"STUDIES ON EFFICACY OF BUPIVACAINE AND ITS COMBINATION WITH DETOMIDINE AND TRAMADOL FOR INDUCING EPIDURAL ANAESTHESIA IN GOATS"

M.V. Sc. THESIS

BY

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INDIRA GANDHI KRISHI VISHWAVIDYALAYA, RAIPUR (C.G.)

By

NARENDRA KUMAR NAIK

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IN

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CERTIFICATE-I

This is to certify that the thesis entitled **"STUDIES ON EFFICACY OF BUPIVACAINE AND ITS COMBINATION WITH DETOMIDINE AND TRAMADOL FOR INDUCING EPIDURAL ANAESTHESIA IN GOATS"** submitted in partial fulfillment of the requirements for the degree of **"Master of Veterinary Science"** of Indira Gandhi Krishi Vishwavidyalaya, Raipur (C.G.), is a record of bonafide research work carried out by **Narendra Kumar Naik**, under my guidance and supervision. The Student's Advisory Committee and the Director of Instruction have approved the subject of the thesis. No part of the thesis has been submitted for any other degree or diploma (certificate awarded etc.) or has been published/published part has been fully acknowledged. All the assistance and help received during the course of investigations have been duly acknowledged by him.

Dated:

(RAJU SHARDA)

Chairman, Advisory Committee

THESIS APPROVED BY STUDENT'S ADVISORY COMMITTEE

Chairman: Dr. Raju Sharda, Associate Professor ----------

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Member: Dr. S. Roy, Professor and Head ----------

Member: Dr.Mohan Singh, Professor and Head ----------

Member: Dr. S. P. Ingole, Professor and Head ----------

CERTIFICATE-II

This is to certify that the thesis entitled **"STUDIES ON EFFICACY OF BUPIVACAINE AND ITS COMBINATION WITH DETOMIDINE AND TRAMADOL FOR INDUCING EPIDURAL ANAESTHESIA IN GOATS"** submitted by **Narendra Kumar Naik** to the Indira Gandhi Krishi Vishwavidyalaya, Raipur (C.G.) in partial fulfillment of the requirements for the degree of **"Master of Veterinary Science"** in the Department of Veterinary Surgery and Radiology, College of Veterinary Science and Animal Husbandry, Anjora, Durg, has been approved by the Student's Advisory Committee after oral examination in collaboration with the external examiner.

External Examiner

Major Advisor

Head of the Department

Dean

Director of Instruction

Dated:

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VITA

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His keen interest in Animal Welfare led him to pursue a career in Veterinary science. He joined College of Veterinary Science and Animal Husbandry Anjora, Durg (C.G.) in the year 2003 and obtained B.V.Sc & A.H. degree with second class in the year 2009. His liking for clinical subjects played a major role in pursuing higher studies in Veterinary Surgery and Radiology in 2010 and completed the requisite course works for M.V.Sc programme.

He has also become "Life Member" of *Indian Society for Veterinary Surgery*.

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CHAPTER I

INTRODUCTION

The tranquilizers and sedatives are required to facilitate restraint and for examination and treatment of animals. A good sedative agent should have analgesic activity, a wide margin of safety, produce minimum side effects and a steady level of sedation without any excitement. India has a large number of different categories of livestock, among which goats play an important role in its economy. Goat population of India is estimated as 124.56 million where as in Chhattisgarh it is approximately 2.3 million. Goat has particular importance in livestock due to its unique qualities such as, high fertility, short kidding interval, good quality chevon, milk and hairs (Mackenzie, 1967). The important role of goat is the production of high quality protein for human consumption. Prevention and treatment of diseases in goat is very essential to obtain maximum milk and chevon production for human consumption. These animals are commonly affected with diseases viz. urolithiasis, ruptured bladder, dystocia, volvulus, strangulation, fracture, ruminal impaction, prolapse of rectum and vagina etc. Majority of these ailments require surgical correction and management which can be accomplished under regional analgesia. The development of new sedatives and analgesics in recent years has greatly contributed to the success of many and even complicated surgical procedures in goats.

The technique of administration of epidural anaesthesia is easy and within the reach of any clinician. The complications associated with general anaesthesia in ruminants like tympany, regurgitation and aspiration can be reduced by

epidural anaesthesia. Its use in veterinary medicine is most common in large animal practice than in small animals. However, it may be distinctly advantageous over general anaesthesia in poor risk animals. Epidural anaesthesia has been used in veterinary practice for diagnostic, obstetric and surgical procedures of pelvic limbs, lower abdomen, flank and perineal region.

Regional anaesthesia is generally preferred in ruminants as they are prone to regurgitation, ruminal tympany, respiratory embarrassment and associated problems during general anaesthesia (Hall and Clarke, 1991). Segmental epidural block is routinely used to block the thoracic, lumbar and sacral nerves so as to desensitize the abdominal region, flank, and perineum for performing surgery of these regions (Tyagi and Singh, 1996). In routine practice, 2% lignocaine hydrochloride is used for local or regional anaesthesia.

Bupivacaine is a local anaesthetic agent which is four times more potent than lignocaine hydrochloride. Its 0.5% concentration is used for usual nerve blocks. The compound is stable and well tolerated by all the tissues (Hall, 1971). The margin of safety is greater and the period of analgesia is at least twice as long as that of lignocaine hydrochloride. Bupivacaine has been extensively used in human medicine for long time but only limited literature is available regarding its clinical application in veterinary practice. It has been used as an epidural and spinal anaesthetic in sheep (Adams *et al.,* 1977), epidural analgesia in cats (Adams *et al*., 1977), caudal lumbar epidural anaesthesia in dogs (Gerlach *et al*., 1983), long acting epidural analgesia in buffaloes (Hussain and Kumar, 1988a), unilateral and bilateral segmental epidural and subarachnoid blockade in buffaloes

(Mishra *et al.,* 1993) and for epidural and subarachnoid anaesthesia in goats (Trim, 1989; Tiwari *et al*., 1989a).

Detomidine HCl is a new alpha2- adrenoreceptor agonist with sedative and analgesic properties (Anonymous, 1996). It is an imidazole derivative and has been developed as a sedative/analgesic for animals. Initially, detomidine was developed to be used as a sedative and analgesic in horse and cattle (Hall and Clarke, 1991; Thurmon *et al,* 1992). It has also been used in laboratory animals (Hall and Clarke, 1991). Limited work has been done on the use of detomidine in goats.

Tramadol is a centrally acting analgesic agent with activity at μ-opioid, adrenergic and 5-hydroxytryptamine (5-HT) receptors. Its analgesic effect is a result of its dual mechanism of action that is, as a re-uptake inhibitor of norepinephrine and serotonin and agonist of the μ-opioid receptor (Ide *et al.*, 2006). Tramadol has been in clinical use for the relief of mild to moderate pain in human and veterinary medicine (Mastrocinque and Fantoni, 2003; Pypendop and Ilkiw, 2008). Tramadol is also used perioperatively in veterinary anaesthesia as it significantly reduces the requirements of volatile anaesthetics and opioid agents (Wordliczek *et al.*, 2002; Seddighi *et al.*, 2009).

The reports regarding epidural use of bupivacaine in combination with tramadol and detomidine in goats are limited. Therefore, the present research work was planned with the following objectives.

1. To find out the optimal dose of bupivacaine and its combination with tramadol and detomidine for epidural anaesthesia in goats.
2. To compare the extent, depth and duration of epidural anaesthesia induced by

bupivacaine alone and in combination with tramadol and detomidine in goats.

3. To evaluate the physiological, haematological and biochemical effects in response to epidural administration of these combination of drugs.

CHAPTER II

REVIEW OF LITERATURE

General anaesthesia is generally not preferred in ruminants due to side effects like regurgitation, salivation, ruminal tympany and respiratory embarrassment. Therefore, regional anaesthesia/epidural anaesthesia is preferred. which is easy and useful in poor risk animals. Lumbar epidural anaesthesia permits the surgery of abdomino-pelvic region in standing position.

Combination of alpha-2 agonists like detomidine or opioid analgesics like tramadol potentiates the local anaesthetic effects, reduces dose requirement and prolongs the duration of action with absence of hind limb weakness. Lumbar epidural analgesia has been used in animals (Valvarade *et al*., 1991, Hendrikson *et al*., 1996). Review of literature has been summarized under following headings.

1. Spread of drug
2. Uptake of the drug
3. Elimination of the drug
4. Bupivacaine
5. Combination of bupivacaine with detomidine.
6. Combination of bupivacaine with tramadol.

2.1 SPREAD OF DRUG

The action of epidural anaesthetics depends partially upon the spread of solution. The spread in lumbar epidural injection occurs at sites other than epidural space, possibly to the sub-arachnoid or subpial space (Bromage, 1979).

Most important escape routes which drain the solution from the epidural space are intervertebral foramina, the extradural venous plexuses, possibly the duramater which acts as a semipermeable membrane allowing penetration of drugs into the CSF (Frumin *et al*., 1953) and diffusion in the epidural fat. If the removal is fast compared with the speed of block, solutions may be removed so rapidly that there is no chance for their spread and induction of widespread blockade. Slow absorption causes more prolonged contact between solution and nerves, so that the extent and intensity of spread is likely to be greater.

Spread of the solution from the site of an epidural injection depends upon:

(i) Spread within the epidural space itself: This depends on factors such as the volume of solution injected, speed of injection, patency of the intervertebral foramina, posture of the animal, gravity and vascular absorption.

(ii) Spread in the subdural and subpial spaces: The amount of drug which reaches the subpial spaces will be proportional to the amount which is able to diffuse through the perineurium into the subperineural spaces. Segmental spread is dependent on the mass of analgesic drug available for transneural diffusion in the epidural space (Hall and Clarke, 1983).

According to Greene (1985) the physical characteristics of spinal anaesthetic solutions that determine spread in CSF are: density of the anaesthetic solution, amount of the anaesthetic given (mg), concentration and volume of the anaesthetic solution injected.

2.2 UPTAKE OF THE DRUG

According to Greene (1983) the uptake of anaesthetic solution by tissues is governed by three factors (a) Accessibility (b) lipoid contact and (c) tissue blood flow.

(a) According to Cohen (1968) more is the exposed nerve tissue in CSF, the more rapid is uptake. The accessibility of spinal cord to anaesthetic solution dissolved in CSF is a function of the number of Virchow-Robin spaces per unit of surface area of cord. The number of spaces of Virchow-Robin is greater anteriorly than posteriorly but concentration gradient of anaesthetic solution is not greater anteriorly than posteriorly because of absorption of the anaesthetic by lipids.

(b) Myelin contains lipid and anaesthetics are highly soluble in lipids. Posterior and lateral spinal cord tracts are more heavily myelinated than anterior tracts. Heavy myelination therefore, increases the uptake of anaesthetics in the neuronal tissue.

During perineural or epidural injections, the presence of nerve sheath and absorption of the anaesthetic by surrounding tissue significantly alters drug availability to the target (Langerman *et al.*, 1994).

(c) Tissue concentrations of local anaesthetics are governed by tissue blood flow because blood flow determines the rate at which local anaesthetics are removed from tissue (Cohen, 1968).

2.3 ELIMINATION OF THE DRUG

During epidural anaesthesia, anaesthetics, gets diffused more rapidly down a concentration gradient from the epidural space through the duramater into CSF. Indeed, the diffusion of anaesthetics into the subarachnoid space from the epidural space is very rapid. But the duramater is not a one-way diffusion barrier. Equally rapid diffusion of anaesthetics along a concentration gradient can occur in the opposite direction from CSF into the epidural spaces, which are then susceptible to vascular reabsorption (Greene, 1983). It results in continuous decrease in CSF concentration of anaesthetics. A concentration gradient is set up in turn between anaesthetic solution in CSF and tissue within the subarachnoid space. It then diffuses down this concentration gradient from tissues to CSF and then to the epidural space. Moore *et al*., (1982). observed that the rate of diffusion was inversely related to the thickness of the dura as cranial dura is thicker than lumbar dura which is thicker than sacral dura.

2.4 BUPIVACAINE HYDROCHLORIDE:

Bupivacaine HCl (1-N-butyl-DL-piperidine-2-carboxylic acid-2, 6-dimethyl anilide hydrochloride). A.F. Ekenston and his coworkers synthesized a long acting anilide in 1957. Its molecular weight is 324.9 and melting point is 247°-252°F. Bupivacaine is white, crystalline substance readily soluble in water. It is available as aqueous solution (Sensorcaine/Anawin*), with 6-6.5pH. Both anaesthetic and toxic index of bupivacaine is 5. Bupivacaine is metabolized by demethylation of piperidine ring and coupling to glucuronic acid in the liver. It is excreted through bile duct and kidney. Bupivacaine hydrochloride is approximately four times as

potent as lignocaine hydrochloride and provides period of analgesia atleast twice as that of lignocaine and is well tolerated by all tissues (Hall, 1971).

Bupivacaine has been extensively used in human medicine for a long time but only limited literature is available regarding its clinical application in veterinary practice. It has been used as an epidural and spinal anaesthetic in sheep (Lebeaux, 1975 and Adams *et al.*, 1977), epidural analgesia in cats (Adams *et al*.,1977), caudal lumbar epidural anaesthesia in dogs (Spicciati and Alvarenga,1977, Alverez *et al*.,1980, Bonath *et al*., 1983 and Gerlach *et al*.,1983), long acting epidural analgesia in buffaloes (Hussain and Kumar,1988a), unilateral and bilateral segmental epidural and subarachnoid blockade in buffaloes (Mishra *et al.*,1993), and for epidural and subarachnoid anaesthesia on goats (Trim,1989, Tiwari *et al*.,1989a). The analgesic potency produced by bupivacaine has been reported to be ten times more than procaine and six times to that of lignocaine (Jenkner, 1977).

Bromage (1969) achieved that good surgical analgesia when 0.5 percent solution of bupivacaine HCl was used, since then the drug has gained a wide acceptance as a regional anaesthetic in veterinary and medical practice.

Lumbar epidural anaesthesia is a technique proposed for accomplishing anaesthesia of the last thoracic and first lumbar nerves for performing rumenotomy and it was first described in cattle by Magda, (1947) and by Buchholz and Koemer, (1948).

Hall (1971) investigated that bupivacaine HCl is well tolerated by all tissues and it is approximately four times more potent than lignocaine HCl, provides longer period of analgesia and is safe in animals.

Skarda and Muir (1979a) observed that injection of 5 to 12 ml of 5% procaine solution at the first interlumbar space produced unilateral or bilateral epidural anaesthesia.

Bonath *et al*. (1983) had observed an insignificant decrease in the mean arterial blood pressure (MAP) and peripheral vascular resistance when bupivacaine was used as epidural anaesthetic in dogs.

Moore and Scurlock (1983) reported that circulatory collapse could be recorded after gross over dose (0.3 to 0.5 ml/ kg body wt 0.1% solution) of bupivacaine when used as epidural injection in dogs.

Gill *et al*. (1984) used that bupivacaine HCl for epidural anaesthesia in dogs with longer duration of action without any side effects.

Pandey *et al*. (1984) administered 0.5% bupivacaine alone @ 0.5, 1 and 1.5mg/kg body weight at lumbosacral epidural space in goats with intramuscular injection of triflupromazine HCL (0.3mg/kg) as premedicant. The complete analgesia was achieved within 4.28, 3.00 and 1.65 min. respectively. The duration of analgesia ranged from 79.07 to 103.36 min. They concluded that the administration of triflupromazine HCL prior to administration of bupivacaine HCL significantly prolonged the duration analgesia and time of recumbency.

Andre *et al*. (1988) investigated the effects of volume and concentration of glucose free bupivacaine in spinal anaesthesia in human patients undergoing transurethral surgery. In patients receiving 2.5 ml of 0.5 percent bupivacaine with epinephrine, analgesia extended up to $T8^{th}$ level whereas, in patients receiving 10 ml of 0.125 percent bupivacaine plus epinephrine, the cranial spread was up to $T9^{th}$ level. It was concluded, that when a constant dose of glucose free bupivacaine was

maintained, it did not affect the extent of analgesia, degree of motor blockade or haemodynamic changes. However, a more predictable level of anaesthesia was found when 0.125 percent bupivacaine solution was hypobaric in contrast to 0.5 percent solution.

Leone *et al.* (1988) reported that myocardial dysfunction could occur with bupivacaine as observed with lignocaine HCl but it doesn`t account for the cardiotoxicity of bupivacaine.

Tiwari *et al*. (1989a) investigated that epidural and subarachnoid anaesthesia induced by bupivacaine HCl causes an initial increase in pulse rate and respiration rate followed by a decrease in rectal temperature in goats which might be due to relaxation of muscles and subsequently lowered muscular activity.

Trim (1989) induced epidural analgesia with 0.75 percent bupivacaine HCl for laparotomy in goats and observed that it provided analgesia of the flank in 13 out of 17 goats. Onset of analgesia from bupivacaine HCl was slow (40 minutes) but the duration of analgesia was several hours as compared to lignocaine HCl induced analgesia.

Katoch and Pandey (1991) compared the epidural effects of bupivacaine along with similar dose rates in goats. The doses were 3 mg, 5 mg and 8 mg /kg b.wt. The onset of analgesia was comparatively quicker and prolonged with delayed recovery in lidocaine as compared to similar dose rate of procaine. The apparent decrease in pulse rate was noticed with all the three treatments. However when bupivacaine was used at the higherdose rate (8mg/kg b.wt.) the drop in pulse rate was observed.

Dela *et al*. (1993) observed that bupivacaine HCl induced bradycardia, prolonged P-R interval and increased left ventricular and diastolic pressure in dogs.

Mishra *et al*. (1993) induced unilateral and bilateral segmental epidural and subarachnoid blockades using bupivacaine hydrochloride (0.5 percent) @ 0.1 ml/kg b.wt. in buffalo calves and reported the onset of analgesia in 10.25 ± 1.49 to 13.75 ± 2.05 minutes in epidural blockade and 5.50 ±1.04minutes in subarachnoid blockade, while duration of anaesthesia was 221.25 ± 33.94 minutes and 227.50 ± 19.98 to 243.00 ± 21.53 minutes in subarachnoid and epidural blockade respectively. The cranial spread was upto T12 in subarachnoid blockade where as it was upto T13 in epidural blockade. No significant changes were observed in heart rate, respiration rate and rectal temperature. There was no significant effect on haemoglobin percentage, packed cell volume, erythrocyte sedimentation rate, total leucocyte count ,differential leukocyte count and biochemical parameters like blood and CSF glucose, total protein, albumin, globulin, blood urea nitrogen, creatinine, sodium, potassium, and chloride upto 72 hours.

McEnvoy, (1995) reported that bupivacaine HCl has been a long acting anilide local anaesthetic agent and it is approximately four times more potent than lignocaine and provided longer duration of action, at least twice as that of lignocaine HCl. Analgesia with bupivacaine HCl occured in 20 to 30 mins and lasted upto 5-7 hrs.

Suresh kumar *et al*. (1995) studied the biochemical alterations after epidural injection of bupivacaine @ 1.5, 2.0, and 2.5 mg/kg b.wt. in 8 mongrel dogs and reported a non-significant increase in blood glucose, total proteins, AST, ALT and

calcium levels. Serum electrolytes i.e. sodium and potassium showed a non-significant reduction whereas chloride values showed a non-significant rise following epidural administration. They concluded that epidural bupivacaine did not produce any significant biochemical alterations and was well tolerated and safe for use as epidural analgesia.

Rao *et al*. (1997a) recorded non-significant changes in haematological parameters following epidural injection of 0.5 percent bupivacaine HCl alone and with amyl alcohol in dogs. The TEC, Hemoglobin, PCV revealed an insignificant fall alongwith non significant variation in ESR and finally the haemogram showed a non significant neutrophilia with mild lymphocytopaenia.

Vessel and Joya (1999) observed a significant increase in heart rate with bupivacaine after epidural administration in goats.

Adetunji *et al.* (2002) compared the xylazine (2% 0.5 mg/kg), bupivacaine (1.7 mg/kg) and bupivacaine/xylazine mixture (0.85/0.25 mg/kg) in goats for epidural anaesthesia. Times to recumbency with Bupivacaine (3.8 ± 0.8min) and xylazine (7.0 ± 2.0min)xylazine/bupivacaine mixture(6.2±1.3min) Duration of analgesia was longest with xylazine (148.0 ± 23.1min), shortest with bupivacaine (90.0 ± 2.15min) and intermediate with xylazine/bupivacaine (139.0 ± 57.6min).

Pathak *et al*. (2002) compared the efficacy of pre-traumatic and post-traumatic neuroaxial blockade with bupivacaine in controlling the post traumatic pain and morbidity in 12 nondescript adult goats of either sex randomly divided into groups A, B and C of 4 animals each. In group A, bupivacaine (@ 1mg/kg) was injected at the lumbosacral space 30 minutes before the injection of turpentine, where as in group B, bupivacaine was injected 2 hours after the

injection of turpentine. Group C was control injected with normal saline. A significant increase in heart rate, respiration rate and rectal temperature in animals of group B and C and only a mild increase in the animals of group A was seen. Maximum increase in swelling, joint warmth, hyperalgesia and pain scores were recorded in group C followed by group B. Least changes were observed in group A indicating minimum discomfort in these animals. It was concluded that, epidural blockade with bupivacaine before trauma preempts the postoperative pain and morbidity to a greater extent and might be used in clinical cases with or without general anaesthesia.

Ozaydin and Kilick (2003a) investigated that 0.5 percent marcaine when injected into lumbosacral subarachnoid space in cattle @ 7 to 15 ml. as total dose it had a rapid, long lasting and safe spinal anaesthetic effect and this occurred within 20 to 60 seconds and duration of anaesthesia was 3.5 to 5 hours.

Derossi *et al*. (2003) studied the antinociceptive and motor blocking effects of subarachnoid injection of 0.5 percent hyperbaric bupivacaine and lidocaine 2 percent in goats. They concluded, that bupivacaine HCl produced 3 times longer regional analgesia than that of lignocaine HCl and it showed superior antinociceptive extension reaching upto T8 level and thus bupivacaine HCl was reported to produce better analgesia both in terms of time and extension as compared to lidocaine with minimal motor effects.

Kumar *et al*. (2005) evaluated the efficacy of bupivacaine and xylazine as epidural agents in pigs and compared with the action produced by xylocaine. Xylocaine (1 ml/kg b.wt.), xylazine (3 mg/kg b.wt.) and bupivacaine (2 ml/5 kg b. wt.) were used to induce lumbosacral epidural anaesthesia in pigs. Results showed

that the period of induction was shortest and duration of analgesia was longest with bupivacaine followed by xylazine and xylocaine.

Murmu *et al.* (2008) reported that addition of hyaluronidase in bupivacaine can reduce the onset of analgesia.

Runa *et al.* (2008) studied the effects of 0.5% bupivacaine HCl on high epidural analgesia in Black Bengal goats alongwith adrenaline, ketamine and diazepam. Bupivacaine HCl significantly decreased respiration rate, rectal temperature. However, there was increased heart rate during high epidural analgesia with prolonged analgesia compared to other drugs.

Dadafarid and Najafpour (2008) evaluated the effects of bupivacaine, ketamine and combination of bupivacaine and ketamine after lumbosacral epidural analgesia in sheep. The onset of analgesia was significantly faster in combination than that in aline. The heart rate increased significantly with bupivacaine at 15 and 20 minutes and respiratory rate showed a significant decrease with ketamine.

Singh *et al.* (2009) concluded that bupivacaine prolongs the extradural analgesia produced by xylazine in buffaloes.

Dhage and Pawshe (2010) used bupivacaine, ketamine and xylazine in three groups of goats and concluded, that respiration rate was significantly decreased in the animals of xylazine group.

Kalim *et al.* (2010) documented that lumbar epidural administration of bupivacaine alone and in combination with medetomidine and fentanyl produces complete analgesia of inguinal, perineum, hind limbs and tail in buffalo calves.

Rao *et al.* (2010) determined the obstetric outcome in terms of duration of labour and mode of delivery between the walking epidural analgesia with 0.1% bupivacaine and 0.5% tramadol and observed markedly reduced duration of labour in humans.

Sonwane *et al.* (2010) reported significant increase in heart rate and respiration rate after lumbar epidural administration of bupivacaine and ketamine combination in buffalo calves.

Ahmad *et al.* (2011) compared the epidural analgesia by bupivacaine (1.7 mg/kg b.wt. Gropup I), ropivacaine (0.6 mg/kg b.wt. Group II) and ropivacaine-xylazine combination (0.6 mg/kg and 0.5 mg/kg bwt.Group III) in goats. The onset of analgesia was faster in ropivacaine-xylazine combination whereas ropivacaine induced longer duration of analgesia. The respiratory and pulse rates and rectal temperature decresed siginificantly in group I and III and were non significantly in group II.

2.5 DETOMIDINE HYDROCHLORIDE: (Alpha -2-agonist)

Detomidine [4(5)-(2, 3-dimethyl benzyl) imidazole hydrochloride] is a new veterinary analgesic and sedative compound. It is a weakly basic and lipophilic in nature, which induces its effect via stimulation of central α-2 adreno receptors (Virtanen *et al*., 1985). Detomidine gets rapidly distributed after parenteral administration. Salonen (1986) studied the pharmacokinetics of detomidine and reported that rapid onset and short duration of action of the drug might be due to rapid redistribution in the body. The maximal concentration was achieved after 0.16 hour in mouse (Ruckebusch *et al*., 1983), 0.5 hour in horse

and 0.26 hour in cattle .The drug is eliminated mainly through the urine, and also in traces in faeces (Salonen,1986).

Ruckebusch *et al*. (1983) observed sedative and analgesic effects after administration of detomidine at the dose rate of 18-20µg/ kg were similar in horse and cattle.

Vainio (1985a) studied the sedative and analgesic effects of detomidine in 103 cattle @ 10-30 µg/kg by I.V. or I.M. injection and performed minor operations like correction of teat stenosis, suturing and radiography. The heart rate and respiratory rate showed a decreasing trend while the rectal temperature remained unaffected. The drug was found to be useful as a sedative.

Jedruch and Gajewski (1986) evaluated the sedative effect of detomidine (@ 50 µg/ kg) in 14 cows in there last trimester of pregnancy. All the cows gave normal birth with no embryonic mortality.

Koichev *et al.* (1988) reported that after I/M detomidine adminstration @ 100 µg/kg b. wt. in sheep and cattle showed a non significant decrease in haemoglobin, total erythrocyte count and packed cell volume and non significant increase in erythrocyte sedimentation rate, and non significant changes in the white blood cell count and also the motility of rumen and reticulum was also greatly affected in cattle.

Romvary *et al.* (1989) assessed the clinical efficacy of detomidine at the dose rate of 20, 40, and 80 µg/ kg b.wt. I.V. as well as I.M. in 45 cattle and reported the duration of sedative, analgesic state ranging from 30 to 120 minutes depending upon the dose. In combination with methadone (@ 0.1-0.2 mg/kg b. wt.) deep sedation and strong analgesic state for 2 hours was achieved.

Skarda (1991) used detomidine @ 60 µg/ kg b.wt. diluted to 10 ml with sterile saline solution through caudal epidural space in 8 mares and reported analgesia of 100.86 ± 10.24 minutes of abdomino-pelvic region with marked sedation, ataxia and cardiopulmonary depression. The degree and duration of analgesia were variable.

Peshin *et al*. (1991) evaluated the sedative effects of detomidine in infant calves at the dose rate of 10, 20, and 40 µg/ kg b.wt I.M. and reported dose dependent sedation. At a dose of 10 µg/ kg, detomidine produced excellent sedation for 30 to 45 minutes without any observable analgesia; @ 20 or 40 µg/ kg, it caused deep sedation, sternal recumbancy and moderate analgesia of trunk.

Sabas *et al*. (1991) performed clinical examination of the painful udders in 38 cows and suturing of wounds using local anaesthesia after intravenous administration of detomidine @ 20-40 µg/ kg b.wt.

Chandrashekhar (1993) also reported non significant changes in haemoglobin, total erythrocyte count, packed cell volume, total leucocyte count and differential leucocytes count during various phases of induced estrus cycle in sheep after intravenous detomidine administration. A non significant change in haemoglobin and packed cell volume after I.V. or I.M. detomidine at 30, 60, and 90 µg/ kg was also been reported in sheep.

Skarda and Muir (1994) induced epidural or subarachnoid analgesia by detomidine hydrochloride @ 30 to 60 µg/ kg b.wt. in 8 adult mares through an indwelling catheter. The maximum analgesia by both the treatments i.e. 30 or 60 µg/ kg detomidine extended from coccygeal to spinal cord segments T15 and T14 at 10 to 25 minutes after epidural and subarachnoid drug administration.

Analgesia at perineal area lasted longer after epidural than after subarachnoid administration (142.80 ± 28.8 minutes vs 127.1 ± 27.7 minutes); however, all mares remained standing.

Kumar *et al.* (1997) assessed the haematological and biochemical changes induced during xylazine and detomidine sedation in goats and found that significant decrease is produced in Hb, PCV and TLC during maximum depth of sedation, however, neutrophilia with relative lymphocytopaenia were observed with either of the sedatives. Hyperglycemia was the only constant finding among biochemical parameters (Albumin, BUN, Creatinine, Na, K, Cl) which were non-significant indicating that it had no harmful effect on liver, kidney, and electrolyte balance.

Singh *et al.* (1997) used detomidine (@ 20 and 40 μg /kg b.wt.) for epidural anaesthesia in dogs and recorded a significant decrease in heart rate and respiratory rate with non-significant decrease in body temperature.

Tiwari *et al.* (1998) evaluated the epidural use of xylazine and detomidine with and without local anaesthetics in buffaloes and found that heart and respiration rates were significantly decreased between 5 and 120 mins after there administration.

Tiwari *et al*. (1999a) studied the haematological and biochemical changes in response to epidural administration of xylazine and detomidine with or without local anaesthetic in buffalo calves and found that haemoglobin, PCV and TEC decreased significantly ($P<0.05$) between 0.5 to2 hours however, ESR showed a significant ($P<0.01$) increase between 0.50 to 2 hours. TLC count showed a slight increase between 0.25 to 1 hour in all treatment groups. Serum glucose

concentration and serum urea nitrogen showed a significant ($P<0.01$) increase from 0.25 to 6 hours in various groups of animals. Serum sodium showed significant ($P<0.01$) increase and potassium showed a corresponding significant ($P<0.01$) decrease between 0.25 to 1 hour in all the treatment groups. Enzymes viz., AST, ALT and alkaline phosphatase showed a non-significant ($P>0.05$) increase in all the groups of animals.

Tiwari *et al*. (1999c) investigated the clinico surgical effects of epidural Xylazine and Detomidine with or without local anaesthetics in buffaloes and found that animals after the onset of sedation /analgesia showed marked sedation, drooping of head, ptosis of lower eyelids, salivation, recumbency, suppression of palpebral reflexes, ruminal stasis, marked diuresis and moaning during the sedation / analgesia period. They finally concluded that Xylazine or Detomidine with local anaesthetics i.e. Lignocaine HCl / Bupivacaine HCl produced complete analgesia of abdomino-pelvic region with rapid onset and longer duration of analgesia.

Abdin (2001) reported after intravenous administration of the alpha 2 agonist detomidine hydrochloride @ 80 µg /kg b.wt in camels, an immediate increase in plasma concentration of glucose and non-esterified fatty acids, was recorded followed by delayed increase in cortisol and 2-deoxycortisol concentrations. The concentration of protein, aspartate aminotransferase, lactic dehydrogenase and creatinekinase remained within physiological limits. It was concluded that detomidine is safe for use in the camel.

Varshney *et al*. (2001) evaluated the analgesic effects of epidural detomidine with and without lignocaine in equines. Eight adult donkeys (140-175

kg b. wt.) were randomly divided into 2 groups of equal numbers. In group I ,detomidine (@ 50µg /kg) was administered , while animal of group II, received a combination of detomidine (@ 50µg /kg) and lignocaine hydrochloride(@ 0.22 mg/ kg). The drugs were diluted with normal saline upto a volume of 4ml prior to epidural administration at the intercoccygeal space. Heart rate was decreased in groups I and II until 60 and 90 minutes respectively. No significant changes were found in the respiratory rate and rectal temperature. The onset of analgesia occurred at 3.75 ± 0.32 and 2.12 ± 0.24 min. and lasted for 110.75 ± 4.97 and 133.75 ± 3.43 min. after drug administration in groups I and II, respectively.

Khan (2003) carried out clinicobiochemical studies on detomidine analgesia and effects of its combination on animals. Clinical trials have proved that detomindine a novel sedative and analgesic is a drug of choice for restraining, examination, and minor and major surgical manipulations on equine, bovine, caprine, ovine and canine species without any untoward effects.

Khan *et al*. (2004) carried out a study on 60 healthy rams and male goats presented for castration. The weight of the animals ranged between 25 and 50 kg and age between 3 and 6 months. The animals were divided into three groups A, B and C, with 20 animals in each group. In group A, castration was performed under detomidine sedation injected at a dose rate of 50 µg/kg body weight intramuscularly. In group B, xylazine was administered at a dose rate of 200 µg/kg body weight intramuscularly. In group C, castration was performed without the use of any sedative agent. From this study it was concluded that detomidine and xylazine produced similar sedative effects but the analgesia was considerably better with the detomidine.

Kariman (2005) evaluated the analgesic effect of detomidine hydrochloride administered by caudal epidural injection on 10 healthy adult Holstein cows. Detomidine, 0.04 mg/ kg (diluted to 5ml normal saline), was injected to the sacro-coccygeal epidural space of the cows. Despite the deep sedation, massive salivation and mild ataxia of the hind limbs, moderate analgesia occurred in perineal region. No ruminal movements were observed after injection. The heart and respiratory rates significantly decreased. However, the rectal temperature was not affected by detomidine. The results of this experiments showed that the epidural injection of detomidine is safe.

Mpanduji *et al*. (2007) recorded analgesia, heart and respiration rates and rectal temperature values after lumbosacral epidural injection of three doses (20, 40 and 80 mg/kg) of detomidine in Small East African goats. All three doses induced adequate analgesia of the flank and perineum within 5 minutes, and persisted for the entire 180 minutes of the observation period. All doses induced significant drop of the mean respiration rate (RR) within 5 to 10 minutes. Significant drop of the mean heart rate (HR) was observed only for the two lower doses of 20 and 40 mg/kg and persisted for 120 and 90 minutes respectively. All three doses induced a considerable rise in rectal temperature (RT) values that was followed by a gradual fall to normal. Two to four fold increase in the dose of detomidine administered through the lumbosacral epidural space does not increase the level and duration of the flank and perineal analgesia in Small East African goats.

Shah (2008) performed comparative studies on sedative and physiological effects of xylazine, detomidine and medetomidine at dose rates of 0.1 mg/kg, 50

pg/kg and 6 lig/kg IV in goats. The pulse and respiratory rate significantly decreased while blood glucose level increased. The duration of sedation was significantly longer with detomidine when compared with xylazine and medetomidine. The onset and duration of analgesia was significantly longer with xylazine than detomidine.

Fischer *et al.* (2009) found that Detomidine @ 0.15 mg /Kg injected epidurally in combination with morphine 90.2 mg /kg) and buprenorphine (0.005 mg / kg) separately in horses undergoing bilateral stifle arthroscopy, produced analgesia similar in intensity and duration.

Sonawane *et al.* (2009) evaluated the efficacy of bupivacaine alone and in combination with detomidine for lumbar epidural analgesia in buffalo calves. The onset of analgesia was earlier as well as the duration of analgesia with recovery time was significantly longer in calves treated with bupivacaine in combination with detomidine

Virgin *et al.* (2010) observed that mares sedated with a continuous IV infusion of detomidine have similar hormonal and behavioral responses to painful stimuli during standing laparoscopic ovariectomy as mares sedated with caudal epidural detomidine. So, sedation using a continuous IV infusion of detomidine can be used for laparoscopic ovariectomy in mares.

2.6 TRAMADOL HYDROCHLORIDE :-

Tramadol is a centrally acting analgesic agent with activity at μ-opioid, adrenergic and 5-hydroxytryptamine (5-HT) receptors. Its analgesic effect is a result of its dual mechanism of action that is, as a re-uptake inhibitor of

norepinephrine and serotonin and agonist of the μ-opioid receptor (Ide *et al.*, 2006). Tramadol has been in clinical use for the relief of mild to moderate pain in human and veterinary medicine (Mastrocinque and Fantoni, 2003; Pypendop and Ilkiw, 2008). Tramadol is also used perioperatively in veterinary anaesthesia as it significantly reduces the requirements of volatile anesthetics and opioid agents (Wordliczek *et al.*, 2002; Seddighi *et al.*, 2009). Transdermal delivery is a new modality of administration of tramadol offering a dual additional opportunity over all its well-known advantages. Tramadol premedication has minimal effects on hemodynamics and respiratory function during anesthesia (Mastrocinque and Fantoni, 2003; McMillan *et al.*, 2008; Seddighi *et al.*, 2009).

Dogs given tramadol premedication showed no significant changes in blood pressure, heart rate, arterial blood gases and pH during isoflurane anesthesia (Mastrocinque and Fantoni, 2003). The higher dose of tramadol resulted in higher and more sustained tramadol plasma concentration (McMillan *et al.*, 2008). Although tramadol has relatively effective analgesic effects, a higher tramadol infusion rate was needed to reduce sevoflurane requirements in dogs (Seddighi *et al.*, 2009).

Lee *et al.* (1993***)*** reported that tramadol can be administrated orally, rectally, intravenously or intramuscularly, and it is principally metabolized in the liver and 90% of it is excreted in urine.

Claudio and Robinson (2000) suggested epidural administration of tramadol and morphine induces long-lasting analgesia in healthy adult horses. Epidural

administration of opiods may provide long-lasting analgesia in horses without excitation of the CNS.

Sandra and Denise (2003) concluded that morphine and tramadol @ 0.2 mg/kg iv administered pre-emptively can be used safely in dogs to control early pain after ovariohysterectomy without significant adverse effects.

Nagaria and Acharya (2006) assessed the efficacy and safety of intramuscular tramadol hydrochloride as an analgesic during labor compared to those of pentazocine. Pain relief was satisfactory in 37% vs 14% ($P<0.002$), moderate 38% vs 34% ($P=0.63$) and mild 16% vs 42% ($P <0.006$) in the tramadol and pentazocine groups respectively.It also significantly shortens the duration of labour.

Dhimar *et al.* (2007) investigated the effect of tramadol and pethidine for control of shivering in 60 human patients. Patients received Tramadol or Pethidine in a dose of 1mg/kg- I.V after the appearance of shivering. Onset of disappearance of shivering was found at 1 minute in Tramadol group (T)($p < 0.05$) and at 3 minutes in Pethidine group (P)($p < 0.05$). The complete disappearance of shivering took 5 minutes in T group while 20 minutes in P group. It was concluded that I.V Tramadol is qualitatively superior to Pethidine for control of shivering.

De Sousa *et al.* (2007) studied the Pharmacokinetics of tramadol and *o*-desmethyltramadol in goats after intravenous and oral administration. The systemic availability was $36.9 \pm 9.1\%$ and half-life 2.67 ± 0.54 h following

tramadol 2 mg/kg orally. Metabolite had a half-life of 2.89 ± 0.43 h following intravenous administration of tramadol.

Natalini *et al*. (2007) reported the effects of morphine 91 mg/kg I/M) or tramadol (1 mg /kg I/M) on thiopental anaesthetic induction dosage and physiologic variables in halothane anesthetized dogs. Tramadol produced no visible sedation and no vomit, while morphine induced a moderate degree of sedation in all dogs and vomition in 62% of them. Clinically, tramadol may be useful for premedication of dogs where vomition is undesirable.

Raina *et al.* (2008) studied the effects of tramadol on ECG, mean electrical axis and respiratory rates in adult kagani goats after intramuscular administration @ 1 mg/ Kg body wt. Except significant reduction in T-wave amplitude at 0.5 h, no other significant changes were observed. The mean electrical axis (56.74) before treatment did not show significant differences up to 3hr of post treatment. No significant change on respiration was observed up to 3hr. post treatment.

Raghuvanshi (2008) concluded that epidural administration of bupivacaine – tramadol combination prolongs the duration of analgesia and causes less alteration in clinical and haemato-biochemical parameters in dog.

Khooshideh and Ali (2009) emphasized that tramadol is a synthetic analog of codeine and a weak opioid agonist, acting centrally by modifying transmission of pain impulse by altering mono amine reuptake mechanisms .

Vettorato *et al.* (2009) reported that intravenous and epidural administration of tramadol (2mg/kg) in dogs undergoing soft tissue and orthopedic surgery provided effective post-operative analgesia.

Vullo (2009) studied the effects and tolerability of endovenous administered tramadol in horses. Following IV administration at 1mg/kg , it was well tolerated without any adverse effects. Few side effects like muscle twitching were observed following administration at dose rate of 2 mg/kg intravenously.

Bandiadam *et al*. (2010) concluded that, there is no significant change in heart rate, respiration rate, temperature and in rumen motility after caudal epidural administration of tramadol in cattle and it induces analgesia with slight to mild sedation and ataxia in cows. Analgesia in affected regions after administration of 2 or 3 mg/kg was considered sufficient to allow common surgical procedures to be performed in standing cattle.

Habibian *et al.* (2010) recorded the onset and duration of aneasthesia produced by tramadol and lignocaine – tramadol combination with that of lignocaine in epidural space of lamb.The tramadol produced a significantly ($P < 0.05$) longer duration of analgesia than lidocaine alone and lidocaine–tramadol combination. Also, lidocaine–tramadol combination produced a significant ($P < 0.05$) longer duration of analgesia than lidocaine alone. Complete analgesia was more delayed in the tramadol treatment than lidocaine–tramadol and lidocaine alone.

CHAPTER III

MATERIALS AND METHODS

3.1 EXPERIMENTAL ANIMALS

Fifteen clinically healthy non-descript, goats ranging from 1 to 2 years of age and 15 to 25 kg of body weight were used in this study. All the animals were dewormed with albendazole[1] @ 7.5mg /kg body weight orally one month before the start of experiment. The animals were stall-fed, provided with clean drinking water, and maintained under uniform managemental conditions throughout the period of observation.

During pre-experimental observation period, the clinical status of animal was assessed by recording heart rate, respiratory rate, rectal temperature and by conducting haematological examination. The animals were kept off-fed for 12 hours and water was withheld for 6 hours prior to the start of the experiment.

3.2 EXPERIMENTAL DESIGN

All the fifteen animals were subjected to the following three treatments. An interval of five days was kept between each treatment. Various drugs and their doses used for lumbar epidural analgesia in different treatment groups are presented in the form of table No. 1.

[1] Albomar: Glindia Ltd. Mumbai.

S.No.	Groups	No. of Replicates	Drugs	Dosage (per kg body-weight)
1	**N1**	**5**	**Bupivacaine[2] (0.5%) (5 mg/ml)**	**1 mg/kg body weight**
2	**N2**	**5**	**Bupivacaine (0.5%) + Detomidine[3] (1 mg/ml)**	**1 mg/ kg + 30μg/kg body weight**
3	**N3**	**5**	**Bupivacaine (0.5%) + Tramadol[4] (50 mg/ml)**	**1 mg/ kg + 2 mg/kg body weight**

GROUP N1 : Bupivacaine[2] (0.5%) 1 mg/kg body weight were given epidurally.

GROUP N2 : Bupivacaine[2] (0.5%) + Detomidine[3] 1 mg/ kg + 30μg/kg body weight were given epidurally.

GROUP N3 : Bupivacaine[2] (0.5%) + Tramadol[4] 1 mg/ kg + 2 mg/kg body weight were given epidurally.

The volume of the drug injected was 6 ml in all the groups after reconstituting with distilled water. The dose of different drugs were computed on the basis of the pilot trials conducted prior to the start of the experiment and by screening literature.

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[2] Anawin*: Neon Laboratories Ltd. Mumbai.
[3] Zyrotram*50:Troikaa Pharma Ltd. Dehradun.
[4] Domosedon: Orion Corporation FARMOS Finland.

3.3 EPIDURAL INJECTION

The animals were restrained in standing position. The lumbar region was clipped, shaved and painted with povidone iodine solution. A 18 gauge, spinal needle was used for lumbar epidural injection. The needle was directed at a 90° angle to the spinal cord along the median plane and was slowly advanced until the lumbar epidural space was reached after penetrating the interarcuate ligament, when the résistance to injection of drug was abolished the drug was injected. All the animals received the drug(s) as per the dose rate, given in the table. All the treatments were evaluated and compared on the basis of following observations.

3.4 PARAMETERS TO BE STUDIED

3.4.1 CLINICAL PARAMETERS: -

Clinical observations were recorded included recording of onset of analgesia, depth of analgesia, area of desensitization, motor incoordination, sedation and salivation before and at 10, 20, 30, 45, 60, 75, 90, 120, 180 and 240 minutes after injection.

(i) Onset of analgesia : - After epidural injection of drug(s), response to pin-prick was recorded at every 15 seconds at flank /abdominal region till the loss of sensation. Time from injection to loss of sensation at flank /abdominal region was considered as time of onset of analgesia.

(ii) Depth of analgesia and area of desensitization :- Depth of analgesia and area of desensitization was recorded at flank, inguinal region, hind limbs,

perineum and tail by observing response to pinpricks at a particular region were graded on a 0 to 3 score scale.

0: No analgesia - Strong reaction to pin pricks.

1: Mild analgesia -Weak response to pin pricks.

2: Moderate analgesia - Occasional response to pin pricks.

3: Strong/ complete analgesia - No response to pin pricks.

(iii) Motor in co-ordination:

Motor incoordination was graded on a 0 to 4 score scale as given below:

0 - Walking without staggering.

1 - Able to stand but walks with little incoordination.

2 - Able to stand but walks with extreme incoordination.

3 - Sternal recumbency but animal is able to flex and extend the limbs if disturbed.

4 - Sternal recumbency and animal is unable to flex or extend its limbs.

(iv) Duration of analgesia: Time from loss of sensation from any region to return of sensation at all the sites was considered as duration of analgesia.

(v) Recovery: All the animals was observed for their standing recovery i.e. time taken for standing, alert and walking without support.

3.4.2 PHYSIOLOGICAL PARAMETERS

(i) Heart-rate (per minute), respiratory rate (per minute) and rectal temperature (^{O}F) were recorded before and at 10, 20, 30, 45, 60, 75, 90, 120, 180 and 240 minutes after injection of drug(s).

(ii) Ruminal movements: Ruminal movements (per 2 min) were recorded at every 30 minutes from paralumbar fossa after the injection of drug(s) upto full recovery and 24 hours after the injection.

(iii) Salivation: It's onset, persistency and cessation was recorded.

3.4.3 HAEMATOLOGICAL PARAMETERS

The blood samples (2ml) were collected in clean dry vials containing EDTA before and at 30, 60, 120, 180 and 240 minutes after injection of drug(s) and were subjected to the estimation of following parameters as per the standard methods as described by Jain (1986).

(i) Haemoglobin (Hb) : The concentration of haemoglobin was estimated by using 0.1N HCL with help of Sahli`s haemoglobinometer. The values were expressed in gm%.

(ii) Packed cell volume (PCV): The packed cell volume was determined by the microhaematocrit method using microcentrifuge at the speed of 10,000 rpm for 5 minutes. The values were expressed in percentage.

(iii) Total leucocyte count (TLC): The total leucocyte count was determined on Neubauer`s chamber using WBC diluting fluid. The results were expressed in thousand cell/cu.mm of blood.

(iv) Differential leucocyte count (DLC): The blood smears were prepared immediately after the blood collection. The smears were fixed in methanol for 1 minute and were stained with Geimsa stain for 30 minutes. The counts were expressed in percentage.

3.4.4 BIOCHEMICAL PARAMETERS

Blood samples (3 ml) were collected in dry test tube before and at 30, 60, 120, 180 and 240 minutes Serum was separated to estimate the biochemical parameters. These parameters were estimated by standard procedures and by using semi-automated analyzer (Logotech teckno-168).

The parameters estimated were as follows:-

(i) Serum glucose (mg/dl)

(ii) Serum total protein (gm/dl)

(iii) Serum urea nitrogen (mg/dl)

(iv) Serum creatinine (mg/dl)

(v) Aspartate Aminotransferase (AST) (U/L)

(vi) Alanine Aminotransferase (ALT) (U/L)

3.5 STATISTICAL ANALYSIS

Mean and standard deviation, standard error and coefficient of variation were calculated using the standard statistical formulae. The data collected by using different combination of anaesthetic drugs in different group of animals were analyzed using Completely Randomized Design (CRD) as described by Snedecor and Cochran (1967).

CHAPTER IV

RESULTS AND DISCUSSION

4.1 CLINICAL OBSERVATIONS

4.1.1 Onset of Analgesia

Mean (±SE) values for onset of analgesia (min) in animals of different groups are represented in table No. 2 and shown in Fig. 1

Animals of group N1 (bupivacaine alone) showed a delayed onset of analgesia at 7.93 ± 0.14 min in comparison to animals of group N2 (bupivacaine in combination with detomidine) 5.08 ± 0.13 min, which was significantly ($P<0.05$) less. In animals of group N3 the onset of analgesia was 6.92 ± 0.17 min where bupivacaine with tramadol combination was used.

4.1.2 Depth of analgesia and area of desensitization

Depth of analgesia and area of desensitization were recorded at thorax, flank, inguinal region, hind limbs, perineum and tail by observing response to pin pricks at a particular region and were graded on a 0 to 3 score scale. Score less than 1 was considered as very mild , between 1 and 2 as mild, between 2 and 3 as moderate and 3 as strong / complete analgesia at a particular region.

For measuring the depth of analgesia, many scoring methods have been devised and used to clinically assess the depth of analgesia by recording response to noxious stimuli in experimental animals by various workers (Aithal *et al*., 1996; Amarpal *et al.*, 2001). A similar scoring method as reported by Amarpal *et*

al. (2001) was used for the assessment of analgesia in the present study which was found quite effective and simple in assessing the depth of analgesia at different sites.

4.1.2.1 Flank

Mean (±SE) score for analgesia at flank region in animals of different groups are represented in table No. 3 and shown in Fig. 2

Bupivacaine alone (group N1), induced very mild to moderate analgesia between 20 to 120 min interval. Animals of group N3 (bupivacaine with tramadol) showed very mild analgesia at 10 min, which gradually increased to moderate level between 30 to 60 min. Thereafter, mild level of analgesia was recorded upto 180 min. Bupivacaine in combination with detomidine (group N2) produced an early onset and longer duration of complete analgesia (30 to 75 min post injection), and moderate analgesia persisted till the 180 min of observation. These observation simulate with the findings of Mpanduji (2007) following the use of detomidine as epidural anaesthesia in small African goats.

Comparison among different groups showed that the combination of bupivacaine with detomidine (group N2) had induced deeper analgesia upto 75 min in comparison to group N1 (bupivacaine alone) and group N3 (bupivacaine with tramadol).

4.1.2.2 Inguinal region

Mean (±SE) score for analgesia at inguinal region in animals of different groups are represented in table No. 4 and shown in Fig. 3

Animals of group N1 (bupivacaine alone) showed very mild degree of analgesia at 10 min post injection, which became mild upto 120 min. of observation with peak effect between 45 to 75 min. Animals of group N3 (bupivacaine with tramadol) induced very mild to mild analgesia from 10 to 30 min interval and moderate analgesia from 45 to 75 min interval. Later on mild analgesia persisted till the 180 min. of observation. Animals of group N2 (bupivacaine with detomidine) induced very mild to mild analgesia from 10 to 20 min interval and moderate analgesia from 30 to 90 min interval. Further mild analgesia persisted till the 180 min. of observation. However, bupivacaine with detomidine (group N2) could produce deeper analgesia upto 60 min in comparison to bupivacaine alone (group N1) and bupivacaine with tramadol (group N3).

4.1.2.3 Hind limbs

Mean (±SE) score for analgesia at hind limbs in animals of different groups are represented in table No. 5 and shown in Fig. 4

Animals of group N1 (bupivacaine alone) showed a very mild analgesia at 10 min post injection. Thereafter, mild analgesia which was maintained at 20 min interval persisted till the 180 min. of observation with peak effect from 45 to 60 min interval. and group N3 (bupivacaine with tramadol) showed a very mild analgesia at 10 to 20 min post injection. Thereafter, moderate analgesia which was at 30 to 90 min interval persisted till the 180 min. of observation with peak effect from 45 min interval. Bupivacaine in combination with detomidine (group N2) showed very mild to mild analgesia from 10 to 20 min interval which became

moderate from 30 to 45 min. Analgesia was then depressed and became mild till the 180 min of observation.

Comparison among different groups showed that the combination of bupivacaine with detomidine (group N2) could produce early onset and deeper analgesia from 60 to 75 min in comparison to bupivacaine alone (group N1) and bupivacaine with tramadol (group N3). Comparison among goats of group N1 and N3 revealed that analgesia was deeper in animals of group N2 as compared to other two groups between 20 to 60 min interval.

4.1.2.4 Perineum

Mean (±SE) score for analgesia at perineum in animals of different groups are represented in table No. 6 and shown in Fig. 5

Animals of group N1 (bupivacaine alone) and group N3 (bupivacaine with tramadol) showed a very mild to moderate analgesia from 10 to 120 min to the end 180 min. of observations with peak effect from 45 to 60 min interval and group N3 (bupivacaine with tramadol) the analgesia was mild from 10 to 20 min, mild to moderate between 20 to 75 min till the end of 180 min. of observations with peak effect from 30 to 75 min interval. Bupivacaine in combination with detomidine (group N2) induced mild analgesia at 10 min interval, which gradually increased and reached peak from 30 to 90 min and later on became mild till the 180min. of observations.

Comparison among different groups revealed that animals of group N2 showed deeper analgesia from 30 to 45 min as compared to group N1 and group N3.

4.1.2.5 Tail

Mean (±SE) score for analgesia at tail in animals of different groups are represented in table No. 7 and shown in Fig. 6

Animals of group N1 (bupivacaine alone) showed very mild to mild analgesia between 10 to 90 min interval post injection. Thereafter, no analgesia was observed till the end of observation. Bupivacaine with tramadol (group N3) showed very mild to mild analgesia between 10 to 180 min interval post injection. Thereafter, no analgesia was observed till the end of observation. and bupivacaine with detomidine (group N2) showed very mild to mild analgesia from 10 to 20 min till the end of observations with its peak effect from 45 to 60 min interval.

Comparison among different groups showed that the combination of bupivacaine with detomidine (group N2) had induced deeper analgesia in comparison to group N1 and N3.

Analgesia of different depth extending from flank, inguinal, hind limbs, perineum and tail were recorded in all the groups. Bupivacaine produced moderate analgesia at flank, inguinal, hind limbs, perineum and tail. Local anaesthetic drugs, if applied locally to nervous tissue or injected spinally in effective concentration, block conduction of impulses from the receptors to the cortex of brain (Booth, 1988). Principle sites of local anaesthetic drugs after

epidural injection are spinal nerves that are blocked distal to the dural sheaths after leaving the intervertebral foramina, producing a multiple paravertebral block (Buchholz and Koener, 1948), dura covered spinal nerve roots within the spinal canal (Saeker and Gaida, 1995) and the neurons (Bromage, 1962). The results of the present study are in conformity with the observations of Pratap *et al*. (2000a) who also reported mild to moderate analgesia of hind quarters after epidural administration of bupivacaine @ 1 mg/kg body wt. in goats.

Bupivacaine with detomidine induced complete analgesia of flank, inguinal and mild to moderate analgesia of hind limbs, perineum and tail. It was observed that detomidine induced deeper and prolonged analgesia. Longer duration of analgesia produced by alpha-2 agonists has been attributed to the fact that alpha-2 adrenoceptor agonists provide a local depot of the drug from where they are released slowly for a longer period of time (Nolan and Erhardt, 1990) . Depth of analgesia was considered sufficient to undertake surgery because animals were non reactive to deep pin pricking at the time of peak effect. It is well known that alpha-2 agonists induce analgesia by stimulating pre and postsynaptic alpha-2 receptors at various sites in the pain pathways at the spinal and supraspinal level (Vitranen, 1989). Since analgesia produced by alpha-2 adrenoceptor agonists in the present study was not generalized, it might have been resulted from inhibition of release of neurotransmitters (Kuraishi *et al*., 1985), decreased neuronal activity (Vainio, 1983) and inhibition of release of substance P (Grubb *et al*., 1993) at the level of substantia gelatinosa of dorsal horn of spinal cord. The alpha-2 agonists have induced regional anaesthesia after epidural administration in sheep (Eisenach *et al*., 1987) in goats (Aithal *et al*., 1996) in

cattle (Jean *et al*., 1990; Lin-huichu *et al*., 1998) and in buffaloes (Pankaj 1990; Pratap *et al*., 2001).

4.1.3 Motor Incoordination

Mean (±SE) score for analgesia at motor incoordination of hind limbs in animals of different groups are represented in table No. 8 and shown in Fig. 7

All the animals of bupivacaine alone (group N1) and bupivacaine with tramadol (group N3) were able to stand during the entire post injection period. However, a very mild incoordination was observed between 10 to 60 min interval. Thereafter, animals remained standing but walked with mild incoordination from 10 to 90 min interval. In animals of (group N2) where bupivacaine was used in combination with detomidine in goats were able to walk without staggering upto 10 min post injection. Thereafter, they were able to stand but walked with mild incoordination upto 20 min and then extreme incoordination from 45 to 75 min interval.

Comparison among different groups revealed that bupivacaine in combination with detomidine (group N2) showed higher score for motor incoordination during the 20 to 90 min interval as compared to group N1 and N3.

Animals of all the groups showed the signs of ataxia and motor incoordination. There was mild to moderate motor incoordination in few animals whereas others showed severe incoordination. Ataxia and motor incoordination recorded in animals of group N2 after the epidural administration of bupivacaine with detomidine could be correlated with the proposed local anaesthetic action on

spinal nerve root (LeBlanc *et al*., 1988). Butterworth and Strichatz (1993) reported that α-2 agonists tend to inhibit A δ and C fibers more potently (responsible for pain perception) than A alpha fibres (responsible for motor function and proprioception). Therefore, the analgesia was complete in the present study but motor incoordination was only partial and a higher dose of the drugs could have probably inhibited the fibers completely leading to recumbancy. Lin-Huichu *et al*. (1998) opined that ataxia caused by epidural detomidine was due to CNS effects. LeBlanc *et al*. (1988) reported that Bupivacaine caused blockade of motor fibers along with sensory fibers.

4.1.4 Sedation

Mean (± SE) score for sedation in animals of different groups are represented in table No. 9 and shown in Fig. 8

All the animals of group N1 (bupivacaine alone) did not show any signs of sedation during first 10 min post injection period. However, a very mild sedation was observed between 20-60 min interval and animals remained alert and standing during entire period of observations.

Bupivacaine with tramadol (group N3) produced a very mild sedation at 10 to 20 min interval which remained mild upto 120 min. of observation. Whereas, bupivacaine in combination with detomidine (group N2) produced very mild sedation from 10 to 30 min interval. There after, mild to moderate sedation was observed upto 180 min interval which gradually became mild at the end of observation.

Comparison among different groups revealed that the onset of sedation was earlier in group N2 animals as compared to group N1 and N3. Combination of bupivacaine with detomidine (group N2) showed higher scores for sedation throughout the period of observation in comparison to other groups.

Wide stance and extreme lowering of head was more common in the animals of group N2 as compared to animals of group N1 and N3. Sedation is a common side effect after spinal administration of α-2 receptor agonists and has been recorded after epidural administration of detomidine in cows (Lin-huichu *et al*., 1998), goats (Kinjavdeker.1998, Tunio, 2003 and Shah, 2008). Sedation in these animals might be attributed to the supraspinal effect of α-2 agonists following their systemic absorption from epidural space as suggested by Smith *et al*., (1992). Detomidine has greater potency and selectivity for α-2 adrenoceptors than xylazine. Evidence exists for central α-2 adrenoceptors mediated sedative and hypnotic activities of detomidine (Doze *et al*., 1989) and the predominant location in the brain is the locus coeruleus (Correa-sales *et al*., 1992) where nonadrenergic neurons are found in high concentration (Probst *et al.,* 1984). Many nerve pathways pass through this region and transmit impulses to the fore brain and limbic system and stimulation of α-2 adrenoceptors in this region hyperpolarizes the neurons, thereby inhibiting the transmission of impulses and producing sedation (Aghajanian and Vander maelen, 1982). Bupivacaine did not show any signs of sedation during the entire period of observation.

4.1.5 Salivation

Mean (±SE) score for salivation in animals of different groups have been represented in table No. 10 and shown in Fig. 9

All the animals of group N1 (bupivacaine alone) and (Bupivacaine with tramadol) group N3 did not show any signs of salivation at any time interval till the end of observation. (Bupivacaine in combination with detomidine) group N2 induced very mild to moderate salivation from 10 to 30 min post injection which became extremely significant ($P<0.01$) between 45 to 90 min interval. Thereafter, mild salivation persisted till the end of observation.

Comparison among different groups revealed that salivation was present in animals of group N2 after bupivacaine and detomidine administration whereas goats of group N1 (bupivacaine alone) and group N3 (Bupivacaine with tramadol) showed no salivation.

Alpha-2 agonists like xylazine has been reported to cause excessive salivation in ruminants due to decreased swallowing (Knight, 1980). Detomidine might have also caused salivation through a similar mechanism involving of CNS effects of α-2 adrenergic agonists leading to the increased salivation. Systemic effects of α-2 agonists like partially closed eyes and excessive flows of saliva were also recorded by Patel *et al*. (1996) in cattle and Lin-Huichu *et al*. (1998) in cows, in goats Shah (2008) Delayed salivation were observed with epidural administration of detomidine which might be due to delayed absorption of drug from the epidural space as also reported by Tiwari *et al*. (1999c) in buffaloes.

4.1.6 Duration of Analgesia

Mean (±SE) values for duration of analgesia (min) in animals of different groups are represented in table No. 2 and shown in Fig. 1

Animals of group N2 (bupivacaine with detomidine), showed significantly ($P<0.01$) longer duration of analgesia (164.20 ± 4.69 min) as compared to animals of group N1 injected with bupivacaine alone (90.00 ± 2.92 min).in goats. Adetunji *et al.* (2002) Duration of analgesia (112.80 ± 2.86 min) in animals of group N3 (bupivacaine with tramadol) was significantly ($P<0.01$) longer as compared to the goats of group N1.

Maximum duration of analgesia was recorded in animals of group N2 (bupivacaine with detomidine) followed by animals of group N3 and N2 respectively.

4.1.7 Complete recovery

Mean (±SE) values for complete recovery (min) in animals of different groups are represented in table no. 2 and shown in fig. 1

Animals of group N1 (bupivacaine alone), showed complete recovery at 124.80 ±3.92 min post injection period. Animals of group N2 (bupivacaine with detomidine) showed complete recovery at 200.32 ± 6.55 in post injection period. Animals of group N3 (bupivacaine with tramadol) showed complete recovery at 147.00 ± 4.08 min. Comparison among different groups revealed that bupivacaine with detomidine combination (group N2) showed a significantly ($P<0.01$) late recovery as compared to other two groups.

The early onset of analgesia in detomidine might be due to high lipophilicity (Vesal *et al*., 1996). Pratap *et al*. (2000a) also recorded slightly earlier onset of analgesia after epidural administration of detomidine in buffalo calves as compared to bupivacaine alone. The difference in the site of injection might be responsible for the difference in the time of onset of analgesia. (Fikes *et al*., 1989). Bupivacaine is a long acting local anaesthetic drug which produces analgesia at least twice as that of lignocaine (Hall, 1971).

4.2 PHYSIOLOGICAL OBSERVATIONS

4.2.1 Heart Rate (Beats/minute)

Mean (± SE) values of heart rate (HR) in different groups have been represented in table no. 11 and shown in fig. 10

In animals of group N1 (bupivacaine alone) and N2 (bupivacaine with tramadol), a significant ($P<0.05$) decrease in heart rate was recorded between 30 to 60 min interval of lumbar epidural injection. Heart rate however showed an increasing trend and returned to near preadministration level by end of observation. In animals of group N3 (bupivacaine with detomidine), a significant ($P<0.05$) decrease in heart rate was recorded after 10 min of lumbo sacral epidural injection which was highly significant ($P<0.01$) between 20 to 90 min interval. However, the values returned to near normal by 240 minutes.

Decrease in HR by bupivacaine alone might be due to paralysis of cardiac sympathetic fibers or a generalized decrease in the sympathetic activity (Lumb and Jones, 1984). Reduction in heart rate after epidural/spinal administration of

bupivacaine has been reported in sheep, (Lebeaux, 1975; Adams *et al*., 1977), goats (Tiwari *et al*., 1989b) and buffaloes (Hussain and Kumar, 1988).

A significant bradycardia was observed between 10 to 90 minutes with maximum decrease at 60 min after lumbar epidural injection of bupivacaine with detomidine (group B) animals and it was more pronounced in comparison to group A and C. The decrease in HR might be attributed to decreased sympathetic outflow from the CNS, inhibition of norepinephrine (NE) release from sympathetic nerve terminals, direct depression of cardiac pacemaker and conduction tissue, increased vagal tone and a direct increase in the release of acetylcholine from parasympathetic nerves in the heart (MacDonald and Virtanen, 1992), potential prejunctional ά 2-inhibition at cardiac pacemaker tissue (Raekallio, 1992) and involvement of baroreceptor reflex induced by ά 2 - adrenoceptor agonists (Sarazen *et al*., 1989).Similar findings were also reported after epidural administration of xylazine in cattle (Jean *et al.*, 1990, Skarda *et al*, 1990, Rehage *et al.*, 1994), in goat (Mpanduji *et al.* 2007 , Shah, 2008 and Ahmad *et al.* 2011).

4.2.2 Respiration Rate (Per minute)

Mean (±SE) values of respiration rate (RR) in animals of different groups are represented in table no. 12 and shown in fig. 11

In animals of group N1 (bupivacaine alone) and N3 (bupivacaine and tramadol combination), a significant decrease ($P<0.05$) in RR was observered from 20 to 60 min which returned to normal at the end of the observation. Animals of group N2 (bupivacaine and detomidine combination), showed a

significant (P<0.01) decrease from 20 min upto 90 min interval. Thereafter, it improved slightly but remained below the base value. The decrease in RR in this group N2 was early in comparison to the goats of group N1 and N3.

Respiratory rate (RR) decreased in all the treatment groups after epidural administration of drugs. The significant decrease in RR could be due to direct depressive effect of detomidine on CNS in general and respiratory center in particular (Tiwari *et al*., 1997) or might be due to hypoventilation, direct depression of the respiratory centre (Kumar and Thurmon, 1979) and decreased cardiac output (Campbell *et al*., 1979). The decrease in respiration rate might also be due to depression of the respiratory centre through stimulation of supraspinal adrenoreceptors following systemic absorption of the drugs as also reported by Lin *et al*. (1998) and Prado *et al*. (1999). Similar observations were also reported by (Mpanduji *et al.* 2007, Runa *et al.* 2008, Shah, 2008 and Ahmad *et al.* 2011,) in goats, Raidurg *et al*. (1993) in calves and Tiwari *et al*. (1999c) in buffaloes.

4.2.3 Rectal Temperature (˚F)

Mean (±SE) values of rectal temperature (RT) in animals of different are been represented in table no. 13 and shown in fig. 12

Rectal temperature showed a non significant decrease in all the three groups at various time intervals. The values ranged from 103.67±0.93 to 102.88 ±1.05 in group N1 , 102.96 ±0.90 to 101.56 ±1.24 in group N2, and 103.64 ±0.74 to 102.48± 0.86 in group N3. However all the values returned to normalcy by 240 min.

The animals of all three groups showed a non significant decrease RT. The decrease in rectal temperature in animals administered with bupivacaine might probably be due to the peripheral vasodilatation in area of block. This finding corroborates with the findings of Mishra *et al*. (1993a) in buffalo calves.

Alpha-2 agonists have been found to activate the hypothalamic- alpha-receptors inhibiting the heat conserving mechanism (Maskray *et al*., 1970). Reduced basal metabolic rate and muscle activities might have led to the production of less heat in the body on the one hand and depression of thermoregulation on the other hand which might have resulted in hypothermia in all the three group of animals. This simulates the findings of Nishimura *et al*. (1993), Tiwari *et al*. (1997) and Thompson and Kresting, (1991). Moreover, detomidine potentiates the effect of epidural anaesthetic (bupivacaine) and accelerates the heat loss through peripheral vasodilatation Similar changes in the body temperature were also recorded by Kinjavdeker *et al*. (1997), Amarpal *et al*. (1997) in calves, (Amarpal *et al*.,1998 Mpanduji *et al.* 2007, Shah, 2008 and Ahmad *et al.* 2011,) in goats, using alpha-2 agonists by various routes.

4.2.4 Ruminal Movements (per two min)

Mean (±SE) values of ruminal movements in animals of different groups are represented in table no. 14 and shown in fig. 13

Animals of group N1 (bupivacaine alone) and group N3 (bupivacaine and tramadol combination) showed a non significant decrease in ruminal movements upto 120 min post injection. Thereafter, the value returned to near normalcy by 360 min. The animals of group N2 (bupivacaine with detomidine) showed

significantly (P<0.05) decreased ruminal movements at 30 to 240 min post injection. However, the value returned to near preadministration level by 24 hrs.

The addition of bupivacaine with alpha-2 agonist (detomidine) further reduced ruminal movements. The decreased ruminal movements might be due to the phenomenon that alpha-2 agonists after quick absorption, gets bound to alpha-2 adrenergic receptors in the CNS and fore stomach muscles, thereby inhibiting reticulo-ruminal contractions as observed by Ruckebusch and Allal, (1987) after administration of alpha-2 agonist in cattle. Decreased ruminal movements were also been reported after epidural administration of detomidine in cows (Prado *et al*. 1999) in buffalo calves (Sonawane *et al.* 2009).

4.3 HAEMATOLOGICAL OBSERVATIONS

4.3.1 Haemoglobin (gm %)

Mean (± SE) values of haemogobin (Hb) in animals of different groups are represented in table No. 15 and shown in Fig. 14

The haemogobin level showed a non significantly decreasing trend from 30 to 60 min, which became significant (P<0.05) at 120 min interval in group N1 (bupivacaine alone) and group N3 (bupivacaine and tramadol combination) animals. However, in animals of group N2 (bupivacaine and detomidine combination), a significant (P<0.05) decrease in haemogobin was observed from 30 min which persisted upto 120 min interval. These values however, returned to near preadministration level by 24 hrs in all the three groups of animals.

Pooling of the circulating blood cells in the spleen or other reservoirs secondary to decreased sympathetic activity might be responsible for decrease in haemogobin as also reported by Soliman *et al*. (1965) after administration of tranquilizers in dog. The decrease in haemogobin during the period of anaesthesia or sedation might also be due to shifting of fluids from extravascular compartment to intravascular compartment in order to maintain normal cardiac output in the animals (Wagner *et al.,* 1991). Similar findings had also been reported after epidural administration of xylazine in cattle (Jean *et al*., (1990), and after epidural administration of detomidine in buffalo calves (Pratap *et al*., 2001), in sheep (Chandrashekhar , 1993).

4.3.2 Packed Cell Volume (%)

Mean (± SE) values of PCV in animals of different are represented in table no. 16 and shown in fig. 15

The PCV level showed a significant ($P<0.05$) decrease at 120 min interval in group N1 (bupivacaine alone), and group N3 (bupivacaine and tramadol combination) animals. However, in animals of group N2 (bupivacaine and detomidine combination), a significant ($P<0.05$) decrease in PCV was observed between 30 to 120 min interval. These values however, returned to near normalcy by 24 hrs in all the three groups of animals.

Pooling of the circulating blood cells in the spleen or other reservoirs secondary to decreased sympathetic activity could be the reasons for decrease in PCV as reported by Soliman *et al*. (1965) after administration of tranquillizers in dog. The decrease in PCV during the period of anaesthesia or sedation might also

be due to shifting of fluid from extravascular compartment to intravascular compartment in order to maintain normal cardiac output in the animal (Wagner *et al.,* 1991). Similar findings have also been reported after epidural administratin of xylazine in cattle (Jean *et al*., 1990), in sheep (Chandrashekhar, 1993).and after epidural administration of detomidine in buffalo calves (Pratap *et al*., 2001).

4.3.3 Total Leucocyte Count (x 10^3cumm^{-1})

Mean (± SE) values of total leucocyte count (TLC) in animals of different groups are represented in table No. 17 and shown in Fig. 16

The TLC showed a non significant decrease at various time intervals in animals of group N1 (bupivacaine alone), group N3 (bupivacaine and tramadol) and group N2 (bupivacaine and detomidine) following epidural anaesthesia respectively .These values however, returned to near preadministration level by 24 hrs in all the three groups of animals.

The decrease in TLC might be due to stress and release of ACTH on account of drug administration (Tiwari *et al*., 1996).The decrease in TLC during the period of anaesthesia or sedation might also be due to shifting of fluids from extravascular compartment to intravascular compartment in order to maintain normal cardiac output in the animal (Wagner *et al.,* 1991). Similar findings were also reported after epidural administration of xylazine in cattle (Jean *et al*., 1990), in sheep (Chandrashekhar 1993).and after epidural administration of detomidine in buffalo calves (Pratap *et al*., 2001).

4.3.4 Differential Leucocyte Count (%)

4.3.4.1 Neutrophils

Mean (± SE) values of neutrophils in animals of different groups are represented in table No. 18 and shown in Fig. 17

The animals of group N1 (bupivacaine alone) and group N3 (bupivacaine and tramadol combination), showed a non significantly increase in neutrophils count at 30 min which become at 60 min. Later on the values returned to normalcy by 24 hrs. Whereas in animals of group N3 (bupivacaine and detomidine combination), neutrophil count increased non significantly between 30 to 120 min interval. Thereafter, it returned to normalcy by 24 hrs.

A rise in neutrophils count might be attributed to the adrenocortical stimulation and subsequent effect of glucocorticoids (Soliman *et al.,* 1965) on circulating neutrophils. Similar observations were also made after administration of xylazine, ketamine and detomidine in goats (Hugar, 1993) ketamine and detomidine in goats (Dilip Kumar, 1993).

4.3.4.2 Lymphocytes

Mean (± SE) values of lymphocytes in animals of different groups are represented in table No. 19 and shown in Fig. 18

The animals of group N1 (bupivacaine alone) and group N3 (bupivacaine and tramadol) showed a non significantly decrease in lymphocytes count at 30 min interval whereas, the decrease was at 60 min interval. The lymphocytes count of group N2 (bupivacaine and detomidine), animals also decreased non

significantly between 30 to 60 min interval. Thereafter, the lymphocytes count increased gradually and returned to resting values within 24 hrs.

There was a corresponding lymphocytopaenia in response to neutrophilia in all the groups of animal after various treatments. A decrease in lymphocytes count might be attributed to the adrenocortical stimulation and subsequent effect of glucocorticoids (Soliman *et al.,* 1965) on circulating lymphocytes. Similar observations were also made after administration of xylazine, ketamine and detomidine in goats (Hugar, 1993) and ketamine and detomidine in goats (Dilip Kumar, 1993).

4.3.4.3 Monocytes

Mean (± SE) values of monocytes in animals of different groups are represented in table no. 20 and shown in Fig. 19

The animals of all the groups showed a non significant decrease in monocytes count from 30 to120 min interval. Thereafter, the monocytes count increased gradually and returned to resting values within 24 hrs in all the groups of animals.

This possibly could be attributed the adrenocortical stimulation and subsequent effect of glucocorticoids (Soliman *et al.,* 1965). Similar observations were made after administration of xylazine, ketamine and detomidine in goats (Hugar, 1993), ketamine and detomidine in goats (Dilip Kumar, 1993) and detomidine in cattle and sheep (Koichev *et al*., 1988).

4.3.4.4 Eosinophils

Mean (± SE) values of eosinophils in animals of different groups are represented in table No. 21 and shown in Fig. 20

The animals of all the groups showed a non significant increase in eosinophils count between 30 to 60 min. However, the values returned to resting values within end of study period.

Eosinophils showed a non significant increase in all the groups of animals after drug administration. This possibly could be attributed to the adrenocortical stimulation and subsequent effect of glucocorticoids (Soliman *et al.,* 1965). Similar observations were made after administration of xylazine, ketamine and detomidine in goats (Hugar, 1993), ketamine and detomidine in goats (Dilip Kumar, 1993) and detomidine in cattle and sheep (Koichev *et al*., 1988).

4.4 BIOCHEMICAL OBSERVATIONS

4.4.1 Serum Glucose (mg/dl)

Mean (±SE) values of serum glucose in animals of different groups are represented in table no. 22 and shown in fig. 21

Serum glucose level were increased in all the groups after epidural administration of drugs. In animals of group A (bupivacaine alone) and group C (bupivacaine with tramadol), there was a significant ($P<0.01$) increase in blood glucose level between 60 to 120 min interval. However, in group B (bupivacaine with detomidine), a significant ($P<0.01$) increase in blood glucose level was observed between 30 to 120 min. Thereafter, it was decreased and returned to

normal by end of study period. Increase in blood glucose level at 30 min interval was more pronounced in animals of group C as compared to group A .

The serum glucose concentration depends upon a wide variety of factors and the concentration at any time is the net result of the rate of entry and removal of glucose into the circulation (Kaneko, 1989). Hyperglycaemia might be due to increased concentration of adreno-cortical hormone in blood or increased sympathetic activity and suppression of microsomal enzymes (Thurmon *et al*., 1978) or increased glucose production in the liver in buffaloes.

Hyperglycaemia, which resulted after α-2 agonist administration has also been reported by Kumar and Singh, (1976) in cattle,. Alpha -2 agonist induced hyperglycaemia in cow has been reported to arise by the combination of increased hepatic glucose production and reduced plasma insulin concentration (Symonds and Mallinson, 1978). Hsu and Hummel, (1981) reported the α-2 agonist induced hyperglycaemia and hypoinsulinaemia might be mediated by α-adrenergic receptors possibly in beta-cells of pancreatic islets which inhibit the release of insulin. The present findings corroborates with the observations of (Balkishan, 1992 and Tiwari *et al*. 1999a) in buffalo calves, (Raidurg *et al*. 1993) in calves. and (Shah, 2008) in goats .

4.4.2 Serum Total Proteins (mg/dl)

Mean (± SE) values of total protein in animals of different groups are represented in table no. 23 and shown in Fig. 22

Total proteins showed a non significant decrease between 30 to 240 min in group N1 (bupivacaine alone) and group N3 (bupivacaine with tramadol). Then it

increased gradually and finally returned to the base value at 24 hrs. The combination of bupivacaine with detomidine (group N2) also showed a significant ($P<0.05$) decrease between 30 to 120 min. Then it increased gradually to return near the base value by 24 hrs.

This decrease in total proteins might be due to the increased levels of glucocorticoids, increased adrenal activity and increased protein turnover resulting in decreased plasma protein and albumin. Decrease in insulin levels might modify the general metabolism and impair protein synthesis (Schumann, 1990). Adrenal steroids also reduce the rate of protein synthesis by antagonizing the effect of insulin (Turner and Bagnara, 1976). Kumar and Thurmon, (1979) also reported a reduction in total proteins after xylazine administration in goats. (Singh *et al*. 1991b) also reported a reduction in total proteins after detomidine administration in buffaloes.

4.4.3 Serum Urea Nitrogen (mg/dl)

Mean (±SE) values of serum urea nitrogen (SUN) in animals of different groups are represented in table No. 24 and shown in Fig. 23

In animals of group N1 (bupivacaine alone) and group N3 (bupivacaine with tramadol) a non significant increase in serum urea nitrogen between 30 min to 120 min was observed. Then it decreased gradually and finally returned to base value by 24 hrs. The combination of bupivacaine with detomidine (group N2) also showed a significant increase ($P<0.05$) between 30 to 120 min interval. which decreased and returned to normal values by end of study period.

The increase in serum urea nitrogen might be attributed to the temporary inhibitory effect of drugs on renal blood flow, which in turn might have caused a rise in serum urea nitrogen (Kinjavdekar, 1998) in goats. Increased hepatic urea production from amino acid degradation could also account for the observed increase in serum urea nitrogen values as has also been recorded by Eichner *et al*. (1979) in beef cattle.

4.4.4 Serum Creatinine(mg/dl)

Mean (± SE) values of serum creatinine in animals of different groups are represented in table no. 25 and shown in fig. 24

Animals of group N1 (bupivacaine alone) and group N3 (bupivacaine with tramadol) a non significant increase in plasma creatinine was observed from 30 to 240 min post injection. The combination of bupivacaine with detomidine (group N2), resulted in a significant ($P<0.05$) increase between 30 to 120 min post injection and then it approached base values by end of the experiment.

The transient increase in serum creatinine might be attributed to the temporary inhibitory effect of these drugs on the renal blood flow and consequent decrease in glomerular filtration rate which in turn might have caused a rise in serum creatinine values. Parenteral administration of xylazine has also been reported to cause a rise in creatinine level in buffaloes (Mottelib and El. Gindhi, 1975, Similar changes in serum creatinine were also observed by (Dilip Kumar, 1993) in goats after systemic administration of α_2 agonists.

4.4.5 Serum Alanine AminoTransferase (ALT) (U/L)

Mean (±SE) values of ALT in animals of different groups are represented in table no. 26 and shown in fig. 25

In animals of group N1 (bupivacaine alone) and group N3 (bupivacaine with tramadol) a significant ($P<0.05$) increase in ALT was observed between 60 to120 min post injection, which returned to the base values by 24 hrs. The animals of group N2 (bupivacaine with detomidine combination), showed a significant ($P<0.01$) increase in ALT between 60 to 120 min interval. The values then returned to the preadministration level by end of study period.

The changes in ALT values might be due to alteration in the cell membrane permeability in response to haemodynamic changes by these anaesthetic agents which may permit these enzymes to leak from the cells with intact membrane (Koichev *et al*., 1988) or due to increased secretion of catecholamines and corticoids (Highman *et al.*, 1969). The increased permeability of ALT through plasma membrane of hepatic cells in anaesthetized animals might have occurred due to oxidative transformation of these drugs in the liver during the process of elimination leading to increased level of activity of these enzymes in the present study (Kaneko, 1989). Similar findings were also observed by Kumar *et al*. (1997) in goats, Tiwari *et al*. (1999a) in buffalo calves.

4.4.6 Serum Aspartate AminoTransferase (AST) (U/L)

Mean (± SE) values of AST in animals of different groups are represented in table no. 27 and shown in fig. 26

In animals of group N1 (bupivacaine alone) and group N3 (bupivacaine with tramadol) a non significant increase in AST was recorded between 30 to 120 min post injection, later on the values decreased and returned to near base value by 24 hrs. The animals of bupivacaine with detomidine combination (group N2), showed a significant ($P<0.05$) increase in AST between 60 to 120 min interval. However, the values returned to normal by end of study period.

Alteration in serum AST and ALT levels is the immediate response to cardiac insufficiency (Lehinger, 1990). The AST is distributed widely in many tissues, but the liver, myocardium and skeletal muscles are rich in this enzyme. When there is stress or any damage to the cells of these tissues, the enzyme escapes into the blood and so the AST enzymatic activity increases. This might be due to the hypoxia produced due to respiratory centre depression in group B due to systemic absorption of Alpha-2 agonists. Alpha-2 agonists including detomidine are potent CNS depressive agents. Some alternations might also take place in cell membrane permeability which may permit these enzymes to leak from the cells with intact membrane. Since the values returned to pre-administration level by 24 hrs of observation and the values were within the normal physiological range, therefore possibility of pathological changes in the liver could be ruled out. It corroborates with the findings of (Koichev *et al*. 1988), and (Samy *et al***.** 1984) after detomidine administration in cattle and sheep.

CHAPTER V

SUMMARY, CONCLUSIONS AND SUGGESTIONS FOR FUTURE RESEARCH WORK

SUMMARY

The present investigation was conducted on fifteen clinically healthy non-descript, goats ranging from 1 to 2 years of age and weighing 15 to 25 kg body weight. All the animals were dewormed with albendazole @ 7.5mg /kg body weight, orally one month before the start of experiment. The animals were stall-fed, clean drinking water was made available, and uniform managemental conditions were maintained throughout the period of observation. Each animal was kept off feed for 12 hrs and water for 6 hrs prior to the start of the experiment.

All the fifteen animals were subjected to the following three treatments. An interval of five days was kept between each treatment. The animals of group N1 were treated with epidural injection of bupivacaine (@ 1 mg/kg body weight), animals of group N2 were treated with epidural injection of bupivacaine (@ 1 mg/kg body weight)along with detomidine (@ 30µgm/kg body weight) and in group N3 animals, a combination of bupivacaine and tramadol was administered (@ 1 mg/kg and 2 mg /kg body weight) respectively. The volume of the drug injected was 6 ml in all the groups after reconstituting with distilled water. The drugs were injected at the lumbo sacral epidural space after taking all aseptic precautions.

The onset, duration of analgesia and complete recovery was recorded in all the treatment groups. The depth, extent of desensitization (at flank, inguinal region,

hind limbs, perineum and tail), sedation and motor incoordination were recorded before and at 10, 20, 30, 45, 60, 75, 90, 120, 180 and 240 minutes post injection .Physiological parameters viz. rectal temperature, heart rate, respiratory rate were recorded before and at 10, 20, 30, 45, 60, 75, 90, 120, 180 and 240 minutes post injection. Ruminal movements were recorded before and at 30, 60, 120, 240, 360 minutes and 24 hours post injection. Haematological parameters viz., haemoglobin, packed cell volume, total leukocyte count and differential leucocyte count and biochemical parameters viz., serum glucose, total proteins, serum urea nitrogen, serum creatinine, Alanine Aminotransferase and Aspartate Aminotransferase were estimated before and at 30, 60, 120, 240, 360 minutes and 24 hours post injection.

The onset of analgesia was quickest in group N2 animals (5.08±0.13min) followed by group N3 (6.92±0.17min) and group N1 (7.93±0.14min). Bupivacaine alone (group N1) and in combination with tramadol (group N3) induced very mild to mild analgesia between 10 to 20 min and moderate analgesia between 30 to 60 min of flank while mild to mild analgesia from 20 min to the end of observation in inguinal, perineum, hind limbs and tail region. Bupivacaine with detomidine induced mild to moderate analgesia between 10 to 20 min and complete analgesia between 30 to 60 min of flank region while mild to moderate analgesia from 20 min till the end of observation in inguinal, perineum, hind limbs and tail region. Duration of analgesia was 90.00±2.92 , 164.20±4.69 and 164.20±4.69 minutes in groups N1, N2 and N3 respectively. All the animals of group N1 and N3 were able to stand during the entire post injection period with a mild incoordination whereas, animals of group N2

showed extreme incoordination and two animals became recumbent also. Sedation was very mild in group N1 animals, mild between 20 to 75 min in group N3 and it was extrime between 45 to 90 min in group N2 animals. Salivation was absent in group N1 and N3, whereas extreme in animals of group N2. The order of complete recovery from analgesia was (124.80 ± 3.92 minutes) for bupivacaine alone followed by bupivacaine in combination with tramadol (147.00± 4.08 minutes) and with bupivacaine and detomidine combination (200.32 ± 6.55 minutes) Ruminal movements decreased non significantly between 30 to 120 min in animal of group N1 and N3 whereas, it was decreased significantly ($P<0.05$) between 30 to 240 min in goats of group N2 animals. However, the values were compensated and returned towards preadministration level by 24 hrs.

The mean respiration rate and heart rate decreased significantly ($P<0.05$) between 30 to 75 min in animals of group N1 and N3 while it was highly significant ($P<0.01$) between 20 to 90 min in goats of group N2. The mean rectal temperature decreased non significantly between 30 to 90 min only in group N2 animals.

Haematological studies revealed a non significant decrease in haemoglobin and packed cell volume at 60 and 120 min respectively while total leucocyte count decreased non significantly between 30 to 120 min in animals of group N1 and N3. Whereas, haemoglobin and packed cell volume decreased significantly ($P<0.05$) between 60 to 120 min and total leukocyte count decreased non significantly between 60 to 120 min in goats of group N2. differential leucocyte count revealed a non significant increase in neutrophils at 60 min in group N1 and N3 and between 30 to

120 min in group N2 with a consequent non significant decrease in lymphocyte count at 60 min in group N1 and N3 and between 30 to 120 min in goats of group N2. However, the values were compensated and returned to wards preadministration level by 24 hrs. monocytes and eosinophils count showed a non significant change at different time intervals in all the three groups.

Among biochemical parameters, serum glucose showed a significant ($P<0.01$) increase between 60 to 120 min in all the three groups while serum total protein showed a non significant decrease in all the treatment groups. The serum urea nitrogen and creatinine values showed a significant ($P<0.05$) increase in animals of group N2 between 30 to 120 minutes post injection. However, the values were compensated and returned towards preadministration level by 24 hrs. Alanine Aminotransferase showed a significant ($P<0.05$) increase between 60 to 120 min in animals of group N1 and N3. In animals of group N2, Alanine Aminotransferase increased significantly ($P<0.01$) at 60 to 120 minutes interval. Aspartate Aminotransferase showed a significant ($P<0.05$) increase between 60 to 120 min in animals of group N2 only.

On the basis of this study, it was concluded that bupivacaine alone and in combination with detomidine and tramadol can be safely used for epidural anaesthesia in goats. However, the changes observed during the observation period were transient, well tolerated by the animals and soon returned to their preadministration level. The combination of bupivacaine and detomidine was proved to be better as it produced effective analgesia with quicker onset and of longer duration.

CONCLUSIONS

1. Epidural administration of bupivacaine with detomidine induced early onset with longer duration of analgesia in comparison to bupivacaine alone and bupivacaine in combination with tramadol.
2. Bupivacaine with detomidine produced complete analgesia of flank, perineum and moderate analgesia of inguinal, hind limbs and tail whereas, bupivacaine with tramadol and bupivacaine alone produced only mild to moderate analgesia of flank , inguinal, perineum, hind limbs and tail regions.
3. Epidural administration of bupivacaine alone and in combination with detomidine and tramadol caused a transient decrease in heart rate, respiratory rate, rectal temperature and ruminal movements which returned near preadministration level by 240 mins. However, their values remained within physiological limits.
4. A transient decrease in haematological profiles viz., haemoglobin, packed cell volume, total leucocyte count and lymphocyte count and slight increase in neutrophils count was observed after lumbo sacral epidural injection of bupivacaine alone and combination with detomidine and tramadol. However, the values were compensated and returned towards preadministration level by 24 hrs.
5. Among biochemical parameters viz., serum glucose, Alanine Aminotransferase, Aspartate Aminotransferase, serum urea nitrogen and creatinine were increased while serum total proteins decreased between 30 to 120 min after epidural administration of bupivacaine alone, and with detomidine and tramadol. However, the values were compensated and returned towards preadministration level by 24 hrs.

SUGGESTIONS FOR FUTURE RESEARCH WORK

1. Cardiopulmonary studies viz- mean arterial pressure, central venous pressure and electrocardiogram may be undertaken using bupivacaine alone or in combination with detomidine and tramadol in goats .
2. Blood gas analysis can be undertaken using above combination in goats and in other species.
3. This combination can also be evaluated in other species like buffaloes, dogs and pigs.

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ABSTRACT

"STUDIES ON EFFICACY OF BUPIVACAINE AND ITS COMBINATION WITH DETOMIDINE AND TRAMADOL FOR INDUCING EPIDURAL ANAESTHESIA IN GOATS"

By

NARENDRA KUMAR NAIK

The present study was undertaken to evaluate the efficacy of bupivacaine alone and in combination with detomidine and tramadol for lumbo sacral epidural analgesia in goats. A total of fifteen clinically healthy non descript, either sex goats aging 1 to 2 years of age and weighing 15 to 25 kg body weight were selected for this study. The animals were randomly divided into three groups and subjected to the following three treatments.

The animals of group N1 were treated with epidural injection of bupivacaine (@ 1 mg/kg body weight), animals of group N2 were treated with epidural injection of bupivacaine(@ 1 mg/kg body weight) with detomidine (@ 30µg/kg body weight) and in group N3 animals, bupivacaine and tramadol combination was administered (@ 1mg/kg and 2mg /kg body weight) respectively. The volume of the drug injected was 6 ml in all the groups after reconstituting with distilled water. The drugs were injected at the lumbo sacral epidural space after taking all aseptic precautions and an interval of five days was kept between each treatment.

The onset, duration of analgesia and complete recovery was recorded in all the treatment groups. The depth, extent of desensitization, (at flank, inguinal region, hind limbs, perineum and tail) sedation and motor incoordination, were recorded before and at 10, 20, 30, 45, 60, 75, 90, 120, 180 and 240 minutes post injection .Physiological parameters viz. rectal temperature, heart rate, respiration rate were recorded before and at 10, 20, 30, 45, 60, 75, 90, 120, 180 and 240 minutes post injection. Ruminal movements were recorded before and at 30, 60, 120, 240, 360 minutes and 24 hours post injection. Haematological parameters

viz- haemoglobin, packed cell volume, total leucocyte count and differential leucocyte count and biochemical parameters viz- serum glucose, total proteins, serum urea nitrogen, creatinine, Alanine Aminotransferase and Aspartate Aminotransferase were estimated before and at 30, 60, 120, 240, 360 min and 24 hours post injection.

The onset of analgesia was quickest in group N2 animals (5.08 ± 0.13 min) followed by group N3 (6.92 ± 0.17 min) and group N1 (7.93 ± 0.14 min). Bupivacaine alone and in combination with tramadol induced moderate analgesia of flank, and very mild to mild analgesia of inguinal, hind limb, perineum and tail region. Whereas, bupivacaine with detomidine induced complete analgesia of flank region, moderate analgesia of inguinal and hind limb regions and mild analgesia of perineum and tail region. Duration of analgesia was 90.00±2.92, 164.20± 4.69 and 112.80± 2.86 minutes in group N1, N2 and N3 respectively. All the animals of group N1 and N3 were able to stand during the entire post injection period with a mild incoordination. Whereas, animals of group N2 showed extreme incoordination and two animals became recumbent also. Sedation was very mild, mild and moderate in group N1, N3 and N2 respectively. Salivation was absent in group N1 and N3 whereas extreme in animals of group N2. The order of complete recovery was (124.80±3.92 min) for bupivacaine alone followed by bupivacaine in combination with detmidine (200.32± 6.55 min) and by bupivacaine and tramadol combination (147.00±4.08min). Ruminal movements were non significantly decreased in group N1 and N3 which was significant ($P<0.05$) in group N2 animals.

The mean respiration rate and heart rate decreased significantly ($P<0.05$) between 30 to 75 min in all the groups. Whereas, the rectal temperature decreased non significantly in all the three group animals.

Haematological studies revealed a non significant decrease in haemoglobin and a packed cell volume in group N1 and N3, a significant ($P<0.05$) decrease in group N2 animals between 60 to 120 min post injection. Total leucocyte count showed a non sinificant decrease in all the three groups. Differential leucocyte count showed a non significant decrease in lymphocyte and increase in neutrophil count at 60 min post injection in all the groups. However,

the values were compensated and returned towards preadministration level by 24 hrs. monocytes and eosinophils count showed a non significant change at different time intervals in all the groups.

Among biochemical parameters serum glucose showed a significant ($P<0.01$) increase between 60 to 120 min in all the three groups while Alanine Aminotransferase showed a significant ($P<0.05$) increase between 60 to 120 min in animals group N1 and N3 which became highly significant ($P<0.01$) between 60 to 120 min in group N2. Aspartate Aminotransferase showed a significant ($P<0.05$) increase between 60 to 120 min in group N2 only. The Serum urea nitrogen and serum creatinine values showed a significant ($P<0.05$) increase in animals of group N2 between 30 to 120 minutes post injection. However, the values were compensated and returned towards preadministration level by 24 hrs. serum total protein showed a non significant decrease in all the three treatment groups.

On the basis of this study, it was concluded that bupivacaine alone and in combination with detomidine and tramadol can be safely used for epidural anaesthesia in goats. However, the changes observed during the observation period were transient, well tolerated by the animals and soon returned to their preadministration level. The combination of bupivacaine and detomidine was proved to be better as it produced analgesia with quicker onset and of longer duration.

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Fig. 1 : Showing Onset, Duration and Complete Recovery of all three groups

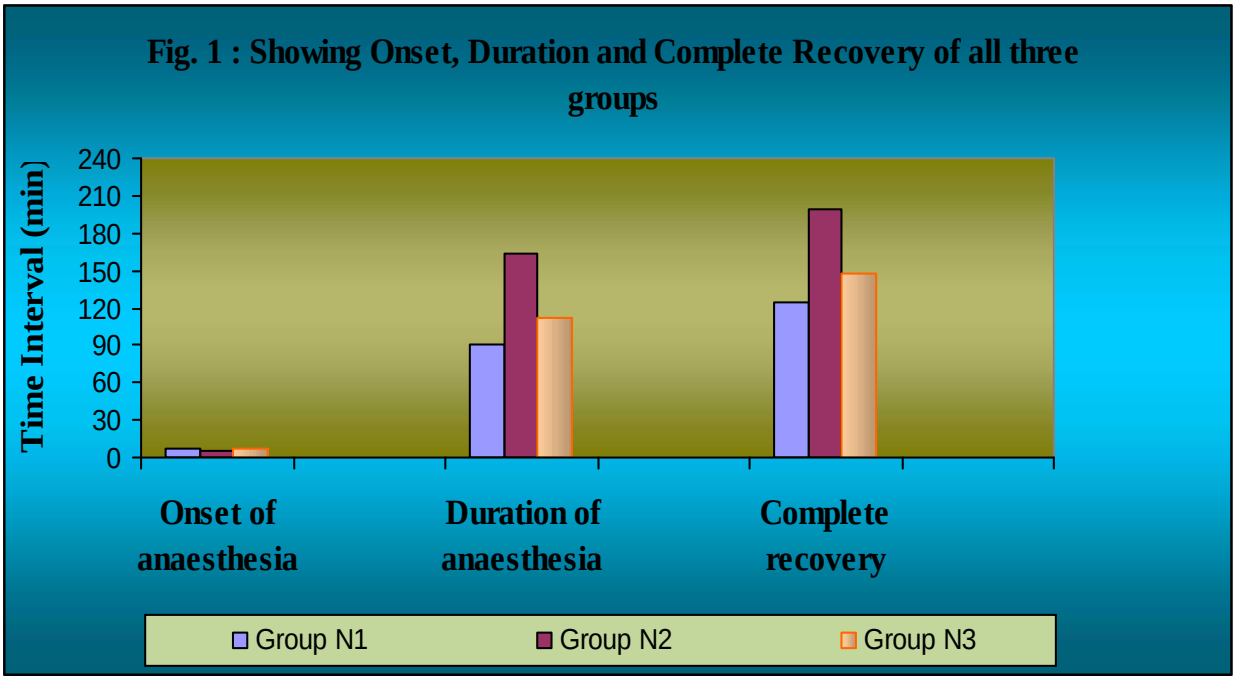
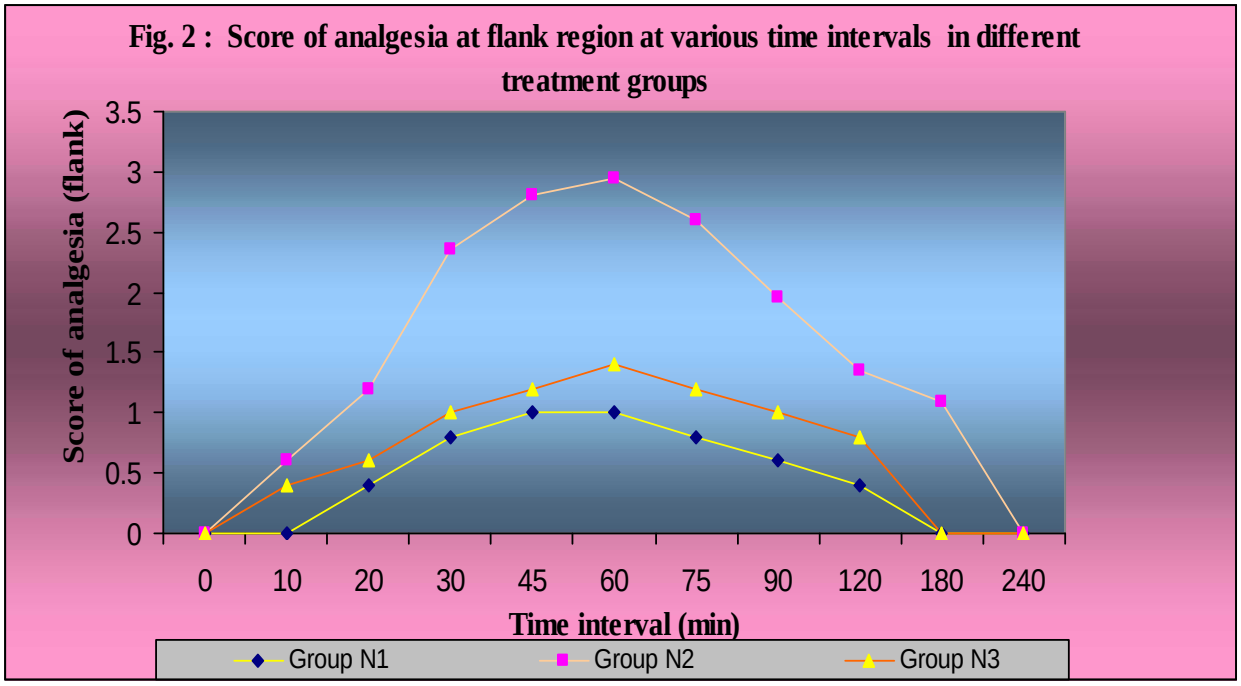


Fig. 2 : Score of analgesia at flank region at various time intervals in different treatment groups



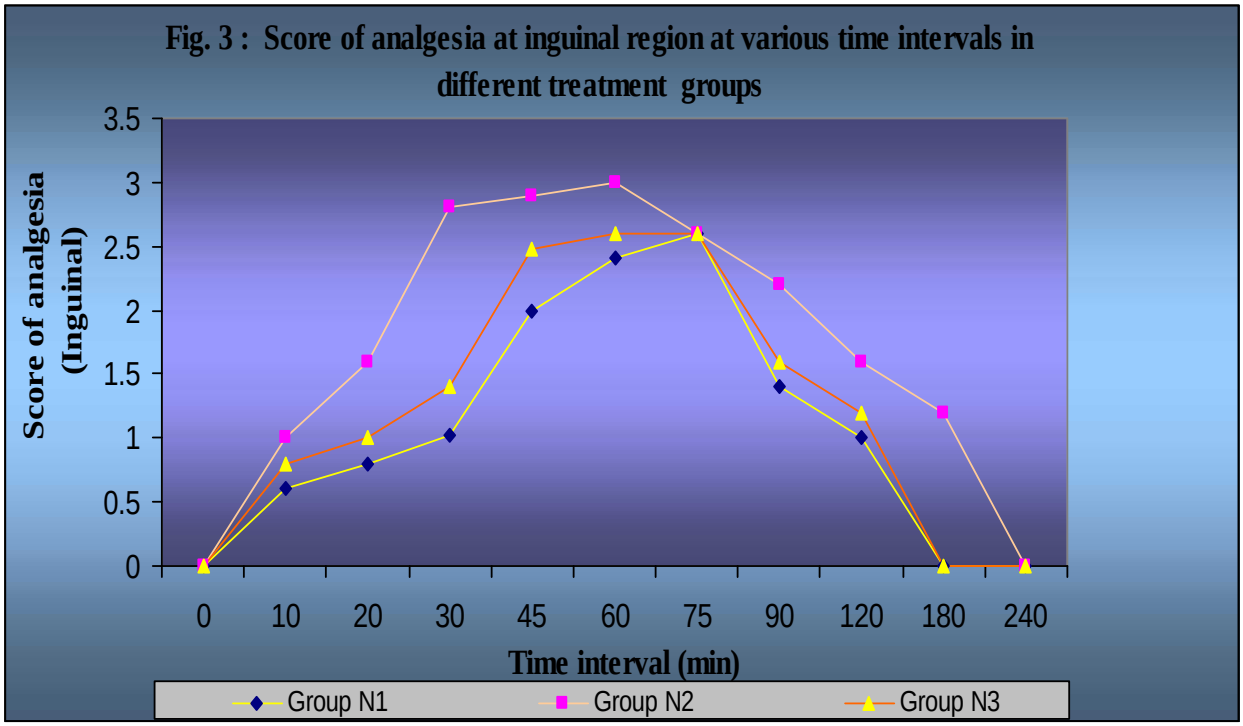


Fig. 3 : Score of analgesia at inguinal region at various time intervals in different treatment groups
Score of analgesia (Inguinal)
3.5
3
2.5
2
1.5
1
0.5
0
0
10
20
30
45
60
75
90
120
180
240
Time interval (min)
Group N1
Group N2
Group N3

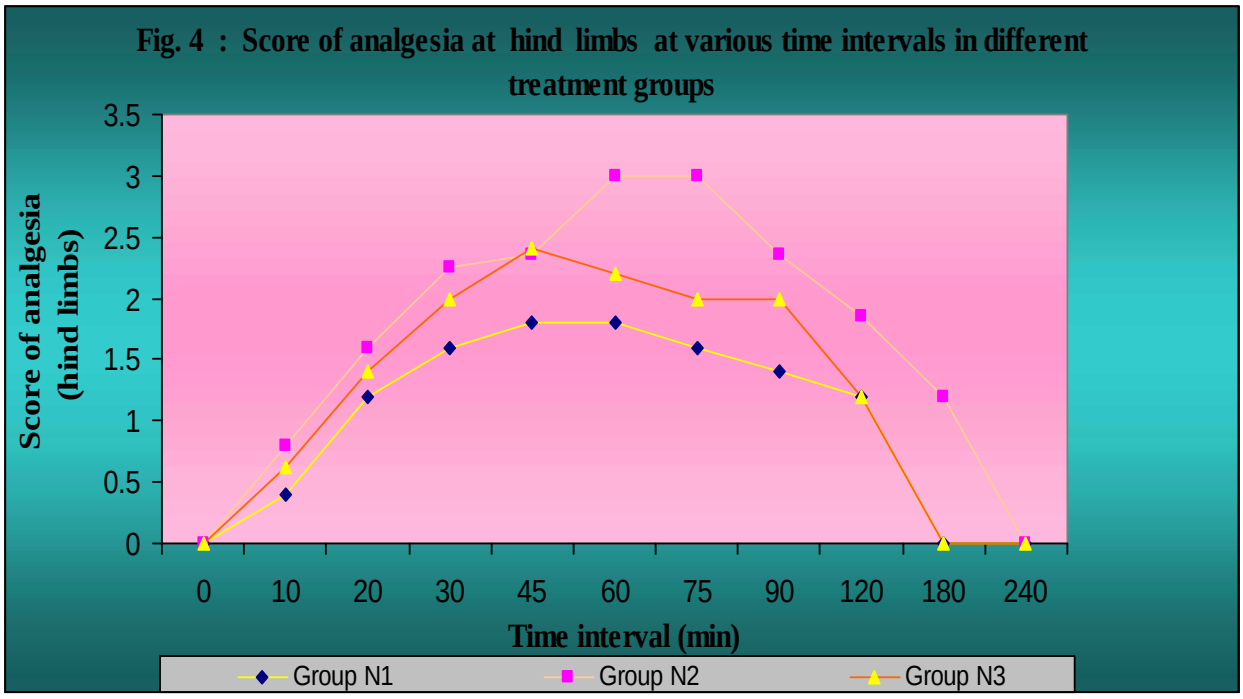


Fig. 4 : Score of analgesia at hind limbs at various time intervals in different treatment groups
Score of analgesia (hind limbs)
3.5
3
2.5
2
1.5
1
0.5
0
0
10
20
30
45
60
75
90
120
180
240
Time interval (min)
Group N1
Group N2
Group N3

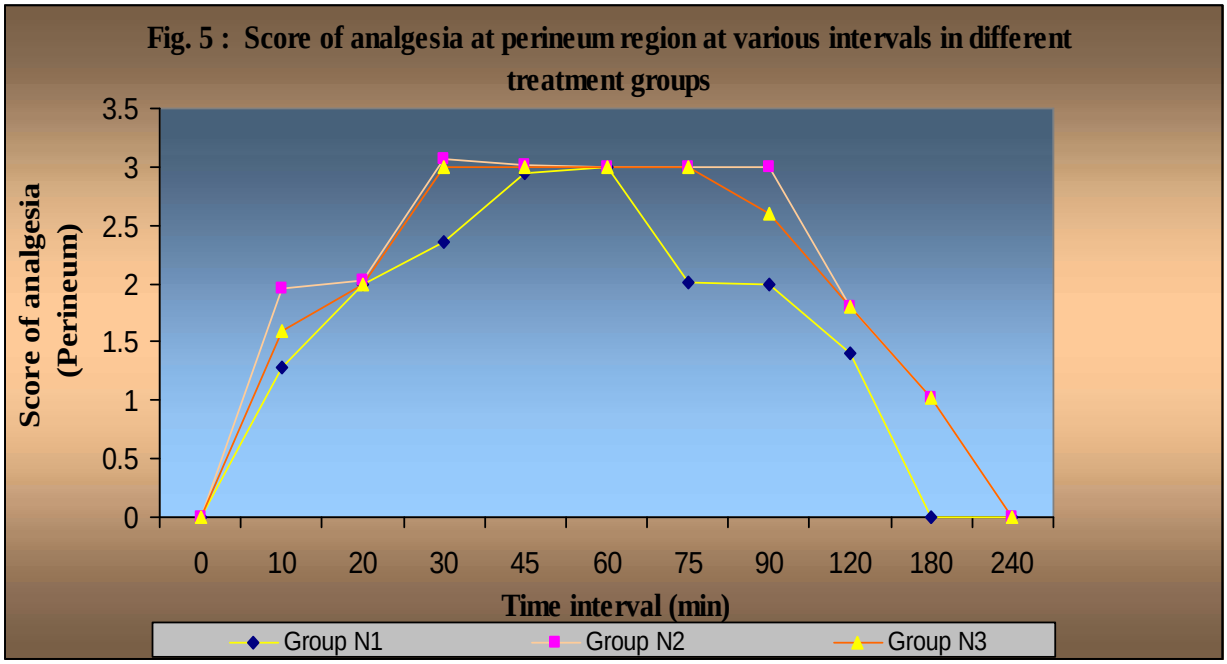


Fig. 5 : Score of analgesia at perineum region at various intervals in different treatment groups
Score of analgesia (Perineum)
3.5
3
2.5
2
1.5
1
0.5
0
0
10
20
30
45
60
75
90
120
180
240
Time interval (min)
Group N1
Group N2
Group N3

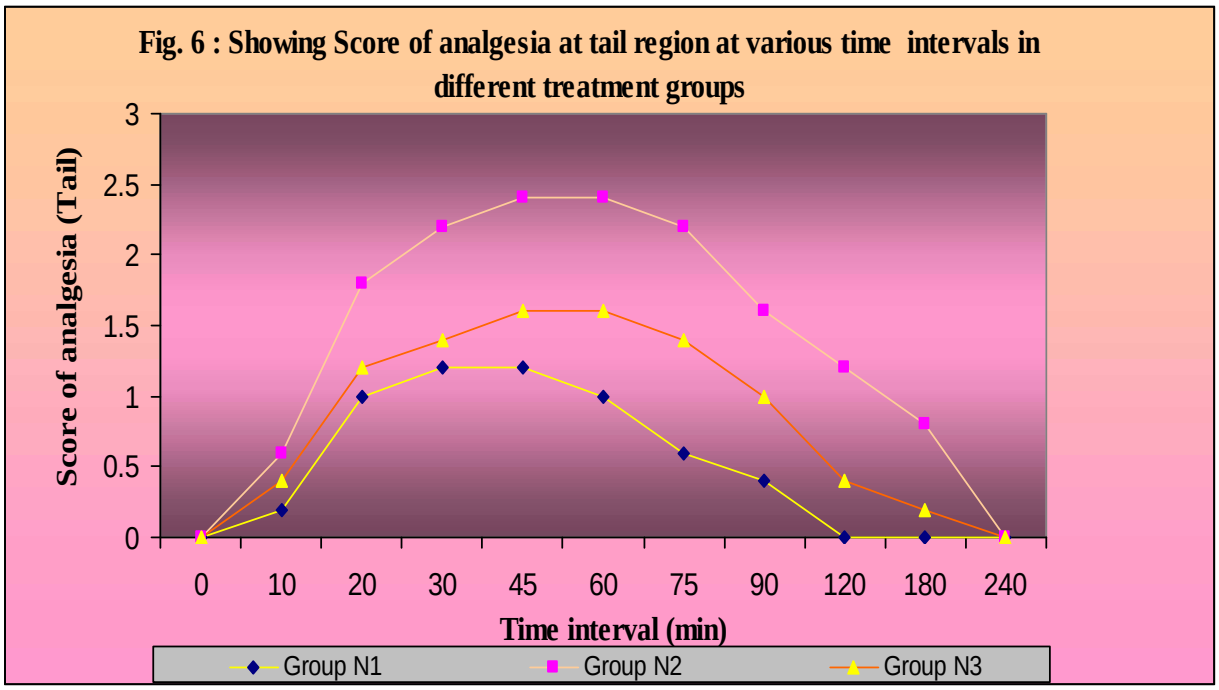


Fig. 6 : Showing Score of analgesia at tail region at various time intervals in different treatment groups
Score of analgesia (Tail)
3
2.5
2
1.5
1
0.5
0
0
10
20
30
45
60
75
90
120
180
240
Time interval (min)
Group N1
Group N2
Group N3

Fig. 7 : Score of motor incoordination at various time intervals in different treatment groups

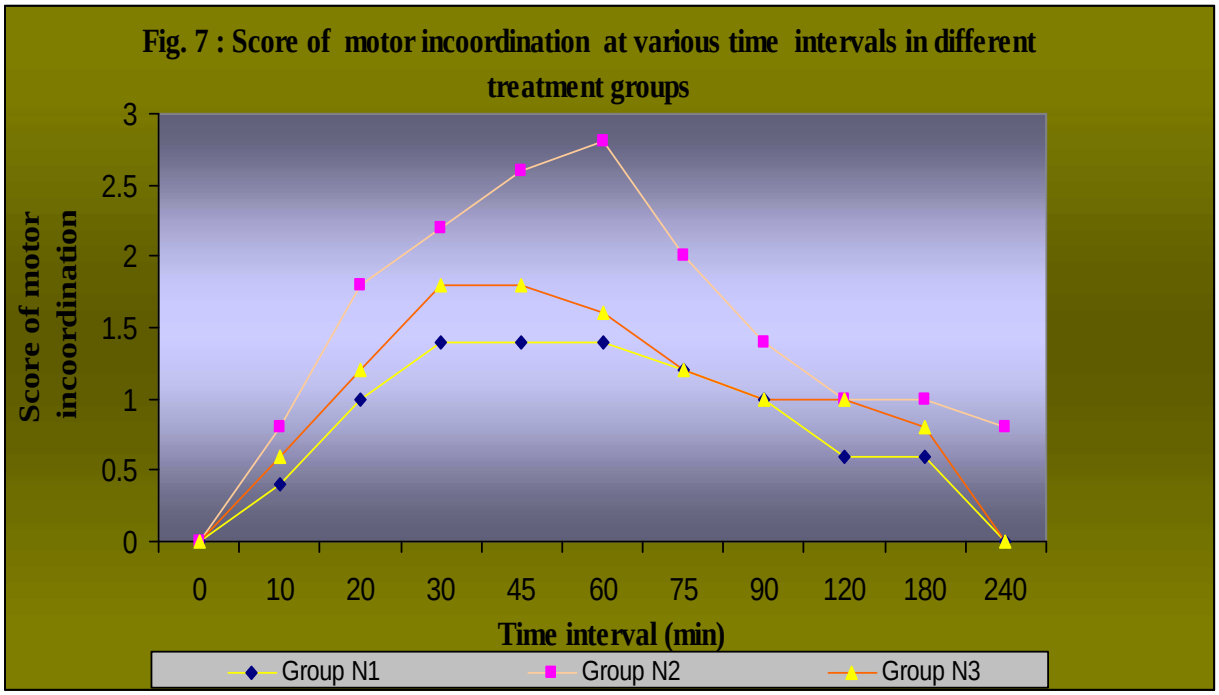
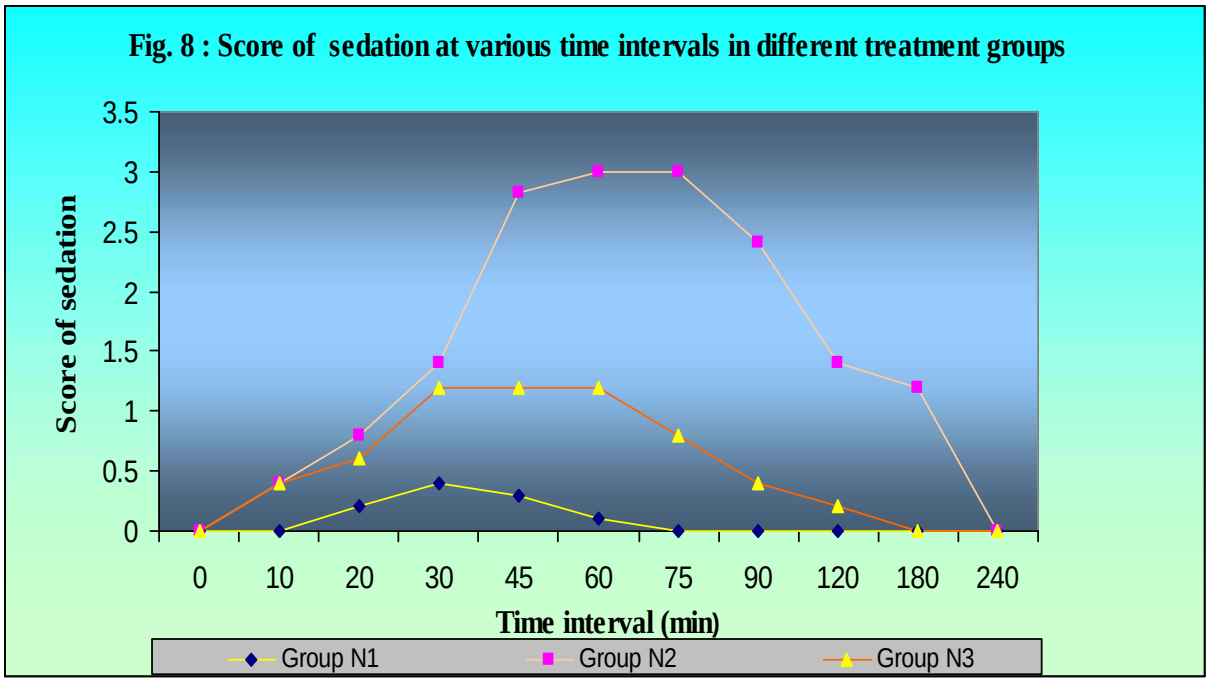


Fig. 8 : Score of sedation at various time intervals in different treatment groups



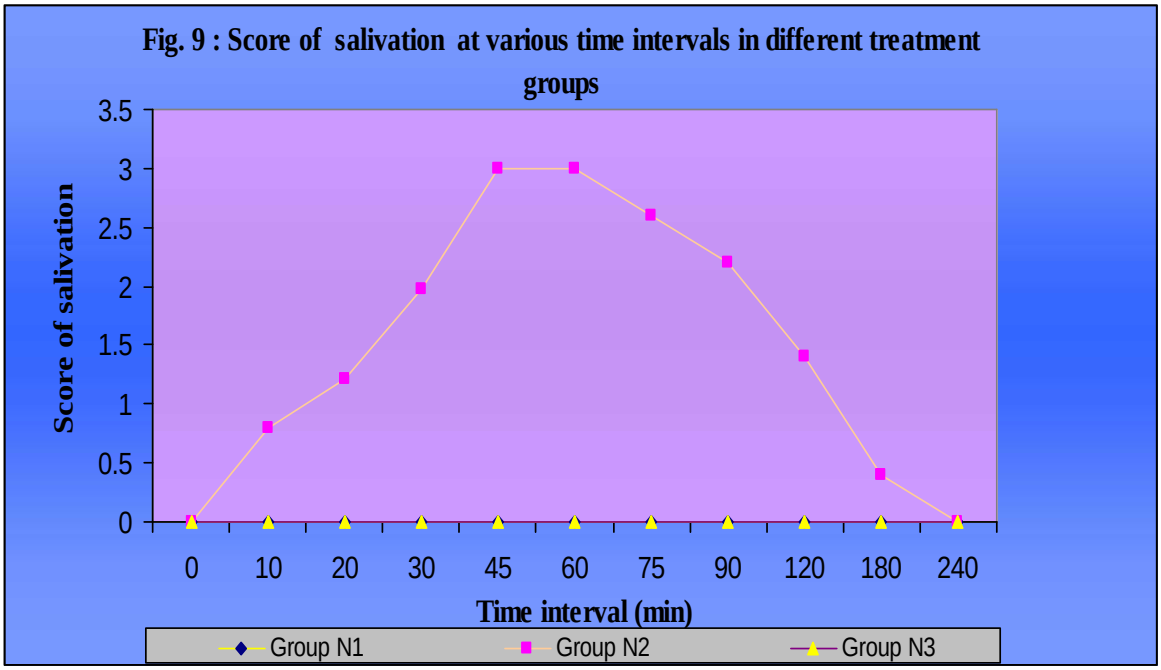


Fig. 9 : Score of salivation at various time intervals in different treatment groups
Score of salivation
3.5
3
2.5
2
1.5
1
0.5
0
0
10
20
30
45
60
75
90
120
180
240
Time interval (min)
Group N1
Group N2
Group N3

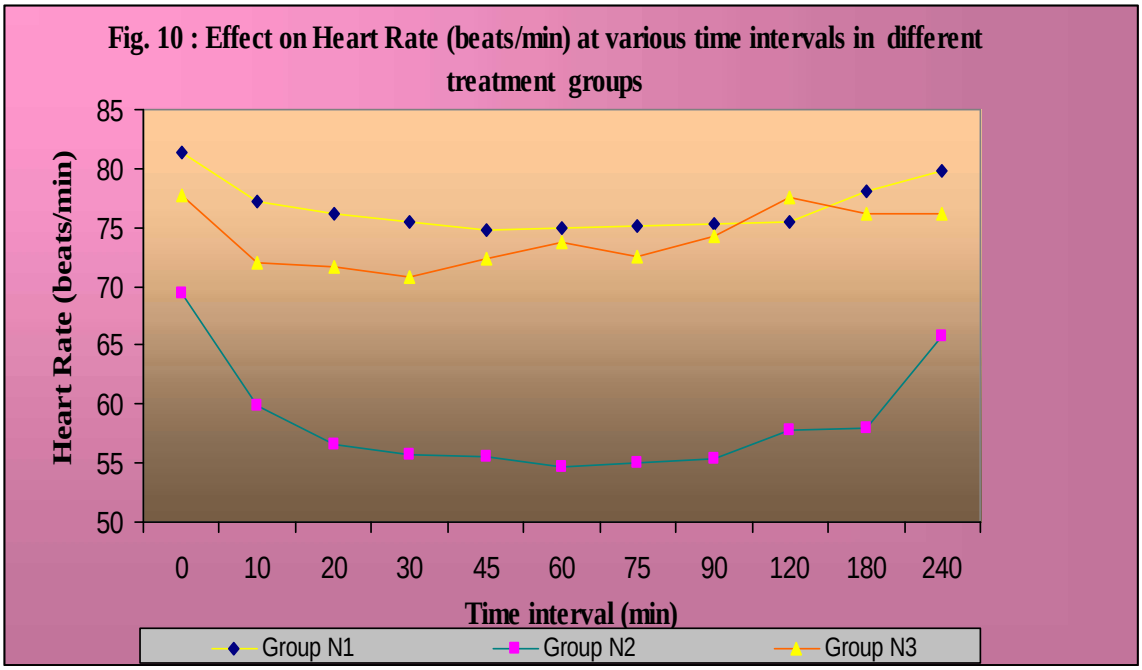


Fig. 10 : Effect on Heart Rate (beats/min) at various time intervals in different treatment groups
Heart Rate (beats/min)
85
80
75
70
65
60
55
50
0
10
20
30
45
60
75
90
120
180
240
Time interval (min)
Group N1
Group N2
Group N3

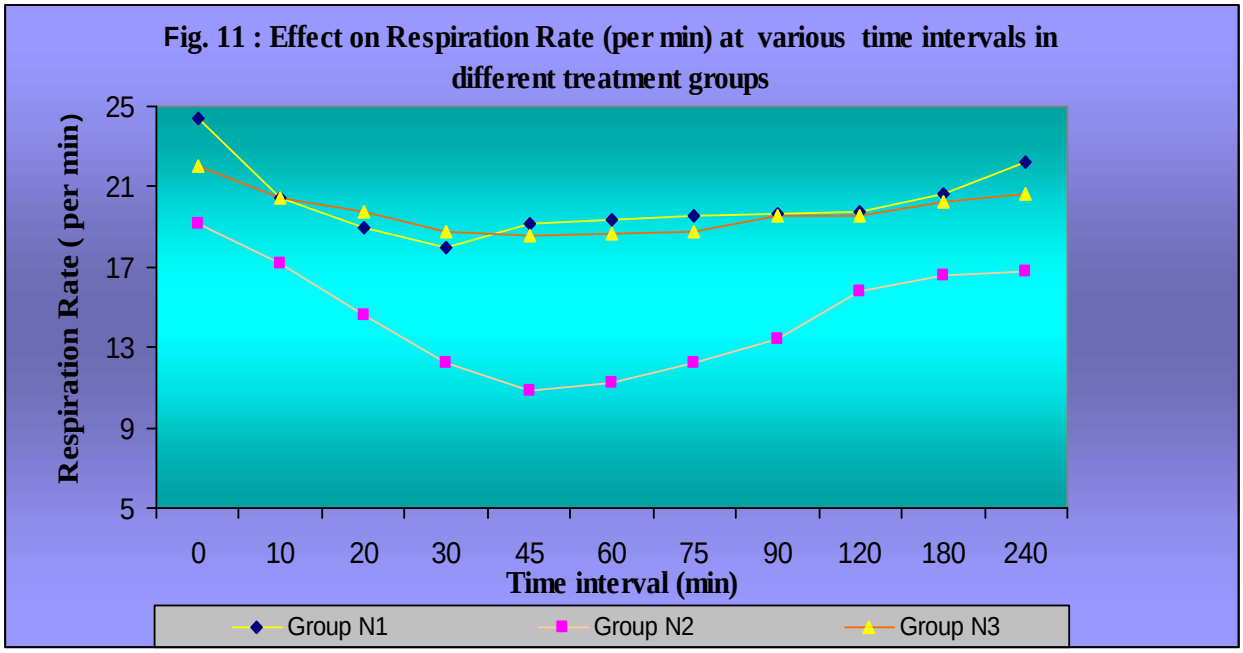


Fig. 11 : Effect on Respiration Rate (per min) at various time intervals in different treatment groups
Respiration Rate (per min)
25
21
17
13
9
5
0
10
20
30
45
60
75
90
120
180
240
Time interval (min)
Group N1
Group N2
Group N3

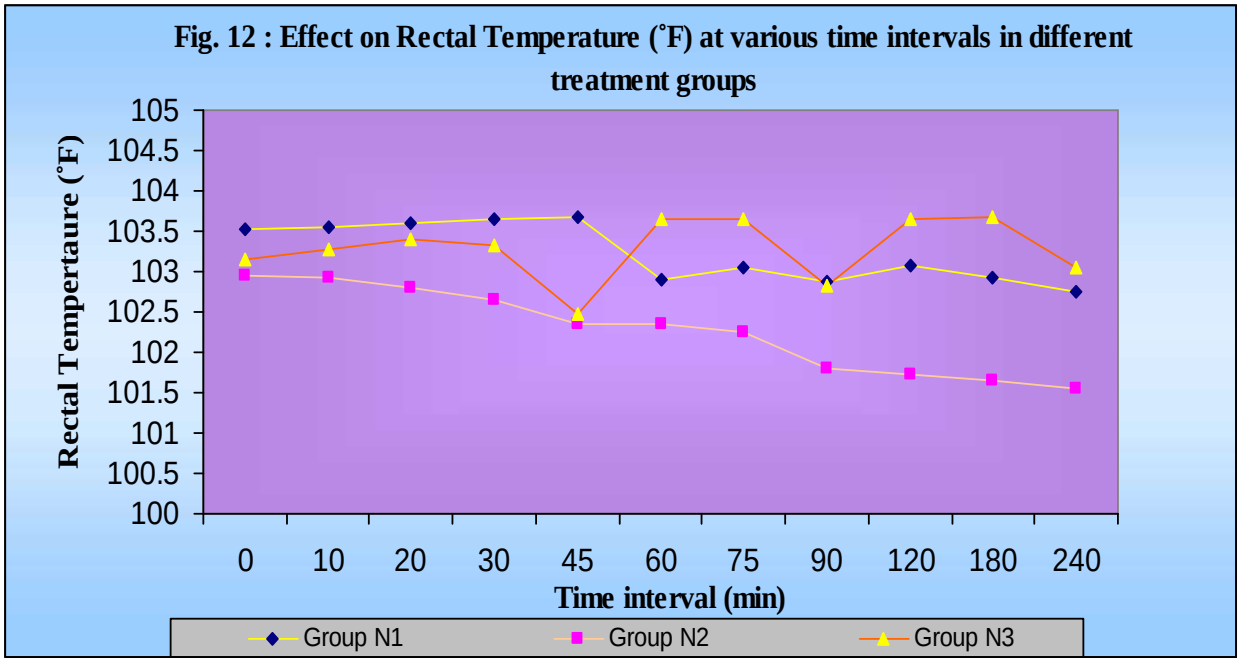


Fig. 12 : Effect on Rectal Temperature (˚F) at various time intervals in different treatment groups
Rectal Tempertaure (˚F)
105
104.5
104
103.5
103
102.5
102
101.5
101
100.5
100
0
10
20
30
45
60
75
90
120
180
240
Time interval (min)
Group N1
Group N2
Group N3

Fig. 13 : Effect on ruminal movement (per 2 min) at various time intervals in different treatment groups

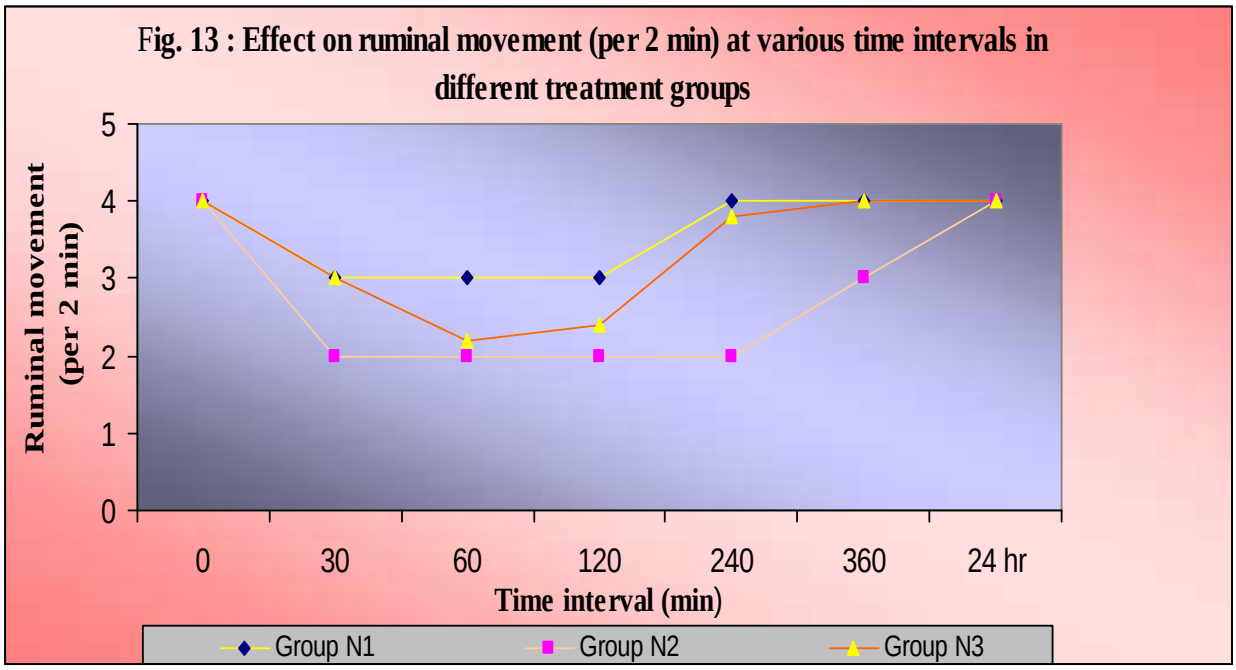
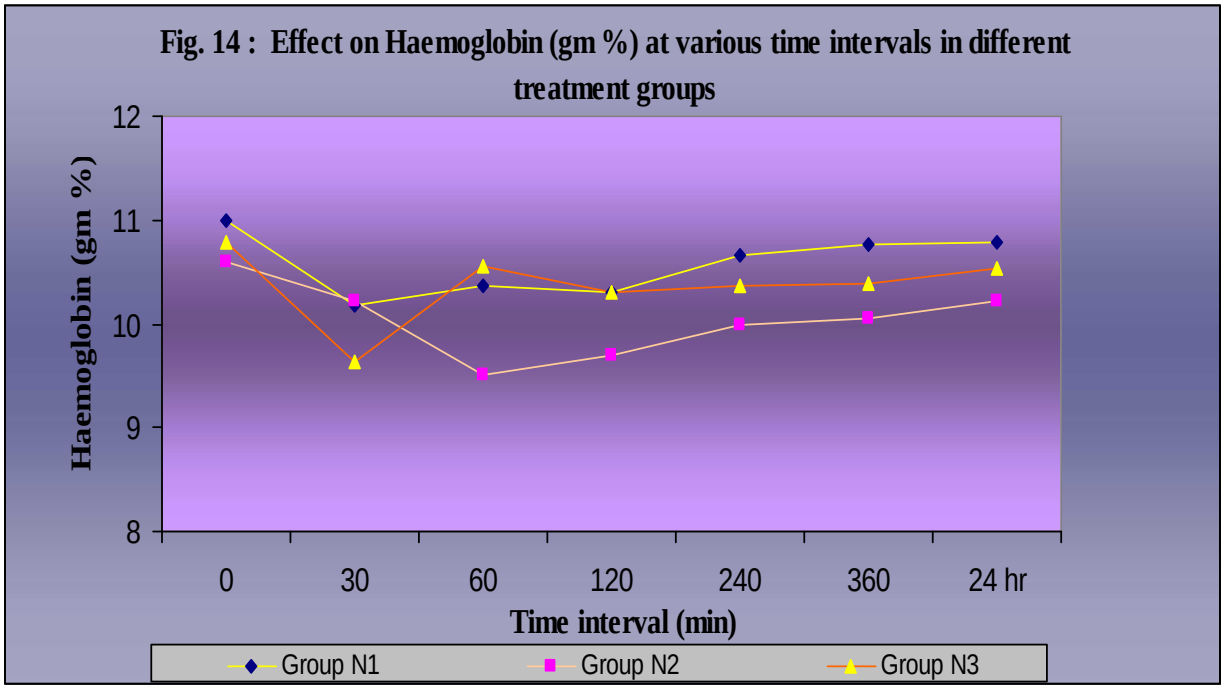


Fig. 14 : Effect on Haemoglobin (gm %) at various time intervals in different treatment groups



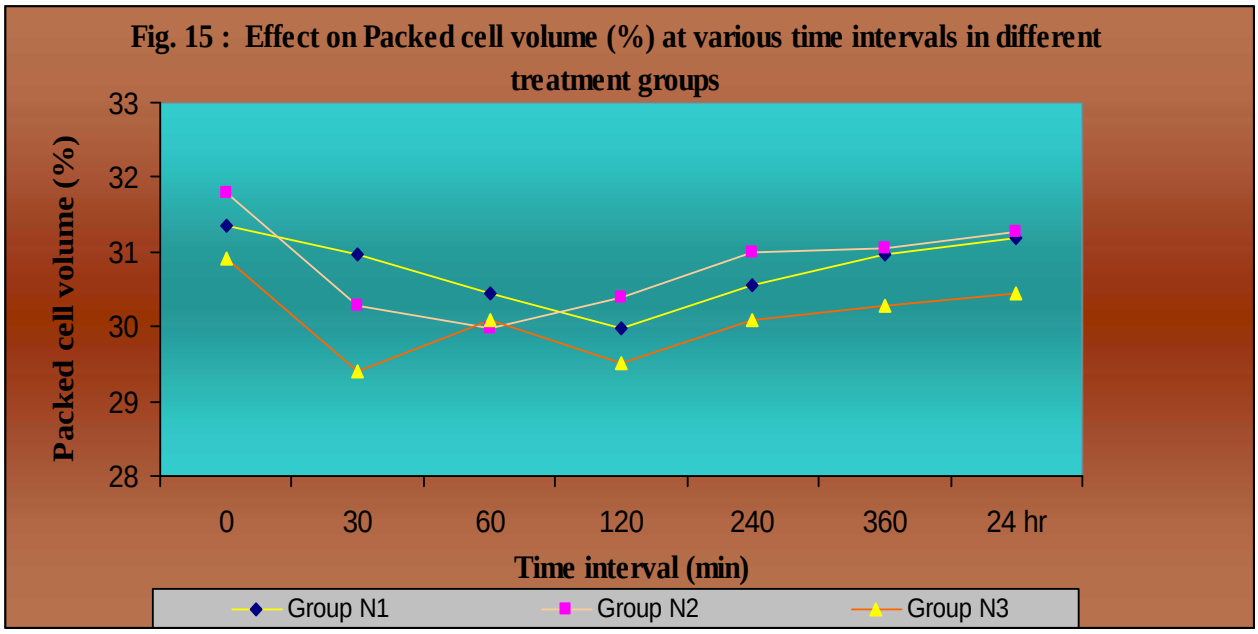


Fig. 15 : Effect on Packed cell volume (%) at various time intervals in different treatment groups
Packed cell volume (%)
33
32
31
30
29
28
0
30
60
120
240
360
24 hr
Time interval (min)
Group N1
Group N2
Group N3

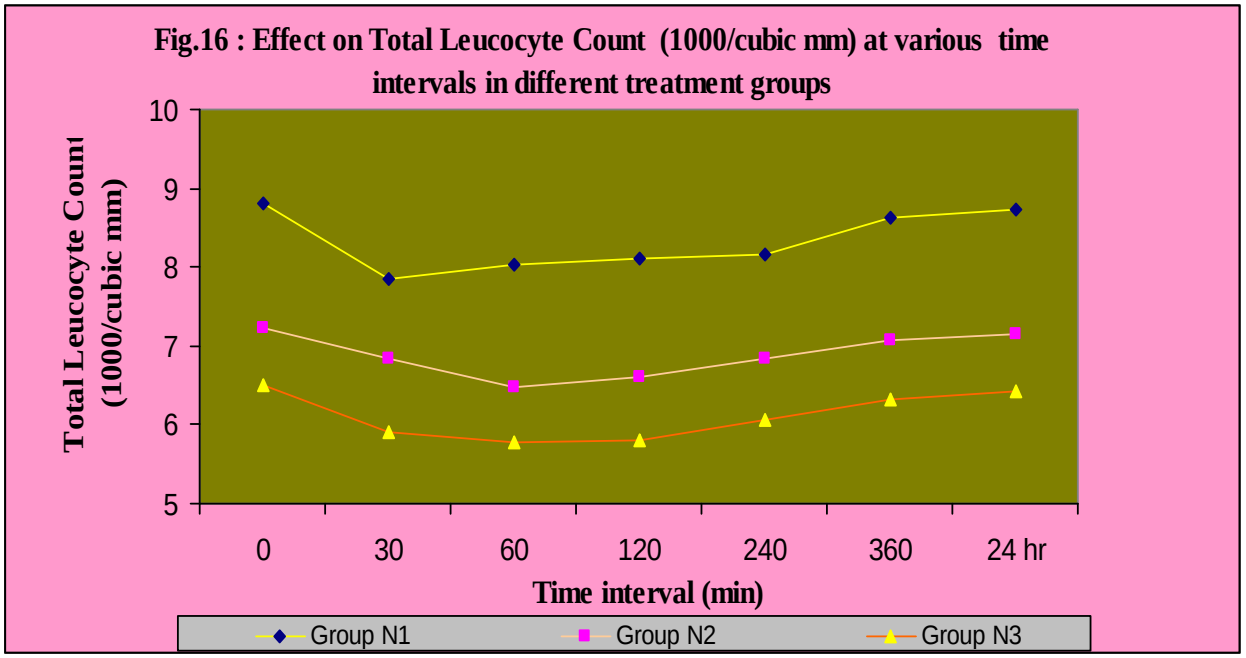


Fig.16 : Effect on Total Leucocyte Count (1000/cubic mm) at various time intervals in different treatment groups
Total Leucocyte Count (1000/cubic mm)
10
9
8
7
6
5
0
30
60
120
240
360
24 hr
Time interval (min)
Group N1
Group N2
Group N3

Fig. 17 : Effect on Neutrophils (%) at various time intervals in different treatment groups

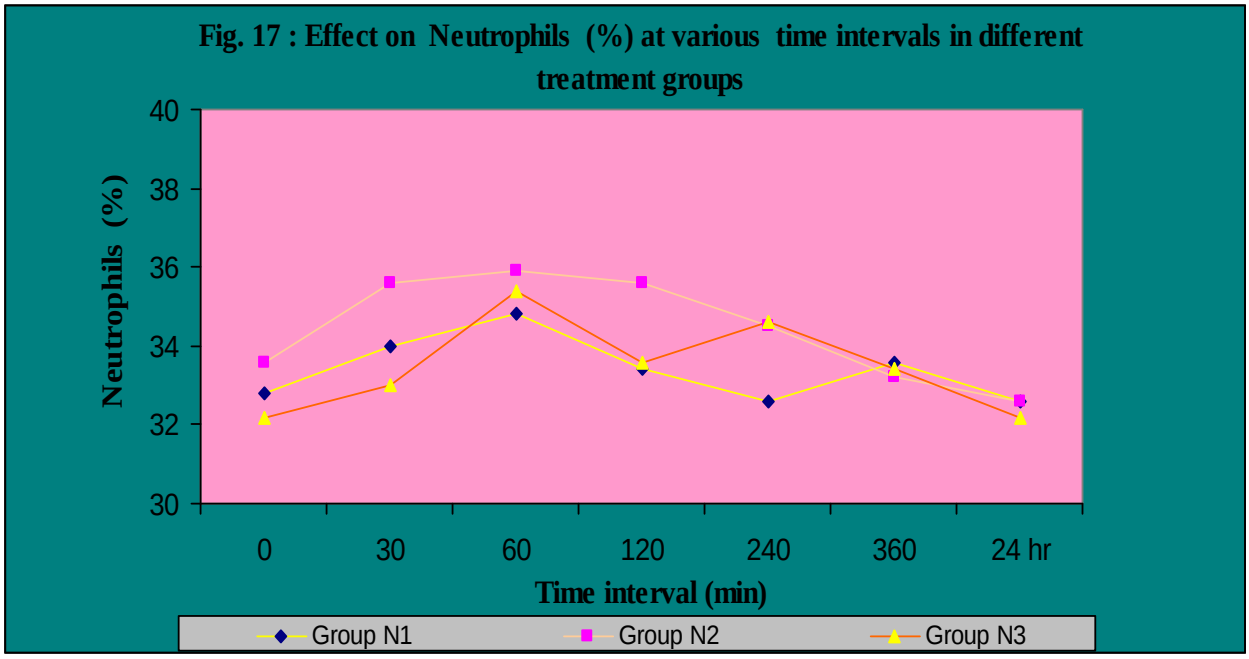


Fig. 18 : Effect on Lymphocytes (%) at various time intervals in different treatment groups

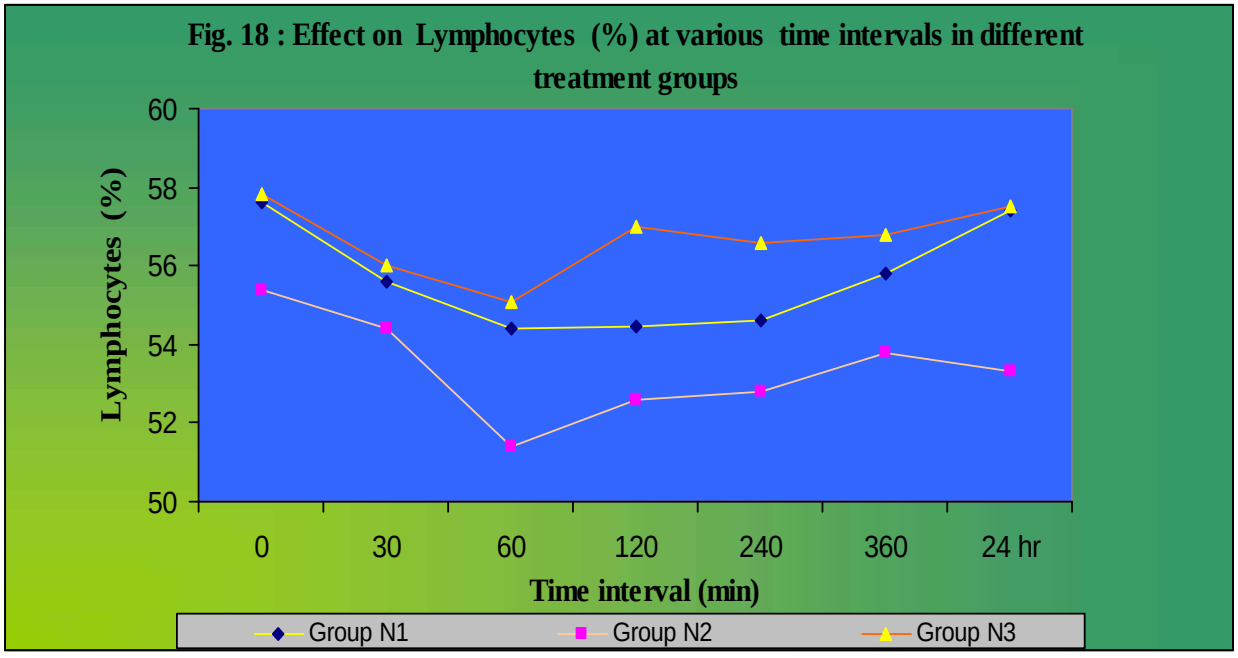


Fig. 19 : Effect on Monocytes (%) at various time intervals in different treatment groups

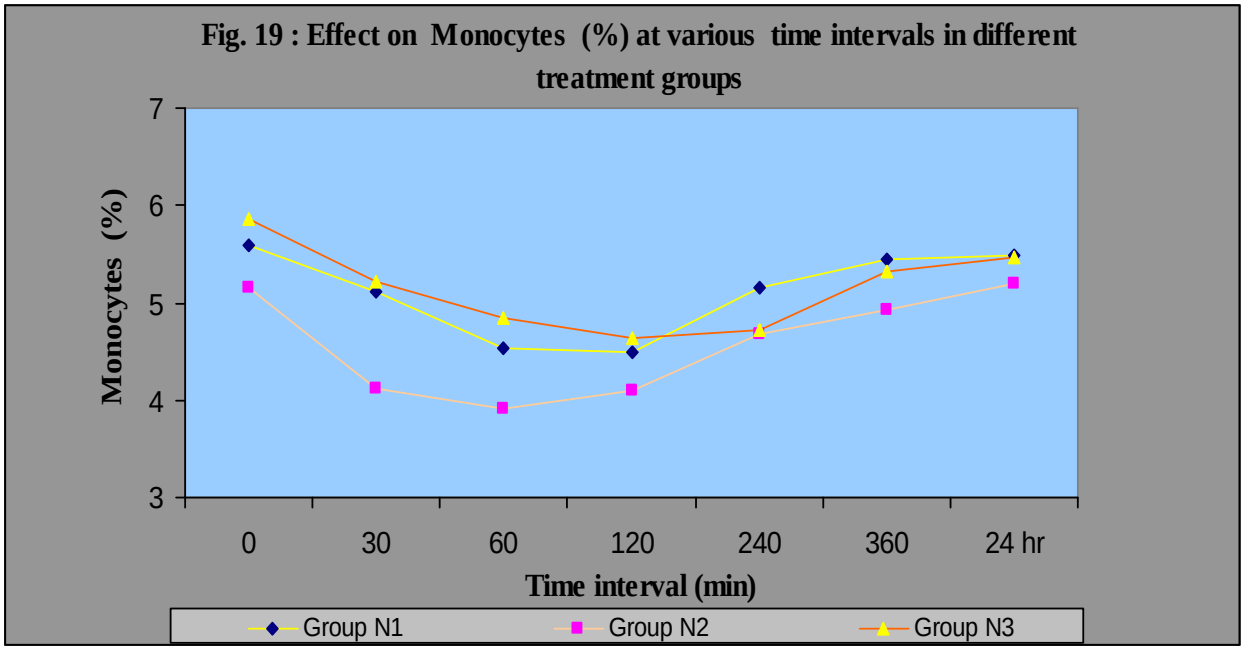
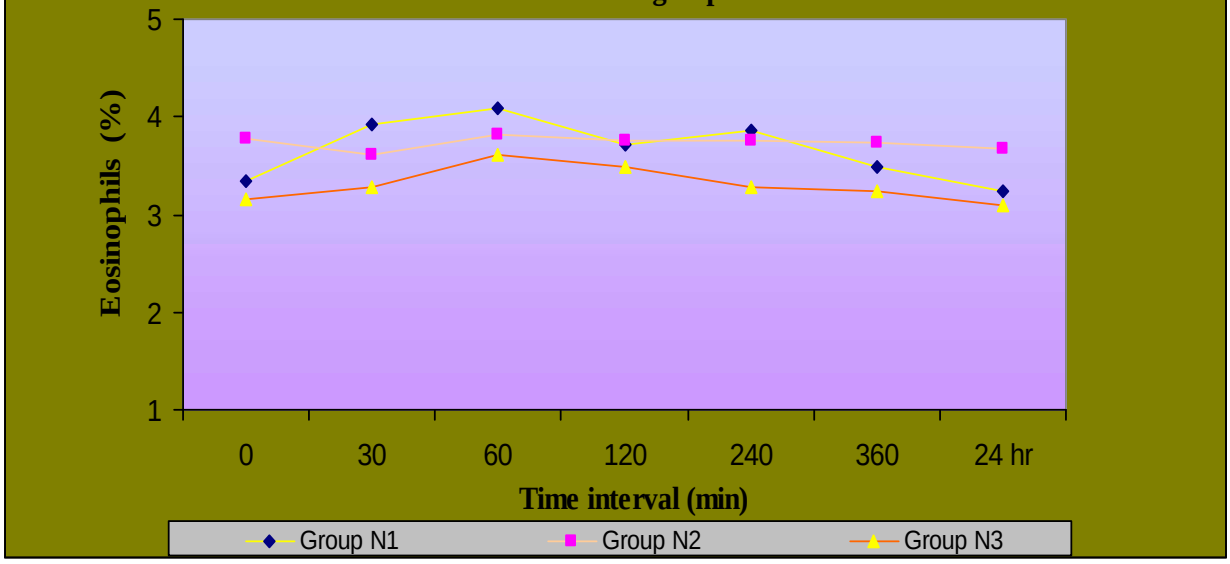


Fig. 20 : Effect on Eosinophils (%) at various time intervals in different treatment groups



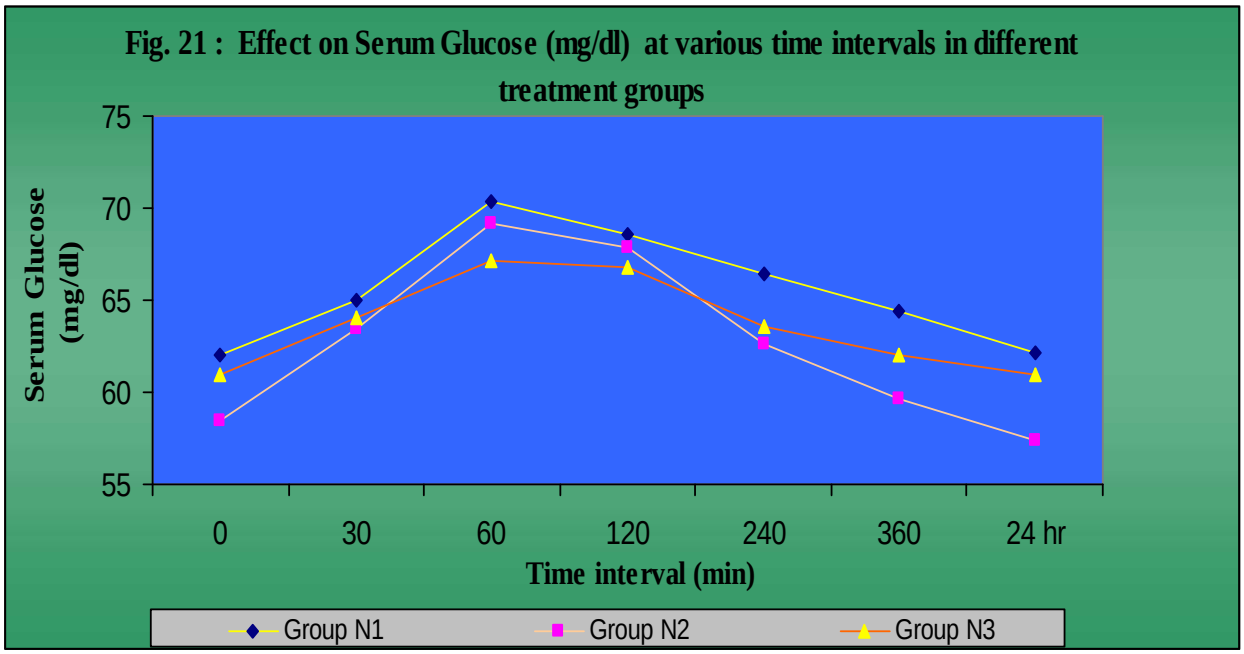


Fig. 21 : Effect on Serum Glucose (mg/dl) at various time intervals in different treatment groups
Serum Glucose (mg/dl)
75
70
65
60
55
0
30
60
120
240
360
24 hr
Time interval (min)
Group N1
Group N2
Group N3

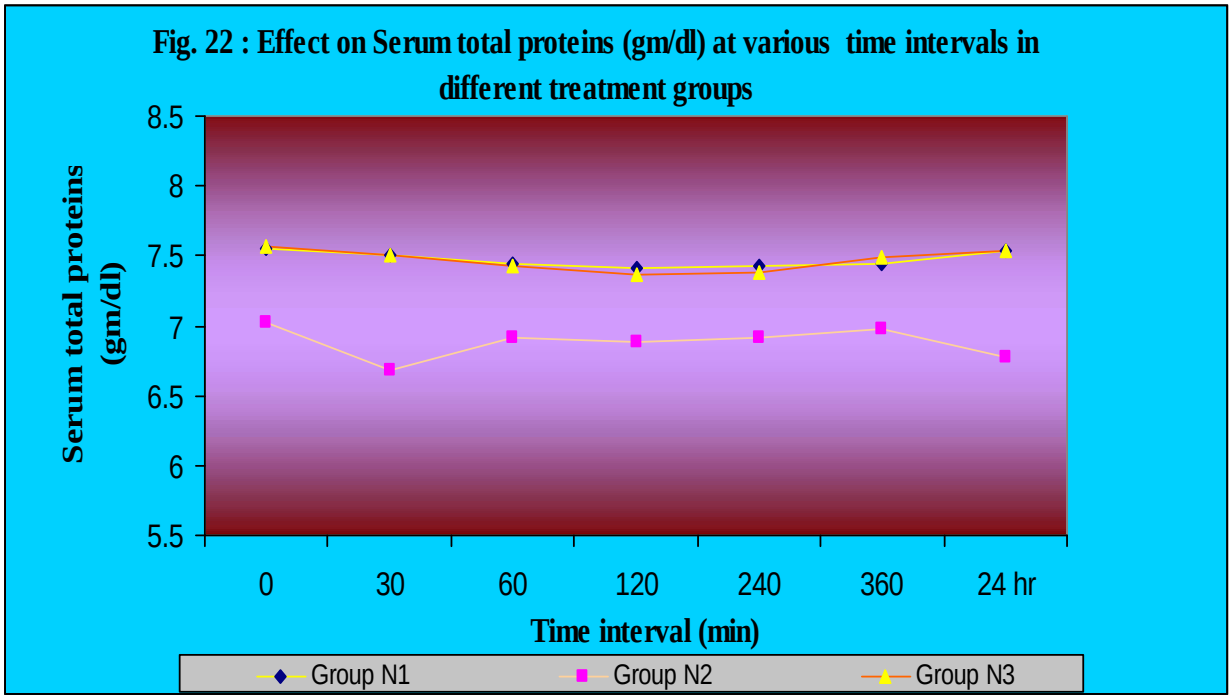


Fig. 22 : Effect on Serum total proteins (gm/dl) at various time intervals in different treatment groups
Serum total proteins (gm/dl)
8.5
8
7.5
7
6.5
6
5.5
0
30
60
120
240
360
24 hr
Time interval (min)
Group N1
Group N2
Group N3

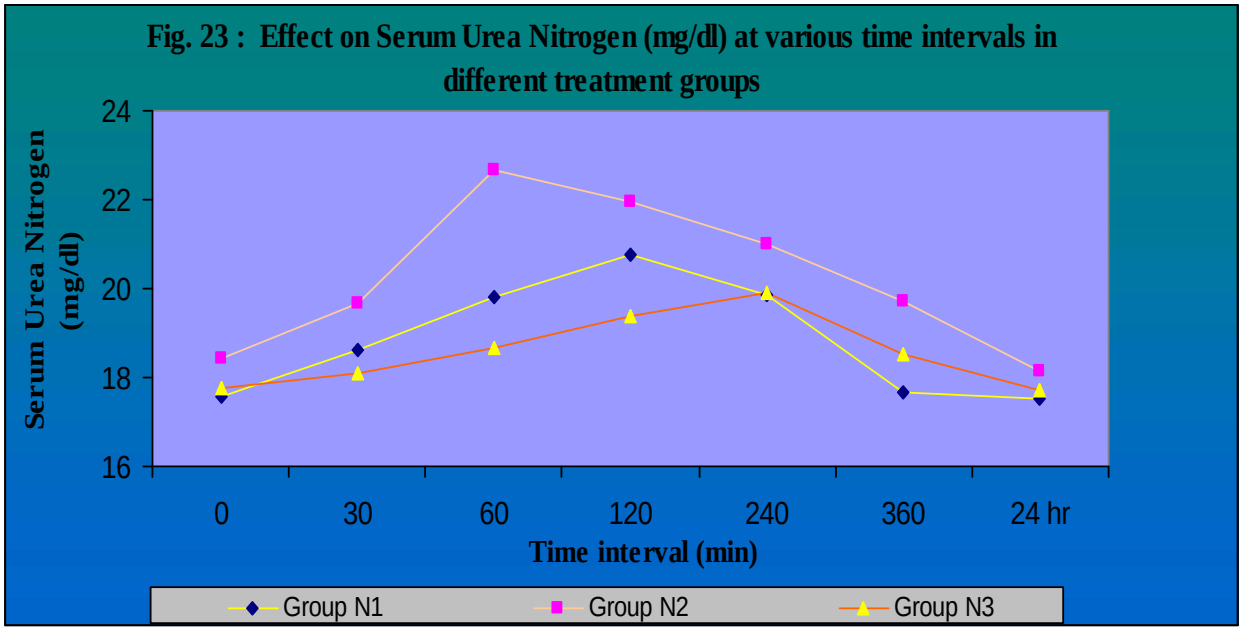


Fig. 23 : Effect on Serum Urea Nitrogen (mg/dl) at various time intervals in different treatment groups
Serum Urea Nitrogen (mg/dl)
24
22
20
18
16
0
30
60
120
240
360
24 hr
Time interval (min)
Group N1
Group N2
Group N3

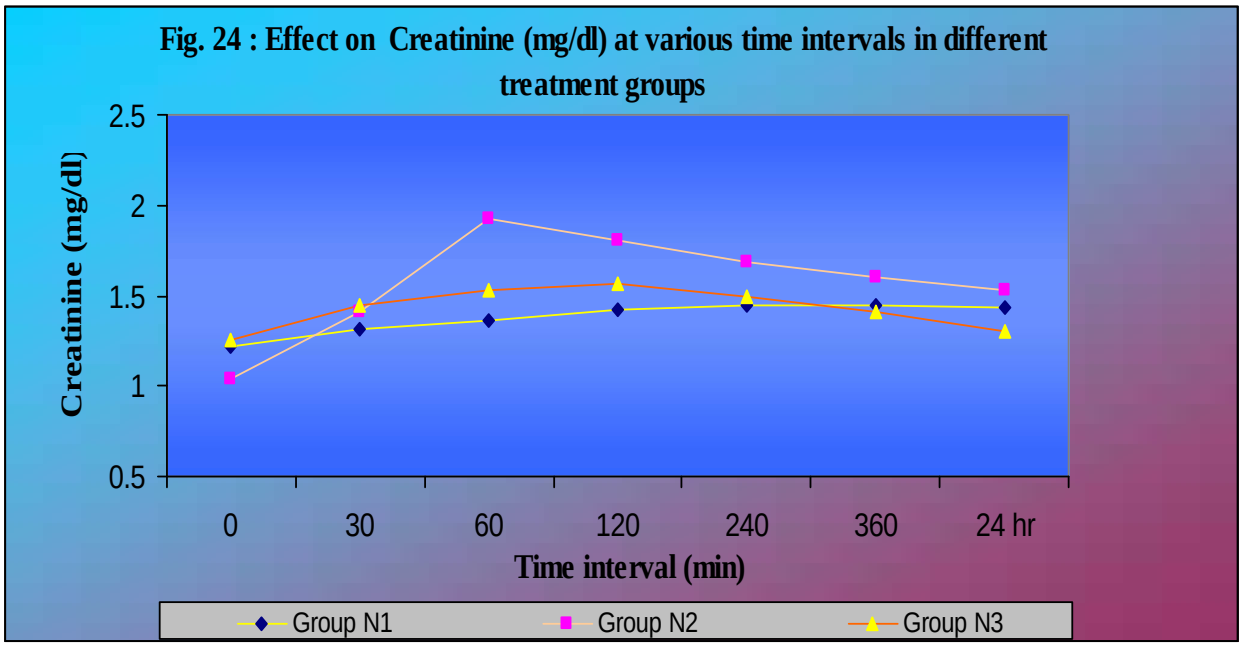


Fig. 24 : Effect on Creatinine (mg/dl) at various time intervals in different treatment groups
Creatinine (mg/dl)
2.5
2
1.5
1
0.5
0
30
60
120
240
360
24 hr
Time interval (min)
Group N1
Group N2
Group N3

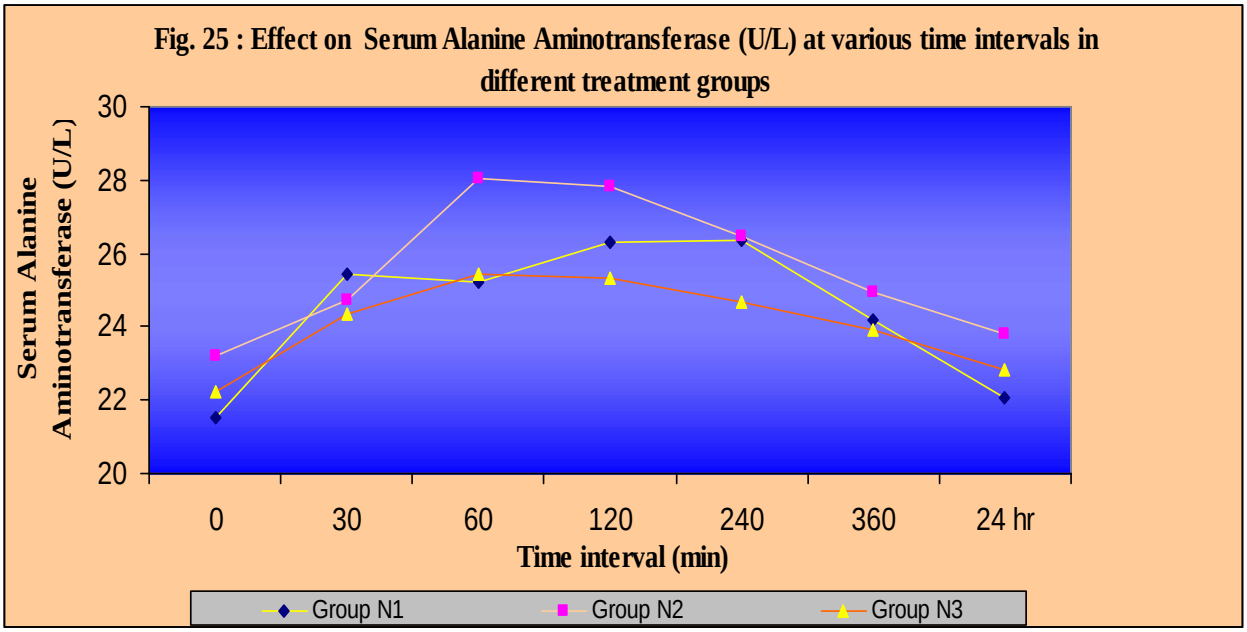


Fig. 25 : Effect on Serum Alanine Aminotransferase (U/L) at various time intervals in different treatment groups
Serum Alanine Aminotransferase (U/L)
30
28
26
24
22
20
0
30
60
120
240
360
24 hr
Time interval (min)
Group N1
Group N2
Group N3

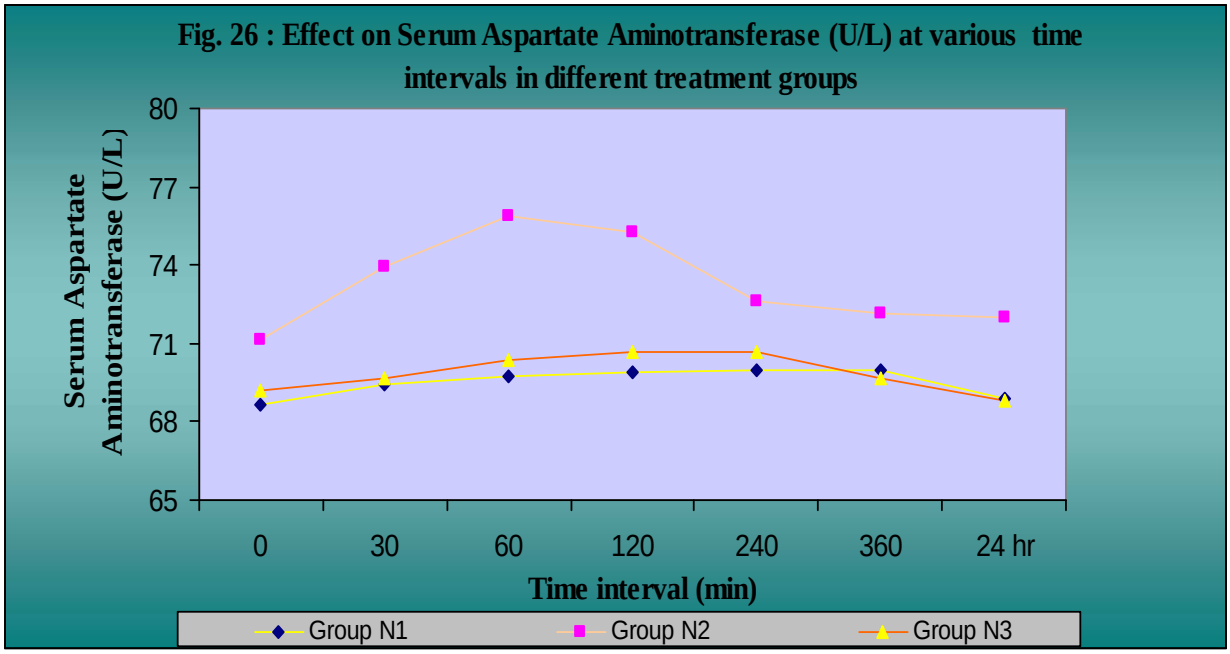
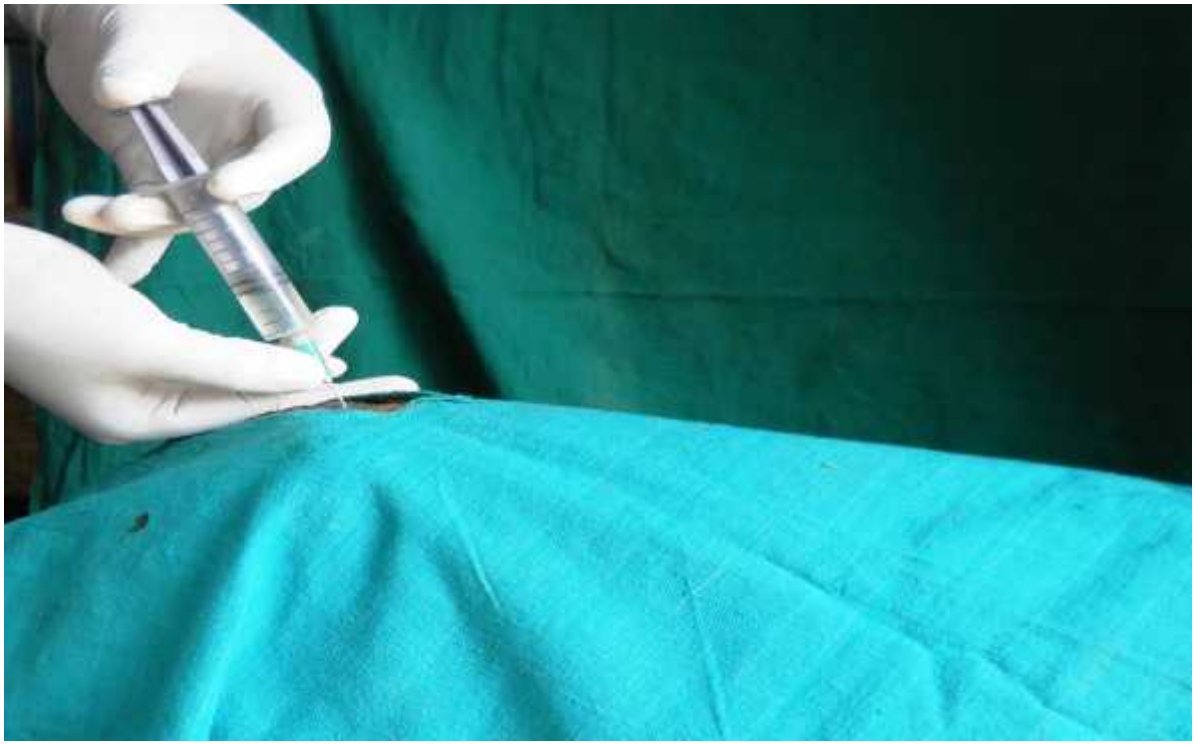


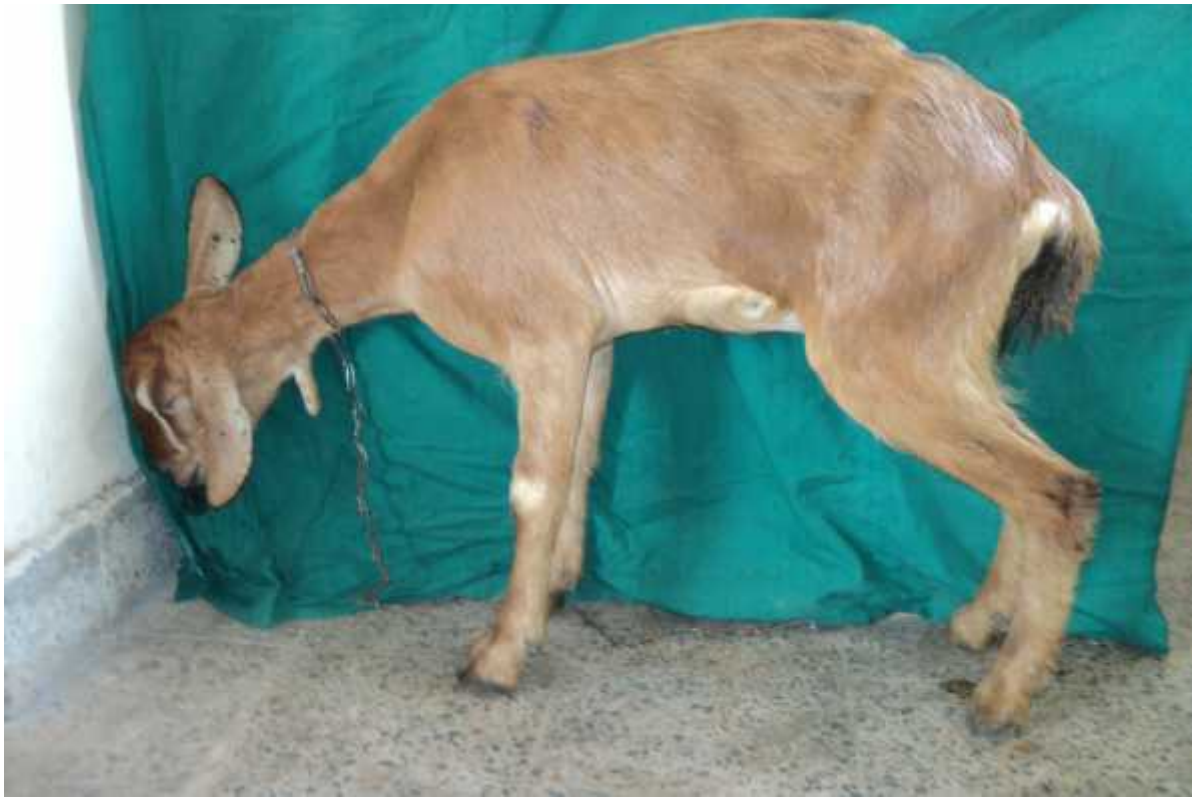
Fig. 26 : Effect on Serum Aspartate Aminotransferase (U/L) at various time intervals in different treatment groups
Serum Aspartate Aminotransferase (U/L)
80
77
74
71
68
65
0
30
60
120
240
360
24 hr
Time interval (min)
Group N1
Group N2
Group N3

PHOTOGRAPH-1 SHOWING THE DRUGS USED IN THE PRESENT STUDY

PHOTOGRAPH-2 WEIGHING OF THE EXPERIMENTAL ANIMAL



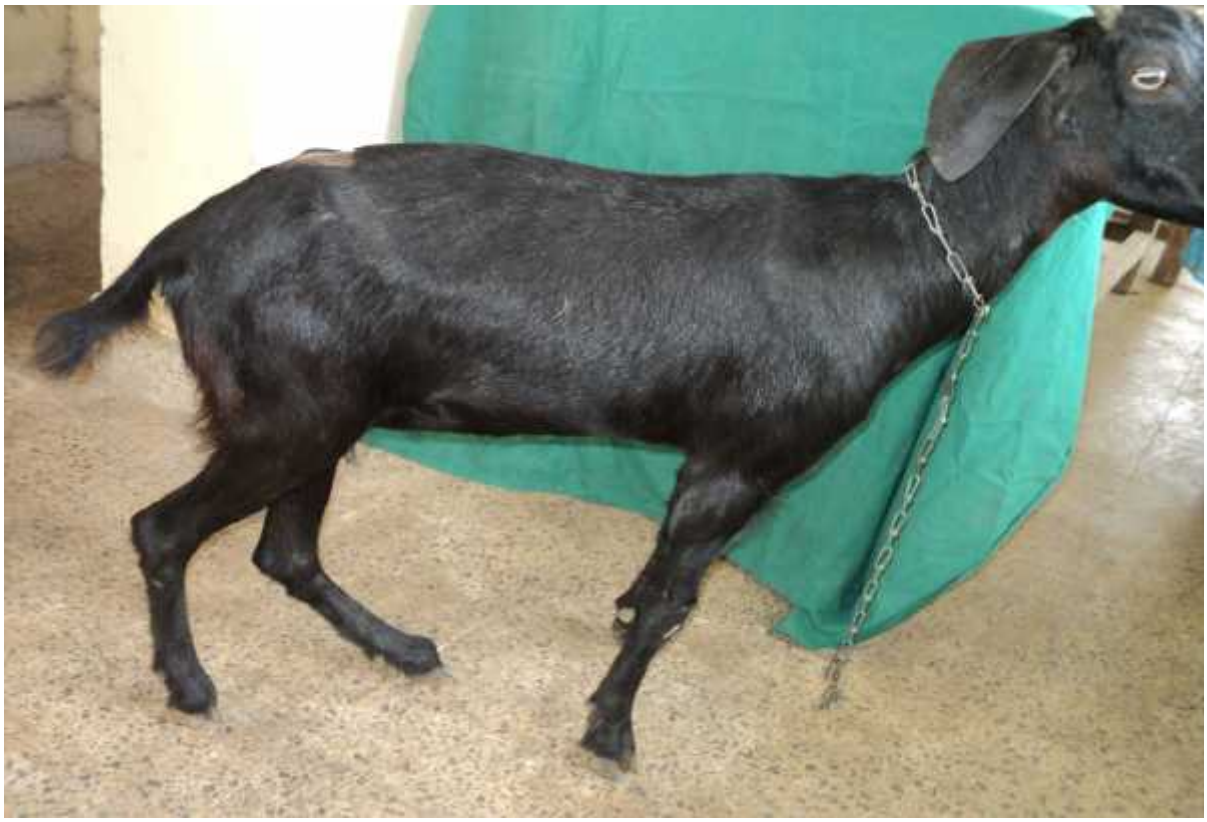
PHOTOGRAPH-3 SHOWING THE SITE OF INJECTION OF EPIDURAL ANAESTHESIA



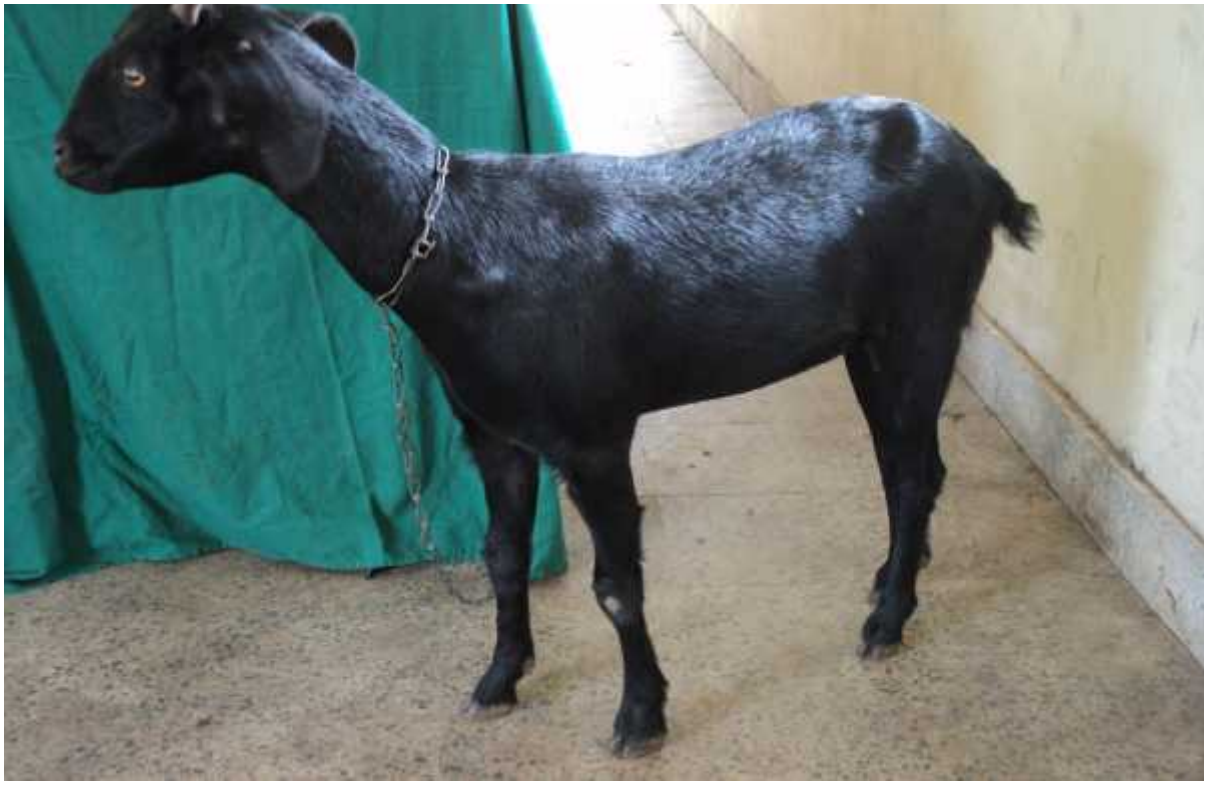
PHOTOGRAPH-4 SHOWING MOTOR INCORDINATION AND SEDATION AFTER EPIDURAL ANAESTHESIA USING BUPIVACAINE

PHOTOGRAPH-5 SHOWING THE MOTOR-INCOORDINATION AFTER EPIDURAL ANAESTHESIA USING BUPIVACAINE-DETOMIDINE COMBINATION

PHOTOGRAPH-6 SHOWING EXCESSIVE SALIVATION WITH ZERO-HEAD TO GROUND DISTANCE AFTER EPIDURAL ANAESTHESIA USING BUPIVACAINE-DETOMIDINE COMBINATION



PHOTOGRAPH-7 SHOWING THE MOTOR-INCOORDINATION AFTER EPIDURAL ANAESTHESIA USING BUPIVACAINE-TRAMADOL COMBINATION



PHOTOGRAPH-8 SHOWING GOAT AFTER COMPLETE RECOVERY

Table No. 2 : Effect on clinical parameters after epidural administration of Bupivacaine alone, and its combination with detomidine and tramadol in goats.

Parameters	Groups (n=5)		
	N1	N2	N3
Onset of anaesthesia (min)	7.93±0.14	5.08±0.13*	6.92±0.17*
Duration of anaesthesia (min)	90.00±2.92	164.20±4.69**	112.80±2.86**
Complete recovery (min)	124.80±3.92	200.32±6.55**	147.00±4.08**

* P < 0.05 = Significant at 5% level when compared to base value
** P < 0.01 = Significant at 1% level when compared to base value

Table No. 3 : Score of analgesia at flank region at various time intervals in different treatment groups.

Groups	Time Intervals(min)										
	0	10	20	30	45	60	75	90	120	180	240
N1	0.00 ±0.00	0.00 ±0.00	0.40 ±0.24	0.80 b ±0.22	1.00 b ±0.08	1.00 b ±0.16	0.80 b ±0.25	0.60 ±0.24	0.40 ±0.24	0.00 ±0.20	0.00 ±0.00
N2	0.00 ±0.00	0.60 ±0.24	1.20 b ±0.25	2.36 ab ±0.23	2.80 ab ±0.22	2.80 ab ±0.20	2.60 ab ±0.24	1.95 ab ±0.05	1.35 ab ±0.33	1.10 b ±0.10	0.00 ±0.00
N3	0.00 ±0.00	0.40 ±0.24	0.60 ±0.24	1.00 b ±0.08	1.20 b ±0.20	1.40 b ±0.24	1.20 b ±0.22	1.00 b ±0.08	0.80 ±0.22	0.00 ±0.00	0.00 ±0.00

Means bearing different superscripts differ significantly at corresponding intervals

Table No. 4 : Score of analgesia at inguinal region at various time intervals in different treatment groups.

Groups	Time Intervals(min)										
	0	10	20	30	45	60	75	90	120	180	240
N1	0.00 ±0.00	0.60 ±0.26	0.80 ^{b} ±0.22	1.02 ^{b} ±0.16	2.00 ^{ab} ±0.08	2.40 ^{ab} ±0.26	2.60 ^{ab} ±0.27	1.40 ^{b} ±0.30	1.00 ±0.08	0.00 ±0.00	0.00 ±0.00
N2	0.00 ±0.00	1.00 ±0.08	1.60 ^{ab} ±0.26	2.80 ^{ab} ±0.22	2.90 ^{ab} ±0.13	3.00 ^{ab} ±0.08	2.60 ^{ab} ±0.24	2.20 ^{ab} ±0.15	1.60 ^{ab} ±0.25	1.20 ^{b} ±0.22	0.00 ±0.00
N3	0.00 ±0.00	0.08 ±0.20	1.00 ^{b} ±0.08	1.40 ^{b} ±0.24	2.47 ^{ab} ±0.22	2.60 ^{ab} ±0.24	2.60 ^{ab} ±0.26	1.60 ^{ab} ±0.24	1.20 ^{b} ±0.22	0.00 ±0.00	0.00 ±0.00

Means bearing different superscripts differ significantly at corresponding intervals

Table No. 5 : Score of analgesia at hind limbs at various time intervals in different treatment groups.

Groups	Time Intervals(min)										
	0	10	20	30	45	60	75	90	120	180	240
N1	0.00 ±0.00	0.40 ±0.24	1.20 ^{b} ±0.20	1.60 ^{b} ±0.24	1.80 ^{b} ±0.20	1.80 ^{b} ±0.20	1.60 ^{b} ±0.24	1.40 ^{b} ±0.26	1.20 ±0.20	0.00 ±0.00	0.00 ±0.00
N2	0.00 ±0.00	0.08 ±0.20	1.60 ^{b} ±0.26	2.25 ^{ab} ±0.19	2.35 ^{ab} ±0.27	2.80 ^{ab} ±0.00	2.70 ^{ab} ±0.08	2.35 ^{ab} ±0.27	1.85 ±0.22	1.20 ±0.20	0.00 ±0.00
N3	0.00 ±0.00	0.62 ±0.25	1.40 ^{b} ±0.26	2.00 ^{b} ±0.00	2.40 ^{ab} ±0.26	2.20 ^{ab} ±0.20	2.00 ^{b} ±0.00	2.00 ^{b} ±0.00	1.20 ±0.20	0.00 ±0.00	0.00 ±0.00

Means bearing different superscripts differ significantly at corresponding intervals

Table No. 6 : Score of analgesia at perineum region at various time intervals in different treatment groups.

Groups	Time Intervals(min)										
	0	10	20	30	45	60	75	90	120	180	240
N1	0.00 ±0.00	1.28 ±0.16	2.00 ^{b} ±0.03	2.35 ^{ab} ±0.22	2.95 ^{ab} ±0.06	2.99 ^{ab} ±0.04	2.01 ^{b} ±0.02	2.00 ^{b} ±0.03	1.40 ^{b} ±0.04	0.00 ±0.00	0.00 ±0.00
N2	0.00 ±0.00	1.95 ^{b} ±0.05	2.02 ^{ab} ±0.02	3.07 ^{ab} ±0.05	3.02 ^{ab} ±0.11	3.00 ^{ab} ±0.08	3.00 ^{ab} ±0.05	3.00 ^{ab} ±0.08	1.80 ±0.22	1.02 ±0.02	0.00 ±0.00
N3	0.00 ±0.00	1.60 ^{b} ±0.24	2.00 ^{b} ±0.08	2.40 ^{ab} ±0.06	2.60 ^{ab} ±0.24	2.80 ^{ab} ±0.08	2.93 ^{ab} ±0.08	2.60 ^{ab} ±0.24	1.80 ^{b} ±0.20	1.02 ±0.08	0.00 ±0.00

Means bearing different superscripts differ significantly at corresponding intervals

Table No. 7 : Score of analgesia at tail region at various time intervals in different treatment groups.

Groups	Time Intervals(min)										
	0	10	20	30	45	60	75	90	120	180	240
N1	0.00 ±0.00	0.20 ±0.20	1.00 ^{b} ±0.08	1.20 ^{b} ±0.20	1.20 ^{b} ±0.20	1.00 ^{b} ±0.08	0.60 ±0.24	0.40 ±0.24	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00
N2	0.00 ±0.00	0.60 ±0.24	1.80 ^{b} ±0.25	2.20 ^{ab} ±0.20	2.40 ^{ab} ±.0.24	2.40 ^{ab} ±0.24	2.20 ^{ab} ±0.20	1.60 ^{b} ±0.24	1.20 ^{b} ±0.20	0.80 ±0.22	0.00 ±0.00
N3	0.00 ±0.00	0.40 ±0.24	1.20 ^{b} ±0.20	1.40 ^{b} ±0.24	1.60 ^{b} ±0.24	1.60 ^{b} ±0.24	1.40 ^{b} ±0.24	1.00 ^{b} ±0.08	0.40 ±0.24	0.20 ±0.20	0.00 ±0.00

Means bearing different superscripts differ significantly at corresponding intervals

Table No. 8 : Score of motor incoordination of hind limbs at various time intervals in different treatment groups.

Groups	Time Intervals(min)										
	0	10	20	30	45	60	75	90	120	180	240
N1	0.00 ±0.00	0.40 ±0.26	1.00 [b] ±0.16	1.40 [b] ±0.24	1.40 [b] ±0.24	1.40 [b] ±0.26	1.21 [b] ±0.22	1.00 [b] ±0.08	0.60 ±0.26	0.60 ±0.24	0.00 ±0.00
N2	0.00 ±0.00	0.80 ±0.22	1.80 [b] ±0.22	2.20 [ab] ±0.20	2.60 [ab] ±0.24	2.80 [ab] ±0.25	2.00 [ab] ±0.20	1.40 [b] ±0.24	1.10 [b] ±0.25	1.00 ±0.16	0.80 ±0.22
N3	0.00 ±0.00	0.60 ±0.24	1.20 [b] ±0.20	1.80 [b] ±0.25	1.80 [b] ±0.25	1.60 [b] ±0.29	1.20 [b] ±0.22	1.10 [b] ±0.08	1.00 ±0.08	0.80 ±0.22	0.00 ±0.00

Means bearing different superscripts differ significantly at corresponding intervals

Table No. 9 : Score of sedation at various time intervals in different treatment groups.

Groups	Time Intervals(min)										
	0	10	20	30	45	60	75	90	120	180	240
N1	0.00 ±0.00	0.00 ±0.00	0.20 ±0.20	0.40 ±0.24	0.30 ±0.25	0.10 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00
N2	0.00 ±0.00	0.40 ±0.24	0.80 ±0.20	1.40 [b] ±0.24	2.82 [ab] ±0.21	3.00 [ab] ±0.08	3.00 [ab] ±0.08	2.40 [ab] ±0.24	1.40 [b] ±0.24	1.20 [b] ±0.20	0.00 ±0.00
N3	0.00 ±0.00	0.40 ±0.24	0.60 ±0.25	1.20 [b] ±0.20	1.20 [b] ±0.21	1.20 [b] ±0.21	0.80 ±0.20	0.40 ±0.24	0.20 ±0.20	0.00 ±0.00	0.00 ±0.00

Means bearing different superscripts differ significantly at corresponding intervals

Table No.10 : Score of salivation at various time intervals in different treatment groups.

Groups	Time Intervals(min)										
	0	10	20	30	45	60	75	90	120	180	240
N1	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00
N2	0.00 ±0.00	0.80 ±0.21	1.22 ±0.23	1.98 ±0.04	3.00** ±0.08	3.00** ±0.08	2.60** ±0.26	2.20** ±0.20	1.40 ±0.26	0.40 ±0.24	0.00 ±0.00
N3	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00

** P < 0.01 = Significant at 1% level when compared to base value

Table No. 11 : Effect on Heart Rate (Beats/ minute) at various time intervals in different treatment groups.

Groups	Time Intervals(min)										
	0	10	20	30	45	60	75	90	120	180	240
N1	81.40 ±4.45	77.20 ±3.90	76.20 ±3.56	75.40* ±2.88	74.80* ±1.92	75.00* ±2.92	75.20 ±3.27	75.35 ±3.24	75.50 ±3.36	78.00 ±2.74	79.80 ±3.83
N2	69.40 ±6.99	59.80* ±5.22	56.60** ±4.88	55.80** ±6.26	55.60** ±6.27	54.60** ±5.55	55.00** ±6.40	55.40** ±6.13	57.80** ±6.80	58.00 ±5.57	65.80 ±6.34
N3	77.80 ±6.72	72.00 ±7.58	71.60 ±4.62	70.80* ±5.17	72.40* ±4.62	73.80* ±3.49	72.60* ±2.95	74.20 ±2.17	77.60 ±2.61	76.20 ±1.92	76.20 ±1.92

* P < 0.05 = Significant at 5% level when compared to base value

** P < 0.01 = Significant at 1% level when compared to base value

Table No. 12 : Effect on Respiration Rate (per minute) at various time intervals in different treatment groups.

Groups	Time Intervals(min)										
	0	10	20	30	45	60	75	90	120	180	240
N1	24.40 ±1.67	20.40 ±3.44	19.00 ±3.74	18.00* ±3.16	19.20* ±2.28	19.40* ±3.51	19.60 ±2.77	19.68 ±2.57	19.80 ±2.17	20.60 ±3.16	22.20 ±3.54
N2	19.20 ±2.39	17.20 ±3.83	14.60 ±3.22	12.20** ±3.35	10.80** ±3.70	11.20** ±3.03	12.20** ±2.86	13.40 ±1.82	15.80 ±2.86	16.60 ±2.41	16.80 ±2.70
N3	22.00 ±3.54	20.40 ±3.21	19.80 ±3.27	18.80* ±2.55	18.60* ±3.05	18.75* ±3.21	18.80 ±4.32	19.60 ±3.91	19.60 ±4.88	20.20 ±4.21	20.60 ±2.88

* P < 0.05 = Significant at 5% level when compared to base value

** P < 0.01 = Significant at 1% level when compared to base value

Table No. 13 : Effect on Rectal Temperature (˚F) at various time intervals in different treatment groups.

Groups	Time Intervals(min)										
	0	10	20	30	45	60	75	90	120	180	240
N1	103.80 ±0.72	103.56 ±0.74	103.44 ±0.79	103.32 ±0.89	103.24 ±0.93	102.92 ±0.83	103.04 ±0.82	102.88 ±1.05	103.08 ±0.77	102.92 ±0.72	102.76 ±0.43
N2	102.96 ±0.90	102.92 ±0.81	102.80 ±0.71	102.64 ±.75	102.36 ±.0.79	102.36 ±0.73	102.24 ±0.79	101.80 ±1.19	101.72 ±1.29	101.64 ±1.13	101.56 ±1.24
N3	103.54 ±1.17	103.28 ±1.25	103.40 ±1.16	103.32 ±1.15	102.48 ±0.86	103.64 ±.0.84	103.64 ±0.74	102.82 ±.0.66	103.64 ±0.83	103.68 ±0.76	103.06 ±0.91

Table No. 14 : Effect on Ruminal Movements at various time intervals in different treatment groups.

Groups	Time interval(min)						
	0	**30**	**60**	**120**	**240**	**360**	**24 hrs**
N1	4.00 ±0.32	3.00 ±0.06	3.00 ±0.32	3.00 ±0.32	4.00 ±0.32	4.00 ±0.06	4.00 ±0.32
N2	4.00 ±0.06	2.00* ±0.06	2.00* ±0.32	2.00* ±0.13	2.00* ±0.06	3.00 ±0.32	4.00 ±0.06
N3	4.00 ±0.06	3.00 ±0.32	2.20 ±0.20	2.40 ±0.24	3.80 ±0.24	4.00 ±0.32	4.00 ±0.06

* $P < 0.05$ = Significant at 5% level when compared to base value

Table No. 15 : Effect on Haemoglobin (gm %) at various time intervals in different treatment groups.

Groups	Time interval(min)						
	0	**30**	**60**	**120**	**240**	**360**	**24 hrs**
N1	11.00 ±0.15	10.17 ±0.09	10.36 ±0.42	10.30 ±0.46	10.67 ±0.27	10.76 ±0.17	10.79 ±0.15
N2	10.60 ±0.16	10.22 ±0.23	9.50* ±0.26	9.69* ±0.22	10.00 ±0.00	10.06 ±0.02	10.21 ±0.23
N3	10.79 ±0.19	9.64 ±0.12	10.56 ±0.11	10.30 ±0.16	10.36 ±0.13	10.39 ±0.07	10.54 ±0.15

* $P < 0.05$ = Significant at 5% level when compared to base value

Table No. 16 : Effect on Packed Cell Volume (%) at various time intervals in different treatment groups.

Groups	Time interval(min)						
	0	**30**	**60**	**120**	**240**	**360**	**24 hrs**
N1	31.34 ±1.15	30.98 ±1.05	30.44 ±1.07	29.98* ±1.05	30.56 ±0.88	30.96 ±0.85	31.20 ±0.84
N2	31.78 ±0.82	30.28 ±0.82	29.98* ±0.82	30.38* ±0.82	30.99 ±0.84	31.06 ±0.82	31.26 ±0.82
N3	30.90 ±1.14	29.40 ±1,14	30.08 ±1.08	29.50* ±1.15	30.08 ±1.11	30.29 ±1.11	30.45 ±1.11

* $P < 0.05$ = Significant at 5% level when compared to base value

Table No. 17 : Effect on Total Leucocytes Count (x 10^3cumm^{-1}) at various time intervals in different treatment groups.

Groups	Time interval(min)						
	0	**30**	**60**	**120**	**240**	**360**	**24 hrs**
N1	8.82 ±0.02	7.84 ±0.01	8.03 ±0.02	8.11 ±0.02	8.15 ±0.03	8.63 ±0.02	8.73 ±0.01
N2	7.23 ±0.02	6.83 ±0.19	6.48 ±0.02	6.60 ±0.17	6.83 ±0.05	7.08 ±0.11	7.16 ±0.30
N3	6.50 ±0.31	5.91 ±0.07	5.79 ±0.06	5.81 ±0.09	6.05 ±0.17	6.33 ±0.12	6.43 ±0.01

Table No. 18 : Effect on Neutrophils (%) at various time intervals in different treatment groups.

Groups	Time interval(min)						
	0	**30**	**60**	**120**	**240**	**360**	**24 hrs**
N1	32.80 ±0.55	34.00 ±1.22	34.80 ±1.84	33.40 ±0.45	32.60 ±0.24	33.62 ±0.55	32.61 ±0.55
N2	33.60 ±0.64	35.61 ±1.55	35.90 ±1.52	35.61 ±0.35	34.50 ±0.65	33.20 ±0.55	32.60 ±0.24
N3	32.20 ±0.84	33.00 ±0.18	35.40 ±0.36	33.60 ±0.55	34.62 ±0.55	33.40 ±0.34	32.20 ±0.45

Table No. 19 : Effect on Lymphocytes (%) at various time intervals in different treatment groups.

Groups	Time interval(min)						
	0	**30**	**60**	**120**	**240**	**360**	**24 hrs**
N1	57.60 ±0.63	55.60 ±0.55	54.40 ±0.72	54.45 ±0.84	54.60 ±0.83	55.80 ±0.46	57.40 ±0.76
N2	55.40 ±0.52	54.40 ±0.43	51.40 ±0.22	52.60 ±0.55	52.80 ±0.43	53.80 ±0.32	53.30 ±0.21
N3	57.80 ±0.95	56.00 ±0.82	55.06 ±0.45	57.00 ±0.71	56.60 ±0.55	56.80 ±0.43	57.50 ±0.24

Table No. 20: Effect on Monocytes (%) at various time intervals in different treatment groups.

Groups	Time interval(min)						
	0	**30**	**60**	**120**	**240**	**360**	**24 hrs**
N1	5.60 ±0.16	5.12 ±0.21	4.53 ±0.21	4.50 ±0.19	5.16 ±0.15	5.44 ±0.12	5.49 ±0.22
N2	5.15 ±0.26	4.12 ±0.09	3.92 ±0.10	4.10 ±0.10	4.68 ±0.12	4.92 ±0.13	5.19 ±0.34
N3	5.86 ±0.15	5.21 ±0.16	4.84 ±0.12	4.64 ±0.13	4.73 ±0.13	5.33 ±0.19	5.46 ±0.10

Table No. 21 : Effect on Eosinophils (%) at various time intervals in different treatment groups.

Groups	Time interval(min)						
	0	**30**	**60**	**120**	**240**	**360**	**24 hrs**
N1	3.34 ±0.46	3.92 ±0.45	4.08 ±0.23	3.72 ±0.30	3.85 ±0.28	3.48 ±0.17	3.23 ±0.40
N2	3.78 ±0.17	3.61 ±0.17	3.82 ±0.25	3.76 ±0.19	3.75 ±0.21	3.73 ±0.21	3.68 ±0.27
N3	3.16 ±0.14	3.28 ±0.14	3.62 ±0.14	3.48 ±0.17	3.29 ±0.18	3.24 ±0.16	3.09 ±0.24

Table No. 22 : Effect on Serum Glucose (mg/dl) at various time intervals in different treatment groups.

Groups	Time interval(min)						
	0	**30**	**60**	**120**	**240**	**360**	**24 hrs**
N1	62.80 ±1.92	65.00 ±2.24	70.40** ±1.67	68.60** ±1.14	66.40 ±1.34	64.40 ±1.95	62.20 ±1.48
N2	58.40 ±1.14	63.40* ±1.14	69.20** ±0.84	68.80** ±1.92	62.60 ±2.88	59.60 ±2.07	57.40 ±1.14
N3	61.00 ±2.45	64.00 ±3.16	67.20** ±2.77	66.80** ±2.77	63.60 ±3.21	62.00 ±2.24	61.00 ±2.25

* $P < 0.05$ = Significant at 5% level when compared to base value
** $P < 0.01$ = Significant at 1% level when compared to base value

Table No. 23 : Effect on Serum Total Protein (gm/dl) at various time intervals in different treatment groups.

Groups	Time interval(min)						
	0	**30**	**60**	**120**	**240**	**360**	**24 hrs**
N1	7.55 ±0.12	7.51 ±0.14	7.44 ±0.19	7.41 ±0.15	7.43 ±0.09	7.45 ±0.11	7.53 ±0.08
N2	7.02 ±0.32	6.68 ±0.31	6.92 ±0.28	6.89 ±0.34	6.91 ±0.35	6.97 ±0.34	6.78 ±0.18
N3	7.57 ±0.44	7.51 ±0.43	7.43 ±0.41	7.37 ±0.41	7.38 ±0.39	7.49 ±0.46	7.54 ±0.45

Table No. 24 : Effect on Serum Urea Nitrogen (mg/dl) at various time intervals in different treatment groups.

Groups	Time interval(min)						
	0	**30**	**60**	**120**	**240**	**360**	**24 hrs**
N1	17.59 ±0.07	18.64 ±0.27	19.82 ±0.61	20.74 ±1.21	19.86 ±1.08	17.66 ±0.72	17.51 ±0.41
N2	18.41 ±0.46	19.69* ±0.42	22.66* ±0.69	21.94* ±1.09	21.02 ±0.86	19.73 ±0.48	18.15 ±0.14
N3	17.07 ±0.22	18.29* ±0.50	18.65* ±0.25	19.37* ±0.79	19.92 ±1.18	18.51 ±0.53	17.70 ±0.34

* $P < 0.05$ = Significant at 5% level when compared to base value

Table No. 25 : Effect on Serum Creatinine (mg/dl) at various time intervals in different treatment groups.

Groups	Time interval(min)						
	0	**30**	**60**	**120**	**240**	**360**	**24 hrs**
N1	1.22 ±0.10	1.32 ±0.10	1.36 ±0.11	1.42 ±0.14	1.45 ±0.14	1.45 ±0.12	1.44 ±0.11
N2	1.04 ±0.03	1.41* ±0.09	1.92* ±0.04	1.80* ±0.10	1.69 ±0.11	1.27 ±0.06	1.53 ±0.11
N3	1.26 ±0.04	1.45 ±0.08	1.53* ±0.10	1.57* ±0.08	1.50 ±0.08	1.41 ±0.10	1.30 ±0.11

* $P < 0.05$ = Significant at 5% level when compared to base value

Table No. 26 : Effect on Serum Alanine Aminotransferase(U/L) at various time intervals in different treatment groups.

Groups	Time interval(min)						
	0	**30**	**60**	**120**	**240**	**360**	**24 hrs**
N1	21.50 ±1.22	25.44 ±1.63	25.24* ±3.34	26.32* ±2.51	26.34 ±2.13	24.20 ±1.48	22.04 ±1.05
N2	23.20 ±1.01	25.74 ±0.82	28.04** ±0.64	27.82** ±1.09	26.48 ±1.12	24.92 ±1.87	23.82 ±1.79
N3	22.22 ±0.93	24.36 ±1.19	25.42* ±1.54	25.30* ±1.15	24.66 ±0.52	23.94 ±0.61	22.82 ±0.87

* $P < 0.05$ = Significant at 5% level when compared to base value
** $P < 0.01$ = Significant at 1% level when compared to base value

Table No. 27 : Effect on Serum Aspartate Aminotransferase (U/L) at various time intervals in different treatment groups.

Groups	Time interval (min)						
	0	**30**	**60**	**120**	**240**	**360**	**24 hrs**
N1	68.68 ±3.12	69.40 ±2.69	69.77 ±1.75	69.92 ±1.39	69.94 ±1.25	69.94 ±0.55	68.86 ±2.33
N2	71.12 ±1.33	73.92 ±1.23	75.88* ±1.30	75.28* ±1.79	72.58 ±1.67	72.12 ±1.69	72.00 ±1.60
N3	69.18 ±2.65	69.70 ±2.38	70.38 ±2.22	70.68 ±2.40	70.64 ±2.81	69.66 ±2.82	68.84 ±2.87

* $P < 0.05$ = Significant at 5% level when compared to base value