CLINICO-PHYSIOLOGICAL STUDIES OF XYLAZINE AND DEXMEDETOMIDINE WITH PROPOFOL AND ISOFLURANE ANAESTHESIA IN DOG

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By

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BIHAR VETERINARY COLLEGE, PATNA-800014

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CERTIFICATE- I

This is to certify that the thesis entitled, **"CLINICO-PHYSIOLOGICAL STUDIES OF XYLAZINE AND DEXMEDETOMIDINE WITH PROPOFOL AND ISOFLURANE ANAESTHESIA IN DOG"** submitted in partial fulfilment of the requirement for the award of the degree of Master of Veterinary Science in the discipline of **VETERINARY SURGERY AND RADIOLOGY** of the faculty of Post-Graduate Studies, Bihar Animal Sciences University, Patna, is a bonafide research work carried out by **Dr. KUMARI PRASHANSA SINHA, Registration No-VM0022/2019-20**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 investigation have been fully acknowledged.

Place: Patna **(Mithilesh Kumar)**

Date: (Major Advisor)

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Place: - Bihar Veterinary College, Patna

Place _____

Date _____ **(*Kumari Prashansa Sinha*)**

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ABBREVIATIONS

%	Percent
/	Per
@	At the rate
<	Less than
=	Equal to
>	Greater than
±	Plus, or minus
°F	Fahrenheit
µL	Micro liter
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
ECG	Electrocardiography
ELISA	Enzyme- linked immune sorbent assay
et al	And others
Fig.	Figure
g/dl	Gram per deciliter
g/L	Gram per liter
GABA	Gamma Amino butyric acid
Hb	Haemoglobin
HR	Heart rate
IM	Intramuscular
IV	Intravenous
L/L	Liter per liter
MAP	Mean arterial pressure
mg/kg	Milli gram per kilogram
Min	Minute
Mm Hg	Milli meter of mercury
mmol/L	Milli mole per liter
µg/kg	Micro gram per kilogram

µIU	Micro international units
µmol	Micromole
NIBP	Non invasive blood pressure (monitor)
nmol	Nano mole
(nmol/l)	Nano mole per liter
PCV	Packed cell volume
pmol/L	Pico mole per liter
RBC	Red blood corpuscle
RR	Respiration rate
RT	Ractal 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 liter
WBC	White blood corpuscle

DEPARTMENT OF VETERINARY SURGERY AND RADIOLOGY

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Title of thesis**: CLINICO-PHYSIOLOGICAL STUDIES OF XYLAZINE AND DEXMEDETOMIDINE WITH PROPOFOL AND ISOFLURANE ANAESTHESIA IN DOG**

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ABSTRACT

The present study was carried out on eighteen clinically healthy female canines to evaluate balanced anaesthetic techniques and the suitability of xylazine and dexmedetomidine along with atropine sulphate and butorphanol as pre-anaesthetic to propofol and isoflurane anaesthesia for elective surgery in canines. Animals were randomly divided into three groups.

All animals were pre-medicated with atropine sulphate @ 0.04 mg/kg b.wt IM , after 10 minute butrophanol @ 0.2mg/ kg b.wt IM and just after xylazine @ 1 mg/kg b.wt IM in group A and dexmedetomidine @ 5µg/kg b.wt and 10 µg/kg b.wt in B and C groups respectively. The induction of anaesthesia was achieved by propofol as per requirement. The maintenance of anaesthesia was achieved by isoflurane. The study was compared on the basis of clinic physiological, haemato biochemical, haemodynamic, and electrocardiographic parameters. Adequate sedation, depth of analgesia and muscle relaxation were observed in the animals of all the groups during surgery.

Significantly lower doses of propofol were needed for induction in the groups of B and C (1.86 ± 0.16 mg/kg and 1.35 ± 0.22 mg/kg) as compared to group A (2.85 ± 0.11 mg/kg). Incidence of apnea recorded in groups A, B and C was 33.33%, 20%, and 0%, respectively soChances of apnea were more with xylazine as compared to dexmedetomidine Recovery time recorded in the canines of group B (12.4 ± 1.26 min) had non – significantly lower recovery time in comparison to group A (13.6 ± 1.32 min) and C (15.2 ± 1.14 min). Atropine sulphate – butorphanol - dexmedetomidine (10µg/kg) combination provided excellent hemodynamic stability when used as a pre- anaesthetic for induction with propofol and maintenance of anaesthesia with isoflurane than other combination.

On the basis of clinical, biochemical and cardiovascular stability 10 µg/kg dexmedetomidine is better in comparison of premedication with xylazine and 5 µg/kg dexmedetomidine along with butrophenol and atropine for induction with propofol and maintenance with isoflurane in elective surgery.

1. INTRODUCTION

Anesthesia is very important for successful surgical intervention. It must provide complete immobilization relaxation and unconsciousness. In spite of discovery of new anesthetic agents, it is difficult to achieve appropriate anesthesia by using a single anaesthetic agent. Therefore obtain perfect anesthesia developed a technique known as balanced anesthetic technique. Balanced anesthesia is the anesthetic technique in which drugs with different pharmacological groups are combined to achieve optimum anesthesia.

Atropine is the most commonly used anticholinergic drug. It blocks muscarinic receptors at the postganglionic terminations of cholinergic fibers in the autonomic nervous system. Atropine increases the incidence of cardiac dysrhythmia and sinus tachycardia in dogs (Muir, 1978). Anticholinergic have been used to preventvago-vagal reflexes and bradycardia caused by administration of α2- agonists in dogs (Ko *et al.,* 2001).Butorphanol is a synthetic opioid with agonist-antagonist properties. The analgesic potency of butorphanol is 3-5 times that of Morphine. In dogs, butorphanol causes minimal cardiopulmonary depression (Cornick and Hartsfield, 1992). Butorphanol has minimum effect on heart rate, respiratory rate and cardiovascular system (Garcia-Pereira *et al.,* 2007).Alpha-2 adrenoreceptor agonists are most commonly used sedatives in both small and large animal patients for sedation, muscle relaxation and analgesia. α-2 adrenoreceptors are located throughout the body in most organs, nervous tissue, extrasynaptically in neural tissue and vascular system.Most commonly used alpha-2 agonists in veterinary practice are xylazine, medetomidine, romifidine and dexmeditomidine.Dexmedetomidine and levomedetomidie is enantiomers of medetomidine, in which levomedetomidine pharmacologically inactive component (Mac Donald *et al*.,1991). Selectivity of alpha2 receptor than the alpha1 receptor dexmedetomidine is greater than other alpha2 agonist (Aantaa *et al*.,1993).Dexmedetomidine, an alpha 2-adrenoreceptor agonist is usually administered via the intravenous (IV) or (IM)routes in humans and animals. It produced dose-related changes in cardiopulmonary function (Granholm *et al.*,2007., Jayaraman *et al.,* 2013 and Pascoe 2015).

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).

In veterinary medicine inhalation anesthetics are widely used for the maintenance of anaesthesia. Elimination of inhalant anaesthetic agent is independent on hepatic and renal system. This is the basic advantage of these anesthetics, compared to other anesthetics

biotransformation. Morbidity and mortality of inhalant anesthetic is very low in comparison to systemic general anaesthetic agents (De Mattos *et al.,* 2011 and Steffey *et al.,* 2007).Isoflurane has highest safety margin and minimum cardiovascular effect with excellent muscle relaxation properties (Eger *et al.,* 1995). Keeping in view the characteristic features of propofol and isoflurane it is hypothesized that it can be used with opoids and alpha-2 agonists pre-anesthetic agents in dogs. The present study will therefore be designed with the following objectives.

OBJECTIVES

- **1. To evaluate the clinico–physiological, haemato-biochemical and hemodynamic effect of xylazine and dexmedetomidine with on propofol and isoflurane anaesthesia in dog.**

- **2. To study dose sparing effect of xylazine and dexmedetomidine on induction dose of propofol and incidence of apnea.**

2. REVIEW OF LITERATURE

The ideal sedative or premedication regimen would provide reliable sedation, anxiolysis, muscle relaxation and analgesia, while the influence on the haemodynamic and pulmonary function would be minimal. In addition, it would be reversible. Atropine causes blockade of acetyl choline at cholinergic fibres of CNS which reduces gastric and respiratory secretion and dilates bronchioflung. Alpha-2 adrenoceptor agonists' agents are extensively used in veterinary anaesthesiology since the late sixties with the advent of xylazine and use in cattle and horses (Clarke and Hall, 1969). Currently, α-2 adrenoceptor agonists are used in domestic and several wild species due to their effects on centrally located α-2 adrenoceptors causing sedation and analgesia.

Atropine:

Parasympatholytic or anticholinergic agent such as atropine block the cholinergic muscarinic receptors, inhibit muscarinic effects of acetylcholine. These substances also block muscarinic effects caused by stimulation of cholinergic nerves, mainly pre-sympathy postganglionic fibres (Tripathi K. D. 2013). Effects of parasimpatholytic agents like atropine sulfate block the vagus nerve stimulation and prevent the bradicardia (Alvaides *et. al.,* 2008). Atropine is an equal mixture of d and l- hyoscyamine, in which dextro form of hyoscyamine is biologically inactive. Atropine sulphate has been used as a pre-anaesthetic agent in small animals to antagonise the muscarinic effects of acetylcholine (Brock,2001). Duration of action of atropine sulphate is 60 to 90 minutes. In the dog, atropine disappears quickly from the blood, part being excreted in the urine unchanged or atropine and part metabolized by liver (Lumb and Jones, 1984).Atropine increases the heart rate, decreases myocardial oxygen supply and increase myocardial oxygen demand (Blanck and Lee, 1994). IUPAC name of atropineis (1R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]3- hydroxy-2-phenylpropionate. It is an anticholinergic agent that acts as a competitive antagonist of acetylcholine at the muscarinic receptors (Ali-Melkkila *et al.,* 1993) Intravenous administration of atropine induces its,action within 3 minutes ,whereas 10 minutes are required after intramuscular route and the effect last for 45 to 65 minutes in canines (Ko *et al*., 2012). Atropine can also be given via endotracheal tube to produce the same degree of tachycardia but shorter time of onset of tachycardia in comparison to the intravenous route. Atropine is extensively used as a premedication agent to prevent or minimize the vagal stimulation induced bradycardia. It is also used to reduce potential muscle spasm, gastrointestinal motility, salivation and respiratory secretion as well as to decrease tears production during anaesthesia (Liga and Edite, 2011).

Butorphanol:

Butorphanol is a synthetic agonist-antagonist opioid analgesic commonly used in both veterinary and human practice (Gourdon, 2008). Butorphanol provides sedation, and limited

duration analgesia for painful surgical procedures. Butorphanol is anagonist antagonist opioid extensively used in different species of animal. Butorphanol extensively used as analgesic agent in canine, feline and equine (Smith, 2008).Addition of butorphanol for basal anesthesia reduced the amount of ketamine required for induction and maintenance of anaesthesia (Rafee *et al.*, 2015). Butorphanol is biotransformed and cleared in hepatic tissue by hydroxylation, dealkylation and conjugation (Kumari *et al.*, 2017).

Butorphanol is chemically described as 1-N-cyclobutylmethyl–6,10aB–dihydroxy1,and 2,3,9,10,10 ahexahydro-(4H)10,4 aimino ethanophenanthrenetartrate. The molecular formula of butorphanolis $C_{12}H_{29}NO_2C_4H_6O_6$. Butorphanolis structurally associated with morphine and is a mixed agonist/antagonist opioid. It has potent agonist activity for k' and ó receptors and low intrinsic activity form μ receptor and it is nearly 3 to 5 times more potent with comparison to morphine (Smith, 2008).

Xylazine:

Xylazine and dexmedetomidine are α2-adrenergic receptor agonists mediate sedative, anxiolytic and analgesic effects (Pertovaara, 2013). Xylazine premedication prolonged the propofol anaesthesia in dogs. Propofol alone reduced blood pressure and transiently raised heart rate and these effect minimized, when xylazine used as pre-anaesthetic agent.

According to Dewangan *et al. (*2010), when xylazine was used as a pre-anaesthetic before propofol-isoflurane anaesthesia, time for onset of sedation, induction time, duration of anaesthesia and recovery time were 3.33±0.48 minutes, 58.50±1.54 seconds, 67.17±12.50 minutes and 18.17±1.83 minutes respectively. Jena *et al*. (2014), observed that administration of xylazine-propofol induced onset of sedation in 5.50±0.22 minutes and reported duration of anaesthesia and recovery time 72.50±3.35 and 11.17±1.14 minutes respectively under xylazine-propofol anaesthesia in dogs. Bradycardia is a common feature in canines following administration of xylazine or medetomidine. Cullen *et al.* (1993) observed hypertension in all the dogs following medetomidine administration Xylazine (2.2 mg/kg IM) provided the highest pain threshold for the first 60 minutes and a sedative effect for 105 minutes in ponies. The effects for superficial pain and visceral pain persisted 3 hours and 4 hours, respectively, and also xylazine decreased systolic, diastolic, and mean arterial blood pressures (Kalpravidh *et al.*,1984). Angel and Langer (1988) reported xylazine induces an increase in serum glucose by suppressing insulin release and stimulating glucagon release or both in β and α cells of the pancreas respectively.

Dexmedetomidine:

Dexmedetomidine generally combined with butorphanol for premedication prior to induction of general anaesthesia using propofol. Most anaesthetic drugs, such as propofol, thiopental, isoflurane and halothane have cardiovascular and respiratory side effects that are dose-dependent. Therefore, a reduction in the dose of these agents can lead to improved cardiovascular stability and contributes to the provision of balanced anaesthesia (Kuusela *et al.* 2001a). Dexmedetomidine and medetomidine produce deep sedation, muscle relaxation and analgesia and also reduce the dose of general anaesthetic agent (Dart, 1999 Murrell)

Currently dexmedetomidine is the newest and most selective α-2 adrenoceptors agonist drug used in small animals (Seddighi, 2014). It is a potent and selective α2-adrenergic agonist, the active enantiomer of medetomidine (Panzer *et al.,* 2011). The α2/α1-receptor binding selectivity indicates that the dexmedetomidine is more selective and specific α2-adrenergic receptor agonist than xylazine (Scheinin *et al*., 1989).However, similar to other α-2 adrenoceptor agonists, dexmedetomidine is associated with marked adverse effects of the cardiovascular system, which make unsuitable for administration in younger than 6 months or patient with cardiovascular disease (Ko *et al.,* 2009). Alpha-2 agonist exerts cardiovascular effect through stimulation of central and peripheral adrenoreceptors (Cullen *et al*., 1996). The main negative cardiovascular effects of all α 2-agonists include bradycardia and associated bradyarrhythmias (1st and 2nd degree atrio-ventricular heart block), a dramatic reduction in cardiac output (CO) by up to 50% and an increase in systemic vascular resistance (SVR) (Kumar *et al.,* 2020). Dexmedetomidine causes biphasic changes in arterial blood pressure (ABP) (Bloor *et al.,* 1992).It causes preoperative sympatholysis and decrease blood pressure by stimulating central alpha 2 and imidazoline receptor (Bekker *et al*., 2001 and Mack *et al*., 2004). Dexmedetomidine preserves blood flow to the most vital organs like brain, heart, liver and kidney, at the expense of organs like skin and pancreases and this distribution of blood flow is not affected by the type of anaesthesia (Kumar *et al*., 2020).Dexmedetomidine decreases vasodilatation and the subsequent reduction of MAP in isoflurane-anesthetized dogs (Ohata *et al*., 1999). It is a good anaesthetic adjuvant for general anaesthesia which reduces intra-operative isoflurane consumption, provides analgesic-sparing effect without affecting postoperative recovery profile (Muniyappa *et al*., 2016). Lower doses of dexmedetomidine (5-10 μg/kg in dogs and 10-20 μg/kg in cats) have been combined with opioid analgesics with the expectation of achieving a synergistic analgesic effect. In cats only the highest dose of dexmedetomidine (40 μg/kg) showed antinociceptive effects as observed by thermal stimulus applied on the skin (Slingsby and Taylor, 2008). Both medetomidine and

dexmedetomidine reduce the respiratory rate (Lerche and Muir 2004 and Acevedo-Arcique *et al.,* 2014).

Induction agent

General anesthesia is a total loss of all feeling in organism. It is accompanied with annihilation of pain feeling, free movements muscle relief and total loss of reflexes. During this retardation the essential body life activities are safe. Propofol has many characteristics of the ideal iv anesthetic, including a rapid, smooth induction of the anesthesia and rapid clearance from the body. Inhaled anesthetics are preferred for maintenance of anesthesia because they allow a more precise control of the anesthetics state and do so at low cost.

Propofol:

Propofol 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). Propofol infusion as 1% emulsion may be used as part of TIVA regime and has established itself as a qualified maintenance anaesthetic with a good quality recovery (De Vries *et al.,* 2013). Propofol as sole agent for TIVA is generally unsatisfactory, since its poor analgesic property. Consequently, it is necessary to supplement propofol with an analgesic and muscle relaxant (Kurum *et al*., 2013). 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). Extra hepatic mechanism contributes to the total clearance of propofol from the blood (Adam *et al.,* 1983). No significant changes in heart rate and systolic blood pressure in dogs following propofol injection (Kittleson and Oliver, 1983). Pharmacokinetic properties of propofol in human patients and stated that propofol had a very rapid rate of metabolic clearance from the body (Cockshott *et al.,*1985).Kittleson and Oliver (1983) reported no significant changes in heartrate andsystolicblood pressurein dogs following propofol injection. Searl *et al.* (1985) reported non-significant alterations either in hematological or biochemical parameters following propofol anesthesia.Dundee *et al.* (1986) observed no abnormalities in liver function following propofol anaesthesia.

Propofol is a unique non-barbiturate, non-steroid, short-actingnon-water-solublehypnotic general intravenous anaesthetic agent (Hofmeister *et al*., 2008).The empirical formula of propofol is C12H18O(2,6-diisopropylphenol) 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*etal*.,2015).

\Maintenance of anesthesia

Isoflurane:

Isoflurane has been used frequently as an inhalant anesthetic in animals and human because of it physical and chemical properties, such as low blood gas partition coefficient and it has no anycardiac arrhythmogenic effect (Steffey *et al.,*1977 and Eger, 2005). Brain and tissues, establishing the anesthetic state more consistently and faster than administration through the lungs (Eger and MacLeod, 1995). Furthermore, it has been suggested that the amount of anesthetic drug necessary to establish anesthesia may be significantly reduced, which may potentially decrease both the incidence of side effects and costs (Krahn *et al.,* 2012).

Isoflurane decreases cytokine production in lymphocytes and NK cell activity (Markovic *et al*., 1993) and can also induce apoptosis of lymphocytes (Matsuoka *et al*., 2001).Inhalant anesthetics for maintenance of anesthesia is preferred because of better quality and control over anaesthetic depth and ability to accurately titrate the dose administered (Pottie*et al*., 2007) as compared to intravenous anaesthesia or, even total intravenous anesthesia.Although induction with short acting intravenous anesthetics agents and maintenance with inhalant anesthetics is the preferred method of general anaesthesia in most species of animals, but it is not practicable under field conditions especially in India where the costly equipment required for administration of inhalant anesthetics is not available (Dar K. H. and Gupta A. K. 2015).

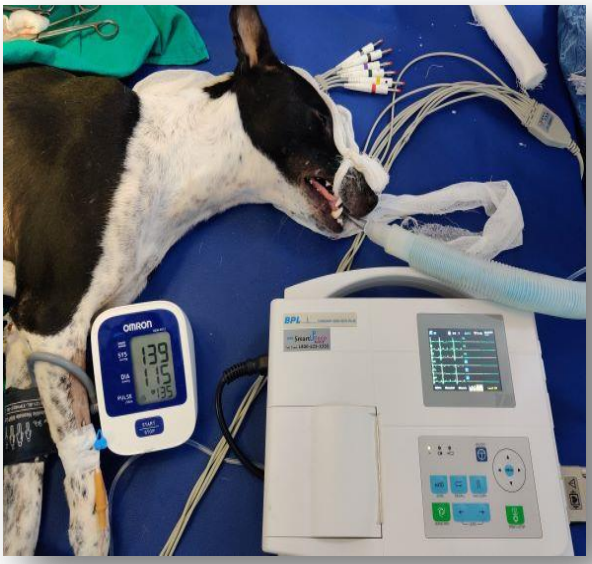

Image 1. Recoding of BP and ECG

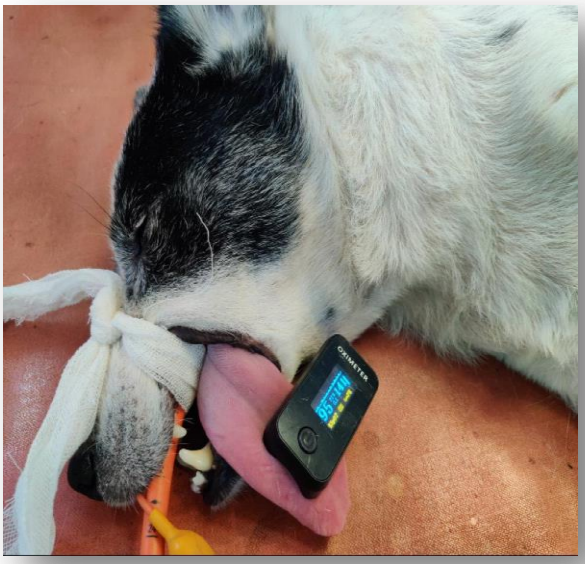

Image 2. Recoding of SPO2

Image 3. Haematological parameter evaluated auto analyzer

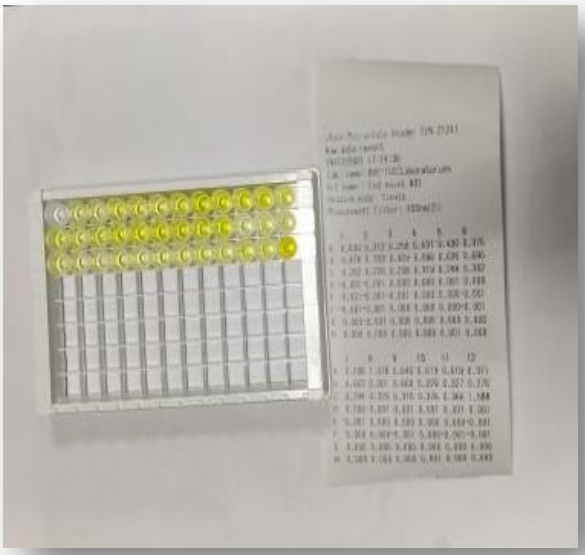

Image 4. Result of ELISA

3. MATERIALS AND METHODS

The research work was done in the Department of Veterinary Surgery and Radiology, BVC Patna -14. The dogs brought for soft tissue elective surgery scanned with ultrasonography and Radiography for any abnormality for this study after obtaining written consent from the respective owners.

Design and grouping of experiment

The animals was randomly divided into three groups with different Study Population: 18 adult client owned dogs of either sex presented to the department of Veterinary Surgery and Radiology for elective surgery (physical status I as per American Society of Anaesthesiologists Classification), (Daabiss 2011). The animals was randomly divided into 3 groups, viz. Group A, B and C.

Protocol of anesthesia

Table – 1: Anesthetic drug combination used in dog of different groups

Grp	No. of dogs	Premedication agents	Induction agents (IV)	Maintenance agent
A	6	Atropine sulphate@ (0.04 mg/kg b.wt IM) Butorphanol@ (0.2 mg/kg b.wt IM) Xylazine@ (1 mg/kg b.wt IM)	Propofol as per requirement	Isoflurane
B	6	Atropine sulphate@ (0.04 mg/kg.bwt IM) Butorphanol@ (0.2 mg/kg b.wt IM) Dexmedetomidine@ (5µg /kg b.wt IM)	Propofol as per requirement	Isoflurane
C	6	Atropine sulphate@ (0.04 mg/kg b.wt IM) Butorphanol@ (0.2 mg/kg b.wt IM) Dexmedetomidine @(10µg /kg b.wt IM)	Propofol as per requirement	Isoflurane

IM: Intramuscular route, IV: Intravenous route

Pre-operative Preparation

The dog was subjected to preoperative check-upclinical,physiological and haemato-biochemical parameters. The dog was kept in fasting for minimum 12 hours prior to the trial of anaesthesia.

Protocols

Pre-anaesthetic agent

The induction of pre-anaesthetics, first give atropine sulphate @ 0.04 mg/kg b.wt IM in all groups, after 10 minutes give butrophanol @ 0.2mg/ kg b.wt IM in all groups just after give xylazine @ 1 mg/kg b.wt IM in first group and dexmedetomidine @ 5µg/kg b.wt and 10 µg/kg b.wt in second and third group respectively.

Induction and Maintenance of anaesthesia

The induction of anaesthesia was achieved by propofol as per requirement, after premedicated with atropine sulphate- butrophanol and xylazine in Group A and atropine – butorphanol and dexmedetomidine combination in Group B and also Group C. The maintenance of anaesthesia was achieved by isoflurane.

Observation and parameters to be studied

Physiological observations

The Physiological observations such as rectal temperature, respiratory rate, heart rate and oxygen saturation measured before pre-anaesthetic administration,5 minutes after premedication, Immediately after induction with propofol, 20 and 40 minutes during maintenance with isoflurane and just after extubation.

Rectal temperature

The rectal temperature was measured using a clinical thermometer.

Respiratory rate

Respiratory rate (breaths/minute) was recorded by counting the movement of the thorax of animal and rebreathing bag.

Heart rate

Heart rate (beats/minute) was recorded by non- invasive blood pressure (NIBP)

Oxygen saturation of haemoglobin

Oxygen saturation of haemoglobin was recorded by pulse oximeter of veterinary multi- parameter monitor.

Clinical parameters

The clinical parameters such as depth of analgesia, jaw relaxation, salivation measured before pre-anaesthetic administration,5 minute after premedication, Immediately after induction with propofol, 20 and 40 minute during maintenance with isoflurane and just after extubation. Also measured dose of propofol for induction, incidence of apnoea, urination, recovery time, sternalrecumbency time, standing time, duration of surgery and duration of anaesthesia.

Depth of Analgesia

The subjective evaluation of analgesia was graded from 0 to 3 by observing the extent of animal reaction after the pinching of pin at the inter – digital skin of the hind foot of the animal (**Ahmad *et al.*, 2013).**

Subjective observations of analgesia	Score scale
Intact and strong reaction	0
Weak reaction (Canine responding slowly)	1
Very weak reaction (Slow and occasional response)	2
Reaction abolished completely(no response)	3

Jaw relaxation

Relaxation of the jaw was taken as measured of muscle relaxation and was recorded. (**Ahmad *et al.*, 2011).**

Subjective observation of jaw relaxation	Score scale
Not allowing to the open the jaws	1
Resistance to opening the jaws and closed quickly	2
Less resistance to opening of jaws and closed slowly	3

No resistance and jaws remain open	4

Salivation

The subjective observations was graded from 0 to 3 according to the following scales of salivation **(Overall, 2013)**

Subjective observation of salivation	Score scale
No salivation	0
Mild salivation	1
Moderate salivation	2
Excessive salivation	3

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. The reflexes were graded on a1to 4 scoring scales as:

Subjective observation of palpebral reflex	Score scale
Intact and strong reflex (quick blink)	1
Intact but weak reflex (slow response)	2
Very weak reflex (very slow and occasional)	3
Abolished reflex	4

Dose of propofol for induction

Total dose (mg/kg b wt) required for induction in canine with propofol will be recorded in each animal.

Incidence of apnea

Incidence of apnea was recorded during or after induction with propofol.

Recovery time

The time from the closure of supply of isoflurane to time of appearance of pedal reflex.

Duration of anaesthesia

The time from the abolitions of pedal reflex of the animal to the time of reappearance of pedal reflex.

Duration of surgery

Time elapsed from beginning of incision for surgery to till the completion of suturing of skin.

Sternal recumbency time

The time from the closure of supply of isoflurane to spontaneous attaining of the sternal recumbency.

Any other observation:

Urination was also recorded during the period of anaesthesia.

Hematological observation

2.5 ml blood collected in EDTA vial for hematological observation. The collection of blood was done before pre-anaesthetic administration, 5 minutes after premedication, Immediately after induction with propofol and 40 minutes during maintenance with isoflurane and just after extubation. To determine Hemoglobin (Hb), PCV, TLC and DLC using standard procedures.

Haemoglobin (Hb)

Haemoglobin was evaluated by using Auto analyser. Haemoglobin value was expressed in g/L.

Packed cell volume (PCV)

PCV was evaluated by Auto analyser. Packed cell volume was expressed in L/L

Total Erythrocyte count(TEC)

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

Total leukocyte count (TLC)

TLC was evaluated by Auto analyser. The values were expressed as 10^3/µL.

Differentia leukocyte count (DLC)

DLC was evaluated by Auto analyser. The values were expressed in percent (%).

Biochemical observations

The blood samples collected in sodium fluoride vials were centrifuged at 3000 revolutions per minute for 15 minutes. The serum was isolated and samples store dat-20pC until samples assayed for biochemical observations. Serum samples were used for the

estimation of following parameters:

Blood urea nitrogen (BUN)

Blood urea nitrogen was estimated by Auto analyser. The values were expressed in mg/dL.

Blood glucose

The blood glucose was estimated by glucose Auto analyser. The values were expressed in mg/dL.

Plasma creatinine

Plasma creatinine was estimated Auto analyser. The values of plasma creatinine were expressed in mg/dL.

Alanine amino transferase (*ALT*)

ALT was estimated by Auto analyser. The values of ALT were expressed in IU/L.

Serum Aspartate Amino transferase (AST)

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

Cortisol

Cortisol was estimated by ELISA. The values of Cortisol were expressed in (nmol/l)

Insulin

Insulin was estimated by ELISA. The values of Insulin were expressed in (µU/ml)

Hemodynamic observations

Blood pressure

The cuff of the non invasive blood pressure (NIBP) monitor was applied around the limb of animal for monitoring of systolic, diastolic and mean arterial pressures. The recording of these parameter will be done before pre-anaesthetic administration, 5 minutes after premedication, Immediately after induction with propofol, 20 and 40 minutes during maintenance with isoflurane and just after extubation.

1) Systolic Arterial Blood Pressure (SAP) in the mm Hg.
2) Diastolic Arterial Blood Pressure (DAP) in the mm Hg.
3) Mean Arterial Blood Pressure (MAP) in the mm Hg.

Electrocardiographic observations

Electrocardiographic recording was made before pre-anaesthetic administration, 5 min after premedication, Immediately after induction with propofol, 20 and 40 min during maintenance with isoflurane and just after extubation by multi parameter monitor in right lateral recumbency of animal.

P wave :- Amplitude and duration.

R wave :- Amplitude and duration

PR interval

ST interval

QT interval

Amp of T wave

Statistical Analysis

ANOVA (Analysis of variance) and Duncan's multiple range test (DMRT) were used to compare the means at different time intervals between different groups.

(Snedecor and chochran, 1994)

The subjective data generated from the scoring was analyzed by Turkey HSD testing among groups and within each group.

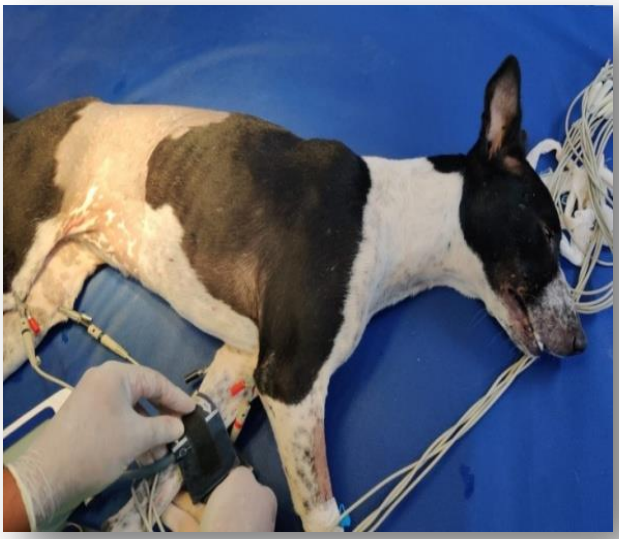

Image 5. Recoding of clinical parameter before surgery

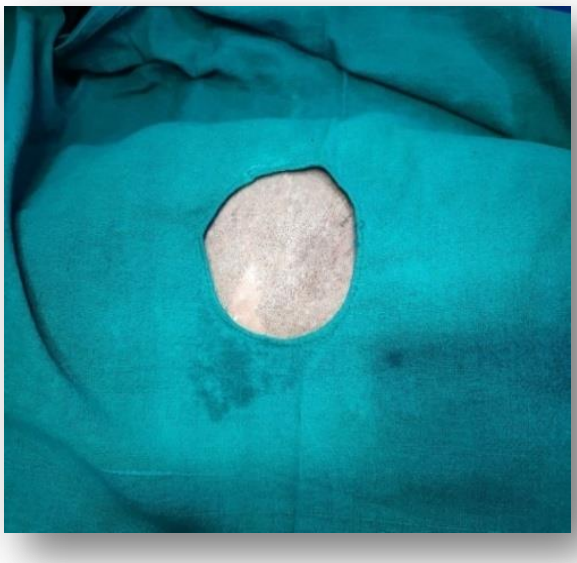

Image 6. Aseptic preparation of surgical site

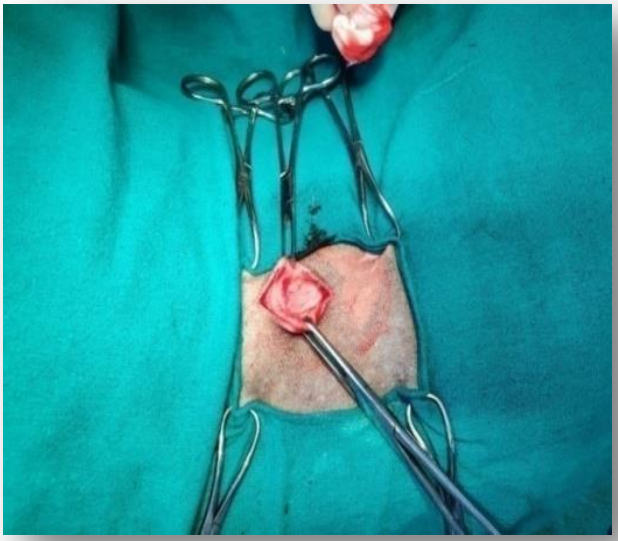

Image 7. Incision on right flank for ovariohysterectomy

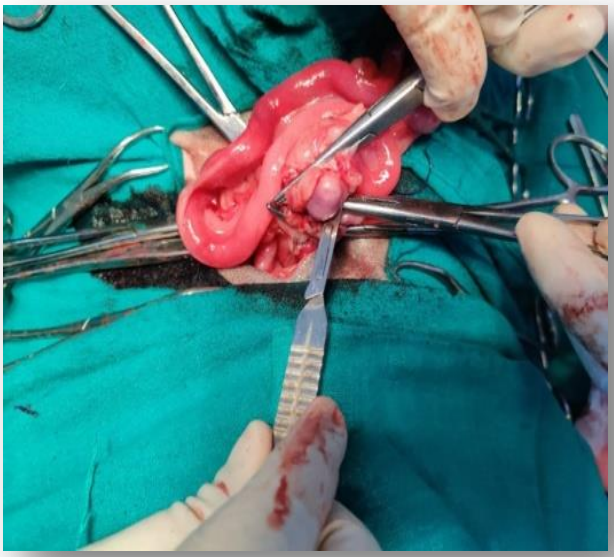

Image 8. ligation of ovarian blood vessels

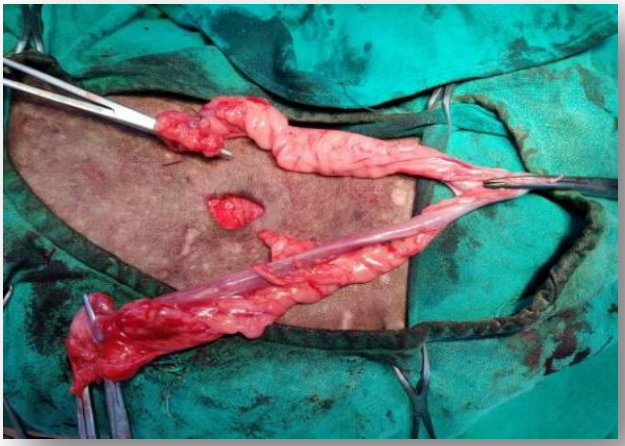

Image 9. Left and right horn of the uterus

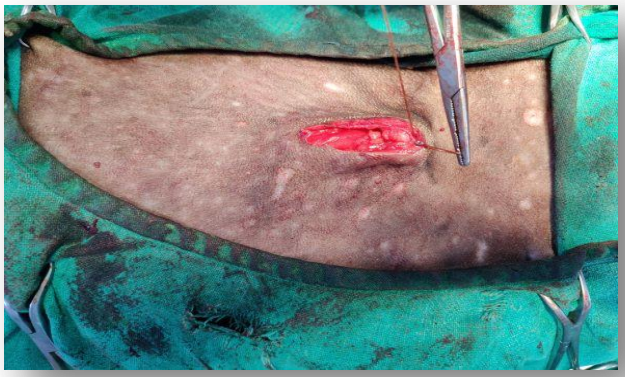

Image 10. Suturing of incision site

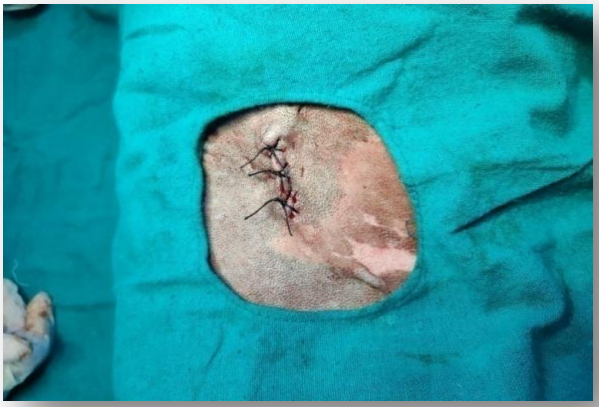

Image 11. Completion of surgery

4. RESULTS

Physiological Observations

Rectal Temperature (^{0}F)

Table 2: Mean ± SE values of the rectal temperature (^{0}F) recorded in all the three groups at different intervals. (Figure no.- 1)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	T40	At extubation
A	101.06^{a}± 0.91	100.78^{a}± 1.06	99.8^{ab}± 3.4	99.12^{ab}± 2.3	97.98^{b}± 3.28	97.9^{b}± 1.07
B	101.64^{a}± 1.31	101.1^{a}±1.13	100.14^{ab}±3.57	98.74^{bc} ±2.38	97.26^{dc}±2.24	96.1^{d}±1.94
C	101.56^{a}± 1.22	100.42^{ab}±2.5	99.4^{bc}±1.78	98.48^{bcd}±1.02	97.18^{d}±1.08	97.46^{c}±0.95

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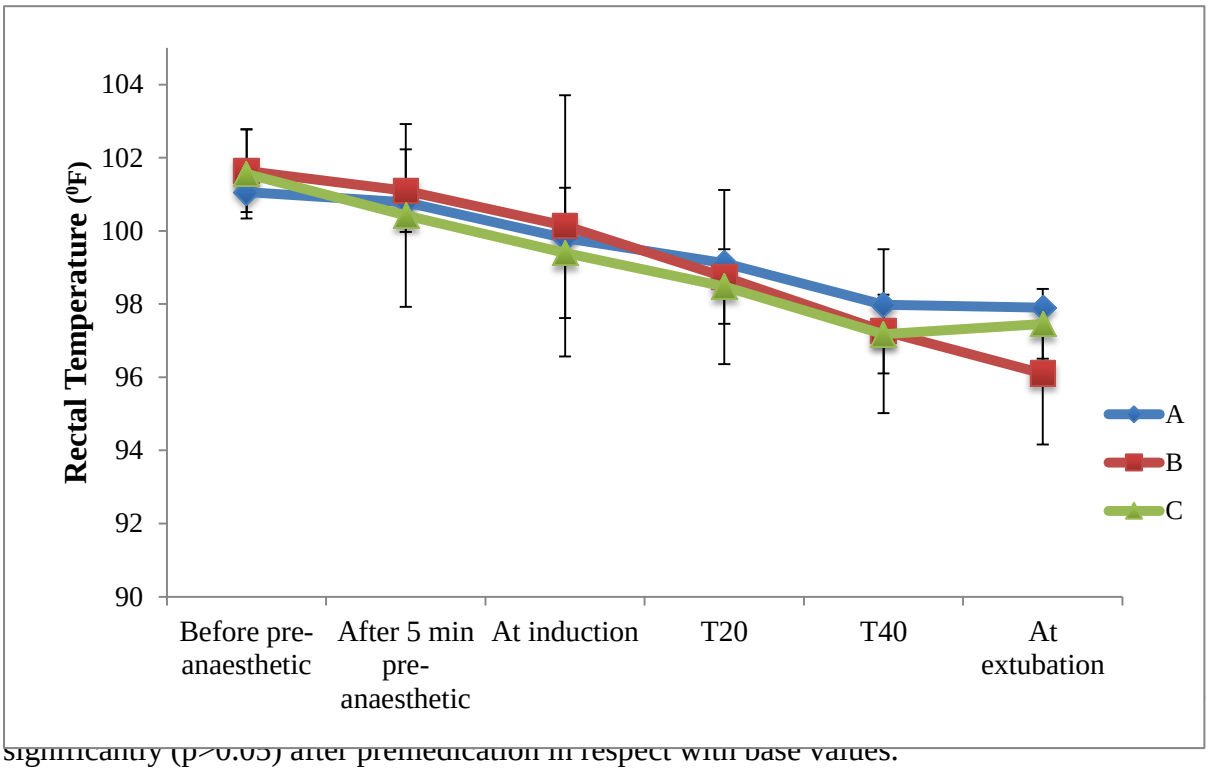

significantly ($p>0.05$) after premedication in respect with base values.

Rectal temperature in group A was decreased non- significantly up to T20 in respect of base values, after that values decreased significantly ($p<0.05$) during observation period. In group B rectal temperature was decreased non- significantly from premedication to induction, after that decreased significantly up to entire observation period. However, in group C decreased was significant from induction to entire observation period in respect to base

values.

Comparison in between the different groups showed that rectal temperature non- significantly ($p>0.05$) changed at various intervals during the observation period.

Respiration Rate

Table 3: Mean ± SE values of respiratory rate (breaths/minute) recorded in all the three groups at different intervals. (Figure no.- 2)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	T40	At extubation
A	$27.2^{a}\pm 1.35$	$21.8^{b}\pm1.28$	$12.2^{c}\pm1.42$	$16.2^{c}\pm0.48$	$15.6^{c}\pm0.67$	$23^{ab}\pm1.09$
B	$26.4^{a}\pm 1.93$	$21.6^{b}\pm1.69$	$12.6^{c}\pm1.4$	$15.4^{c}\pm0.4$	$15.1^{c}\pm0.50$	$21.6^{b}\pm0.81$
C	$27.4^{a}\pm0.74$	$18.4^{b}\pm0.81$	$10^{c}\pm0.70$	$16.4^{b}\pm0.97$	$15.2^{b}\pm0.48$	$22^{d}\pm0.94$

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

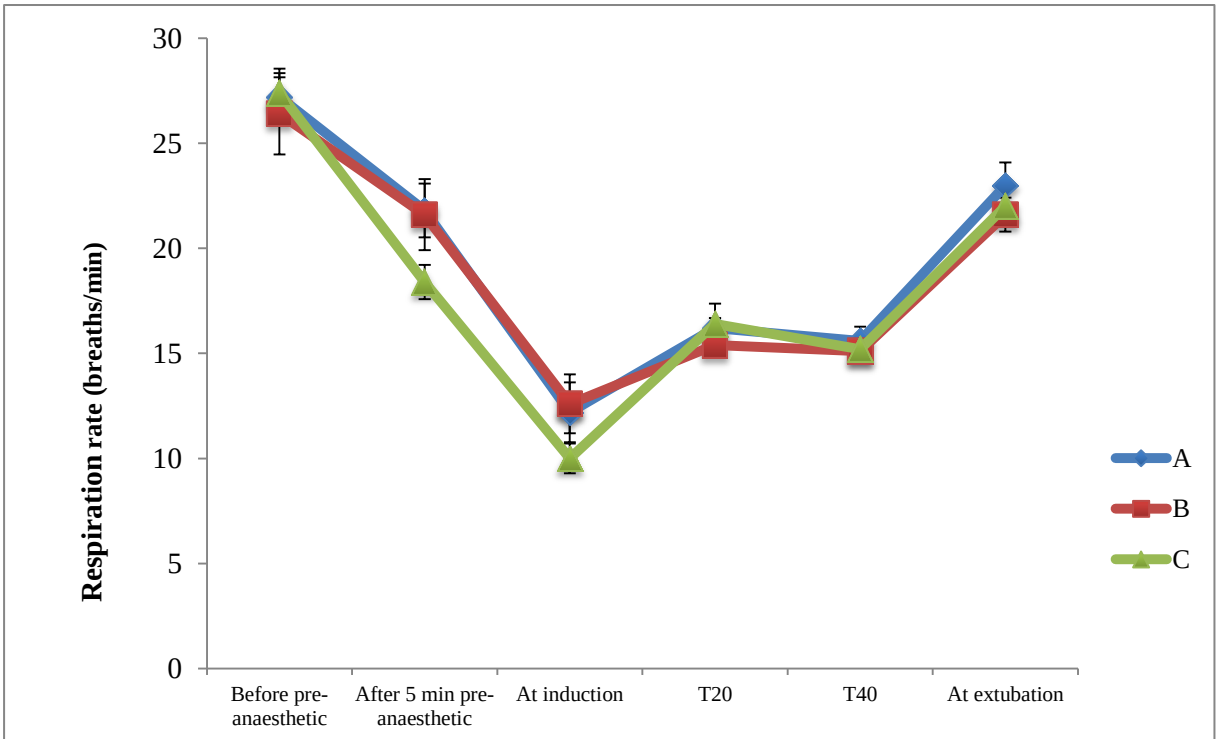

Figure 2: Mean ± SE values of respiration rate (breaths/min) recorded in different groups at various time intervals.

The value of respiratory rate (breaths/minute) in all three group was decreased significantly ($p<0.05$) up to T40 during maintenance of anaesthesia with isoflurane in comparison to base value. Respiratory rate in the groups A was decreased significantly ($p<0.05$) after premedication during observation period except at extubation in comparison to base values. Whereas in the groups B and C respiratory rates were decrease significantly ($p<0.05$) after premedication up to entire observation period in comparison to base value. Result also showed that respiratory rate significantly lower at induction in comparison to premedication in all three groups.

Comparison between different groups showed that respiratory rate (breaths/minute) value was non-significantly ($p>0.05$) change at different stage during the entire observation period.

Heart Rate

Table 4: Mean ± SE values heart rate (beats/minute) recorded in all the three groups at different intervals. (Figure no.- 3)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	T40	At extubation
A	$120.2^{a}\pm1.56$	$119.8^{bc}\pm2.15$	$104.2^{a}\pm1.62$	$105.6^{bc}\pm2.03$	$114.4^{ac}\pm3.31$	$103.6^{bc}\pm2.13$
B	$118.6^{ad}\pm1.72$	$147.4^{b}\pm2.29$	$114.6^{a}\pm3.37$	$104.8^{dc}\pm2.65$	$117.2^{a}\pm4.96$	$100^{c}\pm2$
C	$119.8^{a}\pm1.28$	$136.8^{b}\pm1.98$	$115.8^{a}\pm4.36$	$101.2^{cd}\pm1.85$	$111^{ac}\pm3$	$97.4^{d}\pm1.77$

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

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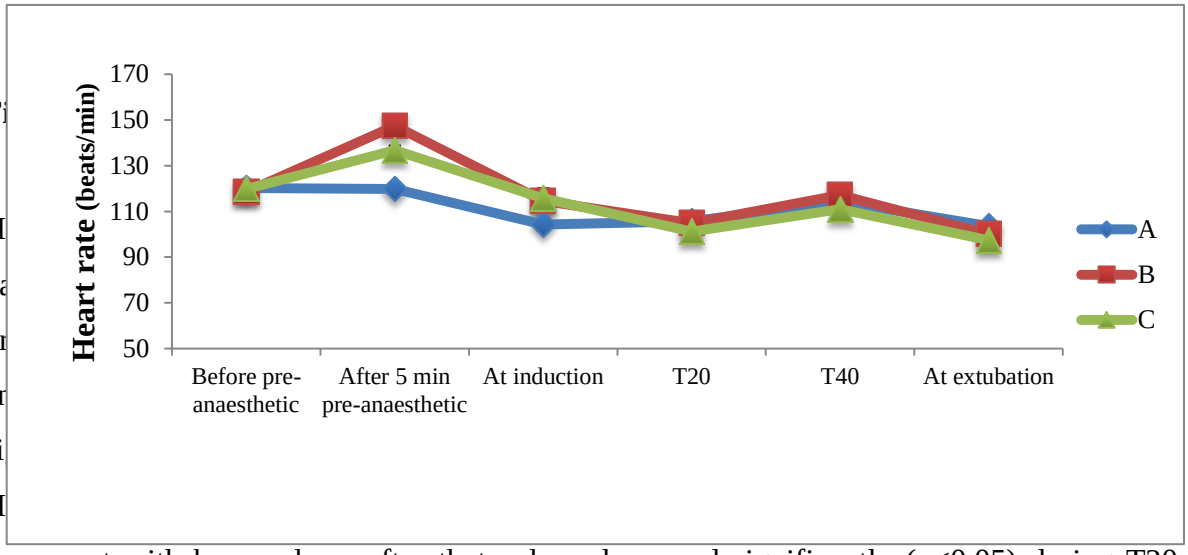

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in respect with base values, after that values decreased significantly (p<0.05) during T20 from pre- anaesthetic than values increased from T20 to T40 significantly in group B and non-significantly in group C, at the time of recovery value was decreased significantly (p<0.05) from T40.

Comparison between different groups showed that Heart rate (beats/minute) value was non-significantly (p>0.05) change at different stage during entire observation period.

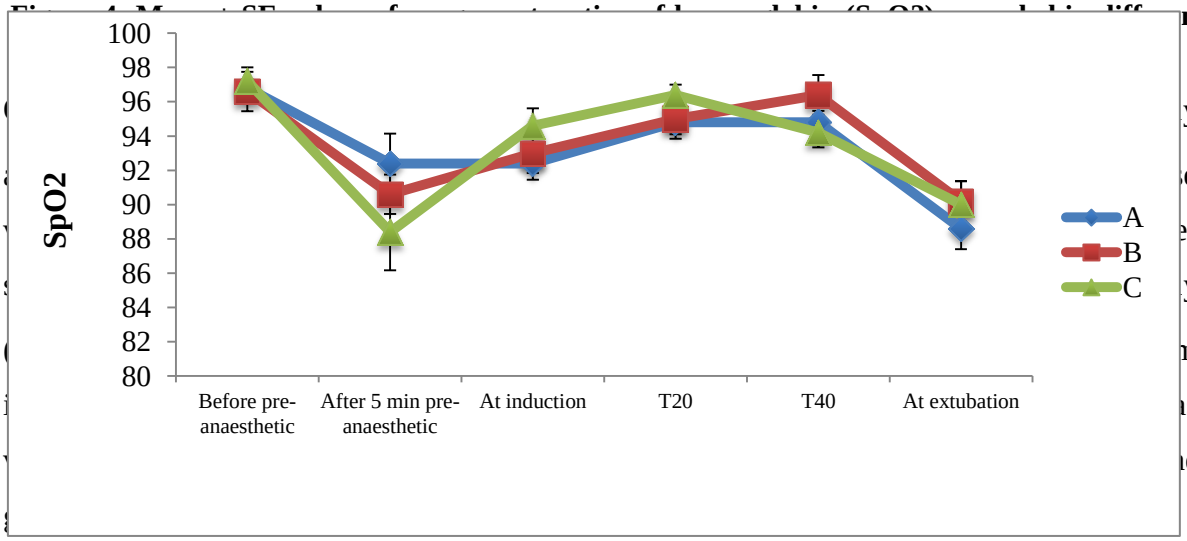
Oxygen Saturation of Haemoglobin (SpO_2)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	T40	At extubation
A	$96.8^{a}\pm0.58$	$92.4^{acA}\pm0.67$	$92.4^{acA}\pm1.50$	$94.8^{ab}\pm1.06$	$94.8^{a}\pm0.73$	$88.6^{c}\pm1.50$

B	96.6 ^{a}±0.50	90.6^{bB}±1.74	93 ^{ab}±0.94	95 ^{a}±0.70	96.4 ^{a}±0.67	90.2^{b}±1.2
C	97.2 ^{a}±0.8	88.4 ^{bC}±2.24	94.6 ^{acB}±1.02	96.4 ^{a}±0.6	94.2 ^{ac}±0.86	90^{c}±1.37

Table 5: Mean ± SE values of oxygen saturation of haemoglobin (SpO_2) recorded in all the three groups at different intervals. (Figure no.- 4)

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



Comparison between different groups showed that Oxygen Saturation of Hemoglobin value was significantly ($p<0.05$) change at 5 minutes after premedication in group A, B and C where as in groups A and C value significant ($p>0.05$) change observed at induction.

CLINICAL OBSERVATIONS

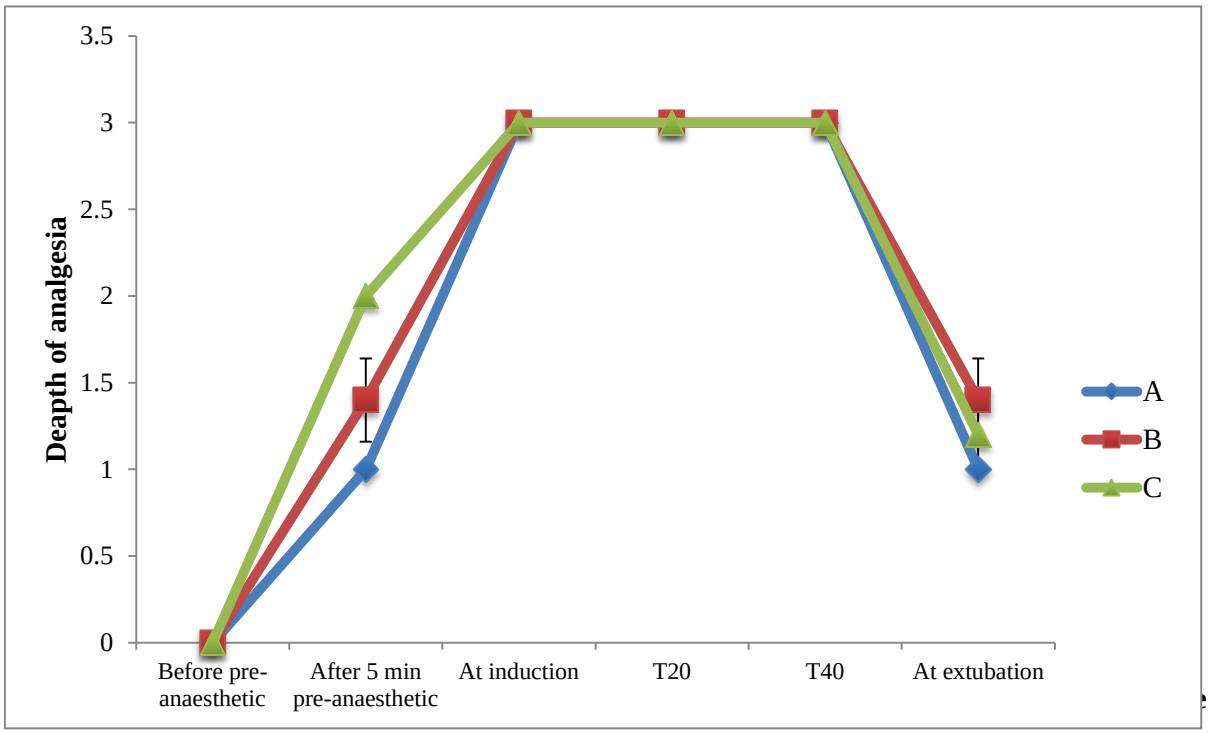
Depth of Analgesia

Table 6: Mean ± SE values of Depth of Analgesia recorded in all the three groups at

different intervals. (Figure no.- 5)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	T40	At extubation
A	$0^{a}\pm0$	$1^{bA}\pm0$	$3^{c}\pm0$	$3^{c}\pm0$	$3^{c}\pm0$	$1^{bA}\pm0$
B	$0^{a}\pm0$	$1.4^{bB}\pm 0.24$	$3^{c}\pm0$	$3^{c}\pm0$	$3^{c}\pm0$	$1.4^{bB}\pm0.24$
C	$0^{a}\pm0$	$2^{bC}\pm0$	$3^{c}\pm0$	$3^{c}\pm0$	$3^{c}\pm0$	$1.2^{dAB}\pm0.2$

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



intervals.

The value of depth of analgesia in all three-group increased significantly ($p<0.05$) after pre-medication in respect to base values. At induction depths of analgesia became maximum

and remain maximum throughout maintenance of anaesthesia. But at the time of recovery value was significantly lower in compare to values at induction to maintenance of anaesthesia.

Comparison between different groups showed that depth of analgesia value was significantly ($p<0.05$) change at 5 minutes after premedication, then value was non – significantly change from induction to maintenance of anaesthesia in between all groups. However, value was significantly ($p<0.05$) higher at extubation in group B comparison to group A.

Jaw relaxation

Table 7: Mean ± SE values of jaw relaxation recorded in all the three groups at different intervals. (Figure no.- 6)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	T40	At extubation
A	$1^{a}\pm0$	$1.8^{bA}\pm0.2$	$4^{c}\pm0$	$4^{c}\pm0$	$4^{c}\pm0$	$2.4^{d}\pm0.24$
B	$1^{a}\pm0$	$2.4^{bB}\pm0.24$	$4^{c}\pm 0$	$4^{c}\pm0$	$4^{c}\pm0$	$2.2^{b}\pm0.2$
C	$1^{a}\pm0$	$3.4^{bC}\pm0.24$	$4^{c}\pm0$	$4^{c}\pm0$	$4^{c}\pm0$	$2.2^{d}\pm0.2$

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

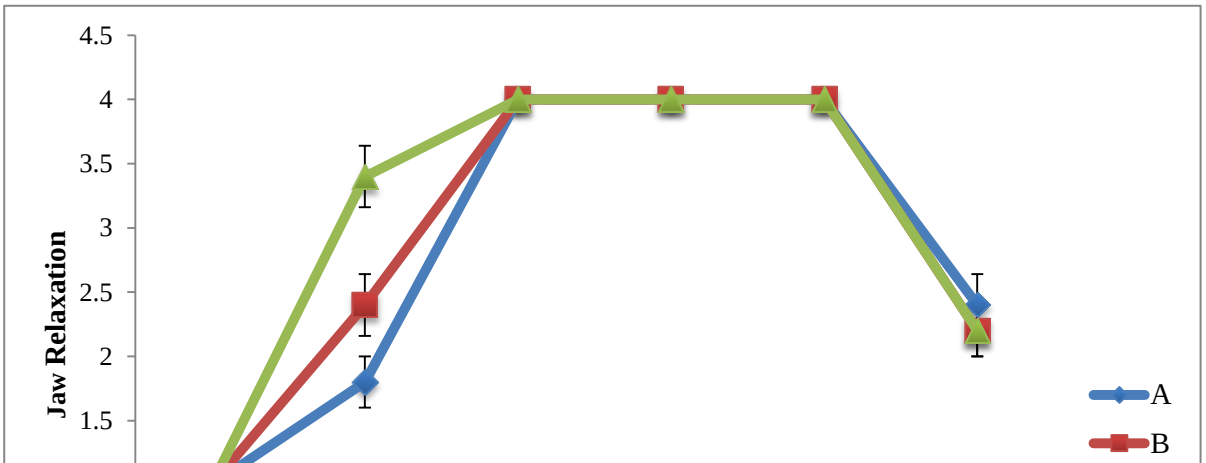


Figure 6: Mean ± SE of Jaw relaxation scores recorded in different groups at various time intervals.

The value of jaw relaxation in all three groups increased significantly ($p<0.05$) are after pre-medication to induction from base value. At induction value is maximum and remain same throughout maintenance of anesthesia. At the time of recovery value is significantly decreased compare to previous value. Comparison between different groups showed that jaw relaxation value was significantly ($p<0.05$) change in the three groups after premedication, whereas value was non – significantly change all the three groups at induction to entire observation at different stage.

Palpebral Reflex (Sedation Score)

Table 8: Mean ± SE values of palpebral reflex recorded in all the three groups at various time intervals. (Figure no.-7)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	T40	At extubation
A	$1^{a}\pm0$	$1.8^{bA}\pm0.2$	$4^{c}\pm0$	$4^{c}\pm0$	$4^{c}\pm0$	$2.4^{d}\pm0.24$
B	$1^{a}\pm0$	$2.4^{bB}\pm0.24$	$4^{c}\pm 0$	$4^{c}\pm0$	$4^{c}\pm0$	$2.2^{b}\pm0.2$
C	$1^{a}\pm0$	$3.4^{bC}\pm0.24$	$4^{c}\pm0$	$4^{c}\pm0$	$4^{c}\pm0$	$2.2^{d}\pm0.2$

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

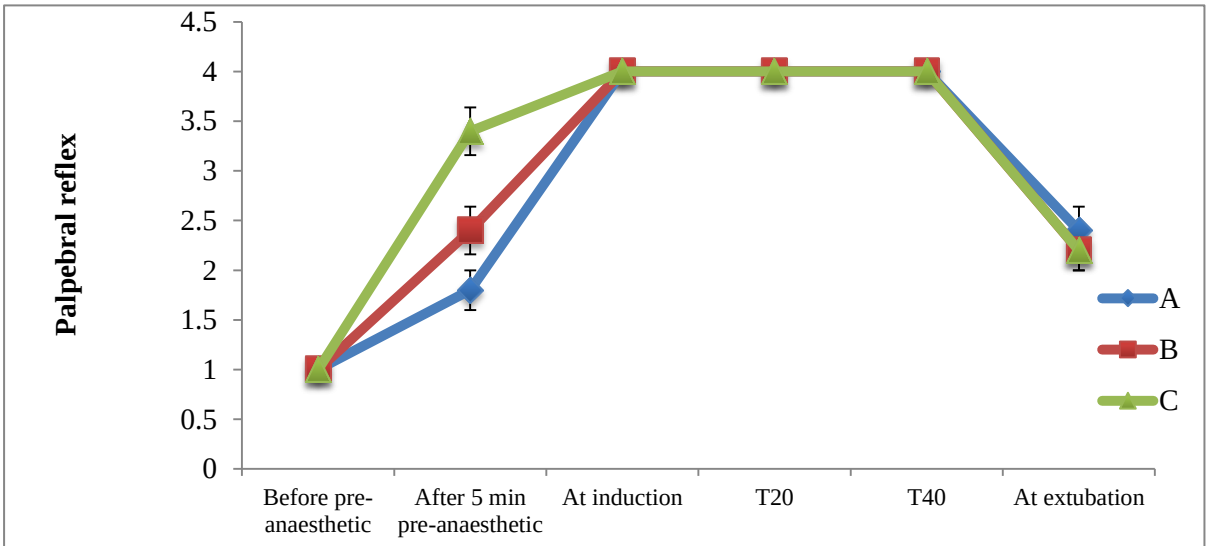


Figure 7: Mean ± SE values of palpebral reflex recorded in all the three groups at various time intervals.

The palpebral reflex in all three groups increased significantly after pre-medication to induction from base value. At induction value is maximum and remain same through out maintenance of anesthesia.

Dose of Propofol

Table 9: Mean ± SE dose of propofol for induction (mg/kg) recorded in all the three groups at different intervals. (Figure no.- 8)

Group	A	B	C
	2.85^{a} ±0.11	1.86^{b} ±0.16	1.35^{b} ±0.22

The means with a different superscript differencing significantly

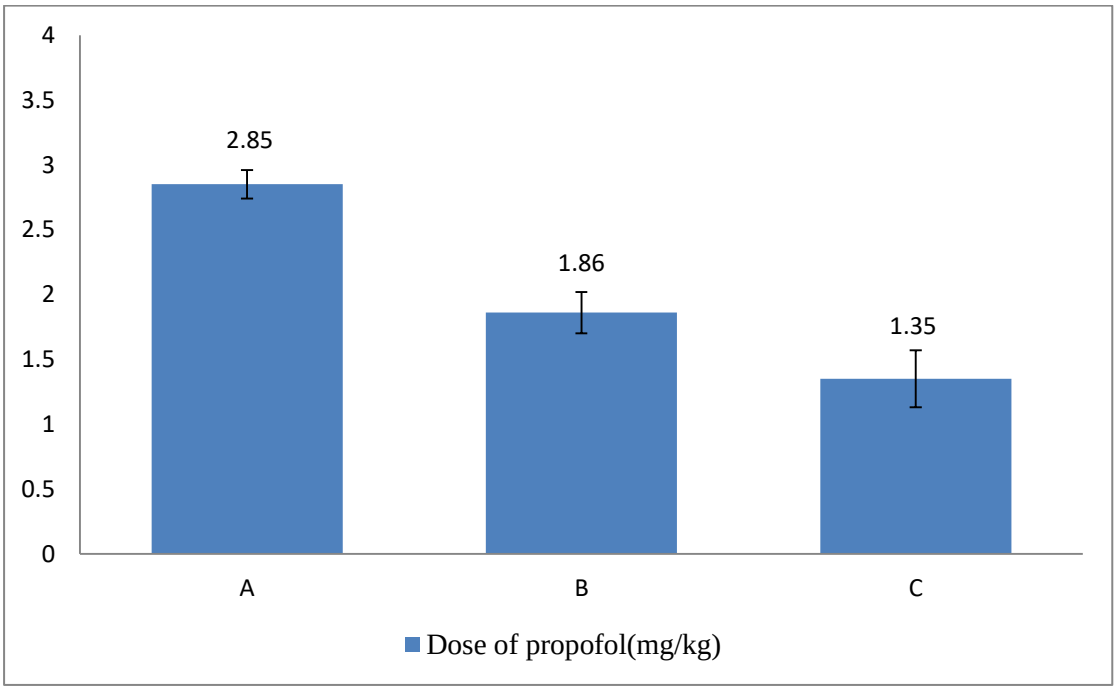


Figure 8: Mean ± SE dose of propofol for induction (mg/kg) recorded in different groups at various time intervals.

Mean ± SE doses of propofol in groups A, B and C were 2.85 ± 0.11 mg/kg, 1.86 ± 0.16 mg/kg and 1.35 ± 0.22 mg/kg respectively.

Comparison between groups showed that dose of propofol for induction of anaesthesia in groups A was significantly($P<0.05$) higher in compare to the groups B and C. comparison between groups also showed that group B required non- significantly higher induction dose of propofol in comparison to group C.

Incidence of apnea

Table 10: Incidence of apnea after induction in all the three groups. (Figure no.- 9)

Group	A	B	C
Yes	2	1	0
No	4	5	6
Total	6	6	6

The means with a different superscript differencing significantly

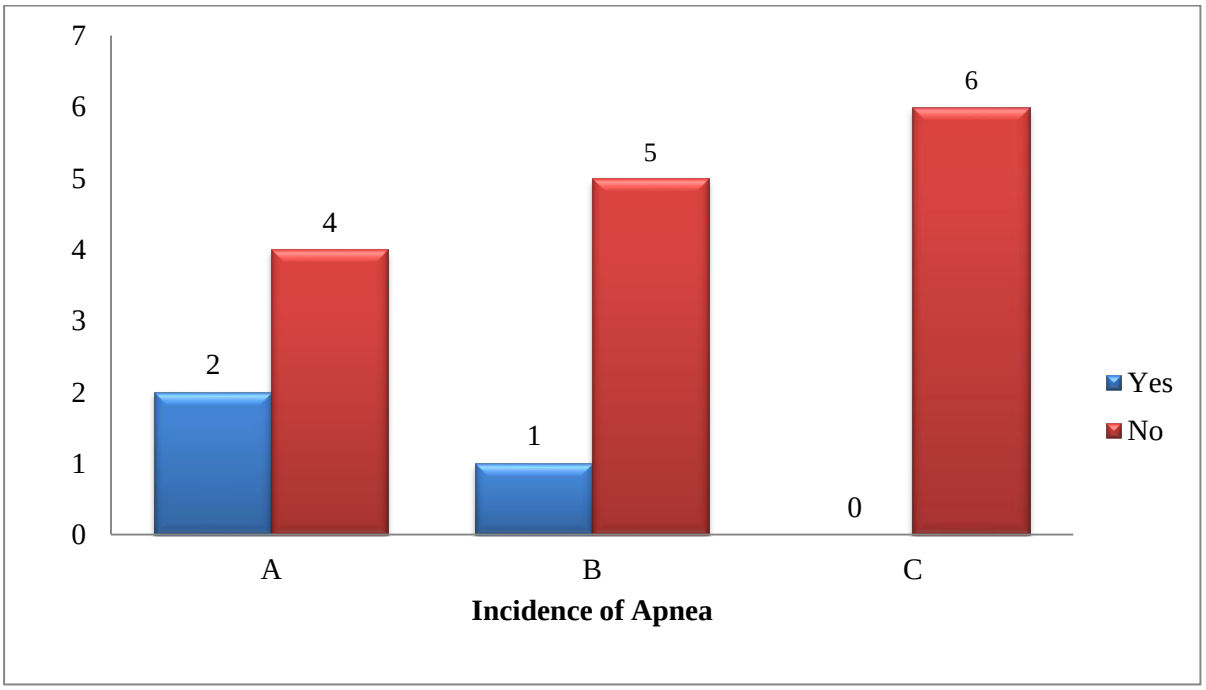


Figure 9: Mean ± SE Incidence of apnoea after induction recorded in all the three groups.

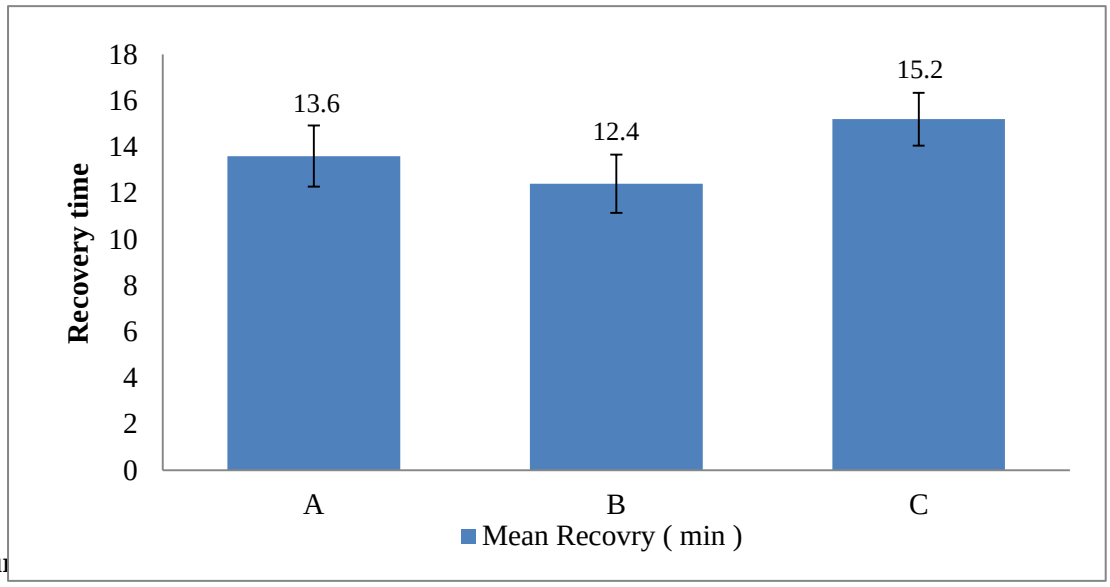
Incidence of apnea recorded in groups A, B and C was 33.33%, 20%, and 0%, respectively.

Recovery Time

Table 11: Mean ± SE of recovery time (min) recorded in all the three groups at different intervals. (Figure no.- 10)

Group	A	B	C
	13.6 ± 1.32	12.4 ± 1.26	15.2 ± 1.14

The means with a different superscript differencing significantly



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time intervals.

Comparison between all the three groups, group B had non – significantly lower recovery time in comparison to group A and C. comparison of group A and C, group C had non - significantly (P>0.05) higher recovery time than group A.

Duration of anaesthesia

Table 12: Mean ± SE duration of anaesthesia (min) recorded in all the three groups. (Figure no.- 11)

Group	A	B	C
	56.2 ± 2.5	56.8 ± 1.85	50.6 ± 2.32

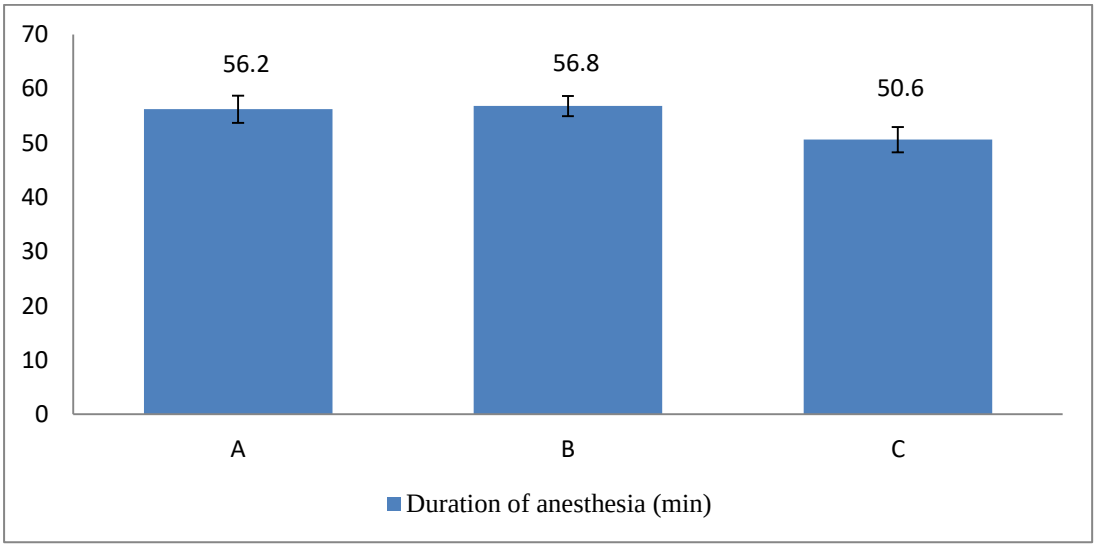


Figure 11: Mean ± SE duration of anaesthesia (min) recorded in different groups at various time intervals.

Comparison between all the three groups, group C had non – significantly lower value of duration of anaesthesia in comparison to group A and B. comparison of group A and B, group B had non - significantly (P>0.05) higher recovery time than group A.

Duration of Surgery

Table 13- Mean ± SE of duration of surgery (min) in all the three groups. (Figure no.- 12)

Group	A	B	C
	43.4 ± 3.93	45.2 ± 4.59	35 ± 4.18

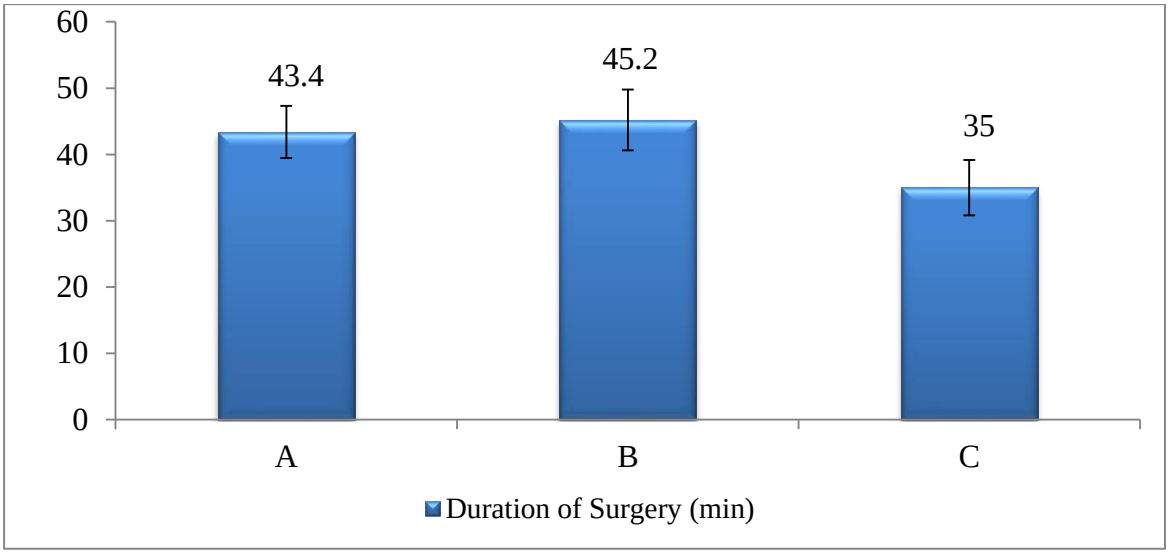


Figure 12: Mean ± S.E. values of duration of surgery time (min) recorded in different groups at various time intervals.

Comparison between all the three groups, group C had non – significantly lower value of duration of surgery in comparison to group A and B. comparison of group A and B, group B had non - significantly (P>0.05) higher recovery time than group A.

Sternal recumbency time

Table 14 : Mean ± SE of sternal recumbency time recorded in all the three groups at different intervals. (Figure no.- 13)

Group	A	B	C
	30 ± 1.7	26.6 ± 1.54	33.2 ± 2.52

The means with a different superscript differencing significantly

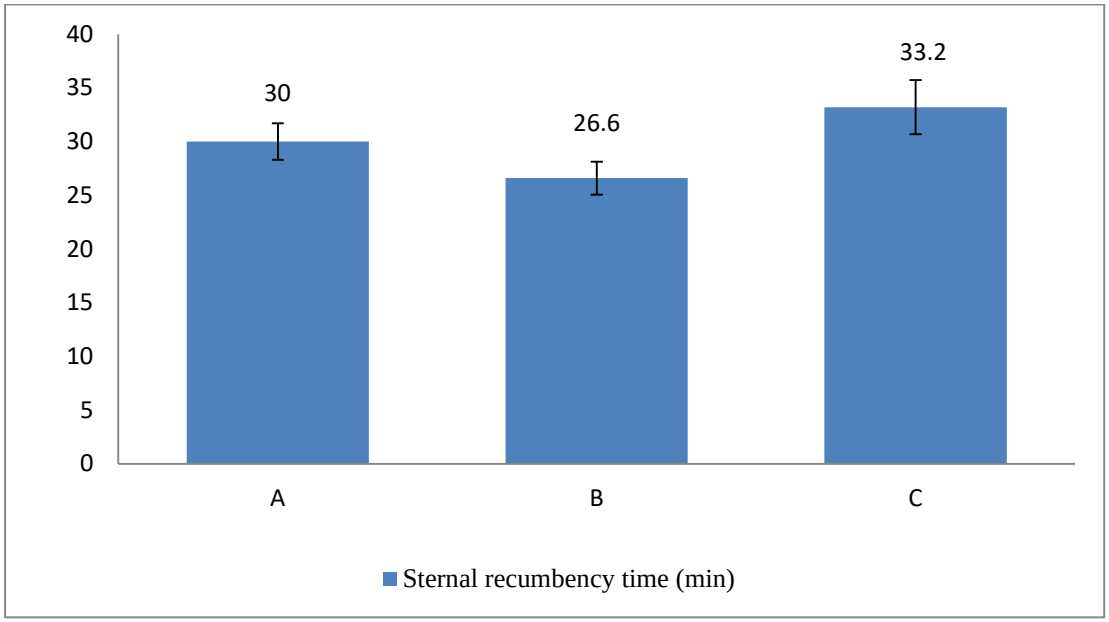


Figure 13: Mean ± S.E. values of sternal recumbency (min) recorded in different groups at various time intervals.

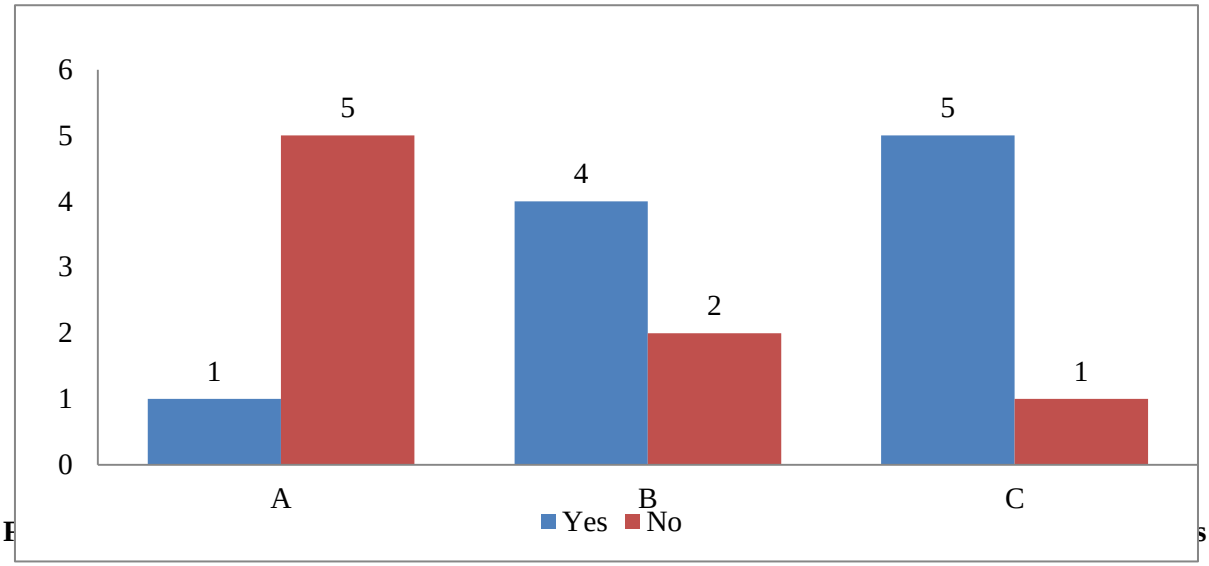
Comparison between all the three group B had non – significantly lower sternal recumbency time in comparison to group A and C. comparison of group A and C , group C had non – significantly (P>0.05) higher recovery time than group A.

Urination

Table 15: Mean ± SE urination recorded in all the three groups. (Figure no.- 14)

Groups	A	B	C

Yes	1	4	5
No	5	2	1
Total	6	6	6



F s time intervals.

Urination recorded after pre-medication in groups A, B and C were16.66%, 66.66% and 83.33% respectively.

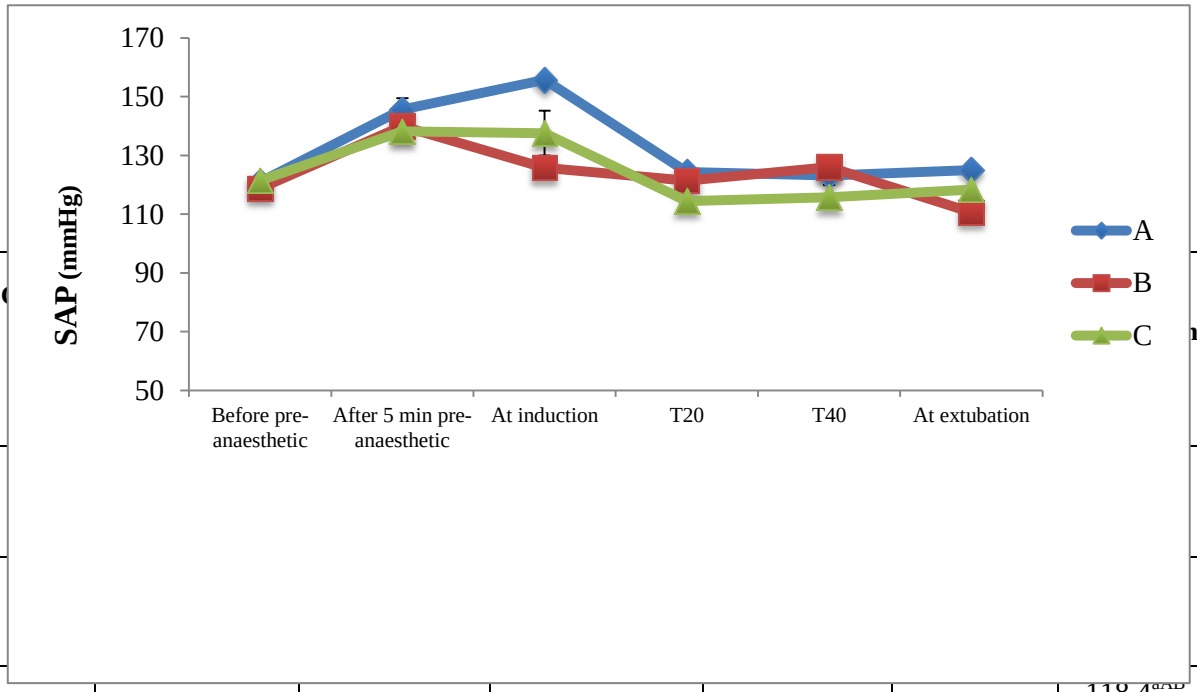
Hemodynamic observation

Blood pressure

Systolic Arterial Pressure (SAP)

Table 16: Mean ± SE values of systolic arterial pressure (mmHg) recorded in all the three groups at various intervals (Figure no.- 15)

The value of systolic arterial pressure in all three groups were increased significantly ($p<0.05$) after 5 minutes of premedication in comparison to base value.



C	121.4^{a} ±1.24	138.2^{b} ±2.1	137.6^{bC} ±7.62	114.4^{a} ±3.96	115.8^{a} ±4.2	118.4^{aAB} ±4.11

Figure15: Mean ± SE values of systolic arterial pressure (mmHg) recorded in different groups at various time intervals.

Group A showed that value was increased significantly after premedication to at induction in comparison to base value. After that value was increased non – significantly At T20during maintenance of anesthesia to entire observation period.

In groups B value was increased significantly after 5 minutes premedication in comparison to base value. After that value was increased non- significantly ($p>0.05$) at induction to entire observation period, except at extubation value was decreased significantly. Group C showed that value was increased significantly after premedication to at induction in comparison to

base value. whereas value was decreased non – significantly At T20 during maintenance of anesthesia to entire observation period.

Comparison between different groups showed that SAP value was non- significantly ($p<0.05$) change in all the three groups after premedication to maintenance of anesthesia, except at induction value was change significantly in all groups.Whereas at extubation SAP value was significant change in group A with respect to group B.

Diastolic Arterial Pressure (DAP)

Table 17: Mean ± SE values of diastolic arterial pressure (DAP) recorded in all the three groups at various intervals. (Figure no.- 16)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	T40	At extubation
A	88.8^{a} ±0.8	104.8^{b} ±2.8	108.6^{cA} ±1.88	92.4^{abA} ±1.93	92.8^{abA} ±1.85	100.2^{abcA} ±1.28
B	86.6^{ac} ±1.53	101.6^{b} ±3.17	93^{abB} ±8.98	81^{acB} ±3.74	81.4^{acB} ±4.66	77.6^{cB} ±1.72
C	88.8^{ac} ±1.09	101^{b} ±3.49	103^{aAB} ±3.06	95.4^{acAB} ±2.22	90.4^{acAB} ±1.72	84.4^{cB} ±1.46

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

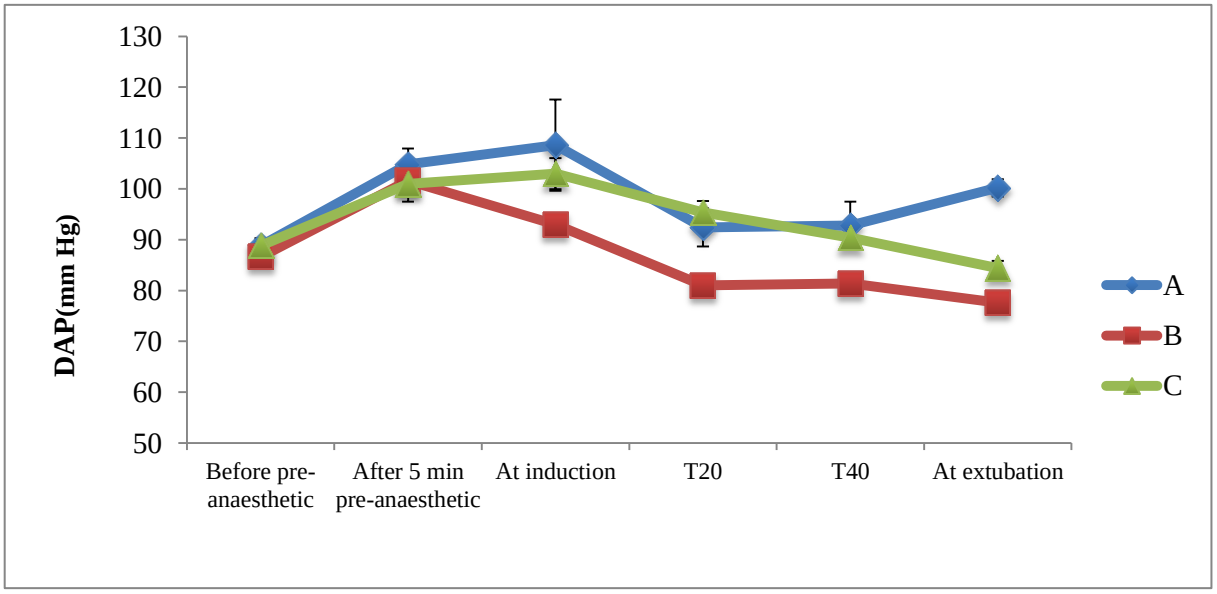


Figure 16: Mean ± SE values of diastolic arterial pressure (mm Hg) recorded in different groups at various time intervals.

The value of diastolic arterial pressure in all three groups were increased significantly ($p<0.05$) after 5 minutes of premedication in comparison to base value.

In group A value was increased significantly ($p<0.05$) after 5 minutes of premedication to at induction in comparison to base value. after that value was increased non - significantly ($p>0.05$) at T20 maintenance of anesthesia to entire observation period.

In group B value was increased significantly after 5 minutes of premedication and non – significantly increased at induction in comparison to bas value. however, value was decreased at T20 maintenance of anesthesia to entire observation period, except at extubation value was significantly lower in comparison base value. In group C value was increased significantly5 minute after premedication in comparison to base value where as value was increased non – significantly at induction to maintenance of anesthesia. At extubation value was significantly lower in comparison base value.

Comparison between different groups showed that diastolic arterial pressure non- significantly ($p>0.05$) change after pre- medication where as value was significantly ($p<0.05$) change in group A and B at induction to at T40 during maintenance of anesthesia, however DAP value significantly ($p<0.05$) change in group A with respect to group B and C at extubation.

MEAN ARTERIAL PRESSURE (MAP)

Table 18: Mean ± SE values of mean arterial pressure (MAP) recorded in all the three groups at various intervals. (Figure no.- 17)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	T40	At extubation
A	100.46^{a} ±1.13	106.92^{ab} ±1.04	114.53^{bAB} ±3.57	101.73^{ab} ±2.38	98.86^{a} ±2.24	95.73^{aA} ±1.94
B	97.33^{ac} ±0.91	114.39^{b} ±1.06	103.93^{abA} ±6.00	94.46^{ac} ±2.30	96.26^{ac} ±3.28	88.59^{cA} ±1.07
C	99.59^{a} ±1.22	111.72^{ab} ±6.30	123.66^{bB} ±1.78	103.06^{a} ± 1.02	102.93^{a} ±1.08	108.46^{aB} ±0.95

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

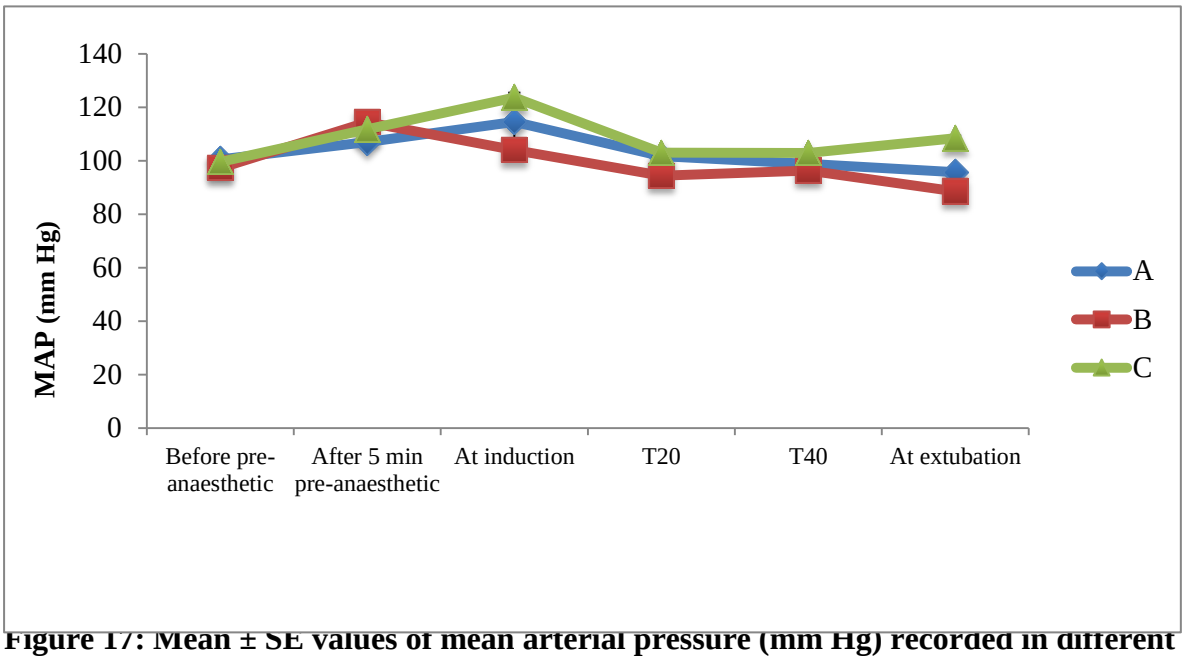


Figure 17: Mean ± SE values of mean arterial pressure (mm Hg) recorded in different groups at various time intervals.

The value of mean arterial pressure in group A increased non - significantly (p>0.05) after 5 minutes of premedication to at T20 maintenance of anesthesia in comparison to base value, except at induction value was significantly where as MAP value was decreased non – significantly at T40 maintenance of anesthesia to at extubation.

In group B MAP value was increased significantly (p<0.05) after 5 minutes of premedication in comparison to base value, after that value was increased non - significantly (p>0.05) at induction, whereas value was decreased non – significantly during maintenance of anesthesia.

At extubation value was significantly lower in comparison base value. In group C value was increased significantly 5 minutes after premedication to entire observation in comparison to base value. except at induction value was significant.

Comparison between different groups showed that mean arterial pressure non- significantly (p>0.05) change after5 minutes of pre- medication to maintenance of anesthesia, except at induction value was significantly (p<0.05) change in group B with respect to group C. However at extubation value was change significantly (p<0.05) in group C with respect to group A and B .

Electrocardiographic (ECG) Observation

Amplitude of P wave

Table19: Mean ± SE values of the amplitude of P wave (mv) recorded in all the three groups at a various interval. (Figure no.-18)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	T40	At extubation
A	0.225^{a} ±0.00	0.208^{ab} ±0.00	0.220^{b} ±0.00	0.231^{ab} ±0.00	0.216^{b} ±0.00	0.199^{ab} ±0.00
B	0.216^{a} ±0.00	0.267^{ab} ±0.00	0.194^{b} ±0.00	0.218^{b} ±0.00	0.212^{b} ±0.00	0.173^{b} ±0.00
C	0.224^{a} ±0.00	0.249^{a} ±0.00	0.221^{a} ±0.00	0.216^{a} ±0.00	0.213^{a} ±0.00	0.165^{a} ±0.00

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

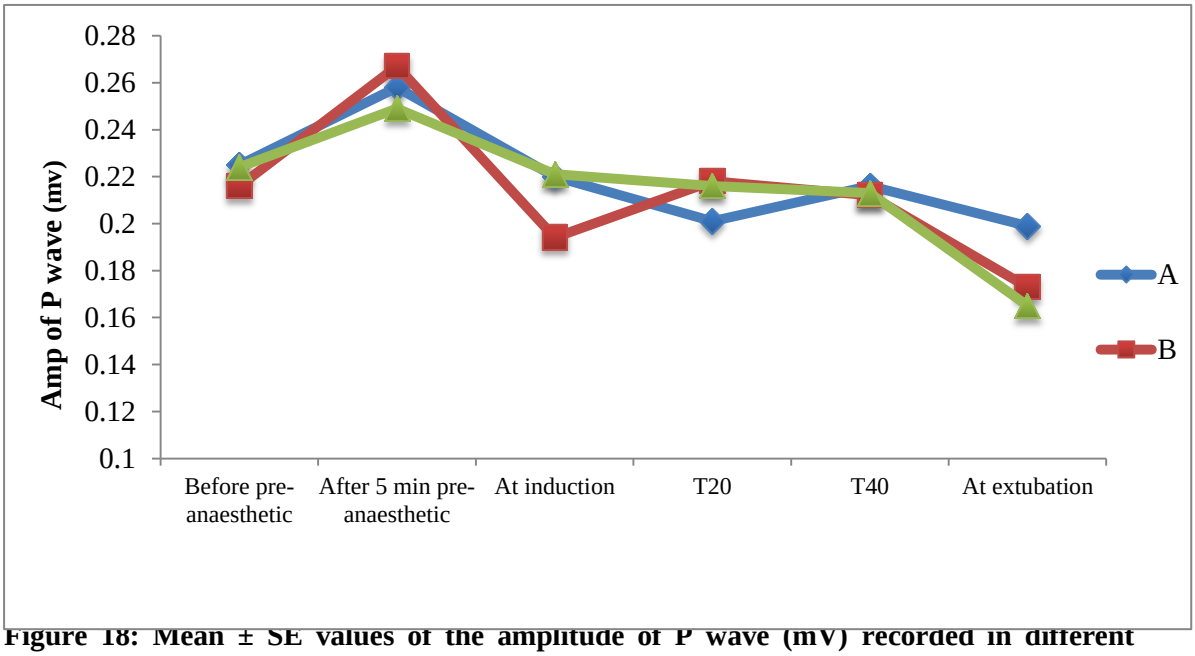


Figure 18: Mean ± SE values of the amplitude of P wave (mV) recorded in different groups at various time intervals.

The value of amplitude of P wave (mV**)** in group A was gradually decreased non-significantly ($p>0.05$) after premedication and become significant at induction in comparison to base value. Group A also that value again becomes non-significant except at T40 during maintenance of anaesthesia in comparison to base values.

In group Band C value was increased non- significantly ($p>0.05$) 5 minutes after premedication in comparison to base value, whereas value was gradually decreased

significantly ($p<0.05$) at induction to entire observation period except at T20 during maintenance of anaesthesia value again become increased.

Comparison between different groups showed that amplitude of P wave (mV**)** value was non-significantly ($p>0.05$) change at different stage.

Duration of P wave

Table 20: Mean ± SE values of duration of P wave (sec) recorded in all the three groups at various intervals. (Figure no.-19)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	T40	At extubation
A	$0.048^{a}\pm0.00$	$0.053^{a}\pm0.00$	$0.063^{b}\pm0.00$	$0.063^{ab}\pm0.00$	$0.065^{b}\pm0.00$	$0.062^{ab}\pm0.00$
B	$0.054^{a}\pm0.00$	$0.060^{ab}\pm0.00$	$0.069^{b}\pm0.00$	$0.069^{b}\pm0.00$	$0.071^{b}\pm0.00$	$0.072^{b}\pm0.00$
C	$0.056^{a}\pm0.00$	$0.059^{a}\pm0.00$	$0.064^{a}\pm0.00$	$0.067^{a}\pm0.00$	$0.061^{a}\pm0.00$	$0.064^{a}\pm0.00$

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

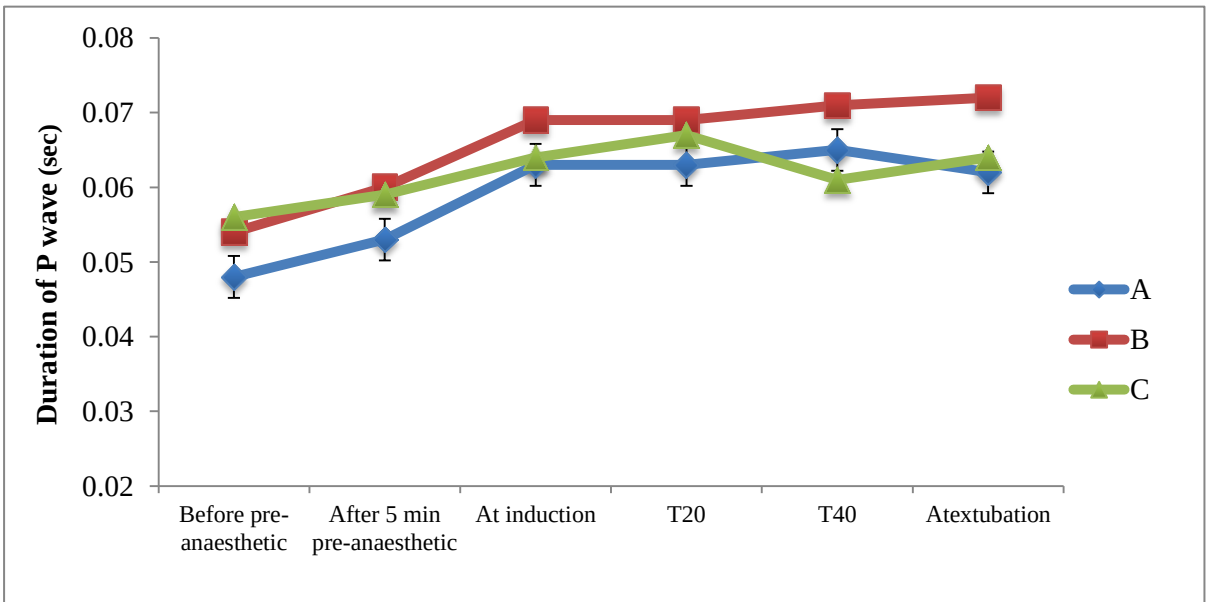


Figure 19: Mean ± SE values of the duration of P wave (sec) recorded in different groups at various time intervals.

The value of duration of P wave in all three groups were increased non- significantly (p>0.05) after 5 minutes of premedication in comparison to base value.

The value of duration of P wave (sec**)** in group A was gradually increased non- significantly (p<0.05) after premedication and become significant at induction an in comparison to base value. Group A also that value again becomes non-significant except at T40 during maintenance of anaesthesia in comparison to base values.

Whereas in group B value was increased non- significantly (p>0.05) after 5 minutes of premedication in comparison to base value, whereas value was increased significantly (p<0.05) at induction to entire observation period. However In group C value was increased non - significantly (p<0.05) after premedication to entire observation period in comparison to

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	T40	At extubation
A	1.075 [a]± 0.04	1.134 [a]± 0.07	1.127 [a]± 0.07	1.17 [a]± 0.06	1.182 [a]± 0.07	1.105 [a]± 0.01

base value.

Comparison between different groups showed that duration of P wave (mV**)** value was non-significantly (p>0.05) change at different stage.

Amplitude of R wave

B	0.997 ^{a}± 0.02	1.202 ^{b}± 0.04	1.171 ^{b}± 0.02	1.219 ^{b}± 0.02	1.308 ^{b}± 0.04	1.189 ^{b}± 0.02
C	0.999 ^{a}± 0.03	1.125^{ab}± 0.02	1.170^{ab}± 0.04	1.21 ^{b}±0.01	1.227 ^{b}±0.02	1.183 ^{b}± 0.01

Table 21: Table Mean ± SE values of the amplitude of R wave (mV) recorded in all the three groups at a various intervals. (Figure no.-20)

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

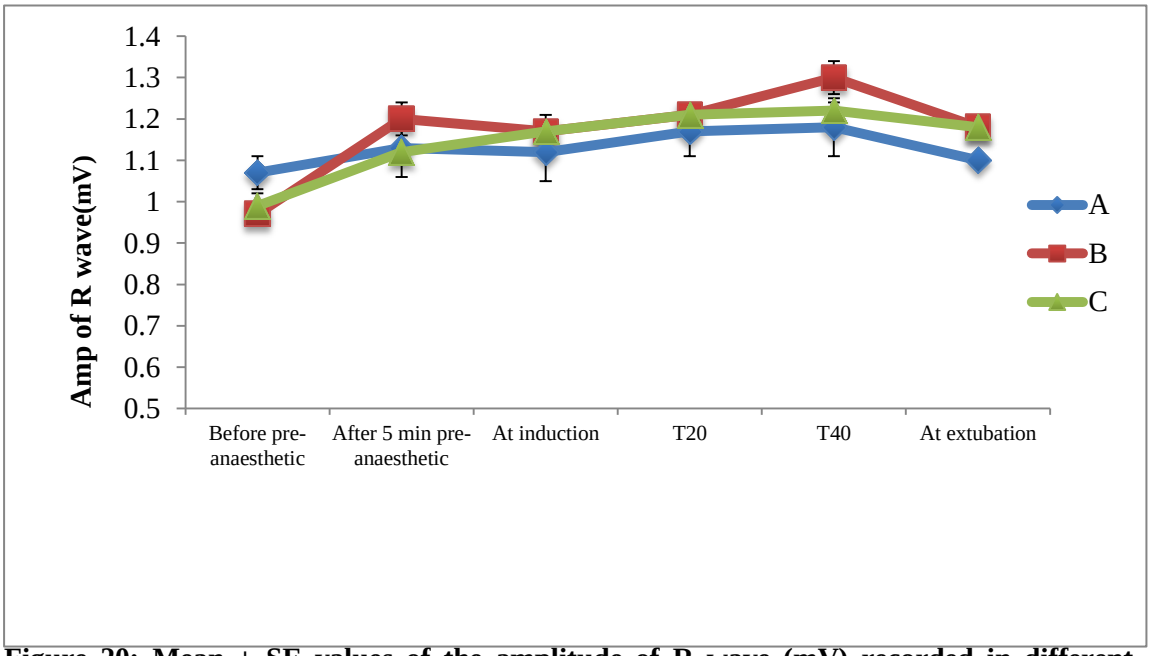


Figure 20: Mean ± SE values of the amplitude of R wave (mV) recorded in different groups at various time intervals.

The value of amplitude of R wave in group A was increased non - significantly (p>0.05) after premedication to entire observation period in comparison to base value. Whereas in group B value was increased significantly (P<0.05) after premedication to entire observation period.

In group C value was increased non – significantly after 5 minutes of premedication to induction in comparison to base value whereas value was increased significantly at T20 during maintenance of anaesthesia to entire observation period.

Comparison between different groups showed that amplitude of R wave (mV**)** value was non-significantly (p>0.05) change at different stage.

Duration of R wave

Table 22: Mean ± SE values of the duration of R wave (sec) recorded in all the three groups at various intervals.(figure no.-21)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	T40	at extubation
A	0.038± 0.00	0.041^{A} ± 0.00	0.039^{A}± 0.00	0.042^{A}± 0.00	0.041^{A}± 0.00	0.045^{A}± 0.00
B	0.048± 0.00	0.052^{B}± 0.00	0.053^{B}± 0.00	0.049^{B}± 0.00	0.053^{B}± 0.00	0.042^{B}± 0.00
C	0.047± 0.00	0.045^{AB} ± 0.00	0.046^{AB} ± 0.00	0.047^{AB} ± 0.00	0.048^{AB} ± 0.00	0.043^{AB} ± 0.00

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

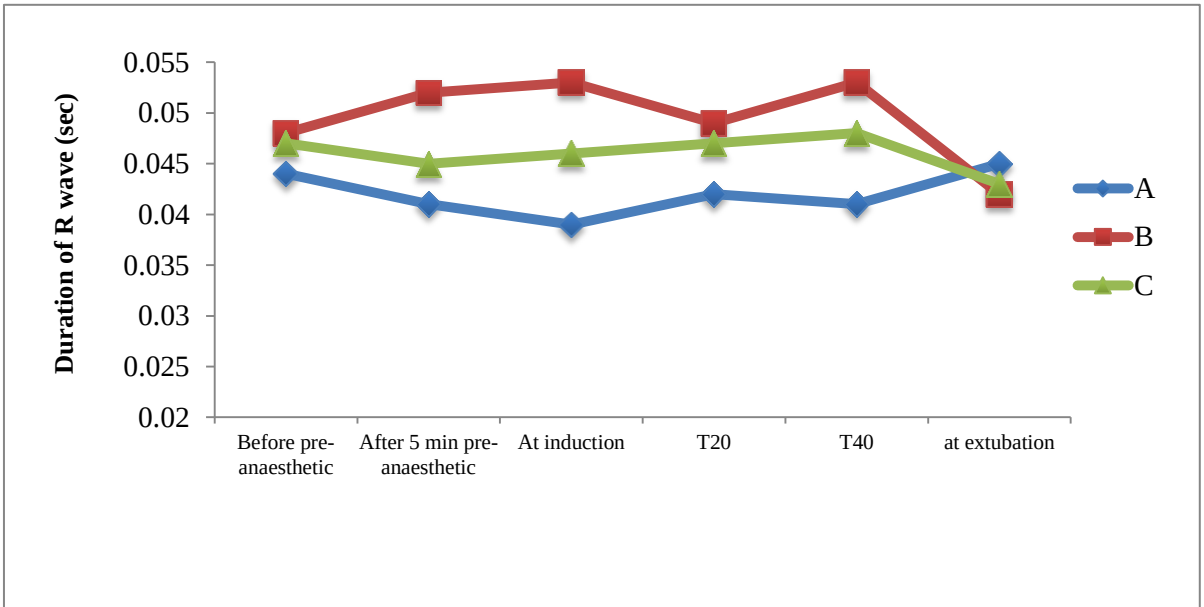


Figure 21: Mean ± SE values of the duration of R wave (sec) recorded in different groups at various time intervals.

The value of duration of R wave in group A and B was increased non - significantly (p>0.05) after 5 minutes of premedication to entire observation period in comparison to base value, except in group B at extubation value was decreased.

In group C value was decreased non - significantly (p>0.05) after premedication to entire observation period in comparison to base value, except at T40 during maintenance of anaesthesia value was increased.

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	T40	At extubation
A	$0.110^{a} \pm 00$	$0.102^{a} \pm 00$	$0.103^{b} \pm 00$	$0.116^{a} \pm 00$	$0.104^{b} \pm 00$	$0.117^{a} \pm 00$
B	$0.104^{a} \pm 00$	$0.088^{b} \pm 00$	$0.109^{a} \pm 00$	$0.122^{c} \pm 00$	$0.122^{c} \pm 00$	$0.124^{c} \pm 00$
C	$0.107^{a} \pm 00$	$0.091^{b} \pm 00$	$0.098^{c} \pm 00$	$0.117^{d} \pm 00$	$0.118^{d} \pm 00$	$0.122^{d} \pm 00$

Comparison between different groups showed that duration of R wave (sec) value was significantly (p<0.05) change in group A with respect to group B after 5 minute of premedication to entire observation period at different stage.

PR-Interval

Table 23: Mean ± SE values of PR interval recorded in all the three groups at various intervals. (Figure no.-22)

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

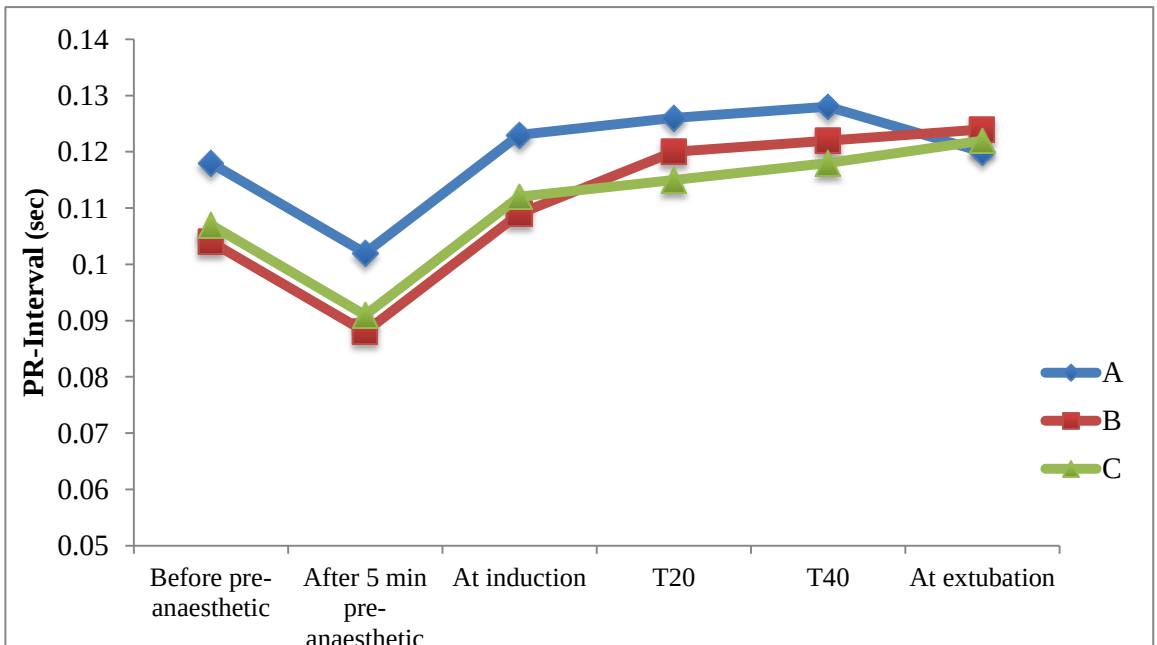


Figure 22: Mean ± SE values of the PR- interval wave (sec) recorded in different groups at various time intervals.

The value of PR-interval (sec**)** in group A was decreased non- significantly (p>0.05) after 5 minute of premedication and become significant at induction in comparison to base value. After that value was gradually increased non - significantly (p>0.05) at T20 during maintenance of anaesthesia to entire observation, except at T40 value was decreased significantly.

In group B value was decreased significantly (p<0.05) after premedication and become increased non- significantly (p>0.05) at induction an in comparison to base value. After that value was gradually increased significantly (p<0.05) at T20 during maintenance of anaesthesia to entire observation. Where as in group C value was decreased significantly after premedication to induction in comparison to base value. After that value was increased significantly at T20 during maintenance of anaesthesia to entire observation.

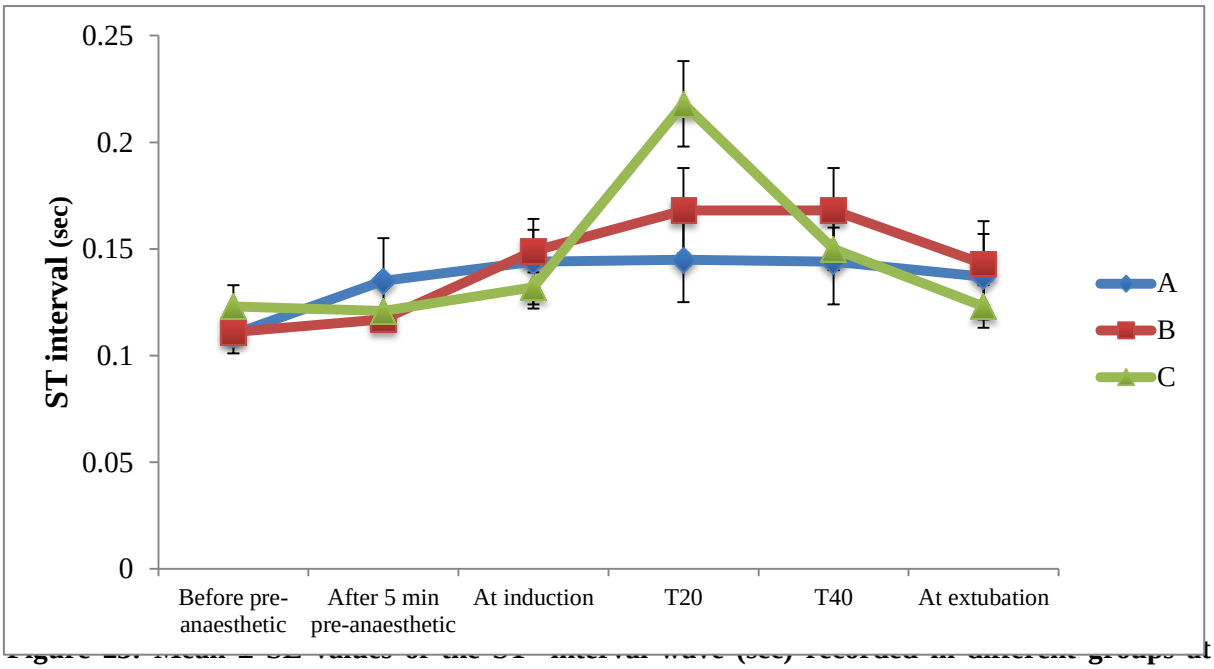
Comparison between different groups showed that PR- interval (sec**)** value was non-significantly (p>0.05) change at different stage.

ST- Interval

Table 24: Mean ± SE values of ST interval (sec) recorded in all the three groups at avarious interval. (Figure no.-23)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	T40	At extubation
A	$0.110^{a} \pm 0.00$	$0.135^{a} \pm 0.02$	$0.144^{a} \pm 0.02$	$0.145^{a} \pm 0.02$	$0.144^{aA} \pm 0.02$	$0.137^{a} \pm 0.02$
B	$0.111^{a} \pm 0.01$	$0.117^{a} \pm 0.00$	$0.149^{a} \pm 0.01$	$0.168^{a} \pm 0.02$	$0.168^{aAB} \pm 0.02$	$0.143^{a} \pm 0.02$
C	$0.123^{a} \pm 0.01$	$0.121^{a} \pm 0.00$	$0.132^{a} \pm 0.01$	$0.218^{b} \pm 0.02$	$0.150^{abB} \pm 0.01$	$0.123^{a} \pm 0.01$

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



various time intervals.

The value of ST interval in the all groups were increased non - significantly (p>0.05) after premedication to entire observation period in comparison to base value, except- in group C at T20 value was significantly increased.

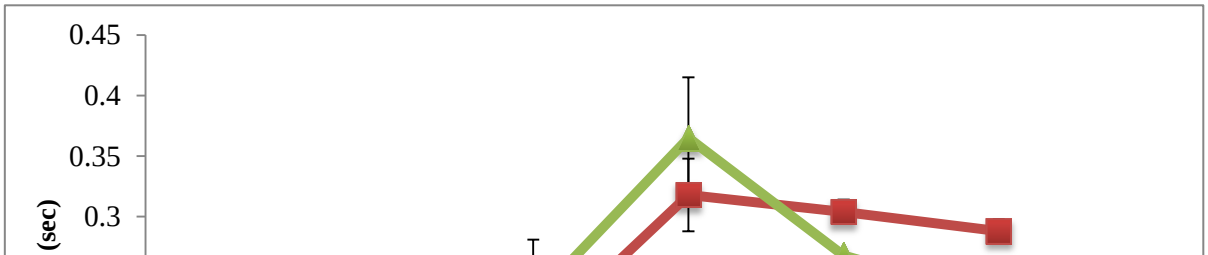
Comparison between different groups showed that ST interval (sec**)** value was non-significantly (p>0.05) change at different stage, except at T40 in group A and C value was significantly change.

QT-Interval

Table 25: Mean ± SE values of QT interval (sec) recorded in all the three groups at a various interval. (Figure no. 24)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	T40	At extubation
A	$0.202^{a} \pm 0.00$	$0.193^{a} \pm 0.00$	$0.208^{a} \pm 0.00$	$0.225^{aA} \pm 0.00$	$0.223^{aA} \pm 0.00$	$0.209^{aA} \pm 0.00$
B	$0.199^{a} \pm 0.00$	$0.187^{a} \pm 0.01$	$0.197^{a} \pm 0.01$	$0.318^{bB} \pm 0.03$	$0.304^{bB} \pm 0.01$	$0.288^{bB} \pm 0.01$
C	$0.193^{a} \pm 0.00$	$0.205^{a} \pm 0.02$	$0.231^{a} \pm 0.05$	$0.365^{bB} \pm 0.05$	$0.268^{aAB} \pm 0.00$	$0.232^{aAB} \pm 0.01$

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



Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	T40	At extubation

Figure 24: Mean ± SE values of the QT- interval wave (sec) recorded in different groups at various time intervals.

The value of QT interval (sec) in group A was decreased non - significantly (p>0.05) after 5 minutes of premedication in comparison to base value. After that value was increased non - significantly (p>0.05) at induction to entire observation period.

In group B value was decreased non – significantly after premedication to at induction in comparison to base value. After that value was increased significantly at T20 during maintenance of anaesthesia to entire observation. Where as in group C value was increased non – significantly after 5 minutes of premedication to at induction in comparison to base value. After that value was increased significantly at T20 during maintenance of anaesthesia to entire observation.

Comparison between different groups showed that QT interval (sec**)** value was non-significantly (p>0.05) change at after premedication to at induction, after that value was at T20 group A change significantly (p<0.05) with group B and C whereas value as change significantly in group A respect to group B at T40 to entire observation period.

Amplitude of T wave

Table 26: Mean ± SE values of amplitude of T wave (mV) recorded in all the three groups at different intervals. (Figure no.-25)

A	0.211[a]± 0.00	0.223[a]± 0.00	0.215[a] ±0.00	0.232 [a]± 0.00	0.223 [a]± 0.00	0.229[a]± 0.00

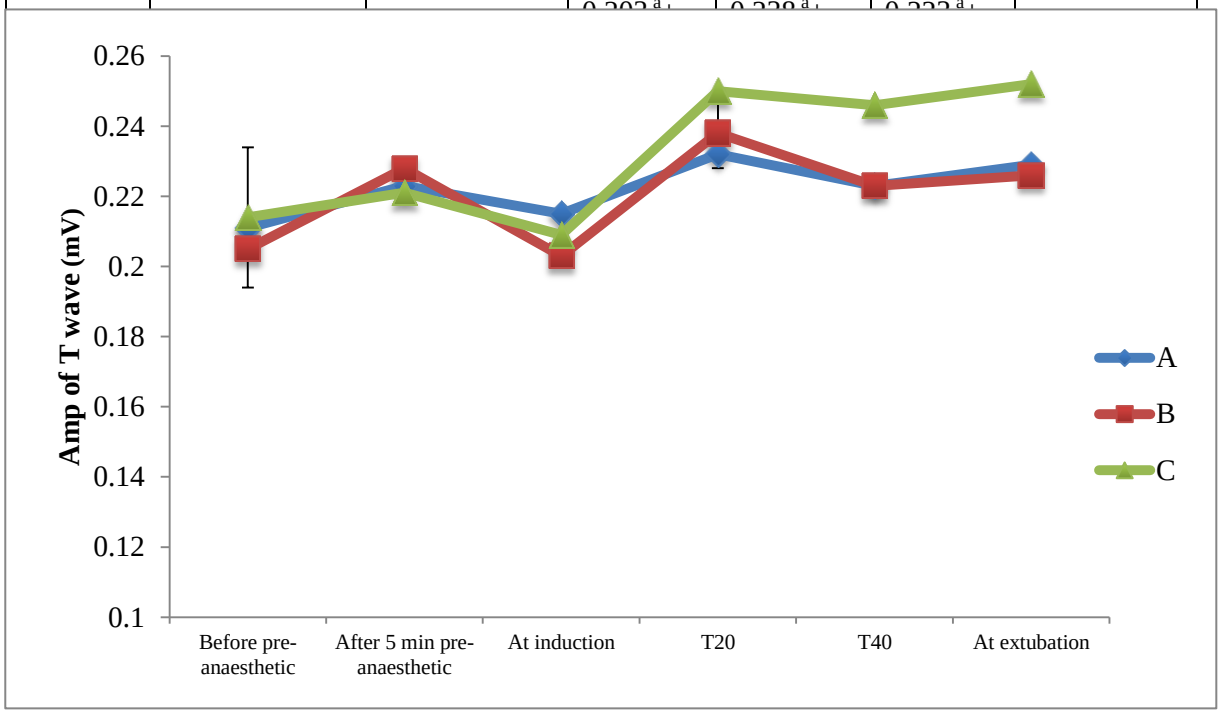


Figure 25: Mean ± SE values of the amplitude of T wave (mV) recorded in different groups at various time intervals.

The value of amplitude of T wave (mV**)** in group A and B was increased non - significantly (p>0.05) after premedication to entire observation period in comparison to base value, except in group B at induction value was decreased.

In group C value was decreased non- significantly after premedication to entire observation period in comparison to base value except at induction value was significantly decreased.

Comparison between different groups showed that amplitude of T wave (mV**)** value was non-significantly (p>0.05) change at different stage.

Haematological Observation

Haemoglobin (gm/dL)

Table 27: Mean ± SE values of haemoglobin (gm/dL) recorded in all the three groups at different intervals. (Figure no.-26)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	At extubation
A	12.80 ±1.01	11.76 ±0.60	10.88 ±0.76	10.32 ± 0.74	10.98 ±0.77
B	12.70±1.04	12.28 ±0.79	12.22 ±0.97	11.30 ±1.00	11.94 ±0.91
C	12.66 ±0.48	10.64 ±0.31	10.44 ±0.27	10.40±0.68	11.10 ±0.68

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

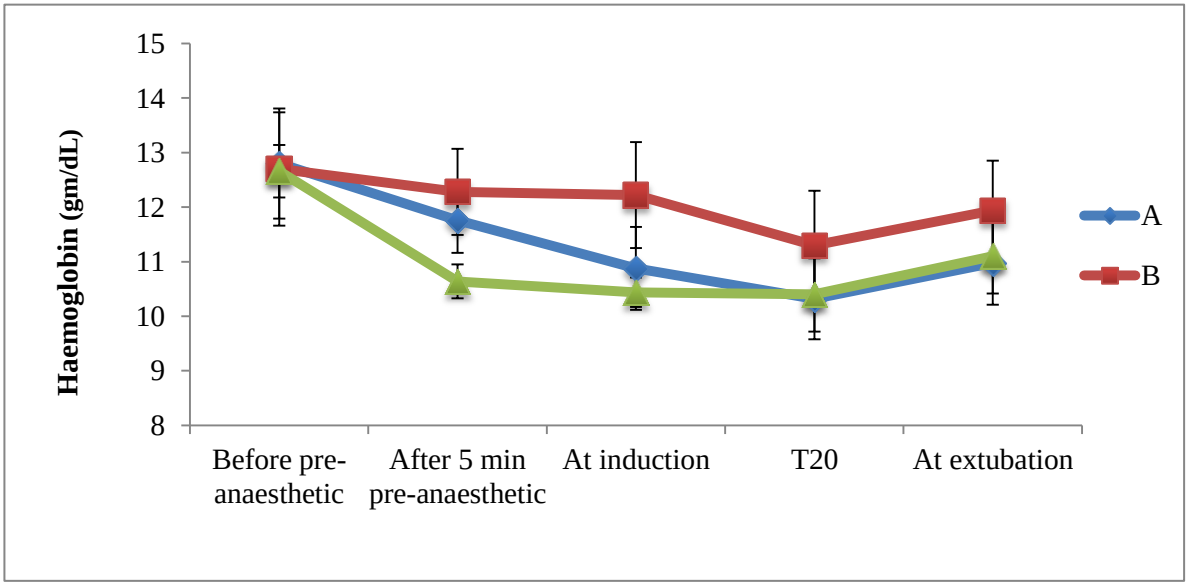


Figure 26 : Mean ± SE values of Haemoglobin (Hb) (g/dl) in different groups at various time intervals.

The value of haemoglobin (Hb gm/dL) in all three groups were decreased non-significantly after premedication to entire observation period in comparison to base value. Result also showed that Hb value increase non- significantly ($p>0.05$) at extubation comparison to value at T20 during maintenance of anesthesia in all three groups. Comparison between different groups showed that haemoglobin (Hbgm/dL) value was non- significantly ($p>0.05$) change at different stage.

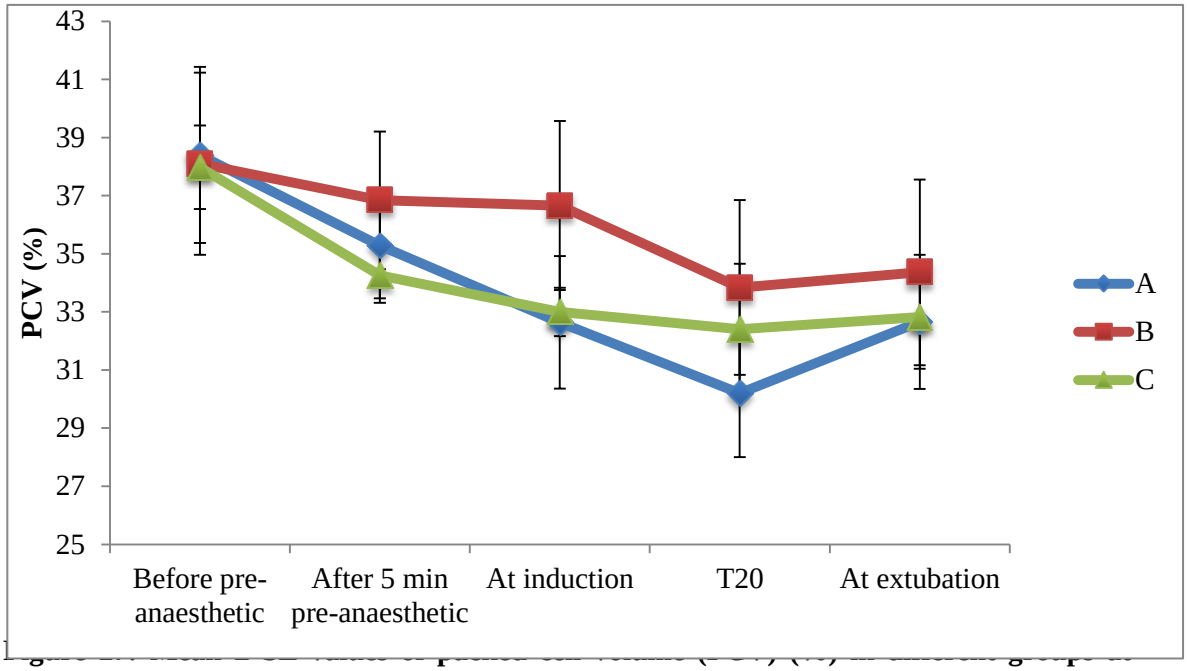
Packed cell volume (PCV %)

Table 28: Mean ± SE values of PCV (%) recorded in all the three groups at a different intervals. (Figure no.-27)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	At extubation
A	38.40±3.03	35.28 ±1.81	32.64 ±2.28	30.20 ±2.20	32.66 ±2.31

B	38.10 ±3.13	36.84±2.37	36.66 ±2.91	33.84 ±3.01	34.36 ±3.20
C	37.98±1.44	34.26 ±0.95	33.00 ±0.83	32.40 ±2.26	32.82 ±1.78

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



various time intervals.

The value of haematocrit (HCT L/L) in all three groups were decreased non-significantly (p>0.05) after premedication to entire observation period in comparison to base value. Result also showed that PCV value increase non- significantly (p>0.05) at extubation comparison to value at T20 during maintenance of anesthesia in all three groups.

Comparison between different groups showed that haematocrit (HCT L/L) value was non-significantly (p>0.05) change at different stage.

Total leukocyte count (TLC)

Table 29: Mean ± SE values of total leukocyte count (TLC 10^3 /µL) recorded in all the three groups at different intervals. (Figure no.-28)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	At extubation
A	11.75 ±0.81	11.44 ±0.74	10.96 ±0.78	11.16 ±0.66	11.26 ±0.65
B	11.70 ±1.08	10.91 ±0.93	9.87 ±0.75	10.59 ± 0.77	9.90 ±0.77

C	11.29 ±0.59	10.94±0.53	10.32 ±0.60	10.62 ±0.50	9.88 ±0.51

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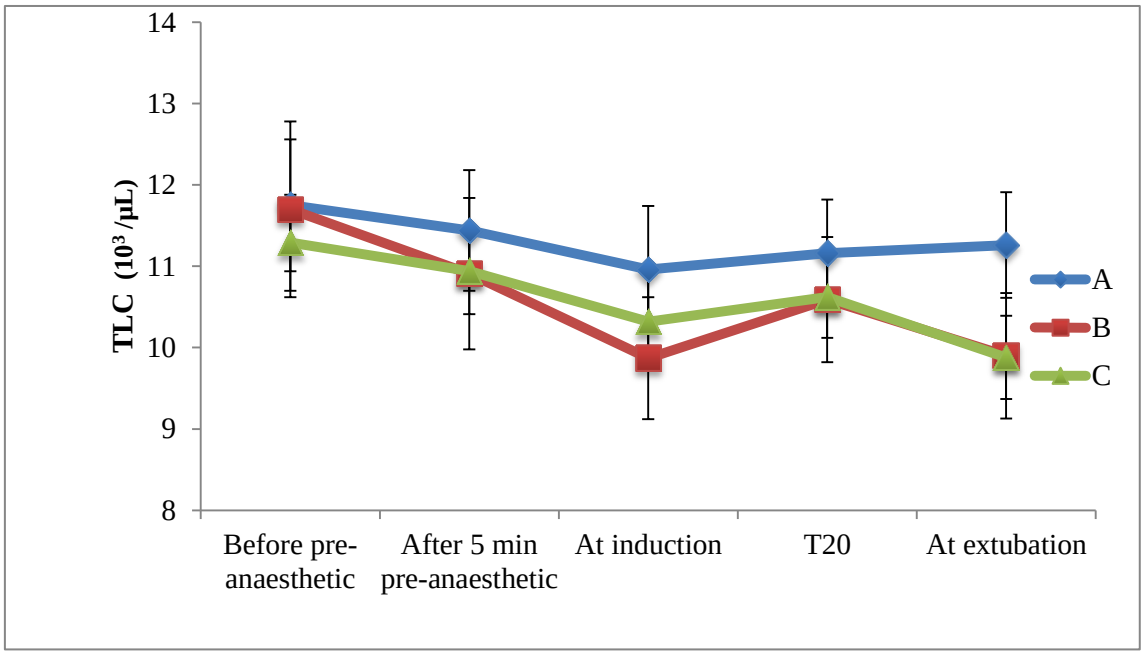


different groups at various time intervals.

The value of total leukocyte count (TLC 10^3 /µL) in all three groups were decreased non – significantly (p>0.05) after pre-medication to entire observation period in comparison to base value.

Comparison between different groups showed that total leukocyte count (TLC 10^3 /µL) value was non- significantly (p>0.05) change at different stage.

Total erythrocyte count (TEC)

Table 30: Mean ± SE values of total erythrocyte count (10^6/µL) recorded in all the three groups at various intervals. (Figure no.-29)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	At extubation
A	5.94^{a}±0.06	4.82^{bA}±0.06	4.24^{cA}±0.09	3.92^{dA}±0.05	4.72^{bA}±0.10
B	6.18^{a}±0.03	5.26^{bB}±0.08	5^{bcB}±0.07	4.76^{cB}±0.14	5.26^{bB}±0.04
C	6.12^{a}±0.05	5.5^{bB}±0.08	5.2^{bcB}±0.05	4.98^{cB}±0.05	5.34^{bB}±0.06

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

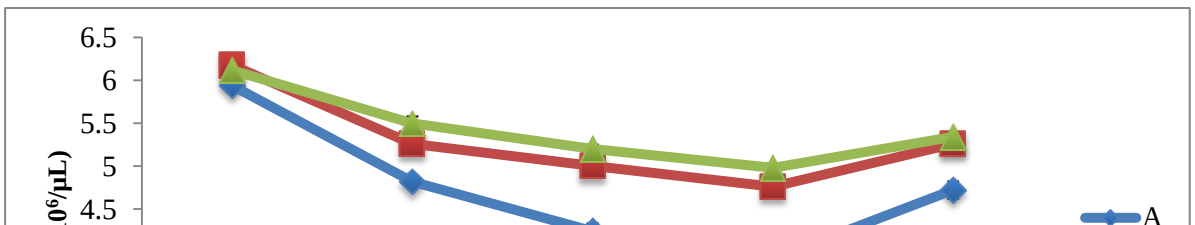


Figure 29: Mean ± SE values of total erythrocyte count (TEC) ($x10^6/\mu L$) in different groups at various time intervals.

The value of total erythrocyte count ($10^6/\mu L$) in all three groups were decreased significantly ($p<0.05$) after pre-medication to entire observation period in comparison to base value. Comparison between different groups showed that total erythrocyte count ($10^6/\mu L$) value was significantly ($p<0.05$) change in group A with respect to group B and C after premedication to entire observation period at different stage

Differential Leukocyte Count (DLC)

Neutrophils

Table 31: Mean ± SE values of neutrophil (%) recorded in all the three groups at various intervals. (Figure no.-30)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	At extubation
A	$71.4^{a}\pm2.94$	$70.8^{a}\pm1.52$	$72.8^{a}\pm2.57$	$72.4^{a}\pm2.50$	$74.4^{a}\pm1.91$
B	$70.2^{a}\pm1.06$	$68.8^{a}\pm1.59$	$71.2^{a}\pm1.82$	$71.6^{a}\pm1.56$	$72.8^{a}\pm1.65$
C	$70.4^{a}\pm0.74$	$72^{ab}\pm0.70$	$75.4^{ab}\pm0.67$	$76.8^{ab}\pm0.66$	$77.8^{b}\pm0.66$

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

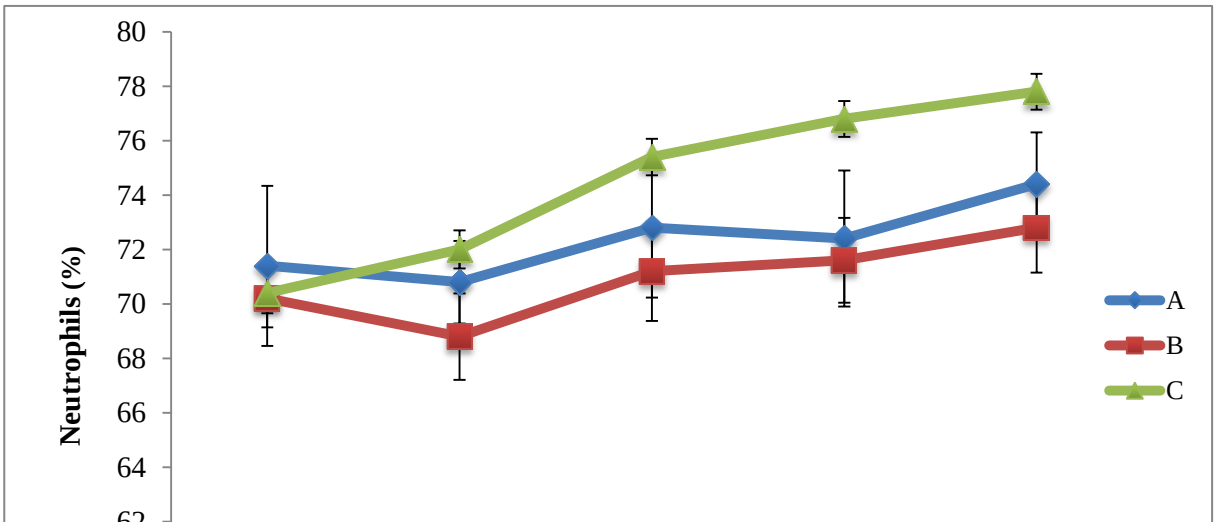


Figure 30: Mean ± SE values of neutrophil (%) recorded in different groups at various time intervals.

The values of neutrophil (%) in group A and B decreased non-significantly ($p>0.05$) after 5 minutes of premedication in respect to base values. whereas value was increased non-significantly at induction to entire observation period in comparison to base value. However in group C neutrophil value was increased non – significantly after premedication to during maintenance of anesthesia in comparison to base value , but at extubation DLC value was significaltly ($p<0.05$) higher in comparison to other stage during observation period.

Comparison between different groups showed that neutrophil (%) value was non - significantly ($p>0.05$) change at different stage.

Monocyte

Table 32: Mean ± SE values of monocyte (%) recorded in all the three groups at various intervals. (Figure no.-31)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	At extubation
A	$3.2^{a}\pm0.37$	$3.6^{aA}\pm0.4$	$3^{aA}\pm0.31$	$3.4^{a}\pm0.24$	$3.8^{a}\pm0.37$
B	$3.2^{a}\pm0.37$	$3.8^{aA}\pm0.58$	$4.6^{a\,B}\pm0.4$	$3.6^{a}\pm0.24$	$4.2^{a}\pm0.48$
C	$4.2^{a}\pm0.2$	$5.2^{abB}\pm0.37$	$5.6^{abB}\pm0.4$	$5.6^{a}\pm0.50$	$3.4^{ac}\pm0.24$

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

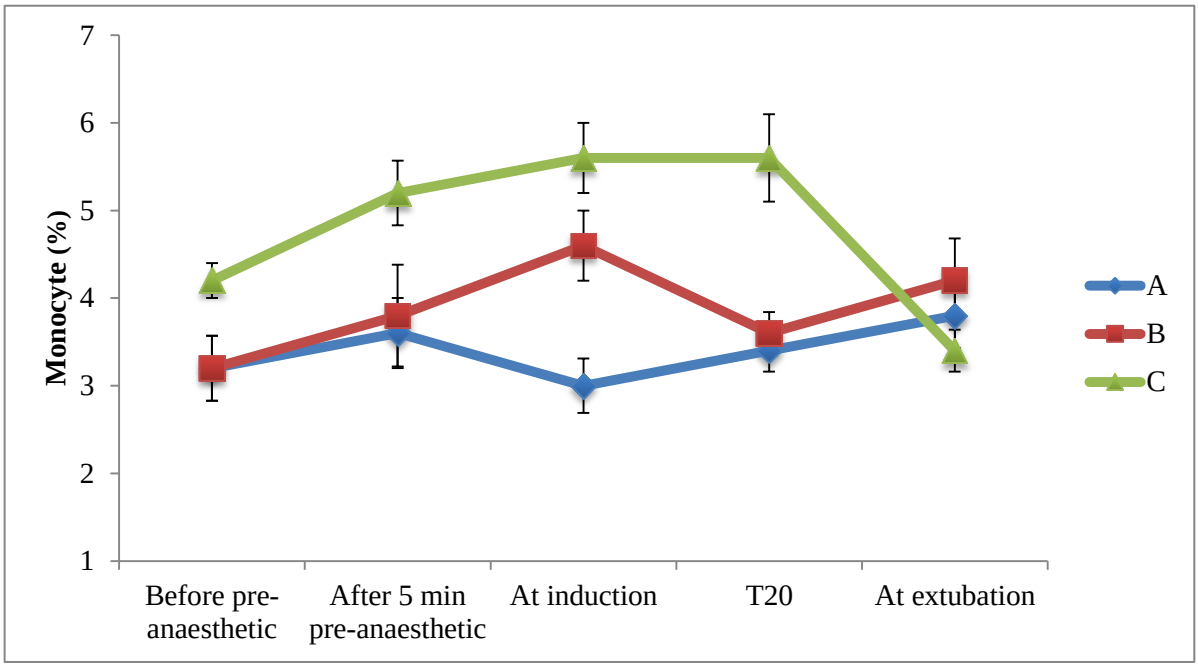


Figure 31: Mean ± SE values of monoyte (%) recorded in different groups at various time intervals.

The value of monocyte (%) in all the three groups were increased non- significantly (p>0.05) after 5 minutes of premedication in comparison to base value.

In the group A value was decreased non- significantly (P>0.05) after premedication to induction in comparison to base value. But value was increased non- significantly at T20 maintenance of anaesthesia to entire observation period comparison to base value. Where as in group B and C value was increased non- significantly after premedication to entire observation period comparison to base value. Result also showed that in group C at extubation value was non – significantly lower in comparison to other stage.

Comparison between different groups showed that monocyte (%) value was significantly (p<0.05) change in group C with respect to the group A and |B after5 minutes of premedication then value was significantly (p<0.05) change in group A with respect to the group B and |C at induction however value was non- significantly (p>0.05) change in all the groups at different stage to entire observation.

Lymphocyte

Table 33: Mean ± SE values of lymphocyte (%) recorded in all the three groups at various intervals. (Figure no.-32)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	At extubation
A	22.4 ^{a}± 2.27	19.4 ^{a}± 2.01	17^{ab}± 1.64	21.8 ^{a}± 2.17	24.6 ^{ac}± 1.53
B	23.8 ^{a}± 1.02	21 ^{a}± 1.14	18.8 ^{a}± 0.58	23.6 ^{a}± 1.65	21.4 ^{a}± 1.69
C	23.2 ^{a}± 1.59	21.2 ^{a}± 1.93	18.8 ^{a}± 1.71	21.4 ^{a}± 1.63	19.2 ^{a}± 1.35

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

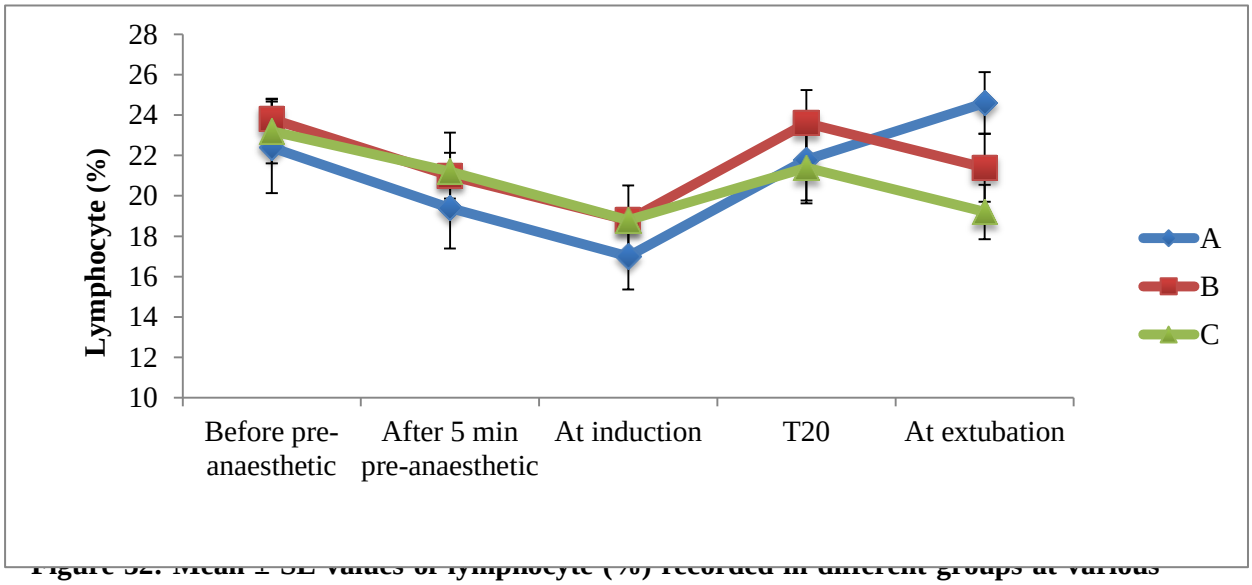


Figure 32: Mean ± SE values of lymphocyte (%) recorded in different groups at various time intervals.

The value of lymphocyte (%) in all three groups were decreased non - significantly (p>0.05) after pre-medication to entire observation period in comparison to base value, except in groups A value was increased at extubation .

Comparison between different groups showed that lymphocyte (%) value was non-significantly (p>0.05) change at different stage.

Eosinophills

Table 34: Mean ± SE values of eosinophil (%) recorded in all the three groups at various intervals. (Figure no.-33)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	At extubation
A	$6.8^{a} \pm 0.24$	$5.2^{ab} \pm 0.37$	$6.2^{a} \pm 0.2$	$5.6^{ab} \pm 0.67$	$4.8^{b} \pm 0.24$
B	$7.6^{a} \pm 0.24$	$5.8^{b} \pm 0.2$	$5.2^{c} \pm 0.2$	$3.8^{c} \pm 0.24$	$4.4^{c} \pm 0.24$
C	$7.4^{a} \pm 0.24$	$6.7^{b} \pm 0.37$	$6.2^{b} \pm 0.37$	$4.4^{dc} \pm 0.24$	$4.8^{d} \pm 0.37$

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	At extubation

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

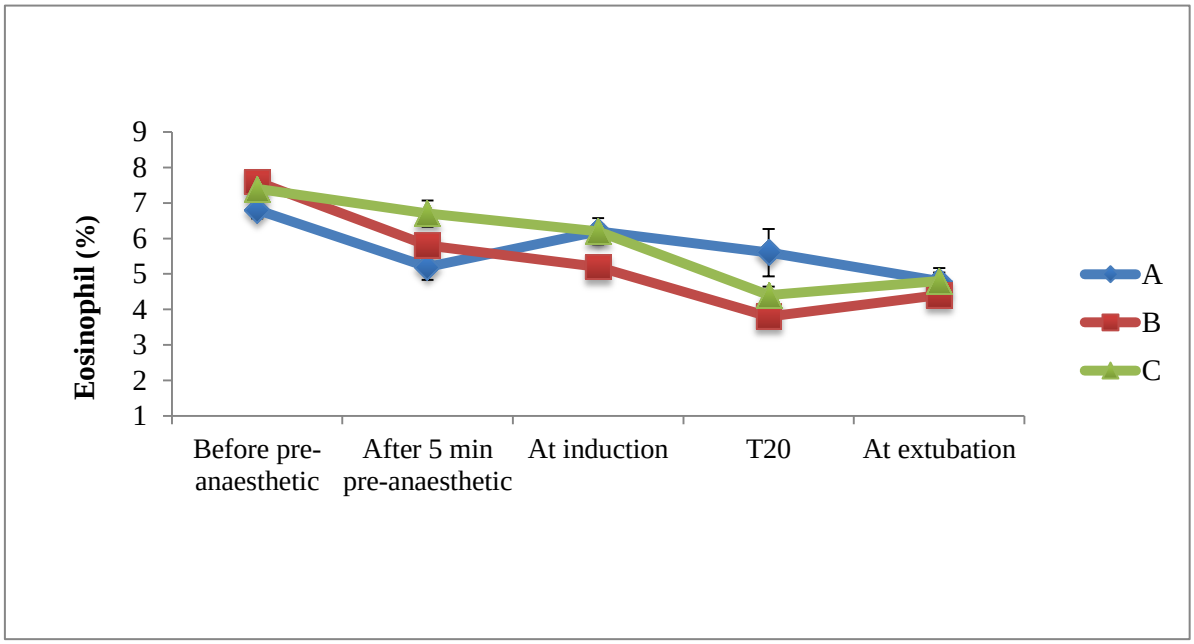


Figure 33: Mean ± SE values of eosinophils (%) recorded in different groups at various time intervals.

The value of eosinophil (%) in group A was decreased non- significantly ($p>0.05$) after pre-medication to entire observation period in comparison to base value except at extubation value was significantly ($p<0.05$) lowered .Where as in group Band C eosinophil (%) value was decreased significantly after premedication to entire observation period .

Comparison between different groups showed that eosinophil (%) value was non-significantly ($p>0.05$) change at different stage.

Biochemical observation

Serum glucose

A	70.2^{a} ±3.55	81.2^{ab} ±4.76	88^{abc} ±4.24	101^{bc} ±3.84	104.8^{cA} ±4.88
B	75.8^{a} ±3.05	84^{ac} ±4.18	78.8^{ac} ±4.63	106.4^{b} ±5.92	96.2^{cAB} ±4.73
C	72.6^{a} ±2.76	78.6^{ab} ±2.89	75.2^{a} ± 2.59	94.2^{b} ±6.47	87.2^{abB} ±6.34

Table 35: Mean ± SE values of serum glucose recorded in all the three groups at various intervals. (Figure no.- 34)

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

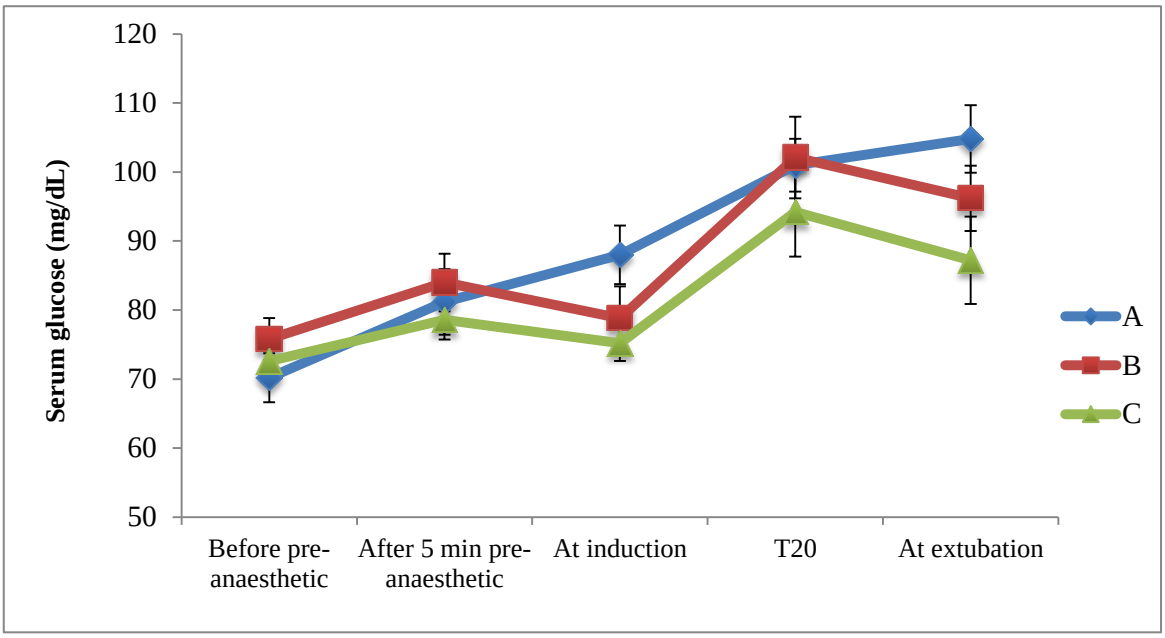


Figure 34: Mean ± SE values of serum glucose (mg/dL) of animals recorded in different groups at various time intervals.

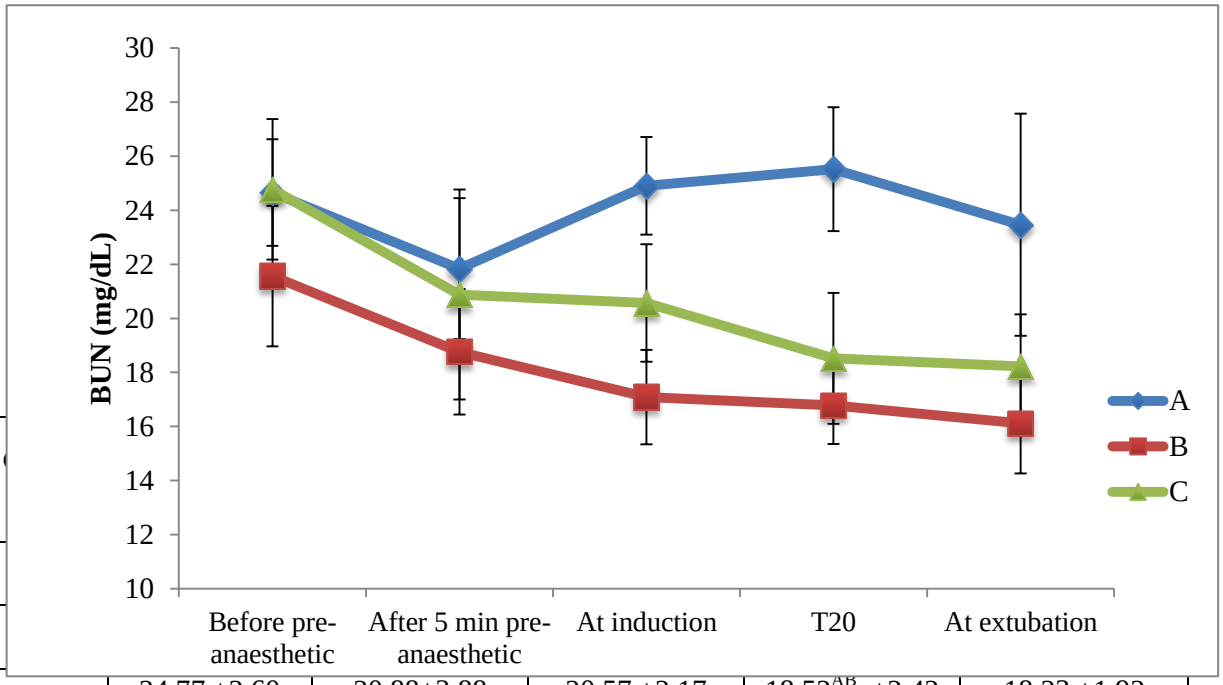
The value of serum glucose in all three groups were increased non- significantly after 5 minutes of premedication to induction in comparison to base value. Similarly In all the three groups value were increased significantly (p<0.05) during entire observation period.

Comparison between different groups showed that serum glucose non- significantly (p>0.05) change after premedication, to entire observation period at different stage, except at extubation significantly (p<0.05) change in group A respect to group B.

Blood urea nitrogen (BUN)

Table 36: Mean ± SE values of serum blood urea nitrogen (BUN) (mg/dL) recorded in all the three groups at various intervals. (Figure no.-35)

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



C	24.77 ±2.60	20.88±3.88	20.57 ±2.17	18.52^{AB} ±2.42	18.23 ±1.92

Figure 35: Mean ± S.E. values of blood urea nitrogen (mg/dL) of animals recorded in different groups at various time intervals.

The values of serum blood urea nitrogen (mg/dL) in the all three groups were decreased non-significantly ($p<0.05$) after premedication in respect to the base values.

In groups A blood urea nitrogen value was non - significantly decreased 5 minutes after pre-medication to entire observation period. except at T20 maintenance of anaesthesia value was Increased non- significantly. In the group B and group C blood urea nitrogen value was decreased gradually from pre-medication to entire observation period in comparison to base values.

Comparison between different groups showed that serum blood urea nitrogen (mg/dL) non-significantly ($p>0.05$) change at different stage during observation period, except at T20 during maintenance of anaesthesia value was significantly ($p<0.05$) lowed in group B with respect to group A.

Creatinine

Table 37: Mean ± SE values of creatinine (mg/dL) recorded in all the three groups at various intervals. (Figure no.-36)

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

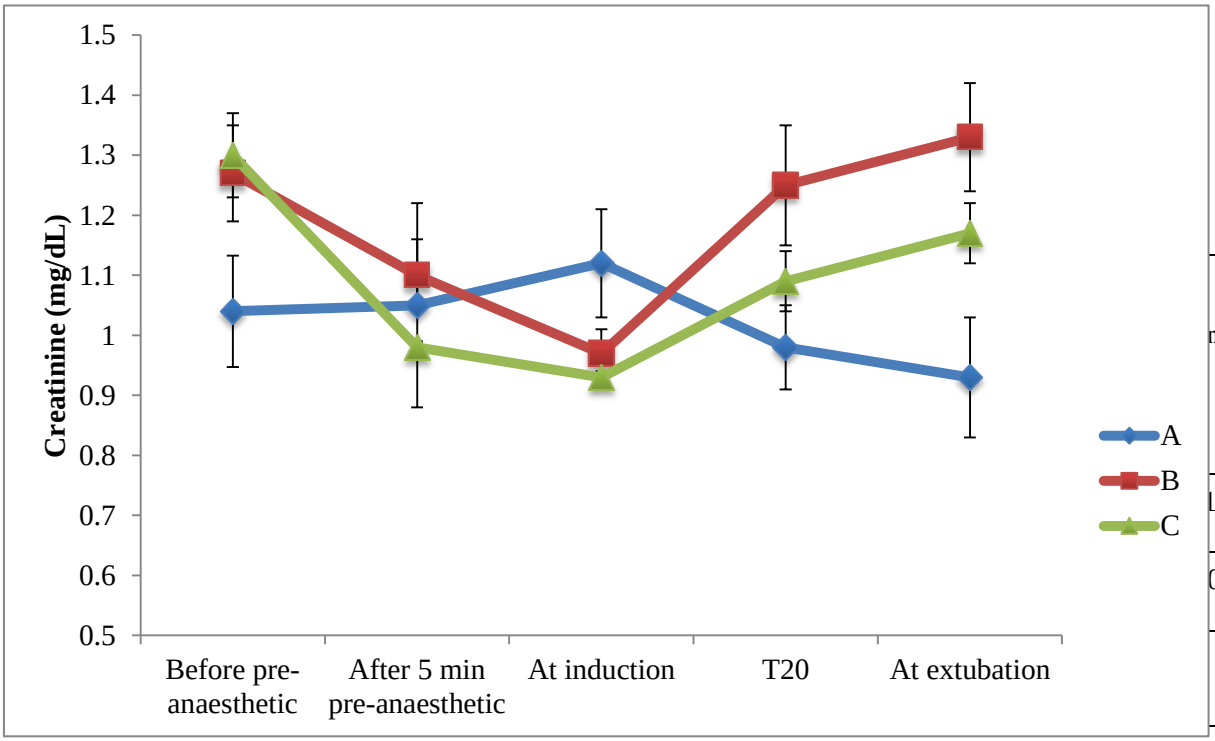


Figure 36: Mean ± SE values of serum creatinine (mg/dL) of animals recorded in different groups at various time intervals.

The value of creatinine (mg/dL) in group A was increased, non- significantly (p>0.05) after premedication to at induction comparison to base value, after that value was decreased non- significantly (p>0.05) at T20 to entire observation period. Where as in group B value was decreased non- significantly after premedication to entire observation period in comparison to base value , except at extubation value was increased, non- significantly (p>0.05). however in group C value was decreased non- significantly after premedication to entire observation period in comparison to base value , except at induction value was decreased significantly .

Comparison between different groups showed that creatinine (mg/dL) value was non-significantly (p>0.05) change at different stage, except at extubation value was significantly (p<0.05) lower in group B with respect to group A.

Alkaline amino transferase (ALT)

Table 38: Mean ± SE values of serum ALT (IU/L) recorded in all the three groups at various intervals. (Figure no.-37)

Groups	Before pre-anaesthetic (0)	After 5 min pre-anaesthetic (15)	At induction (20)	T20 (40)	At extubation (90)
A	37.64 ±1.26	36.96 ± 2.47	32.74^{A}±2.14	30.71^{A} ± 2.47	32.57^{A} ± 2.41
B	29.19 ± 5.38	27.55 ±4.37	22.67^{B} ± 4.16	20.62^{B} ± 5.10	19.12^{B} ± 4.01
C	38.12 ± 2.30	32.41 ± 3.10	34.10^{AB} ± 4.55	30.28^{AB} ± 3.56	33.20^{AB} ±3.75

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

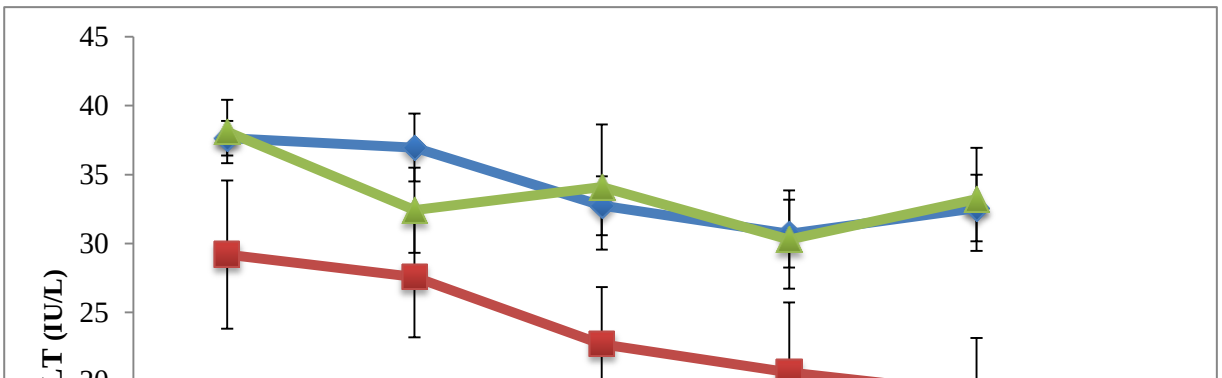


Figure 37 : Mean ± SE values of asparte amino transferase (IU/L) of animals recorded in different groups at various time intervals.

The value of serum ALT (IU/L) in all three groups were decreased non- significantly (p>0.05) after premedication to entire observation period in comparison to base value. Comparison between different groups showed that serum ALT (IU/L) non- significantly (p>0.05) change after 5 minutes of premedication, Where as in group A significantly change with group B at induction to entire observation period at different stage **.**

Aspartate amino transferase (AST)

Table 39: Mean ± SE values of serum AST (IU/L) recorded in all the three groups at various intervals.(Figure no.-38)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	At extubation
A	59.74± 3.58	56.47± 3.33	50.98± 5.16	48.59± 4.29	48.4^{A} ± 3.18
B	58.55± 4.20	57.19± 4.86	56.04± 7.03	54.52± 6.43	55.17^{B} ± 5.71
C	61.67^{a} ± 3.57	54.8^{ab} ± 2.61	46.92^{a} ± 3.51	47.24^{a} ± 2.47	42.75^{acAB}± 3.76

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

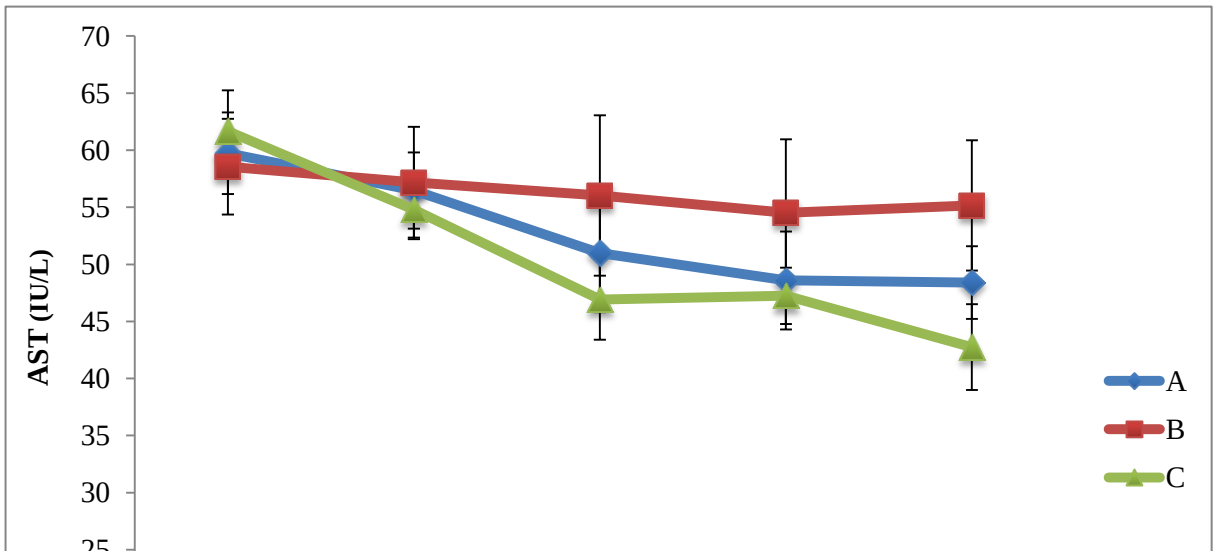


Figure 38: Mean ± SE values of alkaline amino transferase (IU/L) of animals recorded in different groups at various time intervals.

The value of serum AST (IU/L) in all three groups were decreased non- significantly after premedication to entire observation period in comparison to base value. Result also showed that in group C value was significantly lower at extubation comparison to induction.

Comparison between different groups showed that serum AST (IU/L) value was non-significantly (p>0.05) change after premedication to entire observation period at different stage, except at induction value was significantly change in group A with respect to group B.

Cortisol

Table 40: Mean ± SE values of serum Cortisol (nmol/L) recorded in all the three groups at various intervals. (Figure no.-39)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	At extubation
A	86.35^{a} ±4.33	99.71^{abA} ±3.61	106.3^{bcA} ±4.27	113.54^{bc} ±3.30	121.70^{cA} ±3.46
B	78.11^{a} ±3.01	83.32^{aB} ±2.13	80.49^{aB} ±3.73	107.84^{b} ±3.75	100.61^{bB} ±3.01
C	79.33^{a} ±2.07	89.05^{abAB} ±3.09	80.25^{aB} ±3.23	101.37^{b} ±4.50	98.49^{bB} ±3.27

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

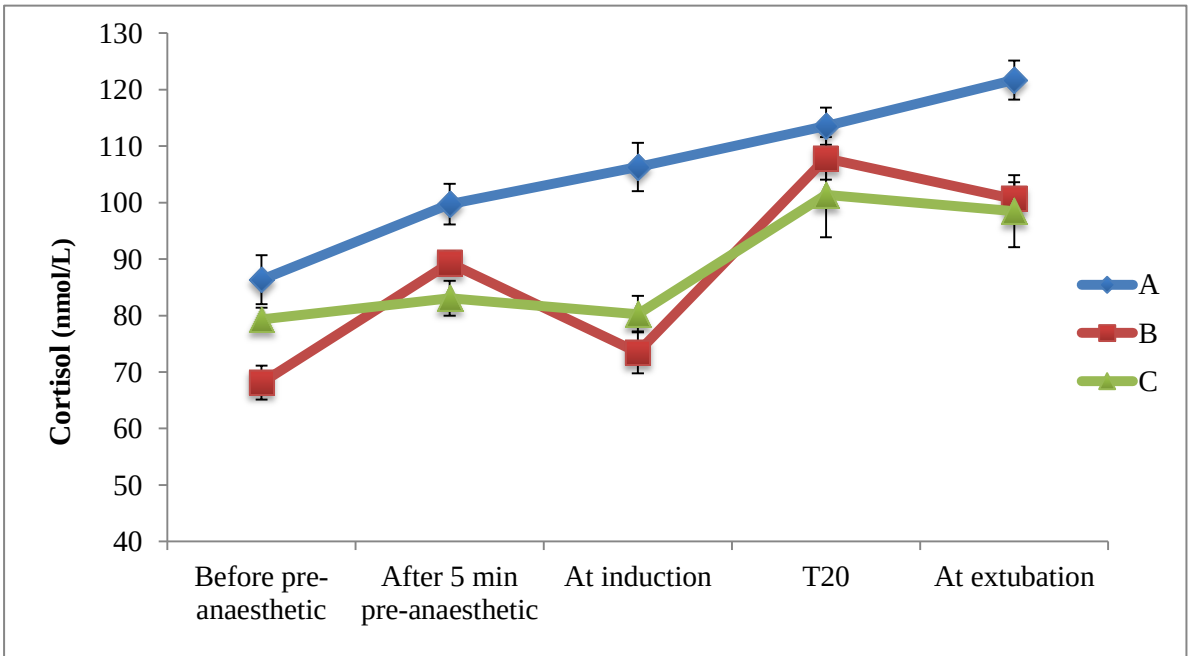


Figure 39: Mean ± SE values of Cortisol (nmol/l) of animals recorded in different groups at various time intervals.

The value of Cortisol in all three groups were increased non- significantly (P>0.05) after premedication to induction in comparison to base value, except in group A at induction value was increased significantly, after that in all the three groups value was increased significantly (p<0.05) at T20 maintenance of anaesthesia to entire observation period.

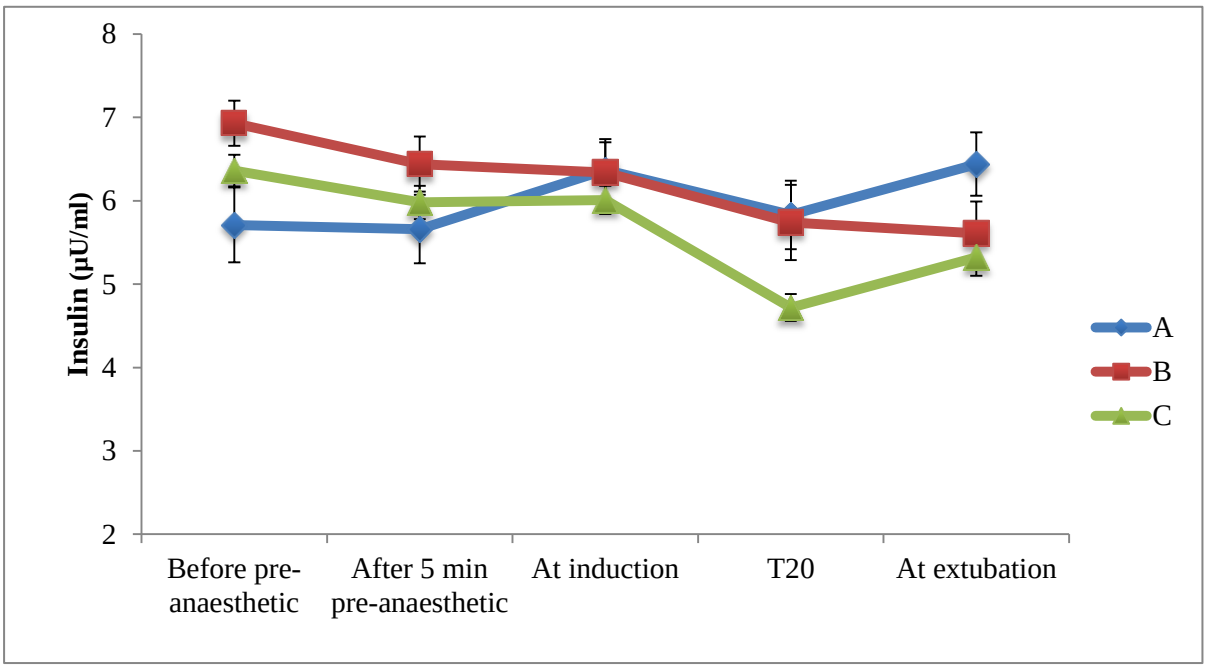
Comparison between different groups showed that cortisol significantly change in group A respect to group C after 5 minutes of premedication, whereas value was significantly (p>0.05) change in group A respect to group B and C at induction to entire observation period except at T20 maintenance of anaesthesia value was non – significantly in all the three groups .

Insulin

Table 41: Mean ± SE values of serum insulin (µU/ml) recorded in all the three groups at various intervals. (Figure no.-40)

Groups	Before pre-anaesthetic	After 5 min pre-anaesthetic	At induction	T20	At extubation
A	5.71^{a} ±0.45	5.66^{abA} ±0.41	6.37^{abA} ±0.37	5.83^{abA} ±0.41	6.44^{bA} ±0.38
B	6.93^{ac} ±0.27	6.44^{abB} ±0.33	6.34^{aB} ±0.36	5.74^{cbB} ±0.45	5.61^{dbC} ±0.38
C	6.36^{a} ±0.19	5.98^{abB} ±0.20	6.01^{aB} ±0.17	4.72^{bB} ±0.16	5.32^{aB} ±0.22

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



at various time intervals.

In group A value was decreased non – significantly (P>0.05) after premedication to entire observation period except at extubation value was significantly lower comparison to base value. In group B value was decreased non- significantly 5 minutes after premedication comparison to base value, whereas value was increased non-significantly at induction to entire observation period, except at T20 value was decreased significantly (P<0.05). In group C insulin value was decreased non – significantly after premedication to at induction in comparison to base value, whereas value was decreased significantly at T20 maintenance of anaesthesia to entire observation period.

Comparison between different groups showed that serum insulin significantly (p<0.05) change in group A respect to group B and C after 5 minutes of premedication, to during maintenance of anesthesia in at different stage, at extubation value was significantly (p<0.05) change in all the three groups.

5. DISCUSSION

Physiological observations

Rectal temperature

The rectal temperature (^{0}F/minute) was decreased non-significantly 5 minutes after premedication and become significant at T40 in group A, T20 in group B and at induction in group C in respect to base values.

Rectal temperature decreased after pre- medication might be combine effect of CNS depression, decrease in muscular activity and basal metabolic rate (Singh *et al*., 2009). Induction of anaesthesia with propofol was caused further depression of rectal temperature but remained within a normal physiological range similar finding also observed Sharma and Bhargava (2007) and Maney *et al*. (2013). Reduction of rectal temperature after induction might be due to the additive effect of pre- anaesthetic agents and propofol (Robertson *et al*., 1992) or due to depression of thermoregulatory system by propofol (Carlson and Champman, 1981). Since Alpha 2 agonist caused decreased in rectal temperature by reducing activity of muscle and heat production by in habiting the thermoregulatory mechanisms of central nervous system (Virtanen,1989), simultaneously alpha-2 agonists also decrease cutaneous losses of heat by peripheral vasoconstriction and redistribution of blood, which may be reason that body temperature remain in normal physiological range.

Opioid reduced body temperature by decreasing basal metabolic rate (Ku-Kanich and Wiese, 2015). After induction with propofol the rectal temperature further decreases in all the groups. This effect may be due to thermoregulatory mechanism depression, vasodilatation, depression of peripheral circulation, inhibition of muscle tone and decrease in metabolic rate after administration of propofol (Ponder and Clarke, 1980 and Gadawski,1998).

Respiratory rate

The respiratory rate (breaths/minute) was decreased significantly in all groups after premedication to T40 during maintenance of anaesthesia with isoflurane in comparison to base value.

Respiratory depression occurred after preanaesthetic administration attributed due to direct depression of respiratory centre (Singh *et al*., 2013). Induction of anaesthesia with propofol caused further depression of respiratory rate (Adetunji *et al*., 2002). Similar to present study Jena *et al*., (2014) reported significant decreased in respiratory rate after 10 minutes of pre-medication with xylazine and dexmedetomidine followed by induction with propofol.

Respiratory depression enhance by opioids through acting on mu and delta receptors of respiratory centres at medulla and mureceptors of chemoreceptor sites (White and Irvine, 1999). Respiratory rate significantly decrease when alpha-2 agonist used in combination with butorphanol reported by Muir *et al*., (1999). Similar to present study Silva *et al*., (2010)

reported pre-medication with dexmedetomidine and induction with propofol anaesthesia in canines caused significantly reduction in respiratory rate as observed in groups C and D. Patond (2016) also observed a significant decreased in respiratory rates by DEX irrespective of the dose that persisted during propofol anaesthesia and surgery. Contrary to present study Rafee *et al*., (2017) reported that respiratory rate declined but non significantly when dexmedetomidine (I/M) and butorphanol used in combination or, dexmedetomidine (I/M) alone.

Heart rate

Heart rate in group A was decreased significantly and in group B and C was increased significantly 5 minute after pre-medication , after that value was non- significantly decreased in group A and C whereas increased in group B at induction in comparison to base values.

Heart rate decreased significantly in group A after IM injection of xylazine might be inhibit both sympathetic and parasympathetic systems that results heart rate decreases. Tranquilli *et al* ., (2007);Plumb , (2008) and Hall *et al* , (2001) also reported that dose dependent effect of xylazine on heart rate. Cardiovascular function affected by alpha 2 agonists (Mc-Sweeney *et al*., 2012), bradycardia develops with increased vagal tone and decreased sympathetic activity (Hayashi and Maze 1993).

Heart rate increased after pre-medication and reached the highest level at15 minute after pre-medication with atropine, butorphanol, and dexmedetomidine combination reported by Rafee *et al*. (2017) as observed in present study. Bradycardia induced by alpha-2-agonist in canine can be reversed by pre-emptive administration of atropine and caused initial tachycardia reported by Alibhai *et al*. (1996).Both butorphanol and dexmedetomidine develops bradycardia by the activation of parasympathetic tone (Ko *et al* ., 2000 and Bloor *et al*.,1992).Mild tachycardia for a short duration develops by Propofol reported by (Kojima *et al*.,2002). Isoflurane also increased heart rate but depends upon alveolar concentration (Picker *et al*., 2001). Consequentlyeffect of these pre-anaesthetic, propofol, and isoflurane could be responsible for changes in heart rate under acceptable limit.

Oxygen Saturation of Haemoglobin

Oxygen Saturation of Haemoglobin (SpO2) in group A was decreased non- significantly however in group B and C SpO2 value was significantly decreased 5 minute after premedication in comparison to base values. However SpO2 remained normal physiological range under entire observation period.

Pulse oximeter shows low reading when arterial oxygenation and tissue perfusion reduced. However, it can also shows due to vasoconstriction (Leppanen *et al*.,2006). In groups B and

C oxygen saturation of haemoglobin initially decreased might be due to vasoconstriction caused by dexmedetomidine (Kuusela *et al*., 2000 and Leppanen *et al*., 2006), it may also due to respiratory depression caused by sedation or due to technical fault (Leppanen *et al*., 2006). Significant decrease in SpO2 observed by Kushwaha *et al*.(2012) after pre-medication with dexmedtomidine followed by induction with propofol. Quandt *et al*. (1998) also reported similar observation, when propofol used for induction. The non- significant changes in oxygen saturation in the present study might be due to all the animals immediately intubate endotracheal tube to maintain airway passage and concurrent administration of oxygen during maintenance of anaesthesia with isoflurane. However , oxygen saturation decreased during maintenance of anaesthesia also observed by Bishnoi and Saini (2005). Bufalari *et al* (1998) reported mean oxygen saturation remained higher than 90% when induced by propofol and maintenance with either halothane or isoflurane.

Similar finding reported by Kuusela *et al*.(2001a) throughout observation period from pre-medication to maintenance of anaesthesia when premedicated with dexmedetomidine followed by induction with propofol and maintenance with isoflurane. However, significant decreased in oxygen saturation (SpO2) after 5 min of anaesthesia with propofol reported by SenandKiliç (2018).

Clinical observations

Depth of Analgesia

Depth of analgesia was increased significantly after premedication to entire observation period in respect to base values. Comparison between different groups showed that depth of analgesia value was significantly lower in group A in comparison to groups B and C.

By measuring withdrawal reflex of limb against a painful stimulation in inter-digital region used to evaluate the depth of analgesia (Poree *et al*. 1998 and Kuusela , 2004). After pre-medication scores for depth of analgesia significantly increased and complete analgesia was observed from induction with propofol to maintenance with isoflurane in all groups. Analgesia produced by butorphanol might be activation of kappa receptors (Monteiro *et al*., 2009), however butorphanol analgesic properties are not potent (Kojima *et al*.,1999a and Murrell, 2007). After systemic administration of DEX alone or with butorphanol pedal reflex was sluggish that was also observed by Rafee *et al* (2017). Similar finding was also observed by Akbar *et al*. (2014) with dexmedetomidine and propofol combination in canines. The

analgesia produced by dexmedetomidine is mediated at the spinal level (Hayashi *et al*., 1995). Alpha-2 agonists interrupt nociceptive pathways on ventral root of dorsal horn and lower the spinal reflex in the animals (Kending *et al*.,1991 and Savola and Virtanen, 1991). Dexmedetomidine induced antinociception might be apart of acetylcholine rescues in the spinal cord (Klimscha *et al*.,1997).

Jaw Relaxation

Jaw relaxation was increased significantly after premedication to entire observation period in respect to base values. Comparison between different groups showed that Jaw relaxation value was significantly higher in group A in comparison to groups B and C.

Jaw tone become sluggish after the administration of xylazine/dexmedetomidine in groups due to inhibition of alpha 2 adrenoceptors in the interneuron level of spinal cord. (Sinclair 2003). Some time jaw tone score was more in the dexmedetomidine groups than the xylazine group due to higher potency of dexmedetomidine. (Scheinin *et al*., 1989)

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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). Higher sedation score with dexmedetomidine could be to central attributed alpha-2 agonists induce deep sedation along with analgesia and relaxation of muscle (Maze and Tranquilli, 1991 and Correa-Sales *et al.,* 1992). Marked synergistic effect was also observed between alpha-2 agonists, and butorphanol (Hammond and England, 1994). This synergistic effect between dexmedetomidine and butorphanol caused deep sedation (Pypendop 2017). Chevallier *et al.,* (2018) also reported that medetomidine and butorphanol combination produced adequate sedation score.

Salivation

In the present study no salivation was observed after pre-premedication to entire observation period in dog. One known side effect of benzodiazepines in canines is hyper salivation (Haskins *et al.,* 1986, Court and Greenblatt, 1992), sometime vomition and salivation were observed even after administration of propofolin canines (Smith *et al.,* 1993). However, Bufalari *et al.,* (1998) reported no abnormal salivation and vomition after induction with propofol. In present study clear view of the larynx was observed without the presence of saliva during intubation in all animals, which might be due to pre-medication with atropine (Lemke, 2007).

Dose of propofol

Doses of propofol in groups A, B and C were 2.85 ± 0.11 mg/kg, 1,86 ± 0.16 mg/kg and 1.35 ± 0.22 mg/kg respectively.

Comparison between groups showed that dose of propofol for induction of anaesthesia in groups A was significantly higher in compare to the groups B and C. comparison between groups also showed that group B required non- significantly higher induction dose of propofol in comparison to group C.

In unpremedicated canines the induction dose of propofol have wide range reported by Jiménez *et al*.(2012) and Robinson and Borer-Weir (2013).For induction the minimum dose of propofol was 2mg /kg (Robinson and Borer-Weir, 2013) , average dose for induction was 6mg/kg in canine (Doebeli *et al*.,2013). Similar induction dose 5.55mg/kg of propofol in canine reported by David (1992) while in sheep as 5 mg/kg (Zama *et al*.,2003) and in goats as 4mg/kg (Amarpal *et al*.,2002). The induction dose of anaesthetic agents markedly reduces by Dexmedetomidine through reducing the central noradrenergic neuro transmission and pharmacokinetic interaction of the drugs (Buhrler *et al*.,1994 and Aantaa *et al*.,1990).

Incidence of Apnea

Incidence of apnoea recorded in groups A, B and C was 33.33%, 20%, and 0%, respectively.

The most common and frequent complication with induction by propofol is Incidence of apnoea that depends on speed and dose of propofol administration (Langley and Heel, 1988; Kojima *et al*., 2002 and Sano *et al*.,2003b). Kuusela *et al* .(2001a) also reported that in 15% canines incidence of apnoea lasted for 1to 2 minutes, after pre-medication with dexmedetomidine (20µgm/kg) accompanied by induction with propofol. By slowly administering of propofols apnoea can be avoided. When propofol is injected too fast, it can develops apnoea (Smith *et al*., 1993). However, due to rapid redistribution and metabolism of propofol, if the propofol is injected too slowly the animal may not anesthetised adequately. So, apnoea can be prevented and induces adequate general anesthesia by proper administration of propofol (Langley and Rennie, 1988).

Recovery time

The mean values of recovery time recorded in canines of all the three groups A, B and C were 13.6 ± 1.36 min, 12.4 ± 1.36 min, and 15.2 ± 1.36 min, respectively.

In many earlier studies in canines (Pires *et al*.,2000; Redono *et al*., 2000; Adetunji *et al*., 2002; Mathews *et al*., 2004; Ajadi *et al*., 2007; Seliskar *et al*.,2007 and Surbhi, 2008) ,

caprices (Carroll *et al*.,1998) and buffalo calves (Ahmad, 2009), Ferre *et al*. (2006) has been reported that Rapid and smooth recovery after anaesthesia is due to the sedative effects of the pre-anaesthetic agents persisted into the recovery period. The relation between potency of CNS depression by pre-anaesthetic medications with induction dose, and the recovery time is very close (Kojma *et al*., 2002). The prolonged recovery time could be depressive effect on central nervous system by the combination of butorphanol and dexmedetomidine (Sharma *et al.,* 2014). Sharma *et al*. (2014) also reported that recovery following anaesthesia with combination of butrophenol, xylazine, ketamine or butrophenol, dexmedetomidine, ketamine was excellent in majority of dog.

Duration of anaesthesia

Comparison between all the three groups showed non-significant difference in duration of anaesthesia. The time gap between absence of pedal reflex and the time of reappearances of pedal reflex of the animal was considered as the duration of anaesthesia (Adetunji *et al*., 2002). it was always noticed that time taken by the animals In gaining pedal reflex after cessation of isoflurane administration that could be important cause of Difference between duration of surgery and duration of anaesthesia.

Duration of surgery

Comparison between all the three groups showed non-significant difference in duration of surgery, since all surgery performed by same team of surgeon.

Sternal recumbency time

The mean values of sternal recumbency time recorded in different groups A, B, and C were 13.6 ± 1.36 min, 12.4 ± 1.36 min and 15.2± 1.36 min, respectively. Comparison between all the three group B had non - significantly lower sternal recumbancy time in comparison to group A and C.

After pre-medication with butorphanol and dexmedetomidine followed by induction with ketamine and maintenance by halothane, sternal recumbancy was 16.47+.97 minutes reported by Sharma *et al.,* (2014). However, when canine is treated with butorphanol and medetomidine sternal recumbency time was 73.5±19 minutes Ko *et al.,* (1996).

Urination time

Urination recorded after pre-medication in groups A, B and C were 16.66% , 66.66% and 83.33% respectively.

Production of urine increases due to the interaction between alpha-2 agonists and antidiuretic

hormone on the renal tubular cells and collecting duct reported by Gellai and Edwards (1988). Increased production of urine by alpha 2 agonists in other study by Duke *et al*., (1994) might be due to osmotic diuretic effect of higher concentration of blood glucose. Similar study in goats reported by Singh *et al.,* (2013). significant increase in urine output as compared to base line and also to control group after treatment with dexmedetomidine reported by Salah *et al., (*2013). Similar diuretic effect after administration of xylazine in goats was reported in several species (Trim and Hanson 1986, Thurmon *et al.,* 1984 and Burton *et al.,*1998). No significant difference in urine production after 24 hour, among the group or, within groups compared to baseline. The diuretic effect induced by administration of medetomidine (10 and 20µg/kg intravenously) that lasted for 4 hours reported by Burton *et al*., (1998).

Haemodynamic Observations

Blood Pressure

Blood pressure (BP) increased after the premedication with xylazine or dexmedetomidine , might be stimulation of peripheral alpha 2B agonist receptors which mediated transient initial hypertension of variable duration (Vainio and Palmu, 1989).The transient hypertension induces a reflex baroreceptor mediated physiological bradycardia (Schmeling *et al*., 1991). Propofol has been reported to decrease systemic arterial BP due to peripheral vasodilation (Sooryadas *et al* ., 2011) direct negative inotropic action and direct decrease of arterial and venous vascular tone (Surbhi *et al*., 2008).

Vasoconstrictive effect of alpha-2 adrenergic receptor agonists was attenuated by isoflurane anesthesia reported by Kenny *et al.,* (1989).The attenuation of the vasopressor effect of isoflurane by the alpha-2 adrenergic receptor agonists was considered to be non-selective and was not affected by the calcium channel blockers. In canines it was also observed that the pre-anaesthetic administration of medetomidine (Keegan *et al.,* 1995) or xylazine (Lemke *et al.,*1993) enhanced vascular tone, so attenuating isoflurane-induced vasodilatation and reducing the isoflurane requirement. Hypertension can also induced byanticholinergics (Alibhai *et al.,* 1996) and due to stimulating alpha -2adrenoceptors of blood vessels byhigher plasma concentration of dexmedetomidine results vasoconstriction and consequently hypertension (Mac Millan *et al.,*1996). After pre-medication with DEX (20µgm/kg) and medetomidine (40µgm/kg) Kuusela *et al*., (2001a) observed that significant elevation in MAP which decreased significantly after induction with propofol. Similarly, dose –dependent effect on MAP and DAP by medetomidine was reported by Ko *et al*., (2001). Regardless of whether dogs had been given saline solution or atropine significant increases in MBP and DBP were observed as the dose of medetomidine increased from 10 to 20µg/kg and from 10 to 40 µg/kg.

The systolic blood pressure was decreased after induction with propofol (Cima *et al.,* 2016).

Rapid reduction in arterial blood pressure occurred with bolus dose of propofol (5mg/kg) administered over 30s intravenously however, cardiac output was well maintained reported by Cattai *et al.* (2018). In canines minimum negative inotropic effect produced when propofol was used within clinical concentrations (Fujinaka *et al.,* 2012 and Ismail *et al.,* 1992). In canines decline in blood pressure occurred mostly due to vasodilatory effect of propofol. The vasodilatory effect of propofol occurred by decrease in sympathetic tone and by direct effect on smooth muscle of blood vessel. In canines induction of anaesthesia by propofol caused reduction of systemic vascular resistance and this reduction vary according to the dose of propofol (Wouters *et al.,* 1995). Cattai *et al.,* (2018) also reported that significant cardiovascular depression during continuous recording of arterial blood pressure.

Electrocardiographic (ECG)

A non-significant difference in amplitude of P wave , duration of QRS complex, duration of P wave, amplitude of R wave except group B ,T wave amplitude, Q-R interval, and S-T interval with their respective base line values and among different groups were observed after premedication. P-R interval non – significant difference in group A and significant difference in group B and C. At induction value was decreased significant amplitude of P wave in group A and B, PR-interval in group A and C, and amplitude of T wave in group C. After that value was increased significantly amplitude and duration of P wave in group B, amplitude of R wave in group B and C, PR- interval in group B and C, QT- interval in group B and C ST- interval in group C At T20 whereas at T40 value was increased significant duration of P wave , amplitude of R wave , PR-interval except in group A.

Tachycardia might be due to the administration of atropine, as an anticholinergic agent increases the heart rate by the muscarinic receptor blocking on the sino- atrial (SA) and auriculo-ventricle (AV) nodes (Ali-Melkkila *et al.,*1993). Present finding in groups C and D were in accordance with Rafee *et al*. (2016) who reported normal rhythm with atropine-dexmedetomidine and butorphanol. It was observed that amplitude of P wave in canines is correlated to heart rate (Avdosko *et al*., 2010). Although the morphology of the P wave corresponds to heart rate however, the P wave is mainly influenced by the autonomic system (Moise, 1998).

In the present study, amplitude of P wave increased possibly due to vagolytic effect of atropine. Ahmad *et al*., (2012) observed that amplitude of P wave decreased in canines following administration of dexmedetomidine and amplitude directly correlated to the heart rate. Hanton and Rabemampianina, (2006) evaluated the effect of anaesthetic agents on AV conduction and reported that for diagnosis of Ist degree AV block PR duration should be compared with their respective base value instead of arbitrary values. Present study was in accordance with

Cardoso *et al.,* (2016) who observed non-significant changes between post-sedation and base line values for P-wave, R-wave, or T-wave amplitude or QRS duration with acepromazine and butorphanol. Kuusela *et al.,* (2002) observed second degree AV block following administration of dexmedetomidine. Ko *et al.,* (1994) observed bradycardia and SA and AV blocks within two minutes after administration of atropine – medetomidine – etomidate in canine show ever; blocks disappeared with in8 minutes after administration of these drugs. Vernooy *et al.* (2006) reported marked increase in ST-segment at the right precordial leads with propofolanaesthesia in humans. The diagnostic value of change in amplitude of T wave in canines is very limited in comparison to humans as morphology of T wave is highly flexible in canines (Martin, 2007). Present Study showed that amplititude of T wave did not exhibit regular pattern but remained within clinically normal range. Amplitude of T may be biphasicorpositive/ negative (Tilley, 1985). Similar amplitude of T wave was observed in the present study. The inverted T wave could be related with hypoxia of the ventricles (Tilley1985). Biphasic T waves in the animal may be related to intra-operative hypokalemia (Tilley1992). Sooryadas *et al.,* (2011) were also reported biphasic T waves with xylazine – propofol anesthesia in canines.

Haematological observations

Haemoglobin (Hb) and packed cell volume (PCV)

Haemoglobin (Hb gm/dL) and PCV value in all three groups were decreased non-significantly after premedication to entire observation periodin comparison to base value. Result also showed that Hb value increasenon- significantly at extubation comparison to value at T20 during maintenance of anesthesia in all three groups.

Hb and PCV value decrease due to haemodilution develops due to fluid therapy (Surbhi *et al.,* 2010b and Singh *et al.,* 2013) or, due to intercompartmental fluid shift in order to maintain normal cardiac out-put (Wagner *et al.,* 1991) or, pooling of circulating erythrocytes in primary and secondary reservoirs to decreased sympathetic stimulation (Surbhi *et al*., 2010b and Singh *et al.,* 2013). Khan *et al*. (2006)also reported that Hb level was decreasedwhen propofol used as anaesthesia. Haemoglobin decrease due to vasodilatation induced by anaesthesia observed by Tranquilli *et al* .(2007). Passage of many red blood cells to microcirculation due to vasodilatation may also causes decrease in haemoglobin level reported by Naghibi *et al.* (2002). Due to intravenous fluid therapy haemodilution develops in animal consequently decrease in Hb and PCV level. Bloodf lowin most vital organs at expense of other non-vital organs as skin and pancreas, secured by dexmedetomidine (Jena *et al.,* 2014 and Sethi *et al.,* 2017).

Total leukocyte count (TLC)

The total leukocyte count (10^3 /µL) in all groups were decreased non significantly 5 minutes after pre-medication to entire observation period in comparison to base value.

Propofol caused a significant (<0.05) decline in TLC in canines, but later gradually increased towards baseline values reported by Anandmay *et al.,* (2016). Similar observation that is reduction in TLC after ovariohysterectomy as compared to the values of pre-ovariohysterectomy is reported by Fazio *et al.,* (2015). Splenic dilatation that causes splenic confinement of erythrocyte results in reduction in total leukocyte count value (Anandmay *et al.,* 2016).

Similar finding of present study in groups B and C reported by Jena *et al.,* (2014) that TLC value declined after pre-medication with dexmedetomidine followed by propofol anaesthesia. Khan *et al.,* (2006) also reported that TLC decreases after propofol anaesthesia in canine .The cause of TLC decreasing be due to elevation of adrenaline or nor-adrenaline concentration in peripheral circulation that depress the leukocyte proliferative activity along with confinement of RBC in spleen and lungs or, rise in plasma volume due to vascular pooling after anaesthetic administration (Komar *et al.,* 2003 and Venugopalan *et al.,* 2002). Similarly, total leukocyte count decrease when alpha2- agonists was used in canines also observed by Amarpal *et al.,* (1998b) and in goats by Hugar (1993) and Kumar and Thurmon (1979) .

Total erythrocyte count (TEC)

The total erythrocyte count (10^6/µL) in all groups were decreased significantly after pre-medication to entire observation period in comparison to base value.

In support of present study decrease in total erythrocyte count was reported by Durrani *et al.,* (2009), Emami *et al.,* (2010), Amarpal *et al.,* (2010) and Mahmud *et al.,* (2014). Non-significant decrease in TEC also reported by Mazumdar *et al.,* (2015) following premedication with dexmedetomidine. Pre- medication with DEX-BUT combination and induction and maintenance with propofol TEC significantly reduced (Mate and Aher, 2018). Due to splenic pooling of erythrocyte and subsequent haemodilution dexmedetomidine reduces the erythrocyte count.

Differential leukocyte count

Present study showed a non-significant difference in differential leukocyte count. The non-significant increased in neutrophil during observation periods might be related to the anaesthetic and surgical stress that causes activation of adrenal cortex and subsequent production of glucocorticoid that acts on the circulating neutrophils (Solimon *et al.,* 1965).

Amarpal *et al.* (1998a) reported that after pre-medication with alpha-2 agonist in canine neutrophil count decreases this is contrary to present study. Chacko (2003) also reported that after epidural use of fentanyl citrate in canines neutrophils count decreases and lymphocytes count increase. Similar finding also observed by Chacko (2003) as present study that is non-significant change in monocyte and basophil count. Increase in neutrophil and decrease in lymphocytes, similar finding observed in canine after systemic administration of propofol by Kelawala *et al., (*1996) and (Surbhi, 2008).

Biochemical observation

Serum glucose

Serum glucose in all groups was increased non- significantly after 5 minutes of premedication to induction and increased significantly during entire observation period, except in group B at extubation in comparison to base value.

During anaesthesia the activation of adrenal medulla and sympathetic nervous system results movement of glycogen from the liver thus increase in serum glucose due release of epinephrine. In the present study increased level of serum glucose in groups B and C was in accordance with Sharif and Abouazra (2009) that reported temporary hyperglycaemia might be due to increased secretion of hormone like Cortisol and growth hormone in canines under stressful conditions, especially during anaesthesia. Alpha-2 adrenergic agonist inhibits insulin production from alpha cell of pancreas, increased secretion of adreno cortical hormones due to traumatic stress and restraining of animals caused sympathetic stimulation ultimately enhancing secretion of hormone from cortex of adrenal gland might be responsible for hyperglycaemia (Mirakhur *et al.,*1984). Kinjavdekar *et al.,* (2000) reported medetomidine- ketamine caused arise in serum glucose in canine. sheep, goats, cattle and buffalo also develops hyperglycaemia after administration of xylazine . Decreased glucose transport by the membrane, insulin activity or increased concentration of adreno cortical hormones and decreased utilization of glucose mediated by dexmedetomidine (Burton *et al.,* 1997 and Restitutti *et al.,* 2012) responsible for further rise in serum glucose level in groups B and C in the present study.

Blood urea nitrogen (BUN)

Serum blood urea nitrogen (mg/dl) in the all groups was decreased non-significantly 5 minutes after premedication to entire observation period in respect to the base values, except in group A at T20 value was increased.

Similar result also reported by Surbhi *et al.*(2010a) in canine operated orthopaedic surgery following premedication with xylazine, medetomidine or dexmedetomidine followed by induction with propofol.

Mukati *et al.* (2004) observed no any change in biochemical parameters in dogs except hyperglycemia propofol anaesthesia. The present study also showed at 5 minutes after pre-medication and just after induction blood urea nitrogen values were remainnearly same. Similar result also reported by Kalaiselvan (2018) following pre-medication with DEX-BUT accompanied by induction and maintenance with propofol and isoflurane respectively. In the present study, decrease in blood urea nitrogen level might be due to continuous intravenous infusion of fluids, which maintained the normal kidney functions results.

Creatinine

The creatinine (mg/dl) in group A was increased, non - significantly Where as in group B and C value was decreased non- significantly 5 minutes after premedication. After that value was decreased non- significantly at induction to entire observation period, except in group A at induction and in group B at extubation increased non- significantly. In group C at induction decreased significantly.

Marginal changes in creatinine in present study may be due to the intrinsic auto regulatory capacity of the kidney that maintain generally constant renal blood flow rate and glomerular filtration rate variations in spite of variations in systemic arterial pressure between 75 and 160 mmHg (Brown, 1993). Even without concurrent intravenous fluid administration sufficient renal function was maintained in healthy canines during elective surgery under general anaesthesia reported by Lobetti *et al*., (2000). Dogs kidney are generally resistant to ischemia that developed by hypotensive shock. Dexmedetomidine preserved blood supply to most vital organs at the cost of non-vital organs, that may be reason behind marginal non-significant decreased in serum creatinine in groups B and C and this redistribution does not depend upon type of anaesthesia used for maintenance (Lawrence *et al.*, 1996). Adequate renal blood flow and normal glomerular filtration to maintain Creatinine values near the base values may be also due to continuous fluid therapy and redistribution of blood supply by DEX. Similar finding was reported by Kalaiselvan (2018). Serum creatinine non-significantly decreased when pre-medication by dexmedetomidine accompanied by induction with propofol also observed by Jena *et al*., (2014).

Aikaline amino transferase (ALT) and Aspartate amino transferase (AST)

Serum ALT (IU/L) in all groups was decreased non- significantly after premedication to entire observation period in comparison to base value.

The value of serum AST (IU/L) in all three groups were decreased non- significantly 5 minutes after premedication to entire observation period in comparison to base value.

After systemic administration of dexmedetomidine non-significant increased in serum ALT levels in the canines similarly reported by Sharma *et al.,* (2014). Non-significant difference in serum AST and ALT in calves caused by medetomidine was reported by Singh *et al*., (2010). However, serum AST and ALT values decline within the clinically normal range during propofol anaesthesia in canines (Kwon *et al.,* 1998).

Cortisol

Cortisol was increased non- significantly after premedication to induction in comparison to base value, except in group A at induction value was increased significantly, after that value was increased significantly at T20 maintenance of anaesthesia to entire observation period in all three groups.

Stress level of the animal can be presumed by the estimation of plasma cortisol value. Levels of stress – related hormones can be reduced by the administration of alpha 2 agonists, thus attenuate the stress response of surgery reported by (Ko *et al*., 2000). Ambrisko *et al*., (2002) reported not any effect on canine cortisol levels following clinical IM dose of racemic medetomidine. Similarly Kuusela *et al.,* (2003) reported that no influence of propofol on plasma Cortisol concentration at the end of anaesthesia and during recovery in dexmedetomidine pre-medicated dogs. The Cortisol levels increased due to the anaesthetic and surgical stresses in the animals even stress attenuation response of xylazine / dexmedetomidine

Insulin

The value of insulin in all three group was decreased non- after 5 minutes of premedication to induction in comparison to base value.

In group A value was decreased non – significantly after premedication to entire observation period except at extubation value was significantly lower comparision to base value. In group B value was increased non- significantly at induction in comparison to base value, after that value was decreased significantly during maintenance of anesthesia where as insulin value was increased non- significantly at extubation in comparison to base value. In group C insulin value was decreased non – significantly after premedication to at induction in comparison to

base value, whereas value was decreased significantly at T20 maintenance of anaesthesia to entire observation period.

Stimulation of glucagon release or suppression of insulin release or, both in alpha and beta cells of the pancreas, develops hyperglycemia following administration of alpha 2 agonists like medetomidine (Surbhi *et al.,* 2010b) and dexmedetomidine (McSweeney *et al.,* 2012) might be reason for hyperglycemia in present study. Significant increase in glucose in present study during anaesthesia might also be due to decreased glucose utilization, impaired insulin activity, decreased membrane transport of glucose and increased blood concentration of adrenocortical hormones as reported in dogs (Restitutti *et al.,* 2012). similar result also reported in dog with propofol anesthesia (Khan *et al.,* 2006).

6. SUMMARY AND CONCLUSIONS

The present clinical study was carried out on 18 clinical cases of female dogs irrespective of age and weight presented for soft tissue surgery i.e. ovariohysterectomy and non – malignant mammary tumor at the Department of Surgery and Radiology, Bihar Veterinary College, Patna to evaluate and compare the effect of xylazine and dexmedetomidine with propofol and isoflurane .

The animals were randomly divided into 3 groups, viz. Group A, B and C with 6 animals in each groups. The animals of different groups were administered the following drugs for pre-medication, induction and maintenance of anaesthesia for elective soft tissue surgery.

All animals were pre-medicated with atropine sulphate @ 0.04 mg/kg b.wt IM in all group, after 10 minute give Butrophanol @ 0.2mg/ kg b.wt IM in all group after give

Xylazine @ 1 mg/kg b.wt IM in first group and dexmedetomidine @ 5µg/kg b.wt and 10 µg/kg b.wt in second and third group respectively. The induction of anaesthesia was achieved by propofol as per requirement. The maintenance of anaesthesia was achieved by isoflurane.

During the present study various physiological, haematological, biochemical, and haemodyamic evaluations were carried out to evaluate and compare the effect of xylazine and dexmedetomidine with propofol and isoflurane anaesthesia. In clinical parameters, sedation score, Jaw relaxation, depth of analgesia, dose of propofol, incidence of apnea and salivation were recorded and evaluated in all groups. Similarly, recovery time, sterna recumbency time, urination 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, Spo2 diastolic blood pressure, systolic blood pressure, mean arterial pressure and ECG were recorded before pre-anaesthetic administration, 5 minutes after premedication, Immediately after induction with propofol, 20 and 40 minutes during maintenance with isoflurane and just after extubation.

Haematological parameters like haemoglobin, PCV, TLC, TEC and DLC and biochemical parameters like serum urea nitrogen, serum glucose, serum Creatinine, ALT, AST, Insulin and cortisol were estimated 5 minutes after premedication, Immediately after induction with propofol and 40 minutes during maintenance with isoflurane and just after extubation.

On the clinical and physiological examination adequate sedation, depth of analgesia and muscle relaxation was observed in the animals of all the groups and this sedation made handling of the animals properly and safe. On clinical parameters, the mean values of recovery time in groups A, B, and C were 13.6±1.32 min, 12.4±1.26 min, and 15.2±1.14 min respectively. The mean values of sternal recumbency time in groups A, B and C were 30±1.7 min, 26.6±1.54 min and 33.2±2.52 min respectively. The mean values of duration of surgery in groups A, B and C were 43.4±3.93 min, 45.2±4.59 min and 35± 4.18 min respectivety. The mean values of urination time in A, B and C were 16.66%, 66.66% and 83.33% respectively. The mean values of doses of propofol in groups A, B and C were 2.85 ± 0.11 mg/kg, 1.86 ± 0.16 mg/kg and 1.35 ± 0.22 mg/kg respectively. Incidence of apnea recorded in groups A, B and C was 33.33%, 20%, and 0%, respectively. In the present study no salivation was observed after pre-premedication to entire observation period in dog.

Decrease in TLC, Hb and PCV were recorded in all the groups after pre-medication in comparison to respective base values. Comparison between different groups showed that value was non- significantly ($p>0.05$) change at different stage. Value of TEC was significantly ($p<0.05$) change in group A with respect to group B and C after premedication to entire observation period at different stage. Slight lymphocytopenia and neutrophilia were observed in all groups after pre-medication. Serum glucose and cortisol increased at different intervals during observation period in comparison to the base line value in all the groups. Whereas insulin value was decreased at different intervals during an observation period in comparison to the base line value in group B and C, in group A during maintenance of anaesthesia value was decreased. Value of ALT in group A significantly changes with group B at induction to entire observation period at different stage. Serum AST value was non- significantly change after premedication to entire observation period at different stage, except at induction in group A and B. However, serum creatinine was decreased during anaesthesia in the animal of all groups. Similarly blood urea nitrogen also decreased in all the groups after pre-medication.

Systolic blood pressure increased after pre-medication in all groups. Comparison between the groups at different intervals recorded that showed SAP was significantly increase in group A with comparison to C at induction. Similarly diastolic and mean blood pressure increased after pre-medication in groups A and B, MAP was significantly increase in group A and C at induction.

A non-significant difference in amplitude of P wave, duration of QRS complex, duration of P wave, amplitude of R wave except group B,T wave amplitude, Q-R interval, and S-T interval with their respective base line values and among different groups were observed after premedication. P-R interval non – significant differs in group A and significant differ in group B and C after 5 minutes of pre-medication. At induction amplitude of P wave was decreased significant in group A and B, PR- interval in group A and C, and amplitude of T wave in group C.

After induction amplitude and duration of P wave and amplitude of R wave were increased significantly in group B, PR- interval in group B and C, QT- interval in group B and C, ST-interval in group C At T20 whereas duration of P wave, amplitude of R wave , PR- interval were increased significant except in group A at T40.

Based on the analysis of various clinico-physiological, haemato-biochemicals, haemodynamic, and electrocardiographic and parameters investigated in the present study, the following conclusions were drawn:

Conclusion

- Premedication with 10 µg/kg dexmedetomidine provided better sedation in the dogs.
- Chances of apnea were more with xylazine as compared to dexmedetomidine.
- On the basis of clinical, biochemical and cardiovascular stability 10 µg/kg dexmedetomidine is better in comparison of premedication with xylazine and 5 µg/kg dexmedetomidine along with butrophenol and atropine for induction with propofol and maintenance with isoflurane in elective surgery.

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RESUME

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Educational Qualifications

S. No.	Exam Passed	School/College	Board/University	Year of Passing	Percentage
1.	B.V.Sc. & A.H.	Bihar Veterinary College	Bihar Animal Sciences University	2019	7.82 OGPA
2.	M.V.Sc	Bihar Veterinary College	Bihar Animal Sciences University	2022	8.52 OGPA

Title of M.V.Sc. thesis: "**Clinico-physiological studies of xylazine and dexmedetomidine with propofol and isoflurane anaesthesia in dog**."

Membership in Professional societies:

1. Member of Bihar Veterinary Council (BVC)
2. Member of Veterinary Council of India (VCI)