.00 ± 1.21^{A}	168.16 ± 5.24^{B}	166.66 ± 7.63^{B}	$173.66\pm3.53^{B}{}_{b}$	$177.16\pm3.58^{B}{}_{b}$	156.33 ± 2.98^{AB}
II	142.50 ± 1.78^{A}	166.16 ± 4.98^{B}	153.50 ± 7.50^{B}	$142.83\pm4.13^{A}{}_{a}$	$129.50\pm3.58^{C}{}_{a}$	148.33 ± 2.98^{AB}
III	144.66 ± 1.94^{A}	164.83 ± 4.65^{B}	163.33 ± 7.52^{AB}	$171.16\pm4.07^{B}{}_{b}$	$172.66\pm4.94^{B}{}_{b}$	168.33 ± 2.98^{AB}

The means with a different upper case superscript in a row differ significantly and the means with a different lower case superscript in a column differ significantly ($p<0.05$).

Table 13: Mean ± SE values of diastolic arterial pressure (mm Hg) recorded in all the three groups at various time intervals.

GROUP	0min	10 min	15 min	30 min	60 min	After Recovery
I	101.00 ± 1.23^{A}	116.16 ± 6.50^{AB}	114.16 ± 6.45^{AB}	$123.5\pm1.40^{B}{}_{b}$	$125.00\pm3.15^{B}{}_{b}$	109.3 ± 2.83^{AB}
II	100.33 ± 1.20^{A}	113.33 ± 6.60^{B}	108.16 ± 4.19^{AB}	$105.66\pm2.95^{AB}{}_{a}$	$102.66\pm1.54^{A}{}_{a}$	110.16 ± 2.12^{B}
III	99.83 ± 1.90^{A}	114.66 ± 3.41^{AB}	111.33 ± 7.83^{AB}	$122.66\pm1.35^{B}{}_{b}$	$122.5\pm3.42^{B}{}_{b}$	107.66 ± 1.11^{AB}

The means with a different upper case superscript in a row differ significantly and the means with a different lower case superscript in a column differ significantly ($p<0.05$).

Table 14: Mean ± SE values of mean arterial pressure (mm Hg) recorded in all the three groups at various time intervals.

GROUP	0min.	10 min	15 min	30 min	60 min	After Recovery
I	115.33 ± 0.58^{AC}	133.00 ± 6.17^{BC}	$132.16\pm4.38^{BC}{}_{b}$	$140.22\pm1.65^{B}{}_{b}$	$142.38\pm3.10^{B}{}_{b}$	125.00 ± 2.24^{C}
II	114.38 ± 1.12^{AC}	130.94 ± 4.73^{B}	$123.27\pm4.38^{BC}{}_{a}$	$121.38\pm2.80^{B}{}_{a}$	$119.27\pm1.72^{BC}{}_{a}$	125.55 ± 2.19^{BC}
III	114.77 ± 1.33^{AC}	$130.88\pm4.27^{BC}{}_{b}$	$129.16\pm5.89^{BC}{}_{b}$	$138.83\pm1.15^{B}{}_{b}$	$139.22\pm3.39^{B}{}_{b}$	123.88 ± 1.46^{C}

The means with a different upper case superscript in a row differ significantly and the means with a different lower case superscript in a column differ significantly ($p<0.05$).

Table 15: Mean ± SE values of hemoglobin (mg/dL) recorded in all the three groups at various intervals of time.

GROUP	0	10	15	30	60	120
I	13.38±1.20	13.36±1.18	13.21±1.08	13.32±1.10	13.25±1.23	13.22±1.13
I	12.93±.64	12.98±.82	12.75±.63	13.23±.73	12.72±.62	13.06±.76
III	12.13±.58	11.95±.68	12.02±.47	12.02±.57	11.92±.56	12.00±.51

The value did not differ significantly ($p>0.05$) within and among the groups.

Table 16: Mean ± SE values of packed cell volume (L/L) in different groups at various time intervals are shown in table.

GROUP	0min.	10 min.	15 min.	30 min.	60 min.	After Recovery
I	40.33±3.63	39.83±3.60	39.66±3.24	39.16±3.19	39.66±3.63	39.83±3.33
II	39.50±1.99	39.83±2.68	38.33±1.68	36.00±2.13	39.16±1.49	40.16±2.07
III	37.33±1.52	36.83±1.77	36.83±1.25	36.83±1.49	35.83±1.74	36.66±1.54

The value did not differ significantly ($p>0.05$) within and among the groups.

Table 17: Mean ± SE values of values total erythrocyte count (x10 ^{12}/L) in different groups at various time intervals are shown in table.

GROUP	0min.	10 min.	15 min.	30 min.	60 min.	After Recovery
I	6.68±.59	6.61±.59	6.58±.53	6.66±.55	6.55±.55	6.63±.57
II	6.56±.31	6.51±.45	6.35±.27	6.55±.36	6.46±.26	6.58±.34
III	6.21±.26	6.10±.31	6.15±.20	6.16±.25	5.95±.28	6.15±.24

The value did not differ significantly ($p>0.05$) within and among the groups.

Table 18: Mean ± SE values of total leukocyte count (x10^9/L) in different groups at various time intervals are shown in table.

Group	0min.	10 min.	15 min.	30 min.	60 min.	After Recovery
I	9491.66	9241.66	9458.33	9366.66	9516.66	9391.66
II	9883.33	9708.33	9891.66	9366.66	9825	10150
III	11550	11483.3	11941.7	11725	11641.7	11518.3

The value did not differ significantly ($p>0.05$) within and among the groups.

Table 19: Mean ±SE values of blood urea nitrogen (BUN) (mg/dL) in different groups at various time intervals are shown in table.

GROUP	0min.	10 min.	15 min.	30 min.	60 min.	After Recovery
I	13.12±3.03	12.88±2.86	12.86±2.56	11.41±2.25	11.14±1.19	10.52±1.28
II	13.75±3.21	13.30±3.19	12.63±2.34	11.01±1.13	10.68±1.29	10.29±1.02
III	12.99±2.95	12.34±2.12	11.45±2.21	11.06±1.10	10.99±1.09	10.83±1.32

The value did not differ significantly ($p>0.05$) within and among the groups.

Table 20: Mean ± SE values of serum creatinine (mg/dL) in different groups at various time intervals are shown in table.

GROUP	0min.	10 min.	15 min.	30 min.	60 min.	After Recovery
I	1.23±.11	1.21±.10	1.22±.12	1.21±.12	1.22±.14	1.24±.19
II	1.38±.22	1.36±.21	1.35±.20	1.33±.16	1.29±.17	1.26±.16
III	1.34±.21	1.31±.21	1.28±.20	1.24±.19	1.21±.19	1.18±.19

The value did not differ significantly ($p>0.05$) within and among the groups.

Table 21: Mean ± SE values of serum glucose (mg/dL) in different groups at various time intervals are shown in table.

GROUP	0min.	10 min.	15 min.	30 min.	60 min.	After Recovery
I	78.96 ± 8.51^{A}	83.63 ± 8.71^{A}	98.34 ± 9.94^{AB}	122.90 ± 12.26^{AB}	145.57 ± 4.29^{AB}	173.38 ± 18.48^{B}
II	86.70 ± 20.79^{A}	91.94 ± 20.50^{A}	108.42 ± 20.08^{AB}	123.89 ± 21.70^{AB}	143.35 ± 5.61^{AB}	159.67 ± 27.69^{B}
III	75.31±9.10	78.88±9.03	85.19±9.94	104.55±9.59	120.59±6.87	135.58±16.20

The means with a different upper case superscript in a row differ significantly and the means with no lower case superscript in a column differ significantly ($p<0.05$).

Table 22: Mean ± SE values of asparte aminotransferase (IU/L) in different groups at various time intervals are shown in table.

GROUP	0min.	10 min.	15 min.	30 min.	60 min.	After Recovery
I	79.85±8.44	80.74±7.81	78.05±6.54	78.61±5.11	78.46±6.49	78.48±8.88
II	67.76±20.50	67.96±19.54	65.70±18.67	68.29±16.03	71.34±13.88	76.78±12.79
III	93.07±30.30	88.64±27.51	80.61±21.16	76.89±18.42	71.79±14.94	68.12±11.16

The value did not differ significantly ($p>0.05$) within and among the groups.

Table 23: Mean ± SE values of lipid peroxidation (mmol/L) in different groups at various time intervals are shown in table.

GROUP	0min.	After recovery
I	0.90±.0.32	0.95±0.26
II	0.88±0.26	0.93±0.23
III	0.45±0.15	0.63±0.27

The value did not differ significantly ($p>0.05$) within and among the groups.

Table 24: Mean ± SE values of Superoxide dismutase (U/ml) in different groups at various time intervals are shown in table.

GROUP	0min.	After recovery
I	31.28±5.2	37.15±5.9
II	27.16±3.4	34.73±9.5
III	28.78±8.5	48.80±11.9

The value did not differ significantly ($p>0.05$) within and among the groups.

Brief Bio-Data

"My final words of advice to you are educate, agitate and organize ; have faith in your self "

11

VITAE

Name	:	**Agyey Pusp**
Father's Name	:	**Sh. Ramdev Rajak**
Mother's Name	:	**Smt.Ram Day Devi**
Date of Birth	:	15.01.1994
Permanent address	:	Vill: Fatehpur, P.O: Suhird Nagar P.S: Muffasil, Dist.: Begusarai,
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Academic	**Educational Qualification**			
	School/College	**Board/University**	**Year**	**Marks (%)**
10th class	Rajkiya Krit Jk H/S Begusarai	Bihar School Examination Board, Patna	2010	66.2
12th class	G.D.College,Begusarari	Bihar School Examination Board, Patna	2012	67.2
B.V.Sc & AH	Bihar Veterinary College, Patna-14	Bihar Animal Sciences University, Patna	2018	6.844 (OGPA)

Awards : 1.3th prize in poster presentation during 27th Annual Convention of ISSGPU, held in Bihar Veterinary College, Patna-14

: 2. Certificate on Bihar State Disaster Management.

: 3. Certificate of Participation of 'National Conference of Agricultural Librarian & Users Community (NCALUC-2018)

(Agyey Pusp)
(अज्ञेय पुष्प)