ROMIFIDINE DEXMEDETOMIDINE AND XYLAZINE SEDATION WITH KETAMINE ISOFLURANE ANAESTHESIA FOR SURGERIES IN CATTLE

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CERTIFICATE

This is to certify that the thesis entitled **"ROMIFIDINE DEXMEDETOMIDINE AND XYLAZINE SEDATION WITH KETAMINE ISOFLURANE ANAESTHESIA FOR SURGERIES IN CATTLE"** submitted by **Mr. VENKATGIRI, I.D. No. DVNK-1605** in partial fulfillment of the requirements for the award of **DOCTOR OF PHILOSOPHY** in **VETERINARY SURGERY AND RADIOLOGY** of the Karnataka Veterinary, Animal and Fisheries Sciences University, Bidar is a record of bona-fide research work done by him during the period of his study in this University, under my guidance and supervision, and the thesis has not previously formed the basis of the award of any degree, diploma, associationship, fellowship or other similar titles.

Bidar,
June, 2019

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(S. M. KARTHIKESH)

Affectionately Dedicated

To,

My Beloved Mother

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%	Per cent
/	Per
@	At the dose rate of
^{0}F	Degrees Fahrenheit
>	More than
±	Plus or minus
≤	Less than or equal to
µg	Microgram
Cm	Centimetre
dL	Decilitre
et al.	Co –workers
IU/ L	International Units/ Litre
kg	Kilogram
lb psi	Pounds per square inch
mg	Milligrams
Min	Minute
mm of Hg	Millimetre of mercury
Sl. No.	Serial Number
SE	Standard Error
Viz.,	Namely

Introduction

I. INTRODUCTION

Cattle being docile animals allow many of the surgical and diagnostic procedures to be performed under physical restraint in conjunction with local or regional anaesthesia blockade with or without sedation. However, the resulting conditions are sub-optimal for a number of situations for complex and prolonged surgical procedures and the use of general anaesthesia is desired (Adetunji *et al.*, 1984).

General anaesthesia is defined as reversible state of unconsciousness, immobility, muscle relaxation and loss of sensation throughout the body produced by administration of one or more general anaesthetic agents (Thomas and Lerche, 2010). Most of the surgical and diagnostic procedures in cattle are to be performed under physical restraint in conjunction with local or regional anaesthesia blockade with or without sedation.

General anaesthesia in cattle involves complexities like regurgitation, bloat, respiratory complication and radial nerve paralysis which are not often encountered in small animals however, carefully selected and properly managed general anaesthetic technique provide optimal conditions for surgery.

In recent years, intravenous anaesthetics with rapid onset, redistribution and clearance have become available, which creates the possibility of maintaining anaesthesia even in large ruminants using these intravenous agents (Malik *et al.*, 2012). Moreover, the use of intravenous anaesthetic agents for induction and maintenance of anaesthesia may facilitate endotracheal intubation, oxygen administration or artificial ventilation if it is required.

Cattle and buffaloes usually accept physical restraint well and that to in conjuction with local or regional anaesthesia is often sufficient for completion of many surgical procedures. However, many times in non co-operative animals and in diagnostic and surgical procedure that are more complex like, diaphragmatic hernia, traumatic pericarditis and orthopedic surgeries where technical and anatomical aspects of the surgical procedures warrant absolute control of movement during surgery (Kumar *et al.,* 2013b). General anaesthesia is required in cattle and buffaloes for complex surgical or diagnostic procedures. Inhalation anaesthesia requires specific equipment and may only be possible in the hospital environment. It is rarely feasible for use in the field.

Alpha- 2-agonists are becoming increasingly popular among veterinarians for inducing sedation as well as analgesia owing to certain advantages they offer in comparison to local anaesthetics.

An ideal sedative agent should produce calming or smoothening effect or should induce sleep. It should have minimum induction time, sufficient analgesia, muscle relaxation, should not disturb cardio-pulmonary system and should also provide smooth recovery.

Romifidine is a drug that is used in veterinary medicine as a sedative mainly in large animals such as horses, although it may be used in a wide variety of species. It is not used in humans, it is closely related in structure to the commonly used drug clonidine. Romifidine acts as an agonist at the α_2-adrenergic receptor subtype (Spadavechia *et al.,* 2005) Side effects can include bradycardia and respiratory depression. It is often used

alongside other sedative or analgesic drugs such as ketamine or butorphanol yohimbine can be used as an antidote to rapidly reverse the effects (Belda *et al.,* 2008).

Romifidine has been available as alpha-2-adrenoreceptor agonist since 1985 and being used for sedation, analgesia and premedication in horses in several countries since 1988.

Romifidine, 2-([2-bromo-6-fluorophenyl] imino) imidazolidine hydrochloride, is alpha-2-agonist with similar sedative effects to other drugs. Romifidine is an imino-imidazolidine derivative, selective and alpha-2-adrenoceptor agonist drug systemically to bring about sedation and analgesia in horses (Gasthuys *et al*., 1996), dogs (England *et al*., 1996a and Amarpal *et al*., 2002), sheep (Celly *et al*., 1997) and in goats (Aithal *et al*., 2001 and Amarpal *et al*., 2002) and is mostly administered like its pharmacological group drugs. Romifidine is a potent and selective alpha 2-adrenoreceptor agonist that is approved for use in several species in European countries, and for use in horses in Canada. It has been demonstrated to be a reliable sedative and analgesic agent after intravenous (England *et al*. 1996a), intramuscular (Lernke, 1999) and subcutaneous administration (England and Thompson, 1997b).

In dogs, romifidine has been found to produce useful sedation with similar actions and adverse effects as other alpha-2-adrenoreceptor agonists at a dosage range of 40 to 120 µg per kg (England *et al.* 1996a). Romifidine (2-[(2-bromo-6-fluorophenyl) imino] imidazole (Sedivet®) is developed from Clonidine, an alpha-2-adrenoreceptor agonist.

Xylazine hydrochloride was the first α-2-adrenergic agonist used as sedative and analgesic by veterinarians. Xylazine hydrochloride is classified pharmacologically as an effective sedative, analgesic, muscle relaxant, immobilizing and hypnotic agent in domestic animals (Gross and Tranquilli 2001). Specific action of xylazine is related to central nervous system depression mediated by stimulation of α-2-receptors and muscle relaxation caused by inhibition of interneural transmission within central nervous system (Brikas *et al.,* 1987). Xylazine produces dose dependent depression of cardiopulmonary function in all species, interfering with normal electrical activity in the heart, especially after intravenous administration (Fani *et al.,* 2008).

Dexmedetomidine hydrochloride is a selective α-2-agonist approved for use in 1999. It has approximately 7 to 8 times the α-2-selectivity than that of clonidine. Dexmedetomidine is the dextroisomer of medetomidine that demonstrates selective α-2-agonist action, which produces sedation, anxiolysis, sympatholysis and possess some analgesic properties. Dexmedetomidine reduces the dose requirements of opioids and anaesthetic agents and attenuates the haemodynamic reponses to tracheal intubation and surgical stimuli (Kumar *et al.,* 2014).

Ketamine hydrochloride is a short acting, non barbiturate, dissociative anaesthetic commonly used alone or in combination with other anaesthetics for chemical restraint, short term anaesthesia and pain management in cats, dogs, horses, cattle, small ruminants, humans and exotic species (Wright, 1982 and Stoelting, 1999b). Ketamine produces a cataleptoid state involving unconsciousness and somatic analgesia, however, fails to produce muscular relaxation. Its main advantage over other central nervous

system depressants such as phenobarbitone are that it tends to stimulate cardiopulmonary function and can be given intramuscularly with a wide margin of safety, thus reducing the need of accurate weight estimation beforehand (Green *et al.,* 1981).

Isoflurane is a halogenated ether and is commonly used as a inhalant general anaesthetic for animals and humans. Inhalation anesthetics are unique among the all anesthetic agents because they are administered and in large part removed from the body via the lungs. Isoflurane is the most widely used inhalation anesthetic in veterinary medicine, having replaced halothane (Steffey and Mama, 2007). It offers the importance of safety of the patient and provides greater control of anesthetic depth to the anesthetist and helps in smooth and quick recovery from the anaesthesia.

In the present study romifidine, xylazine and dexmedetomidine preanaesthetics were used for ketamine induction in cattle and anaesthesia is maintained with isoflurane, an inhalant general anaesthetic agent. There is paucity of reports of usage of romifidine in cattle for ketamine-isoflurane anaesthesia. Hence, the present study was undertaken to study the sedative effects of romifidine, xylazine and dexmedetomidine under ketamine-isoflurane anaesthesia in cattle with the following objectives.

1. To compare an anaesthetic combinations of Romifidine-Ketamine-Isoflurane, Dexmedetomidine–Ketamine–Isoflurane and Xylazine-Ketamine-Isoflurane in cattle undergoing surgery.
2. To study and compare clinical and physiological changes in romifidine-ketamine isoflurane, xylazine-ketamine-isoflurane and dexmedetomidine-ketamine-isoflurane combinations for various surgeries in cattle.

3. To study and compare haematological and biochemical changes in romifidine-ketamine-isoflurane, xylazine-ketamine-isoflurane and dexmedetomidine-ketamine-isoflurane combinations for various surgeries in cattle.

4. To compare haemodynamic parameters in different anaesthetic combinations in cattle undergoing surgeries.

Review of Literature

II. REVIEW OF LITERATURE

In the present study romifidine hydrochloride was compared with dexmedetomidine and xylazine hydrochloride for sedation in clinical cases of cattle. Hence the literature is reviewed under the following headings.

2.1 Romifidine hydrochloride

2.2 Dexmedetomidine

2.3 Xylazine hydrochloride

2.4 Ketamine hydrochloride

2.4 Isoflurane

2.1 Romifidine Hydrochloride

2.2.1 Clinical effects

Voegtli (1988) used intravenously or intramuscularly for sedation or pre-anaesthetic administration in horses.

England *et al.* (1992) reported that the effects of romifidine were similar to those of other α-2- adrenoceptor agonist with only minor differences, while comparing the sedative and analgesic effects of intravenous romifidine and xylazine.

Smith *et al.* (1992) reported that, sedation with romifidine might be attributed to the supraspinal effect following its systemic absorption from the sub archinoid space following epidural administration in goats.

England *et al.* (1996a) reported that, romifidine was an imino-imidazolidine derivative α-2- adrenoceptor agonist drug developed from clonidine.

Naylor *et al.* (1997) recorded that, both xylazine and romifidine drugs were almost equally effective however, romifidine had a slight edge over xylazine in the duration and depth of sedation.

Sharma *et al.* (2004) studied romifidine-ketamine anaesthesia in atropine and triflupromazine pre-medicated buffalo calves and reported that, romifidine- ketamine combination provided excellent analgesia and muscle relaxation as compared to romifidine alone use in buffalo calves.

Marzok and EL-Khodey (2009) evaluated the clinical effectiveness and the sedative and analgesic effects of intravenous romifidine in camels, and observed that, intravenous administration of romifidine caused profound sedation and analgesia and it could be used for clinical restraint for variety of diagnostic and minor surgical procedures in camels.

Rafael De Rossi *et al.* (2009) reported that, the combination of romifidine and butorphenol found to provide better sedation and analgesia than the administration of romifidine or butorphenol alone in horses.

Wypart *et al.* (2011) studied the pharmacokinetic profile and pharmacodynamic effects of romifidine hydrochloride in horses and reported that, the drug produces long lasting sedation in horses that corresponded with the long terminal elimination half life of the drug.

Amin *et al.* (2012) studied clinical evaluation of total intravenous anaesthesia by romifidine premedication with midazolam and ketamine in monkeys and reported that, induction time and recovery time was found to be superior and stable and there were no adverse effects noted following this anaesthetic regimen.

Wolfensberger *et al*. (2014) compared the clinical usefulness of constant rate of infusion (CRI) of romifidine with or without butorphanol for sedation and concluded, romifidine provided effective sedation under clinical condition however for dentistry procedure, the addition of butorphenol was advantageous for extended analgesia and sedation in horses.

Interlandi *et al.* (2017) reported that, romifidine with tramadol provided an effective sedative and analgesic effect and minor ataxia than romifidine alone. This protocol may be usefull for minor surgical procedure in standing calves.

Marzok *et al.* (2017) studied th anti-nociceptive and sedative effect of epidural administration of romifidine and reported that, romifidine induced a longer anti nociceptive effect and more rapid onset of sedation than detomidine. Epidural romifidine might offer better therapeutic benfits in the management of acute post operative pain in buffaloes.

Mullers *et al.* (2017) concluded that, romifidine along with butorphenol would inhibit stress response and combination of romifidine with either midazolam or ketamine would improve the sedation quality for various surgical conditions in horses.

Neomi Romagnoli *et al.* (2017) studied pharmacokinetic profile of romifidine after single intravenous administration in horses and reported that, romifidine produced a satisfactory level of sedation in all the horses, the sedation level was detectable in all horses for up to 105 minutes.

2.2.2 Physiological effects

Amarpal *et al.* (2002) studied analgesic, sedative and heamodynamic effects of spinally administered romifidine in female goats and reported that, there was significant decrease heart rate and respiration in all the animals and slight increase in rectal temperature.

Wolfensberger *et al*. (2002) reported that, there was significantly decrease in cardiac index and mixed venous oxygenation at 15 and 30 minutes after administration of romifidine and also observed that, there was increased systemic vascular resistance and arterial blood pressure initially followed by decreased in later stage of anaesthesia in horses.

Sharma *et al.* (2004) studied romifidine-ketamine anaesthesia in atropine and triflupromazine pre-medicated buffalo calves and reported that, significant bradycardia and respiratory depression and hypothermia was noticed in all the animals at different intervals.

Kinjavdekar *et al.* (2006) evaluated analgesic, sedative and heamodynamic effect of romifidine after sub archinoid administration in goats and reported significant

reduction in heart rate and respiratory rate in all the animals and also observed a significant reduction in mean arterial pressure in all the animals.

Rafael De Rossi *et al.* (2009) reported that, there was decrease in heart rate significantly from basal values and also observed, only romifidine would cause significant decrease in respiratory rate following intravenous administration of romifidine –butorphenol combination in horses.

Wypart *et al.* (2011) analysed pharmacokinetic profile and pharmacodynamic effect of romifidine hydrochloride in horses and reported, romifidine caused a significant reduction in heart rate and cardiac index and increase in mean arterial pressure in horses.

Interlandi *et al.* (2017) studied effect of the combination of romifidine and tramadol drug adminstraion in calves and reported that, both heart rate and respiratory rate were decreased significantly in all the animals.

Marzok *et al.* (2017) studied comparative anti-nociceptive and sedative effect of epidural romifidine and detomidine in buffaloes and reported significant decrease in heart rate as well as non significant effect on respiratory rate and the rectal temperature.

Muller *et al.* (2017) studied the effect of butorphenola on romifidine based sedation in horses and reported that, in all horses, the sedation resulted in a decrease in heart rate and respiratory rate which is well known side effect of alpha-2-agonists.

Venkatgiri *et al. (*2017) reported there was a decrease in the rectal temperature and heart rate in romifidine group of animals as compared to xylazine group following

romifidine –ketamine and xylaxine –ketamine combination for isoflurane anaesthesia in cattle.

Dilipkumar *et al. (*2018) reported there was a non-significant decrease in the rectal temperature, Respiratory rate and heart rate in buffaloes as compared to cattle following surgical repair of various condition under butorphenol romifidine with ketamine induction and isoflurane anaesthesia in cattle and buffaloes.

2.2.3 Hemato-Biochemical effects

Amarpal *et al.* (2002) reported non-significant decrease in heamoglobin and packed cell volume, significant increase in blood glucose following spinally administration of romifidine in goats.

Kinjavdekar *et al.* (2006) reported no significant changes in packed cell volume and heamoglobin was observed following sub-archionoid administration of romifidine along with lidocaine in goat.

Venkatgiri *et al.* (2017) observed there was a non-significant decrease in haemoglobin, packed cell volume, total erythrocyte count and increase in total leucocyte counts in romifidine group of animals as compared to xylazine group following romifidine –ketamine and xylazine –ketamine combination for isoflurane anaesthesia in cattle.

Venkatgiri *et al. (*2017) reported that there was a marginal decrease in haemoglobin, total erythrocyte count, total leucocyte counts in all the groups, and also neutrophilia and lymphocytopaenia in all the three groups following romifidine

dexmedetomidine and xylazine sedation with ketamine isoflurane anaestheia for surgeries in cattle.

Venkatgiri *et al.* (2017) observed there was a non-significant decrease in creatinine and BUN towards the end of anesthetic period in all the groups following romifidine, dexmedetomidine and xylazine sedation with ketamine isoflurane anaestheia for surgeries in cattle.

Dilipkumar *et al.* (2018) observed neutrophilia and lymphocytopaenia in cattles towards end of anaesthesia following surgical repair of various condition under butorphenol romifidine with ketamine induction and isoflurane anaesthesia in cattle and buffaloes.

Dilipkumar *et al. (*2018) studied surgical repair of various condition under butorphenol romifidine with ketamine induction and isoflurane anaesthesia in cattle and buffaloes and reported non-significant decrease in creatinine and BUN in buffaloes compared to cattle.

2.2 Dexmedetomidine hydrochloride

Dexmedetomidine is dextroisomer of medetomidine that demonstrates selective α-2-agonist action, got approval by Food and Drug Administration (FDA) for use in 1999. It has 7 to 8 times the α-2- selectivity than that of clonidine (Mariann, 2008).

Dexmedetomidine is a potent and highly selective α-2-adrenoceptor agonist with sedative-hypnotic and anaesthetic sparing properties, currently utilized for continuous infusion for sedation and analgesia in the intensive care unit (ICU) (Arcangeli *et al.*,

2009). It provides a unique conscious sedation and analgesia without respiratory depression. Because of its sympatholytic activity, it might prove useful in balancing the cardiostimulatory effects and attenuating the adverse central nervous system effects of ketamine (Levanen *et al.,* 1995). Dexmedetomidine hydrochloride is more highly specific to α-2-adrenergic receptors than medetomidne and xylazine hydrochloride (Scheinin and MacDonold 1989).

Maze *et al.* (1991) found that dexmedetomidine and its clinically ineffective enantiomer, levomedetomidine were equally effective in blocking the ACTH stimulated corticosteroid secretion in adrenocortical cells in rats and high dosages of dexmedetomidine inhibit adrenal steroidogenesis.

Asano *et al.* (2000) observed that the dexmedetomidine produced dose dependent antinociceptive effect in rats when given epidurally.

Esmaoglu *et al.* (2005) reported that the addition of dexmedetomidine to local anaesthetic solution in intravenous regional anaesthesia improved the quality of anaesthesia and decreased analgesic requirements; however, it had no effect on the onset and regression times of sensory and motor blocks.

Granholm *et al.* (2007) reported that administration of high dose of dexmedetomidine hydrochloride at the dose rate 20 μg/kg [500 $\mu g/m^2$] body weight intramuscularly in dogs resulted in sedative effects lasting up to 120 minutes, with a peak effect recorded at 30 minutes. Dexmedetomidine hydrochloride was found highly

effective for producing chemical restraint in dogs undergoing short ambulatory procedures such as dental procedures, radiography.

Alvaides *et al.* (2008) stated that administration of dexmedetomidine hydrochloride at the dose rate of 5µg/kg body weight intravenously produced moderate to profound sedation lasting up to 30 minutes in dogs. The combination of dexmedetomidine hydrochloride with acepromazine at the dose rate of 0.05 mg/kg body weight intravenously did not modify the intensity nor prolonged sedative effects.

Konakci *et al.* (2008) observed that epidural administration of dexmedetomidine at 10 µg total dose in rabbits did not produce antinociception to the painful stimulus produced by surgical clamp.

Konakci *et al.* (2008) observed that epidural administration of dexmedetomidine at 10 µg total dose in rabbits did not produce antinociception to the painful stimulus produced by surgical clamp.

Arcangeli *et al.* (2009) demonstrated that dexmedetomidine hydrochloride was an efficacious and safe adjuvant to other sedative and anaesthetic medications in general surgery, neurosurgery, cardiac surgery, bariatric surgery and for procedural sedation and awake fiber optic intubation.

Sano *et al.* (2010) reported the use of dexmedetomidine hydrochloride in veterinary practice as a pre-medicant and adjunct to general anaesthesia in several species.

Barletta *et al.* (2011) suggested that dexmedetomidine-buprenorphine-ketamine was a more suitable injectable anaesthetic combination compared to dexmedetomidine-butorphanol-ketamine and dexmedetomidine-hydromorphone-ketamine combination for castration in dogs.

Khattri *et al.* (2013) used dexmedetomidine hydrochloride in ureamic buffalo calves at the dose rate of 2.5 μg/kg and observed good sedation, analgesia and muscle relaxation.

2.2.1 Clinical effects

Kending *et al.* (1991) reported that dexmedetomidine hydrochloride acts on dorsal horn of spinal cord by interrupting the nociceptive pathway to the ventral root, thus reducing the spinal reflex.

Correa-Sales *et al.* (1992) stated that hypnotic effect of dexmedetomidine hydrochloride was mediated by the hyper-polarization of noradrenergic neurons in the locus ceruleus of the brain stem (a small bilateral nucleus that contains many adrenergic receptors), which was the primary site in modulating wakefulness.

Aantaa *et al.* (1993) studied pharmacological properties of dexmedetomidine hydrochloride and found that dexmedetomidine hydrochloride acts as full agonist on all α-2- adrenoceptor subtypes and have high selectivity for α-2-adrenoceptors and very low affinity for α-1-adrenoceptors.

Aantaa *et al.* (1993) stated that medetomidine was racemic mixture that contains equal parts of two optical enantiomers, dexmedetomidine hydrochloride and

levomedetomidine. Among these, dexmedetomidine hydrochloride was the sedative and analgesic active enantiomer.

Sabbe *et al.* (1994) concluded that intravenous administration of dexmedetomidine hydrochloride produced dose dependent sedation in dogs.

Hayashi *et al.* (1995) reported that the analgesic action of dexmedetomidine hydrochloride was spinally mediated.

Chiu *et al.* (1995) reported that dexmedetomidine hydrochloride binds to α-2-adrenoreceptors on the cell membrane of neurons of locus coeruleus, leading to opening of inward rectifying potassium channels, resulting in hyper polarization of membrane.

Guo *et al.* (1995) implicated the direct action of dexmedetomidine hydrochloride on locus coeruleus, resulting in activation of α-2- receptors in the spinal cord, for the antinociceptive effect of the drug.

Ko *et al.* (1996) and Ahmad *et al.* (2011) were of the opinion that α-2-adrenergic agonists produces profound muscle relaxation when used alone or in combination with opioid agonist-antagonists due to inhibition of α-2-adrenoceptors at the interneuron level of the spinal cord.

Ko *et al.* (2000) reported greater muscle relaxation when dexmedetomidine hydrochloride or medetomidine was combined with opioid or ketamine in cats and dogs.

Kuusela *et al.* (2000) reported that dexmedetomidine caused dose dependent sedation. However, increasing the dose beyond a certain level does not cause a further increase in sedation.

Kuusela *et al.* (2001) stated that higher dose of dexmedetomidine hydrochloride (20 μg/kg) might induce profound hypnosis, there by substantially reduced injectable and inhalant anaesthetic requirements for producing anaesthesia.

Selmi *et al.* (2003) and MacDonald *et al.* (1991) reported that dexmedetomidine hydrochloride was the active optical enantiomer isolated from the racemic compound medetomidine.

Selmi *et al.* (2003) reported greater muscle relaxation when dexmedetomidine hydrochloride or medetomidine was combined with opioid and/or ketamine in cats or dogs.

Ansah (2004) reported that out of all the alpha-2-adrenergic group of drugs available, dexmedetomidine hydrochloride has the highest affinity for alpha-2-adrenergic receptors and the fewest side effects.

Ahmad *et al.* (2011) reported that combination of dexmedetomidine hydrochloride -midazolam-fentanyl-ketamine resulted in excellent analgesia, sedation and muscle relaxation with favorable conditions for intubation in dogs.

Ahmad *et al.* (2011) stated that dexmedetomidine hydrochloride produced profound muscle relaxation when used alone or in combination with opioid agonist in dogs.

Gupta *et al.* (2011) opined that dexmedetomidine hydrochloride premedication effectively and safely attenuated the ketamine induced hemodynamic presser response

and psycomimetic effects. Due to its tendency to cause bradycardia routine use of an anticholinergic drug should be considered.

Monsang (2011) used dexmedetomidine hydrochloride and butorphanol in sheep and observed the synergistic action, like excellent muscle relaxation after anaesthetic induction with propofol.

Santosh (2011) concluded that dexmedetomidine hydrochloride-midazolamketamine combination induced surgical anaesthesia for 20 min in dogs. Increasing the dose of dexmedetomidine hydrochloride neither enhanced the depth nor the duration of anaesthesia.

Singh *et al.* (2013a) observed that there was mild corneal reflex up to 10 minutes after premedication with dexmedetomidine and fentanyl which was completely abolished till the end and was abolished for longer period when compared to buffaloes premedicated with xylazine and fentanyl. They also observed complete abolition of palpebral reflex after premedication with dexmedetomidine and fentanyl. The median recovery time, sternal recumbency time and standing time were 3.00 ± 1.09 min, 13.83 ± 3.04 min and 18.00 ± 3.28 min, respectively, in water buffaloes administered with dexmedetomidine-fentanyl-thiopentone-isoflurane.

Khattri *et al.* (2013) administered dexmedetomidine in buffalo calves at the dose rate of 2.5 μg/kg body weight intravenously and observed mild depression of pedal reflex and moderate depression of palpebral reflex at 5 and 10 minutes of administration. They

also observed good sedation, analgesia and muscle relaxation, however, it caused transient cardiopulmonary depression.

Nour *et al.* (2013) noticed that in dogs epidural dexmedetomidine-bupivacaine produced prolonged motor and sensory blockade, haemodynamic stability compared to fentanyl-bupivacaine or bupivacaine alone, which was due to synergism between local anaesthetic and α-2- adrenoceptor agonist.

Kumar *et al.* (2014) observed that when goats were anaesthetized with dexmedetomidine (2.5 µg/kg body weight) and ketamine, the recovery time, sterna recumbency time and standing time were 7.25 ± 1.76, 21.37 ± 2.46 and 40.50 ± 4.68 minutes, respectively. They also observed mild to moderate degree of jaw relaxation and mild degree of salivation after administration of ketamine, which might be due to delayed effect of α2 agonist i.e., dexmedetomidine or due to decreased swallowing reflex.

2.2.2 Physiological effects

Bloor *et al.* (1990) observed that administration of dexmedetomidine hydrochloride caused increased arterial blood pressure for 5 to 10 minutes followed by decreased arterial blood pressure in humans and rodents.

Flackle *et al.* (1990) concluded that species specific hemodynamic response occurred following administration of dexmedetomidine hydrochloride in animals. No such biphasic response has been reported in dogs and blood pressure remained increased despite a decrease in sympathetic tone.

Bloor *et al.* (1992) stated that bradycardia consequent to dexmedetomidine hydrochloride administration was of parasympathetic origin and not due to reduced sympathetic tone.

Aantaa *et al.* (1993) and Frangoulidou *et al.* (1998) used dexmedetomidine hydrochloride in humans and noticed many advantages in comparison with more commonly used hypnotics. Although it produces sedative, analgesic, and anxiolytic effects, unlike other sedatives, it provides respiratory stability, without causing ventilatory depression.

Ruffolo *et al.* (1993) reported that, premedication with dexmedetomidine hydrochloride resulted in decreased blood pressure and prolonged hypotension.

Sabbe *et al.* (1994) reported that systemic administration of dexmedetomidine hydrochloride resulted in a dose dependent depression in the rate and slope of carbon dioxide response curve whereas, intrathecal or epidural dexmedetomidine hydrochloride caused little change in the rate or slope of carbon dioxide function suggesting that these actions were mediated supraspinally.

Amarpal *et al.* (1996) reported that administration of medetomidine or dexmedetomidine hydrochloride resulted in decreased respiratory rate with minimal effects on blood gases in dogs.

Lawrence *et al.* (1996) reported that when dexmedetomidine hydrochloride was used, blood flow to the most of vital organs (brain, heart, liver and kidney) remained same. The distribution of blood flow was not affected by the type of anaesthesia.

Talke *et al.* (1997) studied the post-operative sympatholytic effects of dexmedetomidine hydrochloride and found that plasma nor-epinephrine and epinephrine concentration decreased by 72% on an average. This attenuated post-operative increase of heart rate and blood pressure, however, did not entirely abolish sympathetic tone, leading to significant hypotension and bradycardia

Frangoulidou *et al.* (1998) observed that dexmedetomidine hydrochloride could be administered as a continuous infusion in humans and was associated with a predictable and stable hemodynamic response.

Ansah *et al.* (1998) and MacDonald *et al.* (1989) used dexmedetomidine hydrochloride in cats and observed decrease in heart rate, they attributed it to known dexmedetomidine hydrochloride induced phenomena: an increase in arterial blood pressure inducing a baroreceptor mediated increase in vagal outflow causing bradycardia or a decrease in sympathetic tone due to dexmedetomidine hydrochloride mediated decrease in nor-epinephrine release in the CNS.

Pagel *et al.* (1998) stated that single dose of dexmedetomidine hydrochloride at the dose rate of 10 μg/kg intravenously induced a transient vasopressor effect, which was characterized by substantial increased systemic vascular resistance (SVR), moderately increased arterial pressure, bradycardia and a decreased cardiac output (CO). Cardiac output was decreased by 50% from baseline values after 5 minutes of dexmedetomidine hydrochloride administration.

Kuusela *et al.* (2001) and Selmi *et al.* (2003) stated that medetomidine and dexmedetomidine hydrochloride caused similar cardiovascular, analgesic and sedative effects in cats.

Kuusela *et al*. (2001) studied various premedicant doses of dexmedetomidine hydrochloride administrated intravenously in dogs and found that, dose level of 20 µg/kg body weight preserved blood pressure whereas, profound bradycardia occurred. Dose level of 2 µg/kg body weight resulted in more stable cardiovascular effects. However, the effect was short term and a stable plane of anaesthesia was difficult to maintain.

Selmi *et al.* (2003) used a single dose of dexmedetomidine hydrochloride in cats and observed a transient decrease in respiratory rate.

Lemke (2004) reported that dexmedetomidine hydrochloride at 20 µg/kg body weight produced hypertension due to vasoconstriction resulting from stimulation of α-2-adrenoceptors in the smooth muscles of blood vessels.

Bettschart-Wolfensberger *et al.* (2005) compared cardiopulmonary side effects of dexmedetomidine hydrochloride-medetomidine-xylazine hydrochloride in horse. Heart rate and cardiac output were reduced non-significantly for the first 10 minutes and arterial blood pressure was initially increased for short duration with dexmedetomidine hydrochloride as compared to medetomidine and xylazine hydrochloride.

Kastner *et al.* (2005) found that dexmedetomidine hydrochloride induced a transient decrease in heart rate and cardiac output in sheep anaesthetized with sevoflurane.

Kutter *et al.* (2006) found that arterial, pulmonary arterial, pulmonary capillary wedge and central venous pressures were increased and heart rate and cardiac output were decreased significantly after dexmedetomidine hydrochloride administration under sevoflurane anaesthesia in sheep and goat.

Leppanen *et al.* (2006) stated that dexmedetomidine hydrochloride at the dose rate of 5-20 µg/kg did not interfere with respiratory function. However, it induced mild to moderate changes in arterial blood gases.

Kastner *et al.* (2006) and Monsang (2011) reported bradycardia following dexmedetomidine hydrochloride administration in goats and sheep.

Alvaides *et al.* (2008) declared that routine anticholinergic administration to prevent dexmedetomidine hydrochloride induced arrhythmias was contraindicated as it produced significant hypertension and might be associated with premature ventricular depolarization.

Mariann (2008) was of the opinion that after administration of dexmedetomidine, an immediate increase in blood pressure might be observed due to stimulation of α-2-b-receptors in vascular smooth muscles, which lasts for 5 to 10 minutes and was followed by a slight decrease in blood pressure due to inhibition of central sympathetic outflow; and he also observed fall in heart rate, which was due to stimulation of pre synaptic α-2-receptors and thereby decrease in epinephrine release.

Gupta (2010) and Surbhi *et al.* (2010) reported decreased respiratory rate following administration of dexmedetomidine hydrochloride along with butorphanol in

dogs. Monsang (2011) and Ahmad (2009) noticed the similar findings in sheep and buffalo.

Ahmad *et al.* (2011) observed that dexmedetomidine (20 µg/kg) administered intramuscularly in dogs caused a significant decrease in heart rate (up to 60 minutes), respiratory rate (at 10 minutes and up to 120 minutes) and rectal temperature (from 60 to 90 minutes). Oxygen saturation did not show any significant changes at different point of time interval after administration of dexmedetomidine.

Khattri *et al.* (2013) used dexmedetomidine hydrochloride in ureamic buffalo calves and they observed good sedation, analgesia, muscle relaxation and transient cardiopulmonary depression.

Singh *et al.* (2013a) reported that in buffaloes premedicated with dexmedetomidine (5 µg/kg, IV) and fentanyl, there was a significant decrease in rectal temperature and mean arterial pressure (up to 75 minutes), and a significant increase in respiratory rate during the entire maintenance period with isoflurane.

Kumar *et al.* (2014) observed that after premedication with dexmedetomidine in goats, there was a significant decrease in respiratory rate and mean arterial pressure. However, after induction of anaesthesia with ketamine, the respiratory rate decreased significantly only at 15 minutes, thereafter, the values were non significantly lower than baseline value up to the end of observation period, which might be due to some degree of hyperventilation induced by ketamine. Mean arterial pressure improved at 15 minutes and onwards after induction of anaesthesia with ketamine. They also observed non significant

decrease in rectal temperature, which decreased significantly after induction with ketamine.

2.2.3 Haematological and Biochemical effects

Wagner *et al.* (1991) reported that the haemoglobin, packed cell volume and total leukocyte count decreased significantly after administration of dexmedetomidine in horses, which might be due to pooling of circulatory blood cells in spleen or other reservoirs secondary to decreased sympathetic activity.

Gupta (2010) reported decreased haemoglobin and packed cell volume after administration of dexmedetomidine hydrochloride in dogs and sheep.

Ahmad *et al*. (2011) reported neutrophilia and lymphocytopaenia after administration of dexmedetomidine hydrochloride or combinations of dexmedetomidine hydrochloride-midazolam-fentanyl in dogs.

Monsang (2011) observed decrease in haemoglobin and packed cell volume following administration of dexmedetomidine in sheep.

Khattri *et al.* (2013) observed neutrophilia and lymphocytopaenia in buffalo calves administered with dexmedetomidine and propofol, which was due to the stress caused by the preanesthetic and anaesthetic drugs and subsequent stimulation of adrenal glands. They also observed a significant increase in blood urea nitrogen from 15 to 60 minutes after administration of dexmedetomidine and propofol, which might be due to temporary inhibitory effects of anaesthetic drugs on the renal blood flow.

Kumar *et al.* (2013) observed non-significant change in plasma urea nitrogen and creatinine values during dexmedetomidine hydrochloride with and without butorphanol for propofol and ketamine anaesthesia in uraemic goats.

Singh *et al.* (2013a) reported that in buffaloes premedicated with dexmedetomidine and fentanyl, there was a significant decrease in haemoglobin, packedcell volume and creatinine from 30 to 90 minutes and significant increase in urea nitrogen at 30, 90 and 1440 minutes of dexmedetomidine-fentanyl-thiopentone-isoflurane anaesthesia.

Sharma *et al.* (2014) observed non-significant change in haemato-biochemical parameters under atropine-dexmedetomidine hydrochloride-butorphanol-ketamine anaesthesia in dogs.

2.3 Xylazine hydrochloride

Xylazine hydrochloride is an analogue of clonidine and is an agonist belonging to the α-2-class of adrenergic receptor. Xylazine hydrochloride was developed in 1962 by Farbenfabrikin Bayer AG, Lever kusen in Federal Republic of Germany for use as an antihypertensive agent, however, it was found to have potent sedative effects in wide variety of domestic and exotic species (Green and Thurmon, 1988). Xylazine hydrochloride is a potent non-narcotic sedative, analgesia and muscle relaxant, chemically designated as 2(2,6-dimethylphenylamino)-4H-5,6-dihydro-1,3-thiazine hydrochloride. The sedative and analgesic activities are related to central nervous system depression mediated by stimulation of α-2- receptors (Hsu and Hummel 1981).

Symonds and Mallison (1978) stated that xylazine induced hyperglycemia in cow was due to combination of increased hepatic glucose production and reduced plasma insulin.

Kumar and Thurmon (1979) and Shokry *et al.* (1976) reported rapid onset of sedation after intramuscular administration of xylazine hydrochloride at the rate of 0.2 mg/kg body weight in sheep.

Hsu and Hummel (1981) stated that xylazine hydrochloride exerts its sedative effects at alpha-2- adrenergic postsynaptic receptors localized in the cell bodies of the locus coeruleus. They also stated that sedative and analgesic activities of xylazine hydrochloride were related to CNS depression and mediated by stimulation of α-2-adrenergic receptors in dogs.

Hall and Clarke (1983) first used xylazine hydrochloride and they said that it was a potent sedative/hypnotic agent. Further studies were conducted by Adams *et al*. (2001), and he reported that xylazine hydrochloride is chemically named as 2(2, 6-dimethylphenylamino)- 4H-5, 6-dihydro-1, 3-thiamine hydrochloride and is pharmacologically classified as an effective sedative, analgesic, muscle relaxant, immobilizing and hypnotic agent used in domestic animals.

Tranquilli *et al*. (1984) reported that xylazine pre-medication dramatically decreases the induction and maintenance of anaesthetic dose requirements in dogs.

Hsu *et al*. (1985) stated that the sedative and analgesic activities of xylazine were related to CNS depression and mediated by stimulation of α-2-adrenergic receptors in dogs.

Haskins *et al*. (1986) recommended that dose of xylazine in dogs as 0.1-0.5 mg/kg body weight by intravenous route and 0.4-0.9 mg/kg body weight by intramuscular route.

Coulson *et al.* (1989) observed sedation for 15 minutes with 0.1 mg/kg of xylazine hydrochloride administered intravenously in sheep.

Carter *et al.* (1990) observed marked sedation with xylazine hydrochloride administered 1.1 mg/kg intravenously in foals.

Caulkett *et al.* (1993) reported that epidural xylazine hydrochloride was an adequate sedative and analgesic agent for caesarean section in cows in addition to a local nerve block or paravertebral or field block using lidocaine.

Patel *et al*. (1996) opined that a dose rate of 0.05 mg/kg body weight xylazine was most suitable for caudal epidural analgesia in cattle.

Perez *et al.* (1997) stated that xylazine should not be administered to pregnant goats in their last trimester of pregnancy because of its oxytocin like effect on uterus.

Paddleford and Harvey (1999) stated that xylazine had favorable muscle relaxant effect and could be used as a pre-medicant in the induction of general anaesthesia.

Gross and Tranquilli (2001) stated that muscle relaxant properties of xylazine hydrochloride was related to the inhibition of intraneural transmission of impulses in the central nervous system.

Ambrisko and Hikasa (2002) noticed that higher dosages of xylazine in dogs induced more alertness, sometimes anxiety and muscle rigidity and hence 4 and 8 mg/kg dosages of xylazine were not recommended for clinical practice.

George *et al.* (2003) stated that after intramuscular injection the absorption and distribution was rapid (although incomplete) however, the half-life was short (36 minutes) in cattle. The intramuscular injection of xylazine hydrochloride (0.2 mg/kg) in calves caused deep sedation, recumbancy, useful analgesia that was evident at 5 minutes and maximum at 10 minutes. Analgesia usually lasted for 30-40 minutes.

Grant and Upton (2004) stated that major effects of xylazine develop in approximately 10 to 15 minutes after intramuscular administration and within 3 to 5 minutes after intravenous administration in sheep.

Frame (2006) recommended caudal epidural analgesia with xylazine hydrochloride for the different management practices of dystocia like episiotomy, fetotomy and caesarian section.

Lemke (2007) recommended the dose range of 0.5-1.0 mg/kg of body weight intramuscular xylazine hydrochloride in healthy dogs.

Abrahamsen (2008) observed recumbancy in 50% of the animals with xylazine administration at the dose rate of 0.05 mg/kg I.V. and 0.1 mg/kg I.M. and almost complete recumbancy with the dose of 0.2 mg/kg I.M. in cattle.

Ruckebusch and Allal (2008) stated that xylazine hydrochloride with dose rate of 0.2 mg/kg caused increase in body temperature. However, it decreased with dose rate of 0.4 mg/kg in cattle. They also noticed reduction in reticular rumen activity leading to bloat.

Vesal *et al.* (2011) suggested that the acepromazine-xylazine combination could be useful for sedation, anxiolysis, muscle relaxation and pre-medication in healthy dogs.

Moolchand *et al.* (2014) stated that xylazine caused increase in urine production by inhibition of anti diuretic hormone release and they also observed some of the side effects of xylazine in sheep such as, staggering, wobbling, head drooping, protrusion of tongue, tail movement, mild tympany, snoring and defecation.

2.3.1 Clinical effects

Sagner *et al.* (1968) reported that muscle relaxant effect of xylazine was due to suppression of the inter-neural transmission of impulses and not due to paralysis of neuro-muscular transmission.

Knight (1980) stated that xylazine caused excessive salivation in ruminants due to decreased swallowing reflex.

Peshin *et al.* (1980) reported that intramuscular administration of xylazine hydrochloride at the dose rate of 3.0 mg/kg body weight in dogs produced sedation and analgesia within 6 to 9 minutes, which lasted up to 60-85 min. The authors observed prolonged recovery between 20 minutes and 4 hours in dogs anaesthetized with xylazine hydrochloride alone. However, tonic and clonic convulsions, vomiting and defaecation were observed following xylazine hydrochloride administration.

Hsu and Hummel (1981) reported that analgesic action of xylazine might be due to stimulation of central pre-synaptic α-2-adrenoceptors which inhibit norepinephrine release from adrenergic nerve terminals.

Lele and Bhokre (1985) reported that xylazine hydrochloride at the dose rate of 3.0 mg/kg body weight had induced sedation within 10-15 minutes after administration by intramuscular route. The duration of anaesthesia lasted for 61.66±7.15 min and recovery were completed within 10-15 minutes.

Jenkins (1986) reported an onset of action at 5-10 min after xylazine hydrochloride injection in cattle and sheep.

Brikas *et al.* (1987) stated that the muscle relaxation produced by xylazine was caused by inhibition of inter neural transmission within CNS in sheep.

Caron and Lebanc (1989) used xylazine hydrochloride in adult Holstein cows through epidural route and observed significantly greater duration of analgesia than epidural lidocaine.

Skarda *et al.* (1990) reported that good analgesia and standing sedation after epidural administration of xylazine (0.05 mg/kg) in cattle, compared to lidocaine hydrochloride (0.2 mg/kg) and opinion that xylazine induced depression of CNS, respiratory and cardiovascular activity and rumen motility was reversed with tolazoline at 0.3 mg/kg.

Bryant *et al*. (1991) observed that at equisedative doses of xylazine and medetomidine, xylazine produced less ataxia and had shorter duration of action as compared to medetomidine in horses.

Mohammed and Yelwa (1993) reported that the onset of action was 7.00 ± 3.11 minutes in Sokoto red goats administered with 0.05 mg/kg body weight of xylazine intramuscularly.

Dilipkumar *et al.* (1995) stated that at equal dose rate of detomidine and xylazine (0.22 mg/kg body weight), detomidine produces better sedation and analgesia as compared to xylazine.

Ko *et al.* (1996) reported that the α-2-adrenergic agonists produced profound muscle relaxation when used alone or in combination with opioid antagonists.

Pandey *et al.* (1996) observed that the recovery in horses administered with xylazine and ketamine was full of excitement and struggling in contrary to the animals which received diazepam-xylazine-ketamine whose recovery was smooth without struggling.

Patel *et al.* (1996) stated that onset, duration, intensity, extent, depth of analgesia, sedation and ataxia were dose dependent following epidural administration of xylazine in cattle.

Tiwari and Amreshkumar (1998) observed that the xylazine in combination with lignocaine and bupivacaine produced a significantly longer duration of analgesia, which lasted for 240 ± 7.07 and 298 ± 6.04 minutes, respectively, as compared to 183 ± 4.63 minutes with xylazine alone when given epidurally in buffalo calves and also stated that the cranial spread and extent of analgesia was more in buffalo calves given with epidural xylazine than detomidine. They also observed a significant decrease in ruminal movements after epidural administration of xylazine.

Varshney (1998) used xylazine hydrochloride at the dose rate of 0.5 mg/kg and 1.1 mg/kg body weight intravenously in ponies and reported that rectal temperature, pulse rate and respiratory rate were lowered at 30 minute after administration of xylazine hydrochloride. The mean duration of analgesia was comparatively more (41.61 minute) in ponies given with xylazine at 1.10 mg/kg body weight than those given at 0.50mg/kg (32.66 minute).

Kinjavdekar *et al.* (2000) used xylazine hydrochloride to induce sacrococcygeal or lumbosacral spinal analgesia in different species of animals to produce a longer duration of regional analgesia.

Nolan *et al.* (2000) explained that xylazine hydrochloride was not an anaesthetic drug, and its analgesic effects were dose dependent and analgesia is seen only in deeply sedated animals.

Singh *et al.* (2003) reported that medetomidine in buffalo calves produced an early onset and more pronounced analgesia than xylazine which could be attributed to its more lipophilic nature. They also stated that medetomidine had greater selectivity and affinity for α-2-adrenoceptors compared to xylazine.

Grant and Upton (2004) noticed onset of sedation in sheep after 10 to 15 min of intramuscular injection and 3 to 5 min following intravenous administration using xylazine hydrochloride.

Talukder and Hikasa (2009) reported that dose dependent diuretic response to xylazine was more profound than that to medetomidine by decreasing the resorption in the narrow tube of glomerulus in dogs.

Gweba *et al.* (2010) administered Sokoto red goats with xylazine at the dose of 0.20 mg/kg body weight intramuscularly and observed the onset of action to be 3.33 ± 0.51 minutes

Pathak *et al.* (2012) stated that epidural xylazine produced a significantly greater duration of analgesia in adult Holstein cows than did epidural lidocaine and the incidence of ataxia associated with epidural xylazine was also less than lidocaine.

Shah *et al.* (2013) observed that the onset of sedation was 29.00 ± 3.74 seconds and duration of sedation was 77.59 ± 4.38 minutes in goats administered with intravenous xylazine at the dose of 0.10 mg/kg body weight and they stated that α-2-agonists produce dose dependent duration of sedation in animals.

Singh *et al.* (2013a) reported that buffaloes anaesthetized with xylazine and fentanyl produced extensive salivation compared to animals anaesthetized with dexmedetomidine and fentanyl.

Mane *et al.* (2014) stated that xylazine produces good sedation and smooth and uneventful induction when compared with acepromazine and midazolam, which produced moderate sedation and moderate excitement during induction in equines. Similarly, calm and smooth recovery was noted and the recovery quality was best with xylazine. Hence, they concluded that xylazine was a better premedicant in terms of clinicophysiological, electrolytic and acid-base status as compared to acepromazine and midazolam for ketamine - isoflurane anaesthesia in horses. They also stated that xylazine was useful in combination with ketamine since its muscle relaxing properties help to reduce the rigidity caused by dissociative agent.

Moolchand *et al.* (2014) reported that the sheep anaesthetized with intravenous xylazine at 0.20 mg/kg body weight, the onset of sedation was 60 seconds and total duration of sedation was 67.13 ± 2.83 minutes and it produced analgesia within 6.00 ± 1.76 minutes which lasted for 10.87 ± 3.19 minutes. They stated that xylazine produced medium to deep degree of sedation which might be useful for physical examination, biopsy, tagging, application of surface medication, preanaesthesia medication, performing diagnostic procedures, dressing of wounds, drainage of abscess, application of plaster casts, passing of urinary catheter, dental problems and removal of stitches.

Nanda *et al.* (2014) studied continuous maintenance of anaesthesia using guaifenesin or diazepam combined with xylazine and ketamine in horse and reported that

higher muscle relaxation score in animals anaesthetized with guaifenesin, ketamine and xylazine than those with diazepam, ketamine and xylazine.

2.3.2 Physiological effects

Khamis and Saleh (1970) reported that xylazine hydrochloride had depressive effects on both heart and respiratory rates in cattle and buffaloes.

DeMoor and Desmet (1971) reported that in cattle xylazine decreased partial pressure of oxygen in arterial blood (Pao_2).

Klide *et al.* (1975) and Haskins *et al.* (1986) reported biphasic blood pressure response (hypertension followed by hypotension) in dogs after intravenous and intramuscular administration of xylazine hydrochloride.

Campbell *et al.* (1979) observed that significant decrease in heart rate following epidural administration of xylazine which could be attributed to decreased sympathetic outflow from the CNS, direct depression of cardiac pacemaker and conduction tissue and increased vagal tone attributable to activation of baroreflex.

Peshin *et al.* (1980) noticed that bradycardia, hypotension and decreased respiratory rate in dogs after administration of xylazine at the rate of 3 mg/kg body weight intramuscularly.

Moreau *et al.* (1983) noticed that the sedative effects of xylazine hydrochloride in dogs decreased when given the same dose a week later thus it indicated that tolerance had developed for xylazine hydrochloride from the single dose injection initially.

Singh *et al.* (1983) reported that intravenous administration of xylazine at 0.22 mg/kg body weight resulted in slight initial transient hypertension followed by sustained hypotension.

Lele and Bhokre (1985) observed that a significant decreased heart rate and respiratory rate with inconsistent effect on blood pressure when xylazine used at the dose rate of 3 mg/kg body weight intramuscularly in dogs.

Jean *et al.* (1990) reported that significant decrease in heart rate, respiratory rate and arterial blood pressure after epidural administration of xylazine in cattle.

Matthews *et al.* (1991), Wagner *et al.* (1991) and opined that peripheral vasoconstriction mediated through α-1 and α-2- receptors was likely responsible for the increase in the systemic blood pressure that was seen immediately after intravenous administration of xylazine, which was transient and blood pressure slowly declined according to the dose.

Mohammed and Yelwa (1993) stated that xylazine caused bradycardia by increasing the vagal tone and decreasing the sympathetic activity.

Kerr *et al.* (1996) observed that the mean arterial pressure was lower than the baseline values at 25 minutes after diazepam and ketamine administration in xylazine premedicated horses.

Tiwari and Amareshkumar (1998) reported significant decrease in heart rate and respiratory rate from 5 to 120 minutes after epidural administration of xylazine at 0.10

mg/kg body weight in buffalo calves. The decrease in respiratory rate was due to direct depressant action of α-2- agonists on CNS, in general and respiratory centre in particular.

Paddleford (1999) used xylazine hydrochloride in small ruminants and observed hyperglycemia due to reduction in insulin release, prolonged recovery and increase urine production by inhibition of antidiuretic hormone release. He also stated that xylazine hydrochloride causes depression of thermoregulation with hypo or hyperthermic effects in sedated patients.

Yamashita *et al.* (2000) concluded that, cardiovascular depression was shorter and milder with xylazine hydrochloride as compared to equipotent doses of medetomidine and detomidine. The author also reported that initial hypertension and rise in peripheral vascular resistance was minimal after xylazine hydrochloride administration.

Hall *et al.* (2001) stated that, the effects of xylazine hydrochloride on the arterial blood pressure depend on the relative effects of the central and peripheral stimulation. There was often an initial hypertensive phase, followed by a more prolonged period of arterial hypotension. The hypertensive phase was not always evident after intramuscular injection, possibly because of reduced peak blood concentrations of the drug.

Gross and Tranquilli (2001) reported that xylazine hydrochloride caused reduction in heart rate, cardiac output, arterial blood pressure and respiratory rate, whereas, increase in urine volume and transient hypoinsulinemia.

Ambrisko and Hikasa (2002) reported excitement and muscle rigidity in dogs administered with xylazine hydrochloride at higher doses of 4-8 mg/kg body weight intramuscularly.

Riazuddin *et al.* (2004) stated that the xylazine induced a fall in mean arterial pressure, probably due to decreased myocardial contractibility and cardiac output, sympatholytic action, inhibition of catecholamine release and blockade of central and peripheral alpha adrenoceptors.

Lemke (2007) reported that, the cardiovascular effects after intramuscular administration of xylazine hydrochloride were less dramatic as compared to intravenous injection.

Abrahamsen (2008) reported that xylazine hydrochloride caused transient reduction in haematocrit values and haemoglobin concentration and increased of uterine tone in late gestation that could lead to abortion in ruminants.

Kanda and Hikasa (2008) reported that xylazine hydrochloride increases blood glucose in various species, including dogs, cats, rats and mice.

Gweba *et al.* (2010) observed that the respiratory rate, heart rate (at 30, 60 and 120 minutes) and rectal temperature (at 120, 180 and 240 minutes) decreased significantly after administration of xylazine at the dose of 0.2 mg/kg body weight, intramuscularly to Sokoto red goats.

Lu *et al.* (2013) observed an immediate decrease in rectal temperature following administration of α-2-adrenoceptor agonists, possibly because of the loss of thermoregulatory control and might also be due to generalized sedation, decreased metabolic rate, muscle relaxation and central nervous system depression.

Singh *et al.* (2013 a) reported that significant decrease in rectal temperature and heart rate (at 5 and 10 minutes up to 30 minutes) in xylazine and fentanyl premedicated buffaloes.

Mane *et al.* (2014) reported that a significant depression in respiratory rate after premedication with xylazine (1.1 mg/kg, IV) in horses which might be due to direct depression of respiratory centres. The heart rate decreased non significantly after premedication followed by non significant increase after induction of anaesthesia with ketamine and isoflurane. Bradycardia might be attributed to direct vagomimetic action of α-2-adrenoceptor agonists.

Sannakki and Ranganath (2016) used xylazine at 0.05 mg/kg body weight as a premedicant intravenously to ketamine (2 mg/kg, IV) and isoflurane (1.00 to1.50%) for general anaesthesia in cattle and reported that non-significant decrease in the mean rectal temperature from 60 to 75 minute, a non-significant decrease in mean heart rate (HR) and mean pulse rate 5 minute after administration of xylazine at these dose. Also reported that mean ± SE value of recovery time was 5.00±0.86 minute.

Venkatgiri *et al*. (2017) observed intermittent apnoea in both xylazine and romifidine group of animals following comparative evaluation of romifidine-ketamine and xylazine-ketamine induction combination for isoflurane anaesthesia in cattle.

2.3.3 Haematological and biochemical effects

Khamis and Selah (1970) reported that xylazine hydrochloride causes a decrease in erythrocyte count, haemoglobin concentration and significant changes in blood acid base equilibrium.

Symonds and Mallison (1978) stated that xylazine induced hyperglycemia in cow was due to combination of increased hepatic glucose production and reduced plasma insulin.

Peshin *et al.* (1980) reported that xylazine hydrochloride administration at the dose rate of 3.0 mg/kg body weight intramuscularly produced a slight decrease in total erythrocyte count, total leucocyte count, packed cell volume, haemoglobin and lymphocytes with subsequent increase in neutrophils. A significant increase in blood glucose and mild increase in serum potassium and chloride concentrations were also observed.

Singh *et al.* (1983) stated that in calves, xylazine caused reduction in blood flow, which possibly occurred due to peripheral sympathetic depression.

Vikers *et al.* (1984) observed that a significant increase in serum glutamic oxaloacetate transaminase (SGOT) and serum glutamic pyruvate transaminase (SGPT) enzymes following epidural xylazine.

Lele and Bhokre (1985) reported that xylazine alone or in combination with various pre-anaesthetics in dogs has no significant influence on blood urea nitrogen

(BUN). However, xylazine with chlorpromazine hydrochloride produced significant changes in blood glucose level.

Angel and Langer (1988) opined that hyperglycemia in xylazine anaesthesia was attributed to adrenergic inhibition of insulin receptor release by stimulation of alpha-2-receptor in the pancreatic β-cells.

Ambrisko and Hikasa (2002) observed that dose dependent increase in plasma glucose level following xylazine administration in dogs.

Kilic (2004) reported that pooling of circulating blood cells in the spleen and other reservoirs secondary to decreased sympathetic activity could be the reason for a decrease in haemoglobin and packed cell volume.

Singh *et al.* (2005) reported that decrease in haemoglobin (Hb), packed cell volume (PCV) and total leukocyte count (TLC) in water buffalo administered with xlazine (0.05 mg/kg) lumbar epiduraly and also found that a significant increase in glucose and BUN level from 30 to 60 minute, creatinine from 30 to 120 minute after injection and all biochemical values came to base line values at 24 hours post injection

Malik and Singh (2007) reported that increased creatinine value in horse administered with xylazine-butorphanol-midazolam-ketamine anesthesia.

Ajadi *et al.* (2008) stated that xylazine hydrochloride in dogs had a tendency to increase the creatinine and blood urea nitrogen levels and hence should not be used in uraemic patients or concurrently with drugs capable of inducing renal depression.

Fani *et al.* (2008) observed a significant decrease in total erythrocyte count, haemoglobin, packed cell volume, total leukocyte count and platelet count after epidural administration of xylazine in dogs, which might be due to an increase in plasma volume on account of sequestration of blood cells in spleen and lungs during anaesthesia and they also observed a significant increase in blood urea nitrogen.

Singh *et al.* (2013 a) observed that significant decrease in haemoglobin, packed cell volume (from 30 to 90 minutes) and creatinine (from 15 to 720 minutes) and significant increase in blood urea nitrogen (from 120 to 1440 minutes) in buffaloes premedicated with xylazine and fentanyl and maintained with isoflurane anaesthesia.

Xiao *et al.* (2013) reported that an increase in blood glucose levels from 58.00 ± 3.00 to 108.00 ± 12.00 mg/dL in normoglycemic monkeys administered with xylazine (1-2 mg/kg) intramuscularly and they concluded that hyperglycemia was due to stimulation of α-2-adrenoceptors and then reducing tissue sensitivity to insulin and glucose uptake.

Kumar *et al.* (2015) reported that a significant increase in plasma glucose after xylazine (0.10 mg/kg IV) administration in buffalo calves.

Sannakki and Ranganath (2016) used xylazine at 0.05 mg/kg body weight as a premedicant intravenously to ketamine (2 mg/kg, IV) and isoflurane (1.00-1.50%) general anaesthesia in cattle and reported that there was a non-significant decrease in mean total erythrocyte count, haemoglobin and packed cell volume values between 60 and 75 minute, 30 and 75 minute, and 45 and 75 minute, respectively.

2.4 Ketamine hydrochloride

Ketamine hydrochloride is an analogue of phencyclidine, induces dissociative state of anaesthesia by interrupting the ascending transmission from the unconscious to conscious parts of the brain, rather than by generalized depression of all brain centres (Corssen *et al.,* 1968). Its chemical name is 2-(O-chlorophenyl)-2-methylamino cyclohexamine hydrochloride (Corssen and Domino, 1966). The ketamine molecule exists as two optical isomers or enantiomers. This racemic mixture is currently used clinically; however, in animals the (+) isomer produces hypnosis lasting nearly twice as long as the (–) isomer (Marietta *et al.,* 1977 and Ryder *et al.,* 1978). The racemic mixture is intermediate in effect. Analgesia with the (+) isomer is more profound, and there is less locomotor activity after anaesthesia (White *et al.,* 1980).

Cohen *et al.* (1974) reported that ketamine was lipid soluble and its lipid solubility was 5 to 10 times greater than thiopental, so it was absorbed quickly after administration.

Waterman (1984) reported that the distribution and elimination half-lives of ketamine were 6.9 min and 60.50 min, respectively, in calves.

Haskins *et al.* (1985) reported that increased temperature, excessive muscle tone and salivation in dogs under ketamine anesthesia

Hui Chu Lin (1996) reported that ketamine produces dose related unconsciousness and analgesia. Ketamine had rapid onset of action, with maximum effect occurring in approximately 1 minute.

Flaherty *et al.* (1997) stated that concomitant infusion of ketamine markedly decreased the blood propofol concentration required to provide surgical anaesthesia.

Orser *et al.* (1997) reported that antagonism of ketamine to the N-Methyl-D-Aspartate (NMDA) receptor had been molecular mechanism responsible for most of its central nervous system actions.

Caulkett *et al.* (2000) stated that quality of immobilization of deer was superior with medetomidine-ketamine, which was characterized by good muscle relaxation no spontaneous movements when compared to carfentanyl-xylazine.

Kathirvel *et al.* (2000) noticed that ketamine added to spinal bupivacaine had local anaesthetic sparing effects in humans.

Bednarski *et al*. (2011) recommended the dose of ketamine as 10-20 mg/kg body weight and could be given subcutaneously, intramuscularly, epidurally or intravenously and as a constant rate infusion at 0.50-1.00 µg/minute in dogs.

2.4.1 Clinical effect

Levinson (1973) used ketamine (5 mg/kg) in pregnant ewes and reported that increased maternal blood pressure slightly (15% from control) and caused no deleterious effects on the foetal cardiovascular or acid-base status. Uterine blood flow increased concomitant with the rise in maternal arterial pressure.

Fuentes and Tellez (1974) observed that the swallowing, palpebral and anal reflexes remained intact under ketamine anaesthesia in cattle.

Flots *et al.* (1975) reported that ketamine induced hypertonicity in dogs could be attributed to the extrapyramidal activation, because of increased electrical activity of basal ganglia.

Muir (1977) observed that excellent analgesia and light anesthesia in all horses anaesthesized with xylazine (1.1 mg/kg) and ketamine (2.2 mg/kg) intravenously and also observed that cardiac output, arterial blood pressure, pulmonary arterial pressure, central venous pressure, and pulmonary arterial wedge pressure remained within normal limits.

Ryder *et al.* (1978) reported that S-ketamine was more potent analgesic than R-ketamin in mice.

Waterman (1981) observed that the duration of anaesthesia was 37.00 ± 7.50 minutes in calves anaesthetized with xylazine (0.20 mg/kg) and ketamine (5 mg/kg) intravenously they also observed the decresase in respiratory and pulse rate after xylazine administration and then increase in these parameters after ketamine injection.

Rings and Muir (1982) reported that significant decrease in mean arterial blood pressure and partial pressure of oxygen (PaO_2) and significant increase in respiratory rate after 15 minute of administration of xylazine (0.08 mg/kg)-ketamine (4.40 mg/kg) drug combination intramuscularly in calves.

White *et al.* (1982) stated that the protective reflexes such as deglutition, corneal and palpebral reflexes remained intact with ketamine whereas, the duration of anaesthesia was very short and hypertonus.

Marsico *et al.* (1999) reported that epidural ketamine produced dose dependent caudal analgesia of tail, anus, perineum and vulva in cow.

Paddleford (1999) reported that during ketamine anaesthesia, eyelid and corneal reflexes remained intact and eyes remain open and laryngeal reflexes were not depressed. Ketamine produced increased muscle tone and limb rigidity, increased salivation and respiratory secretions. It also produced delirium, which might be accompanied by ataxia, increased motor activity, avoidance behaviour, sensitivity to touch, hyper-reflexia, or violent recovery.

Pawde *et al.* (2000). Studied detomidine-diazepam –ketamine anaesthesia in buffaloes and reported that detomidine - diazepam –ketamine combination was safe and suitable for 15 minutes of anaesthesia with excellent muscle relaxation and had only limited cardiorespiratory effects in buffaloes.

Hall *et al*. (2001) opined that, ketamine had cataleptic, analgesic and anaesthetic action without muscle relaxation. There was generally an increased skeletal muscle tone with brisk tendon reflexes with spontaneous tonic-clonic spasms of limb muscles. Although laryngeal and pharyngeal reflexes were retained, the increased salivation could obstruct airways. Although limb movements occurred without external stimuli and were dose related.

Chandrashekar *et al.* (2003) observed that poor muscle relaxation, muscle tremors and hind limb stretching in buffalo calves anaesthetized with ketamine.

Lee *et al.* (2003) observed that good analgesia without sedation at tail and perineum region in cattle administered with 5% ketamine into the first inter-coccygeal (Cy1- Cy2) epidural space after 5 minutes.

Kaur and Singh (2004) stated that the recovery time to sternal recumbency was 40.54 ± 7.25 minutes in bovines anaesthetized with intravenous midazolam (0.1 mg/kg) and ketamine (4.0 mg/kg).

Lin (2007) observed varying degrees of hypertonus and purposeful or reflexive skeletal muscle movements often occurred unrelated to surgical stimulation in ketamine anaesthesia. Dissociative anaesthetics produced rapid onset of action, a dose dependent unconsciousness and brief, however, intense somatic analgesia and rapid recovery. Emergency reactions were characterized by ataxia, increased motor activity, hyperflexia, sensitivity to touch, delirium and violent recovery.

Posner and Burns (2009) were of opinion that analgesic effects of ketamine were partially mediated through activation of opioid receptors. When ketamine was used alone in animals, upper airway muscle tone and reflexes would be preserved.

Sindak *et al.* (2010) used xylazine (1 mg/kg) and ketamine (10 mg/kg) intramuscularly in Greyhound dogs and observed that mean induction time and duration of anaesthesia were 8.33 minute and 55.52 minute respectively.

Kovalcuka *et al.* (2013) observed that substantial increase in the intra ocular pressure 5 minute after ketamine injection in dogs with IOP of 23.20 ± 5.80 mmHg (a

45.00% increase compared to baseline) in the right eye and 22.90 ± 5.90 mmHg (a 43.50% increase) in the left eye.

Kumar *et al.* (2014 a) reported that the onset of sedation, sternal recumbancy and lateral recumbancy were 1.27, 5.34 and 16.57 minute respectively in buffalo calves anaesthetized with midazolam (0.30 mg/kg) and ketamine (6 mg/kg) intravenously.

Kumar *et al.* (2014 b) reported that onset of salivation and recovery time to sternal position were occurred at 5.89±0.73 minutes and 61.33±6.08 minutes in buffalo calves administered with diazepam (0.75 mg/kg body weight) and ketamine (6 mg/kg body weight) intravenously.

Kachari and Sharma (2015) reported that the mean induction time, duration of sedation and recovery time were 2.16±0.21, 60.25±1.47 and 80.66±2.13 minutes respectively in pigs anaesthetized with medetomidine (30 µg/kg) and ketamine (10 mg/kg) imtramuscularly.

Rohith kumar *et al.* (2014) studied clinico-physiological, hematobiochemical and haemodynamic effect of propofol and ketamine with dexmedtomidine in urolithic goat and concluded that, both ketamine and propofol combination are suitable for induction maintenance anaesthesia for one hour with good analgesia haemodynamic stability.

Deepesh guatam *et al.* (2017) studied clinical haematological evaluation of subarachnoid ropivacaine dexmedetomidine and their combination with ketamine for tube cystotomy in urolithic buffalo calves and reported ropivacaine, dexmedetomidine and their combination with ketamine produces only transient and minor changes in

haematological parameters and produces good muscle relaxation and analgesia at lower abdominal surgery in buffalo calves.

2.4.2 Physiological effects

Wilson *et al*. (1968) reported that the effect of ketamine on cardiovascular system was mediated through either one of the three ways; general stimulation of vasomotor centre, peripheral release of nor-epinephrine or decreased baroreceptor activity permitting increased blood pressure or heart rate.

Kelly *et al.* (1971) reported that the respiratory rate and minute ventilation increased in dogs administered with ketamine.

Waterman and Livingston (1978) reported that the intravenous injection of ketamine in sheep gave a brief period of respiratory depression with decrease in the PaO_2, followed by a period of respiratory stimulation with elevated PaO_2 levels. Administration of ketamine caused an initial fall in arterial blood pressure which was dose dependent and short lived.

Altura *et al.* (1980) reported that ketamine caused a short-lived vasodepressor response that was followed by longer lasting potent pressor response. The depressor phase of ketamine anaesthesia occurred within the first few minutes of induction and was due to a direct relaxation of vascular smooth muscles.

Haskins *et al.* (1985) reported that increase in the temperature, heart rate, cardiac output, systemic blood pressure and decrease in breathing rate, minute volume with

excessive muscle tone and salivation in dogs under intravenous ketamine (10 mg/kg) anaesthesia.

Kumar *et al.* (1986) observed a significant increase in heart rate up to 30 minutes, which declined to normal levels by 120 minutes following ketamine administration in goats, which was due to general stimulation of vasomotor centre and peripheral release of nor epinephrine.

Aithal *et al.* (1996) stated that epidural administration of ketamine in goats resulted in analgesia accompanied by cardiopulmonary stimulation.

Muir *et al*. (1999) observed that ketamine administration in horses increased heart rate, cardiac output, arterial blood pressure and body temperature by CNS sympathetic activation.

Caulkett *et al.* (2000) noticed that significant rise in mean arterial pressure in deer during immobilization with medetomidine and ketamine.

Ohata *et al*. (2001) reported that systemic administration of ketamine at 1 mg/kg body weight and 5 mg/kg body weight did not alter any haemodynamic values in dogs.

Chandrashekar *et al.* (2003) observed that accelerated heart rate and pulse rate in buffalo calves administered with intravenous ketamine (5 mg/kg).

Singh *et al.* (2003) opined that ketamine was useful in counteracting some of the depressant action of α-2- agonists on respiratory rate.

Gunay *et al*. (2004) reported that intravenous administration of ketamine in dogs caused an increase in respiratory rate, decrease in body temperature, a significant decrease in systolic pressure, increased diastolic pressure and sinus tachycardia during anaesthesia.

Riazuddin *et al.* (2004) reported that ketamine caused an increase in mean arterial pressure by depression of baroreceptors, negative ionotropic effect on myocardium, increased cardiac output and myocardial output and sympathomimetic action.

Kilic (2008) reported that there was a significant decrease in the mean heart rate, arterial pH, PaO_2 and an increase in $PaCO_2$ within 5 minute of the injection. Respiratory rate increased significantly with time. The body temperature decreased significantly during the anaesthesia from 38.50 ± 0.30^{o}C to 37.90 ± 0.40^{o}C in calves anaesthetized with detomidine (50 μg/g), midazolam (0.50 mg/kg) and ketamine (5 mg/kg), intravenously.

Sindak *et al.* (2010) reported that a significant decrease in mean heart rate at 30-45-minute, respiratory rate at 5-45 minute and rectal temperature at 20-25 minute after anaesthetizing Greyhound dogs with xylazine (1 mg/kg) and ketamine (10 mg/kg) intramuscularly.

Ahmed *et al*. (2015) Evaluated halothane anaesthesia after xylazine-ketamine administration in camels and reported significant decrease in respiratory rate after xylazine and ketamine administration.

Chander Vijay Pal *et al*. (2016) evaluated on anaesthetic combination with triflupromazine –ketamine in buffalo calves and observed increase in heart rate and decrease in respiratory rate along with significant decrease in haemoglobin and packed cell volume was observed.

Sannakki and Ranganath (2016) observed that a non significant increase in the heart rate at 15-30 minute, respiratory rate from 60 to 75 minute and non-significant decrease in the mean rectal temperature in cattle anaesthetized with xylazine (0.05 mg/kg, IV) as a premedication to ketamine (2 mg/kg, IV)-isoflurane (1-2%) general anaesthesia.

Animesh Chandra Roy *et al*. (2017) compared the effect of different local analgesics and ketamine on clinical parameters for cranial epidural analgesia in black Bengal goat and reported that ketamine hydrochloride significantly increased the heart rate and respiratory rate.

Ninu *et al.* (2017) studied the comparison of thiopentone and ketamine as induction and maintenance agent in buffaloes undergoing diaphragmatic hernioraphy and reported that the quality of muscle relaxation was better in ketamine as induction agent used in buffaloes.

2.4.3 Haematological and biochemical effects

Kumar *et al.* (2001) stated that in haloperidol (0.85 mg/kg) premedicated dogs, ketamine anaesthesia caused significant decrease in haemoglobin, total erythrocyte count, total leukocyte count, packed cell volume from 5 to 10 minutes and up to 45 minutes of ketamine administration.

Butola and Singh (2003) administered midazolam at the rate of 0.3 and 0.5 mg/kg body weight intravenously to two groups of dogs followed by slow intravenous injection of ketamine, to effect. Group 1 showed a drop-in serum sodium levels, while Group 2 showed significant decrease in hemoglobin, packed cell volume and serum potassium levels. In both groups there were nonsignificant decrease in total leucocyte count, SGOT, SGPT and significant increase in blood glucose levels, serum creatinine and chloride levels in both groups.

Singh *et al.* (2007) reported that nonsignificant decrease in haemoglobin, packed cell volume and total leucocyte count in goats anaesthetized with xylazine (0.25 mg/kg) and ketamine (2.50 mg/kg) intravenously.

Kilic (2008) used detomidine (50 μg/kg), midazolam (0.50 mg/kg) and ketamine (5 mg/kg) in calves and reported that haemoglobin, PCV, and RBC decreased significantly for a short time. The plasma glucose, creatinine and ALT increased significantly. However, they returned to the baseline values at 24 hours.

Udegbunam *et al*. (2009) observed that haemoglobin, packed cell volume and total erythrocyte count of the splenectomised dogs decreased slightly after ketamine administration and concluded that this might be due to sequestration of red blood cells in non-splenic sites.

Ismail *et al*. (2010) used xylazine (0.10 mg/kg body weight), ketamine (4 mg/kg body weight) and diazepam (0.25 mg/kg body weight) anesthesia in sheep and observed that a significant increase in neutrophil percentages and PCV at 2 hour and 24 hour after

recovery and a leukocytosis at 24 hour. There was a non significant change in hemoglobin, blood urea nitrogen, creatinine, aspartate aminotransferase, alkaline phosphatase, and gamma-glutamyl transpeptidase, total protein, and albumin concentrations during anaesthesia.

Kumar *et al.* (2014 a) reported that a non significant increase in plasma glucose, blood urea nitrogen (BUN) and aspertate transaminase (AST) in buffalo calves anaesthetized with midazolam (3 mg/kg) and ketamine (6 mg/kg) at 87.20 minutes of administration.

Okwudili *et al.* (2014) observed that increase in blood glucose, serum cortisol, blood urea nitrogen (BUN) and alanine transaminase (ALT) and non significant change in serum creatinine in West African Dwarf (WAD) goats anaesthetized with xylazine (0.05 mg/kg, IV) and ketamine (5 mg/kg, IV).

Kumar Amresh et *al*. (2017) evaluated lorazepam –ketamine anaesthesia in buffalo calves and observed relaxation of muscle was good quality and swallowing reflex was absent. A non significant increase in glucose during lorazepam –ketamine anaesthesia.

2.5 Isoflurane

Isoflurane is a nonflammable, nonexplosive inhalant general anesthetic agent. It is clear, colorless and stable liquid containing no additives or chemical stabilizers with mildly pungent etheral odour. It is a halogenated ether, chemically designated as 2-chloro-2-difluoromethoxy-1, 1, 1-trifluoroethane, commonly used for anaesthetizing

domestic and pet animals and humans via inhalational anaesthesia. Induction and recovery from anesthesia with isoflurane were rapid (Auer *et al*., 1978). As anesthetic dose was increased, both tidal volume and respiratory rate decrease and this depression is partially reversed by surgical stimulation even at deeper level of anaesthesia (Steffey and Howland, 1980).

Leonard (1975) reported that halogination with five fluorine and one chlorine renders isoflurane nonflammable over all clinically useful concentrations

Steffey and Howland (1977) stated that the minimum alveolar concentration (MAC) of isoflurane in equines was 1.31%.

Brett *et al.* (1987) reported that for 1.00 MAC isoflurane the end tidal concentration was 1.51% in newborn lambs. Also opined that the myocardial blood flow and oxygen consumption decreased dramatically during 1.00 MAC isoflurane. It did not decrease significantly further during 1.50 MAC.

Antognini (1993) reported that the MAC of isoflurane was 1.50% in sheep and goats.

Hikasa *et al.* (1998) reported that the MAC value of isoflurane was 1.29 ± 0.11% in goats.

Cantalapiedra *et al.* (2000) reported that minimum alveolar concentration of isoflurane was 1.27 % in cattle. They observed that isoflurane provided a smooth induction and rapid recovery from anaesthesia in cattle.

Steffey (2001) mentioned that blood/gas partition coefficient of isoflurane was 1.40 and, fat/blood partition coefficient and minimum alveolar concentration of isoflurane were 4.50 and 1.31, respectively, in horse.

Ball and Westhorpe (2007) stated that isoflurane was isolated in 1965.

Steffey and Mama (2007) and Stoelting (1999a) said that isoflurane exists as a clear, nonflammable, halogenated methyl ethyl ether with a blood-gas partition coefficient of 1.46.

Dzikiti *et al.* (2011) reported that minimum alveolar concentration of isoflurane in goat was 1.40.

Kumar *et al.* (2013b) reported that the inclusion of butorphanol tartrate and buprenorphine hydrochloride in the anaesthetic protocol of cattle had a significant reduction in MAC requirement of isoflurane, which indicated that it had a prominent isoflurane sparing effect.

Shaughnessy and Hofmeister (2014) reported that minimum alveolar concentration of isoflurane in cat was 1.71.

2.5.1 Clinical effects

Brett *et al.* (1987) reported that during both 1.00% and 1.50 % MAC, the regional blood flow, oxygen delivery and cardiac output decreased suggesting that the decrease in oxygen delivery resulted from a decrease in demand during isoflurane anaesthesia in lambs.

Watney *et al.* (1987) observed bronchodilatation in isoflurane anaesthetized ponies, which appeared to occur more rapidly, the maximum degree of bronchodilatation being evident within 5 minutes of exposure.

Antognini (1993) reported that the MAC of isoflurane in goats was 1.50 ± 0.30 (mean ± SE) and also reported the decrease in blood pressure from 98.00 ± 17.00 to 78.00 ± 13.00 at 1 MAC.

Hikasa *et al.* (1998) reported a significant decrease in mean arterial pressure in goats under isoflurane anaesthesia.

Cantalapiedra *et al.* (2000) reported that minimum alveolar concentration (MAC) of isoflurane in cattle was 1.27 ± 0.03%. Time to sternal recumbency and time to standing were 4.60 ± 0.58 minutes and 6.70 ± 1.02 minutes respectively. They also reported that isoflurane provided a smooth induction and rapid recovery from anaesthesia in cattle.

Hikasa *et al*. (2000) recorded that mild salivation under isoflurane anaesthesia without any premedication in sheep.

Steffey (2001) mentioned that blood/gas partition coefficient of isoflurane was 1.40 and fat/blood partition coefficient and minimum alveolar concentration of isoflurane were 4.50 and 1.31 respectively in horse.

Banoub *et al.* (2003) reported a decrease in amplitudes of cortical-somatosensory evoked potentials while an increase in cortical-somatosensory evoked potential latencies after isoflurane administration in humans.

Pascoe *et al.* (2007) reported that the minimum alveolar concentration of isoflurane was significantly decreased by an infusion of ketamine and this was accompanied by an increase in heart rate and blood pressure and prolonged recovery in cats.

Sellers *et al.* (2013) reported that the time to first movement and extubation were 7.56 ± 5.34 minutes and 15.56 ± 8.69 minutes, respectively, in calves under isoflurane anaesthesia.

Singh *et al.* (2013b) stated that isoflurane, in combination with dexmedetomidine, fentanyl and thiopentone provided better clinical, physiological and haemodynamic stability than halothane in buffaloes.

Kumandas and Elma (2015) found that the regaining of swallowing reflex and standing up time in isoflurane anaesthetized goats were 8.43 ± 4.47 minutes and 25.00 ± 8.64 minutes, respectively, and the recovery from anaesthesia was uneventful without any complications.

Chaudhary *et al.* (2016) compared isoflurane and sevoflurane for anaesthesia in buffaloes undergoing diaphragmatic herniorrhaphy and reported there was no significant diference in sedation score degree of muscle relaxation and quality of analgesia between isoflurane and sevoflurane, expect for cost, sevoflurane is a better maintaining agent than isoflurane

Rahime Yayingul *et al*. (2017) compared clinical and hemodynamic effects of isoflurane and sevoflurane anaesthesia in calves and reported the effect of isoflurane and

sevoflurane anaesthesia on the cardiovascular and respiratory system were similar and although the changes that emerged during anaesthesia were statistically significant ,it was non etherless found that the changes were within the physiological limits

2.5.2 Physiological effects

Steffey and Howland (1977) investigated cardiovascular effects of isoflurane in healthy unpremedicated dogs and cats, and found that as anaesthetic dose increased, mean arterial pressure consistently and significantly decreased. Cardiac output was sustained (only during light-moderate level of anaesthesia) because the heart rate significantly increased.

Steffey and Howland (1980) reported dose dependent decreases in mean arterial pressure, cardiac output and stroke volume and respiratory rate under isoflurane anesthesia in horse.

Freisen and Lichtor (1983) noted that mean systemic arterial pressure and heart rate decreased during induction of anaesthesia with isoflurane by amounts similar to those reported during halothane anaesthesia.

Brahim and Paul (1984) reported that a significant decrease in mean arterial pressure (MAP) in dogs anaesthetized with isoflurane from baseline (163.30) to after intubation (99.10), they opinioned it was due to the property of isoflurane which decreasd the systemic arterial pressure.

Brett *et al.* (1987) reported significant decrease in the heart rate and cardiac output along with decrease in the mean arterial pressure under isoflurane anaesthesia in sheep.

Susan (1990) opinion that isoflurane was non-irritating to the respiratory tract and did not increase secretions.

Hikasa *et al.* (1998) stated that isoflurane caused a dose dependent decrease in blood pressure, cardiac output, systemic vascular resistance and respiratory rate in sheep and goats. During spontaneous ventilation in goats, the isoflurane increased at 1 to 2 MAC multiples, which was due to central and peripheral chemoreceptors responding to hypercapnia.

Hikasa *et al.* (2000) reported that significant decrease in the respiratory rate and significant increase in the $PaCO_2$ under isoflurane anesthesia in sheep.

Riazuddin *et al.* (2004) reported that during isoflurane anaesthesia in cattle the mean arterial pressure was higher which could be attributed to better coronary perfusion and protection of myocardium by modifying intracellular calcium transport.

Natalini *et al.* (2008) reported that drop in respiratory rate during maintenance could be attributed to the dose dependent depressing effect of isoflurane anaesthesia on higher respiratory centres in horse.

Onmaz *et al.* (2009) observed that significant increase in heart rate and significant decrease in respiratory rate and temperature in sheep under isoflurane anaesthesia.

Kumandas and Elma (2015) reported that a dose dependent decrease in systemic blood pressure was observed in goats under isoflurane anaesthesia.

Sobayil and Omar (2016) evaluated isoflurane after premedication with ketamine in camels and reported significant decrease in heart rate after xylazine –ketamine administration and also significant decrease in rectal temperature and arterial blood pressure were recorded in camels during isoflurane administration.

2.5.3 Haematological and Biochemical effects

Hikasa *et al.* (2000) reported decrease in the packed cell volume and total erythrocyte count, and non-significant alteration in alanine transaminase, aspertate transaminase, glucose, blood urea nitrogen and creatinine values during isoflurane anaesthesia and up to 3 days post-anaesthesia in sheep.

Topal *et al.* (2003) reported that increased alanine transaminase and aspartate transaminase activities 2 days after isoflurane anaesthesia in dogs.

Onmaz *et al.* (2009) observed that the arterial and venous PCO_2, PO_2 and oxygen saturation values were significantly increased and a significant elevation of packed cell volume in arterial blood compared to venous blood in isoflurane anaesthetized sheep.

Singh *et al.* (2013 a) used fentanyl (5 pg/kg body weight) and xylazine (0.05 mg/kg body weight) as a pre-anaesthetics to 5% thiopental sodium and isoflurane general anaesthesia in water buffalo and observed that a significant decrease in hemoglobin, PCV and TLC up to 90 minute and also observed a significant increase in blood urea up to 120

to 1440 minute. A significant decrease in insulin up to 120 minute, there after a significant increase was recorded at 720 minute and 1440 minute was noticed.

Thangadurai *et al*. (2016) used xylazine hydrochloride (0.10 mg/kg body weight, IV), guaifenesin (50 mg/kg body weight, IV) with ketamine hydrochloride (4 mg/kg body weight, IV) and isoflurane (2%) general anaesthesia in cattle with traumatic pericarditis and observed that significant increase in serum glucose between the stages of anaesthesia and also observed that decrease in total protein, increase in serum urea and aspertate transaminase (AST) enzymes compared to normal values.

Venkatgiri *et al.* (2017) reported decrease in heamoglobin, packed cell volume and total erythrocyte count in all the animals and also observed nuetrophillia and relative lymphocytopenia in all the animals following romifidine-ketamine and xylazine-ketamine induction combination for isoflurane anaesthesia in cattle.

Materials and Methods

III. MATERIALS AND METHODS

The present study was conducted to compare the sedative effects of Romifidine , Xylazine and Dexmedetomidine in cattle presented for various surgical procedures to the Veterinary Clinical Complex (VCC), Veterinary College, Bidar.

3.1 Sources of research animals

The present clinical study was carried out in 18 clinical cases of cattle presented for various surgical procedures to the Department of Surgery and Radiology, Veterinary Clinical Complex (VCC), Veterinary College, Bidar. All the cattle were randomly divided into three groups consisting of six cattle in each group. The details were shown in the Table 1.

3.2 Preparation of animals

Cattle were kept off-feed for 18-24 hours and off-water for 12 hours followed by preparation of surgical site involved series of steps such as clipping of hairs, removal of dirt and oils at the site of surgery, followed by scrubbing was done using chlorhexidine (savlon) and operative site was stained using povidone iodine 0.1% solution.

3.3 Procedure of the study

3.3.1 Sedation and induction

Group I: The animals of group I were pre-medicated with romifidine hydrochloride @ 10 µg/kg body weight intravenously (plate-1). After ten minutes of romifidine administration the animals were restrained in lateral recumbency over the

Table 1: Design of the technical programme of clinical study

Sl. No.	Groups	Number of animals	Surgeries performed for Calf /Cow/Bull /Bullock	Anaesthetic protocol
I	Group-1	06	1) Ventral hernia repair 2) IILN of oblique complete over riding fracture of right femur 3) IILN of simple complete distal metaphysial fracture of left tibia 4) Superficial digital tendon repair in bullock 5) Excision of Pre-scapular lymph node tumor 6) Dehorning in bullock	Induction: Romifidine[1]-10µg/kg I/V Ketamine[2]-3mg/kgI/V Maintenance Isoflurane[3]-(1-2%)
II	Group-2	06	1) Extra luminal intestinal obstruction with paralytic ileus 2) Third eyelid cancer repaire in cow 3) Dehorning in bullock 4) Squamous cell carcinoma in cow 5) Scrotal ablation 6) Bilateral dehorning	Induction: Dexmedetomedine[4]-2.5µg/kg I/V Ketamine[2]-3mg/kgI/V Maintenance Isoflurane[3]-(1-2%)
III	Group-3	06	1) Excision of tumor growth at left abdomen 2) Deep digital tendon repaire in bullock 3) Repaired with wiring complete over riding fracture of right tibia 4) Tibial fracture repair 5) Extirpation of eyeball 6) IILN of left tibial fracture repaire in heifer	Induction: Xylazine[5]-0.1mg/kg I/V Ketamine[2]-3mg/kgI/V Maintenance Isoflurane[3]-(1-2%)

[1] Sedivet (1.0% Injection), Boehringer Ingelheim
[2] Aneket (50 mg/mL), Neon Laboratories Ltd., Mumbai, India
[3] Sosrane, Neon Laboratories Ltd., Mumbai, India
[4] Dextomid (100 µg/mL), Neon Laboratories Ltd., Mumbai, India
[5] Xylaxin (23.32 mg/mL), Indian Immunologicals Ltd., Hyderabad, India

operation table and anaesthesia was induced by administering ketamine at the dose rate of 3 mg/kg body weight intravenously. Then animals were maintained under isoflurane (1-2%) anaesthesia. In this group, six cattle were presented for different surgical conditions and the surgeries performed are mentioned in Table 1.

Group II:

The animals of group II were pre-medicated with dexmedetomidine @ 2.5 µg /kg body weight intravenously (Plate-1). After ten minutes of xylazine hydrochloride administration, anaesthesia was induced by administering ketamine intravenously at the dose rate of 3 mg/kg body weight. Then animals were maintained under isoflurane (1-2%) anaesthesia. In this group, six cattle were presented for different surgical conditions and the types of surgeries performed are mentioned in Table 1.

Group III:

The animals of group III were pre-medicated with xylazine hydrochloride @ 0.1 mg/kg body weight intravenously (Plate-1). After ten minutes of dexmedetomidine administration, anaesthesia was induced by administering ketamine intravenously at the dose rate of 3 mg/kg body weight. Then animals were maintained under isoflurane (1-2%) anaesthesia. In this group, six cattle were presented for different surgical conditions and the surgeries performed are mentioned in Table 1.

Dosages of drugs used in all the three groups were determined based on pilot studies and the available previous literature. After induction a Gunther‟s mouth gag was used to open the jaws for intubation. Endotracheal intubation with cuffed Murphy type

endotracheal tube of appropriate size (Plate 2) was accomplished in all the animals by digital palpation of the epiglottis to direct endotracheal tube into the trachea (Plate 3). The endotracheal tube‟s cuff was inflated to provide a secure leak–free airway. The endotracheal tube was then tied to the mouth gag. The correct placement of the endotracheal tube was confirmed by observing the passage of air through the endotracheal tube upon compressing the chest. The endotracheal tube was connected to the Y-piece of the breathing tube of anesthetic machine

3.3.2 Maintenance of anaesthesia

The large animal anaesthetic machine (Plate 4) was used to maintain anaesthesia with isoflurane. Closed system was used for all animals. The 100% oxygen was given with flow rate set at 10 liters per minute for the first two minutes to increase the fraction of inspired oxygen concentration. The oxygen flow rate was then reduced to five to eight litres per minute based on the size of the animal. Initially isoflurane was given with higher concentration at 5% until downward rotation of eyeball. Later isoflurane concentration was reduced to 1-2%. The vapourizer setting was altered during anaesthesia as and when required to maintain uniform surgical plane of anaesthesia.

After completion of surgery, isoflurane was stopped by setting the vapourizer at 0%. Oxygen (100%) was given until the restoration of swallowing reflex. After reappearance of swallowing reflex “Y” piece was disconnected from endotracheal tube. After deflation of cuff of endotracheal tube, it was removed immediately to restore normal respiration.

Plate 1: Photograph showing the drugs used in present study; Romifidine Dexmedetomidine, Xylazine, Ketamine and Isoflurane

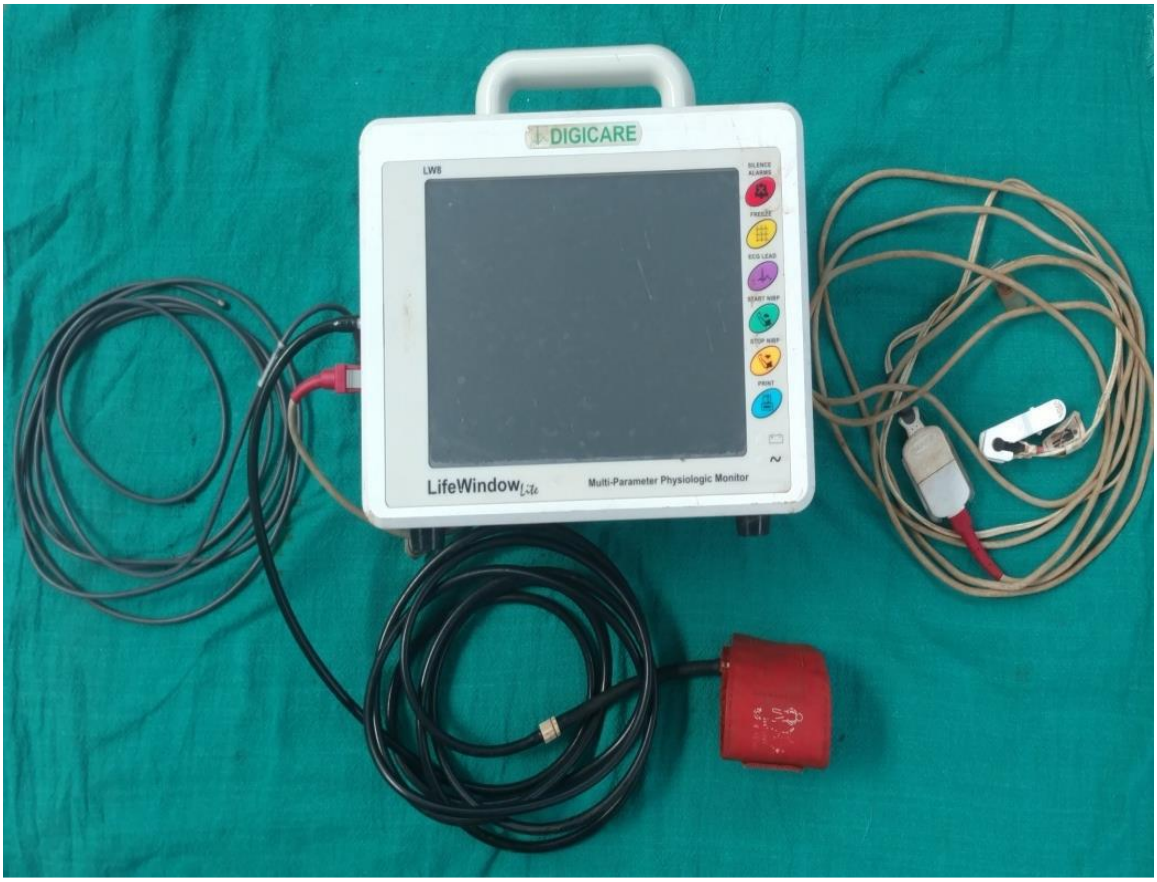
Plate 2: Photograph showing the instruments used in the present study

Plate 3: Photograph showing endotracheal intubation in cattle

Plate 4: Large animal anaesthetic machine used in the present study[6]

[6] Mallard Medical Model 8300C, Redding CA, USA

Plate 5: Photograph showing multi-parameter physiological monitor used in present study[7]



[7] LW8 Lite, Digicare Biomedical Technology, Inc., Florida, USA

3.4 Clinical evaluation

To evaluate the efficacy of anaesthetic protocol the following parameters were recorded before, during and after anaesthesia.

3.4.1 Onset of sedation (Minutes)

The time taken from administration of preanaesthetic drug *viz.*, romifidine (group I), xylazine (group II) and dexmedetomidine (group III) to the development of ataxia, drooping of eyelids and drowsiness in animals was considered as onset of sedation.

3.4.2 Induction time (Seconds)

The time taken for the injecting induction agent to the intubating endotrecheal tube after sedation in romifidine (group I) or xylazine (group II) dexmedetomidine (group III) was considered as induction time. Onset of symptoms such as ataxia, drooping of eyelids and drowsiness were considered to acertain the induction time.

3.4.3 Recovery time (minutes)

The time taken by the animal from discontinuation of inhalant agent to the spontaneous regaining to sternal recumbency was considered as recovery time to sternal recumbency.

3.4.4 Degree of analgesia

The degree of analgesia caused either by romifidine (group I), xylazine (group II) and dexmedetomidine (group III) was measured by needle pricks and response of animal during surgery. The analgesia was graded as following.

0 - No analgesia

1 - Mild analgesia

2 - Moderate analgesia

3 - Good analgesia

3.4.5 Abolition of reflexes

Abolition of palpebral and animal behaviour were evaluated at 10 minutes after premedication and at 30, 60 and 120 minutes after induction of general anaesthesia.

3.4.6 Degree of muscle relaxation

Degree of muscle relaxation was assessed in both the groups administered with sedatives by observing relaxation of abdominal muscles and reduced resistance to passive flexion of the limb. This was observed at 0 minute, 10 minutes, 30 minutes, 60 minutes and 120 minutes of interval after induction of general anaesthesia in both the groups and was graded as following

0 - Absence of muscle relaxation

1 - Mild muscle relaxation

2 - Moderate muscle relaxation

3 - Excellent muscle relaxation

3.5 Physiological parameters

3.5.1 Rectal temperature (°F)

The rectal temperature was recorded before sedation (0 minute) and at 10 minutes, 30 minutes, 60 minutes and 120 minutes interval after induction of general anaesthesia in all the three groups.

3.5.2 Heart rate (beats/minute)

The heart rate was monitored before sedation (0 minute) and at 10 minutes, 30 minutes, 60 minutes and 120 minutes of interval after induction of general anaesthesia in all the three groups.

3.5.3 Respiratory rate (breaths/minute)

The respiratory rate was monitored before sedation (0 minute) and at 10 minutes, 30 minutes, 60 minutes and 120 minutes interval after induction of general anaesthesia in all the three groups.

3.6 Haemodynamic changes

Haemodynamic observations were recorded using multi-parameter physiologic monitor (Plate 5) before premedication (0 minute), 10 minutes after premedication and at 30, 60 and 120 minutes after induction of general anaesthesia

3.6.1 Mean Arterial Pressure (mm of hg)

Mean arterial pressure (MAP), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded using a non-invasive blood pressure monitor before sedation (0 minute) and at 10 minutes, 30 minutes, 60 minutes and 120 minutes after induction of general anaesthesia in all the three groups The blood pressure cuff was placed around the base of the tail to record the mean arterial pressure. The values were expressed in mm of Hg.

3.6.2 Haemoglobin oxygen saturation (SpO2) (%)

The haemoglobin oxygen saturation (SpO_2) was recorded by applying the sensor of the pulse oxymeter on the vulval lips in female animals or to the ears in male animals at (0 minute) and at 10 minutes, 30 minutes, 60 minutes and 120 minutes in all the three groups.

3.7 Haematological estimations

Following haematological observations were estimated before sedation (0 minute), and at 10 minutes, 30 minutes, 60 minutes and 120 minutes interval after induction of general anaesthesia in all the three groups of cattle.

3.7.1 Haemoglobin (g/dL)

Haemoglobin was estimated by Sahli" s haemoglobinometer as per the standard method recommended by Schalm *et al.* (1975).The values are expressed in g/dL

3.7.2 Total Erythrocyte Count ($x10^6$ /µL)

Total erythrocyte count (TEC) was estimated by procedure described by Schalm *et al*. (1975) using Neubauer**,** s slide and values were expressed in million cells per microlitre of blood.

3.7.3 Total Leukocyte Count ($x10^3$ /µL)

Total leucocyte count (TLC) was estimated as procedure described by Jain (1986) and the values were expressed as thousand cells per microlitre of blood.

3.7.4 Differential Leukocyte Count (%)

Differential leukocyte count (DLC) was estimated by staining the blood smear with Giemsa stain and 100 leucocytes were counted using Battlement method as described by Jain (1986).

3.7.5 Packed cell volume (%)

Packed cell volume was estimated by microhaematocrit as described by Benjamin (1985) and the values were expressed in percentage.

3.8 Biochemical estimations

Blood samples were collected before premedication (0 minute), 10 minutes after premedication, and at 30, 60 and 120 minutes after induction of general anaesthesia. Serum was separated for the estimation of following biochemical parameters.

3.8.1 Serum creatinine (mg/dL)

Serum creatinine level was estimated by autoanalyser. The values were expressed in mg/dL.

3.8.2 Alanine transaminase (IU/L)

Alanine transaminase level was estimated by autoanalyser. The values were expressed as IU/L.

3.8.3 Aspartate transaminase (IU/L)

Aspartate transaminase level was estimated by autoanalyser. The values were expressed as IU/L.

3.8.4 Serum urea nitrogen (mg/dL)

Serum urea nitrogen was estimated by autoanalyser. The values were expressed in mg/dL.

3.9 Statistical analysis

The mean and standard error of all parameters were computed as per Snedecor and Cochran (1994). The variations in clinical, physiological, haemodynamic, haematological and biochemical parameters were compared at different time intervals within the group and between the groups and were analyzed using student‘t’ test as described by Snedecor and Cochran (1994).

Results

IV. RESULTS

The present study was conducted in 18 clinical cases of cattle of either sex presented for various surgical procedures to the Department of Veterinary Surgery and Radiology at Veterinary Clinical Complex (VCC), Veterinary College, Bidar. They were randomly divided into three groups consisting of six cattle in each group. The animals of group I were administered with romifidine (10 µg/Kg, I/V) followed by ketamine hydrochloride (3 mg/Kg, I/V) and maintained with isoflurane (1-2%). The animals of group II were administered with xylazine hydrochloride (0.1 mg/Kg, I/V) followed by ketamine hydrochloride (3 mg/Kg, I/V) and maintained with isoflurane (1-2%). The animals of group III were administered with dexmedetomidine (10 µg/Kg, I/V) followed by ketamine hydrochloride (3 mg/Kg, I/V) and maintained with isoflurane (1-2%). The sedative effects of preanaesthetics *viz.*, romifidine, xylazine and dexmedetomidine for ketamine-isoflurane general anaesthesia in cattle were compared. The results of the study are presented under the following headings.

4.1 Clinical evaluations

4.1.1 Onset of sedation (Minutes)

In group-I animals, onset of sedation ranged from 0.40 minutes to 1.30 minutes, with a mean onset of sedation of 1.19±0.46 minutes. In group-II animals, onset of sedation ranged from 1.5 minutes to 2.8 minutes, with a mean onset of sedation of 2.49±0.48 minutes and in group-III animals, onset of sedation ranged from 1.10 minutes to 2.2 minutes, with a mean onset of sedation of 2.16±0.20 minutes The onset of sedation

was significantly faster ($p \leq 0.01$) in group-I animals as compared to group-II and group-III animals.

4.1.2 Induction time (seconds)

In group-I animals, induction time ranged from 29 to 34 seconds, with a mean induction time of 32.00±0.85 seconds. In group-II animals, induction time ranged from 38 to 42 seconds, with a mean induction time of 38.00±0.60 seconds and in group-III animals, induction time ranged from 33 to 38 seconds, with a mean induction time of 35.00±0.32 seconds. The induction of anaesthesia was significantly earlier ($p \leq 0.01$) in group-I as compared to that of in group-II and group-III animals.

4.1.3 Recovery time (Minutes)

In the group-I animals, recovery time ranged from 8 minutes to 12 minutes, with mean recovery time of 10.50±0.88 minutes. In the group-II animals, recovery time ranged from 12 minutes to 16 minutes, with a mean recovery time of 12.85±0.21 minutes.

In the group-III animals, recovery time ranged from 9 minutes to 14 minutes, with a mean recovery time of 10.83±0.79 minutes. The comparison between the groups revealed that there was no statistical significant ($P \geq 0.05$) difference in the recovery time.

Table 2: Mean ±SE values of clinical parameters at different intervals in different groups

Sl. No.	Parameter	Group I	Group II	Group III
1	Onset of Sedation (Minutes)	1.19 ± 0.46^{a}	2.49 ± 0.48^{a}	2.16 ± 0.20^{b}
2	Induction time (Seconds)	32.00 ± 0.85^{a}	38.00 ± 0.60^{b}	35.00 ± 0.32^{b}
3	Recovery time (Minutes)	10.50±0.88	12.85±0.21	10.83±0.79

Mean bearing superscript a, b differs significantly ($P \leq 0.01$) from each other

Fig. 1: Mean ± S.E of onset of sedation (minutes) in Group I, II and III

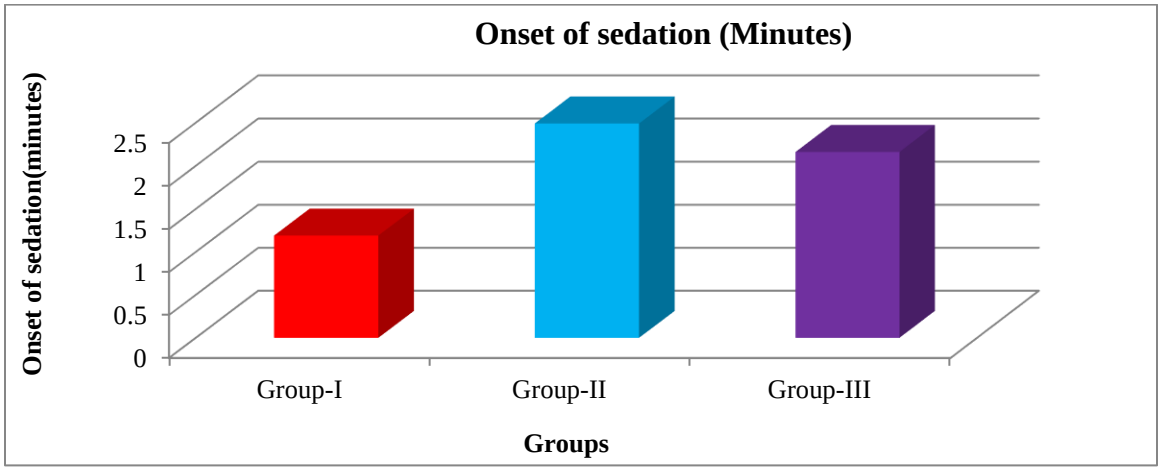


Fig. 2: Mean ± S.E of induction time (seconds) in Group I, II and III

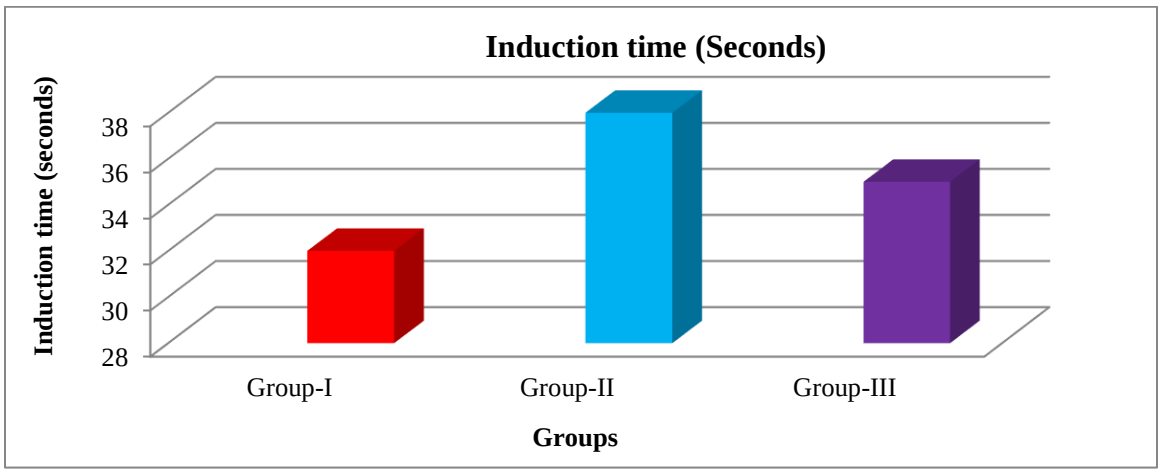
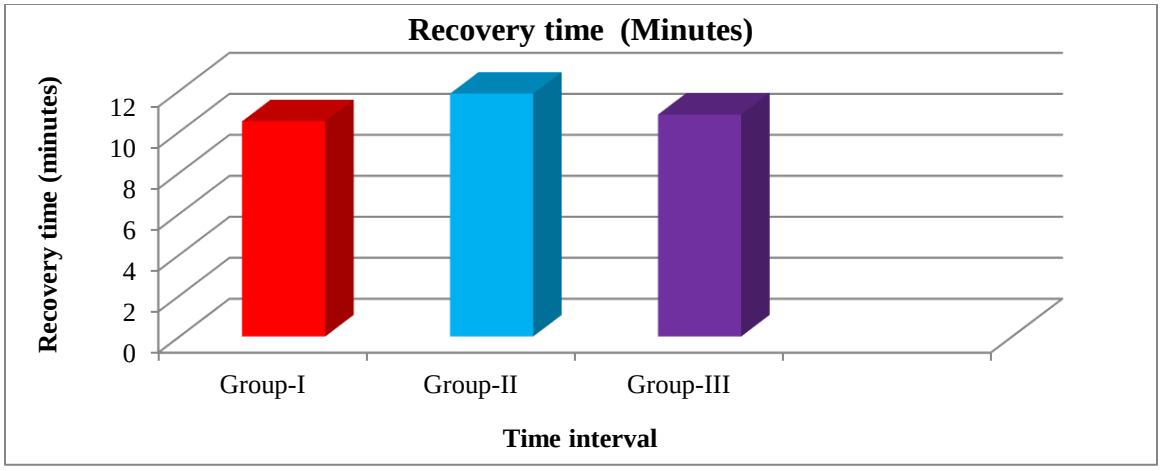


Fig. 3: Mean ± S.E of recovery time (minutes) in Group I, II and III



4.1.4 Degree of analgesia

The Mean ±SE values of analgesic score in cattle of Group I animals, before induction, immediate after 10 minutes, 30 minutes, 60 minutes and 120 minutes after induction were; 0.00±0.00, 2.33±0.33, 3.00±0.00, 2.50±0.43 and 2.17±0.31 respectively. The Mean ±SE values of analgesic score in cattle of group II animals, before induction, immediate after 10 minutes, 30 minutes, 60 minutes and 120 minutes after induction were; 0.00±0.00, 2.67±0.21, 2.50±0.22, 2.33±0.33 and 2.67±0.21 respectively.

The Mean ±SE values of analgesic score in cattle of group III animals, before induction, immediate after 10 minutes, 30 minutes, 60 minutes and 120 minutes after induction were; 0.00±0.00, 1.17±0.17, 2.00±0.00, 2.33±0.33 and 2.83±0.60 respectively.

The analgesia was absent before anaesthesia in all the groups of animals. Pain was significantly abolished from 10 minutes to 120 minutes in all three groups. The level of significance was at ($p \leq 0.01$) all the intervals in all the groups except that it was significant at ($p \leq 0.05$) in group-III animals at 10 minutes. There was non-significant difference in the analgesia level between the groups at all the intervals of study.

4.1.5 Palpebral reflex score

Palpebral reflex was intact even after induction (0 minutes), mild (score =1) to moderate (score =2) abolition in the animals of all three groups.

In the Group-I animals, complete abolition of palpebral reflex (score = 3) was recorded at 30 minutes of post induction, except one animal showed moderate (score = 2) abolition of palpebral reflex. At 60 minutes of post induction all the animals of group-I

showed complete abolition of reflex. At 120 minutes after induction all six animals showed moderate palpebral refex.

In the Group-II animals, complete abolition of palpebral reflex (score = 3) was recorded at 30 minutes of post induction in three animals, another three-animal showed moderate (score = 2) abolition of palpebral reflex. At 60 minutes of post induction all the animals of group-II showed complete abolition of reflex. At 120 minutes after induction three animals showed moderate palpebral refex and another three animals showed mild palpebral reflex.

In the Group-III animals, complete abolition of palpebral reflex (score = 3) was recorded at 30 minutes of post induction in three animals, another three-animal showed moderate (score = 2) abolition of palpebral reflex. At 60 minutes of post induction all the animals of group-II showed complete abolition of reflex. At 120 minutes after induction three animals showed moderate palpebral refex and another three animals showed mild palpebral reflex. The variation in palpebral reflex is due to variation in potency of drugs used in the study.

4.1.6 Degree of muscle relaxation

The Mean ±SE values of degree of muscle relaxation in cattle of Group-I animals, before induction, immediate after 10 minutes, 30 minutes, 60 minutes and 120 minutes after induction were; 0.00±0.00, 2.86±0.23, 2.92±0.17, 2.63±0.31 and 0.00±0.00 respectively.

The Mean ±SE values of degree of muscle relaxation in cattle of group-II animals, before induction, immediate after 10 minutes, 30 minutes, 60 minutes and 120 minutes after induction were; 0.00±0.00, 1.83±0.17, 2.67±0.33, 2.50±0.22 and 0.00±0.00 respectively.

The Mean ±SE values of degree of muscle relaxation in cattle of group-III animals, before induction, immediate after 10 minutes, 30 minutes, 60 minutes and 120 minutes after induction were; 0.00±0.00, 2.67±0.21, 2.83±0.17, 2.33±0.21 and 0.00±0.00 respectively.

The degree of muscle relaxation was significantly (P≤0.01) higher in all the groups of animals between 10 to 60 minutes of the study.

Comparission between the groups showed non significant difference.

Table 3: Mean ±SE values of analgesic score and muscle relaxation at different intervals in different groups

Parameters	**GROUPS**	**Time interval (minutes)**				
		Before (0minute)	**10**	**30**	**60**	**120**
Analgesic Score	**Group-I**	0.00±0.00	2.33±0.33**	3.00±0.00**	2.50±0.43**	2.17±0.31**
	Group –II	0.00±0.00	2.67±0.21**	2.50±0.22**	2.33±0.33**	2.67±0.21**
	Group- III	0.00±0.00	1.17±0.17**	2.00±0.00**	2.33±0.33**	2.83±0.60**
Degree of Muscle Relaxation	**Group-I**	0.00±0.00	2.86±0.23**a	2.92±0.17**	2.63±0.31**	0.00±0.00
	Group –II	0.00±0.00	1.83±0.17**b	2.67±0.33**	2.50±0.22**	0.00±0.00
	Group- III	0.00±0.00	2.67±0.0.21**c	2.83±0.17**	2.33±0.21**	0.00±0.00

The mean bearing superscript ** differ significantly (P≤0.01) from pre-adminstration level to different intervals within in the groups.
Means bearing a, b, c differs significantly (P≤0.05) between the groupsat different intervals

Fig. 4: Mean ± S.E of analgesic score in Group I, II and III

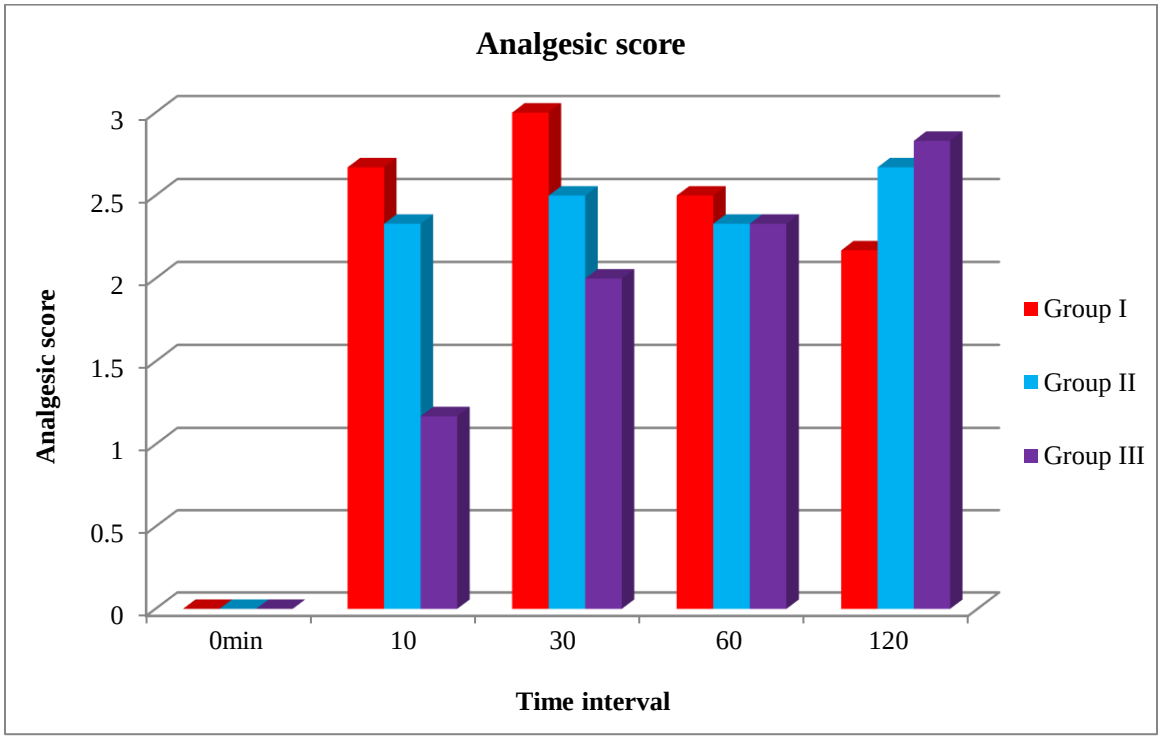


Fig. 5: Mean ± S.E of degree of muscle relaxation in group I, II and III

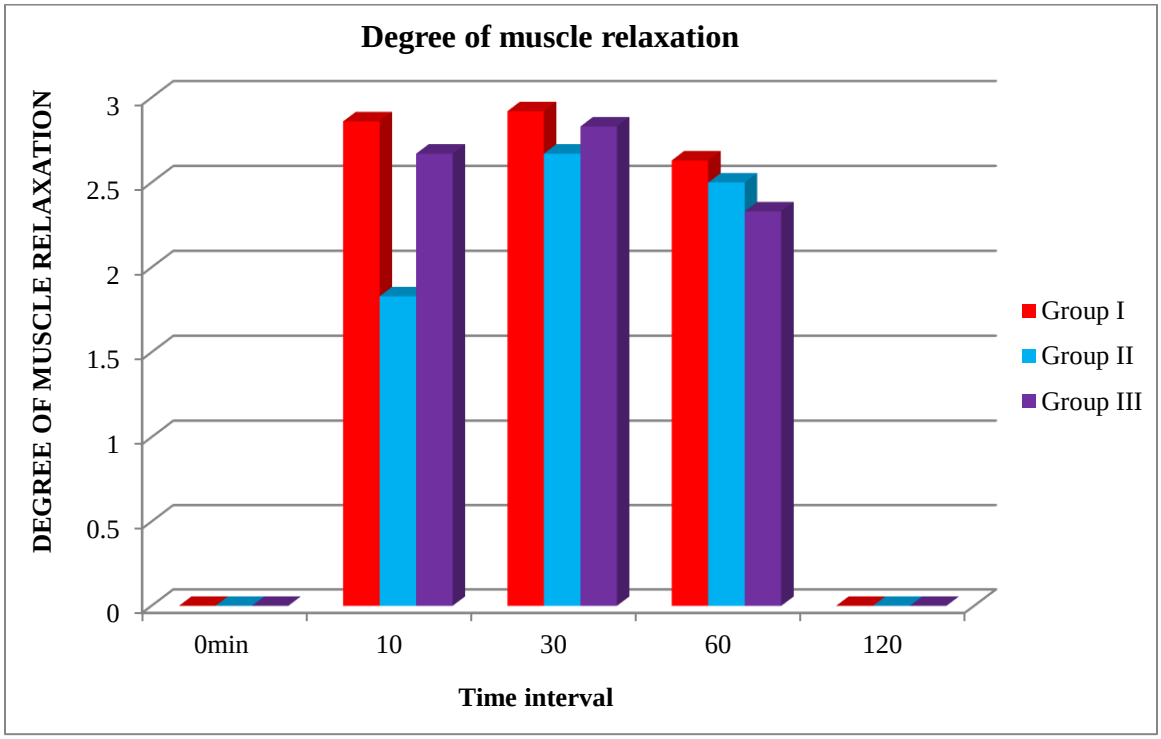


Plate 6: Photograph showing sedation at 10 minutes after administration of romifidine in cattle (Group I) for ventral hernia repair

Plate 7: Intra operative photograph for ventral hernia repair after administering ketamine and isoflurane after romifidine premedication in (Group-I)

Plate 8: Pre-operative photograph showing deep sedation immediately after administering ketamine and isoflurane after romifidine premedication for IILN of right femur fracture repair in calf (Group-I)

Plate 9: Intra-operative photograph for IILN of right femur fracture repair in calf (Group-I) after administering ketamine and isoflurane after romifidine premedication

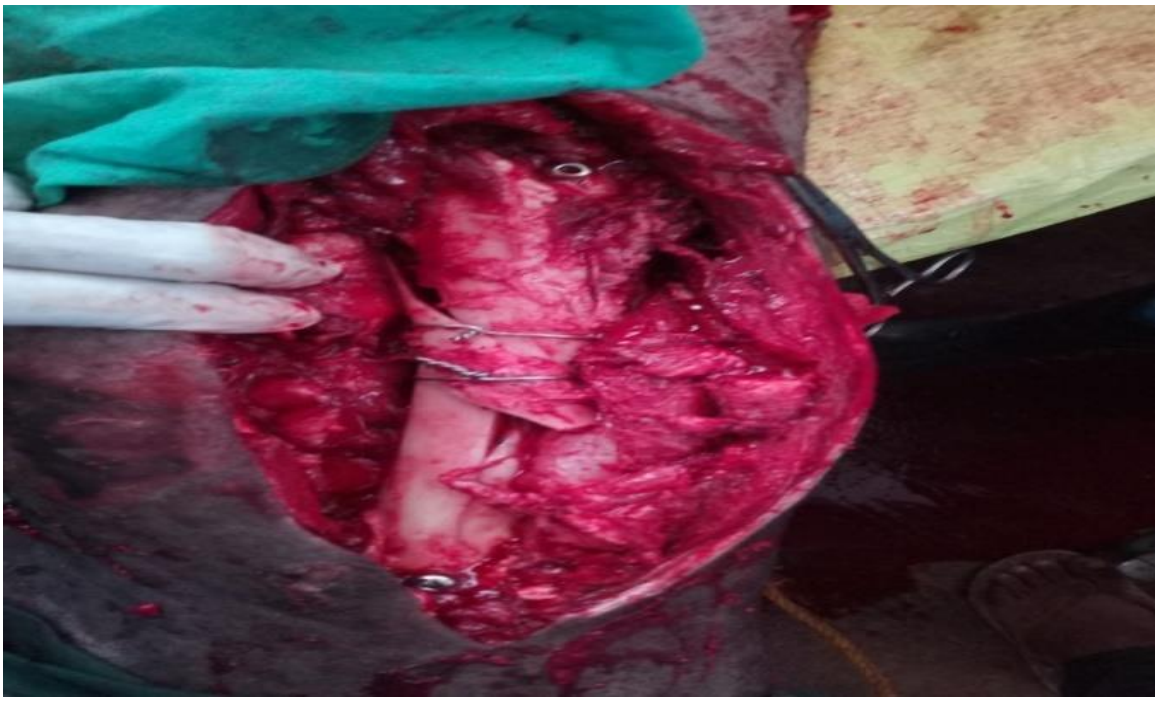


Plate 10: Bullock showing satisfactory anaesthesia under romifidine-ketamine-isoflurane (Group I) anaesthesia. (at 30 minutes)

Plate 11: Calf showing satisfactory anaesthesia under romifidine-ketamine-isoflurane (Group I) anaesthesia for IILN of left tibial fracture repair (at 10 minutes)

Plate 12: Intra-operative photograph for calf showing satisfactory anaesthesia under romifidine-ketamine-isoflurane (Group I) anaesthesia and operated for IILN of left tibial fracture repair (at 30 minutes)

Plate 13: Pre-operative photograph for bullock showing repair of superficial digital tendon under romifidine-ketamine-isoflurane (Group I) anaesthesia in bullock (at 30 minutes)

Plate 14: Intra-operative photograph showing repair of superficial digital tendon under romifidine-ketamine-isoflurane (Group I) anaesthesia in bullock (at 45 minutes)

Plate 15: Photograph showing pre-operative pre-scapular lymph node tumar under romifidine-ketamine- isoflurane anaesthesia (Group I)

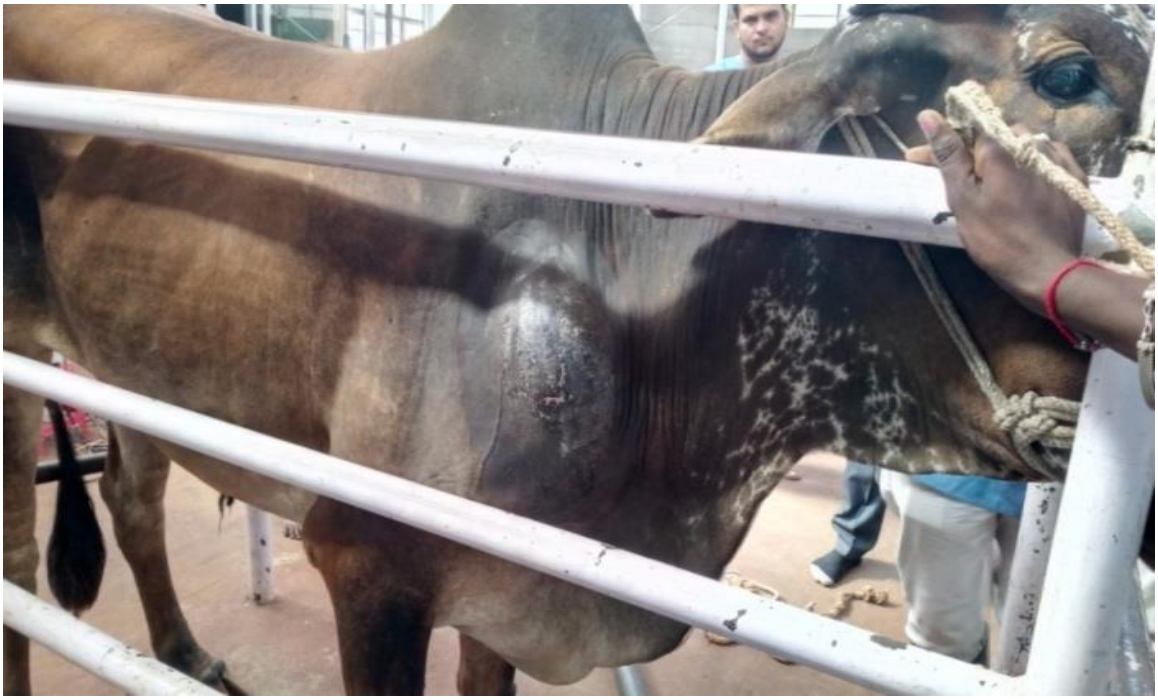


Plate 16: Photograph showing post-operative pre-scapular lymph node tumar under romifidine-ketamine- isoflurane anaesthesia (Group I)

Plate 17: Photograph showing intra-operative dehorning in bullock under romifidine-ketamine- isoflurane anaesthesia (Group I)

Plate 18: Photograph showing post-operative dehorning in bullock and recovery of animal with sternal recumbency from anaesthesia (at 60 minutes, group I)

Plate 19: Photograph showing pre-operative extra-luminal intestinal obstruction with paralytic ileus under dexmedetomidine ketamine-isoflurane anaesthesia (Group II)

Plate 20: Photograph showing intra-operative extra-luminal intestinal obstruction with paralytic ileus under dexmedetomidine ketamine-isoflurane anaesthesia (at 40 minutes, group II)

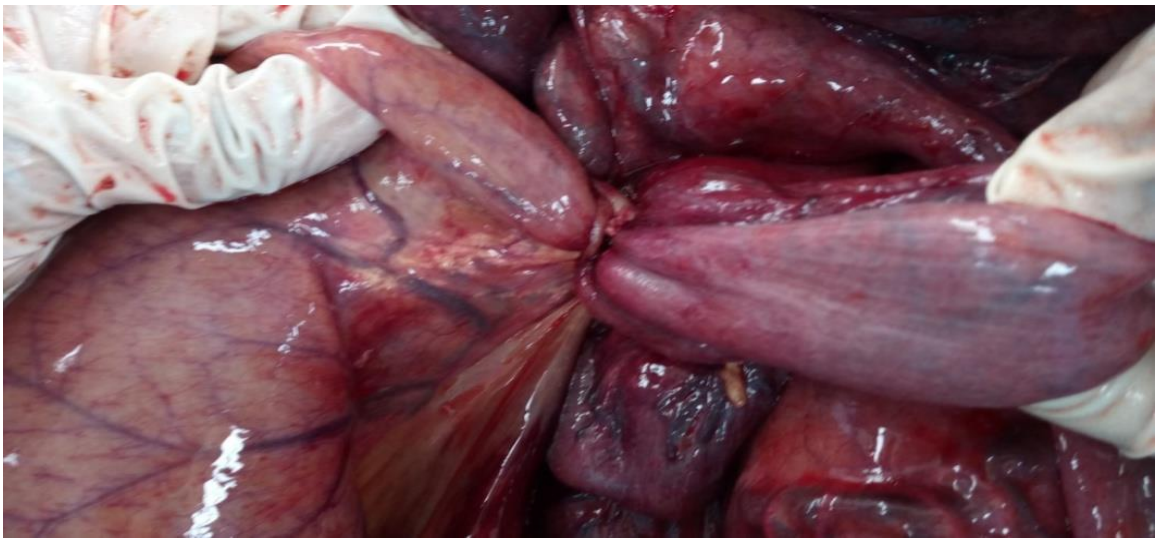


Plate 21: Photograph showing Cow in standing position after sedation for third eyelid cancer repair under dexmedetomidine-ketamine-isoflurane anaesthesia (Group II)

Plate 22: Photograph showing intra-operatve third eyelid cancer repair under dexmedetomidine-ketamine-isoflurane anaesthesia in cow (at 40 minutes, group II)

Plate 23: Photograph showing intra-operative satisfactory anaesthesia under dexmedetomidine-ketamine-isoflurane (group II) anaesthesia and operated for dehorning and recovery after isoflurane disconnection (at 30 minutes)

Plate 24: Photograph showing post-operated anaesthesia for dehorning and recovery after isoflurane disconnection (at 60 minutes) under dexmedetomidine-ketamine-isoflurane (Group II)

Plate 25: Photograph showing cow sedating with dexmedetomidine for operating Squamous Cell Carcinoma for right eye (at 10 minutes, Group II)

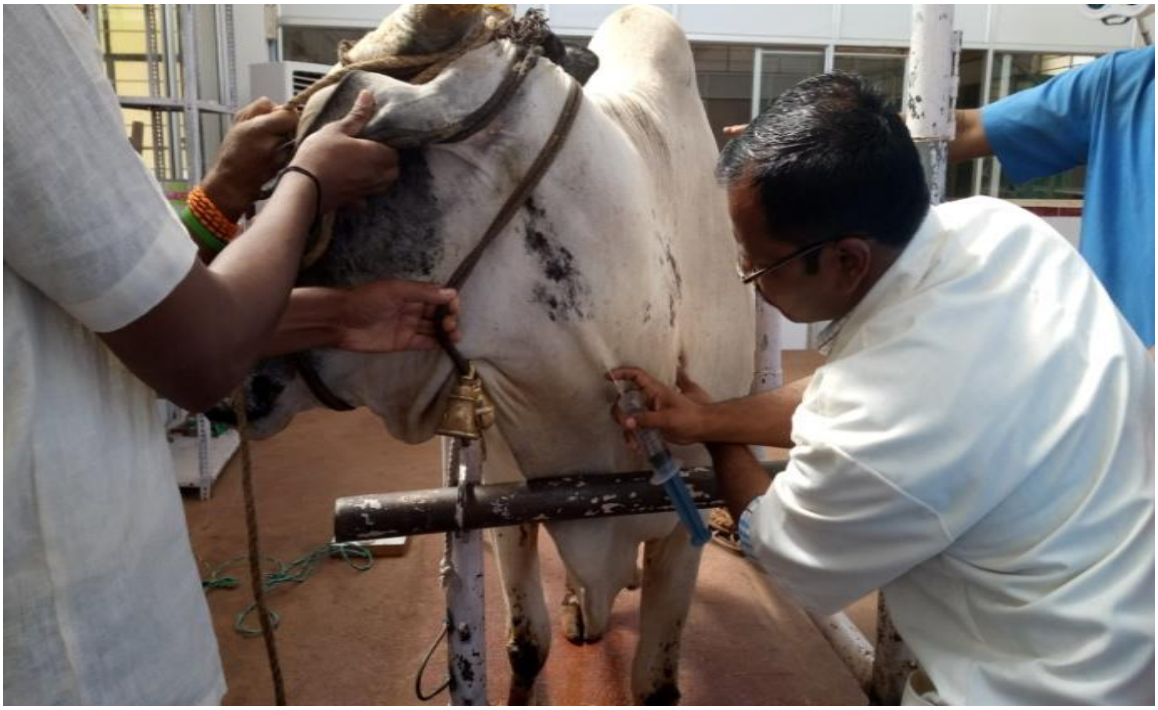


Plate 26: Photograph showing intra- operative Squamous Cell Carcinoma for right eye in cow under dexmedetomidine-ketamine-isoflurane (at 30 minutes, Group II)

Plate 27: Photograph showing pre-operative condition for scrotal ablation (group II) under dexmedetomidine- ketamine and isoflurane

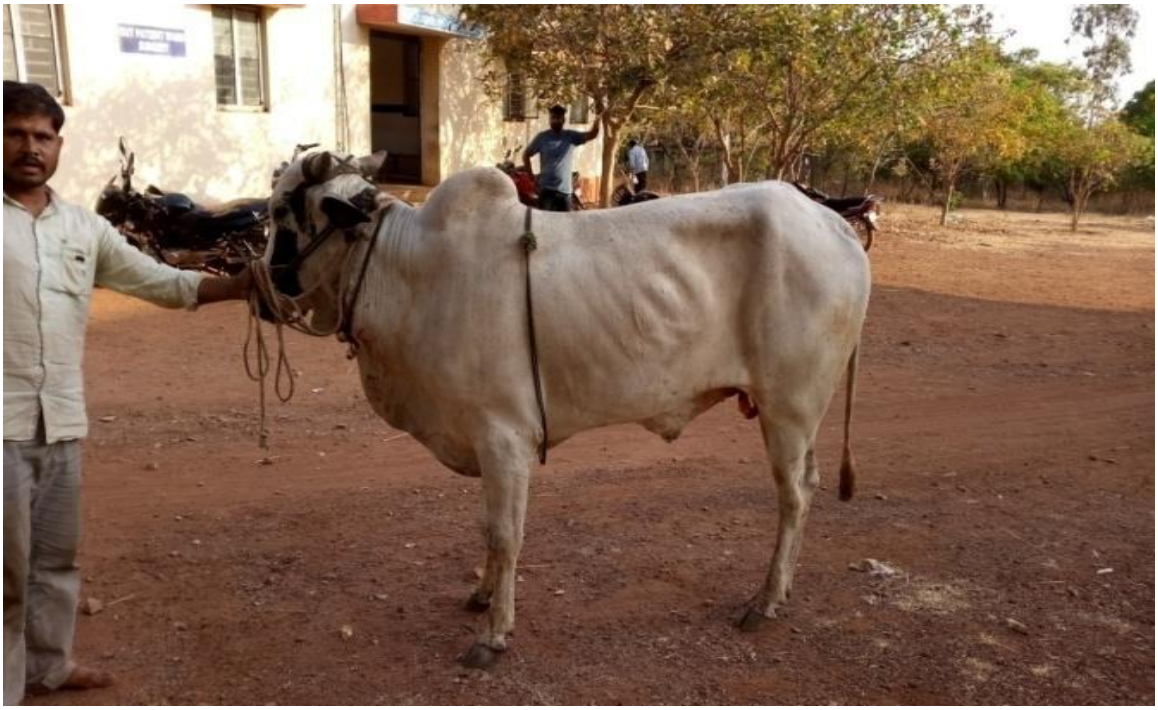


Plate 28: Photograph showing intra-operative scrotal ablation in bullock operated under dexmedetomidine- ketamine and isoflurane for scrotal ablation (Group II)

Plate 29: Photograph showing immediately after administering ketamine and isoflurane after dexmedetomidine premedication for operating bilateral horn fracture (Group II)

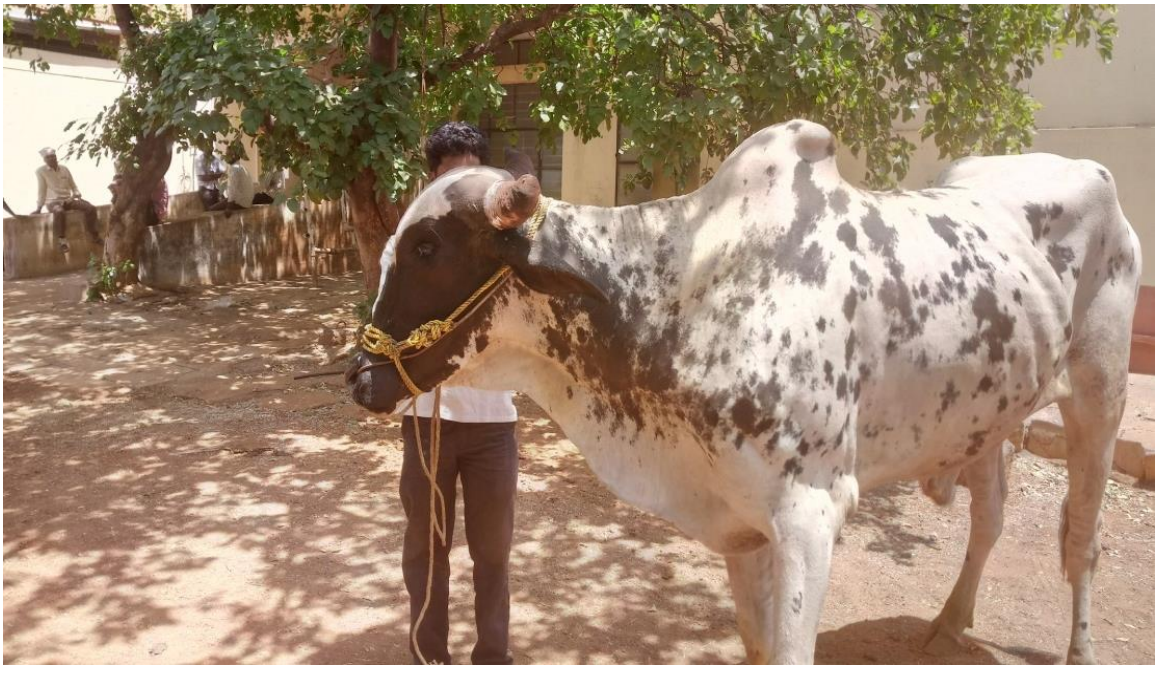


Plate 30: Photograph showing immediately after bilateral dehorning recovery following administering ketamine and isoflurane after xylazine premedication (Group II)

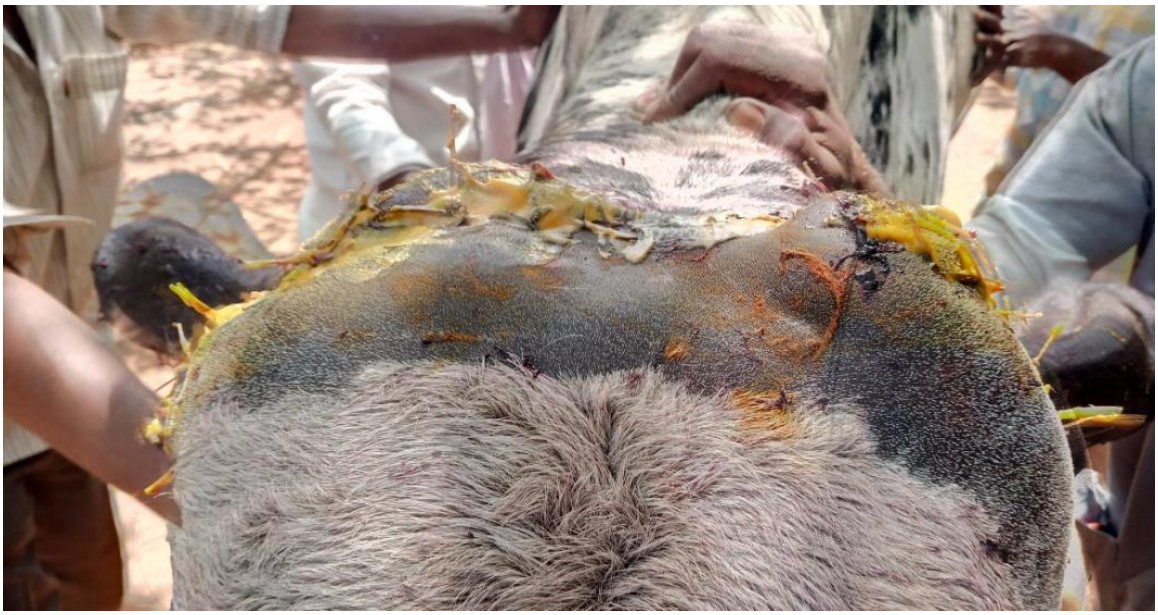


Plate 31: Photograph showing pre-operative excision of tumar growth at left abdomen in bullock operated under xylazine-ketamine-isoflurane (group III) anaesthesia

Plate 32: Photograph showing intra-operative excision of tumar growth at left abdomen in bullock operated under xylazine-ketamine-isoflurane (group III) anaesthesia

Plate 33: Photograph showing pre-operative deep digital tendon repair under xylazine-ketamine-isoflurane (group III) anaesthesia in bullock (at 10 minutes)

Plate 34: Photograph showing post-operative deep digital tendon repair under xylazine-ketamine-isoflurane (group III) anaesthesia in bullock (at 50 minutes)

Plate 35: Photograph showing pre-operative right tibial fracture repair with wiring in calf under xylazine-ketamine-isoflurane (Group III) anaesthesia

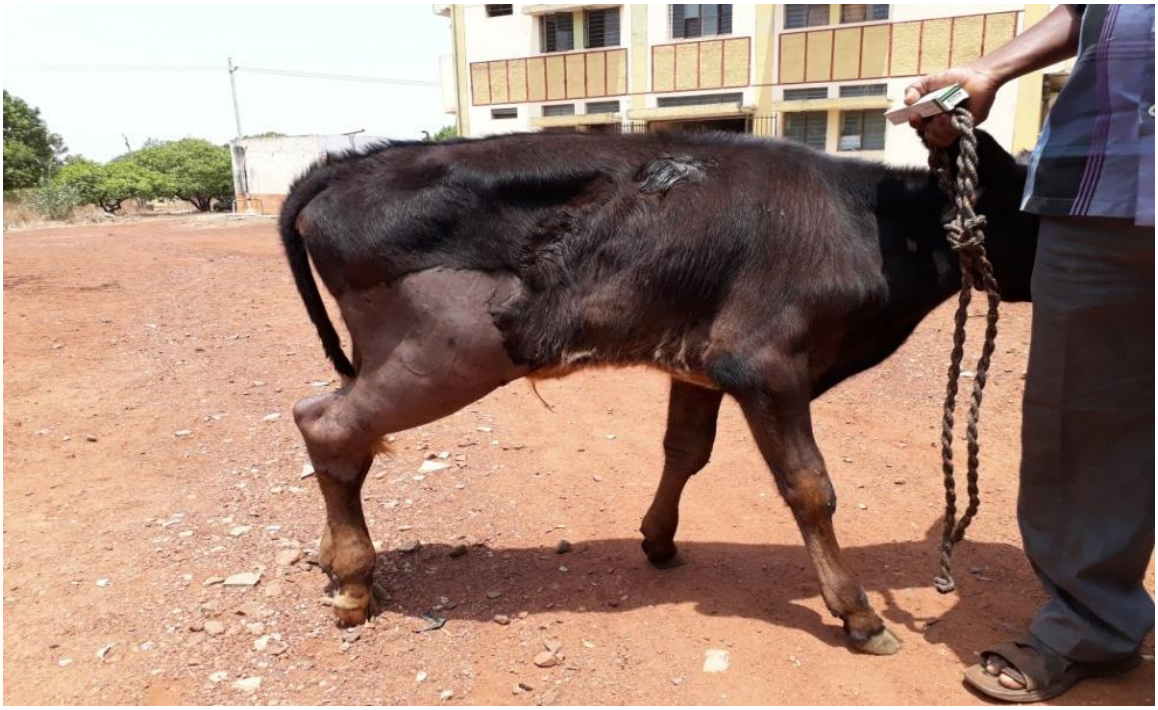


Plate 36: Photograph showing intra-operative right tibial fracture repair with wiring in calf under xylazine-ketamine-isoflurane (Group III) anaesthesia in calf

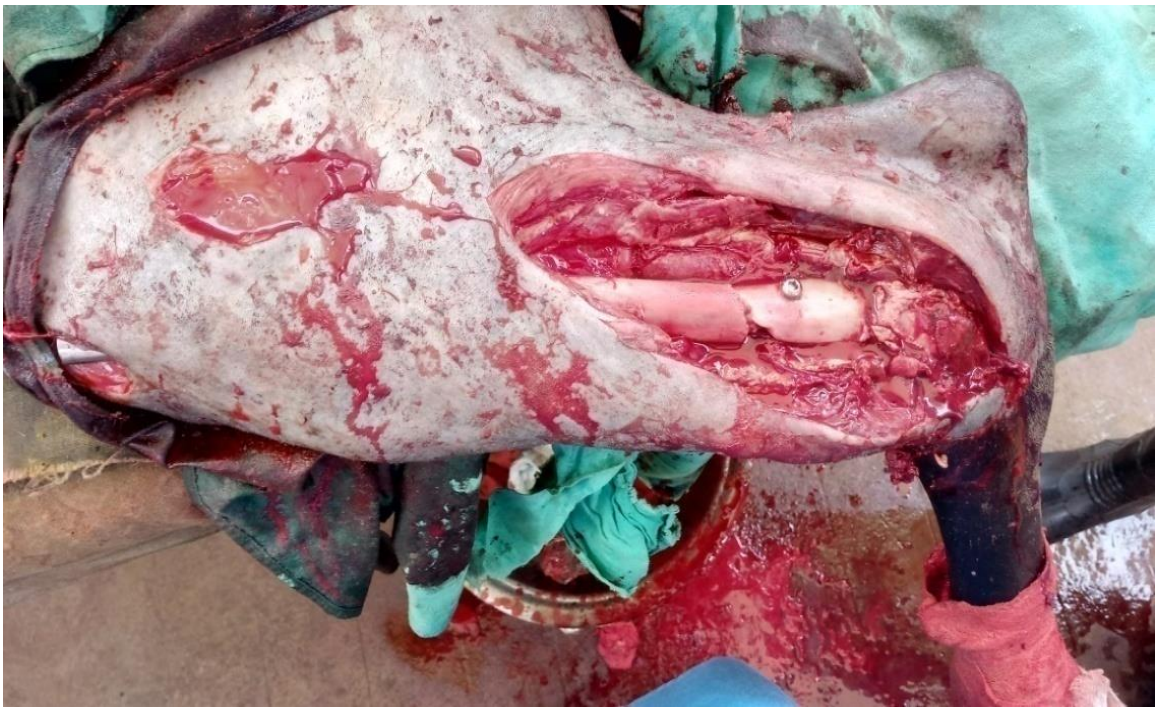


Plate 37: Photograph showing pre-operative IILN of left tibial fracture repair under xylazine-ketamine-isoflurane (group III) anaesthesia in heifer

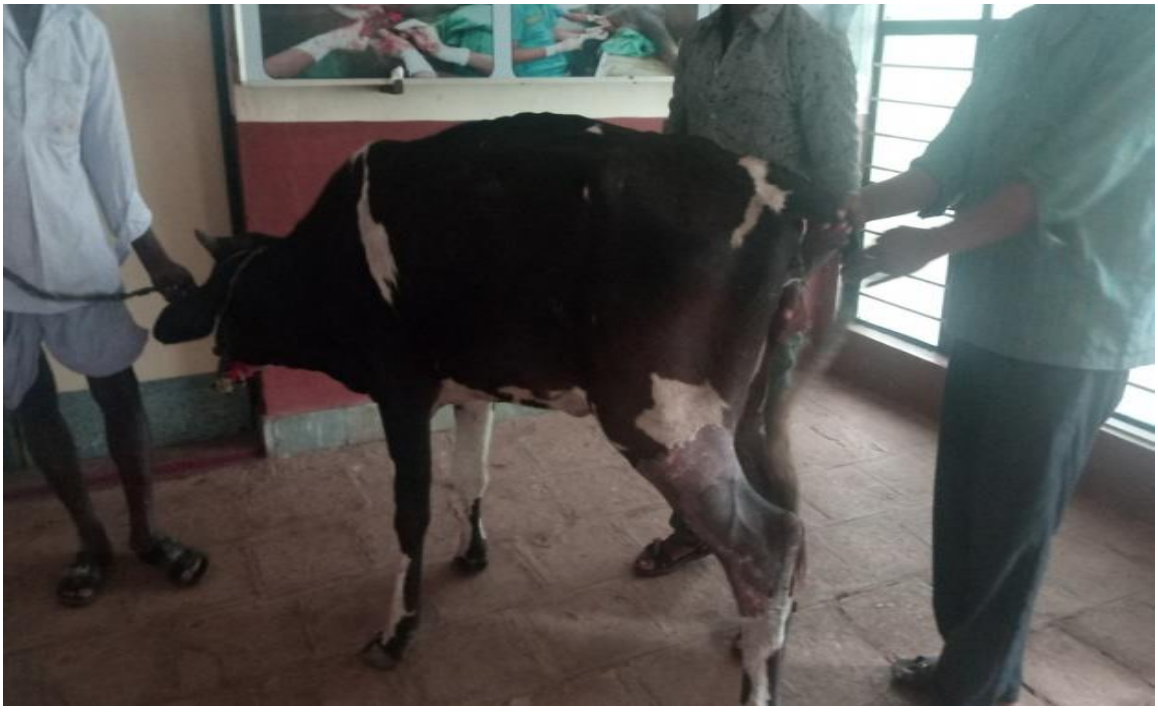


Plate 38: Photograph showing intra-operative IILN of left tibial fracture repair under xylazine-ketamine-isoflurane (Group III) anaesthesia in heifer

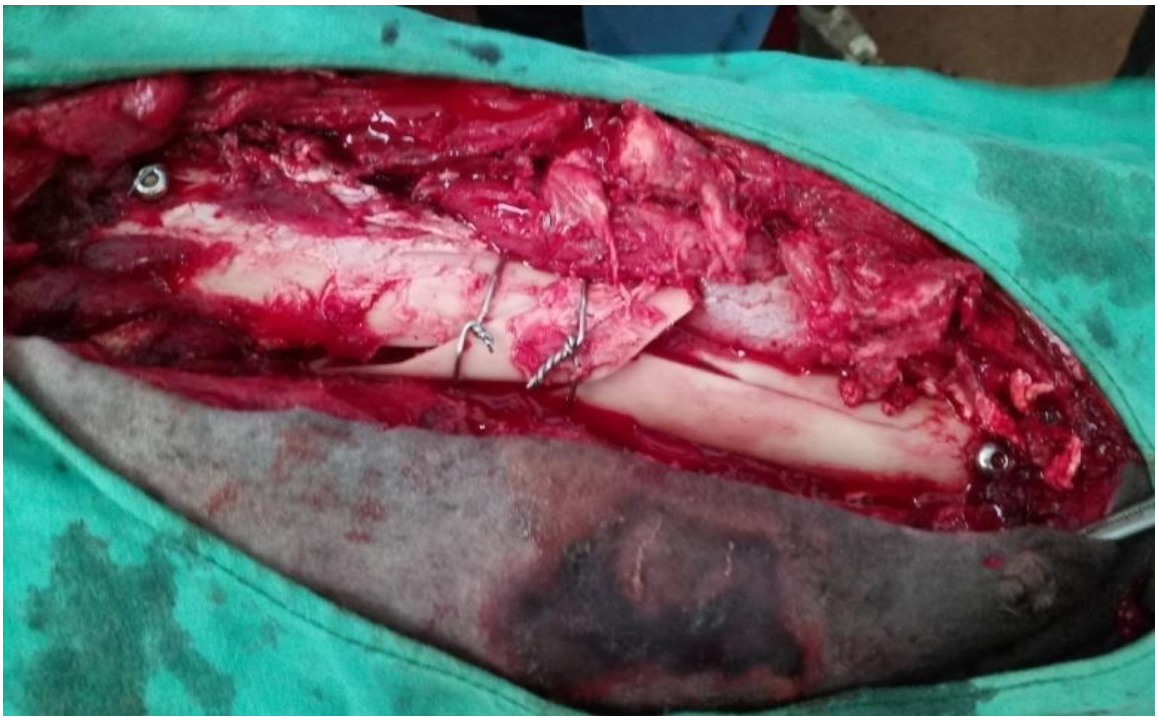


Plate 39: Photograph showing pre-operative extripation of eye ball in bullock procedure under xylazine-ketamine-isoflurane (at Group III)

Plate 40: Photograph showing intra-operative extripation of eye ball in bullock procedure under xylazine-ketamine-isoflurane (at Group III)

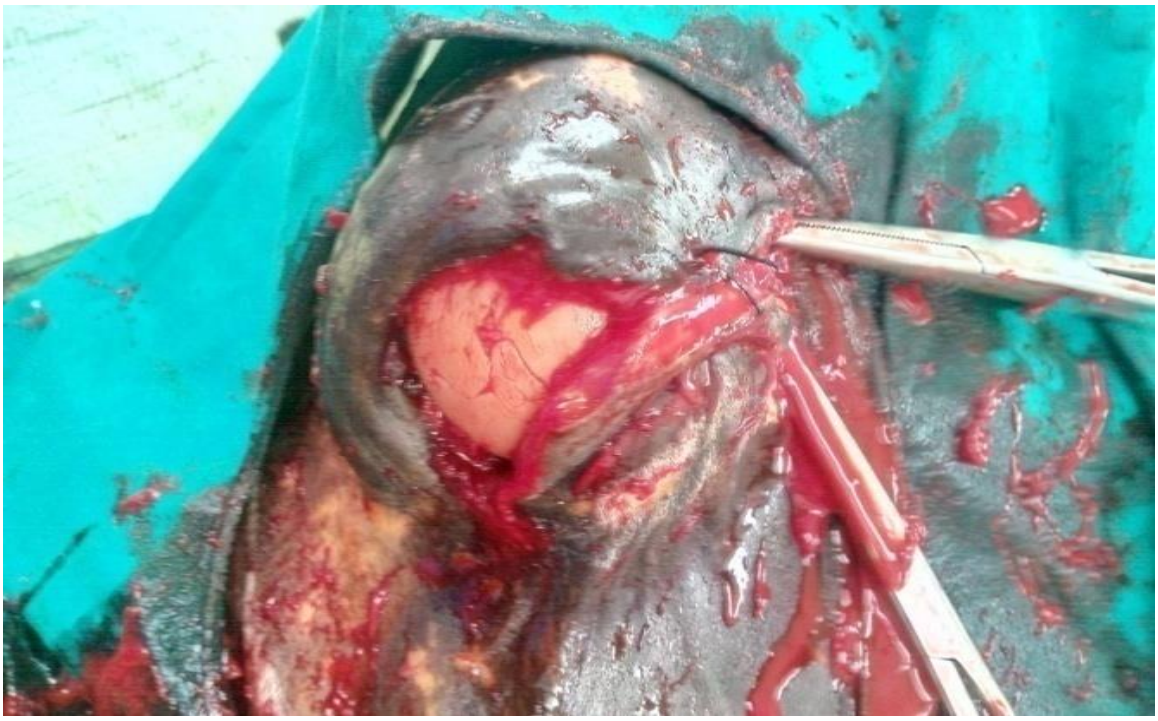
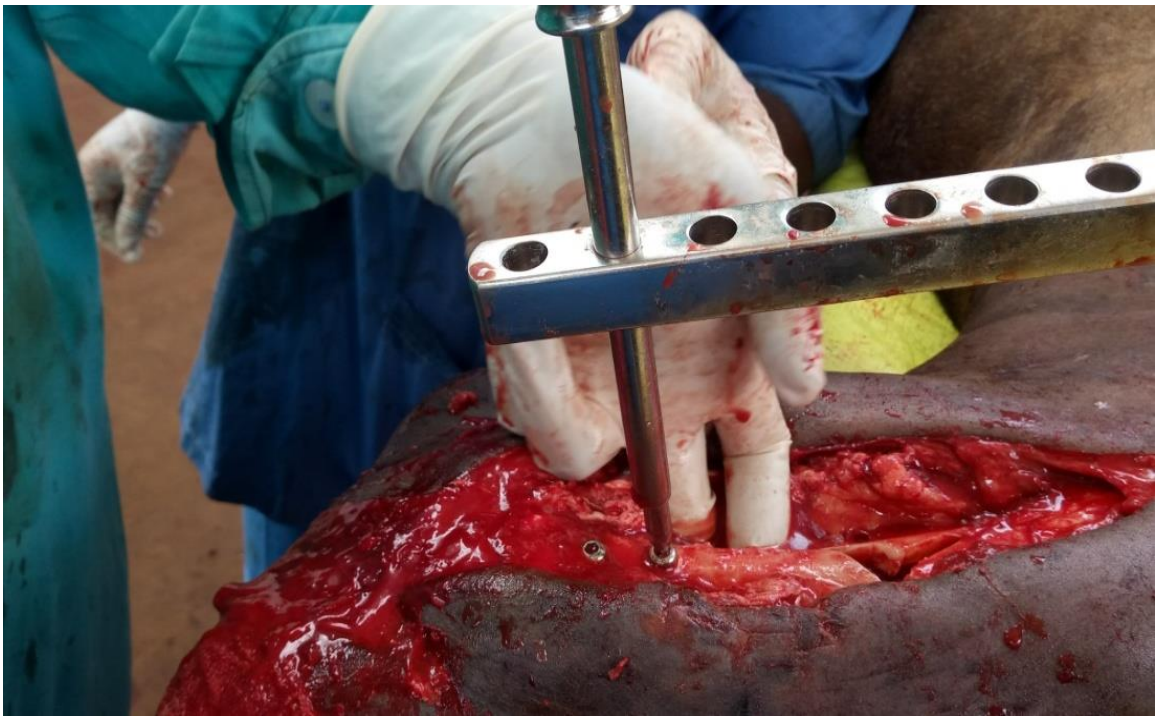


Plate 41: Photograph showing intra-operative IILN of left tibial fracture repair in heifer under xylazine-ketamine-isoflurane (at 50 minutes, Group III)



4.2.1 Physiological Parameters

4.2.1 Rectal Temperature (ºF)

The Mean ± S.E values of rectal temperature (^{0}F) at different intervals in cattle of groups I, group II and groupIII are given in Table 4 and in Fig. 6.

The Mean ± S.E., values of rectal temperature before premedication (0 minute), 10 minutes after premedication and at 30, 60 and 120 minutes after induction of general anaesthesia in cattle of group I were 102.25±0.15, 101.93±0.10, 100.53±0.33, 100.85±0.24 and 101.61±0.14 respectively. The corresponding values in cattle of group II were 101.47±0.37, 100.85±0.81, 101.25±0.29, 101.32±0.40 and 101.37±0.42 respectively and the corresponding values in cattle of group III were 101.55±0.23, 101.93±0.10, 100.53±0.33, 100.85±0.24 and 101.65±0.14 respectively.

Rectal temperature fluctuated within normal physiological limit in all the groups at different intervals of the study.

The rectal temperature did not vary between groups at different interval

4.2.2 Heart Rate (beats/min)

The Mean ± S.E values of heart rate (Beats/minute) at different intervals in cattle of groups I and II are given in Table 4 and in Fig.7.

The Mean ± S.E., values of heart rate (Beats/minute) before premedication (0 minute), 10 minutes after premedication and at 30, 60 and 120 minutes after induction of general anaesthesia in cattle of group I were 66.16±1.35, 55.50±1.66, 57.00±1.90, 59.50±1.90 and 63.00±1.60 respectively. The corresponding values in cattle of group II

were 65.21±1.42, 59.10±1.72, 58.12±1.85, 61.32±1.96 and 65.16±1.65 respectively and the corresponding values in cattle of group III were 66.16±1.35, 55.50±1.66, 57.00±2.00, 59.50±1.91 and 63.12±1.63 respectively.

Bradycardia ($P \leq 0.01$) was observed at 10 minutes of interval in all the three groups, there after heart rate fluctuated within normal range.

Comparissoin between the groups showed non significant variation at all the intervals of study

4.2.3 Respiratory Rate (breaths/min)

The Mean ± S.E values of respiratory rate (Breaths/minutes) at different intervals in cattle of groups I and II are given in Table 2 and in Fig. 8.

The Mean ± S.E., values of respiratory rate (Breaths/minutes) before premedication (0 minute), 10 minutes after premedication and at 30, 60 and 120 minutes after induction of general anaesthesia in cattle of group I were 25.80±1.88, 19.66±1.62, 26.66±1.02, 28.33±2.13 and 32.33±1.49 respectively. The corresponding values in cattle of group II were 24.20±1.80, 20.19±1.72, 27.42±1.15, 29.16±2.14 and 31.18±1.78 respectively and the corresponding values in cattle of group III were 25.83±1.83, 19.66±1.62, 26.66±1.07, 28.33±2.13 and 32.33±1.49 respectively.

The respiratory rate decreased significantly at 10 minutes in all the groups of animals when compared to before administration of premedicants.

The comparission between the groups showed non significant differences.

Table 4: MEAN±SE of physiological parameters at different intervals in cattle of group- I, II and III

Sl. No	Parameter	Time	Group I	Group II	Group III
1	Rectal Temperature (^{0}F)	0min	102.25±0.15	101.47 ± 0.37	101.55±0.23
		10min	101.93±0.10	100.85 ± 0.81	101.93±0.10
		30min	100.53±0.33	101.25 ± 0.29	100.53±0.33
		60min	100.85±0.24	101.32 ± 0.40	100.85±0.24
		120min	101.61±0.14	101.37 ± 0.42	101.65±0.14
2	Heart Rate (Beats/minutes)	0min	66.16± 1.35	65.21±1.42	66.16±1.35
		10min	55.50± 1.66**	59.10±1.72**	55.50±1.66**
		30min	57.00±1.90	58.12±1.85	57.00±2.00
		60min	59.50±1.90	61.32±1.96	59.50±1.91
		120min	63.00±1,60	65.16±1.65	63.12±1.63
3	Respiratory Rate (Breaths/minutes)	0min	25.80±1.88	24.20±1.80	25.83±1.83
		10min	19.66±1.62**	20.19±1.72**	19.66±1.62**
		30min	26.66±1.02	27.42±1.15	26.66±1.07
		60min	28.33±2.13	29.16±2.14	28.33±2.13
		120min	32.33±1.49	31.18±1.78	32.33±1.49

Mean values bearing superscript**differ significantly ($p \leq 0.01$) from interval to 'before' within the group.

4.3 Heamodynamic Parameters

4.3.1 Mean Arterial Pressure (mm of Hg)

The Mean ± S.E values of mean arterial pressure (mm of Hg) at different intervals in cattle of groups I, II and III are given in Table 5 and in Fig.9.

The Mean ± S.E., values of mean arterial pressure (mm of Hg) before premedication (0 minute), 10 minutes after premedication and at 30, 60 and 120 minutes after induction of general anaesthesia in cattle of group I were 85.83±2.71, 79.83±3.40*, 88.65±5.05, 84.44±2.38 and 88.66±5.85 respectively. The corresponding values in cattle of group II were 89.48±1.95, 81.21±2.68, 85.35±4.98, 86.17±2.12 and 89.45±5.48 respectively and the corresponding values in cattle of group III were 85.83±2.71, 79.83±3.75, 88.65±5.05, 84.44±2.38 and 88.66±5.85 respectively.

The mean arterial pressure decreased significantly ($P \leq 0.01$) at 10 minutes of interval in all the group of animals, there after it fluctuated within normal limit in all the group of animals.

The comparission between the groups showed non-significant variation in all the intervals of the study.

4.2.2 Haemoglobin Oxygen Saturation (SPO_2) (%)

The Mean ± S.E values of heamoglobin oxygen saturation (SPO_2) (%) at different intervals in cattle of groups I , II and III are given in Table 5 and in Fig.10.

The Mean ± S.E., values of heamoglobin oxygen saturation (SPO_2) (%) before premedication (0 minute), 10 minutes after premedication and at 30, 60 and 120 minutes

after induction of general anaesthesia in cattle of group I were 96.16±1.22, 97.16±1.04, 95.66±1.33, 93.33±1.76 and 94.16±1.66 respectively. The corresponding values in cattle of group II were 98.20±1.12, 97.50±1.06, 97.64±1.20, 95.18±1.62 and 93.23±1.52 respectively, and the corresponding values in cattle of group III were 96.16±1.22, 97.16±1.04, 95.66±1.33, 93.33±1.76 and 94.16±1.66 respectively.

Heamoglobin oxygen saturation (%) within the group and between the groups comparisssion showed that, there was non-significant variation.

The heamoglobin oxygen saturation (%) fluctuated within normal physiological limits.

Table 5: Mean ± S.E. of Haemodynamic observations at different intervals in cattle of group I, II and III

Sl. No.	Parameter	Time	Group I	Group II	Group III
1	Mean Arterial Pressure (mm of Hg)	0min	85.83±2.71	89.48±1.95	85.83±2.71
		10min	79.83±3.40*	81.21±2.68*	79.83±3.75*
		30min	88.65±5.05	85.35±4.98	88.65±5.05
		60min	84.44±2.38	86.17±2.12	84.44±2.38
		120min	88.66±5.85	89.45±5.48	88.66±5.85
2	Haemoglobin oxygen saturation (SpO_2) (%)	0min	96.16±1.22	98.20±1.12	96.16±1.22
		10min	97.16±1.04	97.50±1.06	97.16±1.04
		30min	95.66±1.33	97.64±1.20	95.66±1.33
		60min	93.33±1.76	95.18±1.62	93.33±1.76
		120min	94.16±1.66	93.23±1.52	94.16±1.66

Values bearing superscript*differ significantly (P≤0.05) from interval to ‘before’ within the group.

Fig. 6: Mean ± S.E of rectal temperature (^{0}F) in group I, II and III

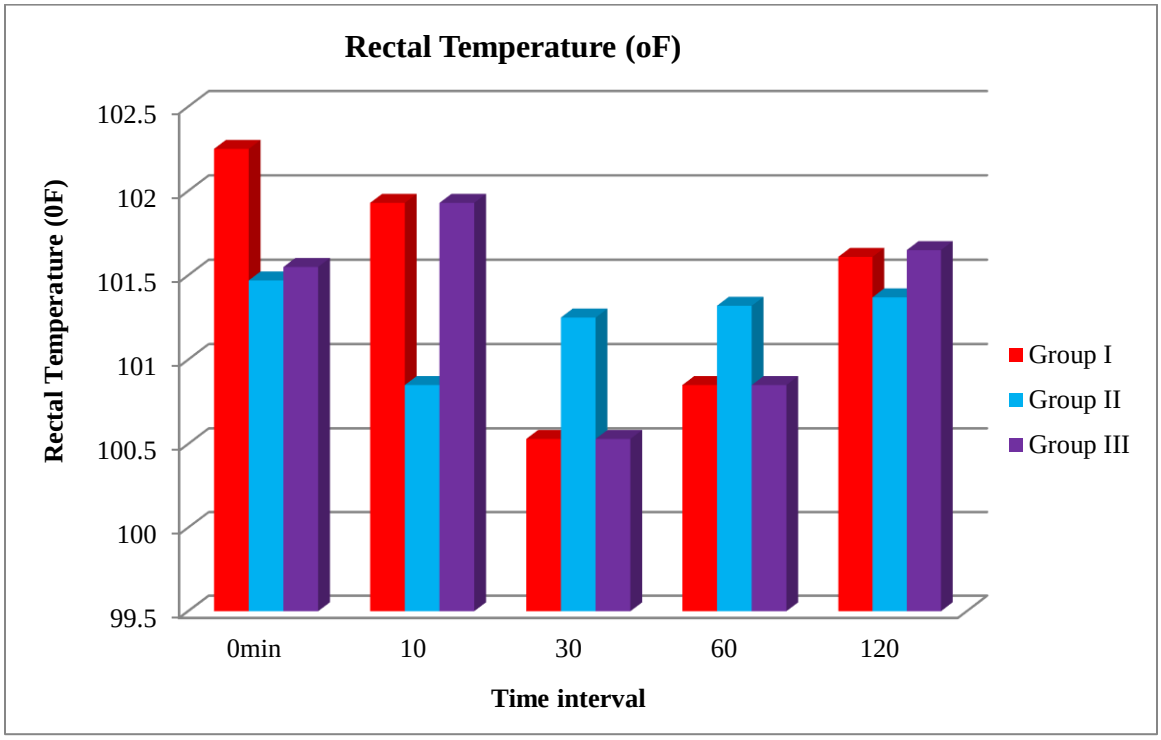


Fig. 7: Mean ± S.E of heart rate (Beats/minutes) in group I, II and III

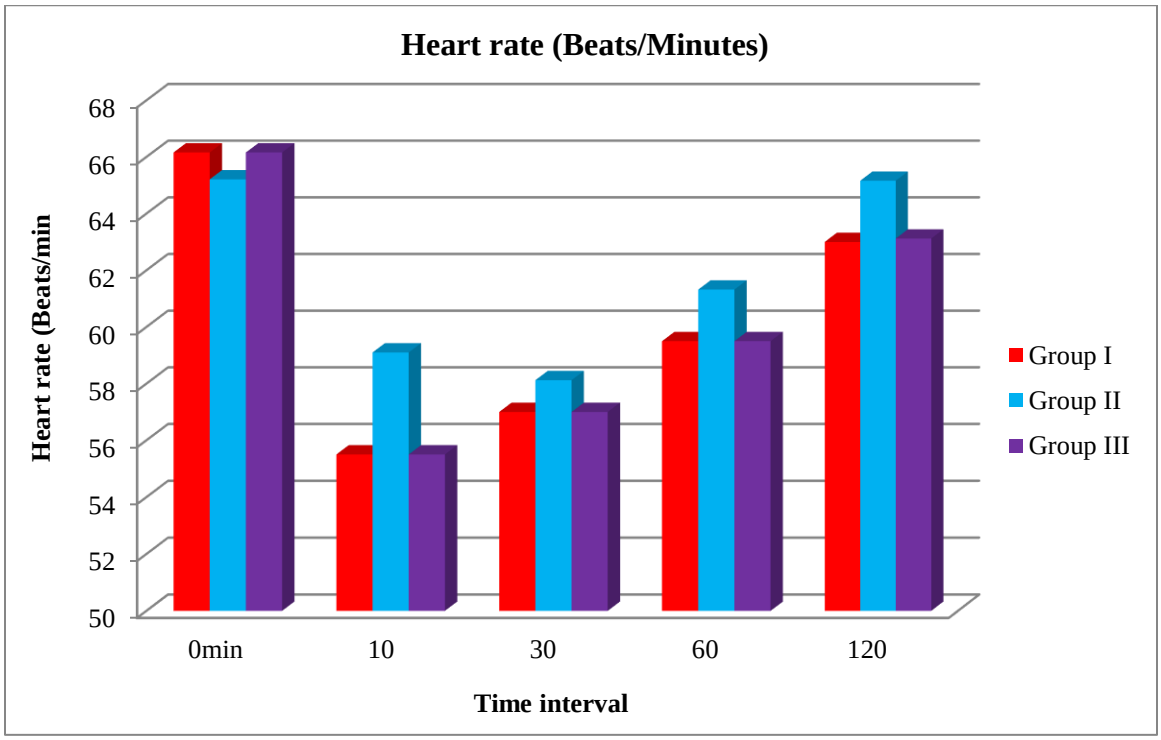


Fig. 8: Mean ± S.E of respiratory rate (Breaths/minutes) in group I, II and III

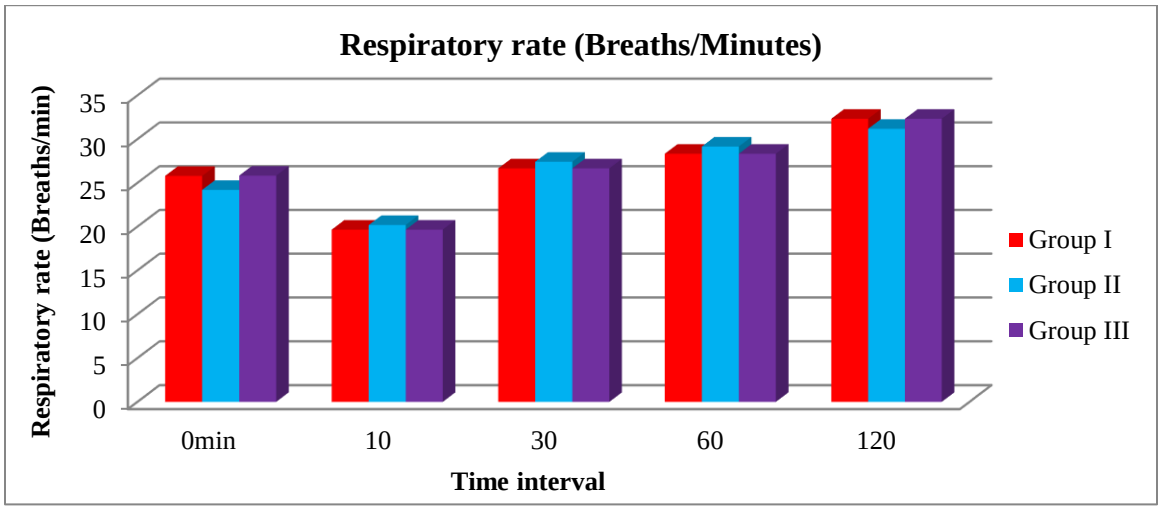


Fig. 9: Mean ± S.E of mean arterial pressure in group I, II and III

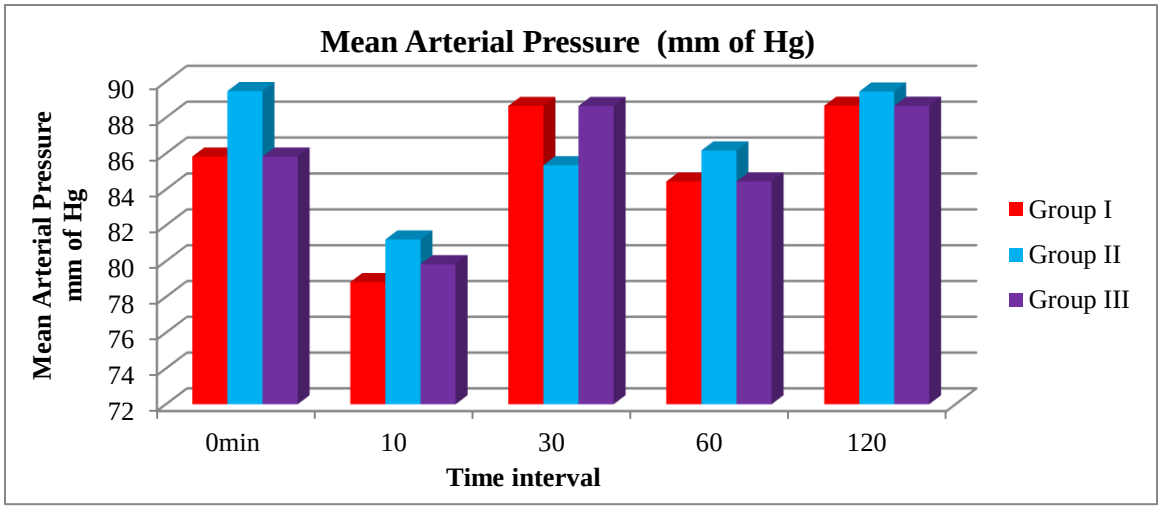
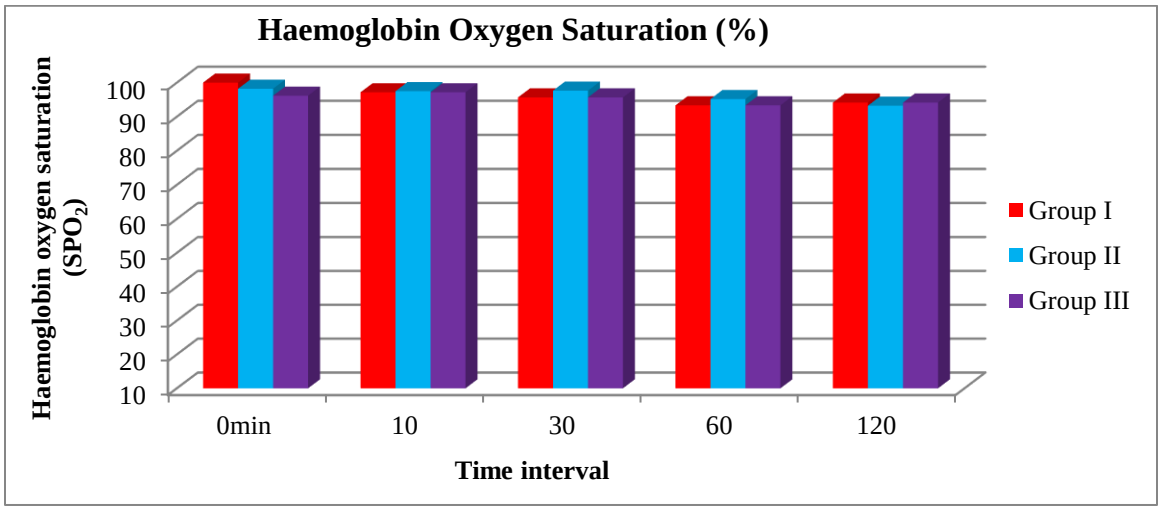


Fig. 10: Mean ± S.E of heamoglobin oxygen saturation in group I, II and III



4.3 Haematological observations

4.3.1 Heamoglobin (g/dL)

The Mean ± S.E values of heamoglobin (g/dL) at different intervals in cattle of groups I, II and III are given in Table 6 and in Fig.11.

The Mean ± S.E., values of heamoglobin (g/dL) before premedication (0 minute), 10 minutes after premedication and at 30, 60 and 120 minutes after induction of general anaesthesia in cattle of group I were 15.10±0.36, 14.96±0.32, 14.45±0.29, 14.26±0.30 and 14.18±0.31 respectively. The corresponding values in cattle of group II were 14.95±0.21, 14.56±0.36, 14.68±0.25, 14.42±0.32 and 14.68±0.28 respectively and the corresponding values in cattle of group III were 14.16±0.36, 14.23±0.32, 13.95±0.29, 14.11±0.30 and 14.48±0.31 respectively.

The heamoglobin fluctuated within normal physiological limits and there was no variation at different intervals within the group of animals.

Comparison between the groups showed non-significant variation at all interval of schedule.

4.3.2 Packed Cell Volume (%)

The Mean ± S.E values of packed cell volume (%) at different intervals in cattle of groups I, II and III are given in Table 6 and in Fig.12.

The Mean ± S.E., values of packed cell volume (%) before premedication (0 minute), 10 minutes after premedication and at 30, 60 and 120 minutes after induction of

general anaesthesia in cattle of group I were 40.96±1.11, 40.10±1.10, 39.96±1.13, 37.78±1.15 and 39.75±1.13 respectively. The corresponding values in cattle of group II were 41.20±1.14, 41.10±1.16, 40.40±1.18, 38.18±1.18 and 38.82±1.18 respectively. The corresponding values in cattle of group III were 40.96±1.11, 39.36±1.10, 40.26±1.13, 39.78±1.15 and 37.95±1.10 respectively.

In group-I, the Mean±SE values of packed cell volume showed that, there were no significant changes observed. Similar trend was observed in group-II and group-III animals with scheduled time intervals.

Comparison between the groups showed non-significant variation at all interval of study.

4.3.3 Total Erythrocyte Count ($\times 10^6$/µL)

The Mean ± S.E values of total erythrocyte count ($\times 10^6$/µL) at different intervals in cattle of groups I, II and III are given in Table 6 and in Fig.13.

The Mean ± S.E., values of total erythrocyte count ($\times 10^6$/µL) before premedication (0 minute), 10 minutes after premedication and at 30, 60 and 120 minutes after induction of general anaesthesia in cattle of group I were 8.75±0.09, 7.85±0.04, 7.65±0.10, 8.13±0.13 and 8.42±0.18 respectively. The corresponding values in cattle of group II were 8.81±0.06, 8.20±0.09, 7.72±0.16, 8.56±0.12 and 8.92±0.18 respectively. The corresponding values in cattle of group III were 8.55±0.03, 8.15±0.01, 7.45±0.14, 8.63±0.11 and 8.82±0.16 respectively.

In group-I, the Mean±SE values of total erythrocyte count was calculated and there were no significant changes were observed. Similar trend was observed in group-II and group-III animals with scheduled time intervals.

Comparison between the groups showed non-significant variation at all interval of schedule.

4.3.4 Total Leucocytes Count ($\times 10^3/\mu L$)

The Mean ± S.E values of total leucocytes count ($\times 10^3/\mu L$) at different intervals in cattle of groups I, II and III are given in Table 6 and in Fig.14.

The Mean ± S.E., values of total leucocytes count ($\times 10^3/\mu L$) before premedication (0 minute), 10 minutes after premedication and at 30, 60 and 120 minutes after induction of general anaesthesia in cattle of group I were 10.45±0.40, 10.91±0.35, 11.16±0.30, 11.61±0.31 and 12.10±0.28 respectively. The corresponding values in cattle of group II were 10.12±0.18, 10.68±0.21, 11.21±0.23, 11.65±0.45 and 12.46±0.36 respectively. The corresponding values in cattle of group III were 10.18±0.10, 10.40±0.15, 11.13±0.18, 11.43±0.21 and 11.96±0.18 respectively.

In Group-I, the Mean±SE values of total leucocyte count was showed that, there was no significant changes in total leucocytes count were observed. Similar trend was observed in group-II and group-III animals with scheduled time intervals.

Comparison between the groups showed non-significant variation at all interval of schedule.

4.3.5 Neutrophils (%)

The Mean ± S.E values of neutrophils (%) at different intervals in cattle of groups I, II and III are given in Table 6 and in Fig. 15.

The Mean ± S.E., values of neutrophils (%) before premedication (0 minute), 10 minutes after premedication and at 30, 60 and 120 minutes after induction of general anaesthesia in cattle of group I were 32.17±2.04, 34.50±2.06, 39.33±3.16, 33.50±2.58 and 32.17±2.04 respectively. The corresponding values in cattle of group II were 33.12±1.62, 34.10±1.82, 39.65±2.21, 35.68±2.32 and 33.26±2.08 respectively.

The corresponding values in cattle of group III were 33.00±1.53, 35.00±1.67, 41.00±2.02*, 33.33±2.23 and 33.00±1.53 respectively.

The comparison within the groups at different interval revealed that, the nuetrophils count increased significantly ($P \leq 0.01$) at 30 minutes after post-induction when compared to pre-anaesthetic level in all three groups, remaining intervals it fluctuated within normal physiologicls limit.

The comparison between the groups at different interval revealed that, there was non-significant ($p \geq 0.05$) difference in neutrophils count at different intervals of study.

4.3.5 Lymphocytes (%)

The Mean ± S.E values of lymphocytes (%) at different intervals in cattle of groups I, II and III are given in Table 6 and in Fig. 16.

The Mean ± S.E., values of lymphocytes (%) before premedication (0 minute), 10 minutes after premedication and at 30, 60 and 120 minutes after induction of general anaesthesia in cattle of group I were 45.45±0.85, 45.65±0.84, 42.80±79, 44.10±0.81 and 46.40±0.77 respectively. The corresponding values in cattle of group II were 48.21±0.68, 49.10±0.42, 41.11±0.53, 46.32±0.58 and 46.82±0.67 respectively. The corresponding values in cattle of group III were 41.21±1.19, 41.51±1.17, 39.71±1.17, 44.00±1.15 and 46.50±1.09 respectively.

The lymphocyte level fluctuated within normal physiological limits at all the intervals of study.

The comparison between the groups at different interval revealed that, there was non-significant ($P \geq 0.05$) difference in lymphocyte count.

Table 6: Mean±SE of Haematological parameters at different intervals in cattle of group- I, group- II and group-III

Sl. No.	Parameter	Time	Group I	Group II	Group III
1	Hb (g/dL)	0min	15.10±0.36	14.95±0.21	14.16±0.36
		10min	14.96±0.32	14.56±0.36	14.23±0.32
		30min	14.45±0.29	14.68±0.25	13.95±0.29
		60min	14.26±0.30	14.42±0.32	14.11±0.30
		120min	14.18±0.31	14.68±0.28	14.48±0.31
2	Packed Cell Volume (%)	0min	40.96±1.11	41.20±1.14	40.96±1.11
		10min	40.10±1.10	41.10±1.16	39.36±1.10
		30min	39.96±1.13	40.40±1.18	40.26±1.13
		60min	37.78±1.15	38.18±1.18	39.78±1.15
		120min	39.75±1.13	38.82±1.18	37.95±1.10
3	TEC ($x10^6$ /µL)	0min	8.75±0.09	8.81±0.06	8.55±0.03
		10min	7.85±0.04	8.20±0.09	8.15±0.01
		30min	7.65±0.10	7.72±0.16	7.45±0.14
		60min	8.13±0.13	8.56±0.12	8.63±0.11
		120min	8.42±0.18	8.92±0.18	8.82±0.16
4	TLC ($x10^3$ /µL)	0min	10.45±0.40	10.12±0.18	10.18±0.10
		10min	10.91±0.35	10.68±0.21	10.40±0.15
		30min	11.16±0.30	11.21±0.23	11.13±0.18
		60min	11.61±0.31	11.65±0.45	11.43±0.21
		120min	12.10±0.28	12.46±0.36	11.96±0.18
5	NEUTROPHILS (%)	0min	32.17±2.04	33.12±1.62	33.00±1.53
		10min	34.50±2.06	34.10±1.82	35.00±1.67
		30min	39.33±3.16	39.65±2.21	41.00±2.02*
		60min	33.50±2.58	35.68±2.32	33.33±2.23
		120min	32.17±2.04	33.26±2.08	33.00±1.53
6	LYMPHOCYTES (%)	0min	45.45±0.85	48.21±0.68	41.21±1.19
		10min	45.65±0.84	49.10±0.42	41.51±1.17
		30min	42.80±79	41.11±0.53	39.71±1.17
		60min	44.10±0.81	46.32±0.58	44.00±1.15
		120min	46.40±0.77	46.82±0.67	46.50±1.09

Values bearing superscript*differ significantly (P≤0.05) from interval 'before' within the group.

Fig. 11: Mean ± S.E of Heamoglobin (g/dL) in Group I, II and III

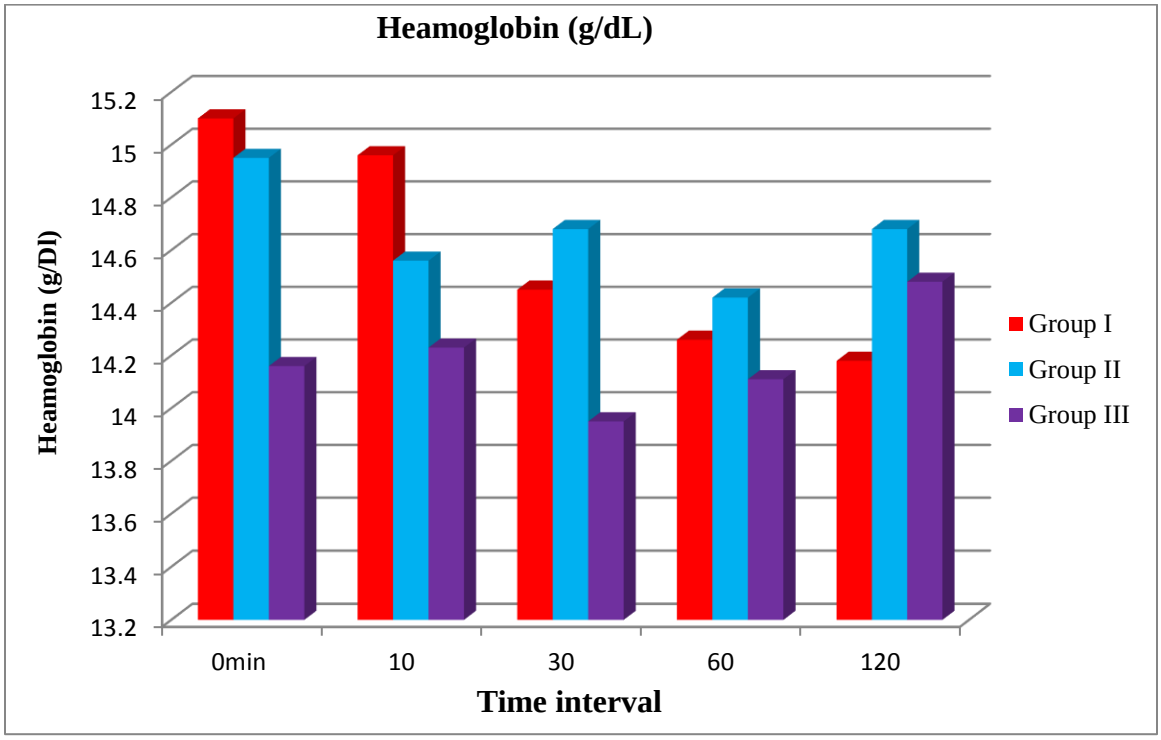


Fig. 12: Mean ± S.E of Packed cell volume (%) in Group I, II and III

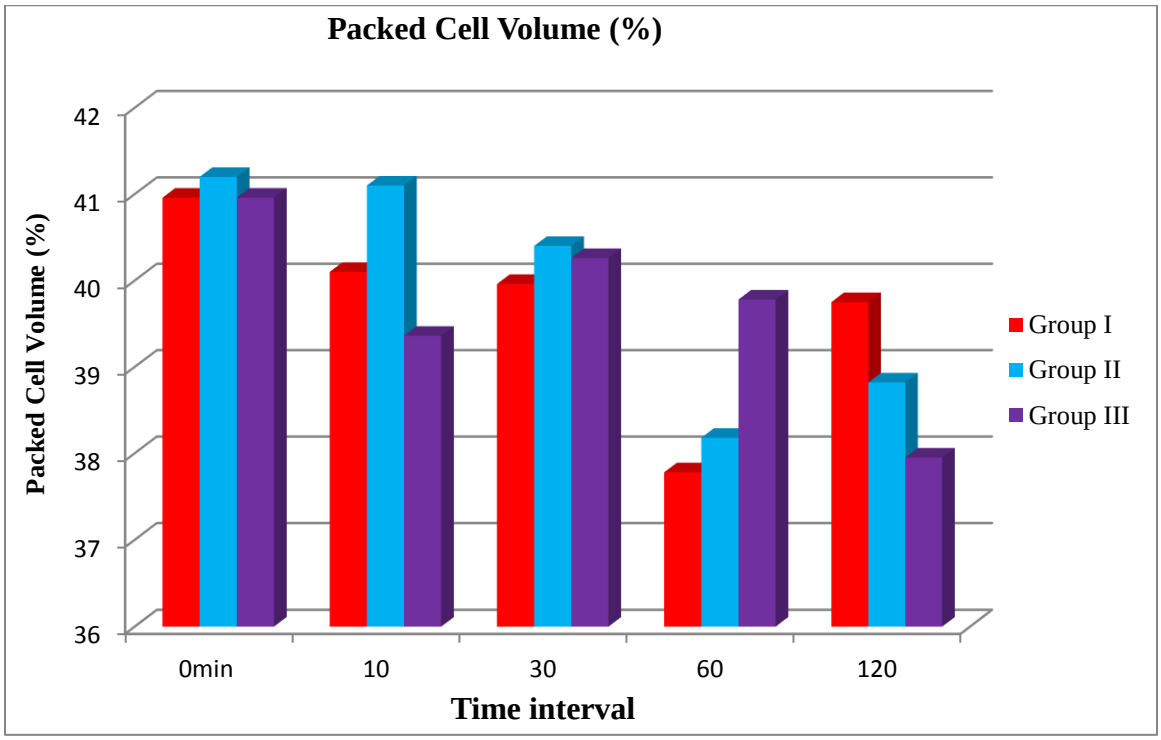


Fig. 13: Mean ± S.E of Total erythrocyte count (x10^6 /µL) in Group I, II and III

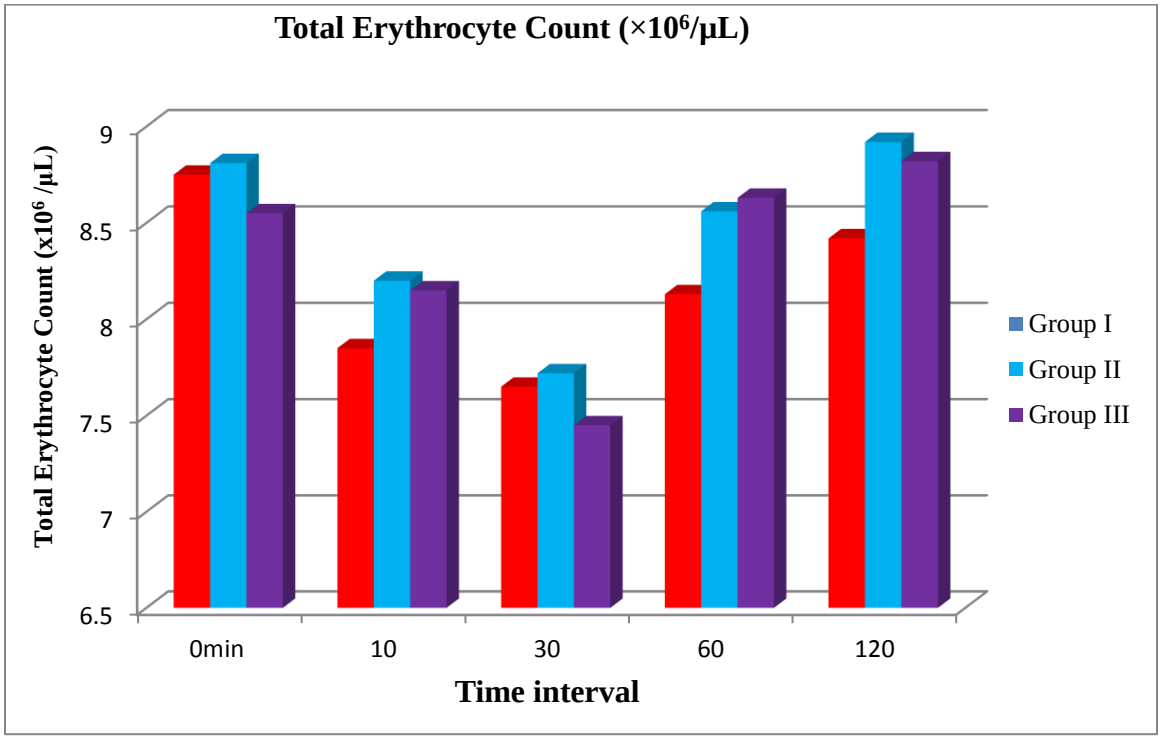


Fig. 14: Mean ± S.E of Total leucocytes count (x10^3 /µL) in Group I, II and III

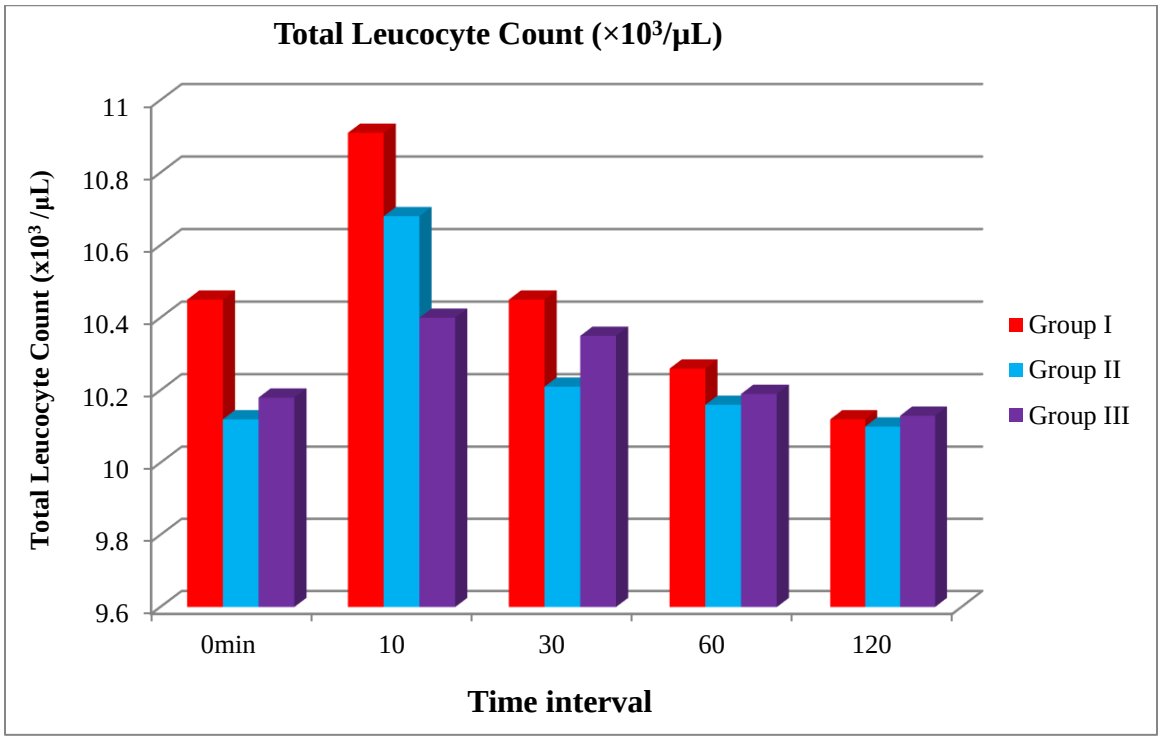


Fig. 15: Mean ± S.E of Nuetrophils (%) in Group I, II and III

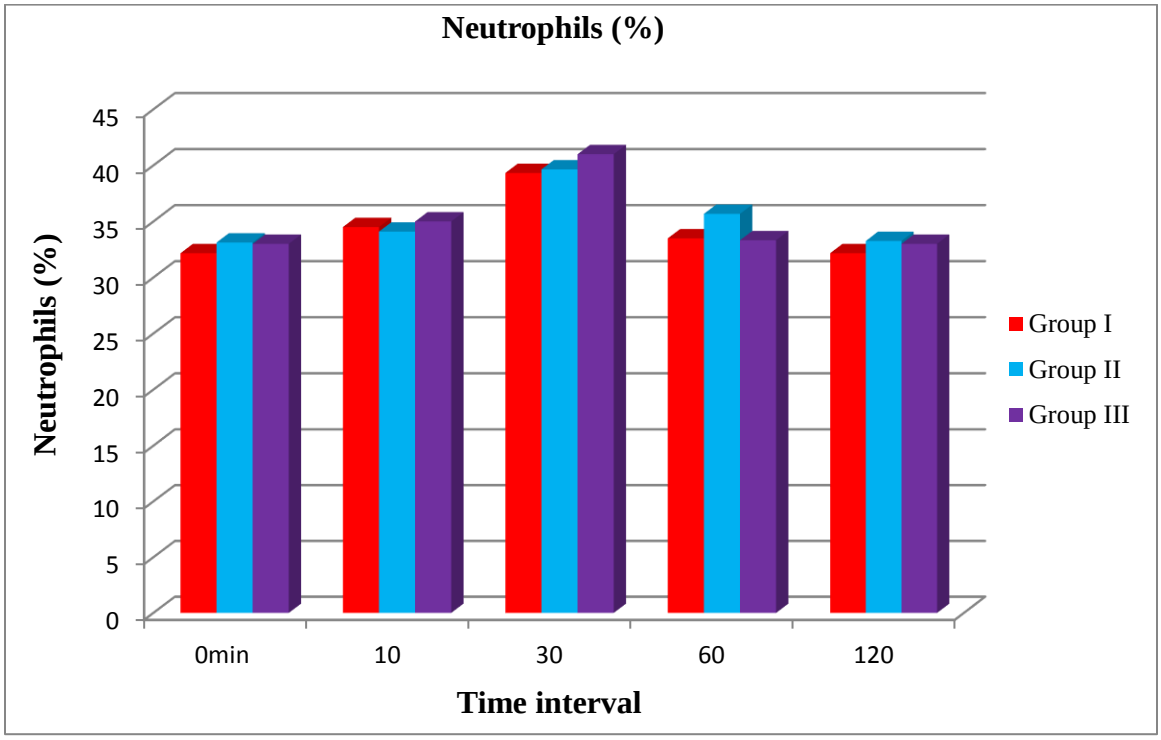
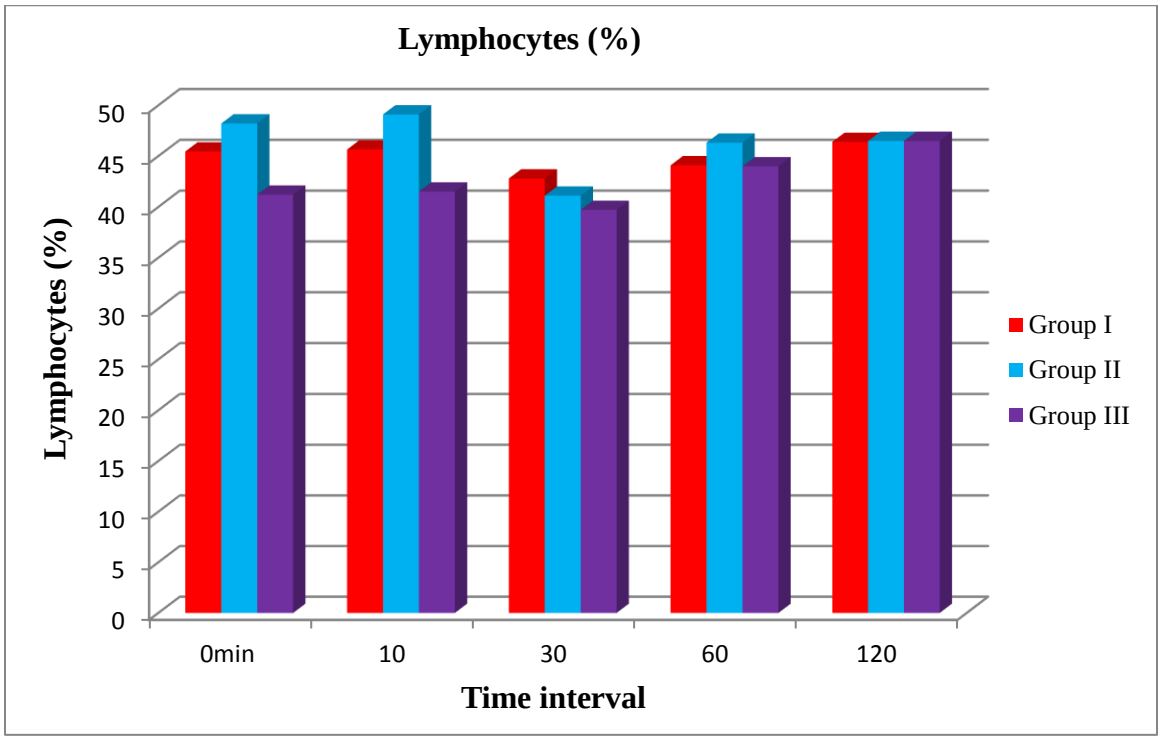


Fig. 16: Mean ± S.E of Lymphocytes (%) in Group I, II and III



4.4 Biochemical observation

4.4.1 Creatinine (mg/dL)

The Mean ± S.E values of Creatinine (mg/dL) at different intervals in cattle of groups I, II and III are given in Table 7 and in Fig.17.

The mean ± S.E, values of Group-I animals before anaesthesia, 10 minutes after pre-anaesthetic administration, and then at 30 minutes, 60 minutes and at 120 minutes after induction were;1.30±0.13, 1.18±0.12, 1.23±0.12, 1.21±0.16, 1.20±0.11 respectively. The corresponding interval values in group-II animals were; 1.25±0.16, 1.20±0.13, 1.21±0.10, 1.23±0.11, 1.22±0.15 respectively. The corresponding interval values in group-III animals were; 1.28±0.12, 1.21±0.11, 1.17±0.07, 1.20±0.07, 1.21±0.11 respectively. The craetinine value fluctuated within normal physiological limits in all the three groups. There was no significant difference ($p \geq 0.05$) within the groups or between the groups at all intervals of the study.

4.4.2 Alanine transaminase (ALT) (IU/L)

The Mean ± S.E values of alanine transaminase (ALT) (IU/L) at different intervals in cattle of groups I, II and III are given in Table 7 and in Fig.18.

The Mean ±SE values before pre-anaesthetic administration ,10 minutes after pre-anaesthetic administration, 30 minutes, 60 minutes and 120 minutes after induction in group-I animals were; 31.00±2.28, 29.67±2.08, 30.00±3.72, 28.17±3.60 and 29.67±1.78 respectively. The corresponding interval values in group-II animals were; 31.28±2.75, 30.25±2.48, 30.20±2.36, 31.27±2.36 and 31.45±2.61 respectively. The corresponding

interval values in group-III animals were; 33.33±2.75, 31.67±2.59, 30.50±3.19, 31.17±2.96 and 31.67±2.59 respectively.

The serum alanine transaminase value fluctuated within normal physiological limits in all the three groups. There was no significant difference (P≥0.05) within the groups or between the groups at all the intervals of the study.

4.4.3 Aspartate transaminase (AST) (IU/L)

The Mean ± S.E values of aspartate transaminase (AST) (IU/L) at different intervals in cattle of groups I, II and III are given in Table 7 and in Fig.19.

The Mean ±SE values before pre-anaesthetic administration ,10 minutes after pre-anaesthetic administration, 30 minutes, 60 minutes and 120 minutes after induction in group-I animals were; 25.50±2.71, 24.67±1.45, 24.67±2.19, 27.17±2.68 and 25.50±2.71 respectively.

The corresponding interval values in group-II animals were; 26.37±2.80, 26.42±2.40, 25.67±2.20, 31.27±3.72 and 27.48±2.65 respectively. The corresponding interval values in group-III animals were; 28.17±17, 28.33±2.35, 26.67±2.56. 33.67±4.61 and 28.33±2.55 respectively.

The serum aspartate transaminase value fluctuated within normal physiological limits in all the three groups. There was no significant difference (P≥0.05) within the groups or between the groups at all the intervals of the study.

4.4.4 Serum Urea Nitrogen (mg/dL)

The Mean ± S.E values of serum urea nitrogen (mg/dL) at different intervals in cattle of groups I, II and III are given in Table 7 and in Fig.20.

The Mean ±SE values before pre-anaesthetic administration ,10 minutes after pre-anaesthetic administration, 30 minutes, 60 minutes and 120 minutes after induction in Group-I animals were; 17.58±2.77, 17.32±2.66, 15.65±2.27, 17.32±3.08 and 17.62±2.11 respectively.

The corresponding interval values in group-II animals were; 18.16±2.11, 17.62±2.16, 16.23±1.97, 18.26±2.14 and 19.28±1.96 respectively. The corresponding interval values in group-III animals were; 19.18±1.91, 18.32±1.92, 18.13±1.87, 18.35±2.34 and 19.18±1.91 respectively. The serum urea nitrogen fluctuated within normal physiological limit indifferent intervals of all three groups. Comparision between groups showed non-significant variation.

Table 7. Mean ±SE values of biochemical parameters at different intervals in different groups

Sl. No.	Parameter	Time	Group I	Group II	Group III
1	Creatinine (mg/dL)	0min	1.30±0.13	1.25±0.16	1.28±0.12
		10min	1.18±0.12	1.20±0.13	1.21±0.11
		30min	1.23±0.12	1.21±0.10	1.17±0.07
		60min	1.21±0.16	1.23±0.11	1.20±0.07
		120min	1.20±0.11	1.22±0.15	1.21±0.11
2	Alanine transaminase (ALT) (IU/L)	0min	31.00±2.75	31.28±2.75	33.33±2.75
		10min	29.67±2.08	30.25±2.48	31.67±2.59
		30min	30.00±3.72	30.20±2.36	31.87±2.56
		60min	28.17±3.60	31.22±2.36	30.50±3.19
		120min	29.67±1.78	31.45±2.61	31.17±2.59
3	Aspartate Transaminase (AST) (IU/L)	0min	25.50±2.71	26.37±2.80	28.17±3.60
		10min	24.67±1.45	26.42±2.40	28.33±2.55
		30min	24.67±2.19	25.67±2.20	26.67±2.56
		60min	27.17±2.68	31.27±3.72	33.67±4.61
		120min	25.50±2.71	27.48±2.65	28.33±2.55
4	Serum Urea Nitrogen (mg/dL)	0min	17.58±2.77	18.16±2.11	19.18±1.91
		10min	17.32±2.66	17.62±2.16	18.32±1.91
		30min	15.65±2.27	16.23±1.97	18.13±1.87
		60min	17.32±3.08	18.26±2.14	18.35±2.34
		120min	17.62±2.11	19.28±1.96	19.18±1.91

Fig. 17: Mean ± S.E., of creatinine in Group I, II and III

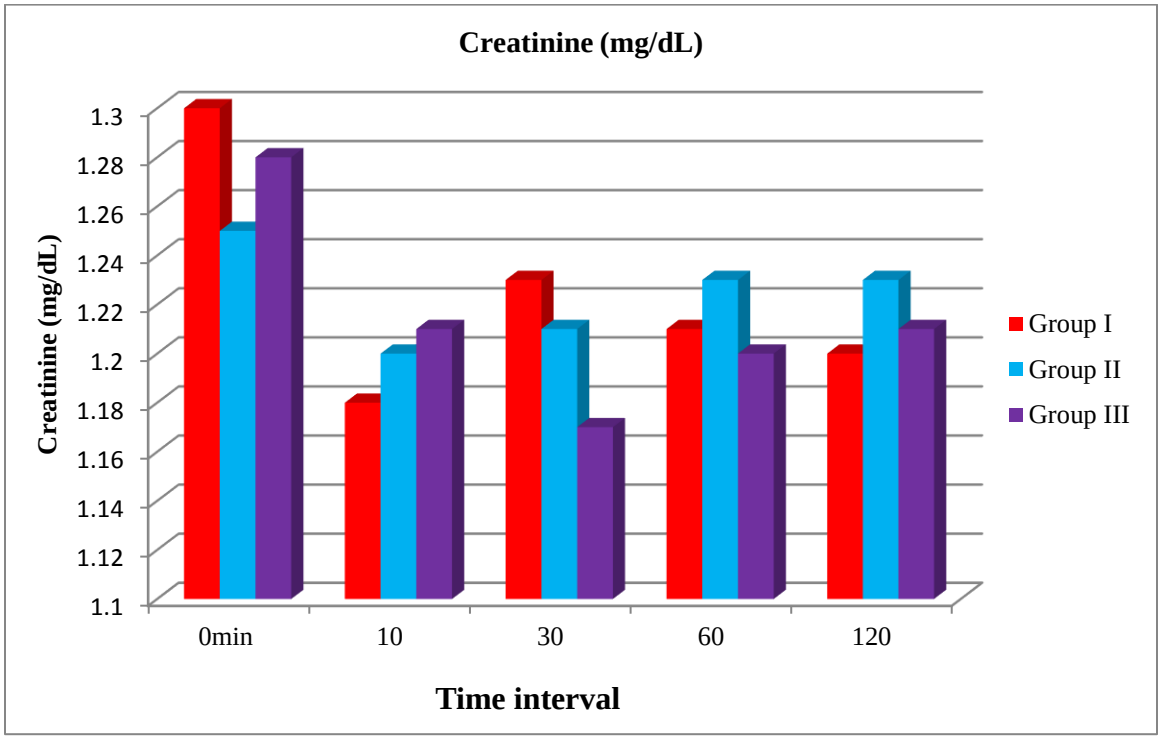


Fig. 18: Mean ± S.E., of alanine transaminase in Group I, II and III

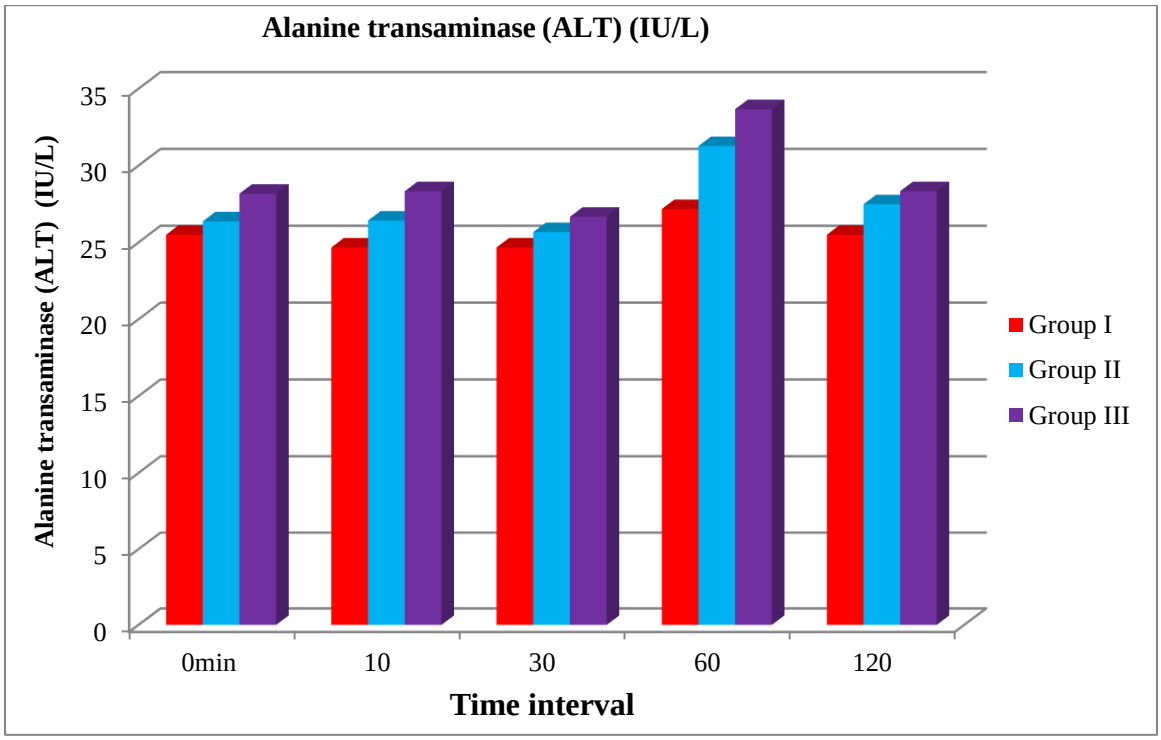


Fig. 19: Mean ± S.E., of aspartate transaminase in Group I, II and III

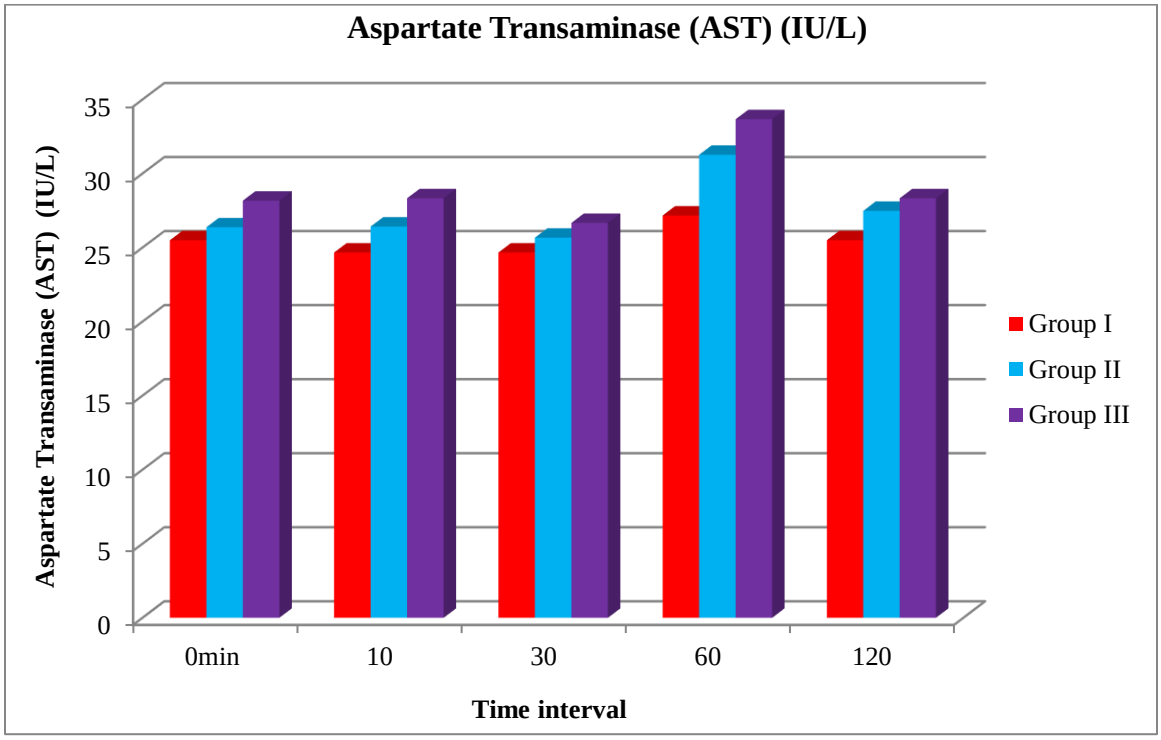
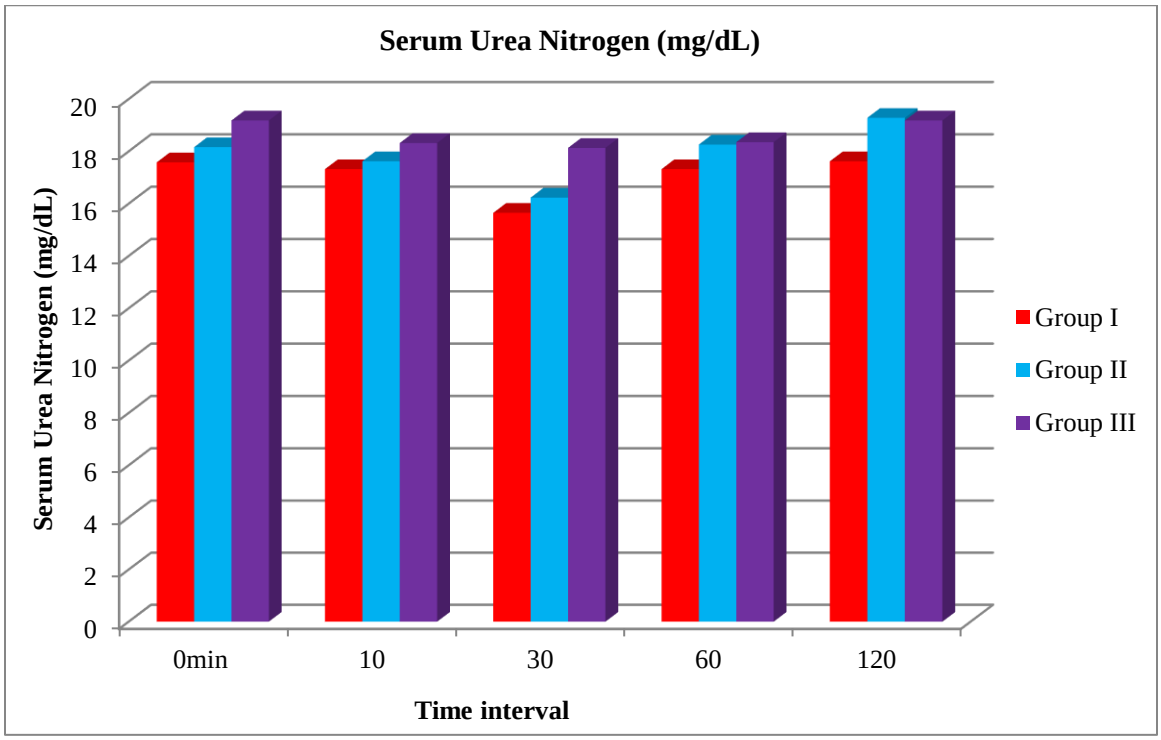


Fig. 20: Mean ± S.E., of serum urea nitrogen in Group I, II and III



Discussion

V. DISCUSSION

The present study was undertaken to compare the sedative effects of Romifidine hydrochloride (10 µg/Kg, I/V) (Group- I), Dexmedetomidine hydrochloride (2.5 µg/Kg, I/V) (Group-II) and Xylazine hydrochloride (0.1 mg/Kg, I/V) (Group-III) for Ketamine - Isoflurane general anaesthesia in cattle undergoing various clinical surgeries. The results of the study were evaluated and discussed under following headings.

5.1 Clinical Observation

5.1.1 Induction time (seconds)

The induction time was significantly quicker in the animals pre-medicated with Romifidine –Ketamine –Isoflurane combination as compared to that in the animals pre-medicated with xylazine -ketamine-isoflurane and demedetomidine-ketamine However, in the present study quick induction in group-I animals might be due to administration of ketamine after induction was smooth in both groups, which are in agreement with observation made by Kour and Singh (2004) who used midazolam-ketamine combination in buffalo.Riazuddin *et al*. (2004a) reported 2.21±0.11 minutes as induction time under xylazine –guaifensen-ketamine anaesthesia as a triple drip in cattle.

5.1.2 Onset of sedation (minutes)

Onset of sedation was characterized by lowering of head, drooping of eyelids, mild drowsiness and ataxia.

In romifidine sedation animals, onset of sedation was earlier as compared to that of dexmedetomedine and xylazine group animals. It could be due to high lipophilic

properties and rapid biotransformation of alpha-2-adrenergic groups. Rapid onset of sedation recorded in the present study was confirmed to the observation made in earlier studies following the administration of medetomidine /dexmedetomidine in dogs (Amarpal *et al.*, 1996, Kuushal *et al.*, 2000 and Ahmad *et al.*, 2011). Mane *et al.* (2014) observed a smooth and uneventful induction in horses premedicated with xylazine during ketamine-isoflurane anaesthesia. Santhosh *et al.* (2011) reported the onset of action at 3.25 ± 0.25 minutes in dogs administered with dexmedetomidine (20 μg/kg body weight) and midazolam (0.4mg/kg) intramuscularly.

5.1.3 Recovery time (minutes)

Statistically there was non-significant difference between the groups in the time taken for the animals to recover after discontinuing the isoflurane. The Mean±SE values of recovery time were: 10.50±0.88, 11.85±0.21 minutes and 10.83±0.79 minutes in group-I, group-II and group-III animals respectively.

The recovery was smooth and uneventful in the animals of all the groups, Moolchand *et al.* (2014) reported that xylazine caused hyperglycemia by reduction in insulin release and prolong recovery in sheep. Recovery time was less in romifidine and xylazine sedated animals as compared to cattle sedated with dexmedetomidine. This might be due to rapid biotransformation of xylazine with elimination half life of 30.10 minutes as compared with dexmedetomidine which is having elimination half life of 47 minutes (Kuusela *et al.*, 2000).

5.1.4 Degree of analgesia

An excellent analgesia was recorded at maximum depth of anaesthesia in all three groups of animals. The pain was significantly abolished from 0 to 60 minutes in all the groups. There was non-significant difference in the analgesic level produced between the groups at all the intervals of study.

The analgesic action might be due to stimulating central pre-synaptic alpha-2-adrenoceptors which inhibits nor-epinephrine release from adrenergic nerve terminals (Hsu, 1981) and interruption of nociceptive pathway to the ventral root of the dorsal horn (Kending *et al.,* 1991 and Ahmad *et al.,* 2011). Similar finding was recorded (Pawde *et al.,* 2000). Degree of analgesia was significantly greater in group-I when compared with group-II and group-III at 10 minutes after premedication. Further, the degree of analgesia was better in group-I at 30 minutes when compared with group-II and group-III. This suggested that romifidine provided better analgesia during ketamine-isoflurane anaesthesia in cattle. However, xylazine and dexmedetomidine can be used as an alternative during ketamine-isoflurane anaesthesia.

5.1.5 Palpebral reflex score

The present study showed that, in all the groups of animals, the palpebral reflex was brisk and present before induction of anaesthesia. A sluggish palpebral reflex was present even after induction in all animals, similar findings were recorded, after xylazine-ketamine anaesthesia in buffalo calves (Chandrashekhar *et al.,* 2003) and after midazolam-ketamine induction in buffalo (Amandeep and Singh, 2004). However, two to five minutes after starting administration of isoflurane at 4 to 5 per cent, the palpebral

reflex started testing negative in most of the animals. Similar observation during maintenance of anaesthsia with isoflurane, was recorded by Singh *et al.* (2013) after thiopental induction in buffalo. Mane *et al.* (2014) reported suppression of palpebral reflex and corneal reflex during the entire anaesthetic period of xylazine-ketamine-isoflurane anaesthesia in horses. Khattri *et al.* (2013) observed a mild depression of pedal reflex and a moderate depression of palpebral reflex at 5 and 10 minutes of dexmedetomidine administration in buffalo calves.

5.1.6 Degree of muscle relaxation

The muscle relaxation was moderate to excellent at 10 minutes in cattle of group-I animals premedicated with romifidine. In cattle of group-II premedicated with dexmedetomidine, the muscle relaxation was mild to moderate at 10 minutes after premedication. The muscle relaxation was moderate to excellent at 10 minutes in cattle of group-III animals premedicated with xylazine. The degree of muscle relaxation was significantly increased from 0 to 60 minutes in all the groups. There was non-significant difference in the degree of muscle relaxation level produced between the groups at all the intervals of study. All alpha-2- agonist are known to produce good muscle relaxation (Lemke, 2004) which could be due to inhibition of interneuronal transmission of impulses at the level of CNS. The findings of present study were confirmed to the observation of earlier researcher, who reported greater muscle relaxation when dexmedetomidine or medetomidine was combined with opioid and /or ketamine in cats or dogs (Ko *et al.,* 2000 and Selmi *et al.,* 2003). Mane *et al.* (2014) reported that xylazine was useful in combination with ketamine since its muscle relaxing properties helped to reduce the rigidity caused by dissociative agent.

5.2 Physiological Parameters

5.2.1. Rectal Temperature (ºF)

The non-significant decrease in rectal temperature in present study could be due to the reduced muscle tone, reduction of metabolic rate and CNS depression by anaesthetic agent (Lu *et al.,* 2013) and depression of thermo-regulatory centre. A significant decrease in rectal temperature was reported by Singh *et al.,* (2012). The decreased temperature might also be due to generalized sedation, decreased metabolic rate, muscle relaxation and central nervous system depression (Khattri *et al.,* 2013).

A significant decrease in the rectal temperature was observed after administration of xylazine in goats (Gweba *et al.,* 2010). Chandrashekar *et al.* (2003) observed a drop-in mean rectal temperature following xylazine – ketamine administration in buffalo calves. Muir *et al*. (1999) reported an increase in body temperature after ketamine administration in dogs and horses, respectively.

5.2.2 Respiratory Rate (breaths/min)

There was non-significant difference was observed between the groups. The respiratory rate was significantly decreased at 10 minutes after romifidine induction as well as dexmedetomidine and xylazine induction. The Bradypnoea statistically significant at 10 minutes ($p \leq 0.05$), it could be due to depression of CNS by xylazine or romifidne (Amreshkumar *et al.,* 1979) and due to activation of α-2-adrenergic pathway, leading to inhibition of local coeruleus neurons (Guo *et al.,* 1995). After 30 minutes of induction in all the three groups respiration regain to normal. This may be due to some degree of hyperventilation induced by ketamine (Kumar *et al.,* 2014). Respiratory depression was

observed after administration of xylazine in goats (Gweba *et al.,* 2010), horses (Mane *et al.,* 2014), which may be due to direct depression of respiratory centres. Singh *et al.* (2003) stated that ketamine is useful in counteracting some of the depressant action of α2 agonists on respiratory rate.

5.2.3 Heart Rate (beats/min)

Bradycardia was observed from 10 minutes intervals in all the three groups of animals, however the bradycardia was statistically non significant after 10 minutes to 60 minutes of interval in all the groups. It could be due to reflex bradycardia as a result of α-2- agonist induced vasoconstriction (Lemke, 2007), the results in agreements with earlier study by Haskins *et al.* (1985) in dogs and by Stegmann (1998) and Ahmad (2013) in goats. Kastner *et al.* (2006) observed profound dose related bradycardia, accompanied by atrio-ventricular blocks after administration of dexmedetomidine hydrochloride in sheep. Mohammed and Yelwa (1993) and Mane *et al.* (2014) reported that xylazine causes bradycardia by increasing the vagal tone and decreasing the sympathetic activity. The bradycardia was more severe in cattle premedicated with xylazine at 10 minutes after premedication when compared to cattle premedicated with dexmedetomidine.

5.3 Haemodynamic Observations

5.3.1 Mean Arterial Pressure (mm of Hg)

Mean arterial pressure (MAP) fluctuated within the physiological limit throughout anaesthetic interval, however at 10 minutes after administration of sedative agents in all the three groups of animals, decrease in mean arterial pressure was observed which might be due to central vegal effect on heart and direct action on vasculature (Peshin *et al.,*

1980) reported significant decrease in the mean arterial pressure in sheep. Riazuddin *et al.* (2004) reported that the fall in the mean arterial pressure induced by xylazine was probably due to decreased myocardial contractility and cardiac output, sympatholytic action, inhibition of catecholamine release and blockade of central and peripheral alpha adrenoceptors.

Although all the pre-anaesthetic and isoflurane used had depressant effect on MAP as reported by earlier workers (Steffey and Mamma, 1977; Perry *et al.*, 1982 and Nain *et al.*, 2010). Mariann (2008) observed that after administration of dexmedetomidine, there was an immediate increase in blood pressure, which might be due to stimulation of alpha-2b-receptors in vascular smooth muscles, which lasts for 5 to 10 minutes, and is followed by a slight decrease in blood pressure due to inhibition of central sympathetic outflow. Ruffolo *et al.* (1993) reported that premedication with dexmedetomidine hydrochloride results in prolonged hypotension. A significant decrease in mean arterial pressure was observed after dexmedetomidine administration in buffaloes (Singh *et al.*, 2013b) and goats (Kumar *et al.*, 2014). Kumar *et al.* (2014) reported a significant decrease in mean arterial pressure in goats after premedication with dexmedetomidine, which improved at 15 minutes and onwards after induction of anaesthesia with ketamine.

5.3.2 Haemoglobin Oxygen Saturation (SPO_2) (%)

The haemoglobin oxygen saturation decreased non-significantly at 10 minutes, 30 minutes and 60 minutes after anaesthesia in all the groups. It started to increase towards normal in both the groups at 120 minutes. There was no significant difference between

the groups at all the intervals. Khattri *et al.* (2013) reported a significant decrease in oxygen saturation at 15 and 20 minutes after dexmedetomidine administration in buffalo calves which is possibly due to a certain degree of respiratory depression caused by α_2 agonists. Ahmad *et al.* (2011) did not notice any significant changes at different intervals after administration of dexmedetomidine in dogs. Shah *et al.* (2013) reported that detomidine and medetomidine alsoproduce severe hypoxaemia when administered intravenously at equipotent sedative doses in sheep.

5.4 Haematological Observations

5.4.1 Haemoglobin

The haemoglobin level decreased non-significantly at 10 minutes after premedication in all the three groups. The haemoglobin level decreased non-significantly from 30 to 120 minutes during ketamine-isoflurane anaesthesia in all the groups. The comparison between the groups at different intervals did not reveal significant difference in the haemoglobin value.

The decrease in haemoglobin during anaesthesia might be caused by the shifting of fluid from the extravascular compartment in order to maintain normal cardiac output (Wagner *et al.,* 1991), Udegbunam *et al*. (2009) observed a decrease in haemoglobin in splenectomised dogs after ketamine administration and attributed to sequestration of red blood cells in non-splenic sites.

Monsang (2011) observed a decrease in haemoglobin after injecting dexmedetomidine in sheep.

Peshin *et al.* (1980) observed a slight decrease in haemoglobin following administration of xylazine in dogs. Singh *et al.* (2013b) observed a significant decrease in haemoglobin in buffaloes anaesthetized with xylazine-fentanyl-thiopentone-isoflurane.

The decreased haemoglobin has been reported after administration of dexmedetomidine in dogs (Gupta, 2010) and sheep (Monsang, 2011). Singh *et al.* (2013b) reported decreased haemoglobin in buffaloes premedicated with dexmedetomidine and fentanyl.

5.4.2 Packed Cell Volume

Packed cell volume decreased non significantly at 10 minutes after premedication in both the groups. The packed cell volume decreased non-significantly at 30- and 60-minutes during ketamine-isoflurane anaesthesia in both the groups. There was no significant difference in packed cell volume between the groups at all the intervals of anaesthesia.

Similar findings were observed by Peshin *et al.* (1980) who reported a significant decrease in packed cell volume after administration of xylazine in dogs. Packed cell volume was also found reduced with xylazine-fentanyl-thiopentone-isoflurane in buffaloes (Singh *et al.*, 2013b). The decreased packed cell volume has been reported after administration of dexmedetomidine in horses (Wagner *et al.*, 1991), dogs (Gupta, 2010) and sheep (Monsang, 2011). Kumar *et al.* (2001) observed a significant decrease in packed cell volume from 5 to 45 minutes after ketamine administration in dogs premedicated with haloperidol. Hikasa *et al.* (2000) reported a decrease in packed cell volume in sheep under isoflurane anaesthesia and up to 3 days post anaesthesia. The

decrease in packed cell volume may be probably due to the stress caused by the sedative drugs (Bollwahn *et al.,* 1970), decreased heart rate and blood pressure (Khamis and Selah, 1970) and haemodilution by infiltration of interstitial fluids during anaesthesia.

5.4.3 Total Erythrocyte Count

The total erythrocyte count decreased non significantly at 10 minutes after premedication in both the groups. The total erythrocyte count non-decreased significantly from 10 to 60 minutes during ketamine-isoflurane anaesthesia in all three groups. The comparison between the groups at different intervals did not reveal significant difference in the total erythrocyte count.

Amreshkumar *et al.* (1979) stated that the decrease in total erythrocyte count during xylazine-ketamine anaesthesia could be due to the result of animal response to stress caused by anaesthetic drug. The decrease in total erythrocyte count was reported after administration of xylazine in dogs (Peshin *et al.*, 1980) and caprines (Dehghani *et al.,* 1991b and Kumar and Thurmon, 1979). Kumar *et al.* (2001) observed a significant decrease in total erythrocyte count in dogs administered with haloperidol and ketamine. Monsang (2011) observed a decrease in total erythrocyte count after injecting dexmedetomidine in sheep. Hikasa *et al.* (2000) reported a decrease in total erythrocyte count in sheep under isoflurane anaesthesia.

5.4.4 Total Leukocyte Count

The total leukocyte count decreased non-significantly at 10 and 120 minutes in cattle of group I (romifidine-ketamine-isoflurane) from 10 to 120 minutes in cattle of

group II (dexmedetomidine-ketamine-isoflurane) and (xylazine-ketamine-isoflurane) of group-III during ketamine-isoflurane anaesthesia.

However, the comparison between the groups at different intervals did not reveal significant difference in the total leukocyte count. The decrease was not alarming to suggest any pathological condition and was probably due to extravascular shift of fluid as a response to blood loss during surgery. Similar findings were reported after administration of xylazine in dogs (Fani *et al.,* 2008) and goats (Kumar and Thurmon, 1979). A significant decrease in total leukocyte count was reported after administration of dexmedetomidine in sheep (Monsang, 2011) and horses (Wagner *et al.,* 1991). Kumar *et al.* (2001) observed a significant decrease in total leukocyte count from 5 to 45 minutes during haloperidolketamine anaesthesia in dogs.

5.4.5 Neutrophills and Lymphocytes

A significant increase in neutrophils with a subsequent non-significant decrease in lymphocytes was observed under ketamine-isoflurane anaesthesia in cattle of all three groups, from 30 to 120 minutes. The comparison between the groups at different intervals revealed no significant difference in the differential leukocyte count. These changes were nearer to normal levels and were probably related to response of animal to anaesthesia and surgery. Peshin *et al.* (1980) reported a decrease in lymphocytes with subsequent increase in neutrophils in dogs administered with xylazine. Khattri *et al.* (2013) reported neutrophilia and lymphocytopenia in buffalo calves administered with dexmedetomidine and propofol which may be due to the stress caused by the preanesthetic and anaesthetic drugs and subsequent stimulation of adrenal glands. Similar findings have been reported

after administration of dexmedetomidine in dogs (Ahmad *et al.,* 2011) and sheep (Monsang, 2011), or combinations of dexmedetomidine-midazolam-fentanyl in dogs (Ahmad *et al.,* 2011).

5.5 Biochemical Observation

5.5.1 Creatinine

Creatinine value remained within normal limits and no significant changes in the value were observed throughout anaesthesia in all animals. Similar findings were recorded after midazolam –ketamine anaesthesia in goats (Ahmad, 2012) and isoflurane anaesthesia in sheep (Hikasa *et al.,* 2000). However, increase in the creatinine value were reported after acepromazine-ketamine and diazepam-ketamine anaesthesia in goats (Akhare *et al.,* 2003), xylazine-butorphenol-midazolam-ketamine anaesthesia in horse (Malik and Singh, 2007), detomidine-midazolam-ketamine anaesthesia in calves and dexmedetomidne-butorphanol-ketamine combinations in dogs (Sharma *et al.,* 2004).

5.5.2 Alanine transaminase

Alanine transaminase (ALT) fluctuated within normal limits in all the animals. Ahamad (2013) observed no significant change in the alanine transaminase and aspertate transaminase during midazolam and ketamine anaesthesia in goats. All general anaesthetics lower the circulation to liver (Malik and Singh, 2007) and changes in alanine transaminase and aspertate transaminase during present study might be due to this fact. Hikasa *et al.* (2000) reported non significant alteration in alanine transaminase during and up to three days after isoflurane anaesthesia in sheep.

5.5.3 Aspartate transaminase

The serum aspartate transaminase increased non-significantly at 60- and 120-minutes during ketamine-isoflurane anaesthesia in cattle premedicated with xylazine (group III). In cattle of group II premedicated with dexmedetomidine, Topal *et al.* (2003) reported increased aspartate transaminase activities up to two days after isoflurane anaesthesia in dogs. However, Hikasa *et al.* (2000) observed non significant alteration in aspartate transaminase in sheep anaesthetized with isoflurane. Butola and Singh (2003) observed non significant decrease in aspartate transaminase in dogs administered with midazolam and ketamine. All the general anaesthetics lower the circulation to liver (Malik and Singh, 2007), and the changes in alanine transaminase and aspartate transaminase during the present study might be due to this response.

5.5.4 Serum Urea Nitrogen

The serum urea nitrogen increased non-significantly at 60- and 120-minutes during ketamine-isoflurane anaesthesia in cattle premedicated with xylazine (group III). In cattle of group II premedicated with dexmedetomidine, the serum urea nitrogen increased non-significantly at 120 minutes during ketamine-isoflurane anaesthesia. Singh *et al.* (2013a) reported a significant increase in urea nitrogen in buffaloes anaesthetized with xylazine-fentanyl-thiopentone-isoflurane (from 120 to 1440 minutes) and dexmedetomidine-fentanyl-thiopentone-isoflurane (at 30, 90 and 1440 minutes). Kumar *et al.* (2013a) observed non-significant change in plasma urea nitrogen in uraemic goats administered with dexmedetomidine-propofol-ketamine. Khattri *et al.* (2013) reported a significant increase in urea nitrogen from 15 to 60 minutes after administration of dexmedetomidine and propofol, which might be due to temporary inhibitory effects of anaesthetic drugs on the renal blood flow.

Summary

VI. SUMMARY

The present clinical study was carried out in 18 clinical cases of cattle of either sex presented for various surgical procedures to Department of Surgery and Radiology at Veterinary Clinical Complex (VCC), Veterinary College, Bidar. The sedative effects of Romifidine, Dexmedetomidine and Xylazine for Ketamine-Isoflurane general anaesthesia in cattle were compared. They were randomly divided into three groups consisting of six cattle in each group. The animals of group I were administered with romifidine (10 µg/Kg, I/V) followed by ketamine hydrochloride (3 mg/Kg, I/V) and maintained with isoflurane (1-2%). The animals of group II were administered with xylazine hydrochloride (0.1 mg/Kg, I/V) followed by ketamine hydrochloride (3 mg/Kg, I/V) and maintained with isoflurane (1-2%). The animals of group III were administered with dexmedetomidine (2.5 µg/Kg, I/V) followed by ketamine hydrochloride (3 mg/Kg, I/V) and maintained with isoflurane (1-2%). The sedative effects of preanaesthetics *viz.*, romifidine, dexmedetomidine and xylazine for ketamine-isoflurane general anaesthesia in cattle were compared. Major surgeries were performed to treat several conditions in these cattle and the anaesthetic combinations were evaluated based on clinical, physiological, haemodynamic and haematobiochemical observations.

Clinical observations revealed that the onset of sedation in cattle of group I, group II and group III was seen in 1.19±0.46 minutes, 2.49±0.48 minutes and 2.16±0.20 minutes respectively. The onset of sedation was significantly faster ($p \leq 0.01$) in group-I animals as compared to group-II and group-III animals.

The Mean±SE values of recovery time were: 10.50±0.88, 11.85±0.21 minutes and 10.83±0.79 minutes in group-I, group-II and group-III animals respectively. The recovery was smooth and uneventful in the animals of all three groups. The recovery time was less in romifidine group of animals as compared to other two groups of animals.

An excellent analgesia was recorded at maximum depth of anaesthesia in all three groups of animals. The pain was significantly abolished from 0 to 60 minutes in all the groups. There was non-significant difference in the analgesic level produced between the groups at all the intervals of study. The muscle relaxation was moderate to excellent at 10 minutes in cattle of group-I animals premedicated with romifidine. In cattle of group-II premedicated with dexmedetomidine, the muscle relaxation was mild to moderate at 10 minutes after premedication. The muscle relaxation was moderate to excellent at 10 minutes in cattle of group-III animals premedicated with xylazine. The degree of muscle relaxation was significantly increased from 0 to 60 minutes in all the three groups.

The present study showed that, in all the groups of animals, the palpebral reflex was brisk and present before induction of anaesthesia. A sluggish palpebral reflex was present even after induction in all animals,

Physiological observations revealed that, the rectal temperature showed non-significant declining trend and they were fluctuated within normal physiological limits.

The Mean±SE values of respiratory rate decreased significantly ($p \leq 0.05$) after 10 minutes of romifidine induction as well as dexmedetomidine and xylazine administration, there after it showed increase trend which was statistically significant ($p \leq 0.05$) only at

120 minutes after ketamine administration. Similar trend was observed in group-II and group-III animals. Comparison between the groups showed non-significant variation at all the interval of study. There was non-significant difference observed between the groups.

Bradycardia was observed from 10 minutes intervals in all the three groups of animals, however the bradycardia was statistically non significant after 10 minutes to 60 minutes of interval in all the groups.

Haemodynamic observations revealed that in all the groups, the mean arterial pressure (MAP) fluctuated within the physiological limit throughout anaesthetic interval, however at 10 minutes after administration of sedative agents in all the three groups of animals, decrease in mean arterial pressure was observed.

The haemoglobin oxygen saturation decreased non-significantly at 10 minutes, 30 minutes and 60 minutes after anaesthesia in all the groups. It started to increase towards normal in both the groups at 120 minutes. There was no significant difference between the groups at all the intervals. The decrease in SpO2 after sedation recorded in both groups was possibly due to certain degree of respiratory depression.

The haemoglobin level fluctuated within normal physiological limit in all the group of animals. The comparison between the groups at different intervals did not reveal significant difference in the haemoglobin value.

Packed cell volume fluctuated within normal physiological limits in all the group of animals.There was no significant difference in packed cell volume between the groups at all the intervals of anaesthesia.

The total erythrocyte count fluctuated within normal physiological limits in all the group of animals. The comparison between the groups at different intervals did not reveal significant difference in the total erythrocyte count.

A significant increase in neutrophils with a non- subsequent significant change in lymphocytes was observed under ketamine-isoflurane anaesthesia in cattle of all three groups, at 30 minutes. The comparison between the groups at different intervals revealed no significant difference in the differential leukocyte count. These changes were nearer to normal levels and were probably related to response of animal to anaesthesia and surgery.

Based on the above findings, following conclusions were made:

1. All the three anaesthetic protocols in the present study *viz.*, premedication with of Romifidine @ 10 µg/kg body weight IV (group I), Dexmedetomidine (2.5 µg/kg, I/V) (group II), and Xylazine @ 0.1 mg/kg body weight IV (group III) .for anaesthetic induction with ketamine (3 mg/kg, I/V) and maintenance of anaesthesia with isoflurane (1-2%) provided satisfactory surgical plane of anaesthesia in cattle.

2. Onset of sedation and down time to sternal recumbency were faster in the cattle premedicated with romifidine, as compared to the cattle premedicated with Dexmedetomidine or Xylazine for Ketamine isoflurane induction combination.

3. The induction time was significantly quick in the animals pre-medicated with Romifidine – Ketamine combination, as compared to that in the animals pre-medicated with Dexmedetomidine or Xylazine – Ketamine isoflurane induction combination.

4. Degree of analgesia and muscle relaxation was excellent in cattle sedated with Romifidine (Group I) and was significantly greater when compared to cattle sedated with Dexmedetomidine (Group II) and Xylazine (Group III).

5. The recovery was smooth and uneventful in the group of animals, the recovery time was significantly less with romifidine when compared to Dexmedetomidine and Xylazine.

6. The respiratory depression, bradycardia and decrease in mean arterial pressure were more severe in cattle premedicated with Romifidine when compared to cattle premedicated with Dexmedetomine and Xylazine during ketamine-isoflurane anaesthesia.

7. Haematological and biochemical parameters fluctuated within normal physiological limits indicating combination of all the three groups were safer for clinical use.

8. Hence Romifidine was more potent sedative than Dexmedetomidine and Xylazine in the present study.

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Abstract

VIII. ABSTRACT

ROMIFIDINE DEXMEDETOMIDINE AND XYLAZINE SEDATION WITH KETAMINE ISOFLURANE FOR SURGERIES IN CATTLE

Student	June	Major Advisor
Venkatgiri	2019	Dr. Dilipkumar, D.

The study was carried out to evaluate the feasibility of Romifidine, Dexmedetomidine and Xylazine sedation for Ketamine-Isoflurane general anaesthesia for various surgeries in cattle. The study was carried out in 18 clinical cases of cattle presented for various major surgical procedures randomly divided into three groups consisting of six cattle in each group. The animals of Group I were administered with Romifidine (10 µg/Kg, I/V) followed by Ketamine hydrochloride (3 mg/Kg, I/V) and maintained with Isoflurane (1-2%). The animals of Group II were administered with Xylazine hydrochloride (0.1 mg/Kg, I/V) followed by Ketamine hydrochloride (3 mg/Kg, I/V) and maintained with Isoflurane (1-2%). The animals of Group III were administered with Dexmedetomidine (2.5 µg/Kg, I/V) followed by Ketamine hydrochloride (3 mg/Kg, I/V) and maintained with Isoflurane (1-2%). Faster induction time, early onset of sedation, early recovery time to regain sternal position and to assume standing position were noticed in cattle premedicated with romifidine than cattle premedicated with Dexmedetomine and Xylazine for Ketamine-Isoflurane general anaesthesia. Romifidine as a premedicant provided better analgesia, degree of sedation and muscle relaxation compared to dexmedetomidine and Xylazine whereas, after induction of general anaesthesia it was excellent in all the groups. Respiratory depression, bradycardia and decrease in mean arterial pressure were more severe in cattle premedicated with Romifidine and Xylazine when compared to cattle premedicated with Dexmedetomidine for Ketamine-Isoflurane anaesthesia. Heamato-biochemical parameters fluctuated within normal limits. Hence in present study we can conclude that, Romifidine was more powerful sedative than Xylazine and Dexmedetomidine, during Ketamine-Isoflurane induced general anaesthesia in cattle.