DEVELOPMENT OF BALANCED SPINAL ANALGESIC TECHNIQUES IN URAEMIC BUFFALO CALVES

Thesis

SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF

Doctor of Philosophy

IN

VETERINARY SURGERY

By

Dr. Rekha Pathak

Roll No. 599

TO

DEEMED UNIVERSITY

INDIAN VETERINARY RESEARCH INSTITUTE

IZATNAGAR - 243 122, U.P., INDIA

2005

Dedicated to....

My Son Aditya

&

My Husband Pankaj

Dr (Maj.) K. Pratap, M.V.Sc., Ph.D.
Principal Scientist
Division of Surgery
Indian Veterinary Research Institute,
Izatnagar-243 122, U.P.

Dated: 8 June, 2005

Certificate

Certified that the research work embodied in this thesis entitled "**Development of balanced spinal analgesic techniques in uraemic buffalo calves**" *submitted by Dr. Rekha Pathak for the award of Doctor of Philosophy Degree in Veterinary Surgery at Indian Veterinary Research Institute, Izatnagar, is the original work carried out by the candidate herself under my supervision and guidance.*

It is further certified that Dr. Rekha Pathak has worked for more than 34 months in the Institute and has put in more than 34 months attendance under me from the date of registration for the Doctor of Philosophy Degree in this Deemed University, as required under the relevant ordinance.

(Dr. (Maj.) K. Pratap)
Chairman
Advisory Committee

Certificate

Certified that the thesis entitled, "**Development of balanced spinal analgesic techniques in uraemic buffalo calves**"*submitted by Dr. Rekha Pathak,* Roll No. 599, *in partial fulfilment of Doctor of Philosophy degree in* **Veterinary Surgery** *at Indian Veterinary Research Institute, embodies the original work done by the candidate. The candidate has carried out her work sincerely and methodically.*

We have carefully gone through the contents of the thesis and are fully satisfied with the work carried out by the candidate, which is being presented by her for the award of ***Ph.D. Degree*** *of this Institute.*

It is further certified that the candidate has completed all the prescribed requirements governing the award of ***Ph.D. Degree*** *of the Deemed University, Indian Veterinary Research Institute, Izatnagar.*

Signature of the ~~External~~ Examiner

Date : 12/01/05

(Dr. (Maj.) K. Pratap)
Chairman
Advisory Committee

Date : 08/01/05

MEMBERS OF STUDENT'S ADVISORY COMMITTEE

Dr. P. Kinjavdekar, Sr. Scientist, Div. of Surgery .....

Dr. Amarpal, Sr. Scientist, Div. of Surgery .....

Dr. D.C. Shukla, Head, Div. of Physiology & Climatology .....

Dr. O.P. Paliwal, Head, Div. of Pathology .....

Dr. D. Swarup, Head, Div. of Medicine .....

Dr. Satish Kumar, Pr. Scientist, Div. of Animal Reproduction .....

ACKNOWLEDGEMENT

I convey my deepest sense of gratitude and indebtness to my advisor ***Dr. (Maj.) Krishna Pratap*** *for his valuable suggestions, empathetic care, generous help and excellent encouragement in conducting this research work. An immence affection and warmth from him and his family is greatly acknowledged.*

I am extremely grateful to my Head of the division, ***Dr. Gajraj Singh*** *for his constructive counsel, inspiration, affection and constant encouragement throughout the course of this investigation.*

A formal statement of acknowledgement will hardly meet the ends of justice in the matter of expression of my deeply felt sincere gratitude to my esteemed advisory committee member ***Dr. Amarpal,*** *Senior Scientist, Division of Surgery, for his scholistic guidance, diligent help and of the most a critical editing of this manuscript.*

I owe special gratitude and feel highly esteemed to thank the other members of my advisory committee, ***Dr.(s) Kinjavdekar, D. C. Shukla, O.P. Paliwal, Satish Kumar*** *for their help and valuable suggestions during my research work.*

It is a great pleasure to record deep sense of gratitude and sincere thanks to all the reverend scientists, ***Dr.(s) O.P. Gupta, A.K. Sharma, M.Hoque, S.K. Maithi, A.M. Pawde, Naveen Kumar*** *and* ***H.P. Aithal*** *for their timely help and cooperation during the course of this study.*

Words are inadequate for me to appreciate unselfish and untiring help given by my Junior ***Dr. Manpreet Singh*** *to whom I am highly indebted. I would like to specially acknowledge* ***Dr. V.P. Varshney,***

Principal Scientist, Division of Physiology and ***Munna Pathak*** *Bhaiyya for their help in biochemical estimation and radioimmunoassay for cortisol estimation.*

Extremely helping attitude of my well wishers need special mention which includes a list of following friends. ***Dr.(s) Sanjeev Kumar Singh, N.K. Singh, Abhijit Dutta, Tarunbir Singh, Ram Bilas Kushwaha, Prassanna, Ramesh Tiwari, Mukesh, Prakash, Selvan, Amburaja, Ajit, Kailash*** *and* ***Natrajan****.*

My gratitudes are due to my in-laws and parents without whose blessings and support it would have been impossible to reach this far in life.

I also thank ***Mr. Dharmendra*** *Ji,* ***Aamil*** *ji and* ***Kamal Verma*** *Ji for framing this manuscript with their meticulous and artistic typing.*

I have no words to pay heart felt regards, love and affection to my husband ***Pankaj*** *and my son,* ***Aditya*** *who had been the most innocent sufferer during the course of present study, for their cooperation, involvement, understanding, failing which it would not have been possible to carry out this work.*

During the course of my present study, I have received help from many people in some way or the other. It is extremely difficult to thank all of them individually by name. This short coming may please be pardoned.

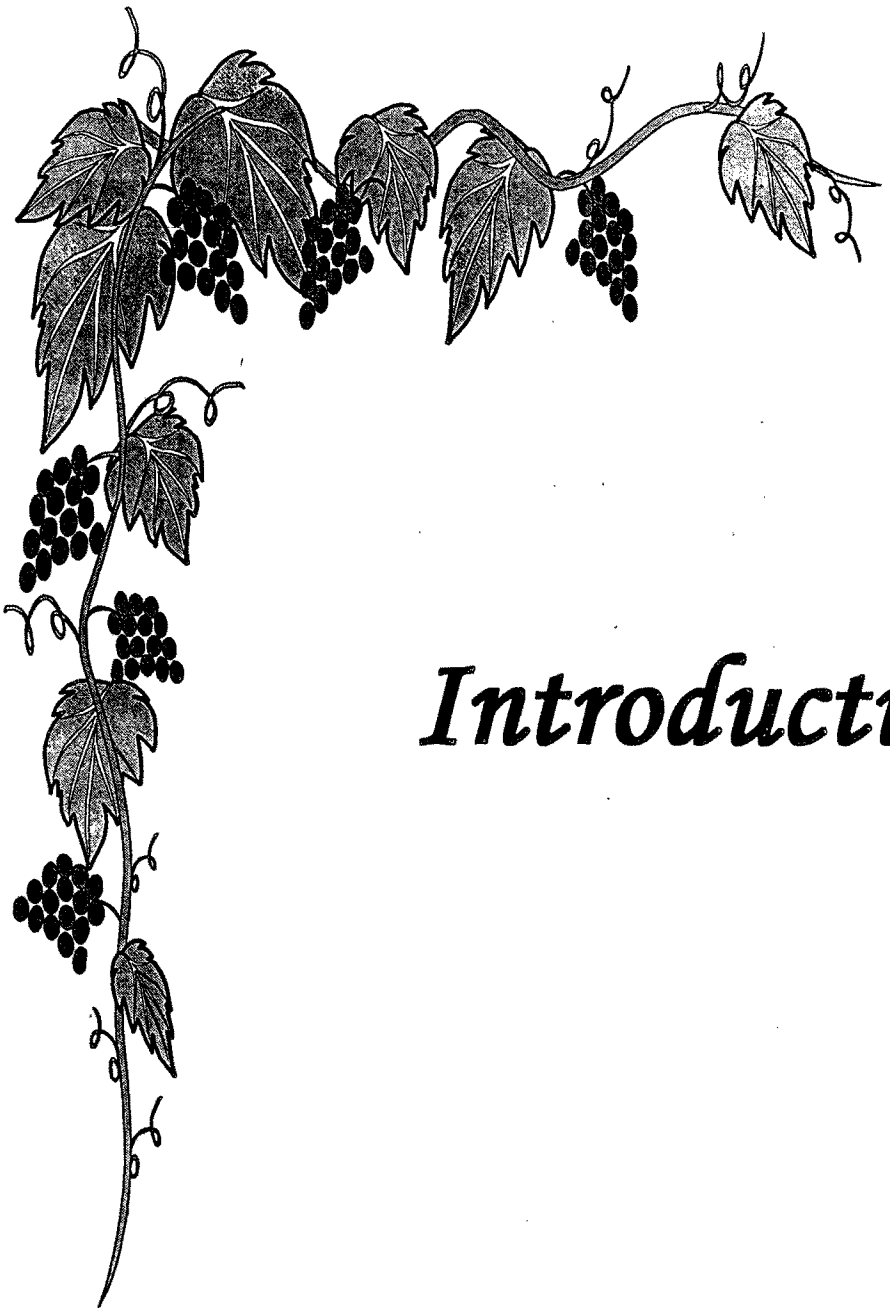
(Rekha Pathak)

Contents

ABBREVIATIONS

µg	Microgram
µL	Microlitre
ADH	Antidiuretic hormone
Ca	Calcium
Cl^-	Chloride ions
CSF	Cerebrospinal fluid
CVP	Central venous pressure
dL	Decilitre
DLC	Differential leukocyte count
DMRT	Duncan's multiple range test
ECG	Electrocardiograph
EDTA	Ethylenediamine tetra acetic acid
Fig.	Figure
FMD	Foot and mouth disease
g	Gram
GGT	Gamma glutamyl transferase
Hb	Haemoglobin
HCl	Hydrochloric acid
HCO_3^-	Bicarbonates
HR	Heart rate
hr	Hour
K^+	Potassium
Kg	Kilogram
L	Litre
MAP	Mean arterial pressure
mEq	Milli equivalent
mg	Milligram
MI	Motor Incoordination
min	Minute
mL	milli litre

mmol	milli mole
Na^+	Sodium ions
NMDA	N-Methyl D-asparate
^oF	Degree farenheit
PCV	Packed cell volume
PUN	Plasma urea nitrogen
RR	Respiratory rate
RT	Rectal temperature
SE	Standard error
Sec	Seconds
TLC	Total leukocyte count
U	Units
α_2	Alpha-2
δ	delta



Introduction

INTRODUCTION

Uraemia is a common clinical condition of almost all domestic animals (Blood and Radostits, 1989), with a higher incidence in bovine and caprine. The onset of uraemia following urolithiasis does not appear to be acute but once the accumulation of urine in the bladder starts, a definite sequence of events take place which ultimately leads to a continuous blood circulation to kidneys without any glomerular filtration resulting eventually in retention of waste metabolites like urea, creatinine and others, which are supposed to be excreted. Since these cases are under severe stress due to dehydration, continued pain, long standing inappetance and uraemia, special care is to be taken for assigning an anesthetic protocol.

Prolonged hypotensive anaesthesia can cause a decrease in renal function and may cause pre-renal uraemic and/or acute renal failure (Stone *et al.,* 1981). Even slight hypotension in animals with uraemia may prove fatal as the animals are already dehydrated, hence anaesthetic agents with minimal effects on cardiovascular and renal functions should be selected for uraemic patients.

It was found that the duration of thiopental narcosis was increased in uraemic animals. Even in minimal doses, thiopental produced prolonged hypotension leading to varied renal blood flow followed by temporary oligouria (Hall *et al.,* 2001). Other general anaesthetics also affect cardiovascular system in animals. General anesthesia should thus be avoided in patients with increased blood urea nitrogen level (Lumb and Jones, 1984). Local and regional anesthesia would be a better choice in such patients.

Regional anesthesia, like epidural /spinal anesthesia has been shown to have less cardiopulmonary and other systemic side effects than general anesthesia in ruminants (Hall *et al.,* 2001). When xylazine and ketamine combination was administered epidurally, both being acting at different sites, showed synergism thereby inducing more profound and prolonged analgesia with reduced cardiopulmonary depression in different animal species (Aithal *et al.,* 1997; Amarpal *et al.,* 1997; Kinjavdekar *et al.*, 1999; Pathak, 1999; Singh *et al.,* 2004).

In an earlier study, it was observed that local anaesthetics, bupivacaine and ropivacaine produced shorter duration and lesser depth of analgesia in uraemic animals as compared to healthy animals (Singh, 2003). In such cases thus the duration of analgesia and depth of analgesia could be enhanced by the use of balanced epidural analgesia using a combination of drug, so that better analgesia could be achieved without increasing the dose of single drug.

Epidural analgesia with 0.75% bupivacaine, a long acting Local anaesthetic was used in human beings for upper abdominal surgery (Mogensen and Bartholdy, 1992), as preemiptive, post-traumatic analgesics and in laparotomy in goats (Trim, 1981; Pathak, 1999). Epidural opioids have been used since long in human beings for relieving of post-operative pain (Lanz *et al.,*1982). Buprenorphine is a partial mu opioid and a weak kappa agonist. It has high affinity for the μ receptors, with slow dissociation resulting in a long duration of action. At higher doses, its agonist effects plateu and it begins to behave more like an antagonist, limiting the maximal analgesic effect. Thus, it has a very wide margin of safety. (Sporer, 2004).

Ketamine has been used to enhance the depth of epidural analgesia produced by xylazine in animals and that produced by local anaesthesia in human beings. Further, ketamine has been reported to have least cardiopulmonary effects when used epidurally. The present study therefore, was designed to evaluate the utility of ketamine to enhance the spinal analgesia produced by bupivacaine, buprenorphine, xylazine and to evaluate these combinations for spinal anaesthesia in the clinical cases of uraemia in buffalo calves with the following objectives :

1. *To compare the analgesic potency and clinical effects of bupivacaine, buprenorphine and xylazine in healthy buffalo calves.*

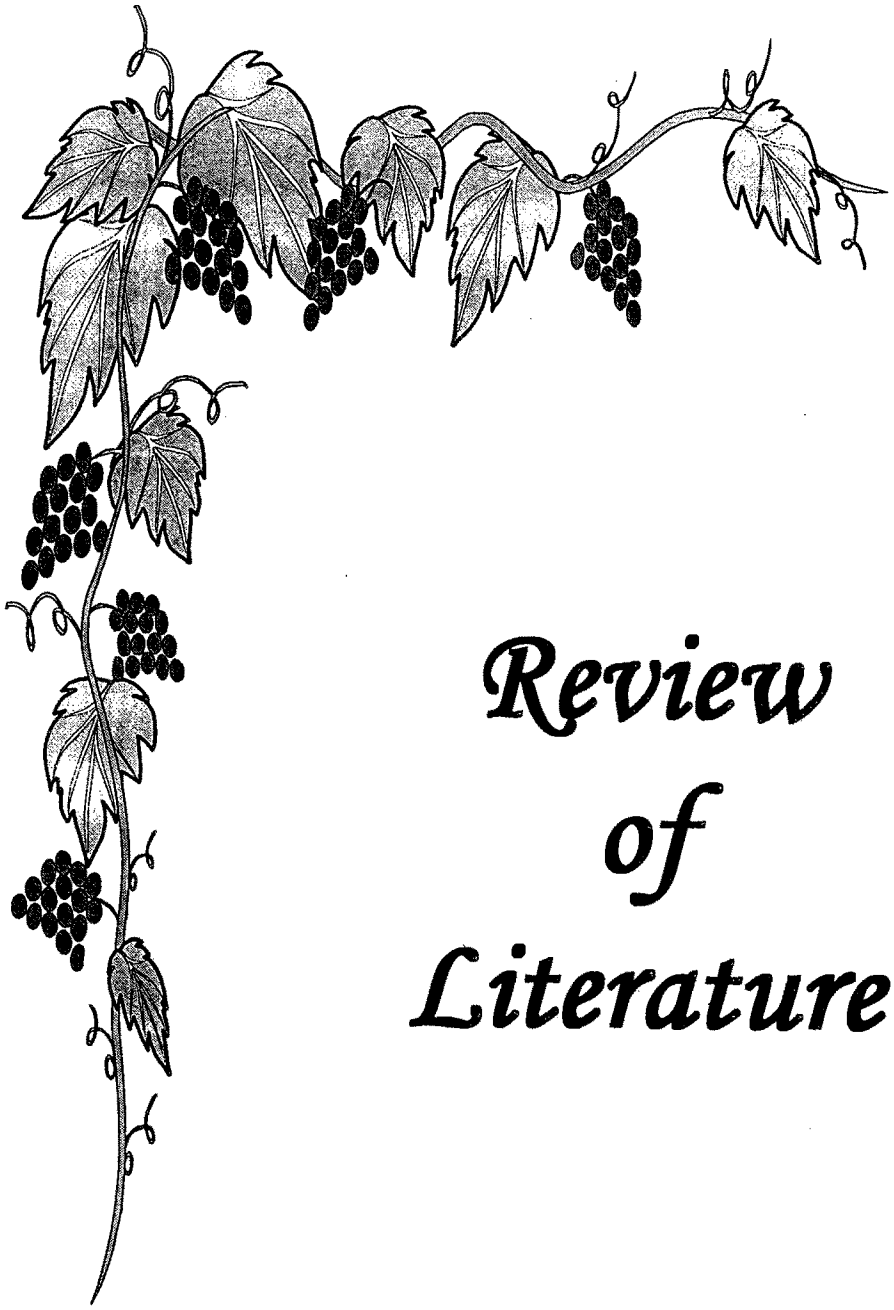
2. *To evaluate the efficiency of ketamine for potentiation of analgesia produced by bupivacaine, buprenorphine and xylazine.*

3. *To study the safety of spinal bupivacaine , buprenorphine and xylazine and their combinations with ketamine using haemato-biochemical parameters.*

4. *To investigate haemodynamic and ECG changes induced by combinations of spinal ketamine with bupivacaine, xylazine and buprenorphine.*

5. *To evaluate the suitability of these combinations in clinical cases of urolithiasis in buffalo calves.*

❑❑❑



Review of Literature

REVIEW OF LITERATURE

Uraemia is a toxemic syndrome resulting from the retention of NPN substances including urea, creatinine, uric acid, ammonia etc. and which may ensue in the development of acidosis.

It is a fairly common condition that may develop due to pre-renal, renal and post renal causes.

I. The pre-renal causes include

a) Lowered B.P. due to shock, trauma, intestinal haemorrhage, which lead to decreased glomerular filtration pressure and waste products of protein metabolism thus retained, aggravates the condition.

b) Diarrhoea, vomition and intestinal obstruction.

c) Fever, large infarcts, gangrene, diabetes, high protein intake or increased protein destruction.

II. The renal lesions resulting in uraemia may be

a) Glomerulonephritis b) Chronic interstitial nephritis (small granular contracted kidney) c) Toxic tubular necrosis and d) Extensive amyloidosis.

III. Post-renal causes include

Urinary tract obstruction by calculi, post-inflammatory strictures, carcinoma of bladder, prostratic enlargement and congenital defects.

In chronic diseases body condition is poor, probably due to continuous loss of protein in the urine, dehydration and anorexia. The most important effects of uremia are

1. Generalized edema resulting from water and salt retention.
2. Acidosis resulting from the failure of the kidneys to get rid the body of normal acidic products.
3. High concentrations of non-protein nitrogens, especially urea, creatinine and uric acid, resulting from failure of body to excrete the metabolic end products of proteins.
4. High concentration of other urinary retention products including phenols, guanidine bases, sulfates, phosphates and potassium.

Uremic coma : After a week or more of renal failure the sensorium becomes clouded and the patient progresses into a state of coma. The acidosis is believed to be principal factor responsible for the coma because acidosis caused by other conditions, such as severe diabetes mellitus a'so causes coma. The respiration usually remains deep and rapid in coma, which is a respiratory attempt to compensate for the metabolic acidosis. Death occurs usually when the pH of the blood falls to about 6.8 (Guyton, 1991).

Anemia and osteomalacia are the other sequlae of uremia.

The animal becomes recumbent and comatose in the terminal stages (Blood and Radostits, 1989). In animals most common cause of uraemia is obstructive urolithiasis. If the treatment of urolithiasis is delayed then it leads to development of uraemia. The uraemic animal is depressed and anorexic with dehydration, muscular weakness and tremor.

In a study in felines, it was found that the continuous urethral obstruction (more than 24 hrs) resulted in rapidly progressing uraemia with significantly increased blood urea and creatinine, signs of anorexia, vomiting, dehydration, bradycardia or tachycardia,

polypnoea and hypothermia. When blood urea level exceeds 50 mmol/L, uraemic comma may occur (Simeonova *et al.*, 2001). Once there is complete obstruction to urine flow, surgical intervention is must.

Anaesthetic and surgical management of veterinary patients with compromised renal function incorporates methods to prevent acute renal failure. Renal ischemia in the dogs is produced by occlusion of the renal artery or by systemic hypotension. In dogs hypotensive anaesthesia with halothane and surgery decreased the glomerular filtration rate and serum urea nitrogen and creatinine increased consequently one day after hypotensive anaesthsia (Stone *et al.*, 1981).

General anaesthetics causes depression of many central functions including the respiratory and cardiovascular centres. Subanaesthetic doses of general anaesthetics are not analgesic and indeed produce hyperalgesia. Cerebral blood flow and metabolism are reduced, the force of cardiac contraction and therefore, cardiac out put is reduced. There is a dilation of the peripheral capacitance vessels with a fall in blood pressure and reduction in renal blood flow (Lumb and Jones, 2001).

General anaesthesia is to be avoided, if at all possible, in animals with an elevated blood urea nitrogen. It is reported in another study that nephrotoxicity with necrosis of collecting ducts and loops of Henle developed unexpectedly in dogs undergoing thoracotomy under GA with methoxyflurane and muscle relaxation with gallamine (Mathews *et al.*, 1990). Local, regional or epidural anaesthesia should therefore, be used whenever possible (Lumb and Jones, 2001). The technique of epidural anaesthesia can be very useful especially for patients suffering from renal dysfunction or urinary tract obstruction (Klide, 1984). Since uremic animals could be considered critically ill patients, they need special care while selecting the anaesthetic protocol. Balanced regional anaesthesia with combination of two or more drugs may be more useful in such cases to avoid side effects of over dosing of single drug. Local and regional analgesia are comonly used for surgical procedures in food animals because the techniques are safe, economical and reliable. Furthermore, local and regional analgesia induce minimal cardiopulmonary alterations and require fewer veterinary personnel and

limited amounts of equipment. Epidural analgesia has been used commonly to perform obstetric and surgical procedures in cattle from perineal region to the cranial portion of the abdomen (Skarda and Muir[a], 1979). Lumbosacral epidural analgesia for ventral abdominal surgery has been reported in pigs (Ko *et al.*, 1992), sheep (Lebeux, 1975), and goats (Pathak *et al.*, 2002; Singh *et al.*, 2002).

However, hypotension after spinal anaesthesia is nevertheless a frequent problem with an incidence of 15.3% (Tarkkila and Jsola, 1992) to 33% (Carpenter *et al.*, 1992). This may cause major adverse outcomes as perfusion pressure decreases to less than the limits for autoregulation of vital organs, and it also may produce minor, but significant, discomfort e.g. post operative nausea, vomiting or dizziness (Tarkkila and Jsola, 1992). The risk of major complication (cardiac morbidity or mortality) attributable to hypotension during either regional or general anaesthesia is very small. Thus, only patients with prolonged hypotension during anaesthesia have an increased risk of major sequelae (Klasen *et al.*, 2003). Protective measures against hypotention after spinal puncture have not been effective. Pre-hydration with large amounts of intravenous fluid has been challenged (Jackson *et al.*, 1995).

Since morphine stimulates secretion of ADH from posterior pituitary, it is contraindicated in uraemia (Lumb and Jones, 2001). Ketamine at a dose rate of 1-2 mg/ kg body weight has been successfully used in cats with uropathy . Alpha-2 agonist xylazine has been used in camel suffering from urolithiasis (Singh *et al.*, 1983).

Spinal analgesia has been defined by Westhues and Fritsch (1964) as being either epidural (i.e. extradural) as a result of injection into the osseous spinal canal but outside the duramater, or subarachnoid (i.e. true spinal) as a result of injection into the cerebrospinal fluid for all procedures caudal to the diaphragm and has been used extensively in small aniamls and cattle. Muscle relaxation and analgesia are excellent allowing for easy visceral manipulation and patient comfort. Spinal analgesia is well tolerated by geriatric patients and in those with systemic disease, which precludes the use of general anaesthesia.

Various drugs, which are used epidurally include α_2-agonists, opioids and local anaesthetic agents, which provide not only excellent surgical anaesthesia but also effective analgesia during the perioperative period (Cousins and Mather, 1984; Skarda and Muir, 1992). The onset, depth, extent and duration of spinal/epidural anaesthesia is contingent upon factors like, spread of the drug. The physical characteristics of spinal anaesthetic solutions are major determinants of their spread in CSF and they are :

1. Density of the anaesthetic solution

The effect of density of anaesthetic solutions on spread of the drugs can be studied directly by relying upon baricity, the ratio between the density of the anaesthetic solution and the density of CSF.

Intrathecal injection of 2.5% procaine in water, was fasterdiluted in CSF and thus resulted in anaesthesia of very brief period (Greene, 1985). A 2% lignocaine in water is functionally isobaric, but after dilution by CSF following injection it becomes too weak to provide anaesthesia for more than short periods (Greene, 1985).

2. Dose of the anaesthetic agent

Bengtsson *et al.* (1984) concluded that dosage (in mg) is more important than either volume or concentration in determining spread of dextrose free bupivacaine solutions.

Similarly, in another study by Shesky *et al.* (1983), the levels of anesthesia were significantly higher in patients given 15 or 20 mg bupivacaine than the patients given 10 mg bupivacaine. Further, the level of anaesthesia was similar in patients who were given the same amount of bupivacaine even though the concentration of bupivacaine and volume injected differed.

However, Pflug *et al.* (1976) found that dose has no effect on distribution of the drug. In their study, 7.5 and 15.0 mg of 0.75% hyperbaric bupivacaine resulted in similar levels of anaesthesia.

3. Volume of the drugs

The injection of a spinal anaesthetic solution into the subarachnoid space causes displacement of CSF away from the site of injection. This causes changes in neurologic function at the site of injection (Greene, 1985). Only excessive fat depots are the barriers to prevent flow of anaesthetic solution forward in the epidural space. The volume of the epidural space is greatest in young adults, and decreases with age (Greene and Thurmon, 1985). In addition to physical characteristics of drugs, there may be several factors that may affect spread of anaesthetics in spinal space. The spread of local anaesthetic was significantly increased with increasing age, weight, body mass-index, addition of fentanyl, higher site of injection, decreasing height, and increasing volume per spinal segment and pregnancy (Bromage, 1962; Curatolo *et al.*, 1994). Age, weight and volume are the predictors of the level of analgesia following epidural injection of bupivacaine (Busoni and Andreuccetti, 1986).

The animals position also effects the spread of the drug. The rear end when lower than the fore end, makes the solution stay in the posterior epidural space (Booth, 1988).

4. Concentration of anaesthetic

The level of anaesthesia was significantly higher in the patients given 0.75% bupivacaine than in those given 0.5% solution (Shesky *et al.*, 1983).

5. Uptake of the drug

To exert the effect, the drug must cross all the spinal meninges, the duramater, arachanoid and piamater to reach the dorsal horn of the spinal cord and exert its effects. Permeability of the drug depends on its hydrophobicity (Bernards and Hill, 1992).

Among the drugs, commonly used epidurally, lignocaine and morphine have much lower distribution coefficients, while fentanyl and sufentanyl have much higher coefficients and are outside the optimal permeability range (Bernards and Hill, 1992).

The distribution coefficient is a measure of solutes relative hydrophobicity and the larger ratios indicate greater hydrophobicity when compared with hydrophillic substances, which have lower coefficients (Bernards and Hill, 1992).

According to Greene (1983) the uptake of anaesthetic solution by tissues is governed by three factors :

a. Tissue blood flow : All the nerve fibres and tracts are not simultaneously and equally blocked during onset of spinal anaesthesia (Cohen, 1968). The higher blood flow to the anterior cord might be responsible for lower concentration of local anaesthetics anteriorly than posteriorly in the cord during spinal anaesthesia.

b. Lipid content : Posterior and lateral spinal cord tracts are more heavily myelinated than at anterior tracts. Heavy myelination, therefore, increases the uptake of local anaesthetics in the neuronal tissue (Cohen, 1968). Epidural fat and veins influenced the spread and the pharmacokinetics of xylazine solution injected into the dorsolumbar epidural space in cattle. The faster onset and longer duration of analgesia with wide area could be obtained by deeper adminsitration under the epidural fat. This technique could be used clinically for flank laparotomy in the standing position in cattle (Lee *et al.*, 2003).

c. Accessibility : Nerve roots are exposed to CSF for considerable distances as they cross the subarachnoid space from the cord to their points of exit through the dura. Cohen (1968), reported that the 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 the 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 anaesthetics by lipids.

Elimination of the drug

The anaesthetic solutions are removed from the subarachnoid space by diffusion and vascular absorption (Greene, 1983). Anaesthetics move rapidly down. A

concentration gradient from duramater into the CSF and diffusion in the opposite direction is also quite rapid along a concentration gradient i.e. from CSF into the epidural space, which are then susceptible to vascular reabsorption (Greene, 1983).

The duration of spinal anaesthesia is usually considered to be shorter than the duration of epidural anaesthesia (Covino and Vassallo, 1976). The shorter duration of spinal anaesthesia reflects the small dose of anesthetic agent employed and the inherent dilutional effects of the CSF, which will tend to further reduce the critical concentration at the site of injection. The duration of spinal anaesthesia depends on two factors : concentration of anaesthetic solution into the CSF and vascular absorption of the anaesthetics. The greater the concentrations; the larger the duration (Greene, 1983).

Evaluation of patients with uremia/renal failure

Preoperative

For patients with GFR > 50 cc / min, no special precautions but for patients with GFR < 50 cc/min, physical examination, electrolytes, glucose, BUN, creatinine, calcium, phosphorus, albumin, etc. should be estimated. Ensure optimal dialysis, euvolemia, normal serum K, blood pressure, pH and serum Na. If bleeding risk for procedure is high and anemia is severe, iron/erythropoietin should be considered (Daugirdas, 1994).

Intraoperative

The fluid replacement is restricted to blood losses, insensible losses and urine out put if patient is clinically euvolemic.

The nephrotoxins like NSAIDS, IV contrasts agents, and aminoglycosides should be avoided. The potassium level should be monitored and avoid K containing intravenous fluids (including Lactated Ringers), drugs which can affect perioperative K levels (NSAIDS, Beta-Blockers, heparin and succinylcholine). Tissue trauma, hypercatabolism and sepsis can cause hyperkalemia (Daugirdas, 1994). Intraoperative hemofiltration have been performed during long or complicated cases to maintain metabolic and volume control (Ilson *et al.*, 1992).

Bicarbonate alone is not effective in treating hyperkalemia but can cause volume overload and or hypernatremia (Daugirdas, 1994).

Post-operative

Monitoring of fluids, electrolytes and hemodyanamic status is essential. Try to avoid NSAID (unless patient makes no urine), morphine etc. Buprenorphine and Fentanyl are considered safe in such patients (Daugirdas, 1994; Lewis and Swan, 1997).

The unique feature of spinal opioid analgesia is the lack of sensory, sympathetic or motor block, which allows patient to ambulate without the risk of hypotension or motor incoordination usually associated with epidural local anaesthetics or parenteral opioids. The intrathecal or epidural doses of opioids are far less than usual parenteral doses and the anaesthesia provided is also prolonged. Morphine, meperidine, fentanyl, lofentanil and sufentanil have been used spinally in laboratory animal species (Yaksh and Reddy, 1981) and humans (Coombes *et al.,* 1985). Relative hydrophilicity of morphine results in slower efflux from the spinal cord and CSF resulting in greater migration to the brain (Tamsen *et al.,* 1983).

Presynaptic and postsynaptic opiate receptors (mu, delta and kappa) in the substantia gelatinosa of the dorsal horn of the spinal cord are major sites of action of spinally administered opioids. Intrathecal administration of opioids reliably attenuates the response of the animals to a variety of unconditioned somatic and visceral stimuli in a variety of species including the rat and rabbits (Yaksh and Reddy, 1976), primate (Yaksh and Reddy), 1981), mouse (Hylden and Wilcox, 1983) and dog (Sabbe *et al.,* 1994).

Mu, delta and kappa agonists in dorsal horn neurons exerted a suppressive effect upon the nociceptive component of the nociceptive specific neurons or WDR neurons in Lamina I. Kappa agonists had no effect. In Lamina II, mu and delta agonists were with minimal effects, while kappa agonist caused a selective inhibition of the nociceptive component.

The binding of the opiate agonists was limited for the most part of the upper laminae located in the substantia gelatinosa (Stevens *et al.,* 1991) and dorsal root ganglia (Fields *et al.,* 1980). This suggests that opiates might exert a portion of their activity by a presynaptic effect upon primary afferents and a postsynaptic effect upon dorsal horn projection neurons.

Opiates *in vitro* and *in vivo* would reduce the release of primary afferent peptide transmitters such as substance P, which by preventing the opening of Ca^{2+} channels reduces the release (Amione and Yaksh, 1989). A post-synaptic action was demonstrated by the ability of opiates to block the excitation of dorsal horn neurons evoked by glutamate through activation of K^+ channel and hyperpolarization, presumably reflecting a direct activation of the dorsal horn neurons (Zieglgansberger and Bayerl, 1976).

The joint ability of mu and delta opiates to reduce the release of excitatory neurotransmitters from C fibres as well as decrease the excitability of dorsal horn neurons is believed to account for powerful and selective effects upon spinal nociceptive processing. Studies using intrathecally applied opioids showed, that they had considerably lower potency than that of the α_2-agonists in sheep (Livingston *et al.,* 1992).

Although other studies (Brandt and Livingston, 1990) showed that the sheep has a lower density of opioid receptors in the spinal cord, but lack of activity can not be attributed to lack of receptors and is probably associated with the ability of the drug to penetrate the spinal cord from the intrathecal route.

New effective analgesics are needed for the treatment of pain. Buprenorphine, is classified as as a partial mu (μ) opioid agonist and weak kappa antagonist. It has a high affinity for the mu-receptor, with slow dissociation resulting in a long duration of action and an analgesic potency 25 to 40 times more than morphine. At higher doses, unlike full mu-opioid agonists, buprenorphine's agonist physiological and subjective effects, including euphoria reach a plateu i.e. it begins to behave more like an antagonist,

limiting the maximal analgesic effect and respiratory depression. This ceiling effect confers a high safety profile and limits the abuse potential limits. Buprenorphine has been used for the treatment of acute and chronic pain, as a supplement to anaesthesia, and for behavioural and psychiatric disorders including treatment for opioid addition, (Neilan *et al.,* 2004; Sporer, 2004; Umbright *et al.,* 2004; Johnson *et al.*, 2005).

Buprenorphine and fentanyl are considered safe and are recommended by many authors in uremic patients (Daugirdas, 1994; Lewis and Swan, 1997). The analgesic effects of a combination of epidural bupivacaine and buprenophine were found to be effective and similar to that of morphine in a study in rats (Morimoto *et al.,* 2001). Medetomidine with buprenorphine was recommended as a good anaesthetic premedication that induces profound sedation and analgesia in dogs (Soontornvipart *et al.,* 2003) and combination of detomidine-buprenorphine in horses during standing surgery (Dijk *et al.,* 2003). Buprenorphine and fentanyl alleviated mechanical sensitivity and prevented weight loss associated with the surgery (0 to 3 days) in spared nerve injury model of neuropathic pain in rats (Stewart and Martin, 2003). Combination of preemptive epidural xylazine and buprenorphine could be an effective technique in minimizing post-operative pain for upto 6 hours in dogs (Halder and Bose, 2001). An effective post-operative analgesia was provided in dogs and cats with cardiovascular disease with buprenorphine intravenously in a study by Skarda *et al.* (1996).

In an another study where the effects of buprenorphine (intramuscularly) oxymorphone hydrochloride and ketoprofen for post-operative analgesia after orchiectomy and sterilization in cats were compared. It was inferred that, buprenorphine demonstrated the highest efficacy with the lowest cummulative pain scores and serum cortisol levels (Dobbins *et al.,* 2002). Buprenorphine appeared to provide better post-operative analgesia than morphine and may also have a longer duration of action in cats (Stanway *et al.,* 2002). Preventive analgesia by direct transoperational block on nerves with buprenorphine is effective with low level of systemic morbidity in cancer patients (Gonzalez *et al.,* 2004; Skaer, 2004). Buprenorphine may play an important role in the

puffy hand sign, because buprenorphine is poorly soluble, it causes lymphatic obstruction and results in puffy hand sign in human beings (Simonnet *et al.*, 2004).

Buprenorphine is a partial opioid agonist, which binds tightly to the mu receptors and antagonises any morphine present at the receptor and has a long duration of action (Hensen, 1994) and suggested in rats that the antinociceptive mechanisms of buprenorphine may be different from those of morphine and methodone (Bulka *et al.*, 2004). Buprenorphine has shown not to interfere with intracranial pressure. However, the marked decrease in arterial pressure due to buprenorphine administration caused a reduction of the cerebral perfusion pressure in dogs anaesthetized with desflurane (Souza *et al.*, 2004). Buprenorphine was reported to produce lesser hyperglycemia in arthritic goats indicating its better analgesic effects (Singh *et al.*, 2002).

The analgesic effects of epidural buprenorphine appear similar to those of epidural morphine. The occurrence of urinary retention is less likely with buprenorphine since its intrathecal injection has minimal effects on urodyanamics in dogs (Drenger and Magora, 1989). Its long duration of action (Known to be about 8 hrs in man) is due to its slow dissociation from receptors and analgesia remains long after it can no longer be detected in the blood by the most assay methods. On its own, in clinical doses, it doesn't appear to cause sedation, or to cause excitement in susceptible species of animal, but its use towards the end of surgery slows recovery from anaesthesia. Its effects on the cardiovascular system are minimal (Hall and Clarke, 2001). As compared to methadone, it was less frequently related to sexual side effects in men (Bliesener *et al.*, 2005) and indicated in opioid dependants where methadone is poorly tolerated (Kristensen *et al.*, 2005).

In a study of post-operative pain relief in dogs, undergoing cranial cruciate ligament rupture repair, it was found that buprenorphine was as effective as epidural morphine for the relief of post-operative hindlimb orthopaedic pain in dogs and also buprenorphine appears to be an effective opioid for epidural use in healthy dogs. It may offer certain

advantages over morphine for epidural use, such as lower abuse potential and in some clinics, reduced cost and less wastage of drug (Smith *et al.*, 2001). Preemptive epidural administration of morphine with or without bupivacaine was found to be safe and effective method of inducing long lasting analgesia in dogs and cats (Troncy *et al.*, 2002).

Similar haemodynamic and electroencephalographic effects of epidural and intramuscular injection of buprenorphine suggested the systemic effects of epidural buprenorphine in sheep undergoing orthopaedic hind limb surgery (Otto *et al.*, 2000).

In arthritic goats lesser hyperglycaemia was noticed with epidural buprenorphine as compared to epidural xylazine-ketamine combination, bupivacaine and systemic diclofenac, suggesting its better analgesic effects (Singh *et al.*, 2002).

α_2 agonists

α_2-adrenoceptors are member of the G-protein coupled family of membrane receptors (Birnbaumer *et al.*, 1989) and stimulation of α_2-adrenoceptors in the brain induces a characteristic pattern of behavioural physiological and neurochemical responses, including sedation, analgesia, hypothermia and inhibition of noradrenaline turn over.

α_2-agonists, like xylazine, detomidine and medetomidine are centrally acting non-narcotic analgesics with sedative, myorelaxant and local anaesthetic properties (Knight, 1980). Intraspinal (epidural or subarachnoid/intrathecal) administration of α_2-adrenergic agonists to produce selective analgesia without motor and autonomic blockade has been investigated only in recent years (Eisenach, 1992). These drugs are therefore, becoming increasingly popular for epidural/spinal use (Tendillo *et al.*, 1995).

Epidural administration of some α_2-adrenergic agents result in profound analgesia in a number of animal species (LeBlanc *et al.*, 1988). This effect is mediated by spinal α_2-adrenergic receptors as evidenced by observations that analgesia is antagonized by α_2-antagonists, but not α_1 or β antagonists (Fleetwood-Walker *et al.*, 1985).

Experiments have demonstrated that direct intrathecal application of adrenergic agonists in rats, cats and primates, will produce a significant elevation of the nociceptive threshold to otherwise aversive stimuli (Reddy and Yaksh, 1980; Yaksh and Reddy, 1981). There's strong evidence that the primary site of antinociceptive action of α_2-agonists after intrathecal delivery is at α_2-adrenergic receptors in the substantia gelatinosa of the spinal cord (Unnerstall *et al.*, 1984; Yaksh, 1985) and resulting analgesia can be attenuated by α_2-antagonists (Yaksh and Reddy, 1981).

α_2-adrenoreceptor agonists provide analgesia when administered systemically by binding to α_2-adrenergic receptors in the brain and spinal cord (Lawhead *et al.*, 1992).

These drugs are becoming increasingly popular for epidural/spinal use as they produce analgesia without affecting autonomic or lower motor neurons (Tendillo *et al.*, 1995). These agonists have been shown to bind to receptors in the dorsal horn of spinal cord on epidural administration (Murata *et al.*, 1989). After binding, these drugs inhibit the release of neurotransmitters, such as norepinephrine and substance P and decrease the neuronal activity (Pernow, 1983; Howe *et al.*, 1987). LeBlanc *et al.* (1988) first reported the use of xylazine epidurally to provide local analgesia in the perineal region in horses as an alternative to local anaesthetics. Waterman *et al.* (1987a) used xylazine intrathecally in experimental sheep and showed its potent analgesic properties when used in this manner. Epidurally administered xylazine produces longer duration of analgesia probably due to the fact that it provides a local depot of drug (Nolan *et al.*, 1990). Prevalence of hind quarter ataxia is lesser with xylazine as compared to that produced by lignocaine (Grubb *et al.*, 1992) and may be due to local anaesthetic property of xylazine attributed to its structural similarity with lignocaine (Antonaccio *et al.*, 1973). The rate of ruminal contraction were markedly decreased in cattle after epidrual administration of xylazine (Jean *et al.*, 1990; Skarda *et al.*, 1990; Rehage *et al.*, 1994) due to stimulation of alpha-2 adrenergic receptors in the fore stomach musculature (Ruckebusch and Allal, 1987). However, LeBlanc and Eberhart (1990) found no measurable changes in cardio pulmonary parameters after caudal epidural anaesthesia in horses. The underlying

mechanisms for the bradycardiac effect of xylazine could be attributed to decreased sympathetic outflow from the CNS, direct depression of respiratory centres (Kumar and Thurmon, 1979; Rings and Muir, 1982). There are only few reports on the use of α-2 agonist for post-operative pain management, epidural clonidine used as a sole analgesic agent during and after abdominal surgery in human beings provided dose dependent control of the haemodynamic changes associated with surgical stimulation. It also produced dose dependent post-operative analgesia without major side effects (Dekock *et al.,* 1997). Epidural xylazine hydrochloride used for castration of mature bulls was also reported to provide some level of post-surgical analgesia (Caulkett *et al.,* 1993). Epidural administration of medetomidine induced prolonged analgesia that was suitable for perineal surgery, post operative analgesia and relief of continuous straining (Lin-Huichu *et al.,* 1998). It has been suggested that use of high doses raised the possibility of α_1-participation in the analgesic effect. Waterman *et al.* (1988), however, suggested that the possibility of α_1-participation is minor because intravenously administered idazoxan (an α_2-adrenoceptor antagonist), has been proved to be effective in abolishing the analgesic activity of intra-thecally administered xylazine and clonidine in sheep.

Xylazine shows large interspecies variation in potency. The plasma concentration of drug needed for sedation is 10 times higher for horses than for cattle. There was no variation in the density or the subtype pattern of the alpha-2 adrenoceptors that could explain the species variation recorded in vivo as a homogenous population of the α-2 A/D subtype (200-300 fmol/mg protein was found in all species. Thus, a species variation in efficacy at the molecular level, if evident, must include the interaction between the α-2 A/D receptor and xylazine further down stream the effect cascade e.g. involing the G-proteins (Torneke *et al.,* 2003). If the binding to the G-protein is totally inhibited, the agonist binding will resemble that of an antagonist (Rouot *et al.,* 1982).

In human beings, the number of α_2-adrenoceptors apparently increased in the sacral part of the spinal cord, compared with the thoracic or lumbar parts of the spinal

cord. A predominantly α_2-subtype receptor is found in the dorsal horn of spinal cord (Lawhead *et al.,* 1992). The density and subtypes of α_2-adrenergic receptors in the spinal cord of various animal species and selectivity of agonist for these receptors are unknown, but may have clinical implications on the site and response to administration (Skarda and Muir, 1994). Xylazine, on epidural administration, in horses and cattle selectively blocks the sensory fibres and produces significantly longer duration of analgesia as compared to lignocaine (Skarda and Muir, 1992).

Epidurally administered xylazine produces longer duration of analgesia probably due to the fact that it provides a local depot of drug (Nolan and Erhardt, 1990). Subarachnoid administration of xylazine in goats resulted in longer duration of analgesia of the tail, perineum, hind limbs, flank and caudodorsal rib areas than ketamine or lignocaine (De Rossi *et al.,* 2003). Xylazine produced lower mean HR, RR and RT longer duration of analgesia, muscle relaxation and patient immobility, as well as, greater systemic depression and longer recovery time than epidurally administered lignocaine in cats (Adentunji *et al.,* 2002). Xylazine helps to reduce rope restrained stress in cattle with significantly lower cortisol levels than control (Lee and Chunsik, 2001). Preoperative epidural xylazine didnot appear to improve post-surgical analgesia but reduced the distress of anaesthetic injection and surgical manipulation as a result of sedation (Chavelier *et al.,* 2004).

Xylazine has been used for lumbar epidural analgesia in sheep (Eisenach *et al.,* 1987), goats (Kinjavdekar, 1998), lumbosacral epidural analgesia in rabbits (Youssef, 1992), dogs (Greene *et al.,* 1995), goats (Aithal *et al.,* 1997a), in calves (Raidurg *et al.,* 1995), cattle (Caron and LeBlanc, 1989; Rehage *et al.,* 1994), horses (Skarda and muir, 1996) and buffaloes (Singh, 1999) to produce analgesia of perineal, abdominal regions and hind limbs. Prevalence of hind quarter ataxia is lesser with xylazine in comparison to lignocaine HCL (Grubb *et al.,* 1992), which could be due to local anaesthetic property of xylazine attributed to its structural similarity with lignocaine HCL (Antonaccio *et al.,* 1973). Bladder repair, through intra-and cystorrhaphy employing xylazine HCL for epidural anaesthesia in better (Deshmukh and Bhokre, 2002).

The added advantage in the use of alpha-2 agonist is prolonged post operative analgesia and the availability of specific antagonists; however, the onset after epidural xylazine is delayed in comparison to lignocaine HCL in different species of animals and various α_2-agonist when used alone, cause respiratory and cardiac depression.

Heart rate, respiratory rate and arterial blood pressure decrease after epidural administration of xylazine in cattle (Jean *et al.*, 1990; Rehage *et al.*, 1994; Skarda *et al.*, 1990) and buffaloes (Tiwari *et al.*, 1996). α_2-agonists have also been found to depress the hypothalamic non-adrenergic α_2-receptors to cause hypothermia (MacDonald *et al.*, 1988).

Pooling of circulating erythrocytes in the spleen or other reservoirs secondary to decreased sympathetic activity may explain the decrease in haematocrit and haemoglobin concentration recorded after epidural xylazine (Skarda and Muir, 1996).

NMDA antagonists

The NMDA receptor mediates wind-up and long term potentiation in the responses of cells to prolonged stimuli, thus it is responsible for the induction and the maintainence of enhanced responses for prolonged periods of time (Pockett, 1995).

Ketamine selectively reduces the responses of spinal and central neurons to NMDA (Yamamura *et al.*, 1990) and blocks the NMDA channel at subanaesthetic doses (Dickenson, 1995) and when administered epidurally helps in pain alleviation (Naguib *et al.*, 1986); without respiratory depression or other side effects like neurologic sequelae and urinary retention (Islas *et al.*, 1985). It was reported that addition of adrenaline to ketamine upon intrathecal administration resulted in complete motor blockade which was not achieved otherwise, with ketamine alone and also intensified the sensory blockade (Bion, 1984). Intrathecally administered ketamine shows local anaesthetic effects in both animals and human being (Gebhardt, 1994). The analgesic effects of ketamine administered intrathecally are spinally mediated (Crisp *et al.*, 1991) and when it was injected intra cerebroventricularly in rats, even high doses failed to produce

analgesia (Smith *et al.,* 1985). Low dose of ketamine (1-2 mg/kg) has been successfully used in cats with obstructive uropathy (Raffee, 1984) and intrathecally or epidurally in experimental animals (Baha and Melbert, 1991; Aithal *et al.,* 1996) and clinical cases in dogs (Aithal *et al.,* 1999), and goats (Aithal *et al.,* 1996) for hind quarter analgesia without side effects. Although, there are reports of ketamine having produced spinal neurotoxicity (Malinovsky *et al.,* 1991). Epidural administration of ketamine is suggested to produce local spinal analgesia and CNS depression in dogs with marked cardiovascular stimulatory effects (Sarafzadeh, 1999); shorter duration without cardiopulmonary depression in buffalo claves (Singh *et al.,* 2004).

From the above mentioned mechanisms of pain induction there is considerable evidence that in excitation, amino acids and neuropeptides are involved in nociceptive transmision in the dorsal horn of the spinal cord (Besson and Chaouch, 1987). The excitatory amino acids implicated in nociception are glutamate and aspartate, and the peptides are tachykinins, calcitonin generated peptide, somatostatin, vasoactive intestinal polypeptide, alanin, bombesin and neurotensin. All of these are present in the afferent fibers and are released by noxious stimulation (Dickenson, 1995). The actions of excitatory amino acids are mediated by N-methyl D-aspartate (NMDA) receptor and non-NMDA receptors. The ketamine molecule structurally resembles with phencyclidine and cyclohexamine. The commercial product is a 50:50 racemic mixture (Ryder *et al.,* 1978). The (+) isomer is more potent than (-) isomer for analgesic properties (Ryder *et al.,* 1978; White *et al.,* 1980).

Racemic ketamine HCL is a dissociative anaesthetic agent, which exhibits analgesic properties in almost all species including rodents (Ryder *et al.,* 1978) and humans (White *et al.,* 1980).

Opioids

Opioids have been the drug of choice for control of post-operative pain in human being and animals for very long time. Morphine, oxymorphine, meperidine, codeine and fentanyl are some of the narcotic agonist, which have been used in veterinary medicine (Kuchinka and Riedesel, 1995).

These agonist activate mu (μ) and kappa (κ) receptors and are most effective for control of moderate to severe pain (Hardie, 1996). Pre-synaptic and post-synaptic receptors in the substantia gelatinosa of dorsal horn of spinal cord are the major sites of action of spinally administered opioids which are capable of relieving both visceral pain such as after abdominal or thoracic surgery(Glynn *et al.,* 1981; Torda and Pybus, 1981) and also somatic pain after orthopaedic surgery (Ebert and Varner, 1980; Glynn *et al.,* 1981).

Post-operative pain relief of 4-6 hrs with different dosage of morphine was reported by Hughes and Lang (1983). Taylor *et al.* (1984) and Bromage *et al.* (1989), however, reported that morphine produced control of pain for 18 hours as compared to 6 and 11 hours by methadone and hydromorphone, respectively. Morphine has been used for the relief of post-operative pain through various other routes because rapid intravenous administration of morphine may cause histamine release resulting in hypotension, respiratory depression, urinary retention, dysphoria, pruritis, nausea and vomiting (Hardie, 1996).

Hanning *et al.* (1988) used morphine hydrogel suppositories transrectally and recorded less post-operative pain and nausea in comparison to patients where morphine was given by injection. Intra-articular administration of morphine in human beings is reported to provide significant and prolonged duration of analgesia (Stein *et al.,* 1991).

Fentanyl and sufentanyl are absorbed transdermally and have been recognised for their rapid onset and short duration of action. Sufentanyl is better suited for transdermal use than fentanyl for acute post-operative pain control (Roscow, 1985) because sufentanyl is absorbed quickly than fentanyl (Roy and Flynn, 1989). However, it is excreted rapidly than fentanyl (Sebel *et al.,* 1987).

Oxymorphone intramuscularly or intravenously, methadone subcutaneously and codeine has also been found useful in the treatment of post-operative pain in dogs (Haskins, 1987).

Epidural administration of drugs eliminate most of their side effects and also increase the duration of action (Pascoe, 1992). Describing the utility of epidural morpine, Lanz *et al.* (1982) reported that patients receiving epidural morphine had less intense pain and required lower total dose of opioid analgesics post-operatively as comapred to patients receiving intramuscular morphine.

Epidural morphine has been successfully used in animals also. In dogs epidural morphine caused analgesia of about 22 hours as comapred to 3 hours produced by epidrual bupivacaine (Gerlach *et al.,* 1983). Bonath and Saleh (1985) also reported 23 hrs of analgesia after epidural administration of morphine in dogs. They observed that there was absence of significantly systemic side effects as compared to systemic administration. It also proved an excellent analgesia after thoracotomy in dogs (Pascoe and Dyson, 1993). In another study, morphine and bupivacaine were reported to provide excellent and comparable better analgesia after epidural administration after the completion of abdominal surgery in goats (Hendrickson *et al.,* 1996).

Another opioid agonist used frequently for post-operative analgesia is pethidine which when given @1-4 mg intramuscularly has provided apparent post-operative pain relief for 1-2 hours in dogs (Short *et al.,* 1971). It has local anaesthetic properties at peripheral nerves and can also produce intravenous regional anaesthesia (Acalovschi and Cristea, 1995). Pethidine has been found effective even intra-articularly (Ekblom *et al.,* 1993). Narcotic agonist antagonists (butorphanol, pentazocine, nalbuphine) are useful for moderate pain only (Hardie, 1996). They act as agonists at kappa receptor and antagonist at mu receptors. They have ceiling effect due to their mu receptor antagonism and higher recommended doses will not result in more potent analgesia (Sawyer and Rech, 1987; Hensen, 1994). Abbound *et al.* (1988) compared intravenous and transnasal butorphanol in post-caesarean section patients and reported that transnasal butorphanol was having superior and longer lasting pain relieving effect than intravenous butarphanol, even when total transnasal dose was half that of intravenous dose.

Plasma cortisol concentrations and systemic blood pressure in cats after ovariohysterectomy have been shown to reduce with butrophanol (Fox *et al.,* 1994). Buprenorphine is a partial agonist, which binds tightly to the mu receptors and antagonises any morphine present at the receptor and has a long duration of action (Hensen, 1994).

McQuay *et al.* (1988) demonstrated that preemptive analgesia using opioid premedication before general anaesthesia resulted in 50% decrease in total dose of analgesics and increase in time for first post-operative requirement of analgesic in treated patients as compared to patients with no treatment. The same was confirmed by Kiss and Killian (1992) after preemptive analgesia using pethidine (50 mg) intramuscularly in man (n=98) who underwent the lumbar disc surgery under nitrous oxide/halothane/ enflurane or isoflurane general anaesthesia.

Pre-operative treatment with fentanyl (4 µg/kg) was found to be more effective in reducing pain and analgesic requirement between 12 and 24 hours after thoracotomy than when administered post-operatively (Katz and Nelson, 1992). However, no difference in post-operative analgesia between treated and untreated patients after the use of intravenous fentanyl was found by Campbell and Kendrick, (1990).

Local anaesthetics

Local anaesthetics are generally water-soluble acid salts. When these salts are injected into tissues that normally are slightly alkaline, the acid salt formed of the local anaesthetic is neutralised. This releases the free amine or alkaloidal base through hydrolysis, which is necessary before the drug can penetrate the lipid barrier of the cell membrane to induce anaesthesia (Booth, 1988).

The amino groups of the local anaesthetic drugs interact with the polar groups of the cell membrane to decrease membrane permeability to potassium and sodium ions resulting in cessation of generation and transmission of the nerve impulse (Booth, 1988).

Small dorsal root ganglion (DRG) neurones represent the somata of myelinated A-δ and unmyelinated C-fibre type neurones (Harper and Lawson, 1985) and possibly participate in processing and transducing sensory information. These neurones are involved in peripheral nerve block when exposed to high concentrations of local anaesthetics during spinal and epidural anaesthesia (Butter worth and Strichartz, 1990).

Local anaesthetic drugs, when applied locally to nerve tissue or injected spinally in effective concentrations, provide relief from pain by blocking conduction of impulses from the receptor to the cortex of the brain (Booth, 1988). Any portion of the nervous system and every type of nerve fibre can be affected by these drugs. However, A-δ fibres are blocked first at the lowest concentration (Ford *et al.*, 1984), followed by C fibres. A-δ fibres are blocked at the highest anaesthetic concentrations. Recovery of function, with no apparent damage to the nerve tissue, is achieved in reverse order.

Calcium ions and local anaesthetics injected epidurally acts upon the same mechanism that is necessary for conveyance of sodium ions through the nerve cell membrane. All anaesthetic agents, including local anaethetics administered spinally produce deformation or expansion of the cell membrane that results in anaesthesia (Seeman, 1972). According to Kolwas (1979), binding of local anaesthetic molecules to hydrophobic regions of the cell membrane and expansion of some critical regions in the membrane could also prevent an increase in sodium ion permeability and thus could prevent propagation of an action potential or impulse transmission in nerve fibre. Lee (1976) proposed that in cell membrane site of the sodium channel is surrounded by a ring like structure, which is composed of lipid molecules and exists in a crystalline or gel state. Rigidity of this structure permits the sodium channels to remain open to the flow of sodium ions. In the presence of a local anaesthetic, rigidity of this structure is believed to be reduced from a solid to a liquid crystalline state. This alteration in the sodium channel closes the channel to passage of sodium and depolarization of the neuron can not occur, thus lcoal anaesthesia is induced.

Local anaesthetics were found to block voltage gated K^+ channels (Olschewski *et al.,* 1998; Komai and McDowell, 2001). It has further been reported to inhibit voltage-in sensitive K^+ channel mainly found in their, myelinated fibres in Xenopus Laevis (Nau *et al.,* 1999). Similar to this K^+ channel a recently described new family of two pore domain K^+ selective channels are sensitive to local anaesthetics (Buckler *et al.,* 2000; Meadows and Randall, 2001). The resting potential of the dorsal roof ganglion neurones is determined by the counter balancing action of two different voltage-sensitive conductances, the delayed rectifier pottassium channel and the hyperpolarization-activated inward current (Mayer and Westbrook, 1983). In another finding, important role of the Ih-block by local anaesthetics in the complex mechanism of drug action during epidural and spinal anaesthesia was suggested (Bischoff *et al.,* 2003).

The principal site of neural uptake of drug remains a matter of conjecture. Suggested sites for action of local anaesthetic drugs after epidural injection are (i) nerves that are blocked distal to the dural sheaths after leaving the intervertebral foramina, producing a multiple paravertebral block (Buchholz and Koerner, 1952), (ii) local anaesthetics act directly on duracovered nerve roots within the spinal canal (Saeker and Gaida, 1955), (iii) dorsal root ganglia in the spinal canal (Frumin *et al.,* 1953), (iv) the neuraxis (Bromage *et al.,* 1963), (v) and the spinal cord after diffusing across the duramater into the subarachnoid space and spinal fluid (Frey and Soehring, 1954).

Synaptic transmission in the spinal cord may also be inhibited by local anaesthetics injected spinally through the modifications of postsynaptic receptors as well as blockade of presynaptic Ca^{+2} channels that function to stimulate the release of transmitters. Butterworth and Strichartz (1990) reported that Ca^{+2} dependent release of norepinephrine triggers depolarization of synaptosomes, which are blocked by local anaesthetics, indicating the role of local anaesthetics in direct inhibition of neuronal transmitter release.

It seems likely, therefore, that local anaesthetics also bind to the sites other than Na^+ channels after spinal and epidural injection that may contribute to anaesthesia. The early events in the epidural anaesthesia may be a blockade of impulses in spinal cord but the full effect of local anaesthetics may also involve other sites as the block develops in time and drug diffuses into the cord. Therefore, an encampossing view of local anaesthetic actions within the spinal cord should include their effects on a variety of channels and other membrane related activities that may contribute to spinal and epidural anaesthesia.

As early as 1885, cocaine was used intrathecally in a dog to produce spinal anaesthesia by Corning (Lumb and Jones, 1984). In 1948, lignocaine hydrohloride was synthesized by Lofgren. In humans, this compound is probably the most popular and extensively used local anaesthetic (Kolwas, 1979). It is also widely used in veterinary medicine.

Bupivacaine

Bupivacaine is a long acting anilide local anaesthetic agent excreted through bile duct and kidneys. It is approximately 4 times as potent as lignocaine and provides longer duration of action, at least twice as that of lignocaine. Analgesia with bupivacaine HCl occurs in 20-30 mintues and lasts upto 5-7 hrs (McEnvoy, 1995). It has also been used in different concentrations to produce regional analgesia in animals (Hall *et al.*, 2001). Bupivacaine has also been reported to reduce pain after canine cruciate surgery when placed in the joint prior to closure (Conzemius *et al.* 1994).

Bupivacaine has been used in dogs for epidural analgesia with long duration of action without any side effect (Gill *et al.*, 1984) and brachial plexus block in dogs (Pereira and Carvahlo, 2003). Intraperitoneal and incisional bupivacaine in dogs (Carpenter *et al.*, 2004). In a study, it was found that bupivacaine induced long lasting perineal analgesia with minimal cardiovascular effects. Analgesia was induced faster and lasted longer with bupivacaine (De Rossi *et al.*, 2004).

Bupivacaine produced a regional analgesia that is 3 times longer than that of lignocaine. Motor blocking ended before the anaesthetic effects. Bupivacaine showed superior antinociceptive extention, reaching untill the dermative T8±2, bupivacaine was reported to produce better analgesia both in terms of time and extention as compared with lidocaine with minimal motor effects (DeRossi *et al.*, 2003).

Various surgical procedures were perofrmed as abdominal and pelvic regions using lumbosacral intrathecal anaesthesia with 0.5% bupivacaine solution administered to the animals, with long time effect of anaesthesia on the whole hind limb or a large part of flank. Increase in HR and decrease in RR and RT were observed during anaesthesia (Ozaydin and Kilic, 2003).

No significant difference ($P>0.05$) was observed between the onset and duration of the motor and sensory blockade using 0.25% bupivacaine. However, the duration of the sensory blockade was significantly higher than the motor blockade using 0.75% bupivacaine ($P<0.05$) and it was concluded that solutions of 0.25 and 0.75% bupivacaine without vascconstrictor were efficient for the brachial plexus blockade in cats (Freitas *et al.*, 2002).

Destruction and denervation atrophy in skeletal muscles caused by the injection of local anaesthetics was investigated by injecting lidocaine or bupivacaine around the rabbit facial nerve to produce facial paralysis and it was found that bupivacaine caused less atropic changes and was not found to be associated with muscle degeneration as lidocaine (Calguner *et al.*, 2003).

Bupivacaine was reported to provide an effective brachial plexus block technique for analgesia of front limb dorsal to the shoulder in dogs (Futema *et al.*, 2002).

Preoperative or postoperative subcutaneous infiltration druing cholecystotomy or inguinal hernia repair, with bupivacaine as well as ropivacaine was found to be effective in human beings (Zink and Graf, 2004).

Lumbar epidural post-operative analgesia after knee surgery with combinations of bupivacaine, fentanyl and clonidine was recommend (Srettici *et al.*, 2004).

The addition of epinephrine to solutions containing fentanyl and bupivacaine for epidural infusion has been shown to improve the quality of analgesia in human beings (Priston *et al.*, 2004).

Bupivacaine, when used preemptively as well as post-traumatically as epidural analgesic is reported to be highly effective in the control of pain in arthritic goats (Pathak *et al.*, 2002; Singh *et al.*, 2002).

The efficacy of epidural local anaesthetics can further be increased by using them in combination with other drugs. The combinations have induded local infiltration with bupivacaine and epidural bupivacaine and morphine for upper abdominal surgery (Mogensen and Bartholdy, 1992) and epidural morphine and bupivacaine for prostratectomy (Shapiro *et al.*, 1981).

The toxicity of lidocaine was reported to be higher as compared to bupivacaine when administered intrathecally in rabbits. Intrathecal local anaesthetics signifcantly increased glutamate concentrations. The sensory and motor functions in lidocaine group were significantly worse than in the other groups (Yamashita *et al.*, 2003).

Yamashit *et al.* (2003), a comparison of the neurotoxic effects on the spinal cord of tetracaine, lidocaine, bupivacaine, and ropivacaine administered intrathecally in rabbits.

An early return of peristalsis and passage of flatus was noticed with the bupivacaine injections in the control of post-operative pain. Respiration was enhanced, earlier patient mobility was noted and general depression from injectable analgesics was avoided. Regional and spinal bupivacaine for inguinal hernia repair (Bugedo *et al.*, 1990), and regional analgesia with epidural bupivacaine in combination with systemic analgesic ketoprofen in dehorning in calves (McMeekan *et al.*, 1998a) was used successfully.

Trim (1981) performed nerve block analgesia of flank for laparotomy using 0.75% of bupivacaine. However, more predictable level of anaesthesia was found when 0.125% of bupivacaine solution was used, which may be because this solution was hypobaric in contrast to the 0.5% solution.

Combination techniques

In the combination techniques of anaesthesia the less dose of each drug produces the desired effect with minimum side effects (Solomon and Gebhart, 1994). Indeed, "balanced" epidural analgesic regimens with combinations of opioids and local anaesthetics have been found to be useful in the obstetric and postoperative settings (Chestnut *et al.*, 1988; Dahl *et al.*, 1990).

Animal studies have shown that NMDA receptor antagonists inhibit central sensitization (Woolfand Thompson, 1991) and prevent acute tolerance to opioids (Kissin *et al.*, 2000; Miyamoto *et al.*, 2000) or opioid induced hyperalgesia (Celerier *et al.*, 2000). Analgesia is enhanced, spinal cord hyperexcitability is more profoundly attenauted, respiratory depression is reduced, and opioid induced sedation is not further increased (Lugnbuhl *et al.*, 2003). NMDA receptor antagonists appears to inhibit the neural plasticity underlying some forms opiate tolerance, sensitization and physical dependence, suggesting that NMDA receptors are involved in the develpment of these drugs induced changes in behaviour (Trujillo, 2000). Ketamine and pethidine has preemptive analgesia after epidural administration in dogs (Amarpal *et al.*, 1999; Hansraj *et al.*, 2000; Hansraj *et al.*, 2002).

Similarly, epidural administration of a combination of ketamine and xylazine has been reported in goats (Aithal *et al.*, 1996; Pathak, 1999) and cattle (Amarpal *et al.*, 1997; Singh, 1999) which was found suitable for surgery invovling hind quarters in ruminants (Aithal *et al.*, 1997; Kinjavdekar *et al.*, 1999) where a lesser degree of bradycardia as compared to xylazine alone was observed in cow calves (Amarpal *et al.*, 1997). Onset of anaesthesia is rapid and complete hindquarter analgesia was recorded in goats for

approximately 20-30 min while mild to moderate analgesia persisted for 90 min. suggesting that there may have been a synergistic rather than additive interaction between ketamine and xylazine (Aithal *et al.*,1996). Low dose or high dose xylazine-ketamine combination can be used as per the desired duration of anaesthesia in llamas with supplemental oxygen with high dose (DuBois *et al.*, 2004). Bupivacaine-xylazine mixture seems to have no advantage in goats over the use of xylazine alone, considering their similar duration of analgesia and cardiodepressant action. Its fast recovery makes xylazine appear as a better choice (Adentunji *et al.*, 2002b). The cardiopulmonary depression induced by epidural xylazine or detomidine with and without local anaesthetics was well tolerated by all the treated buffaloes (Tiwari *et al.*, 1999). Combination of epidural xylazine with lidocaine was recommended for flank surgery without additional line block or side effects (Lee *et al.*, 2004). Xylazine and ketamine was also used successfully as GA in large ruminants for orthopaedic manipulations (Aithal *et al.*, 2004).

Combination of xylazine and pentazocine is suitable for prolonging sedation and analgesia during surgery in cattle (Doiphode and Aher, 2003). Improvement in cardiopulmonary effects was found with combined xylazine-guaiphenesin-ketamine (XGK) infusion as compared to xylazine alone or XGK infusion in combination with extradural intercoccygeal lidocaine in calves (Picavet *et al.*, 2004).

Ketamine-xylazine combination in pigs was reported to decrease plasma insulin concentration (Heim *et al.*, 2002). Ketamine/xylazine/acepromazine was regarded as the best intraperitoneal injection anaesthesia regimen in mice (Arras *et al.*, 2001). Intratesticular injections of xylazine / ketamine combination for castration was shown to be advantageous as less inhibition of cardiopulmonary function and fast recovery from anaesthesia without severe complciations (Kim *et al.*, 2004).

Combination of xylazine and lignocaine HCl in horses (Grubb *et al.*, 1992), buffalo (Singh, 1999), llamas (Grubb *et al.*, 1993), Giantrats (Edderai *et al.*, 2001), chicken (Lucky *et al.*, 2001) and produced analgesia of quicker onset than xylazine alone and of

longer duration than either agent given alone (Grubb *et al.*, 1992), however, respiratory and cardiac depression still persisted when these drugs were combined (Kinjavdekar *et al.*, 1999).

Stress response due to surgery and anaesthesia

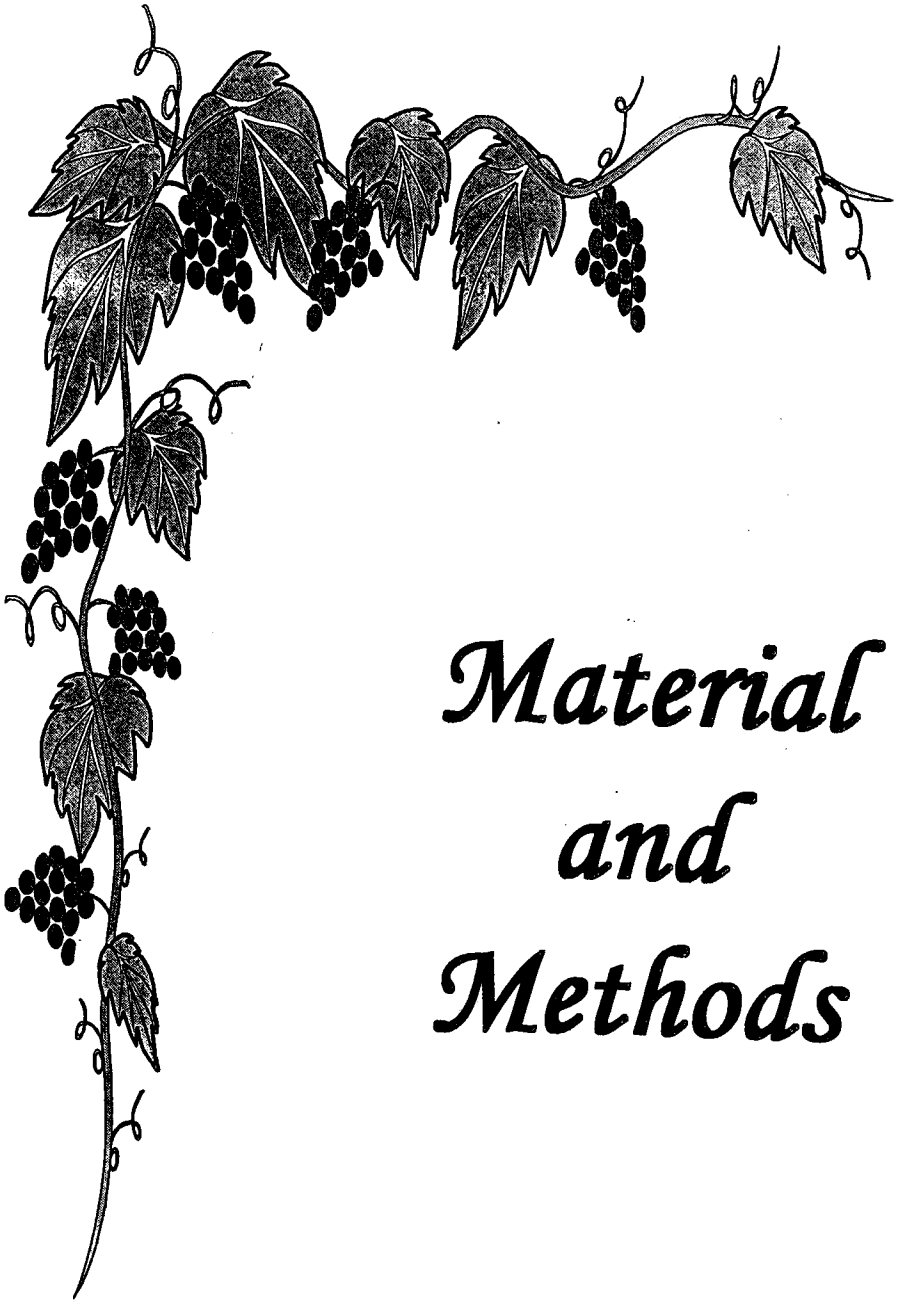
Since uraemic patients are already stressed up with different types of derangements viz. renal and post-renal causes of uraemia. Stress is a reflex reaction as a result of stressors which stimulate homeostatic, physiological and behavioural response in excess of normal.

Cortisol used as an index of physiological stress both in human beings and animals (Domzal *et al.*, 1983; Chastain *et al.*, 1986) has been found to be increased in the blood following surgical procedures in human (Gill *et al.*, 1975). Madsen *et al.* (1977) reported that epidural injection alone can block the rise in cortisol, glucose and cyclic AMP in patients undergoing hysterectomy.

On the other hand Bromage *et al.* (1971) didn't find a significant influence of epidural blockade on blood cortisol response and it was suggested that operative stimulus might have been conducted through vagus nerve, which remained uninterrupted during epidural blockade.

Analysis of clinical and haemato-biochemical data suggested severe post-traumatic changes and stress response in arthritic goats given epidural normal saline, evidenced by increased HR, RR, RT, hyperglycaemia, leucocytosis, neutrophillia, increased trypsin inhibitor and fibrinogen and decreased lymphocytes. The post-traumatic/preemptive treatment with epidural xylazine and ketamine resulted in early suppression of changes in these parameters as compared to that seen with intramuscular diclofenac sodium (Pathak, 1999; Singh *et al.*, 2002).

❑❑❑



Material and Methods

MATERIAL AND METHODS

The research work was carried out in the Division of Surgery and Radiology, IVRI, Izatnagar, Bareilly.

The Animals

The study was conducted on experimental animals as well as in clinical cases of uraemia.

Clinically healthy, male buffalo calves ranging from 6m-8 months of age weighing between 55-75 kgs were used for experimental part of the study. The animals were dewormed with Albendazole @5-10 mg/kg b.w. orally, one month before the start of experiment and vaccinated against infectious and contagious diseases (HS and FMDV).

Each animal was administered with injection oxytetracycline @5-10 mg/kg b.w. intramuscularly for 5 days. All the animals were maintained under uniform feeding and managemental conditions. The animals were stall fed and had free access to feed and clean water. During the period of pre-experimental observation, temperature pulse and respiration were daily recorded for the clinical assessment of the animals. Animals were subjected to fasting for 24 hours and water was withheld for 12 hours prior to the start of the experiment.

Design of the study

The study was conducted in 3 phases

Phase I Clinicophysiological studies.

Phase II Haemodynamic studies

Phase III Clinical studies

Phase I : Cinicophysiological studies

Six healthy male buffalo calves were randomly selected for this phase of study. Each of the six animals was used for six different treatments at weekly intervals according to Latin square design.

The doses of different anaesthetics were selected after conducting pilot trials in a few buffalo calves before the start of the study. The drugs and their doses used in the study are presented in the following table.

Table 3.1 : Anaesthetic drugs in different groups of animals given intraspinally at lumbosacral space.

Sl. No.	Groups	No. of trials	Drugs	Dosage (per kg b.w.)
1.	A	6	Bupivacaine	0.25 mg
2.	B	6	Xylazine	0.05 mg
3.	C	6	Buprenorphine	20 µg
4.	D	6	Ketamine + Bupivacaine	2.5 mg + 0.25 mg
5.	E	6	Ketamine + xylazine	2.5 mg + 0.05 mg
6.	F	6	Ketamine + buprenorphine	2.5 mg + 20 µg

The volume of the drug injected was the same i.e. 6 ml in all the groups.

Administration of drugs

The animals were restrained in standing position. The dorsal lumbosacral region was clipped, shaved and painted with povidone iodine solution. A 10 cm, 18 G, hypodermic needle was used for the subarachnoid injection. The needle was directed

at 60-75° angle to the skin surface along the midline and was slowly advanced untill the lumbosacral subarachnoid space was reached after penetrating the interarcuate ligament and duramater.

Free flow of CSF from the needle hub confirmed the correct positoning of needle and the drugs were then injected slowly as per the dose rate given in table No. 1.

The effect of various drug(s) were then evaluated and compared on the basis of following observations :

Clinical observation

Onset of analgesia

Response to pin pricks was recorded at the perineal region at every 10 seconds until the sensation is lost. The time from the injection to the loss of sensation was considered as time of onset of analgesia.

Depth and extent of analgesia

The extent of analgesia was recorded by making pin - pricks at perineum, inguinal region, tail, flank, abdomen, thorax and upper parts of hind limbs and digits at 0, 5, 10, 15, 20, 30, 45, 60, 75, 90, 105, 120, 130, 150 and 180 minutes after injection of drugs.

Depth of analgesia was graded on a 0 to 3 scale as

0 -	No analgesia	Strong reaction to pin pricks
1 -	Mild	Weak response to pin pricks
2 -	Moderate	Occassional response to pin pricks
3 -	Complete analgesia	No response to pin pricks

The mean values of different scores at different time intervals were calculated. The mean values of >0 to <1 were considered as very mild : mean values of $\geq$ 1 to <2 as mild, mean values of $\geq$ 2 to <3 as moderate and 3 strong/complete analgesia.

Sedation

Sedation was evaluated at 0, 5, 10, 15, 20, 30, 45, 60, 75, 90, 105, 120, 130, 150 and 180 minutes in experimental animals and was graded on a 0-4 scale as,

0 - Standing alert

1 - Standing but tired with slight ptosis of eye lids

2 - Standing with wide stance and extreme lowering of head

3 - Animal attained recumbency but could sit without support

4 - Animal was unable to sit without support and attained lateral recumbency.

Motor incoordination/Ataxia

Motor incoordination of hind limbs was also evaluated at the same time intervals as the sedation and was graded on a 0-4 scale as,

0 - Walking without staggering (Normal)

1 - Walking with staggering (Little incoordination)

2 - Walking with extreme incoordination

3 - unable to walk or sternal recumbency

4 - Lateral recumbency

Duration of analgesia

Time from the loss of sensation to the return of sensation at perineal region was considered as the duration of analgesia.

Recovery time

All the animals were observed for their standing recovery (in min.) when they start walking without support.

Physiological studies

Heart rate (beats / minutes), respiratory rates (breaths / minute) and rectal temperature were recorded at 5, 10,15,20, 30, 45,60, 75, 90, 105 and 120 min were after the injection of drugs.

Haematological studies

A total of 5 ml of venous blood was collected before and at 30, 60, 90, 120 180 minutes and 24 hours after the injection of the drugs. The blood was collected in two separate vials (4 ml in heparin and 1 ml in sodium fluoride). Freshly heparinized blood was used for estimation of the following parameters as per the standard methods.

Haemoglobin (Hb) : Concentration of Hb was estimated by using 0.1 N HCL with the help of Sahli's haemoglobinometer. The values were expressed in g/dl.

Packed cell volume (PCV) : The PCV was determined by the microhaematocrit method (Jain, 1986) using microcentrifuge at the speed of 10,000 rpm for 5 minutes. The values were expressed in percentage.

Total leucocyte count (TLC) : The total leucocyte count was determined on Neubar's chamber using the WBC diluting fluid. The results were expressed in thousand/µl.

Differential leucocyte count (DLC) : DLC was done using the standard method described by Schalm (1975) and the values were expressed in percentage.

Biochemical observations

Blood samples were collected in clean, dry test tubes before and at 30, 60, 120 minutes and 24 hrs after the injection of drugs. Plasma separated by centrifugation of heparinised blood was used for the estimation of BUN, creatinine, plasma cortisol, GGT and that separated with sodium fluoride was used for estimation of glucose.

Glucose : Blood collected in sodium flouride was used for the estimation of glucose by GOD/POD method and the values were expressed in mg per 100 ml.

Plasma Urea Nitrogen : Plasma urea nitrogen was estimated using the DAM (Diacetyl monoxime) method. Values were expressed in B x 0.467 g/L.

Plasma Creatinine : Plasma creatinine was estimated using alkaline picrate method and values were expressed in mg/100 ml.

Plasma cortisol : It was determined by radio immuno assay and values were expressed in nmole/L.

Plasma GGT : was estimated using commercial kits (by carboxy substrate method) and the values were expressed in U/L.

Phase II : Haemodyanamic studies

Three trials each of three treatments (table 2) were conducted in 9 animals, divided into three groups of 3 animals each.

The dosage and volume of different drugs were same as in phase I.

Table 3.2 :

Sl. No.	Groups	No. of trials	Drugs	Dosage (per kg b.w.)
1.	D	3	Ketamine + Bupivacaine	2.5 mg + 0.25 mg
2.	E	3	Ketamine + xylazine	2.5 mg + 0.05 mg
3.	F	3	Ketamine + buprenorphine	2.5 mg + 20 µg

To perform the haemodynamic studies, the animal's jugular vein and carotid artery were catheterised using PVC catheters. The catheter in vein and artery were then advanced into caudal vena cava and the aorta, respectively, to measure the CVP and MAP using water manometer and an anaeroid manometer, respectively.

Spinal injection

Spinal injection in this phase was given while the animal was in recumbency. The method of injection, dosage and volume of the drugs were the same as described in phase I. The following parameters were measured to evaluate the treatments.

Mean arterial pressure (MAP) – Mean arterial pressure (mm Hg) was recorded as per the method described by Hall and Clarke (1983).

Central venous pressure (CVP) – Central venous pressure (cm H_2O) was recorded as per the method described by Hall and Clarke (1983).

Electrocardiogram (ECG) – A lead II ECG was recorded at 1 mV and 25 mm/ s. paper speed before and after injection of drug(s) at 5, 10, 15, 20, 30, 45, 60, 75, 90, 105, 120, 130 and 180 min.

The electrocardiograms were analysed for Heart rate, rythm, duration and amplitude of P-wave, QRS complex, amplitude and duration of T-wave, P-R and Q-T intervals.

The fresh heparinised arterial blood was utilized for the estimation of pH, PO_2, PCO_2, BE, HCO_3^-, Na^+, K^+, CL^- and calcium using blood gas analyzer (Stat profile M Nava Biomedicals, USA). The values were expressed as PO_2: mm Hg, PCO_2: mm Hg, BE : mmol/L, HCO_3^- mmol /L, Na^+: mmol /L, Cl^-: mmol/L, Ca^{++}: mmol/L and K^+: mmol/L. These observations were conducted during haemodyanamic studies at 0, 30, 60, 90, 120 and 180 min intervals.

Phase III

All the combinations of ketamine, tried on the experimental animals were utilized in 36 clinical cases of obstructive urolithiasis of buffalo calves. The animals were randomly divided into 3 groups (G, H and I) with 12 animals in each group. The doses used were similar to doses used in the experimental animals.

Observations

Clinical, physiological, haematological and biochemical, as done in phase I of the study.

After spinal injection of drugs, the animals were secured over the operation table for maximum 30 min during which, paramedian incision was given and a foley's catheter was passed and fixed into the urinary bladder to ensure the outflow of urine. The bladder was repaired if ruptured. Depth, extent of analgesia, sedation and motor incoordination were measured at 0, 5 min after the drug administration followed by immediately after the surgery and then every 15 min till recovery. The various parameters were recorded for a maximum of upto 180 min. Rest of the observations were made at the similar intervals as for phase I of the study.

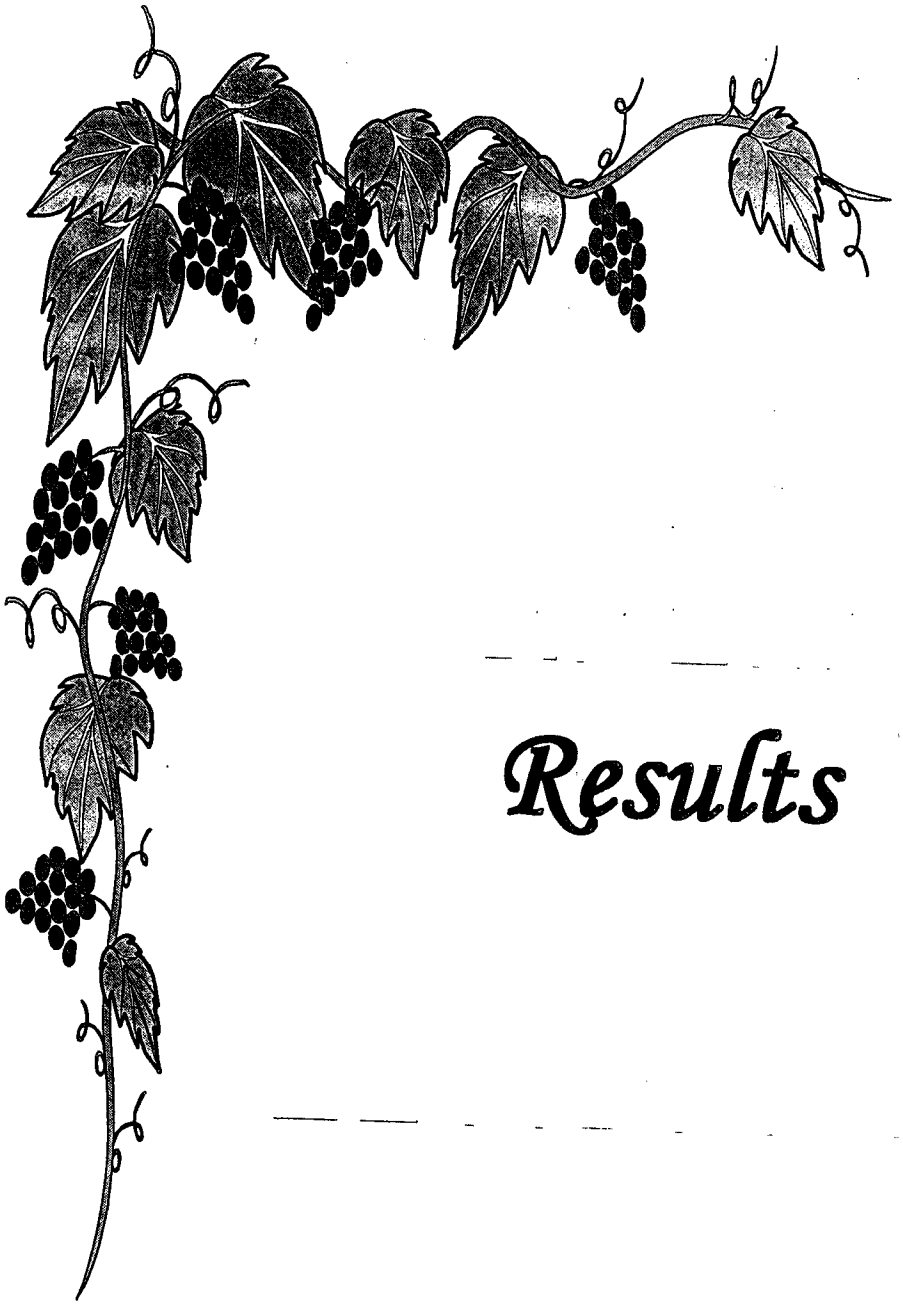
Intraoperative observations

Animal were also observed for their response to skin incision and to any other stimuli during surgery. Additional dose of drug required or use of local anesthetics as infiltration analgesia was also be recorded.

Statistical Analysis

Analysis of variance (ANOVA) and DMRT were used to compare the means among different groups at corresponding intervals and Paired T - test to compare the means among different values with the base value in each group. Kruskal - Wallis's one way test was used to compare the means among the groups of non-parametric observations.

❑❑❑



Results

RESULTS

Phase I

EXPERIMENTAL STUDY

Clinicophysiological studies

Clinical observations

Onset of analgesia

Absence of response to pin pricks at perineal region provided satisfactory indication for the onset of analgesia. The mean±SE values for onset of analgesia (in min) in different groups are presented in Figure 4.1 and Table 4.1.

The onset of analgesia in animals of group A (bupivacaine) and group D (bupivacaine + ketamine) was 6.6±1.02 min and 3.0±0.3 min, respectively. The onset of analgesia in the animals of group B (xylazine) and group E (xylazine + ketamine) was recorded as 16.0±1.86 min and 2.6±0.4 min, respectively. In the animals of group C (Buprenorphine) and group F (buprenorphine + ketamine), the onset of analgesia was recorded in 29.0±5.5 min and 4.0±0.4 min, respectively.

Comparison between the groups revealed that group E had early onset as compared to all the groups and more significantly earlier than groups B and C. The onset of analgesia was significantly ($P<0.05$) earlier in groups A, D, E and F as compared to group B and group C.

In the animals of group C, a significantly ($P<0.05$) longer time was taken for the onset of analgesia as compared to all the groups.

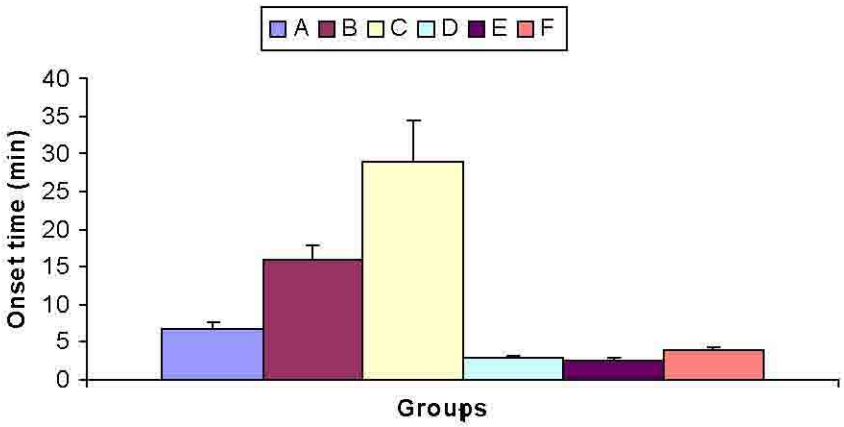


Fig 4.1 : Onset of analgesia in animals of different groups

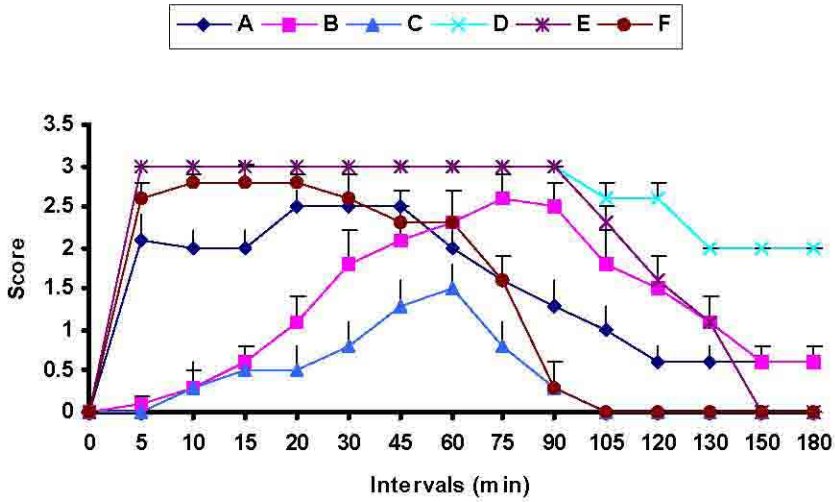


Fig 4.2 : Score of analgesia at perineum in animals of different groups (1-mild, 2-moderate, 3-complete)

Depth and extent of analgesia

Response to pin pricks to record the depth of analgesia in different body regions during the post-injection period also provided indication of extent of analgesia. Mean score at different intervals helped in quantifying the analgesia as absent, mild, moderate and complete analgesia at a particular region.

Perineum

Mean ±SE score for analgesia at perineum region in different groups are presented in Figure 4.2 and Table 4.2.

Bupivacaine alone (group A) produced moderate analgesia of perineum from 5 to 60 min interval post-injection. Thereafter, depth of analgesia started to decline and mild to very mild analgesia was recorded throughout the remaining observation period.

Xylazine alone (group B) produced very mild to mild analgesia of perineum from 5-30 min post-injection which increased gradually to moderate depth by 45 min. and persisted so upto 90 min. Thereafter, the analgesia declined to very mild to mild level and remained so throghout the period of observation.

In the animals of group C where buprenorphine alone was administered, very mild to mild analgesia of perineum was recorded from 10-75 min. Thereafter, depth of analgesia decreased further resulting in complete abolishion by 105 min post-injection.

Complete analgesia of perineum was recorded in the animals of group D and group E only. In both groups complete analgesia of the perineum was recorded within in 5 min after administration of the drugs. Complete analgesia, continued upto 90 min in both the groups. Thereafter, analgesia decreased and moderate depth of analgesia was recorded throughout the period of observation in group D. However, mild to moderate analgesia was seen in group E upto 130 min which weaned off completely by 150 min. In the animals of group F, analgesia quickly achieved moderate depth and remained at

this level from 5-60 min post-injection and complete analgesia could not be recorded at any interval. Analgesia decreased after 60 min remained very mild to mild upto 90 min and was completely abolished at 105 min. Comparison between different groups revealed that group D and group E showed significantly ($P<0.05$) higher level of analgesia of perineum than group C thoughout the period of observation, than group B upto 15 min and than group F after 60 min. The differences among the other groups were not significant ($P>0.05$). Analgesia in group D and E didn't differ significantly ($P>0.05$) from each other but analgesia weaned off in group E at 150 min and continued to persist at moderate level in group D, throughout the observation period. The longest duration of complete analgesia was recorded in animals of group D.

Inguinal region

Mean ±SE score for analgesia at inguinal region in different groups are presented in Figure 4.3 and Table 4.3.

Bupivacaine alone (group A), produced mild analgesia of inguinal region from 5-15 min and moderate analgesia from 20-60 min post-injection. Thereafter, the analgesia declined to remain as very mild to mild throughout the period of observation. Xylazine alone (group B) produced, very mild to mild analgesia for 5-60 min post-injection. Thereafter, the depth of analgesia increased to remain at moderate level from 75-90 min but decreased again to very mild to mild throughout rest of the observation period.

Buprenorphine alone group (C), produced very mild to mild analgesia from 10-90 min post-injection, which was completely abolished at 105 min. In the animals of group D, there was no analgesia of inguinal region at 5 min after the injection but by 10 min of injection a complete analgesia was established which continued upto 105 min post-injection. The analgesia then decreased to mild level and remained so throughout the rest of the observation period.

In the animals of group E, complete analgesia of inguinal region was recorded as early as 5 min and continued so upto 45 min. Thereafter, analgesia declined to remain moderate upto 105 min and weaned off completely by 150 min post-injection.

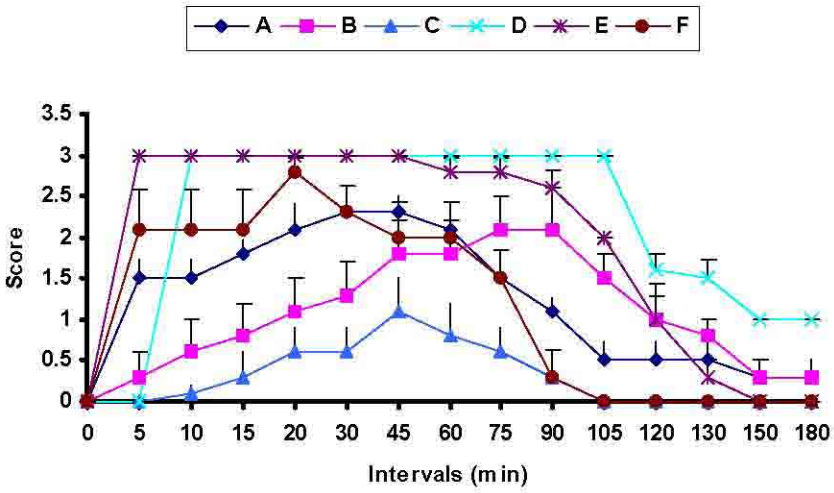


Fig 4.3 : Score of analgesia at inguinal in animals of different groups (1-mild, 2-moderate, 3-complete)

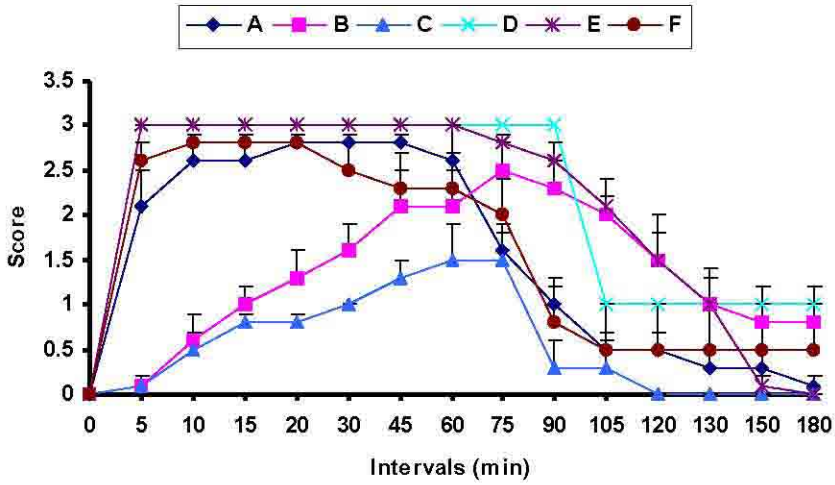


Fig 4.4 : Score of analgesia at tail in the animals of different groups (1-mild, 2-moderate. 3-complete)

Comparison between different groups revealed that group D and group E animals showed significantly ($P<0.05$) higher depth of analgesia as compared to group C throughout the observation period, as compared to group B during initial part of study and as compared to group F towards the end of observation period.

The difference between the other groups were however, non significant ($P>0.05$) at most of the intervals. The longest duration of complete analgesia was recorded in the animals of group D.

Tail

Mean ±SE score for analgesia at tail region in different groups are presented in Figure 4.4 and Table 4.4.

In animals given bupivacaine alone (group A) or ketamine and buprenorphine combination (group F) almost similar depth of analgesia was recorded at the tail. Analgesia was moderate up to 60 min followed by mild analgesia in both the groups. At the end of the observation period very mild analgesia persisted in both groups.

Xylazine alone (group B) produced very mild to mild analgesia of the tail region upto 30 min, which increased gradually to moderate level at 45 min and remained so upto 105 min. Analgesia then decreased gradually and very mild analgesia was recorded at subsequent intervals upto the end of observation.

In group C, where buprenorphine alone was administered, very mild to mild analgesia could be produced upto 105 min which was completely abolished by 120 min.

In groups where ketamine was administered in combination with bupivacaine (group D) or xylazine (group E), complete analgesia of tail region was recorded from 5-90 min in group D and upto 60 min in group E. Thereafter, mild analgesia persisted till the end of observation period in group D and up to 130 min in group E.

Comparison among different groups revealed that combination of ketamine with bupivacaine (group D) or xylazine (group E), produced significantly ($P<0.05$) higher level of analgesia at tail than xylazine alone upto 15 min and buprenorphine alone upto 105 min. Longer duration of complete analgesia was recorded in animals of group D (90 min) than the animals of group E (60 min).

Flank

Mean ±SE score for analgesia at flank region in different groups are presented in Figure 4.5 and Table 4.5.

In animals of group A, where bupivacaine alone was administered, mild analgesia was recorded from 10 min to 60 min which reduced gradually but very mild analgesia was observed upto the end of observation period. Neither xylazine (group B) nor buprenorphine (group C) could produce any level of analgesia of flank region throughout the observation period. In group D, where ketamine and bupivacaine combination was given, very mild to mild analgesia was recorded initially at 5 to 10 min. However, depth of analgesia increased quickly and at 15 to 90 min complete analgesia of flank was recorded. Depth of analgesia decreased again and mild to moderate analgesia was recorded upto the end of observation period. Ketamine and xylazine (group E) when given together, produced very mild to mild analgesia from 10 to 20 min post injection. Thereafter, moderate analgesia persisted from 30 to 105 min which decreased gradually to remain at very mild to mild level upto 130 min and weaned off completely by 150 min post-injection.

In animals of group F, analgesia was very mild to mild from 5 to 105 min and by 120 min the analgesia weaned off completely.

Comparison among different groups revealed that ketamine in combination with bupivacaine (group D) produced significantly ($P<0.05$) higher depth of analgesia of flank region as compared to group B and C up to 180 min and group F at 105-180 min. Complete analgesia of flank was recorded only in the animals of group D.

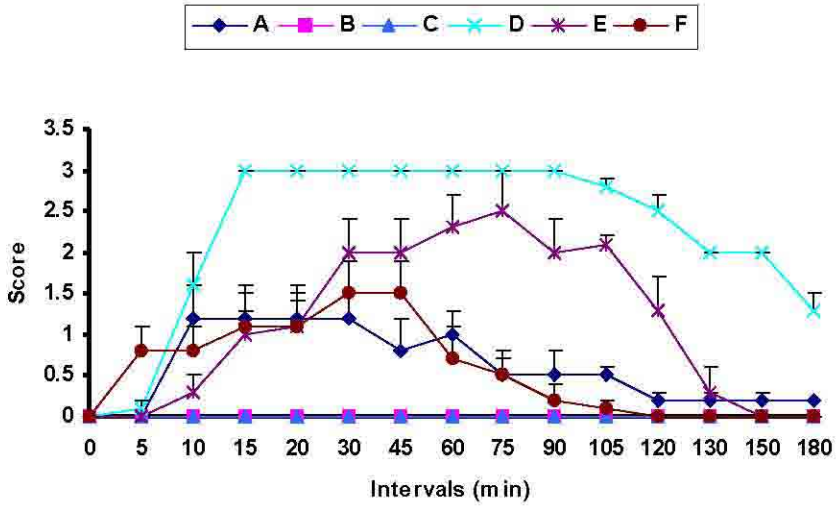


Fig 4.5 : Score of analgesia at flank in animals of different groups (1-mild, 2-moderate, 3-complete)

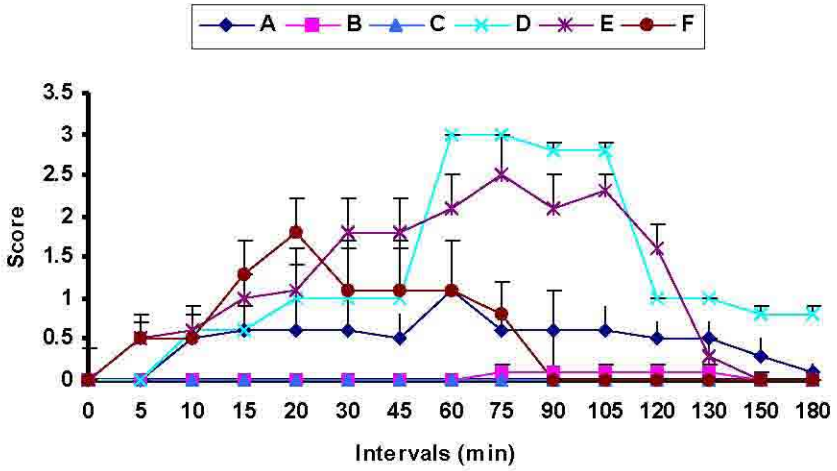


Fig 4.6 : Score of analgesia at abdomen in animals of different groups (1-mild, 2-moderate, 3-complete)

Abdomen

Mean ±SE score for analgesia at abdomen region in different groups are presented in Figure 4.6 and Table 4.6.

In animals of group A (bupivacaine alone), very mild to mild analgesia was recorded from 10 min post-injection, which remained so till the end of observation. Xylazine alone (group B), could produce only very mild analgesia of abdomen from 75 to 130 min. During rest of the observation period animals of this group, exhibited no analgesia. Buprenorphine alone (group C) didn't produce any analgesia of abdomen throughout the observation period.

In the animals of group D, no analgesia of abdomen was recorded upto 5 min post-injection but very mild to mild analgesia of abdomen was apparent from 10-45 min post-injection. Analgesia deepened and complete analgesia was observed from 60-75 min. Analgesia started to decrease gradually and moderate analgesia was then recorded upto 105 min. Thereafter, very mild to mild analgesia persisted throughout the observation period. Group E animals showed very mild to mild analgesia of abdomen at 5-45 min post-injection. Thereafter, moderate analgesia was present for 60-105 min which decreased gradually to get abolished completely by 150 min post-injection. In the animals of group F, very mild to mild analgesia of abdominal region was recorded between 5 and 75 min post injection. The analgesia weaned off completely by 90 min.

Comparison between different groups revealed that animals of group D and group E showed a significantly ($P<0.05$) higher level of analgesia of abdomen than groups B, C and F during most of the time intervals of observation period. However, analgesia in group A animals did not differ significantly from the group D and E. Complete analgesia was seen ony in group D animals.

Thorax

Mean ±SE score for analgesia at thorax region in different groups are presented in Figure 4.7 and Table 4.7.

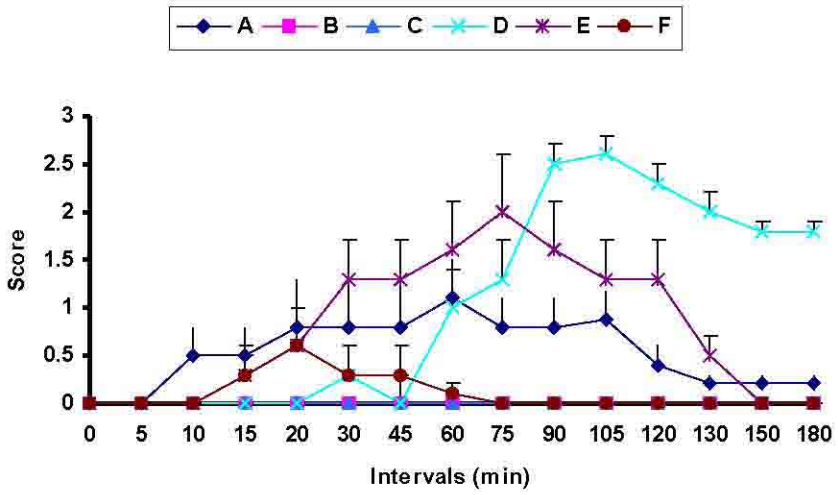


Fig 4.7 : Score of analgesia at throax in animals of different groups (1-mild, 2-moderate, 3-complete)

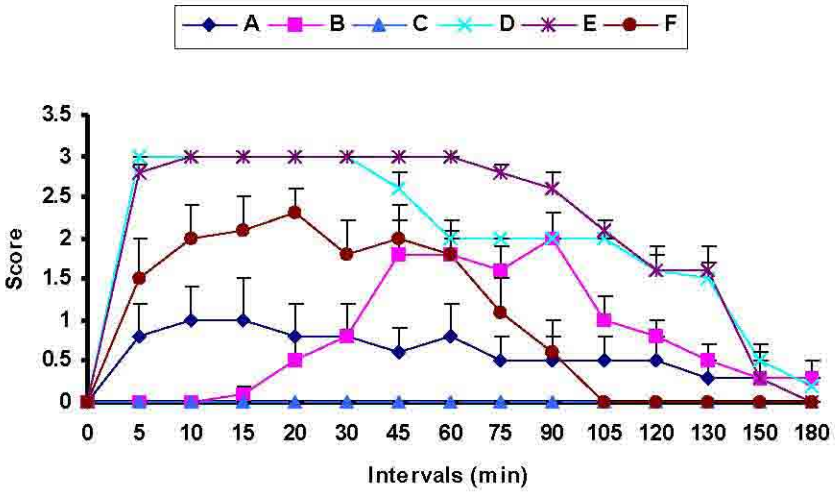


Fig 4.8 : Score of analgesia at hind limb in animals of different groups (1-mild, 2-moderate, 3-complete)

Analgesia of thorax was not complete in any of the groups during entire period of observation. Bupivacaine alone in group A, could produce only very mild analgesia, of thoracic region throughout the period of observation except at 60 min where a mild analgesia was recorded. Xylazine alone (group B) and buprenorphine alone (group C) however, failed to produce any level of analgesia of thoracic region.

In the animals of group D, no analgesia of thorax was present upto 30 min post injection but thereafter a mild to moderate analgesia was recorded from 45-75 min interval, which slightly increased after 90 min and remained mild to moderate throughout rest of the period of observation. No analgesia of thorax in group E animals was recorded upto 10 min. Thereafter, very mild to mild degree of analgesia was recorded from 15 min upto 130 min, which weaned off completely by 150 min. The analgesia in group E, was recorded to be moderate only at 75 min post-injection. In the animals of group F, only very mild analgesia was recorded for a short period from 15 min to 60 min interval. The analgesia at thorax was absent during rest of the observation period.

Comparison between different groups showed that in the animals of group D, significantly ($P<0.05$) higher depth of analgesia of thorax was recorded from 90 to 180 minutes as compared to group B, C and F at corresponding intervals. The analgesia in group A and group E, however, did not differ significantly from all the other groups.

Hind limb

Mean ±SE score for analgesia at hind limb region in different groups are presented in Figure 4.8 and Table 4.8.

In animals of group A, very mild to mild analgesia was recorded from 5 min to 60 min, but thereafter, analgesia decreased further and only very mild analgesia was present till the end of observation period.

In animals of group B, analgesia at the thigh region was almost absent up to 15 minutes. Very mild to moderate anlagesia was then seen up to 75 min. The maximum

analgesia was at 90 min, where the animals showed moderate analgesia. In group C, no analgesia of the hind limbs was recorded throughout the observation period.

In the animals of group D, complete analgesia of the thigh region was recorded as early as 5 min, which remained so up to 30 min. Depth of analgesia then decreased and moderate depth of analgesia from 45-120 min and mild to very mild analgesia from 130 min onwards till the end of observation period was recorded. Animals of group E showed complete analgesia at 10 min which persisted up to 60 min. Depth of analgesia then decreased gradually to completely wean off by 180 min. In group, F, mild to moderate analgesia of thigh region persisted upto 75 min and by 105 min interval pain sensation had returned to normal in the animals of this group.

Comparison among different groups showed that combination of ketamine with bupivacain (group D) or xylazine (group E) produced significantly ($P < 0.05$) higher depth of analgesia at thigh region up to 120 min as comapred to group C and non-significantly ($P > 0.05$) higher than the other groups. The depth of analgesia in group D and E did not differ significantly but the duration of complete analgesia was longer in group E than group D.

Digits

Mean ±SE score for analgesia at digits region in different groups are presented in Figure 4.9 and Table 4.9.

Neither bupivacaine (group A) nor buprenorphine alone (group C) produced any analgesia of digits throught the period of observation. However, xylazine alone (group B), produced very mild to mild analgesia of digits from 30 min till the end of observation period.

Animals of group D and group E showed a complete analgesia of digits as early as 5 min which continued at 30 min and 45 min in group D and E, respectively. Thereafter, the analgesia declined in both the groups to remain as moderate upto 105 min and further declined to remain mild to very mild throughout the observation period. In the

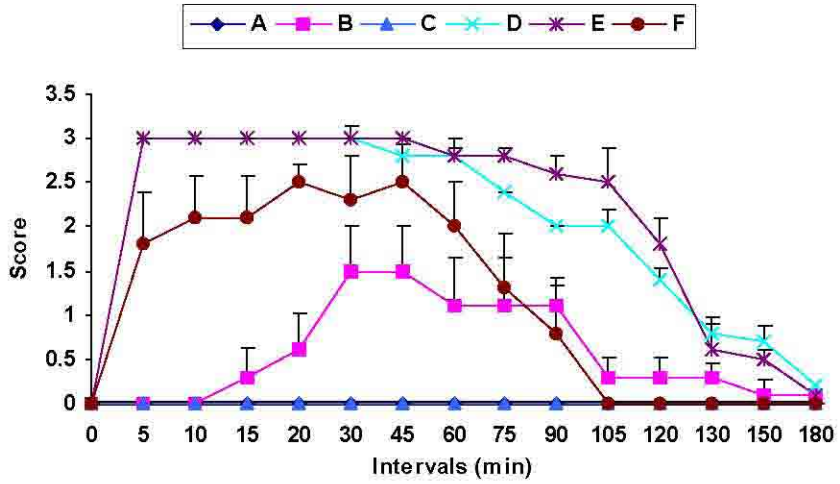


Fig 4.9 : Score of analgesia at digits in animals of different groups (1-mild., 2-moderate, 3-complete)

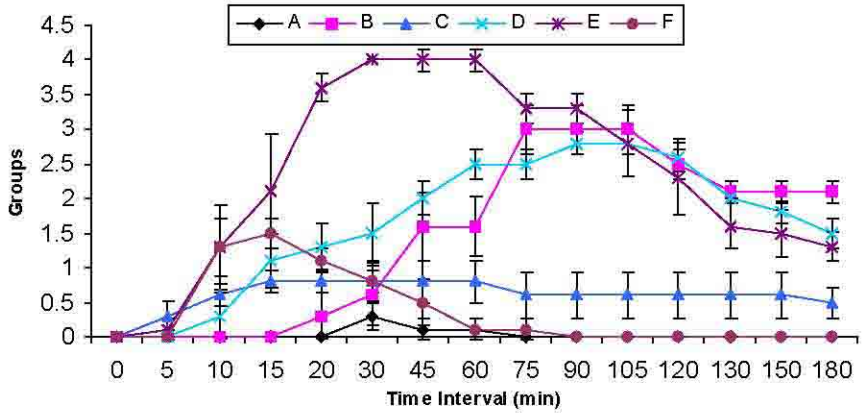


Fig 4.10 : Score of sedation recorded in the animals of different groups (0-standing alert, 1-slight toses of eye lids, 2 extreme lowering of head, 3-recumbent but could sit without support, 4-recumbent laterally

animals of group F, mild to moderate analgesia of digits was recorded from 5 min and 30 to 75 min. At 90 min, very mild analgesia of digits was recorded and analgesia abolished completely at 105 min.

Comparison among various groups revealed that group D and group E animals showed significantly ($P<0.05$) higher depth of analgesia of digits than groups A and C thoughout the observation period at few intervals than the animals of group B. Group D and Group E did not differ significantly ($P>0.05$) from each other as far as the depth of analgesia was concerned. Complete analgesia of digits was observed in group D and E only.

Summary of depth and extent of analgesia

A complete analgesia (score 3) of different regions produced by different anaesthetics and their duration is summarized in Table 4.10.

Bupivacaine in animals of group A couldn't produce any analgesia in digits and could produce a maximum of only mild analgesia of hind limbs, flank and thorax. A maximum of moderate analgesia was recorded in perineum, inguinal and tail region. Xylazine in animals of group B produced no analgesia of thorax and flank and only maximum of mild analgesia of digits and abdomen. A maximum of moderate analgesia was present in perineum, inguinal region, hind limbs and tail region. Buprenorphine in animals of group C could not produce any analgesia of thorax, digits, abdomen, hindlimbs and flank. However, a maximum of a mild analgesia of perineum, inguinal and tail region was seen. Ketamine-bupivacaine in animals of group D produced a maximum of complete analgesia of digits, perineum, inguinal region, abdomen, hind limbs, tail and flank region and moderate analgesia of thorax for varing lengths of time.

Ketamine-xylazine in animals of group E produced a maximum of moderate analgesia of thorax, abdomen and flank and complete analgesia of digits, perineum, inguinal region, hind limbs and tail. Ketamine-buprenorphine in animals

of group F produced a maximum of only mild analgesia of thorax, abdomen and flank and a maximum of moderate analgesia of digits, perineum, inguinal region, hind limbs and tail region.

Sedation

Mean ±SE score of sedation in different groups are presented in Figure 4.10 and Table 4.11.

Group A, animals remained alert throughout the period of observation except for a mild sedative period between 30 to 60 min post injection with slight ptosis of eye lids. Group B, animals showed a mild degree of sedation from 20 to 30 min which increased slowly to become extreme from 75 to 105 min, where the animals were recumbent/ standing with wide stance with lowering of head but could sit without support throughout the period of observation. Group C (Buprenorphine), animals, showed only mild degree of sedation with slight ptosis of eyelids from 5 min onwards to throughout the period of observation. Group D animals, although attained recumbency from 5 min to 90 min post injection but remained less sedated throughout with only lowering of head. Animals in group E, also attained lateral recumbency from 5 min to 75 min postinjection and the animals showed extreme sedation but could sit without support upto 20 min. From 30 to 60 min however, the animals showed highest degree of sedation and couldn't sit without support. This continued to a lesser degree for upto 120 min and thereafter, the animals could walk with staggering at 130 min post-injection. Group F animals remained alert throughout the period of the study except that they showed slight ptosis of eyelids from 10 to 75 minutes post injection.

Comparison among different groups revealed that group A and group C animals were significantly ($P < 0.05$) less sedated throughout the period of observation but group B animals showed significantly ($P < 0.05$) higher degree of sedation from 75 min till 180 min post-injection.

Group D animals showed significantly higher ($P < 0.05$) sedation from 60 to 180 min post injection, as compared to group F, similarly group E (ketamine-xylazine) animals, after a mild phase of sedation showed significantly higher ($P < 0.05$) sedation degree as compared to group F and group A.

Motor incoordination

Mean ±SE score motor incordination in different groups are presented in Figure 4.11 and Table 4.12.

Animals of group A (bupivacaine alone) assumed sternal recumbency from 5 to 45 min post-injection. Thereafter, extreme inccordination of limbs persisted up to 90 min followed by slight staggering of gait till the end of the observation period. Animals of group B (xylazine alone) could walk without staggering for up to 5-10 min and thereafter showed little staggering while walking from 15 to 20 min post injection. Extreme incoordination of gait persisted thereafter, throughout the period of observation. Animals of group C (buprenorphine alone) however, showed little incoordination from 5 to 90 min and extreme incoordination from 105 to 130 min post-injection followed by staggering with little incoordination till the end of observation period. Animals of group D (ketamine and bupivacaine) showed an immediate sternal recumbency from 5 to 15 min and thereafter, attained lateral recumbency from 20 to 45 min post injection. The animals again came back in sternal recumbency and remained so up to 90 min. Thereafter, an extreme incoordination, till the end of the observation period in this group was recorded. Group E (xylazine and ketamine) animals also attained sternal recumbency as early as 5 min and thereafter attained lateral recumbency from 10 to 60 min post-injection followed by attainment of sternal recumbency again at 75 min and thereafter, the score decrease and extreme incoordination of limbs was present at 90-105 min followed by little to very little inccordination of limbs when the animals were made to walk at 120-150 min. However, the animals could walk normally at 180 min post-injection. Group F (ketamine

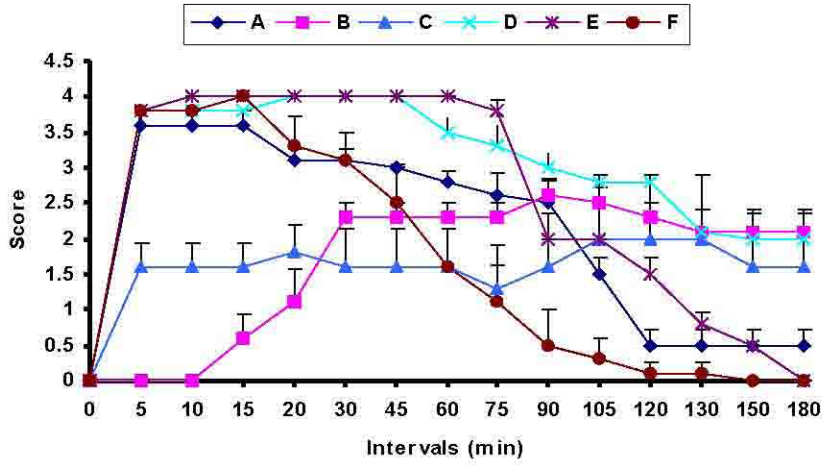


Fig 4.11 : Score of motor incoordination of hind limbs in the animals of different groups (0-normal, 1-little incoordination, 2-extreme incoordination, 3-sternal recumbency, 4-lateral recumbency)

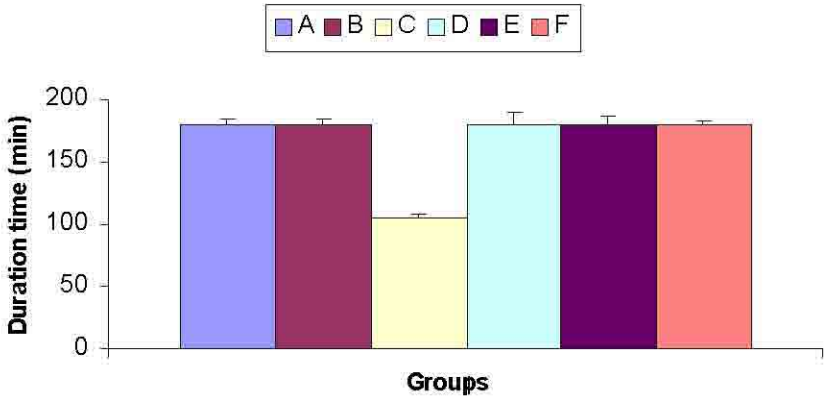


Fig 4.12 : Duration of analgesia in animals of different groups

and buprenorphine) animals, showed sternal recumbency from 5 to 30 min post-injection with lateral recumbency only at 15 min. Thereafter, little staggering persisted upto 105 min and the animals could walk normally by 150 min.

Comparison among various groups revealed that motor incoordination was significantly ($P<0.05$) high in group D, and group E than group B and C at 5 to 45 min and 20 to 75 min respectively. During rest of the period differences remained non-significant. Animals of group F also showed significantly ($P<0.05$) lower motor incoordination as compared to groups D and E from 60 min till the end of obseration period. Motor incoordination of group A was non-significantly different and higher than group B and C at 5 min to 75 min and 5 to 90 min but thereafter vice-versa was true. Thereafter, at the end of observation period animals of group E and F showed no motor incoordination. However, animals of group A showed very mild, animals of group C mild and group B and D moderate degree of motor incoordination.

Duration of analgesia

Mean ±SE values of duration of analgesia (in min) in different groups are presented in Figure 4.12 and Table 4.13.

Duration of analgesia was comparable among different groups. However, the combination of Ketamine with Bupivacaine (D) and Xylazine (E) produced analgesia of all the regions which was non-significantly ($P > 0.05$) of longer duration as compared to that in group A and B, respectively and significantly ($P < 0.05$) of longer duration than group C. Ketamine in combination with buprenorphine (F) however produced a longer duration of analgesia than buprenorphine alone (group C) but its duration was lesser than group D and E. The duration of analgesia was longest in group D among all three groups of experimental animals. On the contrary, group C animals recorded a minimum duration of analgesia as compared to all the groups.

Recovery

The time when the animal was completely alert and had normal gait with absence of analgesia in perineal region, it was considered to have recovered from the effects of the drugs. Recovery took place in the following order. Group C followed by group F, followed by groups A and B, followed by group E, and followed by group D.

Physiological parameters

Heart rate

Mean ±SE values of heart rate in different groups recorded is presented in Figure 4.13 and Table 4.14.

Bupivacaine alone (group A) produced a decrease in the heart rate from 5 to 180 min with the decrease being significant ($P<0.05$) at 15 min 45 min and 75 min post-injection as compared to the base line. The values remained below the base line till the end of the observation period. Group B animals, a non-significant ($P>0.05$) increase in HR was recorded from 5 to 15 min initially followed by a gradual decrease in heart rate from 60 to 180 min post-injection. The decrease was significant ($P<0.05$; $P<0.01$) from 120 to 180 minutes.

In the animals of group C, heart rate increased at 5 min and decreased non-significantly ($P>0.05$) upto 75 minutes with fluctuations. Thereafter, the heart rate fluctuated near the base line at different time intervals during the post-injection period. However, in group D animals a decrease in the heart rate was recorded throughout the observation period. The values of heart rate significantly ($P<0.01$) decreased from 30 to 120 min post-injection. The values remained below the base line even at the end and never returned to pre-adminitration level at 180 min.

In the animals of group E also, a significant ($P<0.05$) decrease in the heart rate from 10-60 min was recorded and continued to be lesser than the base line till the end

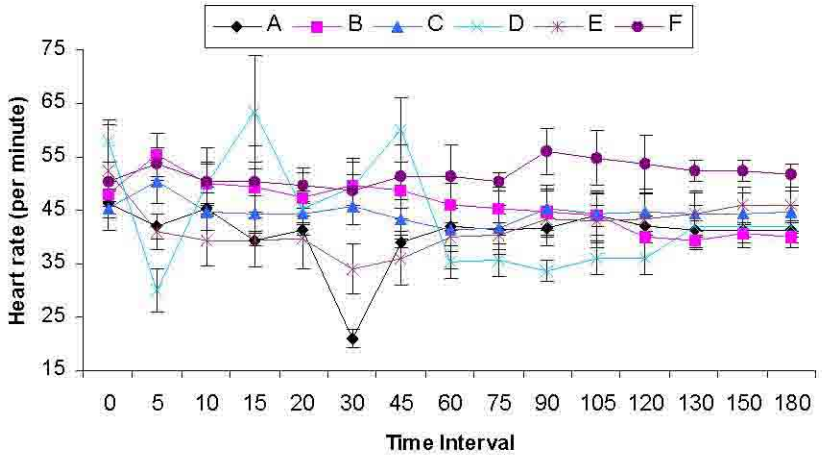


Fig 4.13 : Heart rate (per minute) recorded in the animals of different groups

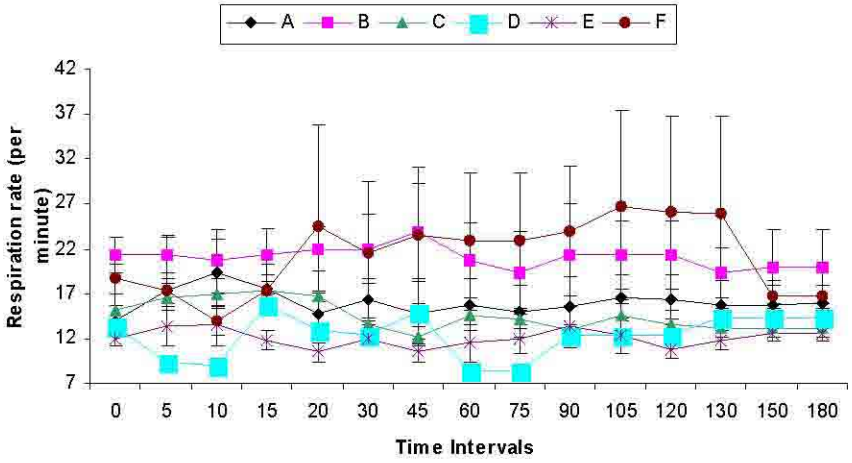


Fig 4.14 : Respiration rate (per minute) recorded in animals of different groups

of observation period. The values of heart rate however, showed a gradual increase after 75 min but remained below the base line at 180 min.

In group F animals no significant (P>0.05) change in heart rate was recorded throughout the observation period. However, the values showed a non-significant increase at some post-injection intervals but the values returned to pre-administration level at the end.

Comparison among various groups revealed that group B animals had significantly (P<0.05) higher HR values at 5 min post-injection as compared to groups A, D and E but non-significantly higher than group F. At 45 min interval, group D revealed a significantly (P<0.05) higher HR value as compared to groups A, C and E and non-significantly (P > 0.05) higher HR than groups B and F.

Heart rate was recorded to be non-significantly (P>0.05) lowest in group E as compared to all the groups at 10 to 45 min. interval and in group D at 60 to 120 min post-injection period. At rest of the intervals of time during the post-injection period the HR values did not differ significantly (P > 0.05) among various groups.

Respiratory rate

Mean ±SE values of respiratory rate in different groups recorded is presented in Figure 4.14 and Table 4.15.

In group.A (bupivacaine alone), there was a non-significant (P > 0.05) increase in the respiratory rate throughout the period of observation. The values remained increased even at the end of observation period and never returned to the base line.

Group B (xylazine alone) animals showed a non-significant (P > 0.05) rise in respiratory rate from 20 to 45 minutes post injection. Thereafter, the values fluctuated near the base line upto 120 min. The RR remained slightly below the base line from 130 to 180 minutes post injection.

Animals of Group C (Buprenorphine alone), showed a non-significant ($P > 0.05$) increase in respiratory rate from 5 to 20 minutes. The respiratory rate then decreased from 30 minutes onwards and remained decreased till the end of observation period.

Group D animals, showed a significant ($P < 0.001$) decrease in the respiration rate for 5 to 10 min post injection. The values then fluctuated between 15 and 45 min. Thereafter, a significant ($P < 0.001$) decrease at 60 and 75 min post injection was recorded. The values, however, increased steadily thereafter and reached near the base line at 130 min. Respiratory rate remained slightly above the base line even at the end of observation period. In group E, there was a transient increase in respiration rate from 5 to 10 min post-injection. The values, however, decreased thereafter upto 60 minutes. Respiratory rate increased from 75 min and fluctuated near the base line till the end of observation period.

Animals of group F showed an initial decrease in respiratory rate from 5 to 15 min post-injection, which was significant ($P < 0.05$) at 15 min. The respiratory rate, thereafter showed a non-significant ($P > 0.05$) increasing trend till 130 min. The rate however, decreased towards the end of observation period and reached near the base line.

Comparison among different groups revealed that no significant ($P > 0.05$) difference in the respiration rate at any time interval was recorded among different groups.

Rectal temperature

Mean ±SE values of rectal temperature in different groups recorded is presented in Figure 4.15 and Table 4.16.

Bupivacaine alone (group A), induced a non-significant ($P > 0.05$) decrease in rectal temperature from 10 to 60 min post-injection. The rectal temperature increased thereafter and the values returned to normal at 75 min and remained near the base line till the end of observation period. Xylazine alone (group B) also produced a non-significant ($P > 0.05$) decrease in rectal temperature from 10 to 30 min post-injection. The values

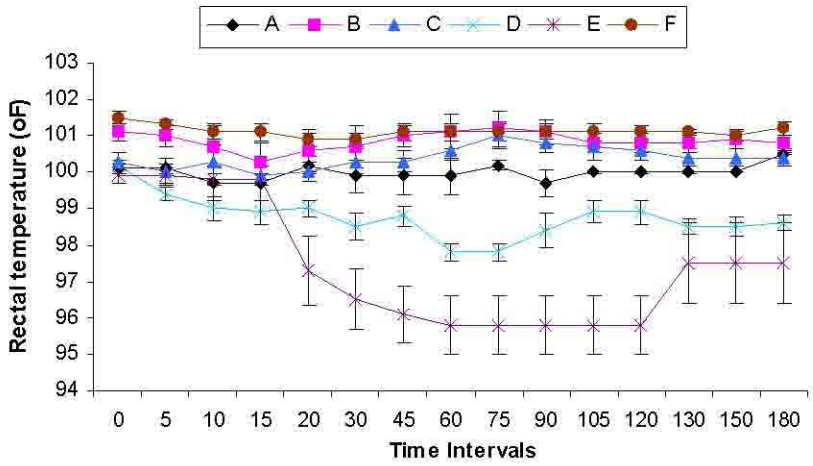


Fig 4.15 : Rectal temperature (oF) recorded in the animals of different groups

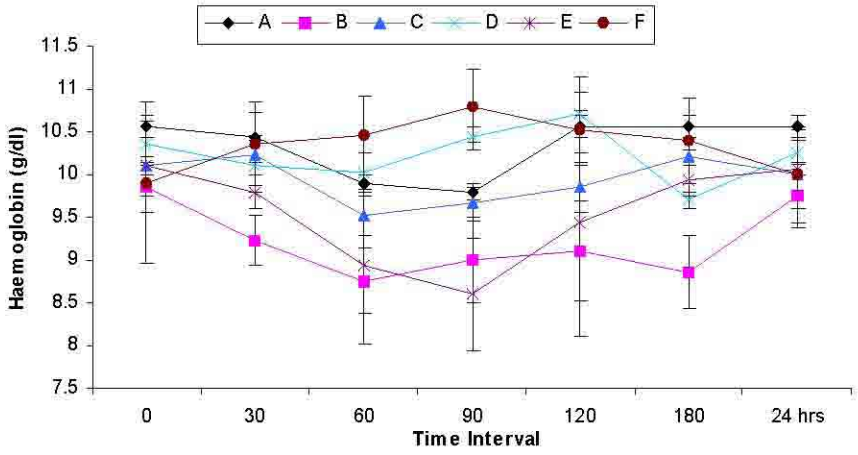


Fig 4.16 : Haemoglobin (g/dl) in the animals of different groups

increased thereafter gradually and remained normal from 45 to 90 min post-injection. The rectal temperature decreased thereafter, gradually till the end of observation period. In group C animals, no significant ($P > 0.05$) difference in the rectal temperature was recorded, throughout the period of observation except for a transient and non-significant ($P > 0.05$) decrease at 15 min post-injection. Group D however, showed a significant ($P < 0.05$) decrease in rectal temperature throughout the period of observation. The decrease was more significant ($P < 0.001$) at 60 and 75 min and from 130 to 180 min post-injection ($P < 0.01$). The values remained decreased and never returned to the base line even at the end of observation period. Group E animals showed a decrease in rectal temperature from 10 min onwards till 120 min post-injection. The decrease was significant ($P < 0.01$) from 30 min to 105 min post-injection. The values, however, started to improve thereafter, but remained lesser than the baseline even at the end of observation period. Group F animals, showed a non-signficant ($P > 0.05$) decrease in rectal temperature from 20 to 30 min. The values significantly ($P < 0.05$) reduced from 45 min to 130 min of observation, which were more significant at 75 min ($P < 0.01$) and 90 min ($P < 0.001$).

Comparison among different groups at different intervals revealed no significant ($P > 0.05$) difference in rectal temperature among groups A, B, C and F. The values in group E (ketamine-xylazine) were significantly ($P < 0.05$) lower during the entire period of observation. The values of rectal temperature in group D were also significantly ($P < 0.05$) lower from 10 min till the end of observation as compared to all the groups. However, as compared to group E, it remained significantly ($P < 0.05$) higher at almost all the intervals of time.

Haematological studies

Haemoglobin

Mean ±SE values of haemoglobin in different groups have been shown in Figure 4.16 and Table 4.17.

Haemoglobin values decreased in groups A, B, C, D and E throughout the period of observation. The decrease was significant ($P < 0.01$) in group A from 60 to 90 min post-injection and in group B ($P < 0.01$) from 30 to 60 min and significantly less ($P < 0.05$) at 180 min post injection. Group C animals showed a significant decrease at 60 min and group D from 30 to 60 min. The haemoglobin values in groups A,B,C,D and E returned to the base line at 24 hrs. There was not much change in the haemoglobin values in group F throughout the period of observation. The values fluctuated near the base line during the post-injection period.

Comparison among various groups revealed that Hb values were significantly ($P < 0.05$) lesser in group F at pre-administration level as well as at the end of observation as compared to all the groups. However, all the values in different groups returned to base levels by 24 hrs.

PCV

Mean ±SE values of haemoglobin in different groups have been shown in Figure 4.17 and Table 4.18.

A decrease in PCV was recorded in group A after injection upto 90 min where the decrease was significant ($P < 0.05$) from base values. The values returned to base line at 120 min and remained so till the end. Group B animals also showed a significant ($P < 0.01$, $P < 0.05$) decrease in PCV from 60 min to 24 hrs. The values remained below the base line at the end of observation period. Animals of group C, showed decrease in the PCV from 60 to 120 min post-injection. The decrease was significant ($P < 0.05$) from 60-90 min. The values, however, returned to base line at 180 min. In groups D and E, the PCV decreased non-significantly ($P > 0.05$) during the post-injection period. The values never returned to the base line even at the end in both the groups. On the other hand, PCV increased non-significantly ($P > 0.05$) in group F during the post-injection period. The values, however, returned to base line at 180 min post-injection.

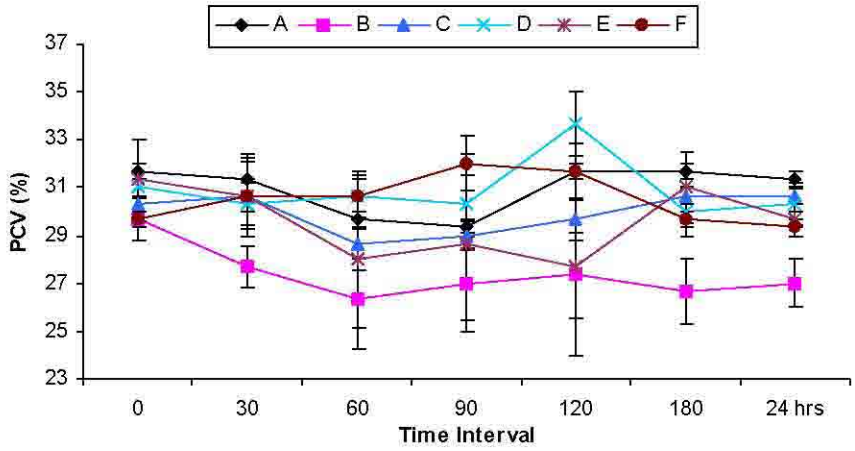


Fig 4.17 : PCV (%) in the animals of different groups

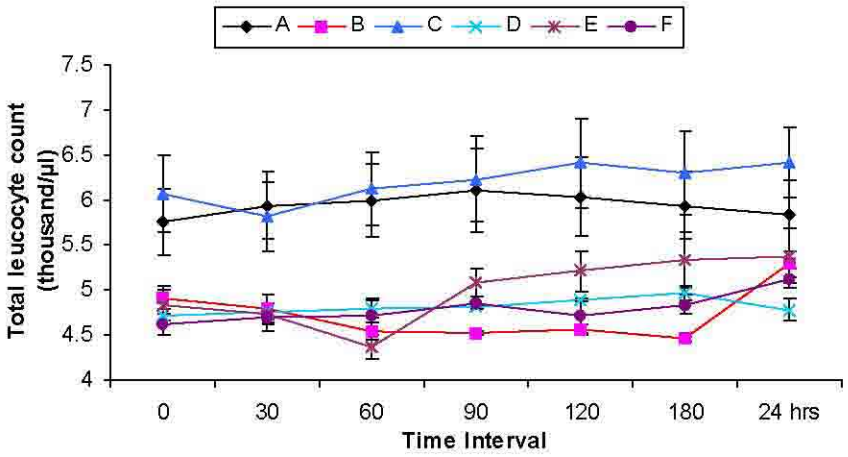


Fig 4.18: Total leucocyte count (thousand/µl) in the animals of different groups

Comparison among different groups revealed that the PCV values were significantly ($P < 0.05$) lower in group B at 180 minutes and 24 hr as compared to rest of the treatment groups. Group D when compared to group E revealed that PCV values in group E was non-significantly ($P > 0.05$) lower in group E as compared to group D at 60 to 120 min post-injection. PCV values of group F was non-significantly ($P > 0.05$) higher than PCV values of group D and E at 90 to 120 min post-injection.

Total leucocytic count (TLC)

Mean ±SE values of total lucocyte count in different groups have been shown in Figure 4.18 and Table 4.19.

The TLC values showed a non-significant ($P>0.05$) increase in group A throughout the period of observation. The values, however, started to decline at 180 min but never reached the pre-administration level till the end of observation (24 hrs). In group B animals, TLC decreased non-significantly ($P>0.05$) from 30 min onwards and continued to decrease significantly ($P<0.05$) at 60 min post-injection. The value increased at 24 hrs and returned to the base line at the end of the observation. Group C animals showed a consistent increase in total leucocyte count during the entire post-injection period and the values remained non-significantly ($P>0.05$) elevated even at the end of the observation period. Group D, animals also showed an increase in TLC upto 180 min. post-injection. The increase was significant ($P<0.05$) at 180 min but declined thereafter at 24 hrs and reached near the base line. Group E animals showed an initial non-significant decrease in TLC at 30 to 60 min which increased above the base line at 90 min. It further increased significantly ($P<0.05$) at 120 min. The values remained elevated and didnot return to the base line even at the end of observation period. Animals of group F, showed a steady increase in the total leucocytic count with a significantly ($P<0.05$) higher leucocytic count at all the intervals as compared to base line values. In this group all the values including the base values were significantly higher as compared to all the treatment groups B, D, E and F. The values at 24 hrs in groups A, B, C, D

and E were non-significantly (P>0.05) higher as compared to base value except in group F where it remained significantly (P<0.05) higher than the base value.

Comparison among different groups revealed that group A and C, showed significantly (P<0.05) different and higher total leucocytic count at all the intervals including the base value as compared to all the treatment groups B, D, E and F.

Differential leukocyte count (DLC)

Neutrophils

Mean ±SE values for neutrophils in different groups have been shown in Table 4.20.

Neutrophil count increased non-significantly (P > 0.05) in all the treatment groups at different intervals during the post-injection period. The count remained elevated at 24 hrs in all the groups and never returned to the base line till the end.

Comparison among various groups revealed that group A had significantly (P < 0.05) lower neutrophil count than all the groups at 120 min and 24 hrs. Group B animals had significantly (P < 0.05) higher count than all the groups except group F at 24 hr interval.

Lymphocytes

Mean ±SE values of lymphocytes in different groups have been shown in Table 4.21.

A non-significant decrease (P>0.05) in lymphocyte count was recorded throughout the period of observation in comparison to the respective base values in all the treatment groups. The values returned to normal at 24 hrs post-injection in all the groups except groups A, C, E and F where they remained non-significantly lesser than the respective base values. In the animals of group A, lymphocyte count remained non-significantly reduced at 30, 90 and 120 min and further decreased at 180 min. It increased at 24 hrs but remained non-significantly (P>0.05) lesser than the base value.

Comparison among different groups did not reveal any signifiacnt (P>0.05) variation at respective time intervals during the post-injection period.

Eosinophils

Mean ±SE values of eosinophils in different groups have been shown in Table 4.22.

There was no significant (P > 0.05) change in the eosinophil count in all the groups at any interval of time during the post-injection period. However, an insignificant increase was seen in group B (xylazine alone) and group C throughout the period of observation.

Comparison among all the groups revealed no significant (P > 0.05) difference at any corresponding interval among each other.

Monocytes

Mean ±SE values of monocytes in different groups have been shown in Table 4.23.

There was no significant (P>0.05) variation in monocyte count within any of the groups as compared to their respective base values at different intervals of time.

Comparison among various groups also revealed no significant (P>0.05) variation at respective time intervals. It remained unchanged throughout the period of observation and the values fluctuated near the base-line during the post-injection period.

Biochemical observations

Plasma glucose

Mean ±SE values of plasma glucose in different groups have been shown in Figure 4.19 and Table 4.24.

In the animals of group A an increase in the plasma glucose was recorded throughout the observation period as compared to the base line. However, the values

returned to the base line by 24 hrs. The increase was significant ($P<0.05$) at 30 min and 180 minutes post-injection. In the animals of group B also an increase in plasma gluocse was recorded throughout the observation period which was significant at 30, 60 ($P<0.05$), 90 ($P<0.001$) and 180 minutes. The values remained elevated above the base line even after 24 hrs. In group C animals, at 30 min, a non-significant decrease in plasma glucose was recorded which thereafter, increased non-significantly ($P>0.05$) and remained slightly elevated above the base line upto 180 min post-injection. Value returned to the base line at the end of obseration. In the animals of group D, a non-significant ($P>0.05$) decrease was recorded throughout the observation period and the values remained decreased even at the end of the observation period than the base line value. Group E animals, also showed a non-significant ($P>0.05$) increase in plasma glucose levels at most of the time intervals and at rest of the intervals values fluctuated close to the base line value till the end of observation. In the animals of group F, a significant ($P<0.05$) increase in plasma gluocse was recorded at 60 min and 90 min. The values returned to the base value at the end of observation period.

Comparison among all the groups revealed that the baseline value of group D was signfiicantly ($P<0.05$) different and higher than all the groups. Groups A, E and F had significantly ($P<0.05$) higher base line values than group B and group C. Group F at 60 minutes interval showed significantly ($P<0.05$) higher plasma glucose values than group C and nonsignificantly higher than all the groups.

Group B and F at 90 min, showed significantly ($P<0.05$) higher plasma glucose values than group C and D and nonsignificantly higher ($P>0.05$) than rest of the groups. Group D as compared to group E had nonsignificantly ($P>0.05$) lower plasma glucose level at 90, 180 min and 24 hrs post-injection. Group B animals showed a significantly ($P<0.05$) higher value at 180 min than group C and D and varied non-significantly ($P > 0.05$) higher than rest of the groups. At 24 hrs post-injection, groups A, C, E and F achieved the base line values but group D remained lower than the base line values and group B remained higher than the base line. Group D at 24 hrs interval showed

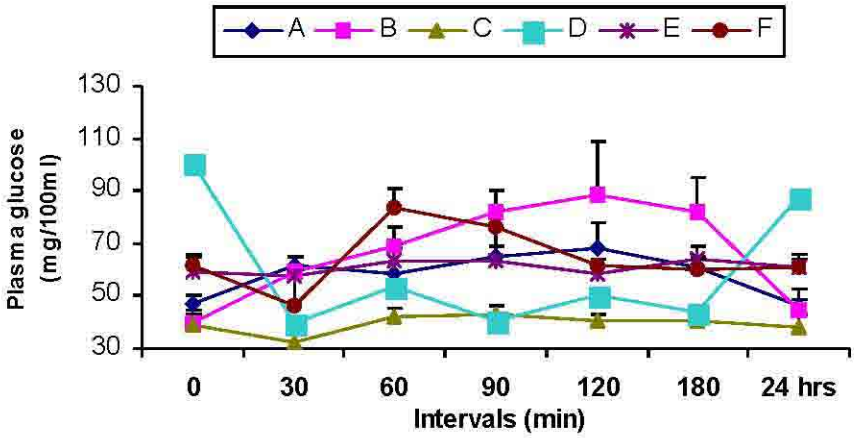


Fig 4.19 : Plasma glucose (mg/100ml) in the animals of different groups

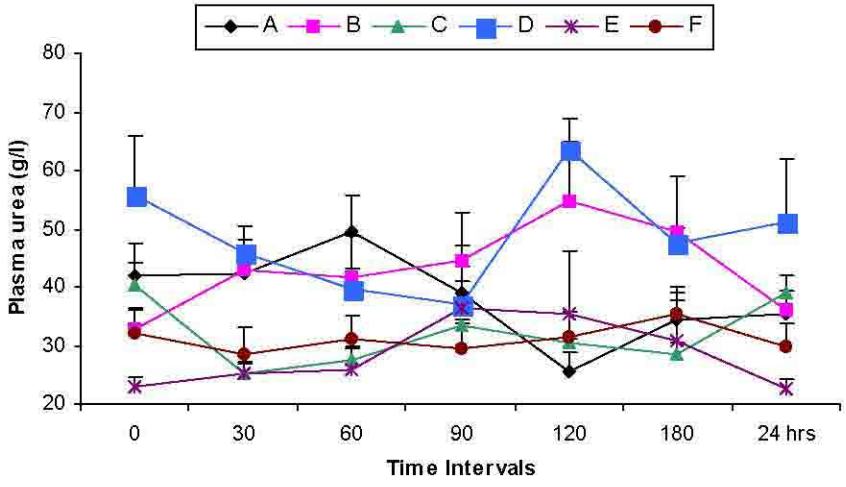


Fig 4.20 : Plasma urea (g/l) in the animals of different groups

significantly (P<0.05) higher plasma glucose than all the groups and groups B and C had significantly (P<0.05) lower glucose levels than groups D and E. Groups A, E and F had no significant difference (P>0.05) among each other at this interval.

Plasma urea nitrogen

Mean ±SE values of plasma urea nitrogen in different groups have been shown in Figure 4.20 and Table 4.25.

Plasma urea nitrogen increased non-significantly (P > 0.05) in group A from 30 to 60 min post-injection. The values decreased from 90 to 180 min post-injection. The decrease was significant (P < 0.05) at 120 min. The values remained decreased and didn't return to the base line at the end of observation period. Xylazine alone (group B) produced an increase in the plasma urea nitrogen throughout the post-injection period. The increase was significant (P < 0.05) at 90 min to 24 hrs post-injection and the values remained below the base line at the end. In group C, where buprenorphine alone was administered, plasma urea nitrogen decreased significantly (P < 0.05) from 30 to 180 min. It increased at 24 hours but remained below the baseline and never returned to the pre-administration level. In group D animals, a non-significant (P > 0.05) decrease in plasma urea nitrogen was recorded from 30 min onwards till 90 min post injection. The values then increased but remained below the base line even at the end of the observation period. In the animals of group E, a non-significant (P > 0.05) increase in plasma urea nitrogen was recorded upto 180 min post-injection. The values however, reached the baseline at the end of the observation period. Group F animals, showed a decrease in urea nitrogen levels throughout the post-injection period. The values never reached the pre-injection level at the end of observation period.

Comparison among different groups revealed that a significantly (P < 0.05) high plasma urea nitrogen concentration was recorded at preadministration levels in group D as compared to group B, E and F. However, at 30 minutes, group A and B animals showed significantly (P < 0.05) higher plasma urea nitrogen than all the groups except

group D. In group C, plasma urea remained significantly ($P < 0.05$) lower as compared to group A and B. At 60 minute interval plasma urea nitrogen was significantly ($P < 0.05$) higher in group A compared to all the groups except groups D and B.

Plasma creatinine

Mean ±SE values of plasma creatinine in different groups have been shown in Figure 4.21 and Table 4.26.

In the animals of group A, plasma creatinine increased at 60 min, 90 min and 24 hrs. The increase was significant ($P<0.05$) at 90 min. The values decreased non-significantly ($P>0.05$) at 30 min, 120 min and 180 min. The values returned to the base line at the end of observation period. In the animals of group B, a significant decrease at 60 min ($P<0.05$) was followed by a non-signfiicant ($P>0.05$) increase from 90 min to 180 min. The values returned to normal at 24 hrs.

In the animals of group C, plasma creatinine levels fluctuated near the base line throughout the observation period with a slight non-significant ($P>0.05$) rise at 30 min, 120 min and 180 min. In the animals of group D, the values fluctuated near the base line except at 60 min where a significant ($P<0.05$) decrease in plasma creatinine levels was recorded. In the animals of group E, a decrease was recorded throughout the period of observation and the values did not return to normal even at the end of the observation period. The decrease was significant ($P<0.05$) at 120, 180 min and 24 hrs post-injection. In the animals of group F, there was a non-signifciant variation of plasma creatinine at various intervals and at the end the values returned back to normal.

Comparison among various groups revealed that group B had significantly ($P<0.05$) higher base line values of plasma creatinine than group A, C and E. Group A and E had significantly higher ($P<0.05$) plasma creatinine values than group C and group C had significantly ($P<0.05$) lower value than all the groups. Plasma creatinine

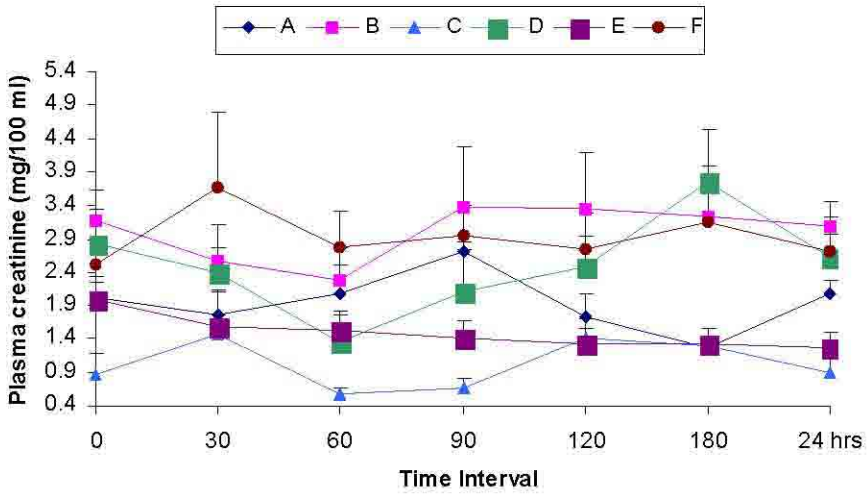


Fig 4.21 : Plasma creatinine (mg/100 ml) in the animals of different groups

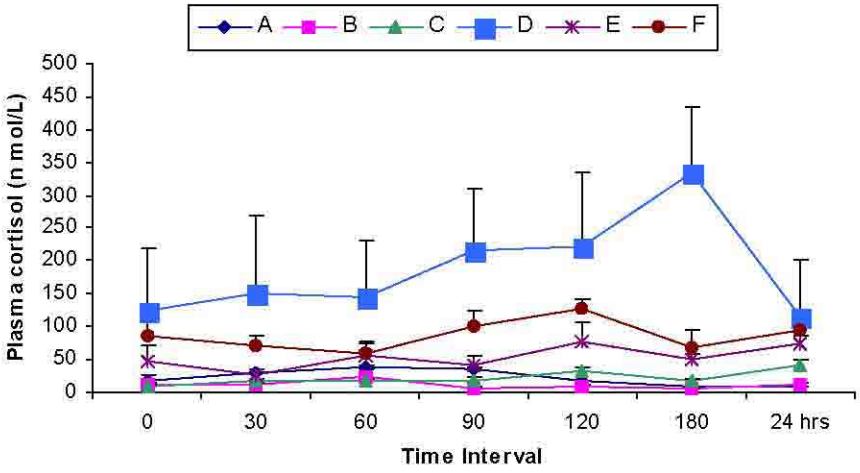


Fig 4.22 : Plasma cortisol (n mol/L) in the animals of different groups

values were significantly higher (P<0.05) in the animals of groups B and F than group C, and E at 120 min. Group A and Group D, however, remained non-significantly (P > 0.05) different from other groups.

Plasma cortisol

Mean ±SE values of plasma cortisol levels in different groups have been shown in Figure 4.22 and Table 4.27.

In the animals of group A, a non-significant (P>0.05) rise in the plasma cortisol levels was recorded at 30 to 90 min. Thereafter, the value decreased and remained less than the preadministration values, even at the end of the observation. The values did not return to baseline. In the animals of group B, a non-significant increase (P>0.05) in plasma cortisol was recorded at 60 min post-injection and thereafter, the values decreased from 90 min till the end of observation period. The decrease was significant (P<0.05) at 90 min. The value remained non-significantly (P>0.05) lesser than the base line even at the end. In the animals of group C, there was a steady rise in the plasma cortisol level at all the intervals. The rise was significant (P<0.05) at 90 min, 120 min and 24 hours post-injection. The values didn't return to the base line even at the end of the observation period. In the animals of group D, a rise in plasma cortisol was recorded upto 180 min post-injection. The rise was significant (P<0.01) at 90 min and 180 min (P<0.05). However, the values at the end of observation remained lesser than the base line. Groups E and F animals, showed a non-significant variation in the cortisol levels with a non-significant (P>0.05) decrease at 30 min and 90 min in group E and 30 and 60 min in group F and increase at rest of the time intervals. The value even at the end of the observation remained elevated than the baseline.

Comparison among different groups revealed that group C and group D had significantly (P<0.05) higher cortisol levels than groups B, E and F. However, group A did not differ significantly (P>0.05) from all the groups. Group F at 180 min had significantly

(P<0.05) higher cortisol level than groups A and B. At 24 hrs time interval, group D animals had significantly (P<0.05) higher cortisol levels than all the groups. Group F had significantly (P<0.05) higher values than group B at this interval. However, groups A, C and E remained non-significantly different (P>0.05) from groups B and F.

Plasma GGT

Mean ±SE values of plasma GGT in different groups have been shown in Figure 4.23 and Table 4.28.

In the animals of group A, no significant change in the GGT levels was recorded throughout the observation period except for a slight non-significant (P>0.05) decrease recorded from 30 min to 180 min post-injection. However, the vlaues returned to the base line at 24 hrs.

In the animals of group D, a non-significant (P>0.05) decrease in GGT was recorded at 30-120 min followed by a significant (P<0.05) decrease at 180 min. In the animals of group B, the GGT values did not change significantly except for a non-significant decrease at 90 and 120 min.

In the animals of group E, the GGT values decreased non-significantly (P>0.05) at 30 min and 60 min and therafter the values started to increase non-significantly (P>0,.05) upto 180 min. In the animals of group C, the GGT values decreased non-significantly (P>0.05) at 30-120 min and thereafter increased non-significantly at 180 min post-injection. In the animals of group F, the GGT values showed non-significant (P>0.05) change throughout the observation period with a non-significant (P>0.05) decrease at 90 min and 120 min. However, in all the groups the values returned to the base line at 24 hrs.

Comparison between the groups revealed that the animals of group F had significantly higher (P<0.05) values at 0 hr, 30 min, 60 min and 24 hrs post-injection values in rest of the groups did not differ significantly from each other.

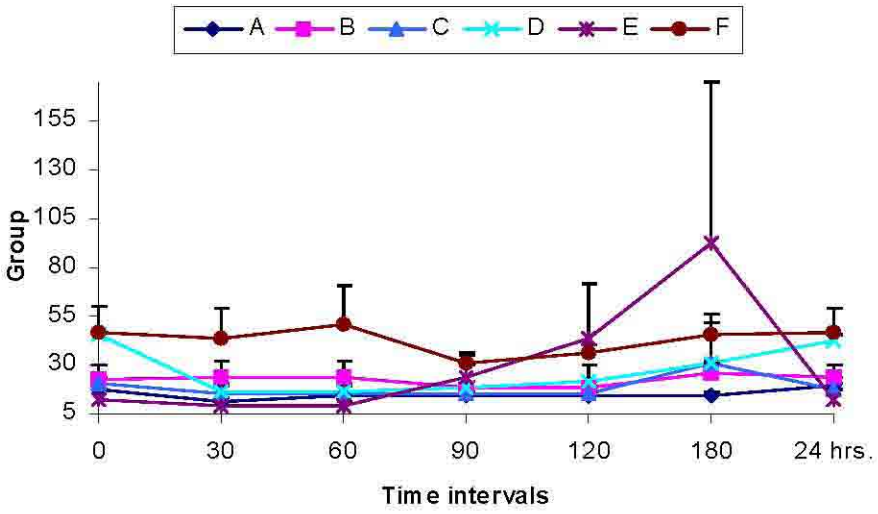


Fig 4.23 : GGT (U/L) in the animals of different groups

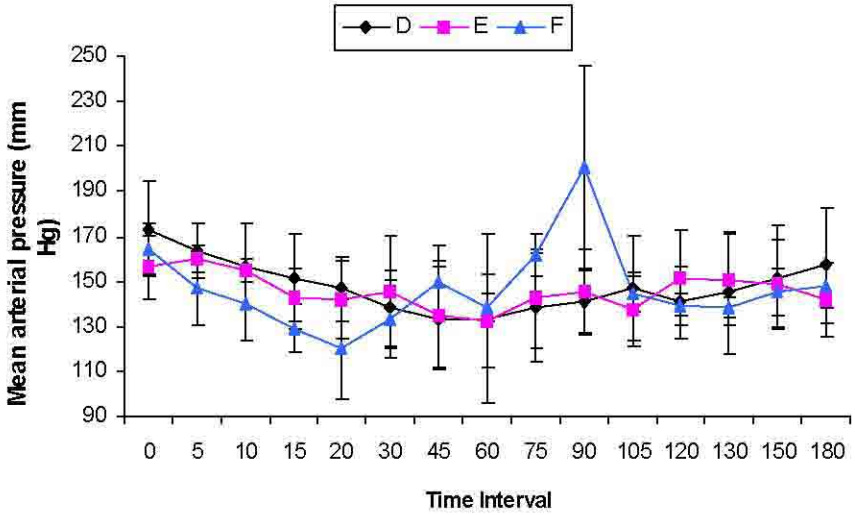


Fig 4.24 : Mean arterial pressure (mm Hg) recorded in the animals of different groups

Phase II

HAEMODYNAMIC STUDIES

Mean arterial pressure (MAP)

Mean ±SE values of mean arterial pressure in different groups have been shown in Figure 4.24 and Table 4.29.

MAP decreased in all the groups throughout the observation period. In group D, the decrease in MAP was recorded from 5 min onwards till the end of observation. The values were signifciantly ($P<0.01$) below the base line from 105 to 150 min. The values increased thereafter but were still below the base line at the end of observation period. In the animals of group E, also same trend of decrease in MAP during the post-injection period was recorded. Significant reduction was recorded at 15 min, 60 min, 105 and 180 min. The values continued to remain below the base level even at the end of observation and never returned to the base line.

Group F animals showed a significant ($P<0.05$) reduction in the MAP values from 5 to 30 min post-injection and then from 105 to 180 min during the post-injection period. At 180 min, it remained significantly ($P<0.01$) below the base values and did not return to the pre-administration level.

Comparison among all the groups revealed no significant difference among each other throughout the observation period. However, group F showed non-significantly ($P>0.05$) lower values from 5 min to 30 min post injection as compared to the remaining groups.

Central venous pressure (CVP)

Mean ±SE values of central venous pressure in different groups have been shown in Figure 4.25 and Table 4.30.

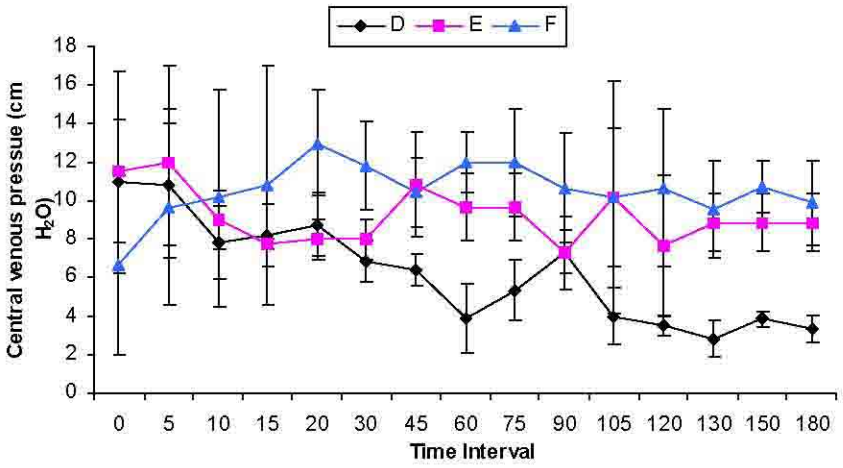


Fig 4.25 : Central venous pressue (cm H2O) recorded in the animals of different groups

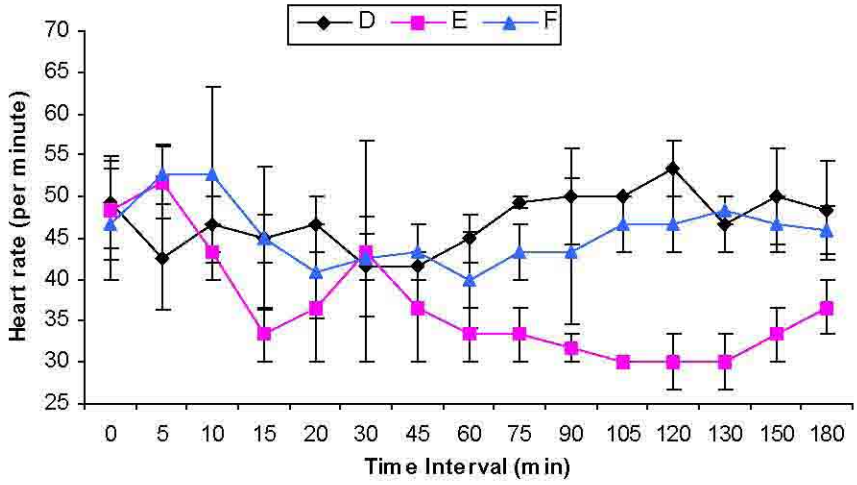
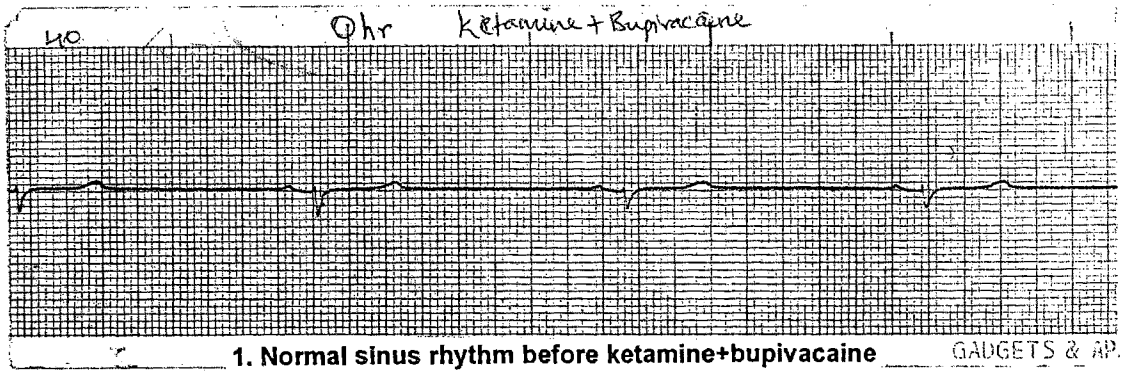
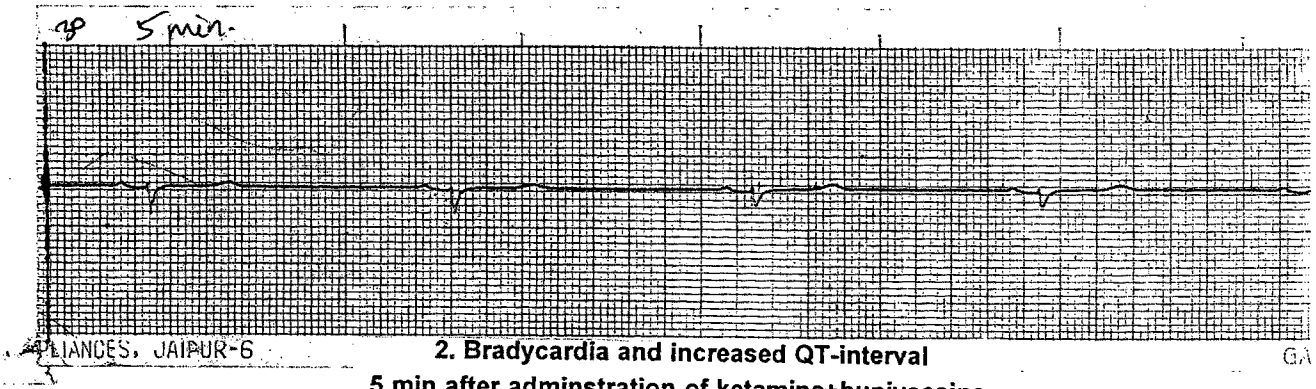


Fig 4.26 : Heart rate of ECG recorded in the animals of different groups

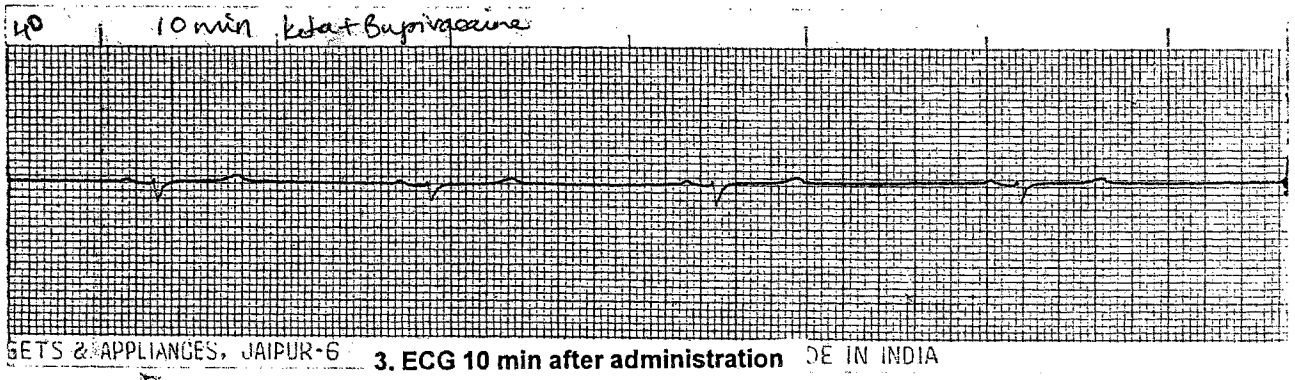
ECG (KETAMINE+BUPIVACAINE) GROUP D



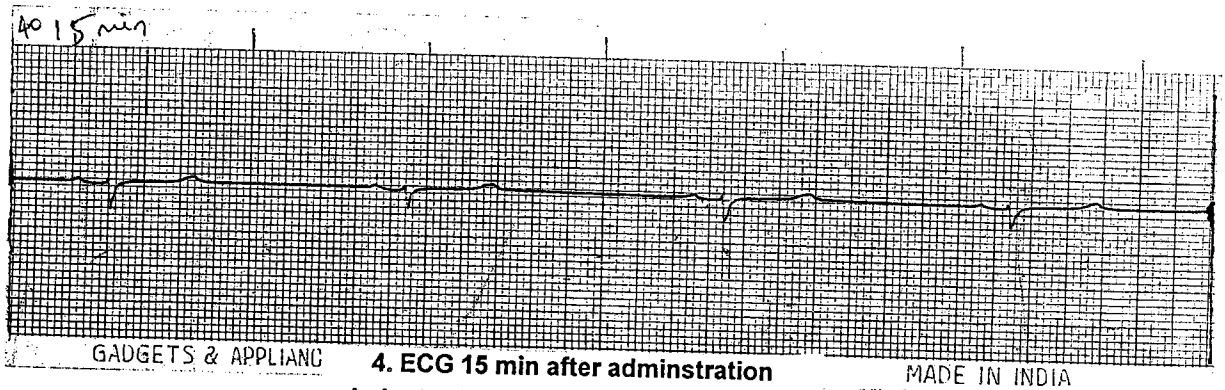
1. Normal sinus rhythm before ketamine+bupivacaine adminstration.



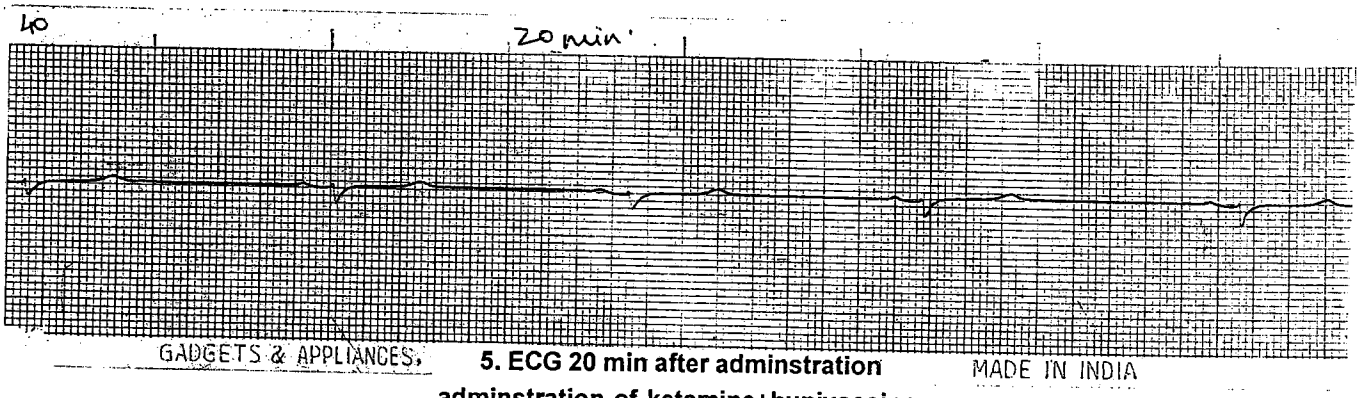
2. Bradycardia and increased QT-interval 5 min after adminstration of ketamine+bupivacaine.



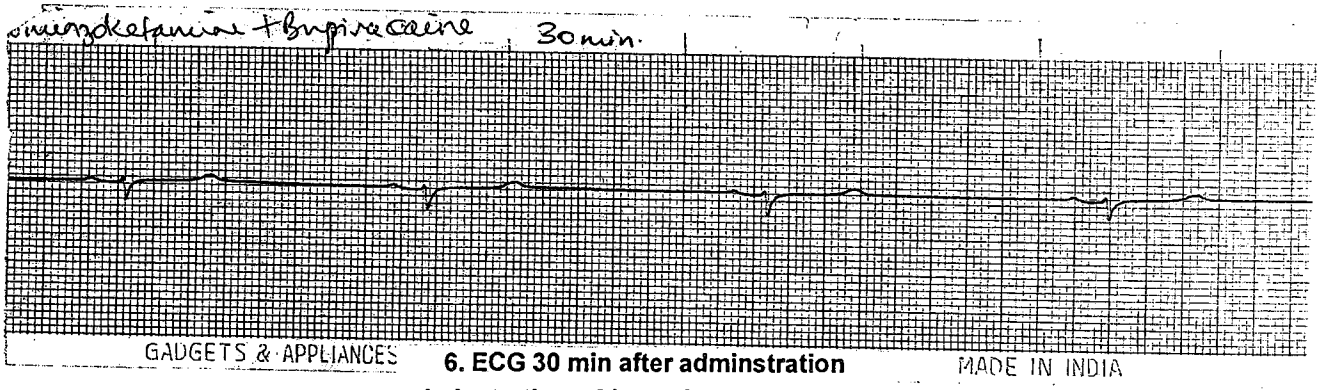
3. ECG 10 min after administration of ketamine+bupivacaine.



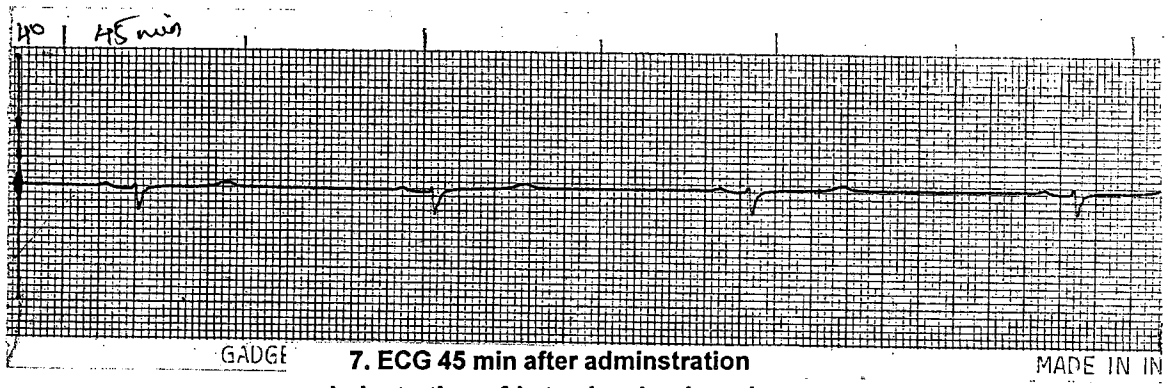
4. ECG 15 min after adminstration adminstration of ketamine+bupivacaine.



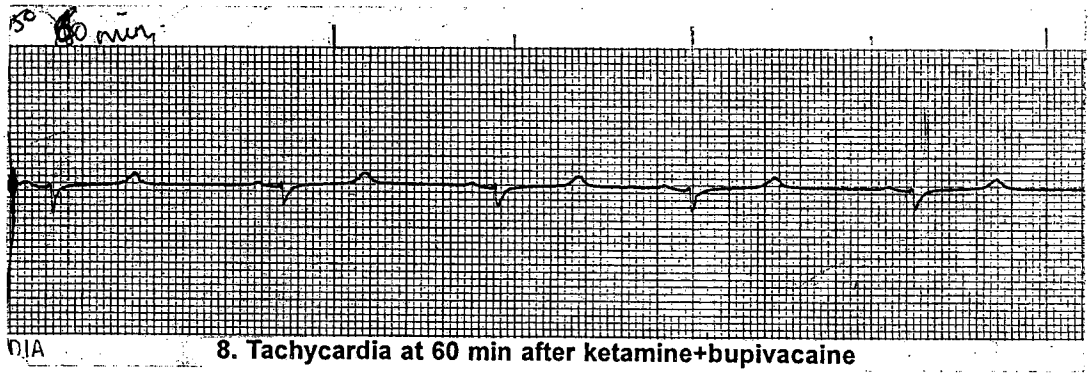
5. ECG 20 min after adminstration adminstration of ketamine+bupivacaine.



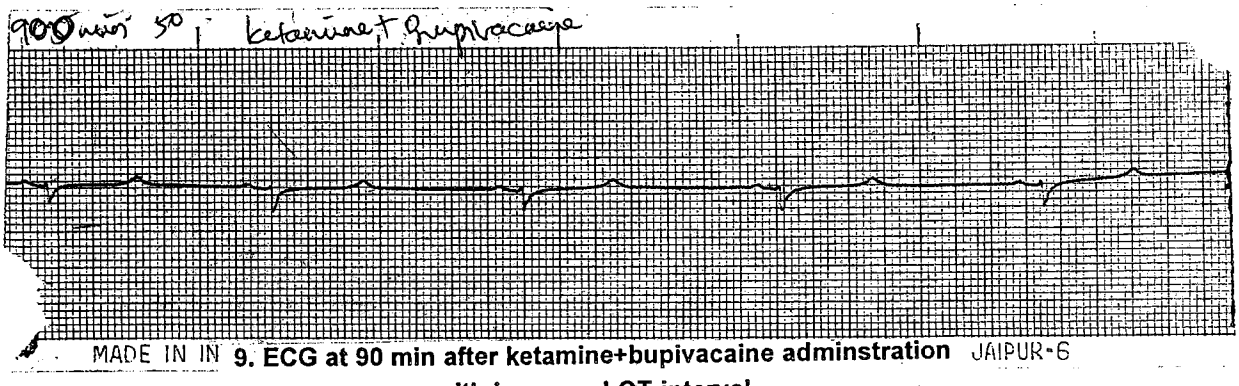
6. ECG 30 min after adminstration adminstration of ketamine+bupivacaine.



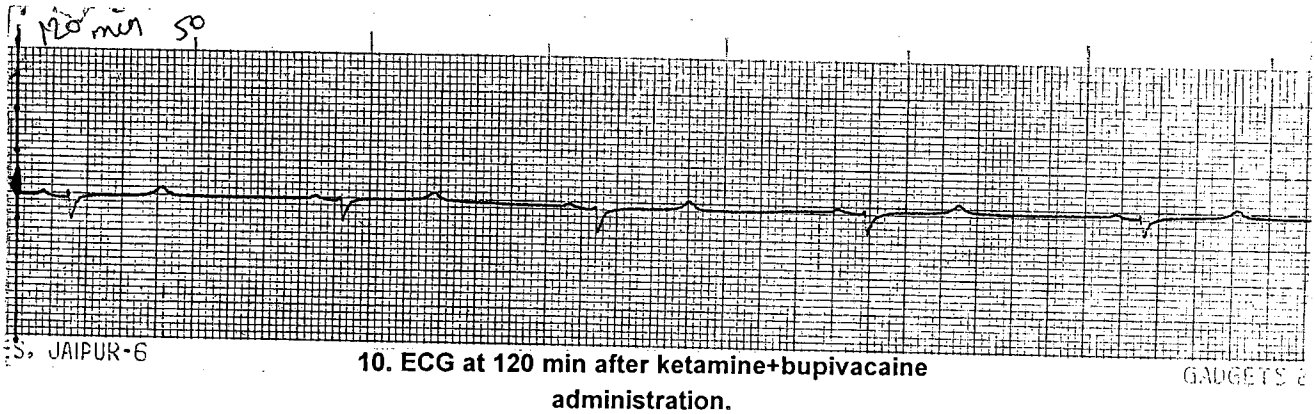
7. ECG 45 min after adminstration adminstration of ketamine+bupivacaine.



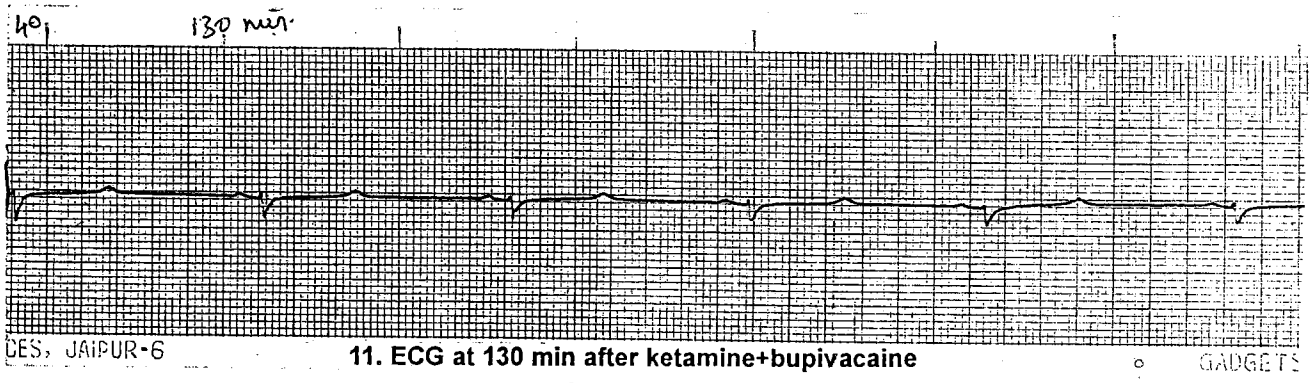
8. Tachycardia at 60 min after ketamine+bupivacaine adminstration



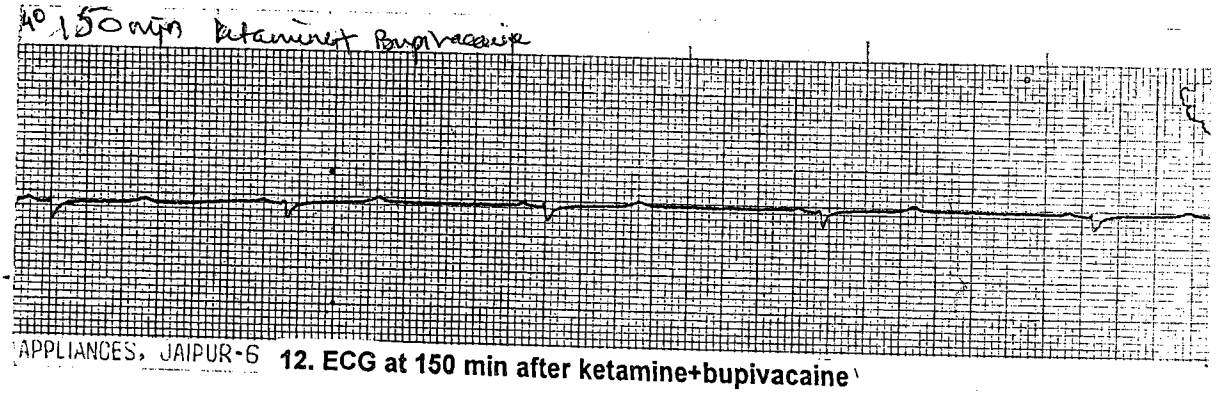
9. ECG at 90 min after ketamine+bupivacaine adminstration with increased QT interval.



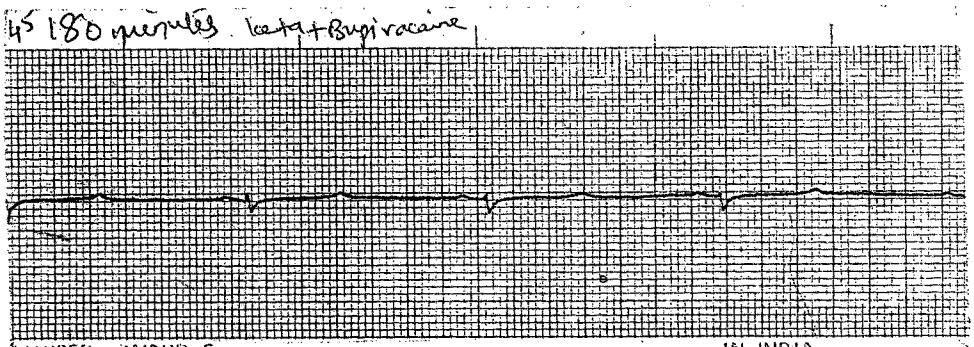
10. ECG at 120 min after ketamine+bupivacaine administration.



11. ECG at 130 min after ketamine+bupivacaine adminstration.

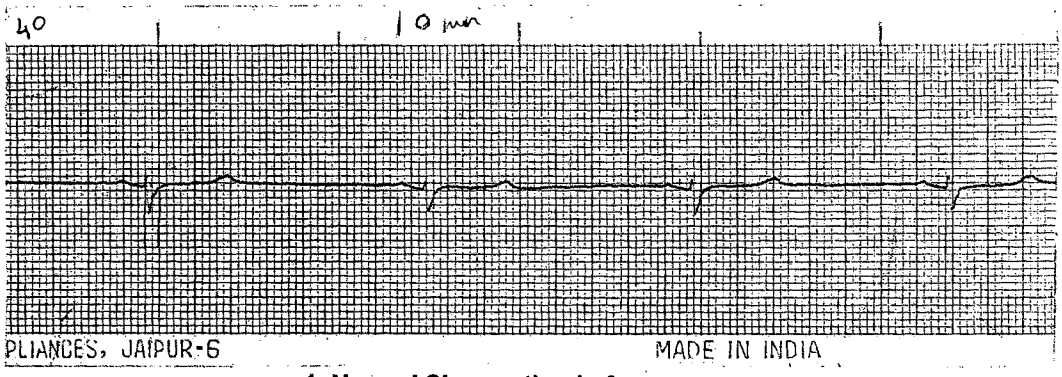


12. ECG at 150 min after ketamine+bupivacaine adminstration.

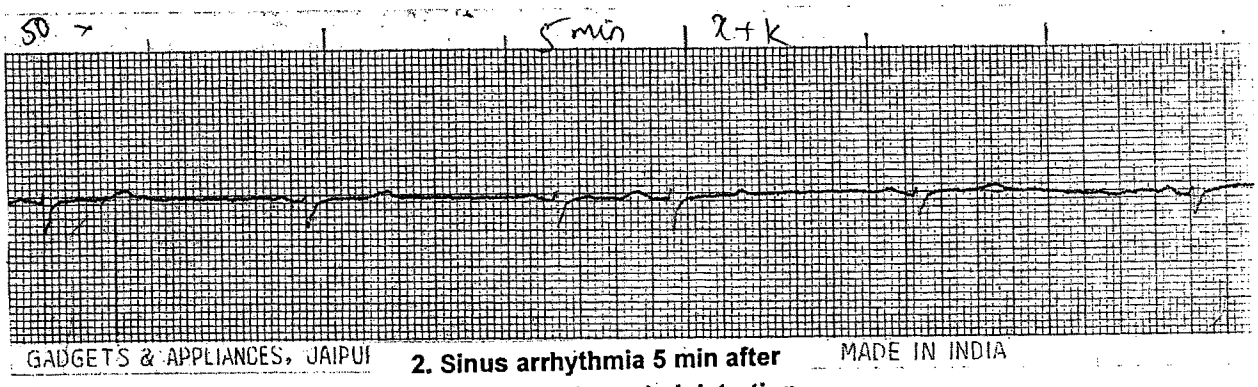


13. Normal sinus rhythm at 180 min after ketamine+bupivacaine adminstration

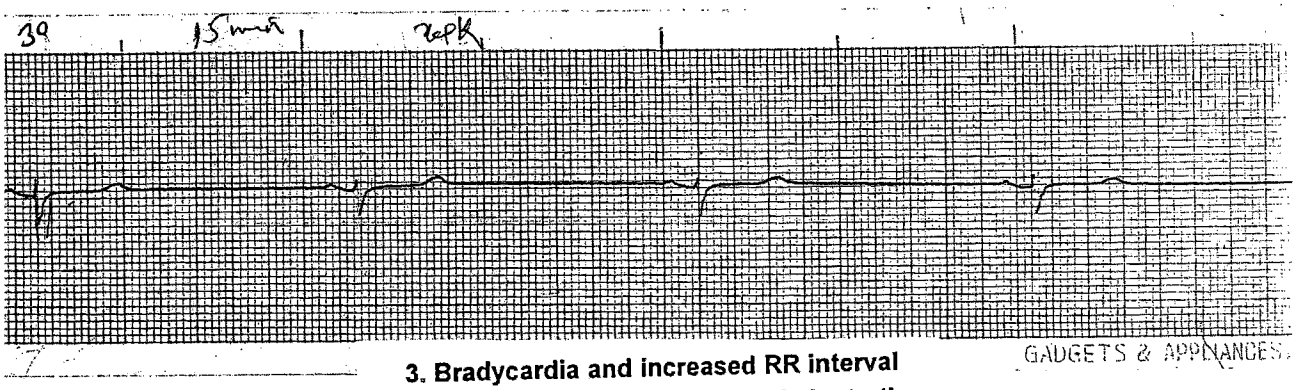
ECG (XYLAZINE+KETAMINE) GROUP E



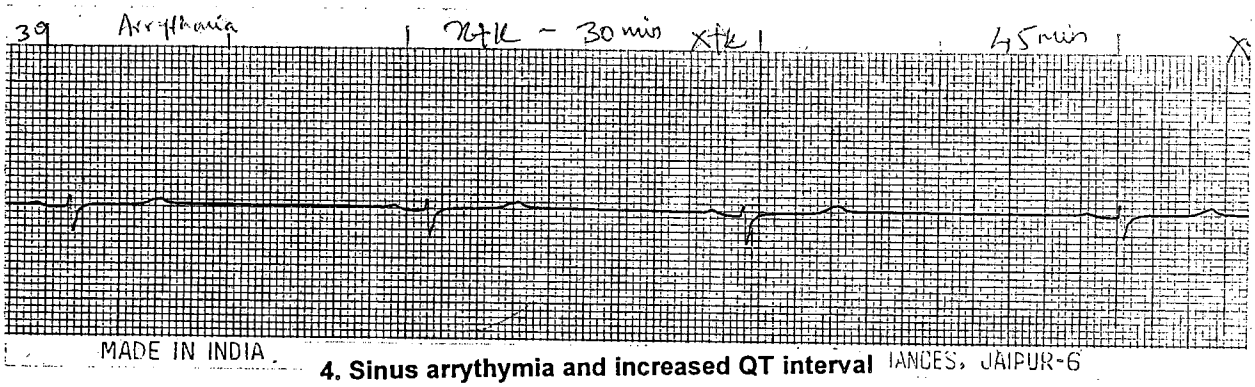
1. Normal Sinus rythm before xylazine+ketamine administration.



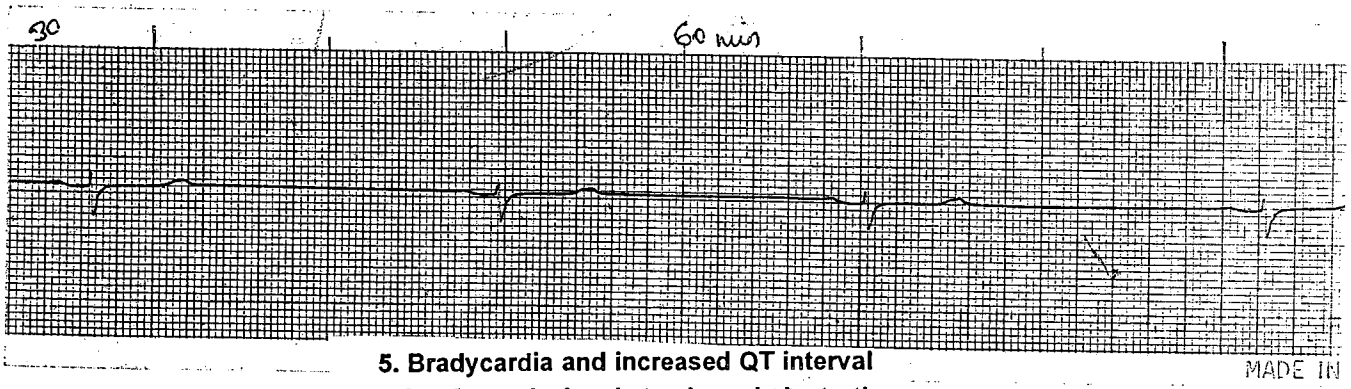
2. Sinus arrhythmia 5 min after xylazine+ketamine administration.



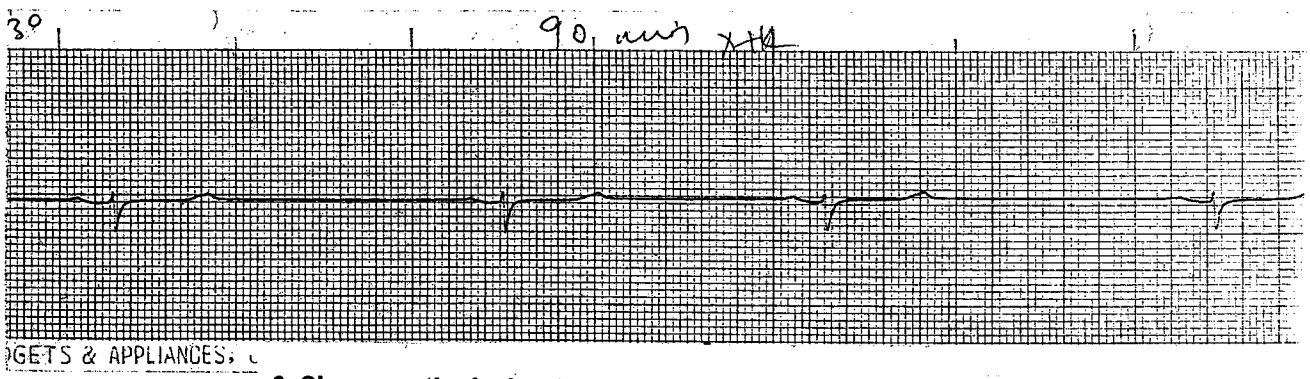
3. Bradycardia and increased RR interval 15 min after xylazine+ketamine adminstration.



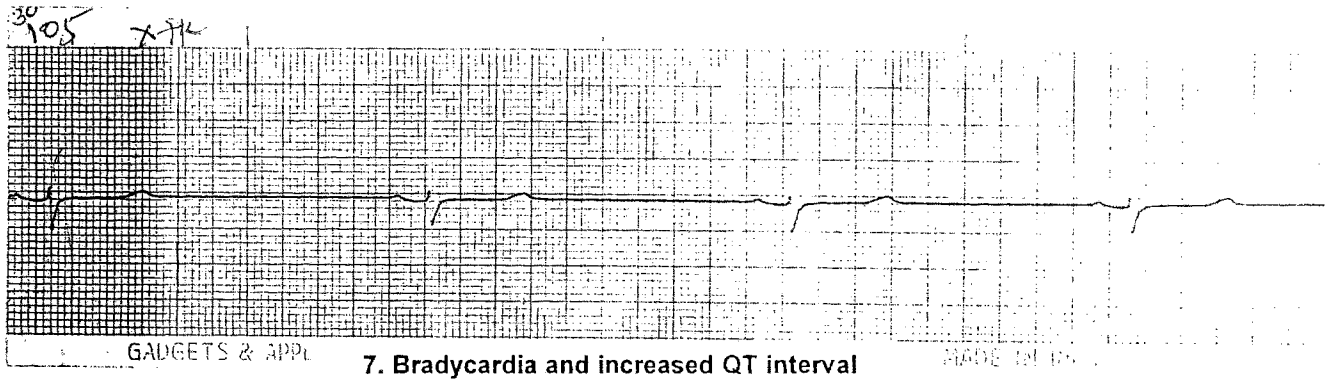
4. Sinus arrythymia and increased QT interval 30 min after xylazine+ketamine adminstration.



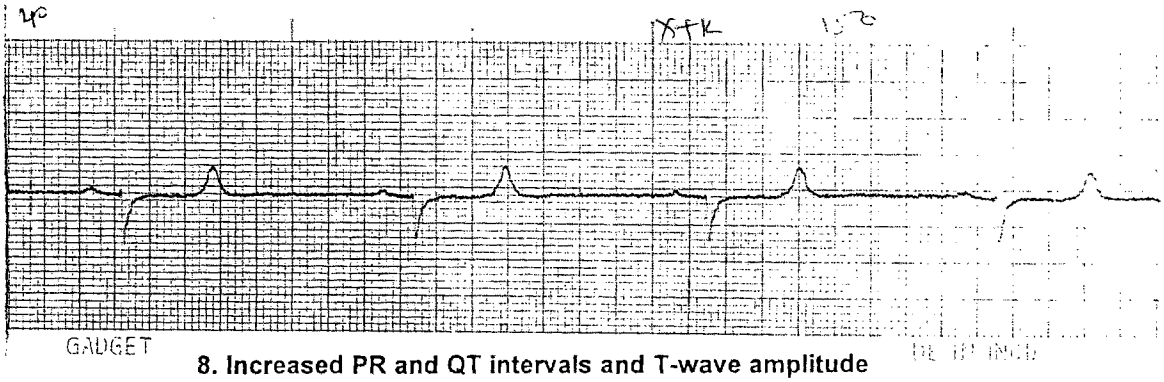
5. Bradycardia and increased QT interval 60 min after xylazine+ketamine adminstration.



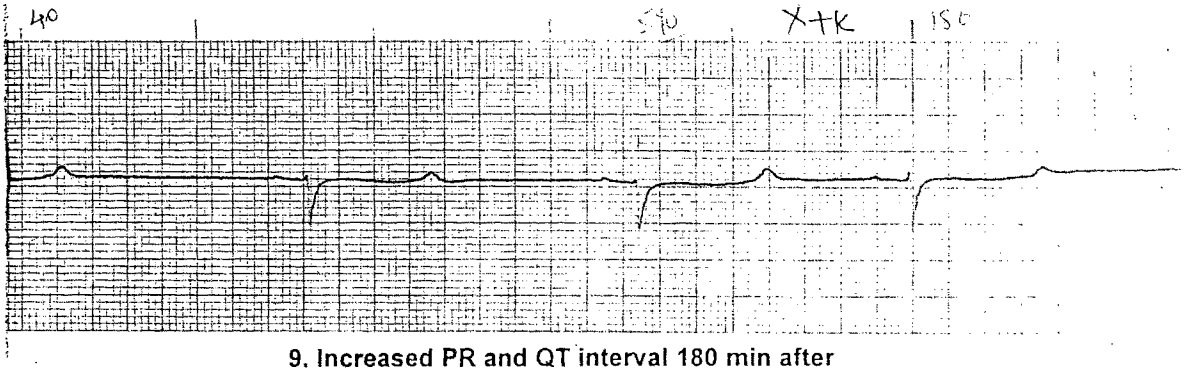
6. Sinus arrythmia, bradycardia and increased QT interval 90 min after xylazine+ketamine adminstration



7. Bradycardia and increased QT interval 105 min after xylazine+ketamine adminstration.

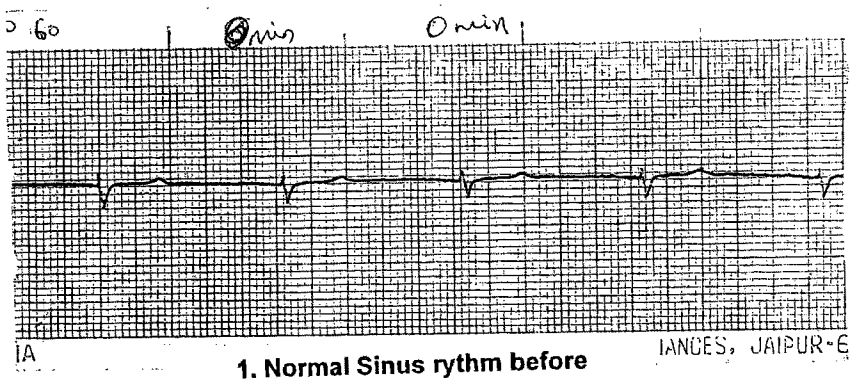


8. Increased PR and QT intervals and T-wave amplitude 150 min after adminstration of xylazine+ketamine.

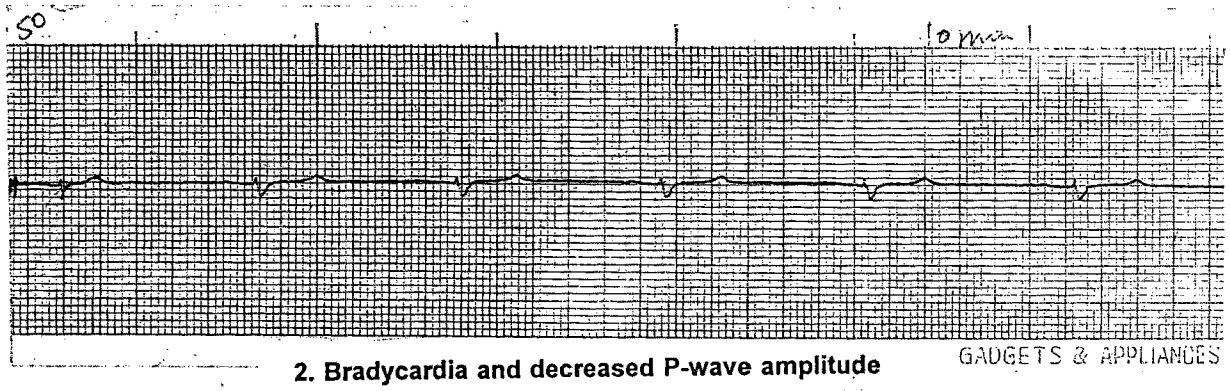


9. Increased PR and QT interval 180 min after adminstration of xylazine+ketamine.

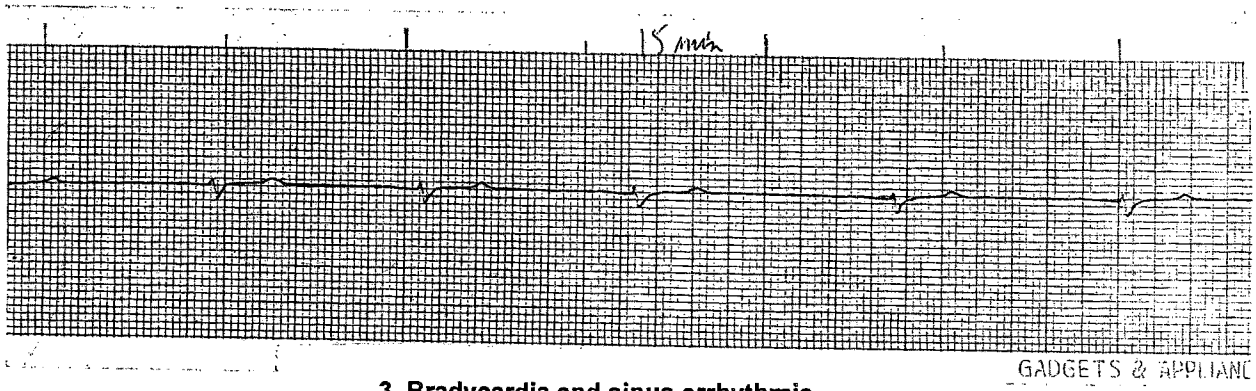
ECG (XYLAZINE+KETAMINE) GROUP E



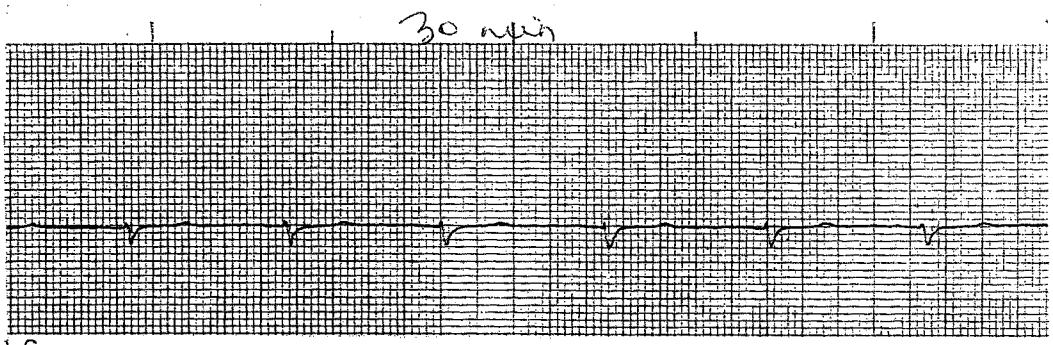
1. Normal Sinus rythm before administration of xylazine+ketamine.



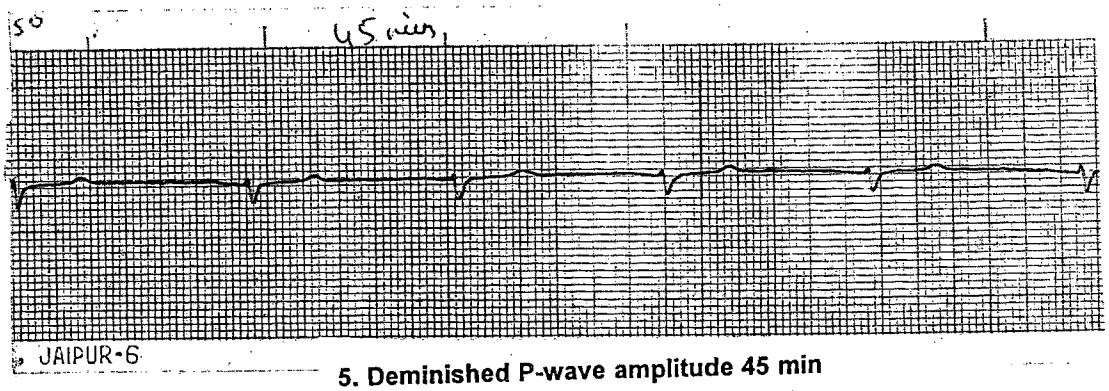
2. Bradycardia and decreased P-wave amplitude 10 min after adminstration of xylazine+ketamine.



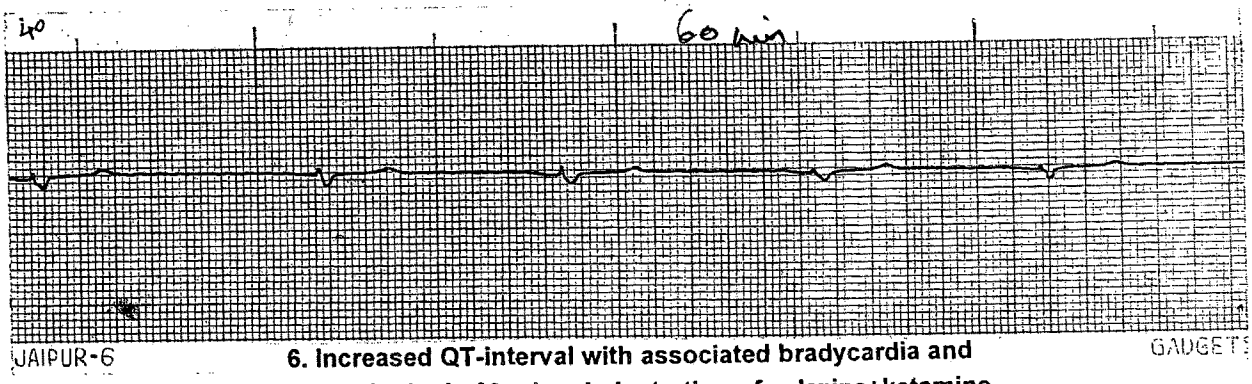
3. Bradycardia and sinus arrhythmia 15 min after adminstration of xylazine+ketamine.



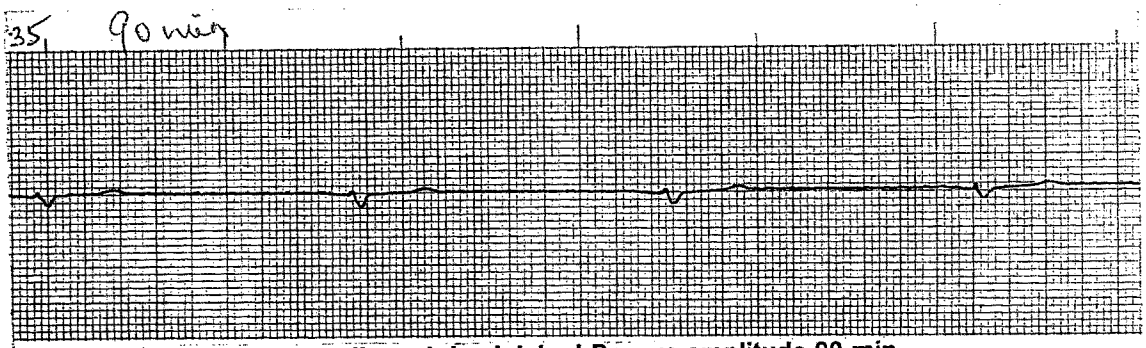
4. Tachycardia 30 min after adminstration of xylazine+ketamine.



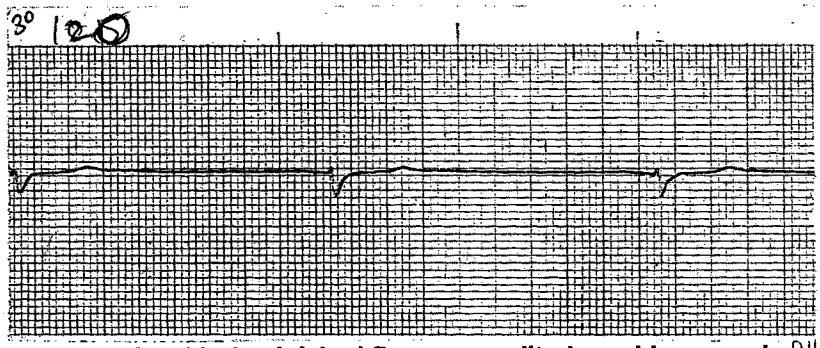
5. Deminished P-wave amplitude 45 min after adminstration of xylazine+ketamine.



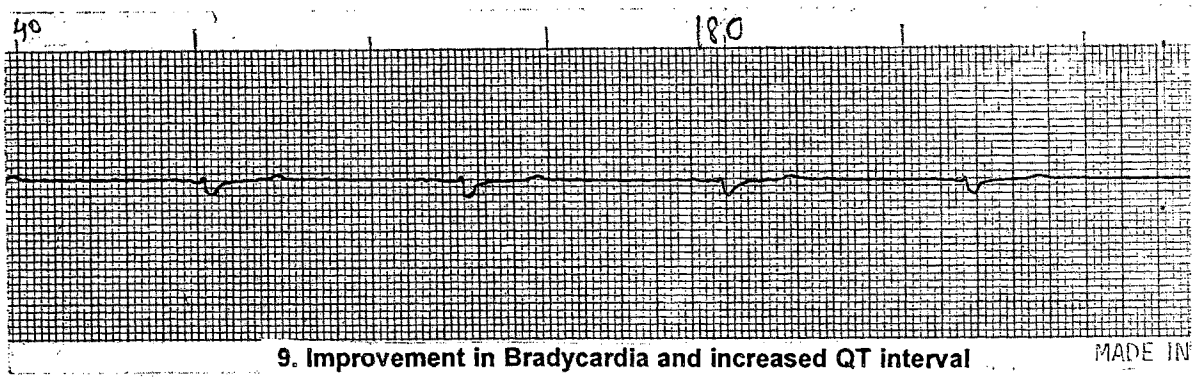
6. Increased QT-interval with associated bradycardia and sinus arrhythmia 60 min adminstration of xylazine+ketamine.



7. Bradycardia and deminished P-wave amplitude 90 min after adminstration of xylazine+ketamine.



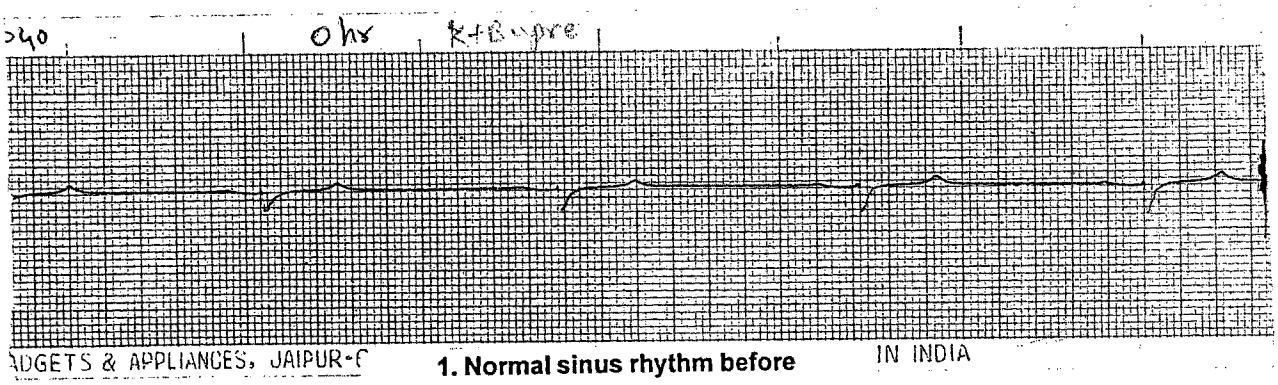
8. Bradycardia with deminished P-wave amplitude and increased QT-interval 120 min after adminstration of xylazine+ketamine.



9. Improvement in Bradycardia and increased QT interval 180 min after adminstration of xylazine+ketamine.

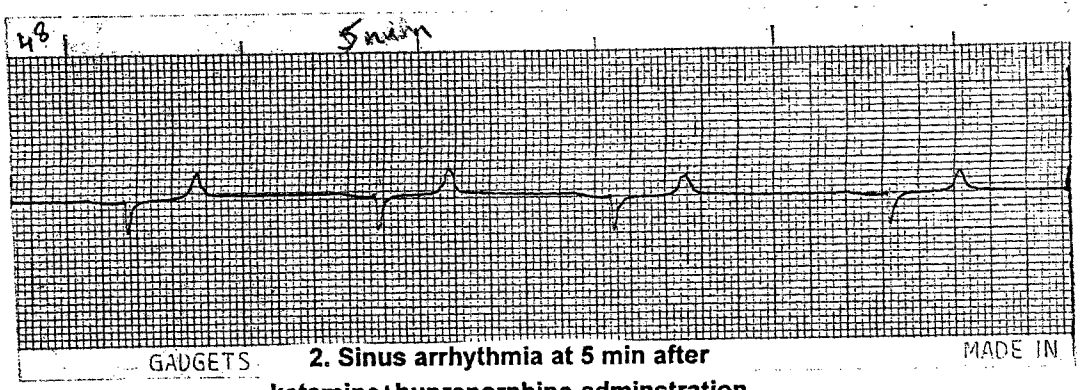
K+Bupre
①

ECG (KETAMINE+BUPRENORPHINE) GROUP F

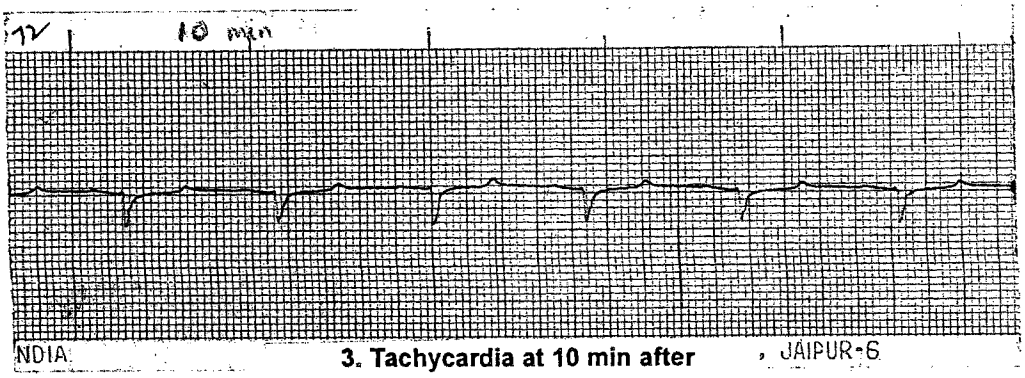


1. Normal sinus rhythm before ketamine+buprinorphine adminstration.

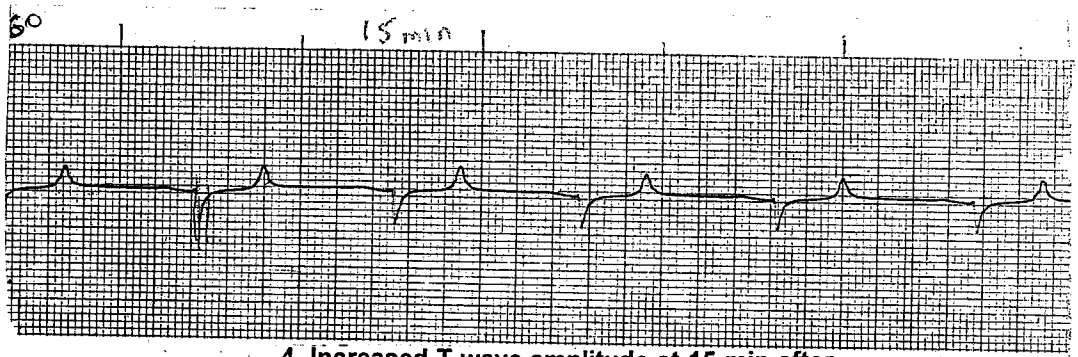
K+Bupre



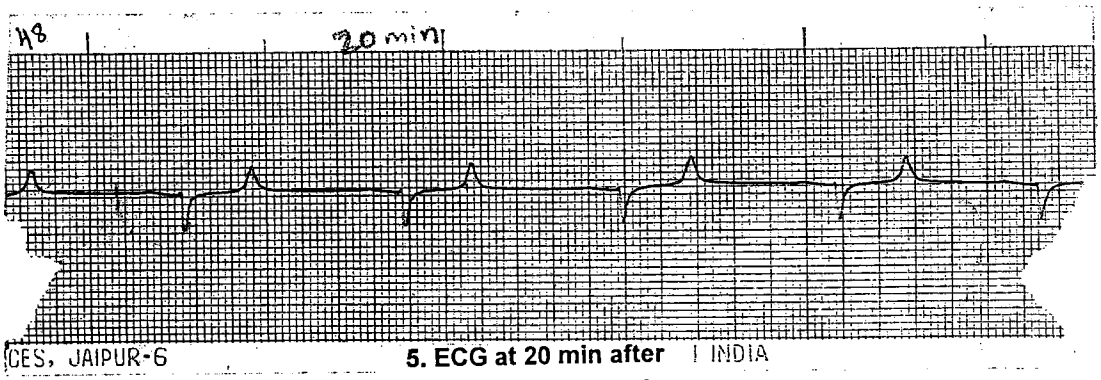
2. Sinus arrhythmia at 5 min after ketamine+buprenorphine adminstration



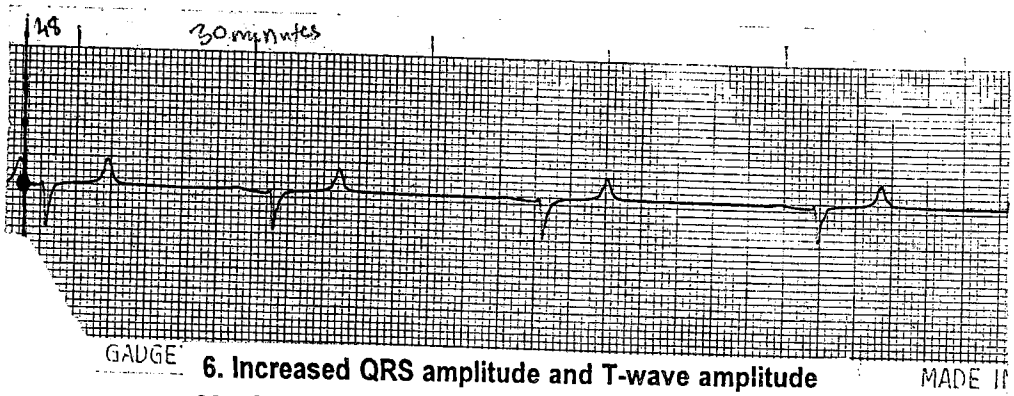
3. Tachycardia at 10 min after ketamine+buprinorphine adminstration.



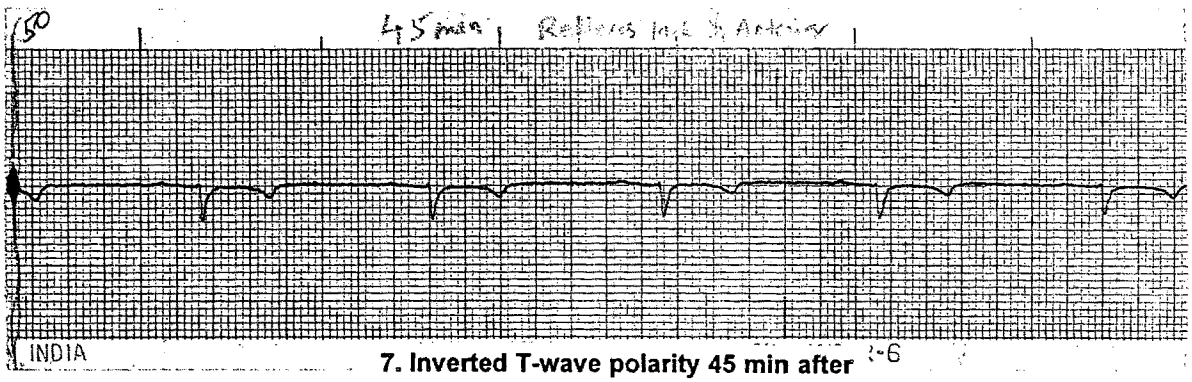
4. Increased T-wave amplitude at 15 min after ketamine+buprinorphine adminstration.



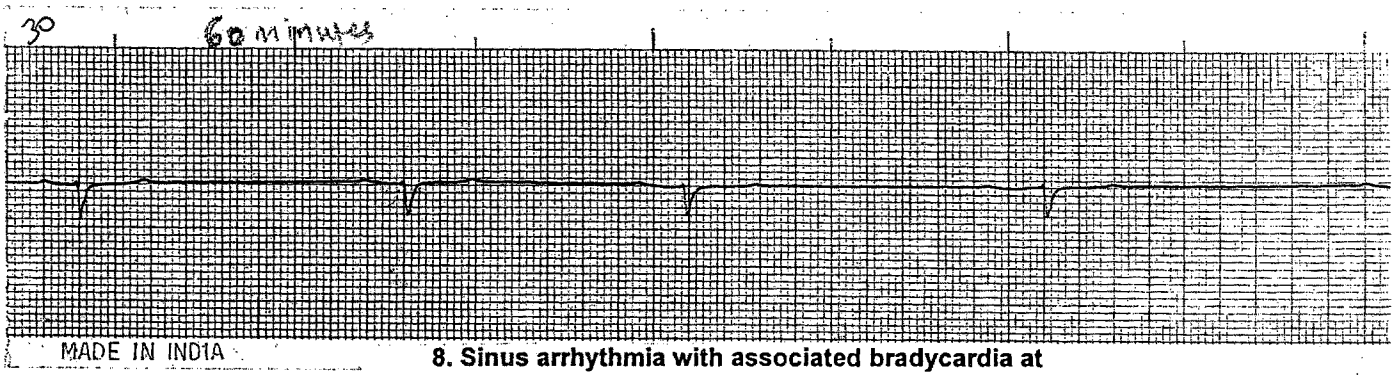
5. ECG at 20 min after ketamine+buprinorphine.



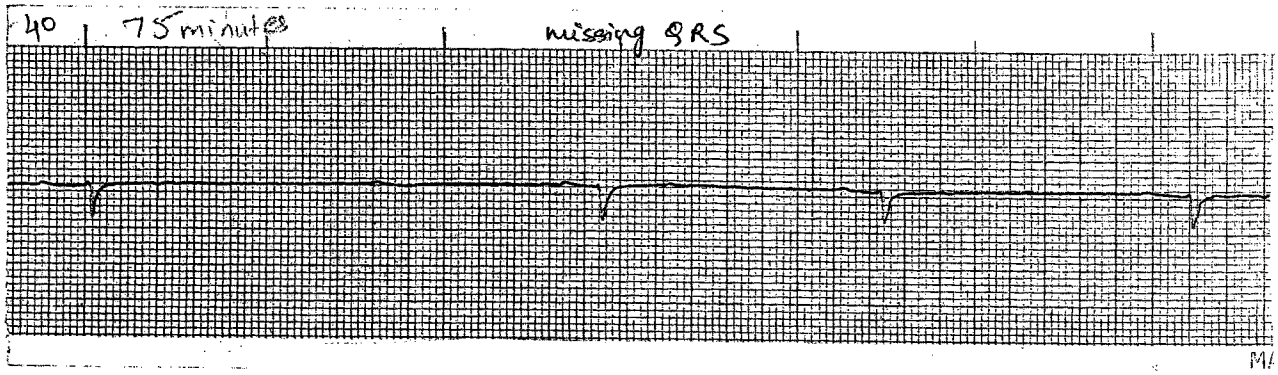
6. Increased QRS amplitude and T-wave amplitude 30 min after ketamine+buprenorphine adminstration



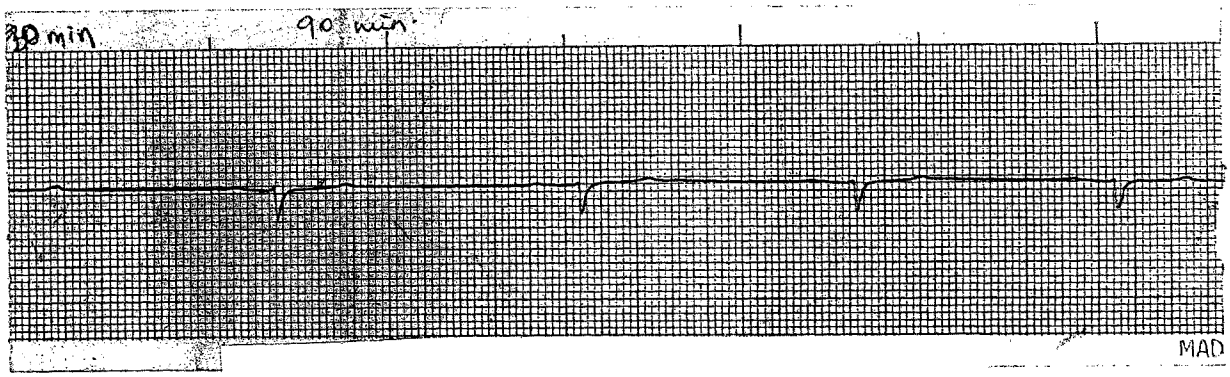
7. Inverted T-wave polarity 45 min after ketamine+buprenorphine adminstration



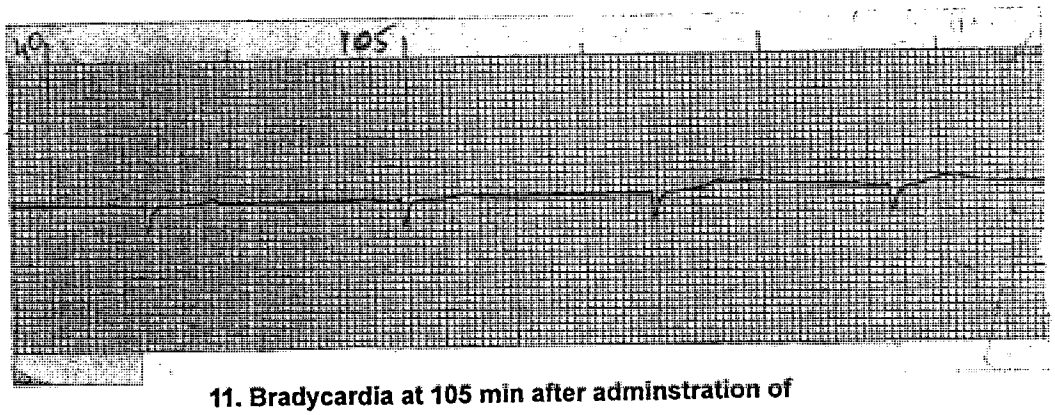
8. Sinus arrhythmia with associated bradycardia at 60 min after ketamine+buprenorphine adminstration



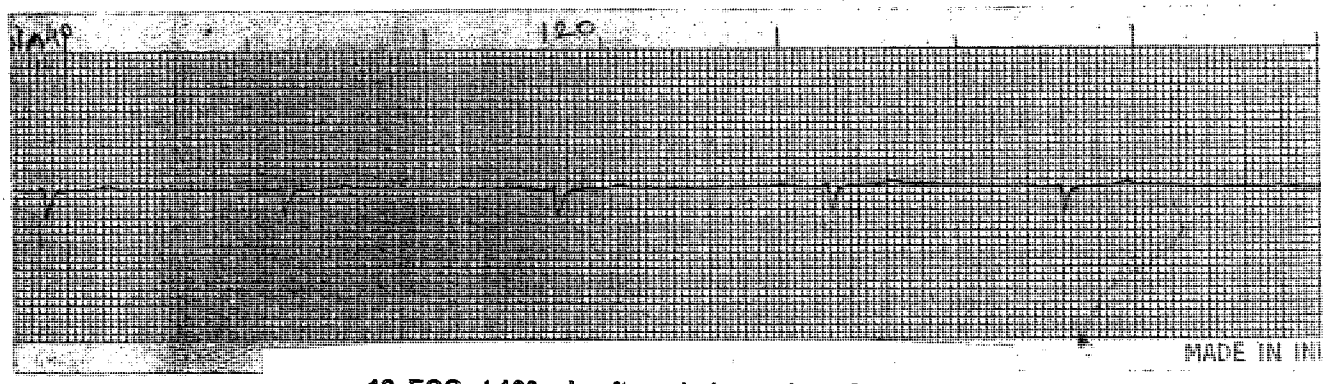
9. Missing QRS at 75 min after adminstration of ketamine+buprenorphine.



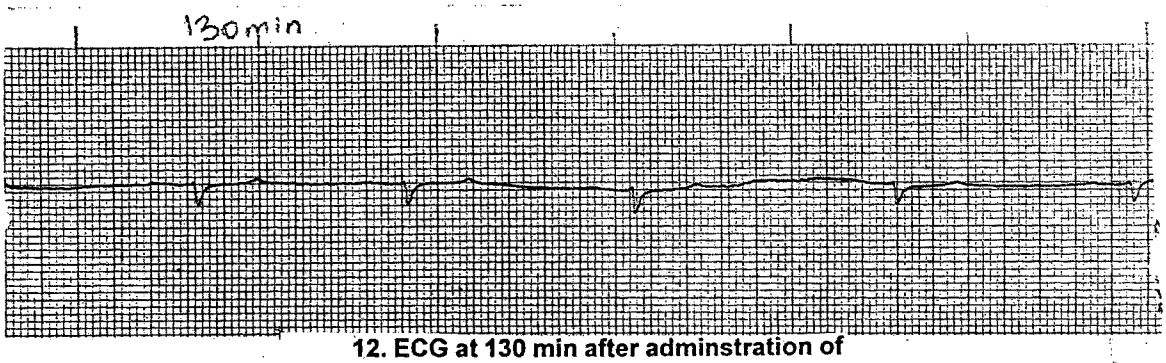
10. Bradycardia at 90 min after adminstration of ketamine+buprenorphine



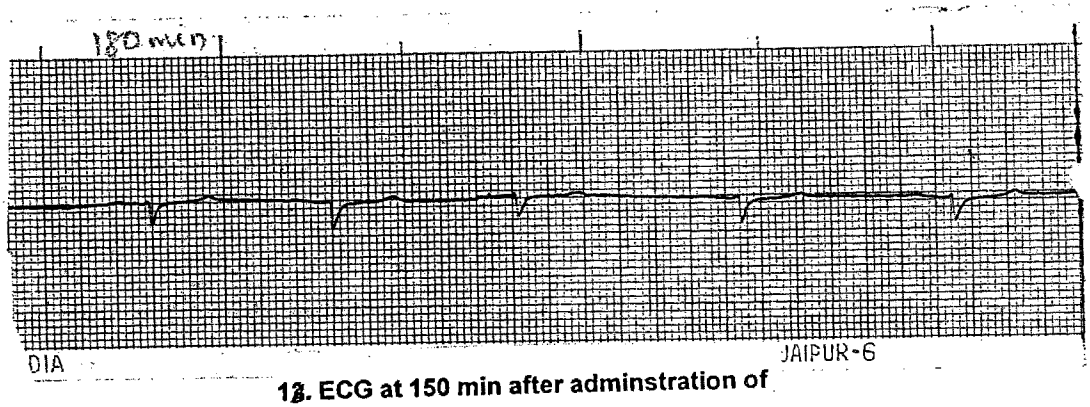
11. Bradycardia at 105 min after adminstration of ketamine+buprenorphine



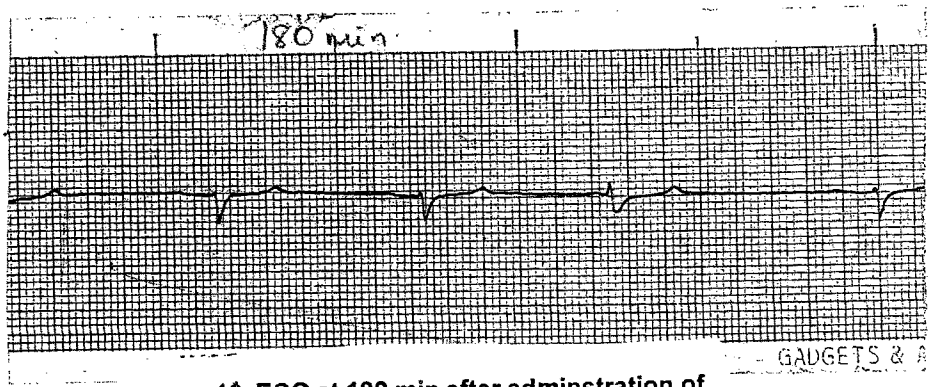
12. ECG at 120 min after adminstration of ketamine+buprenorphine.



12. ECG at 130 min after adminstration of ketamine+buprenorphine.



13. ECG at 150 min after adminstration of ketamine+buprenorphine.



14. ECG at 180 min after adminstration of ketamine+buprenorphine.

There was a non-significant (P>0.05) decrease in CVP in groups D and E except in group F where a non-significant (P>0.05) increase was recorded throughout the period of observation. Bupivacaine and ketamine combination in group D produced a non-significant (P>0.05) gradual decrease in CVP throughout the period of observation. The values remained below the base line even at the end of observation period. Similarly, animals in group E (ketamine + xylazine) also produced a non-significant (P>0.05) decrease in the CVP. The values did not return to the base line and continued to remain below the base line. Group F, however, produced a non-significant (P>0.05) increase in CVP throughout the observation period as compared to the base values.

Comparison among different groups revealed that group F animals recorded significantly (P<0.05) higher CVP values than group E at 10 min and non-signfiicantly higher (P>0.05) CVP than group D at the same interval. Similarly, at 30 min interval, group F animals had a significantly (P<0.05) higher CVP than group D and non-significantly higher than group E. At 60, 130 and 180 min both group E and group F have significantly (P<0.05) higher CVP values than group D.

Heart rate of recumbent animals recorded from ECG

Mean ±SE values of heart rate in different groups have been shown in Figure 4.26 and Table 4.31.

In the animals of group D, a non-significant (P>0.05) decrease in heart rate was recorded from 5 to 60 min. The values fluctuated during this period but stayed below the base line. Thereafter, the values increased and fluctuated near the base line throughout the observation period. In the animals of group E, a transient and non-significant increase (P>0.05) in HR at 5 min was recorded followed by a decrease in the heart rate from 10 min up to the end of the observation period, and the values never returned to normal. The decrease was significant at 15 min (P<0.05), 20 min (P<0.01), 45 min (P<0.01), 60 min to 130 min (P<0.05).

In the animals of group F, non-significant ($P<0.05$) increase in the heart rate was recorded at 5-10 min, followed by a non-significant ($P>0.05$) decrease in heart rate from 15 min to 90 min. Thereafter, the heart rate returned to normal at 150 min post-injection.

Comparison among various groups revealed that group E animals showed lower heart rates as compared to all the groups throughout the observation period and never returned to base line value. The decrease was significant ($P<0.05$) from 75 min to 130 min post-injection. Group D and Group F were, however, having no significant variation from each other except at 5 to 10 min interval where group D showed a decrease in heart rate whereas group F showed an increase in the heart rate.

Rythm of heart (ECG)

The heart rhythm recorded before the injection in all the animals was a normal sinus rhythm. However, Bradycardia was a consistent finding observed in group E where ketamine in combination with xylazine was used, during the post-injection period.

Arrythmia was also seen in all the groups at various intervals of time. In group E arrythmia was recorded at 5 min, 15 min, 60 mins and 90 min even at 180 min. In group D arrythmia was recorded only at 30-60 min and again at 90-105 min but the rhythm and returned to normal. In group F, arrythmia was noticed at 5-10 min, 45-75 min and also at the end i.e. at 180 min.

Amplitude of P-wave

Mean ±SE values of amplitude of P-wave in different groups have been shown in Figure 4.27 and Table 4.32.

A positive P-wave was recorded in all the animals of different groups during the entire period of the study.

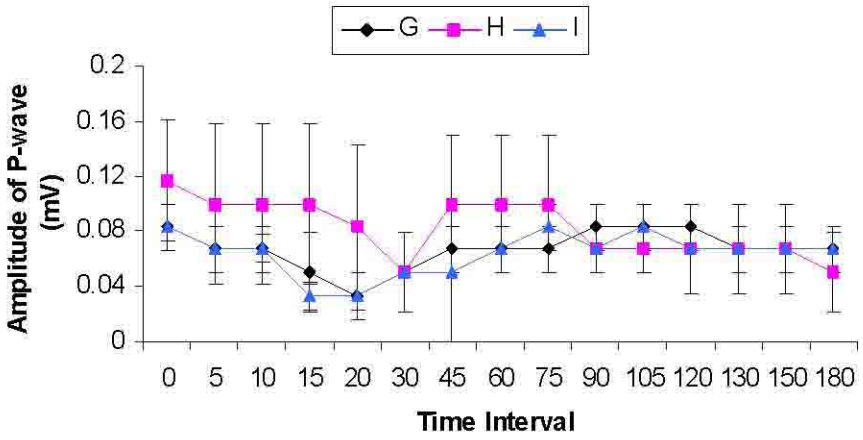


Fig 4.27 : Amplitude of P-wave (mV) recorded in the animals of different groups

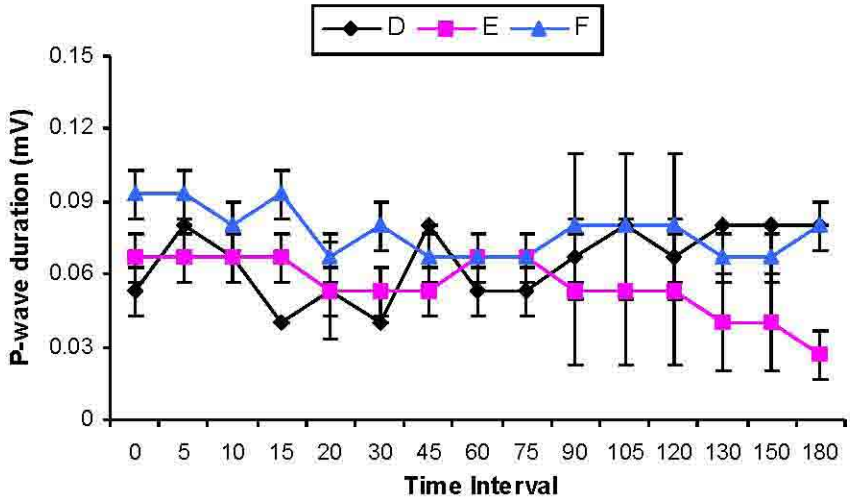


Fig 4.28 : P-wave duration (mV) recorded in the animals of different groups

A non-significant (P>0.05) decrease in the amplitude of P-wave was recorded in all the three groups during the post-injection period in comparison to their respective base values. However, in group E, a significant (P<0.05) decrease was noticed at 30 min post-injection. The amplitude of P-wave became zero in one of the animals of group E from 5 min to 30 min post-injection, thereafter, a lower P-wave amplitude was seen but it again vanished from 120 to 180 min.

Comparison among different groups did not show any significant (P>0.05) difference or variation from each other at different time intervals during the post-injection period.

However, group D and Group F had non significantly lower (P>0.05) P-wave amplitude at 20 min and at 15 to 20 min respectively, as compared to other groups. Group E showed nonsignificantly (P>0.05) lowest amplitude at 180 min inspite of the base line value being the highest.

Duration of P-wave

Mean ±SE values of duration of P-wave in different groups have been shown in Figure 4.28 and Table 4.33.

In the animals of group D, the duration of P wave increased non-significantly at 5 to 10 min and thereafter decreased up to 30 min. The values fluctuated till the end of observation but remained non-significantly (P>0.05) higher than the base-line value. In the animals of group E, also, a non-significant (P>0.05) decrease in the duration of P-wave was recorded at various time intervals and the value remained lower than the base line at the end of observation period. In group F, a non-significant (P>0.05) decrease in duration of P-wave was noticed at few intervals during the post-injection period. At most of the intervals, the values fluctuated near the base line.

Comparison among the groups revealed that group F, showed significantly (P<0.05) longer P-wave duration as compared to group D and group E at 15 min and 30 min post-injection. At 180 min post-injection, group D showed significantly (P<0.05) longer P-wave duration than group E.

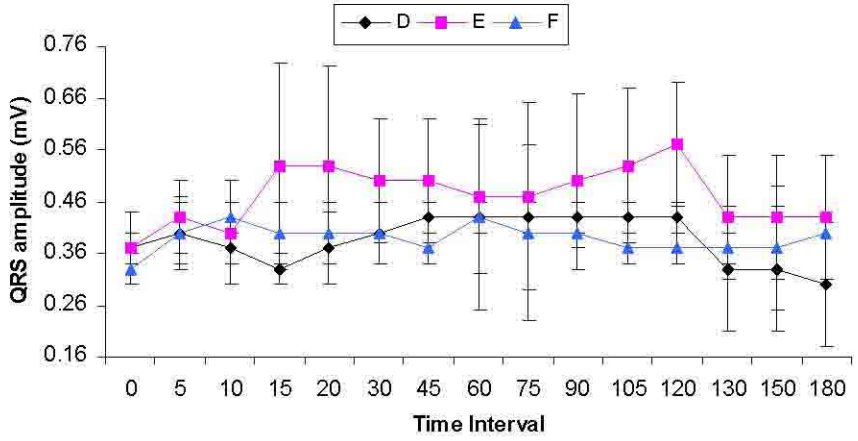


Fig 4.29 : QRS amplitude (mV) recorded in the animals of different groups

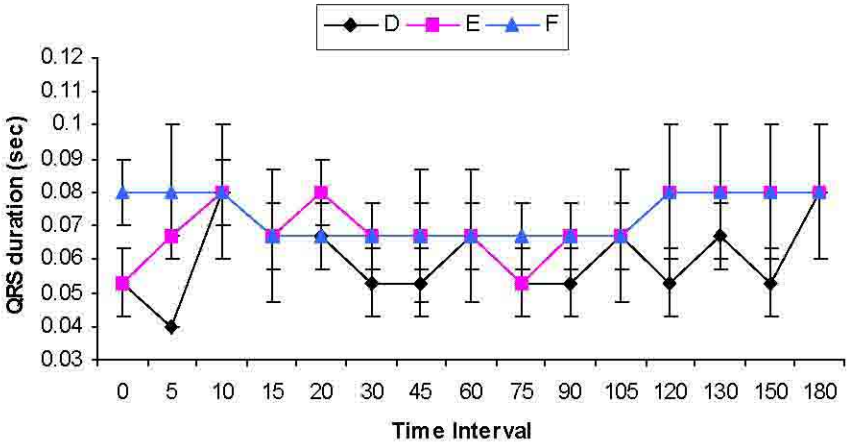


Fig 4.30 : QRS duration (sec) recorded in the animals of different groups

QRS amplitude

Mean ±SE values of QRS amplitude in different groups have been shown in Figure 4.29 and Table 4.34.

In the animals of group D, the amplitude of QRS increased at 5 min and decreased at 15 min from the base-line value. It again started to increase from 30 min to 120 min post-injection but the increase was nonsignificant. Thereafter the values decreased nonsignificantly and remained less than the base line throughout the observation period. The values never returned to the base line.

In the animals of group E, an increase in the QRS amplitude was recorded throughout the observation period which was significant ($P<0.001$) at 10 min and 60 min. The values remained higher than the base line value till the end of observation.

Comparison among different groups didn't reveal significant ($P>0.05$) variation at any time interval. But group D animals showed a non-significantly ($P>0.05$) lower QRS amplitude than group E animals at all the time intervals.

QRS Duration

Mean ±SE values of QRS duration in different groups have been shown in Figure 4.30 and Table 4.35.

The QRS complex pattern were predominantly QS in most of the animals irrespective of the drugs injected. However, QRS pattern was also occasionally seen in some groups at few intervals. There was no significant ($P>0.05$) difference in QRS duration at different intervals in comparison to the base value up to the end of observation period in different groups. However, a nonsignificant ($P>0.05$) increase was recorded in all the groups at different time intervals and the values in all the groups never returned to the base line up to the end of observation period and remained nonsignificantly higher ($P>0.05$) than the base line in all the groups.

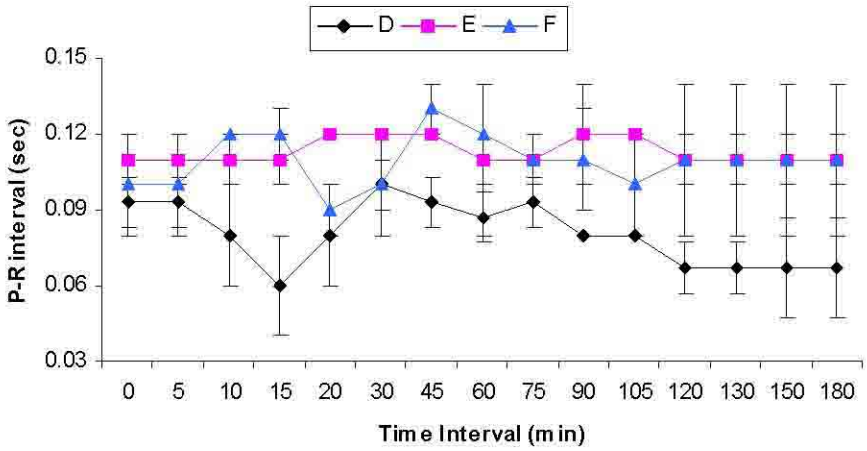


Fig 4.31 : P-R interval (sec) recorded in the animals of different groups

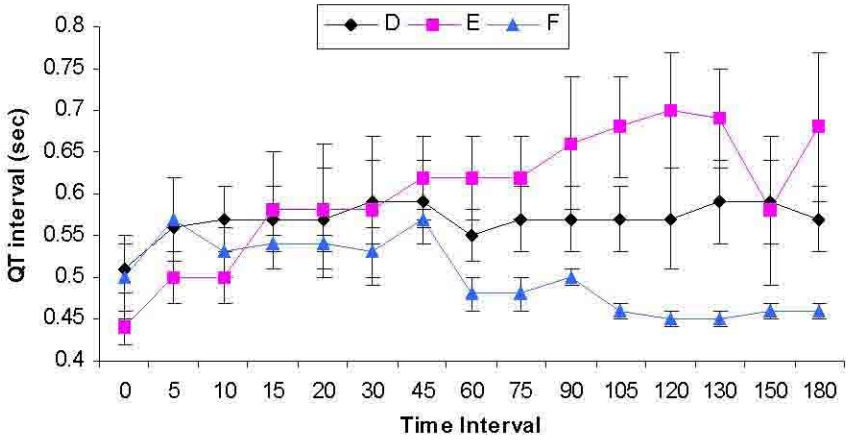


Fig 4.32 : QT interval (sec) recorded in the animals of different groups

Comparison among various groups revealed no significant (P>0.05) variation at any time interval during the post-injection period.

PR-interval

Mean ±SE values of PR-interval in different groups have been shown in Figure 4.31 and Table 4.36.

In the animals of group D, a non-significant (P>0.05) and gradual decrease in PR interval from 90 to 180 min post-injection was recorded. At rest of the time intervals the values of PR interval fluctuated near the base line but remained non-significantly (P >0.05) lower than the base line at the end of observation period. In the animals of group E, the values for PR interval fluctuated near the base line except for a non-significant (P > 0.05) increase at a few intervals during the post-injection period. In group F, the PR interval increased non-significantly (P>0.05) throughout the period of observation. The values remained elevated even at the end of the observation period.

Comparison among different groups revealed that PR intervals was significantly (P<0.05) longer at 45 min in group F than group D and the difference was nonsignificant (P>0.05) from group E. Group D, at end of the observation period showed nonsignificantly (P>0.05) lower PR interval than groups E and F.

QT interval

Mean ±SE values of QT-interval in different groups have been shown in Figure 4.32 and Table 4.37.

There was an increase in the QT interval in all the groups at all the intervals of time than their respective base values except group F where a non-significant decrease (P>0.05) was also recorded at many intervals. Bupivacaine-ketamine (group D) produced a non-significant (P>0.05) increase in QT interval throughout the observation period as compared to the base value. The QT interval remained

elevated at the end of observation period and didn't return to the pre-administration level. Group E animals also showed an increase in the QT interval, which was significant ($P<0.05$) at 5 and 10 min and at 120 min and 130 min post-injection. The values remained elevated and never returned to the base line at the end. Animals in group F (ketamine + buprenorphine), however, produced a non-insignificant increase in QT interval from 5 to 45 min post-injection. Thereafter, the values showed a nonsignificant ($P>0.05$) decrease and didn't return to the pre-administration level.

Comparison among all the groups revealed no significant ($P>0.05$) variation at different time intervals during post-injection period except at 130 min where group E had significantly ($P<0.05$) higher values than group F.

T-wave amplitude

Mean ±SE values of T-wave amplitude in different groups have been shown in Figure 4.33 and Table 4.38.

The T-wave showed different polarities, i.e. positive or negative at different intervals in different groups. A positive T-wave was predominantly seen in most of the animals irrespective of the drugs injected. In the animals of group D, the T-wave amplitude increased (non-significantly ($P>0.05$) from 5 min onwards up to 120 min post-injection. The values, however, decreased from 130 min till the end of observation period and did not return to the base line. In group E, No significant ($P>0.05$) change in T-wave amplitude was recorded throughout the observation period except at the end where a non-significant increase was recorded.

In the animals of group F, the T-wave amplitude initially showed a non-significant increase ($P>0.05$) from 5 to 30 min and reduced from 45 min to 180 min with a significant reduction at 75 ($P<0.001$), and 90 ($P<0.05$) min. The values remained below the base line even at the end of the observation period.

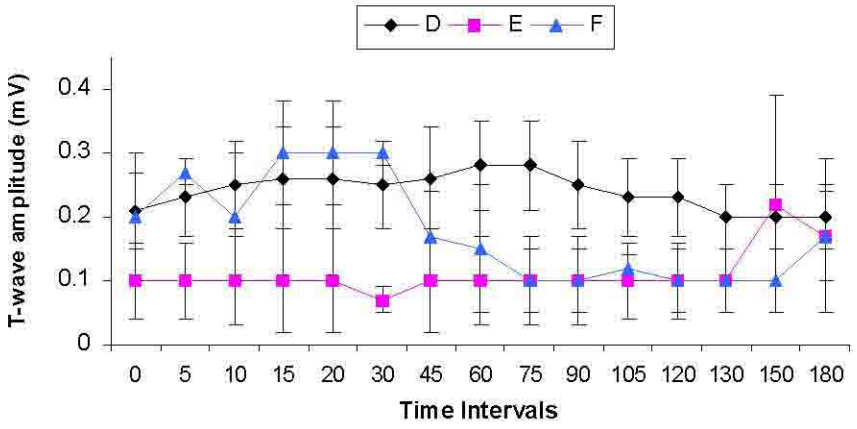


Fig 4.33 : T-wave amplitude (mV) recorded in the animals of different groups

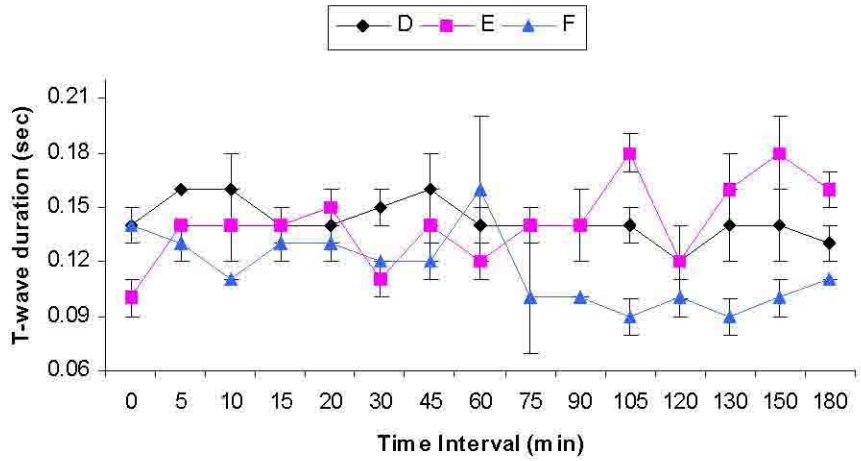


Fig 4.34 : T-wave duration (sec) recorded in the animals of different groups

T-wave duration

Mean ±SE values of T-wave duration in different groups have been shown in Figure 4.34 and Table 4.39.

T-wave duration did not show any significant change (P>0.05) in group D animals during the post-injection period in one animal of group D, the amplitude and duration increased throughout the observation period. The values fluctuated near the base line throughout the period of observation. In the animals of group E, T-wave duration increased throughout the observation period. The increase was significant (P<0.01) at 105 and 150 min post-injection. The values of T-wave duration remained increased at the end of observation period and did not return to the pre-administration level.

In the animals of group F, the T-wave duration decreased throughout the period of observation. The decrease was significant (P<0.05) from 105 to 180 minutes. The values remained below the base line and didnot return to pre-administration level.

Comparison among various groups revealed that T-wave duration of group D and group E animals was longer than group F throughout the observation period. The difference was significant (P<0.05) at 105 minutes interval.

pH

Mean ±SE values of pH in different groups have been shown in Figure 4.35 and Table 4.40.

No definite trend in the pH values was recorded at different time intervals in different groups. No significant (P > 0.05) difference in pH was recorded in any of the combination groups at all the time intervals as compared to the respective base values. Similarly, pH values did not differ significantly between the groups at respective time intervals. The values fluctuated within normal limits and remained near the base line throughout the period of observation.

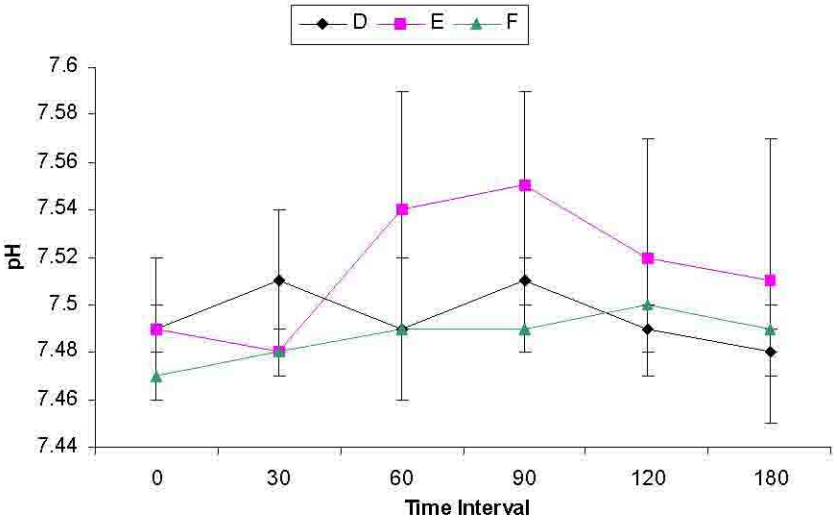


Fig 4.35 : pH in the animals of different groups

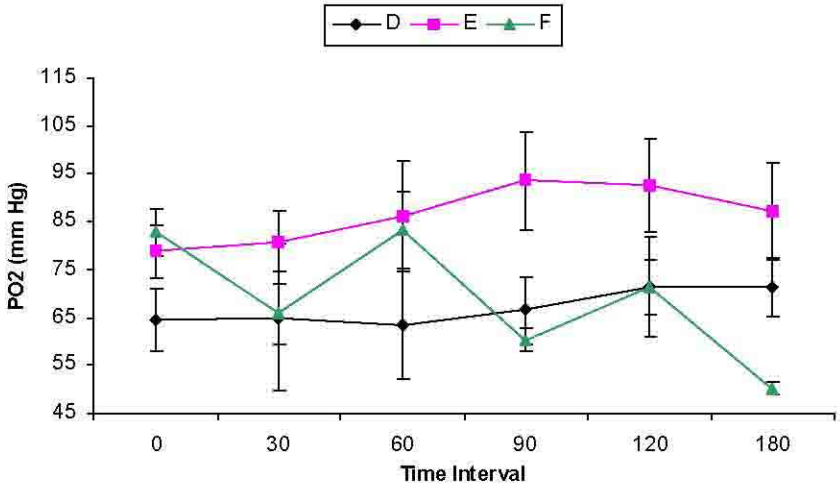


Fig 4.36 : PO_2 (mm Hg) in the animals of different groups

Partial pressure of oxygen (PO_2)

Mean ±SE values of PO_2 in the animals of different groups have been shown in Figure 4.36 and Table 4.41.

In group D (ketamine and bupivacaine) animals, there was a non-significant ($P > 0.05$) increase in PO_2 values from 90 min and onwards as compared to the base value. The values remained elevated even at the end of observation period. Similarly, in group E, a non-significant ($P > 0.05$) increase in PO_2 was recorded at all the time intervals as compared to base values. The values remained increased at the end of the study. In group F, however, the PO_2 concentration decreased and remained below the base line after spinal injection of drugs throughout the period of observation. The decrease was significant ($P < 0.05$) at 90 min and 180 min post-injection. The values never returned to the baseline even at the end.

Comparison among various treatment groups revealed that in animals of group D, the base value of PO_2 was significantly ($P < 0.05$) lower as compared to group F. However, it was non-significantly ($P > 0.05$) lower than group E.

At 90 min, interval, group E animals showed significantly ($P < 0.05$) higher concentration of PO_2 than groups D and F. The difference in PO_2 values between group D and group F was non-significant ($P > 0.05$). Similarly, group D and group E showed significantly ($P < 0.05$) higher values of PO_2 at 180 min as compared to group F.

PCO_2

Mean ±SE values of PCO_2 in the animals of different groups have been shown in Figure 4.37 and Table 4.42.

In group D, there was a non-significant ($P > 0.05$) and transient decrease of PCO_2 at 30 min post-injection followed by an increase at 60 min as compared to the base line values. The values, however, decreased at 90 min and returned to near base

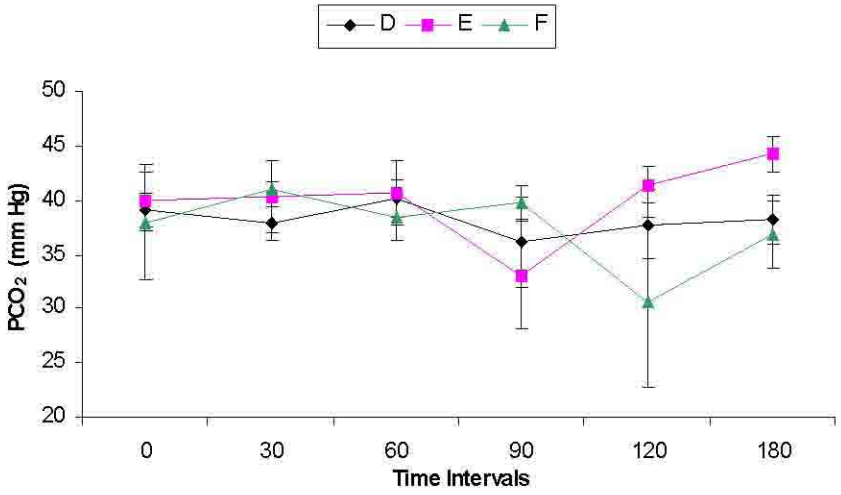


Fig 4.37 : PCO_2 (mm Hg) in the animals of different groups

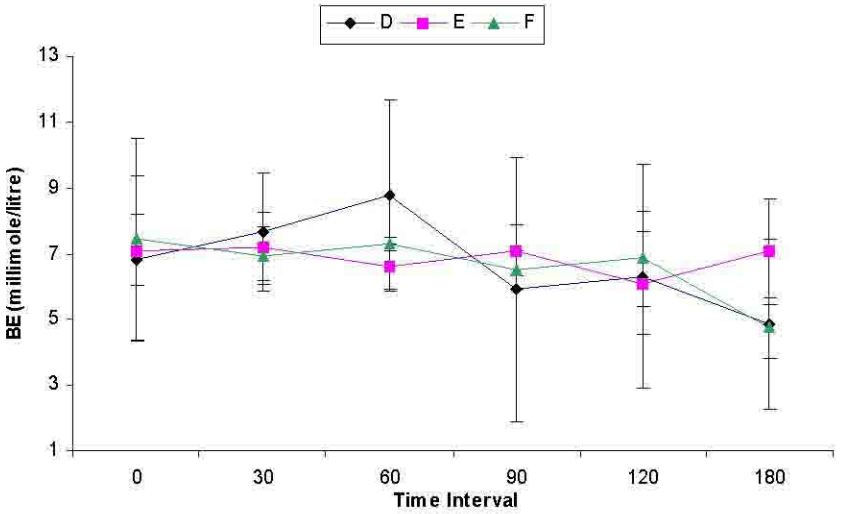


Fig 4.38 : BE-ECF (millimole/litre) in the animals of different groups

line at the end of observation period. The changes in PCO_2 were however, nonsignificant ($P > 0.05$) throughout the observation period in animals of group D. Group E, animals showed non-significant ($P > 0.05$) increase in PCO_2 level at all the time intervals except at 90 min where the level was non-significantly ($P > 0.05$) less than the base values. Group F, animals showed a non-significant ($P > 0.05$) increase throughout the period of observation except at 120 minute and 180 minute interval. The values however, improved and returned to the base line at the end of observation period.

Comparison among different groups revealed that there was no significant difference ($P > 0.05$) in PCO_2 level among different groups at various time intervals during the post-injection period. However, the base values were significantly ($P < 0.05$) higher for group E as compared to group F.

BE-ECF

Mean ±SE values of BE-ECF in the animals of different groups have been shown in Figure 4.38 and Table 4.43.

In group D (ketamine + bupivacaine), there was a non-significant ($P > 0.05$) increase in BE-ECF concentration at 30 min interval, which increased further at 60 min post-injection. At 90 min post-injection the values again decreased than base values and remained lesser than the base values till the end of observation period. In the the animals of group E (ketamine + xylazine) a non-significant decrease ($P > 0.05$) of BE-ECF was recorded at 60 min and 120 min post-injection than the base line values. At rest of the intervals, the values fluctuated near the base line. The values however, returned to the base line at the end of observation period. Group F animals also showed a gradual but non-significant ($P > 0.05$) decrease in BE-ECF at all the time intervals during the post-injection period. The values remained decreased even at the end of the observation period.

Comparison among different groups revealed that group D had significantly ($P < 0.05$) higher BE-ECF value than group F and non-significantly ($P > 0.05$) higher value

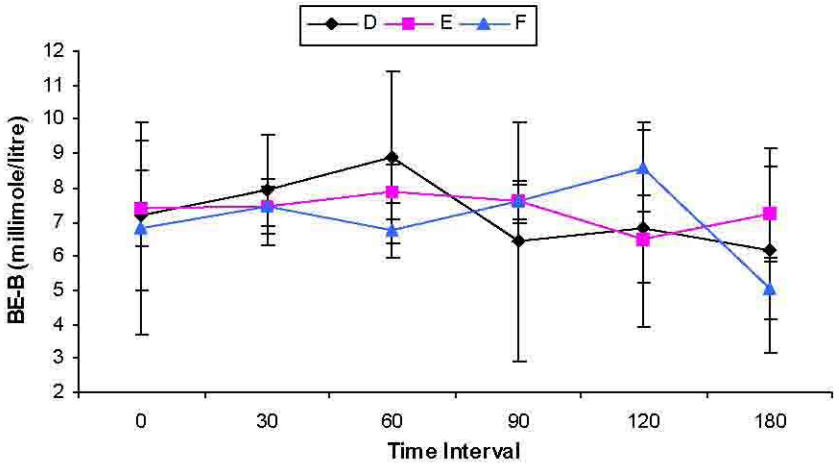


Fig 4.39 : BE-B (millimole/litre) in the animals of different groups

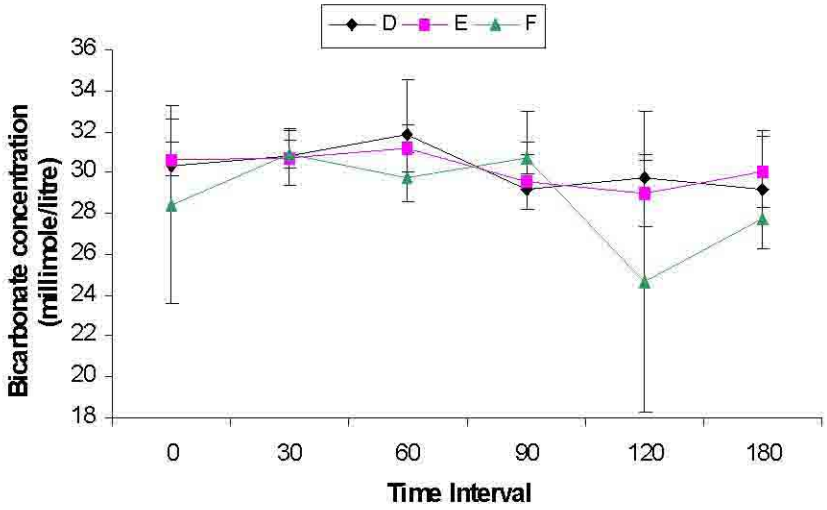


Fig 4.40 : Bicarbonate concentration (millimole/litre) in the animals of different groups

than group E. At 90 min, group D animals showed significantly ($P < 0.05$) lower BE-ECF as compared to group E. However, the difference was non-significant ($P > 0.05$) from the group F.

BE-B

Mean ±SE values of BE-B in the animals of different groups have been shown in Figure 4.39 and Table 4.44.

A non-significant ($P > 0.05$) increase in BE-B was recorded for 60 min post-injection in group D, 90 min in group E and 120 min in group F. The values decreased after those respective intervals till the end of observation period. The values, however, never returned to the preadministration level in any of the groups.

Comparison among different groups revealed that there was no significant ($P > 0.05$) difference in BE-B among different groups at different post-injection time intervals.

Bicarbonate concentration (HCO^-_3)

Mean ±SE values of HCO^{-3} in the animals of different groups have been shown in Figure 4.40 and Table 4.45.

There was no significant ($P > 0.05$) change in the plasma bicarbonate concentration values after spinal injection of the drugs in different groups during the entire period of the study in comparison to the respective base values. However, a transient rise for 30 and 60 min post-injection was recorded in all the groups. The values decreased at 120 min post-injection in all the groups as compared to the base line and remained decreased even at the end of observation period.

There was no significant ($P > 0.05$) difference in the bicarbonate values among different groups at any stage of observation during the post-injection period.

Sodium

Mean ±SE values of sodium in the animals of different groups have been shown in Figure 4.41 and Table 4.46.

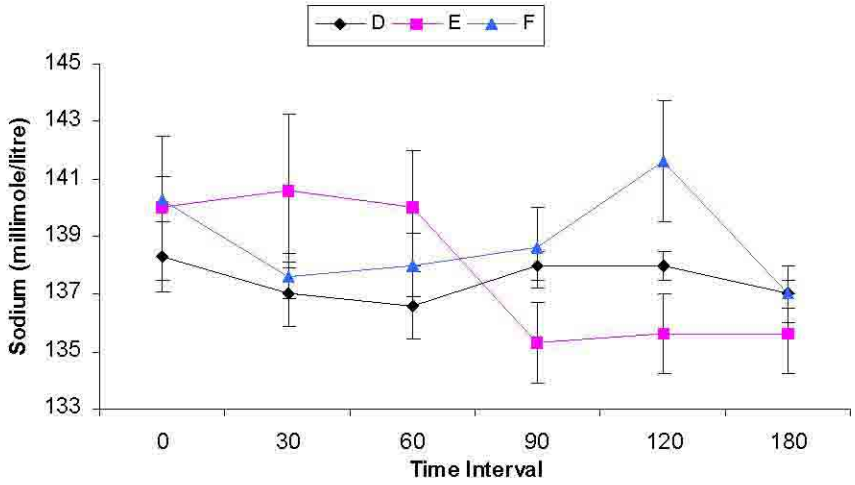


Fig 4.41 : Sodium (millimole/litre) in the animals of different groups

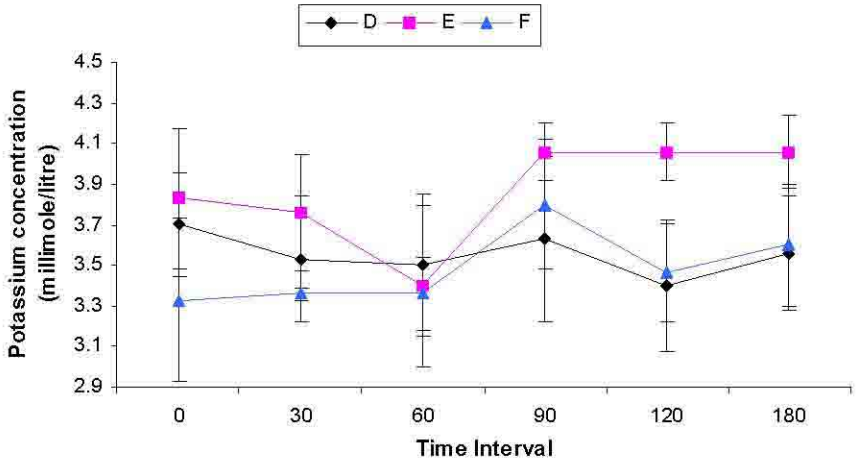


Fig 4.42 : Potassium concentration (millimole/litre) in the animals of different groups

Sodium values in group D did not show any considerable and significant change till the end of the observation period. Group E showed a non-significant ($P > 0.05$) decrease in sodium concentration from 90 to 180 min and the values never returned to the base line even at the end. Group F animals showed a similar non-significant ($P > 0.05$) decrease from 30 to 180 min post-injection.

Comparison among different groups revealed that group E had non-significantly ($P > 0.05$) higher values at 30 and 60 min post-injection and lower values of blood sodium from 90 to 180 minutes post-injection as compared to groups D and F.

Potassium

Mean ±SE values of potassium in the animals of different groups have been shown in Figure 4.42 and Table 4.47.

In group D animals the potassium level decreased non-significantly ($P > 0.05$) throughout the observation period. The values remained lower than the base line even at the end of observation period. In the animals of group E, a slight non-significant ($P > 0.05$) decrease was recorded from 30 to 60 min. The values then increased from 90 min and remained elevated till the end of observation period. In group F, the potassium values increased non-significantly ($P > 0.05$) throughout the period of observation and remained elevated till the end of observation period.

Comparison among different groups revealed that in animals of group E, non-significantly ($P > 0.05$) higher values of plasma potassium were recorded from 90 to 180 min as compared to group D.

Chloride

Mean ±SE values of chloride in the animals of different groups have been shown in Figure 4.43 and Table 4.48.

No significant ($P > 0.05$) change in the chloride concentration in group D animals throughout the post-injection period was recorded. The values remained near the base line at different intervals. Group E animals showed a significant ($F < 0.01$) decrease in

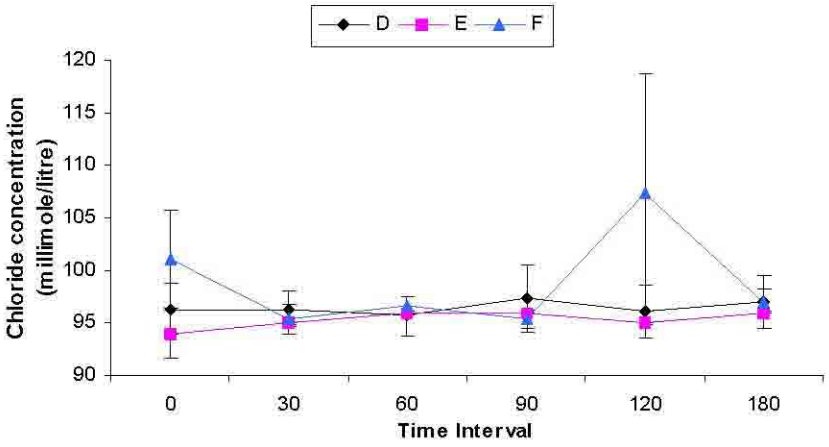


Fig 4.43 : Chloride concentration (millimole/litre) in the animals of different groups

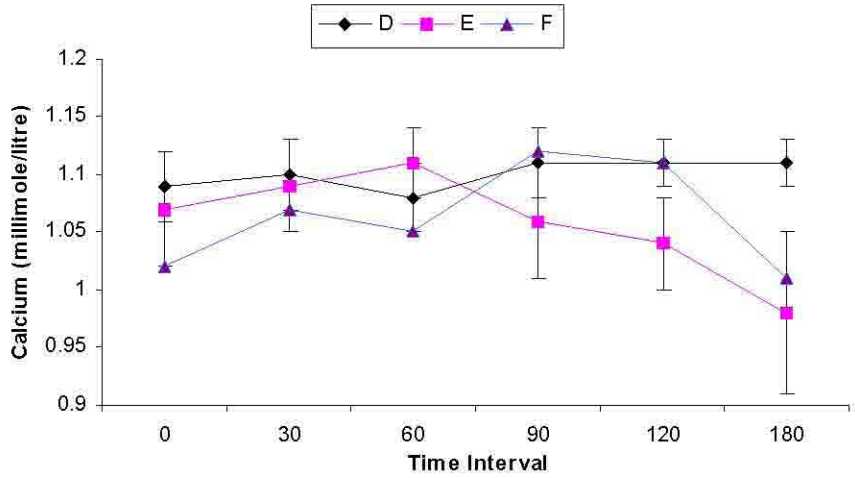


Fig 4.44 : Calcium (millimole/litre) in the animals of different groups

plasma chloride concentration from 30 minutes post-injection up to the end of observation period. Group F, however, showed only a non-significant ($P > 0.05$) decrease in chloride concentration throughout the period of observation. The values remained below the baseline even at the end of observation period.

Comparison among different groups revealed that there was no significant ($P > 0.05$) difference in the chloride values among different groups at any time interval during the post-injection period.

Calcium

Mean ±SE values of calcium in the animals of different groups have been shown in Figure 4.44 and Table 4.49.

No significant ($P > 0.05$) change in the blood calcium levels were found in all the groups of animals at different intervals except in group E where a slight decrease in calcium levels was noticed at 180 minutes post-injection. The values fluctuated near the base line during various post-injection time intervals in all the three groups.

Comparison among different groups revealed that group D at 30 minutes post injection, showed significantly ($P < 0.05$) higher values of blood calcium than group F. Group E however, showed a non-significantly ($P > 0.05$) lower values of calcium from 90 to 180 min post-injection as compared to all the groups.

Phase III

CLINICAL STUDIES

Onset of analgesia

Mean ±SE values onset of analgesia (in min) in different groups are presented in Figure 4.45 and Table 4.50.

In the animals of group G, it took 5.0±0.00 min for the onset of analgesia. The onset of analgesia in the animals of group H took 1.75±0.47 min and in the animals of group I, it took 3.5±0.6 min for the onset of analgesia.

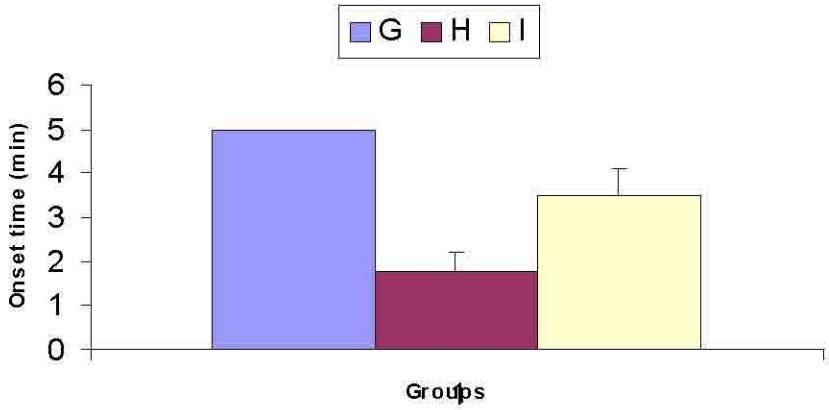


Fig 4.45 : Onset of analgesia in animals of different groups

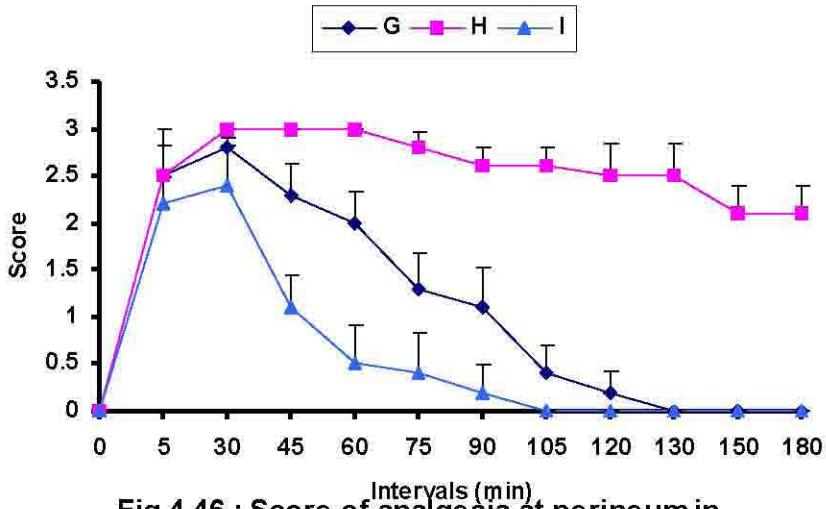


Fig 4.46 : Score of analgesia at perineum in animals of different groups (1-mild, 2-moderate, 3-complete)

Comparison between the different groups revealed that signifiantly (P<0.05) earliest onset of analgesia among clinical groups occurred in the animals of group H. The drugs in animals of group G, caused significantly (P<0.05) later onset than all the groups and in the animals of group I, the onset was significantly (P<0.05) earlier than group G but later than group H.

Depth and extent of analgesia

Perineum

Mean ±SE score of analgesia at perineum region in different groups are presented in Figure 4.46 and Table 4.51.

In the animals of group G, moderate analgesia of perineum was recorded from 5 min. The analgesia thereafter was recorded as moderate for 30-60 min followed by a further decrease to remain as mild to very mild from 75-120 min post-injection. Analgesia weaned off completely by 130 min post-injection. In the animals of group H, moderate analgesia was present at 5 min, which increased further to complete analgesia from 10 min to 60 min. Thereafter, a decrease in analgesia and moderate analgesia was seen throughout the observation period. In the animals of group I, moderate analgesia was recorded from 5 min and at 30 min post-injection. Thereafter, analgesia decreased and remained mild to very mild up to 90 min. Analgesia weaned off completely by 105 min.

Comparison among various groups revealed that group H animals showed significantly (P<0.05) higher analgesia of perineum than group I at 45 min and group G at 105 min and continued to be significantly (P<0.05) higher upto the end of observation period. Group G, however, had non-significantly (P > 0.05) higher analgesia score than group I almost thoughout the period of observation.

Inguinal region

Mean ±SE score of analgesia at inguinal region in different groups are presented in Figure 4.47 and Table 4.52.

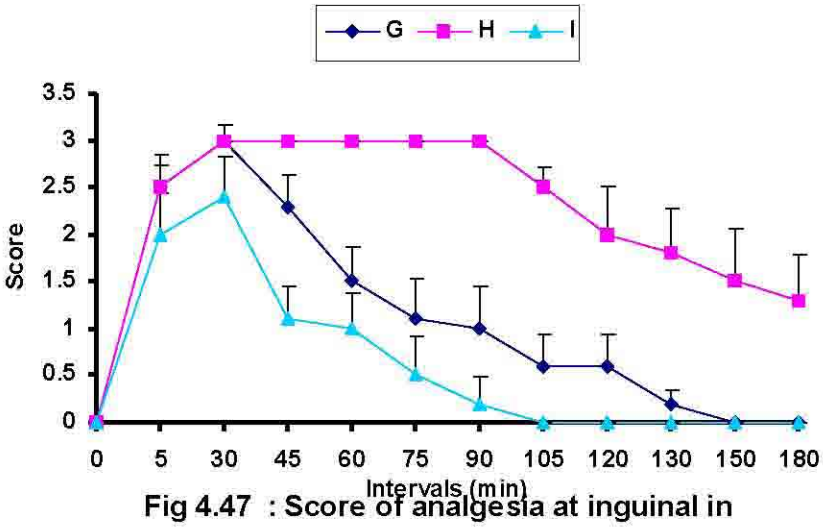


Fig 4.47 : Score of analgesia at inguinal in animals of different groups (1-mild, 2-moderate, 3-complete)

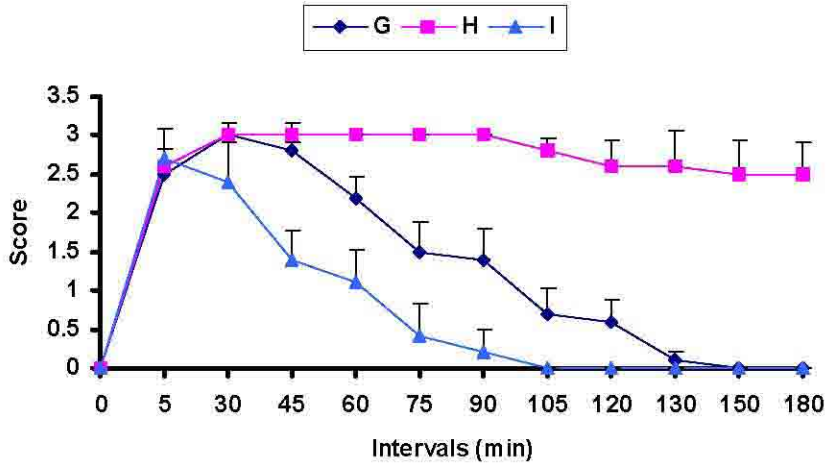


Fig 4.48 : Score of analgesia at tail in animals of different groups (1-mild, 2-moderate, 3-complete)

In the animals of group G, moderate analgesia was present at 5 min which increased to complete analgesia at 30 min. Thereafter, analgesia decreased to mild to very mild depth from 60 to 130 min. Analgesia weaned off completely at 150 min post-injection. In the animals of group H, after a transient phase of moderate analgesia at 5 min, complete analgesia of inguinal region was recorded at 30 min and continued up to 90 min. Thereafter, analgesia declined to remain moderate to mild level from 105 min till the end of observation.

However, the animals of group I didn't show complete analgesia of inguinal region throughout the observation period, where maximum analgesia was recorded as moderate from 5 min and at 30 min. Thereafter, analgesia declined to remain as mild to very mild from 45 till 90 min post-injection. Analgesia weaned off completely by 105 min.

Comparison among various groups revealed that group H animals showed significantly ($P<0.05$) higher level of analgesia of inguinal region than group G and I after 45 min. Group I didnot attain complete analgesia at all.

Tail

Mean ±SE score of analgesia at tail region in different groups are presented in Figure 4.48 and Table 4.53.

In the animals of group G, after an initial phase of moderate analgesia at 5 min, complete analgesia was recorded at 30 min post-injection. Depth of analgesia again decreased to moderate level for upto 60 min. Analgesia then declined further to remain as mild to very mild up to 130 min and then completely abolished by 150 min. A moderate analgesia was recorded in the animals of group H at 5 min which increased further to complete analgesia in 30 min and remained unchanged upto 90 min post-injection. Thereafter, analgesia started to decrease after 105 min but moderate analgesia was still present throughout the rest of observation period. In the animals of group I, also moderate analgesia of tail region was recorded at 5 min and remained

unchanged at 30 min post-injection. Analgesia did not increase further and started to decrease and mild to very mild analgesia was recorded up to 90 min. and weaned off completely by 105 min.

Comparison among different groups revealed that group H animals exhibited significantly ($P<0.05$) higher level of analgesia from 45 min till the end of observation period than group I and from 90 min onward from the animals of group G. Analgesia in animals of group G was higher than group I at most of the observation period but the difference was not significant ($P>0.05$). Duration of complete analgesia was considerably longer in animals of group H as compared to animals of group G.

Flank

Mean ±SE score of analgesia at flank region in different groups are presented in Figure 4.49 and Table 4.54.

Animals of group G, exhibited a moderate analgesia of flank as early as 5 min which continued so from 30 up to 60 min. Thereafter, analgesia decreased gradually and mild to very mild analgesia was recorded upto 120 min and analgesia weaned off completely by 130 min post-injection. The analgesia of flank in group H animals was recorded as mild to moderate at 5 min and from 30 to 45 min which increased further to complete analgesia during 60 to 75 min. Thereafter, moderate analgesia was recorded from 90 min till the end of observation period. In the animals of group I mild to moderate analgesia of flank was reached at 5 and from 30 to 45 min. Thereafter, analgesia declined to very mild for up to 90 min and weaned off completely by 105 min post-injection.

Comparison among various groups revealed that analgesia was significantly ($P<0.05$) higher in the animals of group H than the animals of groups G and I from 60 min till the end of the observation period. However, differences between groups G and I were not significant during the entire period of observation. Complete analgesia of flank was recorded only in the animals of group H for a short period of time.

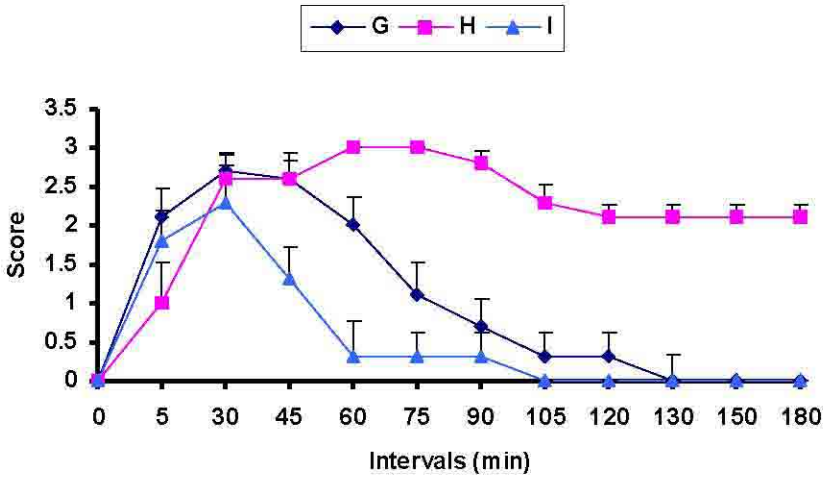


Fig 4.49 : Score of analgesia at flank in animals of different groups (1-mild, 2-moderate, 3-complete)

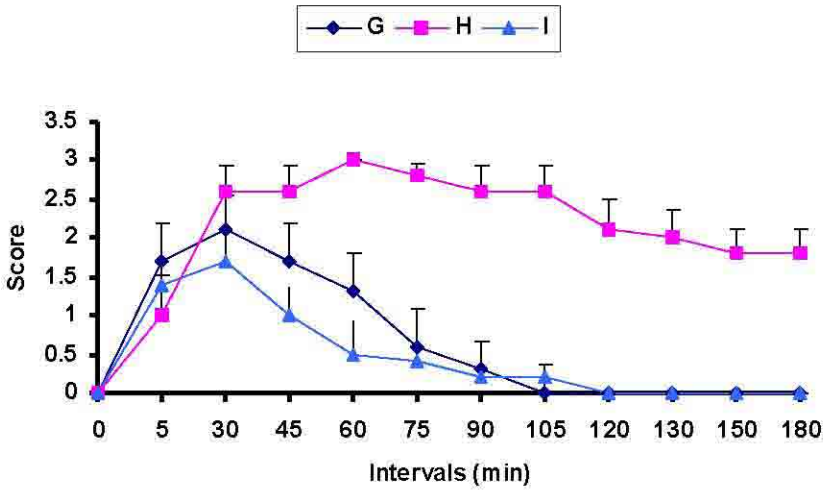


Fig 4.50 : Score of analgesia at abdomen in animals of different groups (1-mild, 2-moderate, 3-complete)

Abdomen

Mean ±SE score of analgesia at abdomen region in different groups are presented in Figure 4.50 and Table 4.55.

In the animals of group G, mild analgesia was recorded from 5 min but thereafter, it increased to remain moderate at 30 min. It declined to remain as mild to very mild up to 90 min post-injection and weaned off completely by 105 min. In the animals of group H, mild to moderate level of analgesia was recorded at 5 to 45 and 30-45 min which increased further to complete analgesia at 60 min post-injection. Thereafter, analgesia declined to moderate to mild throughout the period of observation. In the animals of group I, mild to moderate analgesia of abdomen was seen from 5 min and 30-45 min. Thereafter, analgesia declined to remain as very mild from 60 to 90 min followed by complete abolishment of analgesia by 105 min post-injection.

Comparison among various groups revealed that animals of group H showed significantly ($P<0.05$) higher analgesia scores from 60 min upto end of the observation period than groups G and I. However, analgesia score did not differ significantly between group G and group I. Similarly from 10 to 45 min, the three groups did not vary significantly from each other. Complete analgesia was recorded only in group H at 60 min.

Thorax

Mean ±SE score of analgesia at thorax region in different groups are presented in Figure 4.51 and Table 4.56.

In the animals of group G, only mild to very mild analgesia of thorax was seen at 5 min and 30 to 120 min. Thereafter, at 130 min analgesia was completely abolished. In the animal, of group H, very mild to mild analgesia of thorax was present at 5 min which increased to moderate analgesia from 30 min to 45 min. Analgesia increased further so that complete analgesia was recorded at 60-75 min post-injection. Thereafter, the analgesia declined and moderate to mild depth of analgesia was recorded throughout

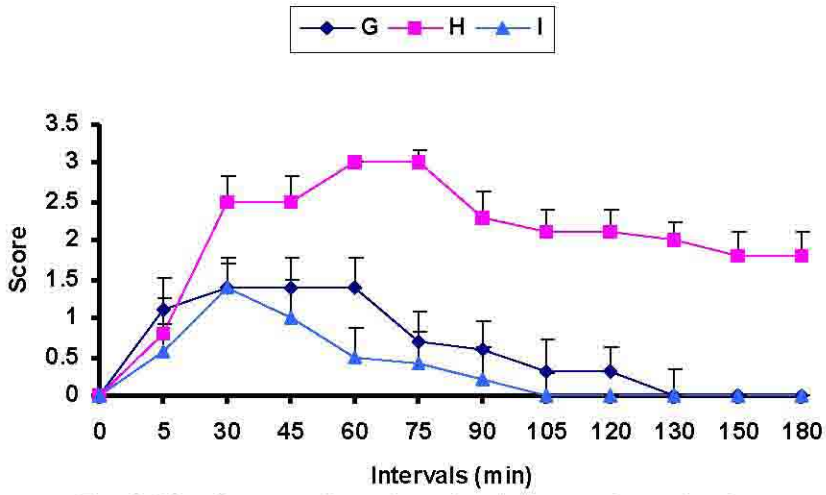


Fig 4.51 : Score of analgesia at throax in animals of different groups (1-mild, 2-moderate, 3-complete

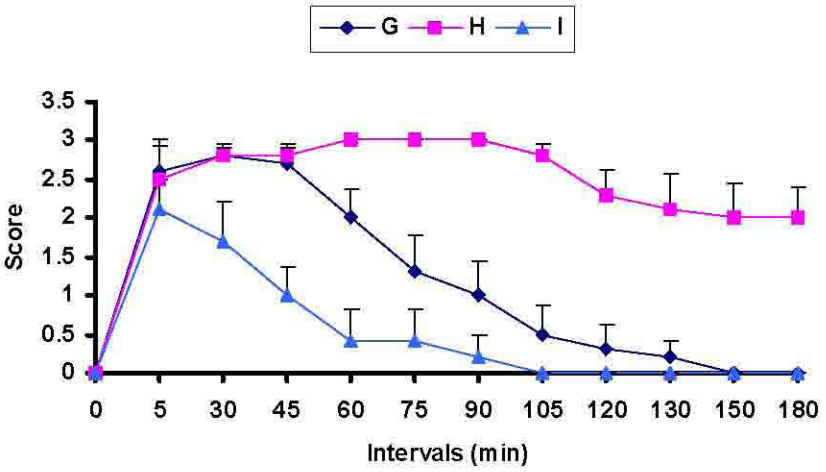


Fig 4.52 : Score of analgesia at hind limb in animals of differnt groups (1-mild, 2-moderate, 3-complete)

the rest of observation period. In the animals of group I, very mild to mild analgesia was recorded at 5 min. The analgesia declined thereafter to remain mild to very mild from 30 min upto 90 min. and weaned off completely by 105 min.

Comparison among different groups revealed that significantly ($P<0.05$) higher depth of analgesia in animals of group H was seen compared to groups G and I from 60 to 180 min. The analgesia between group G and I did not differ significantly ($P>0.05$) during the entire period of observation.

Hind limbs

Mean ±SE score of analgesia at hind limbs region in different groups are presented in Figure 4.52 and Table 4.57.

In the animals of group G, moderate analgesia of hind limbs was recorded as early as 5 min which continued from 30 min up to 60 min. Thereafter, analgesia declined to remain as mild to very mild up to 130 min post-injection and then weaned off completely by 150 min. In the animals of group H, also moderate analgesia was recorded within 5 min which continued to remain so from 30 to 45 min. Analgesia increased further and complete analgesia of hind limbs was recorded from 60 to 90 min. Thereafter, analgesia declined to remain as moderate throughout the observation period. In the animals of group I, moderate analgesia was recorded from 5 min which declined to remain as mild to very mild from 30 upto 90 min. Analgesia completely weaned off at 105 min post-injection.

Comparison among different groups revealed that significantly higher ($P<0.05$) level of analgesia of hind limbs was recorded in group G and H as comapred to group I at 45 min. However, analgesia of group H remained signifiantly ($P<0.05$) higher than group I from during entire period of observation after 45 min interval. Depth of analgesia did not differ significantly between the group G and I. Complete analgesia of hind limbs was recorded in animals of group H from 60 to 90 min.

Analgesia in the animals of group H was also signifiacntly (P<0.05) higher than the animals of group G at 105 min. and remained so till the end of the observation period.

Digits

Mean ±SE score of analgesia at digits region in different groups are presented in Figure 4.53 and Table 4.58.

In the animals of group G, moderate analgesia was recorded at 5 min which increased further to complete analgesia from 30 min upto 45 min. Thereafter, analgesia declined to remain as moderate upto 75 min and decreased further mild to very mild level upto 150 min post-injection. Analgesia weaned off completely at 180 min post-injection. In the animals of group H, moderate analgesia was recorded at 5 min and 30 to 45 min. Thereafter, complete analgesia of digits was produced from 60 min to 120 min which declined slightly to remain as moderate from 130 min upto the end of observation period. In the animals of group I, moderate analgesia of digits was recorded from 5 min to 30 min. Thereafter, analgesia declined to remain as mild to very mild upto 90 min and weaned off completely by 105 min post-injection.

Comparison between various groups revealed that, the depth of analgesia at 5 and 30 min did not differ significantly among the three clincial groups. However, group H, showed a significantly (P<0.05) higher depth of analgesia from 45 min till the end of observation than group I and from 105 to 180 min than group G. Analgesia did not differ significantly between groups G and I.

Summary of depth and extent of analgesia

Complete analgesia (score 3) of different regions produced by different anaesthetics and their duration is summarized in Table 59. Among the clinical groups, a maximum of very mild analgesia of thorax and a maximum of moderate analgesia of abdomen, hindlimbs and flank and complete analgesia of perineum, digits, inguinal and tail was established for varying length of time in animals of group G. In animals of group

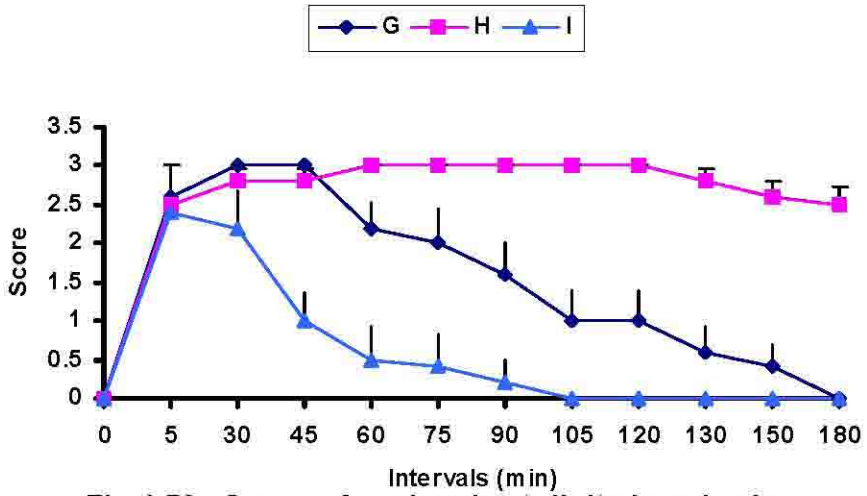


Fig 4.53 : Score of analgesia at digits in animals of different groups (1-mild, 2-moderate, 3-complete)

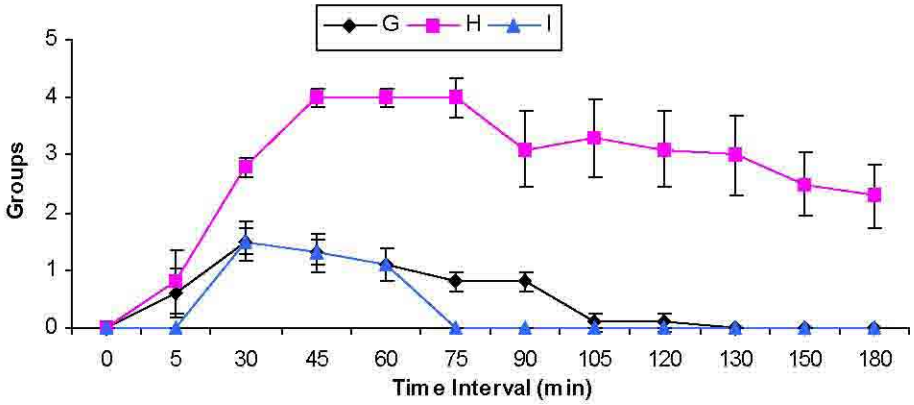


Fig 4.54 : Score of sedation recorded in the animals of different groups (0-standing alert, 1-slight toses of eye lids, 2 extreme lowering of head, 3-recumbent but could sit without support, 4-recumbent laterally

H a maximum of a complete analgesia of all the regions for varying lengths of time was observed. In animals of group I a maximum of moderate analgesia only of thorax, digits, perineum, inguinal region, abdomen, hindlimbs, tail and flank (i.e. of all the recorded regions) was recorded. Complete analgesia was never a feature of this group also.

Sedation

Mean ±SE score of sedation in different groups are presented in Figure 4.54 and Table 4.60.

Group G animals showed sternal recumbency within 5 min after the spinal injection of drugs. Animals looked tired with slight ptosis of eye lids after 120 min thereafter, animals were standing alert.

Group H animals, showed lateral recumbency in 5 min and remained so upto 30 to 60 min. Thereafter, animals became recumbent but could not sit without support from 45 to 75 min post injection. Later on animals were recumbent but could sit without support.

Group I animals showed sternal recumbency from 5 min to 30-45 min post-injection but remained alert upto 10 min and thereafter, showed only mild sedation with slight ptosis of eye lids from 15 to 60 min post-injection and thereafter, animals remained alert upto the end of observation.Comparison among different groups revealed that sedation in animals of group H (Ketamie-xylazine) was significantly ($P < 0.05$) more as compared to all the groups.

Motor incoordination

Mean ±SE score of motor incoordination in different groups are presented in Figure 4.55 and Table 4.61.

In group G, where bupivacaine and ketamine combination was administered intraspinally, animals attained immediate sternal recumbency within 5 min and

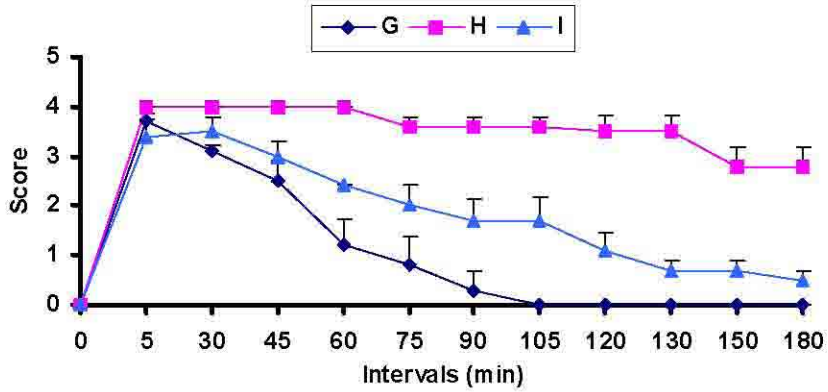


Fig 4.55 : Score of motor incoordination of hind limbs in the animals of different groups (0-normal, 1-little incoordination, 2-extreme incoordination, 3-sternal recumbency, 4-lateral recumbency

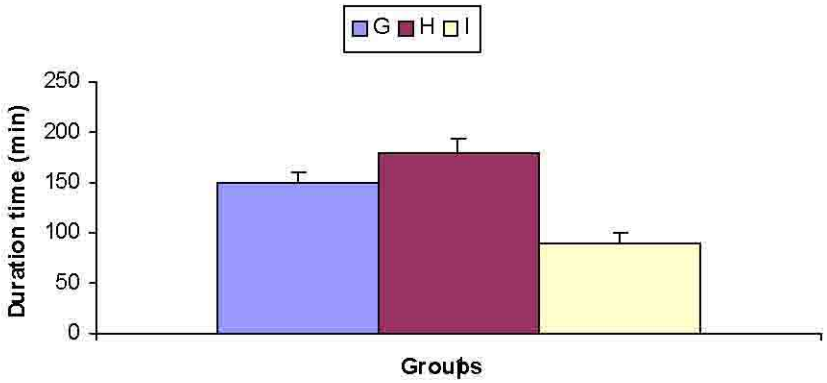


Fig 4.56 : Duration of analgesia in animals of different groups

continued so upto 30 min. Thereafter, the animals showed extreme incoordination of gait at 45 min and the scores further decreased to cause little to very little incoordination when the animals were made to walk at 60 to 90 min. The animals could stand and walk without staggering at 105 min post-injection. In the animals of group H, sternal recumbency was seen as early as 5 min (or less) after the spinal injection and a lateral recumbency at 30 min was recorded which continued till 60 min post-injection and remained so upto 130 min. Thereafter, an extreme incoordination in walk was seen till the end of observation. Similarly in the animals of group I, sternal recumbency was recorded as soon as (5 min. or less) the spinal injection was made and continued upto 45 min post-injection. Thereafter, the animals showed extreme incoordination at 60-75 min. The scores decreased further to cause little to very little incoordination when the animals were made to walk from 90 min upto the end of observation period.

Comparison among various groups revealed that the scores of motor incoordination were higher in group H animals throughout the observation period. It was significant ($P<0.05$) at 30 min till the end, than groups G and I. Group G animals started to walk normally earlier than group H and I. The difference was significant ($P<0.05$) from group H.

Duration of analgesia

Mean ±SE values of duration of analgesia in different groups are presented in Figure 4.56 and Table 4.62.

Among the clinical groups, the duration of analgesia in group H (xylazine-ketamine) was significantly longer than group I and non-significantly longer than group G. Animals of group I (Ketamine + Buprenorphine) showed a shortest duration of analgesia as compared to all the groups.

Recovery

Recovery of the animals of clinical cases took place in the following order.

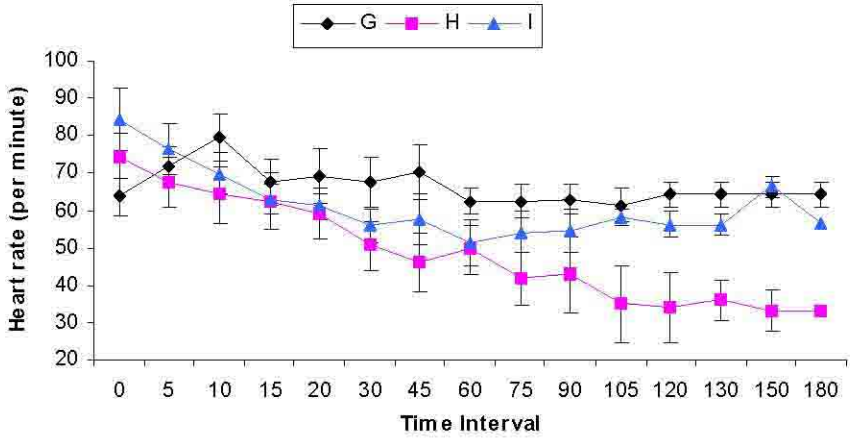


Fig 4.57 : Heart rate (per minute) recorded in the animals of different groups

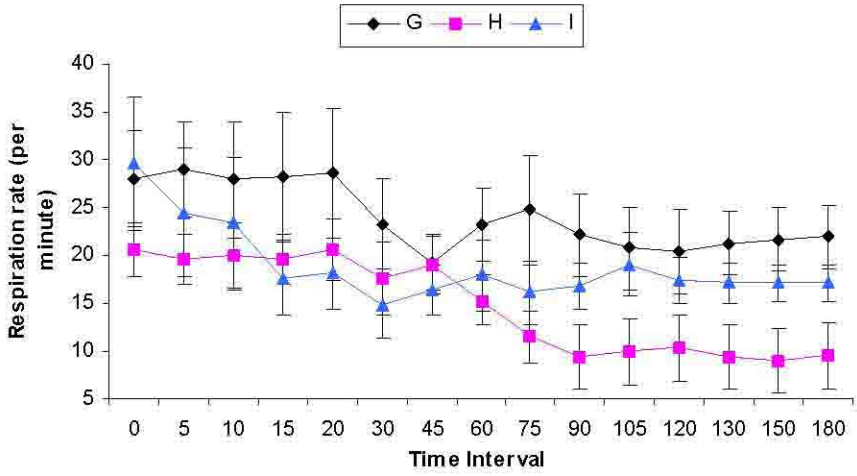


Fig 4.58 : Respiration rate (per minute) recorded in the animals of different groups

Group I followed by group G followed by group H.

Pathophysiological parameters

Heart rate

Mean ±SE values of heart rate in different groups are presented in Figure 4.57 and Table 4.63.

In the animals of group G, an increase in the heart rate from 5 to 45 min post-injection was recorded. The increase was significant ($P < 0.01$) at 10 min. The heart rate then decreased from 60 min onwards till 105 min. Thereafter, the values slightly increased than the baseline value till the end. Group H (ketamine + xylazine) animals showed a rapid decrease in the heart rate from 5 min till the end of observation. The decrease was significant ($P < 0.05$) from 30 to 90 minute and from 150 to 180 minutes as compared to the base values. The heart rate remained decreased and never returned to the base line even at the end. After the administration of spinal drugs, group I (ketamine + buprenorphine) animals showed a steady reduction in heart rate throughout the observation period. The decrease was significant ($P < 0.05$, $P < 0.01$ and $P < 0.001$) from 15 minutes till the end of observation period. The values didn't show any indication of improvement and remained below the baseline even at the end of observation period. Comparison among different groups revealed that group H recorded significantly ($P < 0.05$) lower values of heart rate from 90 minutes to 180 minutes post-injection as compared to all the groups.

The values of heart rate in group H differed significantly ($P < 0.05$) and remained lower during the period as compared to groups G and I.

Respiratory rate

Mean ±SE values of respiratory rate in different groups are presented in Figure 4.58 and Table 4.64.

Group G animals after an initial steady rise from 5 to 20 minutes, showed a decrease in respiration rate from 30 minutes till the end of observation. The decrease in respiration rate was significant ($P < 0.05$) at 30 minutes. The respiration rate remained below the base line value. Group H (ketamine + xylazine) showed a decrease in the respiration rate from 5 minutes post-injection till the end of observation. The fall in respiration rate was significant ($P < 0.01$) from 75 minutes to 180 minutes post injection. The values remained below the pre-treatment value till the end.

Group I (ketamine + buprenorphine) animals showed a decrease in respration rate 5 minutes post-injection till the end of observation. The decrease was significant ($P < 0.05$) at 30 minutes post-injection. The respiration rate showed slight improvement thereafter and remained below the pretreatment value till the end of observation period.

Comparison among different groups revealed that respiration rate in group H was significantly ($P < 0.05$) lower as compared to all the groups between 130 and 180 minutes post-injection.

Rectal temperature

Mean ±SE values of rectal temperature in different groups are presented in Figure 4.59 and Table 4.65.

The clinical cases of uremic animals in group G (ketamine + bupivacaine) showed a decrease in the rectal temperature from 20 min till the end of observation period. The decrease was significant ($P < 0.05$) from 30 to 180 min post injection. The values started to increase at 150 min but remained significantly ($P < 0.05$) below the base line even at the end of observation period. Group H (ketamine + xylazine) animals showed a reduction in rectal temperature from 20 min till the end of observation. The decrease was significant ($P < 0.001$) from 45 min onwards till the end of observation period. Unlike group G, the values didn't improve and remained significantly below the baseline at the end of observation period. In group I (ketamine + buprenorphine) animals, the rectal temperature decreased non-significantly ($P > 0.05$) from 10 min onwards till the end of observation period. The values didn't improve even at the end of the observation period.

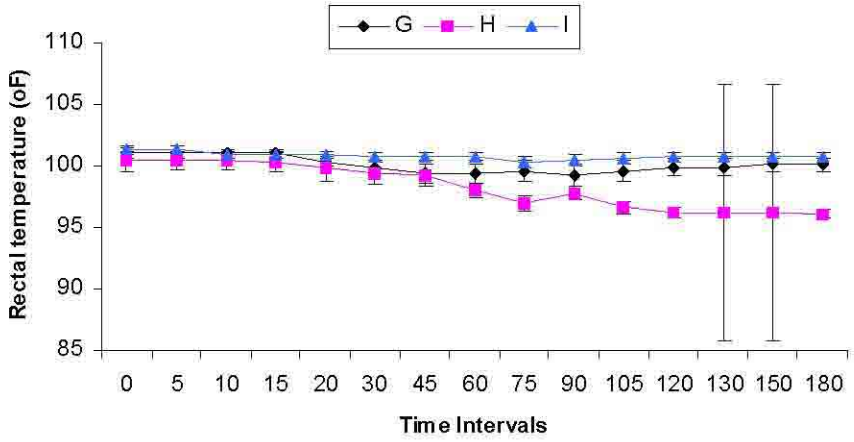


Fig 4.59 : Rectal temperature (oF) recorded in the animals of different groups

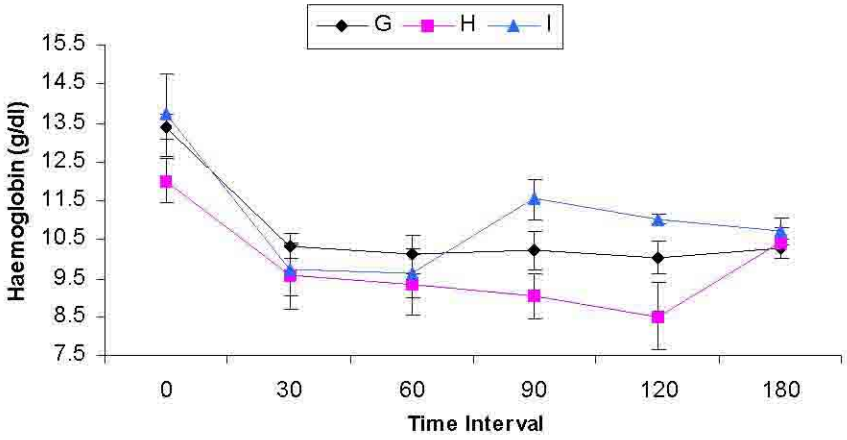


Fig 4.60 : Haemoglobin (g/dl) recorded in the animals of different groups

Comparison among different groups revealed that rectal temperature in group H was recorded as significantly ($P < 0.05$), lesser than group I and non-significantly ($P > 0.05$) lesser than group G at most of the intervals during the post-injection period.

Heaematological studies

Haemoglobin

Mean ±SE values of haemoglobin in different groups are presented in Figure 4.60 and Table 4.66.

Group G animals, showed a significant ($P < 0.01$) decrease in haemoglobin levels at 30 minutes and the values continued to decease significantly ($P < 0.001$) till 180 minutes post injection. The values remained below the base line at the end of observation period. Similarly, Hb levels decreased in group H also significantly ($P < 0.05$, $P < 0.01$, $P < 0.001$) at different time intervals upto the end of observation. The values of 24 hrs were lower than the pre-treatment value. Animals of group I showed an initial significant ($P < 0.05$) decrease in Hb levels at 30 minutes. The decrease in Hb values continued upto the end of observation period. At 24 hrs the values were below the pre-treatment levels. Comparison among different groups revealed that the Hb levels in group I were significantly ($P < 0.05$) high from 90 to 120 minutes post-injection as compared to group H and non-significantly different and higher ($P > 0.05$) than group G.

Packed cel volume (PCV)

Mean ±SE values of packed cel volume in different groups are presented in Figure 4.61 and Table 4.67.

In all the three clinical groups, there was a significant ($P < 0.05$, $P < 0.01$, $P < 0.001$) decrease in PCV from 30 upto 180 minutes. The values remained below the base line at the end of observation period and didn't return to the preadministration level in all the groups during the post-injection period. There was no significant ($P > 0.05$) difference in PCV values among three groups at any interval of time.

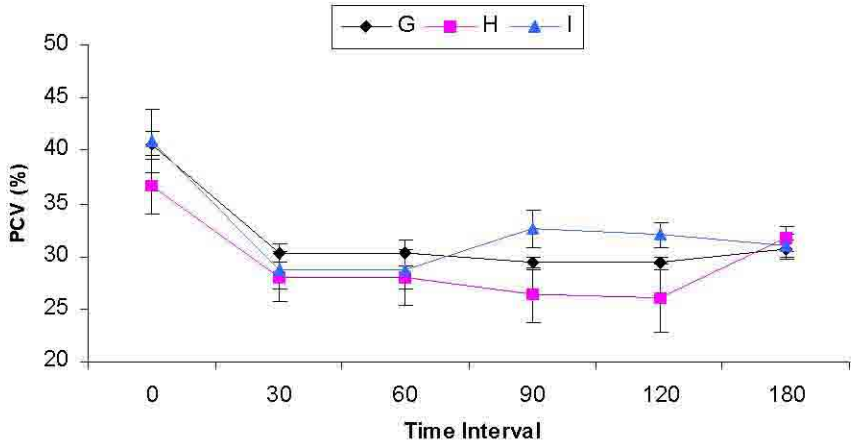


Fig 4.61: PCV (%) recorded in the animals of different groups

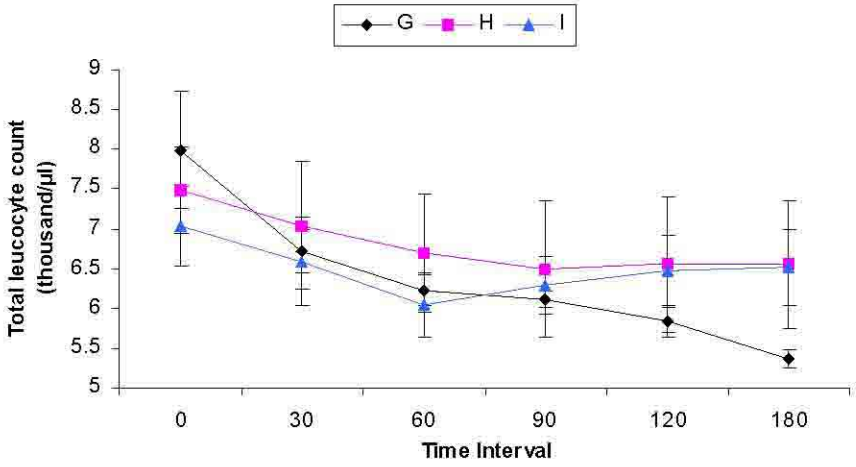


Fig 4.62: Total leucocyte count (thousand/µl) recorded in the animals of different groups

Total leukocyte count (TLC)

Mean ±SE values of total leukocyte count in different groups are presented in Figure 4.62 and Table 4.68.

TLC decreased steadily in all the treatment groups at different time intervals during the post-injection period. The decrease was significant (P<0.05) at 180 min in group I.

Comparison among different groups revealed that in group H a non-significantly (P>0.05) different and higher values of TLC were recorded as compared to all the treatment groups.

Differential leukocyte count (DLC)

Neutrophil

Mean ±SE values of neutrophil in different groups are presented in Table 4.69.

In groups G, H and I, there was a non-significant (P > 0.05) decrease in neutrophil count at different intervals during the post-injection period except at 120 minutes in group I, where the decrease was significant (P < 0.05). The values remained below the base line and did not return to the pre-administration level in all the groups.

Comparison among different groups didn't reveal any significant (P > 0.05) difference at any interval of time during the post-injection period. The values at the end of observation, however, remained non-significantly (P > 0.05) lower than the base line in all the groups.

Lymphocyte

Mean ±SE values of lymphocyte in different groups are presented in Table 4.70.

In all the groups, there was a non-significant (P>0.05) increase in lymphocyte count than the base values till the end of observation. The values remained elevated

even at the end of the observation period and didn't return to the pre-treatment levels in any of the groups. Comparison among different groups revealed no significant (P>0.05) difference at respective time intervals during the post-injection period. However, at 30-180 min post-injection period lymphocyte count was non-significantly (P>0.05) higher in group G than group H.

Eosinophils

Mean ±SE values of eosinophils in different groups are presented in Table 4.71.

The eosinophil count in clinical cases showed no significant (P>0.05) variation within the groups and between the groups at different time intervals during the entire post-injection period. The values fluctuated near the base line during the post-injection period.

Monocytes

Mean ±SE values of monocytes in different groups are presented in Table 4.72.

No significant (P>0.05) difference in the monocyte count was noticed at different time intervals with their respective base values in all the groups and among different groups at any interval of time.

Biochemical studies

Plasma glucose

Mean ±SE values of plasma glucose in different groups are presented in Figure 4.63 and Table 4.73.

In the animals of group G, plasma glucose levels decreased significantly at 30 min (P<0.05). Thereafter, a non-significant increase was recorded continuously up to the end of observation period. The values till the end remained elevated than the pre-treatment value. In the animals of group H, a significant decrease in plasma glucose at 30 min (P<0.01) and 60 min (P<0.05) was recorded. Thereafter, the values started to

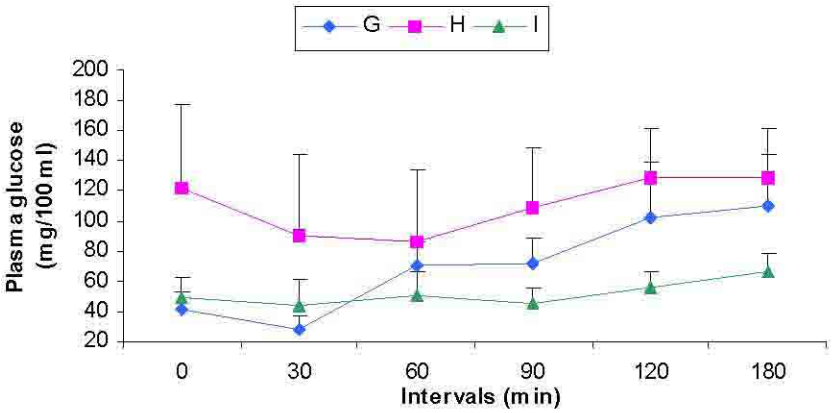


Fig 4.63 : Plasma glucose (mg/100ml) in the animals of different groups

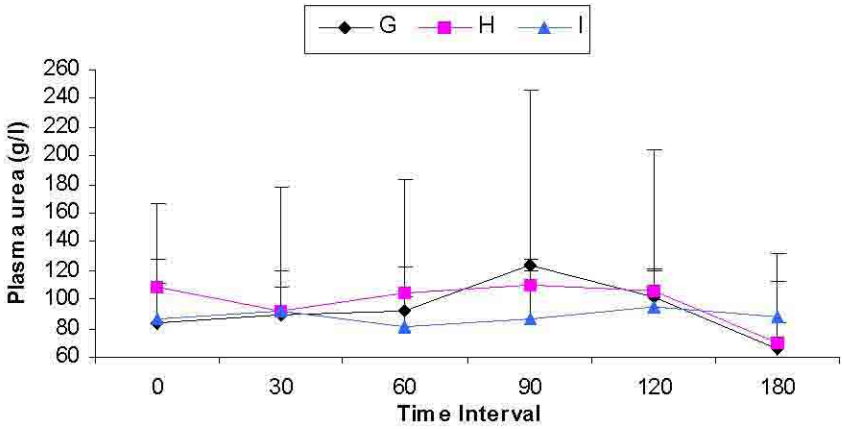


Fig 4.64: Plasma urea (g/l) in the animals of different groups

increase and at the end of observation the values remained higher than the pre-treatment value. In the animals of group I, there was only non-significant (P>0.05) increase in plasma glucose at 60 min, 120 min and 180 min post-injection and the values remained lesser than the pre-treatment value at the end of the observation.

Comparison among various groups revealed no significant difference at any time interval. However, group H animals showed non-significantly higher plasma glucose levels at all the intervals including the baseline than other groups. Group G animals showed non-significantly higher (P>0.05) levels of plasma glucose at 60 to 180 min than group I.

Plasma urea nitrogen

Mean ±SE values of plasma urea nitrogen in different groups are presented in Figure 4.64 and Table 4.74.

Group G showed a non-significant (P > 0.05) increase in plasma urea nitrogen but by the end of observation the values decreased and were recorded to be lesser than the pre-treatment levels. Group H animals showed a significant (P < 0.05) decrease in plasma urea nitrogen at 30 minutes post-injection. The values then increased non-significantly (P > 0.05) upto 120 minutes and again decreased significantly (P < 0.05) at 180 minutes post-injection. The values were lower than the pre-treatment value at the end of the observation period. Group I, showed no significant (P > 0.05) change in plasma urea nitrogen levels throughout the period of observation. The values fluctuated near the base line during different intervals of post-injection period.

Comparison among different groups revealed no significant (P > 0.05) change throughout the period of observation.

Plasma creatinine

Mean ±SE values of plasma creatinine in different groups are presented in Figure 4.65 and Table 4.75.

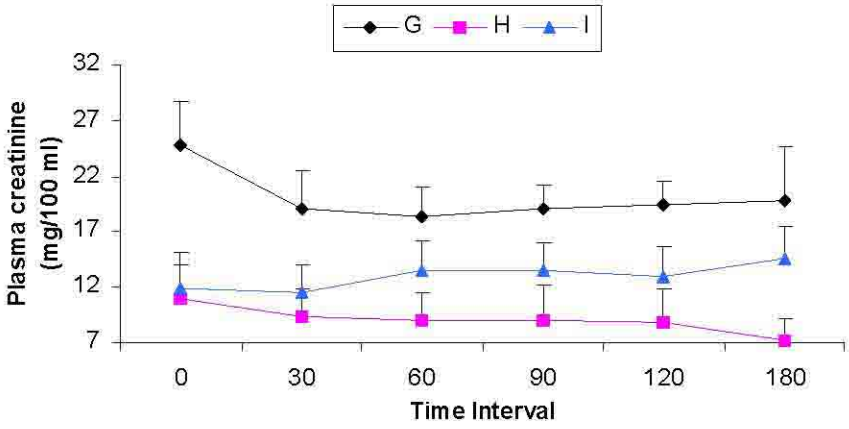


Fig 4.65: Plasma creatinine (mg/100 ml) in the animals of different groups

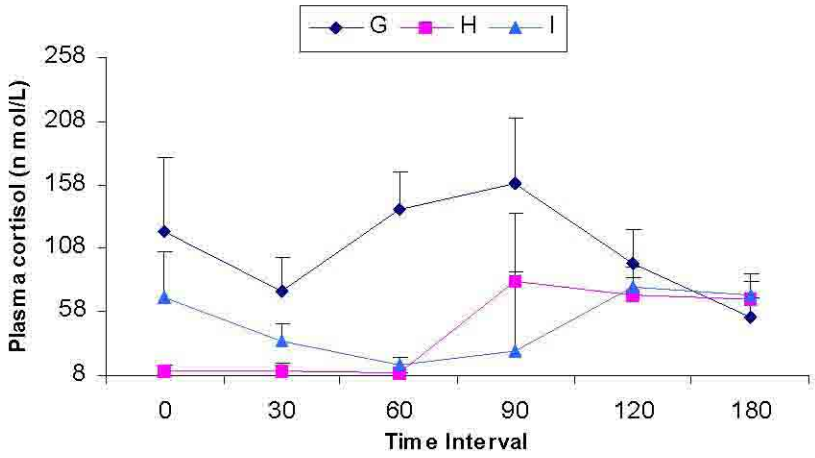


Fig 4.66 : Plasma cortisol (n mol/L) in the animals of different groups

In the animals of group G, there was a decrease in plasma creatinine level throughout the observation period. The decrease was significant at 30 min ($P<0.01$), 60 min ($P<0.05$) and 120 min ($P<0.05$). The values at the end of the observation remained lesser than the pre-treatment value. In the animals of group H, there was a non-significant ($P>0.05$) decrease in plasma creatinine values throughout the period of observation and even at the end of the observation period the values remained lesser than the base line. In the animals of group H, however, a non-significant ($P>0.05$) increase in plasma creatinine was recorded from 60 min till the end of observation period. The values remained non-signficantly ($P>0.05$) higher than the base value even at the end of observation period.

Comparison among various groups revealed that group G animals showed a significantly higher ($P<0.05$) values of plasma creatinine at 90 min, 120 min and at zero hour than group H. Group I remained non-significantly different from the other groups.

Plasma cortisol

Mean ±SE values of plasma cortisol in different groups are presented in Figure 4.66 and Table 4.76.

In the animals of group G, plasma cortisol level decreased non-significantly ($P>0.05$) at 30 minutes post-injection and increased thereafter at 60 and 90 min. The increase was significant at 90 min ($P<0.01$). The cortisol level again declined from 120 min and at the end of observation it remained lesser than the pre-treatment value. In the animals of group H, the cortisol level increased from 90 to 180 min. The increase was signfiicant ($P<0.05$) at 120 min. The value remained elevated above the pre-treatment level. In the animals of group I, plasma cortisol level decreased non-significantly ($P>0.05$) at 30, 60 and 90 min but a non-significant increase ($P>0.05$) was recorded at 120 min. The values returned to the pre-treatment level by 180 min.

Plasma GGT

Mean ±SE values of plasma GGT in different groups are presented in Figure 4.67 and Table 4.77.

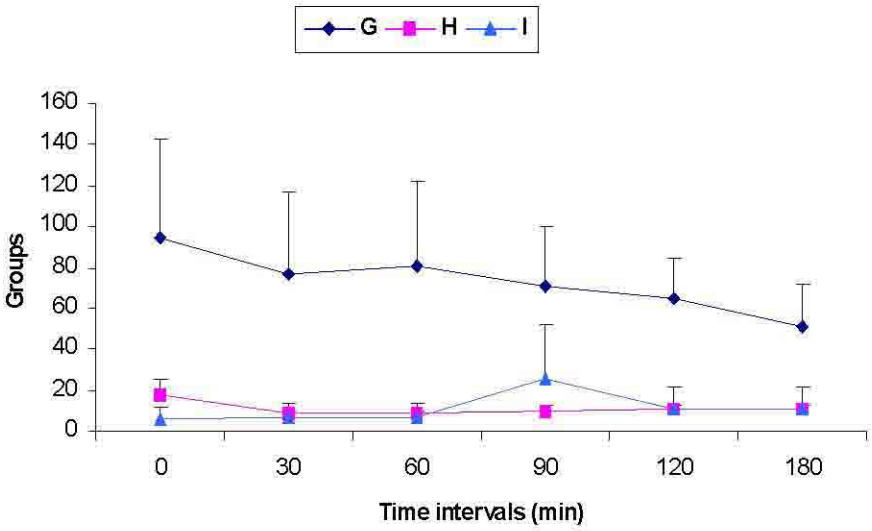
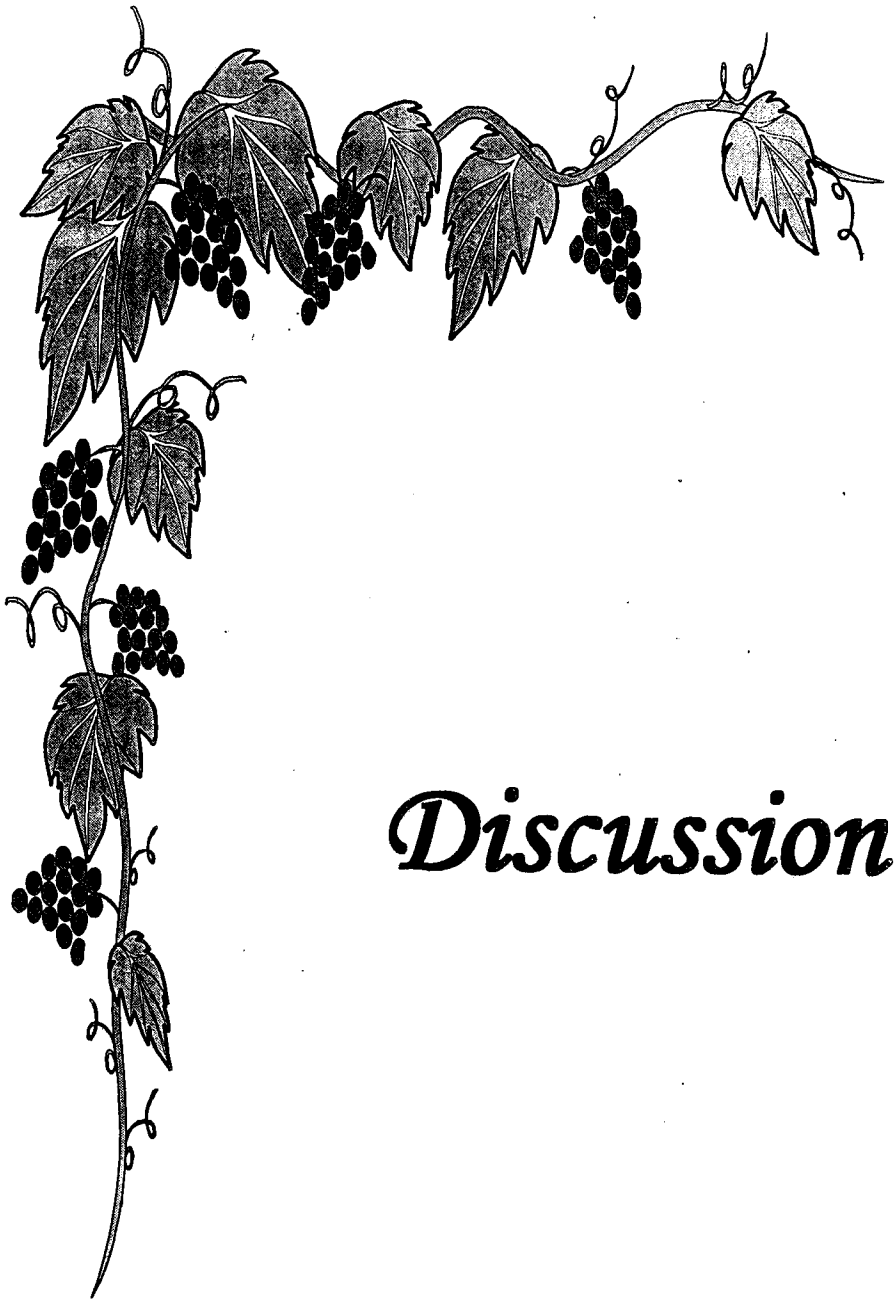


Fig 4.67 : GGT (U/L) in the animals of different groups

GGT values also decreased in the animals of all the clinical groups except group I where after a transient non-significant ($P > 0.05$) decrease of 30-60 min a significant ($P < 0.05$) increase occurred from 120 min - 180 min post-injection.

Comparison among the animals of different groups revealed that group I animals had significantly ($P < 0.05$) higher GGT values as compared to group G at all the intervals including the baseline value.



Discussion

DISCUSSION

Phase I

EXPERIMENTAL STUDY

Group E had early onset as compared to all the groups and more significantly earlier than group B and C. The onset of analgesia was significantly ($P<0.05$) earlier in groups A, D, E and F as compared to group B and group C. In the animals of group C, a significantly ($P<0.05$) longer time was taken for the onset of analgesia as compared to all the groups.

The onset of analgesia in the ketamine combination groups were found to be earlier than the respective groups where the drugs were used alone. This suggested a synergistic/additive action of ketamine with other drugs. The early onset of analgesia with ketamine in comparison to the drugs used alone might be due to its local anaesthetic action at the spinal cord level (White *et al.*, 1982; Crisp *et al.*, 1991) local anaesthetic action has been considered as a reason for early onset after intrathecal and intravenous regional injection of ketamine (Bion, 1984). Buprenorphine took longest time to bring about the onset of anagesia. This might have been due to the analgesia action of it on again receptors due to the (Sporer, 2004). Onset of analgesia was slower with group CPs compared to all the groups. The onset of analgesia depends upon the lipid solubiity of the drug. A slow onset of opioids was also reported by (Hansraj *et al.*, 2000) and Cousin and Mather (1984). The delayed onset in group B (xylazine alone) in comparison to ketamine or local anaesthetics has been reported in different animal species (LeBlanc *et al.*, 1988; Fikes *et al.*, 1989; Aithal *et al.*, 1997a,b).

This has been attributed to the fact that the analgesia induced by xylazine is spinal cord mediated whereas it is spinal nerve mediated in local anaesthetics (LeBlanc *et al.,* 1988). Early onset of analgesia in group E, (xylazine + ketamine), is in accordance with the similar findings of (Kinjavdekar *et al.,* 2000; Singh, 1999; Aithal *et al.,* 1997). Bupivacaine in animals of group A produced mild to moderate analgesia, which extended to tail, perineum, inguinal region, abdomen, flank and thorax. The local anaesthetics after spinal injection, block the conduction of impulses at various sites. The suggested sites include the nerves distal to the dural sheaths after leaving the intervertebral foramina, the dura covered nerve roots and dorsal root ganglion within the spinal canal and the spinal cord itself (Skarda *et al.,* 1981). Lignocaine has been reported to inhibit synaptic transmission in the spinal cord through modifications of pre and post-synaptic receptors (Butterworth and Strichartz, 1990). In the present study, one or a combination of these mechanisms might have played a role in blocking impulse conduction in the nerves or at the spinal cord level. Bupivacaine is approximately 4 times as potent as lignocaine and provides longer duration of action, at least twice as that of lignocaine. The delayed onset and prolonged duration of analgesia with bupivacaine is also recorded in a study by McEnvoy (1995). The analgesia produced by bupivacaine was only mild to moderate which could be attributed to lower dose rate of bupivacaine used in the present study. The lower degree of analgesia of anterior flank, thorax and abdomen, might be due to the decreased concentrations of anaesthetic solution away from the site of injection. Similar observations were recorded by Skarda *et al.* (1981) and Skarda and Muir (1983a) in horses.

Xylazine in the animals of group B produced a mild to moderate analgesia of tail, perineum, inguinal region, hind limbs, digits and abdomen.

Xylazine an α_2-agonist has been reported to produce good spinal analgesia in human beings and animals (Livingston *et al.,* 1992; Singh *et al.,* 2004; Singh *et al.,* 2005). Analgesia was probably due to stimulation of α_2-adrenoceptor at the spinal cord level (Aziz and Martin, 1978), through inhibition of release of neurotransmitters (Kuraishi

et al., 1985) and decreasing neuronal activity (Virtanen *et al.*, 1985; LeBlanc *et al.*, 1988; Kinjavdekar *et al.*, 1999). The primary site of antinociceptive action of α_2-agonists after intrathecal administration is at α_2-adrenergic receptors in the substantia gelatinosa of the dorsal horn of spinal cord (Unnerstall *et al.*, 1984; Yaksh, 1985) where they inhibit the release of substance P, which is involved in pain sensation (Grubb *et al.*, 1993). Xylazine produced analgesia of prolonged duration. It was probably due to the fact that α_2-adrenoceptor agonists provide a local depot of the drug and are released slowly over a longer period of time (Nolan *et al.*, 1987).

Depth and extent of analgesia in xylazine group B supported the observation of Eisenach *et al.*, 1987; LeBlanc *et al.*, 1988; Fikes *et al.*, 1989; Caron and LeBlanc, 1989; Jean *et al.*, 1990; Rehage *et al.*, 1994; Aithal *et al.*, 1997a; and Singh *et al.*, 2004; Singh *et al.*, 2005.

The depth of analgesia at flank and thorax was lesser as compared to the tail and perineum in both group A and B, which could be attributed to difference in concentration of the anaesthetic solution in the CSF. Uptake of anaesthetics was found to be greatest where the concentration of solution was greatest (i.e. at the site of injection) and decreased above and below the site of highest concentration (Greene, 1983). It may, therefore, be inferred that higher degree of analgesia obtained at perineum, inguinal, tail and thigh than abdomen, thorax and flank may probably be due to the highest concentration of anaesthetic at the site of injection i.e. at lumbosacral space from where the spinal nerves, which innervates these regions orginates. Mild relaxation of tail and anal spincter was seen in xylazine group. Relaxation of anal sphincter along with relaxation of constrictor vulvae muscle, rectum, bladder and genitalia has also been reported after epidural administration of xylazine in cattle (Skarda and Muir, 1992) and goats (Aithal *et al.*, 1997a). This may be attributed to blockade of autonomic and motor nerves. (Lee *et al.*, 2004).

Group C (Buprenorphine) animals, showed only mild analgesia of perineum, inguinal and tail region which lasted from 90-105 min duration. Buprenorphine is a partial

mu opioid and a weak kappa agonist. It has high affinity for the μ receptors, with slow dissociation resulting in a long duration of action. At higher doses, its agonist effects plateu and it begins to behave more like an antagonist, limiting the maximal analgesic effect and respiratory depression. This is called ceiling effect (Sporer, 2004). Buprenophine is not appropriate for relief of severe pain, because it is a partial agonist and does not have the full analgesic or intrinsic effects of a pure agonist (Benson and Tranquilli, 1992; Hansen and Hendrix, 2000). This could explain the absence of deep analgesia in animals of group C. Group D animals, (ketamine + bupivacaine), showed complete analgesia of tail, perineum inguinal region and moderate analgesia of thorax. The duration of action or analgesia was also longer (i.e. upto 180 minutes and longer) at all the regions as compared to corresponding regions in animals of group A. A variety of mechanisms have been proposed to underline synergistic antinociceptive interactions between drugs in the spinal cord (Wilcox *et al.*, 1987). The pharmacokinetic and pharmacodyanamic properties of a drug may be altered by co-administration of a second drug. Action of the drugs at separate anatomic sites may lead to show distinct synergistic effects of the drugs (Roerig and Fujimoto, 1989). Ketamine is a potent non-competitive antagonist of NMDA receptors, which are involved in the transmission and modulation of nociceptive information at the spinal cord level (Yamamura *et al.*, 1990). Ketamine and bupivacaine, by acting at two different sites might have had synergistic additive action in the present study and caused a quick onset, higher depth of analgesia and prolonged duration of analgesia. It has been shown that the local analgesic action of ketamine is mediated by various pathways especially opiate receptors (Smith *et al.*, 1985) and lamina specific inhibition of dorsal horn unit activity (Kitahata *et al.*, 1973). Small dorsal root ganglion neurones represent the somata of myelinated and unmyelinated C-fibre-type neurones (Harper and Lawson, 1985) and possibly participate in processing and transducing sensory information. These neurones are involved in peripheral nerve block when exposed to high concentrations of local anaesthetics during spinal and epidural anaesthesia (Butterworth and Strichartz, 1990). Local anaesthetics are reported to block the sodium ion permeability and thus could prevent, propagation of

an action potential or impulse transmission in nerve fibre (Kolwas, 1979). Local anaesthetics were found to block voltage gated K^+ function to stimulate the release of transmitters (Butterworth and Strichartz, 1990).

There may be several mechanisms of action by which ketamine can induce regional analgesia. Higher doses of ketamine may block Na^+ channels (Dowdy and Kaya, 1968) and thus produce regional analgesia in a manner similar to local anaesthetics. It also interacts with opioid, monoaminergic and muscarinic receptors and voltage sensitive Ca^{2+} channels (Segura *et al.*, 1998).

In the animals of group E, a moderate analgesia of thorax and abdomen and a complete analgesia of the rest of the regions for longer duration was recorded. Increased depth and extent of analgesia in group E animals as compared to group B was recorded.

Duration of analgesia was comparable among different groups. However, the combination of ketamine with Bupivacaine (D) and xylazine (E) produced analgesia of all the regions which was non-significantly ($F > 0.05$) longer as compared to that in group A and B, respectively and significantly, ($P < 0.05$) longer than group C. Ketamine in combination with buprenorphine (F), however, produced a longer duration of analgesia than buprenorphine alone (group C) but its duration was lesser than group D and E. The duration of analgesia was longest in group D of experimental animals. On the contrary, among all the groups group C animals recorded a minimum duration of analgesia as compared to all the groups.

Duration of analgesia was comparable among different groups. The combination of ketamine with bupivacaine or xylazine produced analgesia of longer duration as compared to all other groups. However, combination of bupivacaine with ketamine did not effect the duration that was produced by bupivacaine alone. Though, the combination produced deeper analgesia suggesting synergistic interaction. Inability of ketamine to prolong the duration of analgesia produced by bupivacaine could be attributed to very short duration of action of ketamine as compared to bupivacaine. The findings of the

study are in accordance with the observation of earlier workers (Singh *et al.*, 2004; Singh *et al.*, 2005). Similarly, the combination of ketamine with buprenorphine (group F) was having longer duration of analgesia as compared to buprenorphine alone but the difference was not significant.

Buprenorphine is a partial mu opioid and a weak kappa agonist. It has a high affinity for the receptors, with slow dissociation resulting in a long duration of action. At higher doses, its agonist effects plateu and it begins to behave more like an antagonist, limiting the maximal analgesic effects. This is called ceiling effect (Sporer, 2004). Further, ketamine has also been reported to act as agonist of opioid receptor and thus produce spinal analgesia through a mechanism similar to opioids (Yaksh, 1981). This also might have caused a competitive binding of buprenorphine and ketamine for the receptors. This might have been responsible for less difference between group C and F.

The coadministration of ketamine with xylazine resulted in a longer duration of analgesia as compared to all the groups which could be due to longer duration of xylazine and interaction between the two drugs. More synergistic interaction between these two drugs might be due to their ability to produce spinal analgesia through different sites of action. Similar findings have been reported after administration of ketamine with xylazine in buffalo calves (Amarpal *et al.*, 1997; Singh, 1999; Singh *et al.*, 2004, 2005), in goats (Aithal *et al.*, 1996; Kinjavdekar, 1998). The prolonged duration of analgesia suggested synergistic interaction between ketamine and α_2-agonist. Ketamine and xylazine, being acting at different sites, showed synergism additive effect thereby inducing more profound and prolonged analgesia in different animal species (Aithal *et al.*, 1997; Amarpal *et al.*, 1997; Kinjavdekar *et al.*, 1999).

Animals of group F, showed mild analgesia of thorax, abdomen and flank and moderate analgesia of perineum, inguinal region, tail, hind limbs and digits. Complete analgesia of any region was not reached by this group. The animals of combination group (F) had a higher depth and extent and longer duration of analgesia than

buprenorphine alone in group C 45-180 min. This might have been due to the synergistic or additive interaction between ketamine and buprenorphine. Animal studies have shown that NMDA receptor antagonists inhibit central sensitization (Woolf and Thompson, 1991) and prevent acute tolerance to opioids (Kissin *et al.*, 2000; Miyamoto *et al.*, 2000) or opioid induced hyperalgesia (Celerier *et al.*, 2000). Analgesia is enhanced, spinal cord hyperexcitability is more profoundly attenuated, respiratory depression is reduced, and opioid induced sedation is not further increased when ketamine was added to opioid (Martin *et al.*, 2003).

Xylazine alone (group B) or xylazine in combination with ketamine (group E) produced extreme degree of sedation as comapred to other groups. Salivation was also noticed in most of the animals. This indicates that the drug after absorption from the subarachnoid space was distributed to the brain (Skarda *et al.*, 1989). The sedative effect of α_2-agonists is associated with the activation of central α_2-adrenoceptors, which causes decrease in the release and turnover of norepinephrine in the CNS. The sedative effects of epidural administration of xylazine are due to the systemic effect of the drug after absorption through longitudinal epidural veins and possibly the lymphatics (Lee and Chunsik 2001).

The onset of sedation in group B animals started about 20 minutes after the drugs administration i.e. much later than the onset of analgesia. This indicates that the analgesic action of the drug is mediated through spinal action rather than central effect. In group E, the animals attained sternal recumbency immediately after the injection of drugs but showed extreme sedation only from 30-60 min. when the animals could not sit without support. Mild sedation persisted thereafter, till the end of observation. The results suggest that the sedation produced in these groups might be due to the manifestation of central effects of α_2-agonist. In the present study, the degree of sedation produced by α_2-agonists in combination with ketamine was greater in comparison to that produced by xylazine alone. However, comparable degree of sedation was reported

following spinal injection of xylazine alone or ketamine and xylazine combination in goats (Aithal *et al.*, 1997a; Vesal *et al.*, 1998), horses (Yamashita *et al.*, 2002) and cattle (Singh, 1999; Yamagishi *et al.*, 2004).

Frequent urination was noticed in most of the animals after administration of α_2-agonist alone and in combination with ketamine. This might be due to inhibition of production and release of ADH, due to paralysis of sympathetic nerves to the sphincter of the bladder could also have been a cause of micturition as reported by Skarda and Muir (1979). In another study, increased blood glucose by α_2-agonists was attributed for increased urine production, which might have acted as an osmotic diuretic (Duke *et al.*, 1994). Increased urinary output following xylazine (Thurmon *et al.*, 1978; Greene *et al.*, 1986; Kinjavdekar *et al.*, 1999; Ozba *et al.*, 2003) has been reported in different species of animals. However, Singh *et al.* (2005) did not record diuresis after epidural administration of xylazine or medetomidine or their combination at sacrococcygeal space in buffaloes.

Animals of group A (bupivacaine alone), remained alert throughout the observation period except for mild sedation between 30 to 60 min and Group D (Ketamine + bupivacaine) animals remained less sedated throughout the period of observation. The finding was coherent with the observations of Kinjavdekar, (1998) with lcoal anaesthetic in goats and lack of sedation has also been reported by Aithal *et al.* (1997a), Kinjavdekar, (1998) following spinal administration of ketamine. In group C (buprenorphine) and group F (ketamine + buprenorphine) animals, only a mild degree of sedation with slight ptosis of eye lids from 5 min onwards to 180 min and 10 to 75 min respectively was observed. The mild sedation was also accompanied with marked euphoria in the animals of group C and F throughout the period of observation. This euphoria was manifested as paddling of limbs, pressing of head against wall and hitting the head continuously to groundwall. Similar finding was reported in cats with i.m buprenorphine (Robertson *et al.*, 2003). Opioid induced sedation was reported not to increase further when combined with ketamine (Martin *et al.*, 2003) this might have explained comparatively lesser duration of

sedation in group F than group C. Amarpal *et al.* (2003) have also recorded an antagonistic interaction between epidural pethidine and ketamine in dogs when this combination was administered epidurally. Further buprenorphine is lipophillic (Dollery, 1991) and its delayed effect is usually related to slow receptor binding which occurs with partial agonists (Nolan and Others, 1987). Less sedation has also been reported by Robertson *et al.* (2003) with buprenorphine in cats.

Animals of group A and D assumed sternal recumbency from 5 to 45 min and 5 to 15 min after injection. Thereafter, in animals of group A, an extreme incoordination of gait persisted up to 90 min and in group D, lateral recumbency was attained from 20 to 45 min post-injection and animals came back and remained in sternal recumbency up to 90 min. Thereafter, an extreme incoordination persisted till the end of observation period in both groups. Local anaesthetics indiscriminately block the sensory, motor and sympathetic fibres (LeBlanc *et al.*, 1988; Fikes *et al.*, 1989; Grubb *et al.*, 1992). The degree of ataxia also varies with the site of injection of drug and dose rate of the drug used. The indiscriminate blockade of sensory and motor fibers was observed following spinal injection of lignocaine. Similar findings were reported by Skarda and Muir (1983a,b), Makady *et al.* (1990), Grubb *et al.* (1992) and DeRossi *et al.* (2003). Extreme incoordination, sternal and lateral recumbency in group D may be due to the additive or possibly synergistic effect of bupivacaine with ketamine at the spinal level.

Group B animals could walk without staggering for 5-10 min with little staggerring at 15 to 20 minutes and extreme incoordination of gait persisted thereafter throughout the period of observation. The ataxia seen in this study might be related to postulated local anaesthetic properties of xylazine (Le Blanc *et al.*, 1988), probably due to structural similarity with lignocaine (Antonaccio *et al.*, 1973). Xylazine has been shown to have a local anaesthetic effect on frog sciatic nerve trunk preparations similar to that of procaine hydrochloride (Aziz and Martin, 1978). Moderate to marked ataxia has also been observed by many authors when spinal injection of xylazine was made in cattle (Grubb *et al.*, 1993; Aminkov and Huberton, 1995; Raidurg *et al.*, 1995; DeRossi *et al.*, 2003).

Butterworth and Strichartz (1993) have further speculated that local anaesthetic action of α_2-agonists on A-δ and C fibers (responsible for pain perception) might also be responsible for producing analgesia after regional injection of α_2-agonists. Further, these drugs produce inhibition of C fibers more potently than A-δ fibres (responsible for motor function and proprioception) (LeBlanc *et al.,* 1988; LeBlanc and Caron, 1990; DeRossi *et al.,* 2003). Group E (xylazine and ketamine) animals attained sternal recumbency as early as 5 minutes and thereafter, attained lateral recumbency from 10 to 60 min post injection followed by attaiment of sternal recumbency again at 75 min and thereafter, from 90-105 min, extreme incoordination of limb was recorded. The animals, could however, walk normally at 180 min post-injection.

Higher scores of motor incoordination in group E (ketamine and xylazine) as compared to group B (xylazine alone) might be due to additive or possibly synergistic effect of xylazine with ketamine at the spinal level, leading to more intense spinal effect. Similar findings were reported by Aithal *et al.* (1997a) De Rossi *et al.* (2003) in goats, Amarpal *et al.* (1997) in cattle after epidural xylazine and ketamine administration Singh (1999) in buffalo calves and Kinjavdekar *et al.,* 1999 in goats. Moderate to severe hind quarter weakness by ketamine in goats and dogs has been shown in a study by Aithal *et al.* (1997a,b). Intrathecally administered ketamine is reported to have local anaesthetic effect both in animals and human beings which produces complete motor blockade (Gebhart, 1994). Although, the mechanism underlying the motor effect is not clearly understood, most investigators suggest that it is similar to a reversible local anaesthetic block (Altura *et al.,* 1980; Tung and Yaksh, 1981). Increased motor incoordination in combination groups with ketamine in the present study might be due to the additive local anaesthetic action of the drug at spinal cord level.

Animals of group C, showed little incoordination from 5 to 90 minutes followed by extreme incoordination from 105 to 130 minutes post-injection where the animals could walk still with extreme incoordination and animals of group F, showed sternal recumbency from 5 to 30 min after subarachnoid injection and from 60 minutes till 130

min. Slight incoordination persisted at 150 minutes. Opiates have been reported to have local anaesthetic properties (Booth, 1984; Hansraj *et al.*, 2002) due to which motor incoordination occurred. Increased extent of motor incoordination in group F, initially might have been due to synergistic/additive effects of ketamine and buprenorphine since ketamine also has local anaesthetic effect, intrathecally (Gebhart, 1994). The animals of group F, returned to early normal gait as compared to the animals of group C. This finding could be well explained probably by the findings of Amarpal *et al.* (2003), who have recorded an antagonistic interaction between epidural pethidine and ketamine in dogs.

Recovery from the effects of different drugs was in the order as group C followed by group F followed by group A and B followed by group E followed by group D.

Early recovery in group A, B and C where the drugs were used alone than groups D, E and F respectively might have been due to the fact that combination of two drugs used in the study might have acted synergistically to produce a longer duration of analgesia and delayed recovery. Similar observations were made by Singh *et al.* (2004, 2005) in buffalo calves, Aithal *et al.* (1997) in goats, Grubb *et al.* (1992) in horses and Kinjavdekar *et al.* (2000) in goats.

In the animals of group A and D, a significant decrease in HR till the end of the observation period was recorded and values remained below the base line till the end of the observation period. HR of group A was significantly less than group D at 45 min post-injection.

Decrease in HR by bupivacaine might be due to paralysis of cardiac sympathetic fibre or a generalised decrease in the sympathetic activity (Lumb and Jones, 1984). Reduction in HR after epidural/spinal administration of bupivacaine has been reported in sheep, (Lebeaux, 1975; Adams *et al.*, 1977), dogs (Luna *et al.*, 2004), goats (Adentunji *et al.*, 2002), and buffalo (Hussan and Kumar, 1988), however, no significant change in HR was noticed with epidural bupivacaine in horses (DeRossi *et al.*, 2004). In the animals of group B, significant decrease in HR was recorded till later stages of observation

whereas in the animals of group E an early significant decrease of HR was recorded and the values started to improve after 75 min post-injection but remained lesser than the base line value.

Several mechanisms contribute to the α_2-agonist induced bradycardia which include decreased sympathetic outflow from the CNS, inhibtion 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 acetyl choline from parasympathetic nerves in heart (MacDonald and Virtanen, 1992). Similar findings were reported after epidural administration of xylazine in cattle and horses (Jean *et al.*, 1990; Skarda *et al.*, 1990; Rehage *et al.*, 1994; Prado *et al.*, 1999; Lewis *et al.*, 1999; Ozba *et al.*, 2003) sheep (Waterman *et al.*, 1987), mares (Skarda and Muir, 1996), horses (Yamashita *et al.*, 2002; Picavet *et al.*, 2004) and goats (Aithal *et al.*, 1997a; DeRossi *et al.*, 2003). HR in group B did not differ significantly from group E which coincides with the findings of DeRossi *et al.* (2003), that addition of ketamine didn't bring about any increase in the HR. LeBlanc and Eberhart (1990) however, found no measurable change in cardiopulmonary parameters after caudal epidural xylazine in horses and for tortoise (Dennis and Heard, 2002).

In the animals of group C and F no appreciable change in heart rate was observed after spinal administration of buprenorphine alone or in combination with ketamine. Buprenorphine being more lipophillic gets less absorbed into vascular/lymphatic circulation from subarachnoid space (Negus *et al.*, 2002). Buprenorphine i.v. or i.m did not produce alterations in the cardiovascular parameters that could provide any significant clinical effects in dogs (Souza *et al.*, 2004). Buprenorphine was shown to have a ceiling effect for cardio pulmonary depression and high margin of safety even when taken by the i.v. route (Umbricht *et al.*, 2004).

A non-significant increase in respiration rate was recorded throughout the observation period in group A. In the animals of groups B and C, respiration after an

initial rise (P>0.05) decreased (P>0.05) and remained less than the base value till the end of observation period. Group D and E also showed a decrease in the respiration rate but the animals of group F showed an initial decrease (P>0.05) followed by increasing trend till 130 minutes. The non-significant increase might have been due to the handling and restaining of animals and delayed onset of analgesia in group A animals. However, no significant change in respiratory rate was recorded in horses with bupivacaine (DeRossi *et al.*, 2004), rats (Freise *et al.*, 2005) and dogs (Adentuji *et al.*, 2001).

In the animals of group B, there was an initial non-significant increase in respiratory rate. After 45 min the respiratory rate showed a gradual decrease and the values reached below the base line towards the end of observation period. The initial rise in respiratory rate in animals of group B could be due to handling and restraining of the animals. The reduction in RR during later stages could be attributed to CNS effects of xylazine. Significant reduction in RR has been reported after epidural/spinal administration of xylazine in cattle (Jean *et al.*, 1990; Skarda and Muir, 1992; Singh, 1999; Singh, 2001; Picavet *et al.*, 2004), goats (Aithal *et al.*, 1997a; Kinjavdekar *et al.*, 1999), sheep (Waterman *et al.*, 1987), medetomidine in dogs (Vesal *et al.*, 1996), cat (Duke *et al.*, 1994) and romifidine in goats (Amarpal *et al.*, 2001). The respiratory depression in buffaloes could be due to depression of respiratory centre through stimulation of supraspinal adrenoceptors following systemic absorption of the drugs as suggested by Prado *et al.* (1990) and Lin *et al.* (1998).

Similar to group B, animals of group C also showed a non-significant increase in RR followed by a gradual decrease after 30 min of observation period. Epidural or spinal opioids may produce respiratory depression but doesn't produce any changes in cardiovascular or CNS functions (Cousins and Mather, 1984). This is due to sedative ability of opioids through reduction in release of excitatory neurotransmitters from C fibres as well as decrease the excitability of dorsal horn neurons (Livingston *et al.*, 1992).

The animals of group D showed a significant decrease in RR at intervals upto 75 min. Thereafter, the values fluctuated near the base line. However, in group E the

decrease in respiratory rate was only non-significant. The results suggested that ketamine in group D failed to counteract the respiratory depressant action of bupivacaine. It could be due to the fact that bupivacaine induced the decrease in RR through the blockade of nerves innervating the muscles of respiration as suggested by (Blass and Shires, 1986). On the other hand, in group E the respiratory depression produced by xylazine could be well balanced by predominant stimulatory effect of ketamine which balanced the CNS depresant effect α-2-agonists (Kinjavdekar *et al.*, 1999; Singh, 1999; Singh *et al.*, 2005). Contrary to the results of the present study a decrease in RR by xylazine-ketamine has been reported by (Kinjavdekar *et al.*, 1999; Pathak *et al.*, 2003; Reddy *et al.*, 2003). The variation in the results of these studies could be due to difference in species, dose or the site and route of administration of xylazine and ketamine. The results of the study further suggests that RR depression by bupivacaine could be mainly due to the local action at the muscles of respiration. However, xylazine induced RR depression could be due to its cortical effect.

In animals of group F, RR fluctuated near the base line or remained elevated just above the base line. The elevated RR in animals of group F might have been mainly due to the stimulatory effect of ketamine on the respiratory centres (Wright, 1982; Kinjavdekar, 1998). Buprenorphine has been reported to have no effect on RR (Cousin and Mathur, 1984) and rather have a "ceiling effect" on cardiopulmonary depression (Sporer, 2004; Umbricht *et al.*, 2004).

The rectal temperature decreased in all the groups except group C where it did not show any change as compared to base line.

In group D and E, RT reduced significantly for longer duration than the groups A and B respectively. Group E animals showed signfiicantly lower RT than group D. Group F animals, however, showed no significant change throughout the observation period. The decrease in RT might be due to generalized sedation, decrease in metabolic rate, muscle relaxation and CNS depression produced by sedative and analgesic agents.

Decrease in RT by bupivacaine in this study is in accordance with findings of Skarda and Muir (1982a), Mishra *et al.* (1993); Singh *et al.*, (2005) Ozaydin and Kilic (2003). These workers opined that hypothermia after epidural administration of local anaesthetics may be due to heat loss from relaxation of thoracic and abdominal skeletal muscles.

α_2-agonists have been reported to induce prolonged depression of thermoregulation (Ponder and Clarke, 1980) and depress hypothalamic nor-adrenergic α_2-receptors to cause hypothermia (MacDonald *et al.*, 1988). Reduced BMR and muscle activity and depression of thermoregulation additively result in hypothermia (Ponder and Clarke, 1980). Decrease in RT by α_2-agonists is not only related to central α_2-adrenergic mechanisms (Livingston *et al.*, 1984) but probably also related to other depressing CNS mechanisms, because hypothermia could not be prevented by prior administration of Yohimbine (Virtanen, 1986).

Hypothermia observed after the administration of xylazine or bupivacaine in combination with ketamine might also be attributed to the same mechanisms. Aithal *et al.* (1997a) however, did not find any significant change in RT after epidural ketamine administration. Higher degree of depression of RT in group E than group D might be due to the systemic sympatholytic α_2-adrenergic effects of xylazine after absorption into the blood stream. Longer duration of hypothermia in group D as compared to group E could be attributable to longer duration of action of bupivacaine as compared to xylazine (Singh, 2005). The rectal temperature with xylazine and ketamine combination has been shown to decrease by many authors (Aithal *et al.*, 1997a; Kinjavdekar, 1998; Singh, 1999; Jaing-Hwangsoo *et al.*, 2002; Singh *et al.*, 2005) Medetomidine and ketamine in cats (Young and Jones, 1990), minipigs (Vainio *et al.*, 1992), dogs (Reddy *et al.*, 2003), mice (Arras *et al.*, 2001) with xylazine alone (Adentunji *et al.*, 2002b).

The rectal temperature in animals of group C, and group F remained non-significantly elevated as compared to the base line. This correlated with the amount of analgesia and sedation which were also less with these groups. It might have been due

to the less sympatholytic activity of buprenorphine due to more tightly bounded to receptors and hyperalgesia associated with opioids which is neutralised to some extent by ketamine.

Reduction in Hb and PCV was recorded in all the groups except in group F, where the values of PCV and Hb did not change much. The PCV and Hb values returned to the base line in most of the groups towards the end of the observation period. The changes in PCV and Hb were however, non-significant in all the groups.

Pooling of the circulating blood cells in the spleen or other reservoirs secondary to decreased sympathetic activity may explain the decrease in Hb and PCV recorded in this study. Decrease in haematological parameter has been recorded earlier with tranquillizers in dog (Soliman *et al.*, 1965), lumbosacral spinal analgesia with α_2-agonist, lignocaine, ketamine and their combinations in goats (Kinjavdekar, 1998; Pathak, 1999; Singh,1999; Singh, 2001) and I.M. injection of xylazine and ketamine in sheep (Kumar *et al.*, 1974), Peshin and Kumar (1983).

Experimentally, the decrease in Hb and PCV has been reversed by adrenaline injection or by painful stimuli. Similarly, decrease in haematological parameters were not observed in splenectomized sheep (Hawkey, 1985). The retention of red cells in spleen has been suggested to cause a fall in these parameters which was confirmed by Collete and Meriwether (1965) and Monzaly *et al.* (1972) in dogs and goats after chlorpromazine administration. Similar to the findings of present study decrease in Hb and PCV were recroded after epidural administration of xylazine in cattle (Jean *et al.*, 1990; Picavet *et al.*, 2004), horse (Skarda and Muir, 1996a,b,), in neuroleptanalgesia with xylazine and pentazocine in bovine (Doiphode and Aher, 2003), dogs (Kelawala *et al.*, 1996; Reddy *et al.*, 2003). The decrease in PCV and Hb during the period of anaesthesia or sedation may also be due to shifting of fluid from extravascular compartment to intravascular compartment (Wagner *et al.*, 1991) in order to maintain normal cardiac output Minor changes in Hb and PCV in groups C and F could be

attributed to the lesser sedation recorded in buprenorphine group due to its lesser absorption into circualtion vascular/lymphatic from subarachnoid space because of its high lipophillic nature.

TLC decreased in the animals of all the groups except group A and C where a non-significant increase in TLC was observed and group D and F where also an increase in TLC was observed. This also might have been due to the reason cited by Sporer, (2004); Benson and Tranquilli, (1992) and Henson and Hendrix (2000). A significant decrease in TLC with haloperidol on barbiturate anaesthesia in dogs was reported by Soliman *et al.* (1965); Reddy *et al.* (2003).

Less systemic absorption, prolonged activity, and less sympatholytic activities of bupivacaine is reflected in this regard. TLC, PCV and Hb has been shown to decrease with epidural block with lignocaine in buffaloes (Sharda *et al.,* 2001), significantly lower values of TLC with epidural preemptive bupivacaine as compared to post-traumatic bupivacaine in goats (Pathak *et al.,* 2002). However, marked leucocytosis was seen with epidural saline in goats (Pathak, 1999), sedation after xylazine administration in goats (Kumar and Thurmon, 1979), epidural block with xylazine and ketamine in buffaloes (Singh, 1999; Singh, 2001).

A rise in neutrophill count and a decrease in lymphocyte count was recorded in all the groups in the present study. This is possibly attributed to the adrenocortical stimulation and subsequent effect of glucocorticoids (Soliman *et al.,* 1965) on circulating neutrophils. The subcortical pathways which are responsible for the regulation of ACTH secretion are thought to be affected by anaesthetic agents. Similar observations were made after administration of chlorpromazine in dogs (Soliman *et al.,* 1965) and xylazine and local anaesthetics in combination with ketamine in goats (Monzaly *et al.,* 1972; Kinjavdekar, 1998 and Pathak, 1999; Singh *et al.,* 2001), Buffalo calves (Singh, 1999), xylazine in dog (Kelawala *et al.,* 1996), ketamine and medetomidine (Hugar, 1993) and ketamine and detomidine (Dilip, 1993) in goats.

Group B and group F showed higher neutrophillia than other groups in the present study and group A and group D i.e. bupivacaine alone /or in combination with ketamine, have more or less the same effect on haematological parameters. This indicates that combination of bupivacaine with ketamine do not have adverse effect on haemopoitic system and circulating haematological parameters.

Increase in plasma glucose levels after administration of bupivacaine (group A), xylazine alone (group B) or in combination with ketamine (group E) and ketamine-buprenorphine (group F) was recorded. Values returned to base line in group A, E and F but remained elevated in group B even at the end of the observation period. Group C (Buprenorphine) showed no significant variation. Group D (Bupivacaine + ketamine) showed a non-signficant decrease in plasma glucose throughout the observation period.

α_2 adrenoceptor stimulation induces hyperglycaemic responses through a peripheral effect that involves post-synaptic alpha-$_2$ adrenoceptors in the pancreatic beta-cell which are linked to the inhibition of insulin release. (Angel and Langer, 1988) and it is also attributed to an increased glucose production in the liver (Brockman, 1981). However, Mirakhur *et al.* (1984) opined that hyperglycaemia may be due to rise in adrenocortical hormones during stress. There have been many investigations into the hyperglycaemic effects of xylazine (Eichner *et al.*, 1979; Hsu and Hummel, 1981; Brikas *et al.*, 1987; Kijavdekar, 1998; Tiwari *et al.*, 1999; Sharma *et al.*, 1994), medetomidine (Cullen, 1996), medetomidine and ketamine (Singh *et al.*, 2002) spinal romifidine in goats (Amarpal *et al.*, 2001). Glucose concentration in another study has shown a dose dependent increase with epidural xylazine in goats (Sao *et al.*, 2003). Similarly, when medetomidine was compared with xylazine in beagle dogs, the hyperglycaemic effect of medetomidine in contrast with xylazine, was not dose-dependent at the tested doses. The results suggested that the effect of medetomidine an glucose metabolism may not be due only to alpha 2-adrenoceptor-mediated actions (Ambrisko and Hikasa, 2002).

Increase in plasma glucose with bupivacaine is in accordance with the findings of (Hussain and Kumar, 1988 and Krishna *et al.*, 2001) where both plain bupivacaine

and glucose added hyperbaric bupivacaine increased the plasma glucose on epidural administration in buffalo calves. The reason attributed to it was the release of glucocorticoids resulting in hyperglycaemia (Braz-Dent, 1998).

However, no significant effect on plasma glucose after caudal epidural bupivacaine was observed in children (Scull *et al.*, 1998; Schricker *et al.*, 2000; Cucchiaro *et al.*, 2004) and buffaloes (Mishra *et al.*, 1993). Group C and D showed a non-significant variation which reflects less stressfull effect of these drug/comb ination. There was no significant effect on glucose concentrationin spite of the rise in plasma cortisol was recorded in groups C and D upto 24 hrs and 180 min interval respectively. This indicated that release of glucocorticoids as reasoned by Mirakhur *et al.* (1984) and Ravikrishna *et al.* (2001), is not the sole reason for rise in plasma glucose levels but may be conjugated with other factors responsible. Lesser hyperglycaemia recorded in the present study has also been reported by Singh *et al.* (2002) on epidural administration of buprenorphine.

Plasma urea nitrogen values, decreased significantly in group A and C at 120 min and 30-180 min respectively, and didn't return to base line till the end of the observation period. Extradural block with bupivacaine after abdominal surgery significantly reduced the excretion of urea nitrogen-through kidneys (i.e. reduced post-operative protein breakdown) in human beings (Carli *et al.*, 1991).

Similarly, in group D and F a non-significant decrease was recorded in BUN whereas a significant increase in group B ($P<0.05$) and group E (P,0.05) was recorded. The increase in BUN in groups B and E might be attributed to temporary inhibitory effect of drugs on renal blood flow, which in turn might have caused a rise in urea nitrogen. However, it is difficult to ascribe this to possible renal damage, because all the reported values were within normal limits. Increased hepatic urea production from amino-acids and degradation could account for the observed increase in serum urea nitrogen values (Eichner *et al.*, 1979). Similar findings were reported after administration of xylazine (Eichner *et al.*, 1979), epidural administration of xylazine and medetomidine

alone and in combination with ketamine/lignocaine in goats (Kinjavdekar, 1998), xylazine alone or in combiantion with ketamine/lignocaine in buffaloes (Singh, 1999). Decrease in plasma urea nitrogen values in group A and C is in accordance with the findings of (Singh, 2001; Krishna *et al.,* 2001). Group C and F had only little change in BUN. Which could be due to minimal action of buprenorphine or ketamine on renal blood flow and kidney excretary function.

A significant ($P<0.05$) increase in plasma creatinine was recorded in group A animals at 90 min ($P<0.01$) and 180 min ($P<0.05$) . However, the values returned to base line at 24 hrs. In group B a significant decrease at 60 min was followed by a non-significant increase and the values returned to normal. In the animals of group C and F, the values fluctuated near the base line throughout the observation period.

Group D and group E animal showed a significant decrease in plasma creatinine and the values returned to base line in group D whereas in group E values remained lower than base line even at the end of observation period.

The increase in creatinine is attributed to the temporary inhibitory effect of drugs on the renal blood flow which in turn might have caused a rise in serum creatinine value. Increase in creatinine with epidural spinal local anaesthetics, xylazine and ketamine are also reported in goats (Kinjavdekar, 1998) and buffalo calves (Singh *et al.,* 2005). However, no significant changes in serum creatinine was observed with epidural bupivacaine in buffalo calves (Krishna *et al.,* 2001).

The significant decrease in group B, D and E might be due to the blood dilution as a result of fluid shift by increased temporary migration of interstitial fluid to the vascular system. The concurrent decrease in serum electrolytes like calcium chloride,pottassium and sodium, also supported the hypothesis of intercompartmental shift of fluids. The changes in creatinine were corrected earlier in group B and D than group E. This suggested a safety of xylazine, bupivacaine and ketamine drug/drugs on renal functions. Serum creatinine showed a dose depended increase with xylazine in goats (Sao *et al.,*

2003; Kinjavdekar *et al.*, 2000), xylazine-ketamine in buffaloes (Singh *et al.*, 1985). Groups C and F has least effect on plasma creatinine levels which suggested a least deleterious effect of buprenorphine and its combination with ketamine on kidneys by these drug(s).

There was a rise in plasma cortisol level in all the treatment groups. Group A and B showed the rise from 30 and 60 min, respectively. The rise in cortisol continued up to 90 min after which the values decreased and returned to below the base line. Groups C and D showed a steady rise in plasma cortisol till 180 min of observation period, but values returned to less than normal in group D and elevated in group C at 24 hrs than base line values. Animals of groups E and F showed a non-significant decrease in cortisol from 30-90 min followed by increase throughout the observation period. Group C and D had significantly higher cortisol levels than group B, E and F and group F had higher value than group B. Increased cortisol level recorded after epidural injection of drug(s) might be attributed to the stimulation of Hypothalamus Pituitary Adrenal (HPA) axis by restraining, and handling of animals for spinal injection and recording of parameters. Restraining, handling and even isolation has been reported to cause hypercortisolaemia in lambs (Minto and Blecha, 1990), ewes (Niezoda *et al.*, 1987) and rats (Pitman *et al.*, 1995). Cortisol concentrations might also be increased due to direct effect of stress induced by epidural analgesia. Various other techniques have also been reported to induce substantial stress response typified by increased levels of circulating cortisol. Induction with xylazine-ketamine and maintenance with halothane or isoflurane in horses (Taylor, 1987), have resulted in hyper cortisolaemia. Ketamine HCl is also said to induce significant increases in cortisol concentration in male cats (Carter *et al.*, 1984). Ketamine-xylazine was reported to have a little effect on glucocorticoid levels and provide an adequate level of surgical anasthesia, in New Zealand White rabbits (Illera *et al.*, 2000).

The non-significant variation in group F is in accordance with the finding of Dijk *et al.* (2003) when he used detomidine-buprenorphine in standing horses. Least

cumulative pain scores and serum cortisol level was reported with buprenorphine as compared to oxymorphine or ketoprofen for post-operative analgesia after onychectomy or onchectomy and sterlization in cats (Dobbins *et al.*, 2002).

Epidural bupivacaine anaesthesia produced a marked increase in cortical hormone production in non-sedated dogs. Serum cortisol levels were significantly higher for bupivacaine alone as compared to bupivacaine-morphine combination given interpleurally for median sternotomy in dogs (Dhokarikar *et al.*, 1996). It was also shown in a study that long-acting anaesthetics (bupivacaine) do not reduce the overall cortisol response caused by stress in calves (Mc Meekan *et al.*, 1998) whreas a subcutaneous bupivacaine when injected immediately before fitting the ring meant for tail docking in lambs appeared to be effective in reducing the cortisol responses (Grahm *et al.*, 1997).

Group A and B caused a transient stressfull condition and the values returned to decrease than baseline from 90 minutes. Group C and D caused steady increasee of stressull condition but again the values returned back to normal. The stress produced by group E and F continued up to the end of observation period. Group D as compared to group E caused significantly more anaesthetic stress condition which could be correlated to lesser sedation in group D as compared to group E animals.

In all the animals, decrease in GGT was only minor and nonsignificant till 180 minutes and the GGT values returned to baseline in all the groups by 24 hrs. Comparison between the groups revealed that animals of group F had significantly higher values at most of the intervals than other groups.

The importance of serum/plasma GGT estimation in liver dysfunction has been emphasized in horse (McGorum *et al.*, 1999), buffalo (Maru and Pachauri, 1985) and cattle (Baxter and Miert, 1983). In the liver of bovine GGT can be observed in the cytoplasm of the hepatocyte and epithelial cells of the ducts (Albert, 1967). Necrosis due to CCl_4 poisoing induced an internse increase of serum GGT in rabbit (Adjarov *et al.*, 1976) and

sheep (Ford, 1984). The higher GGT of group F as compared to other group could be attributed to metabolic disturbancs in liver (Baxter and Miert, 1983) caused by altered blood flow to liver due to arrhythmia recorded in few animals of this group.

Phase II

HAEMODYNAMIC STUDIES

Mean arterial pressure decreased significantly after spinal administration of drugs in all the groups. The values returned to base line at 150 min in group D but remained lesser than the base line in group E and F even at the end of the observation. Reduction in arterial pressure has been attributed to stimulation of central α_2-adrenergic receptors; peripherally mediated sympatholytic actions and enhanced parasympathetic outflow (Ossipov *et al.,* 1988; Tibirica *et al.,* 1991). Decrease in aortic flow consequent to bradycardia and vasodilation have also been reported to contribute to fall in AP following epidural xylazine in calves (Rings and Muir, 1982). Epidural xylazine (Skarda and Muir, 1996a, b) and detomidine (Skarda and Muir, 1994) in horses exerted a biphasic effect on AP characterized by an initial slight increase, followed by a longer lasting decrease where the initial rise in AP was caused by a direct effect on the post-synaptic α_2-adrenoceptors in vascular smooth muscles (Sympathomimmetic action) resulting in peripheral vasoconstriction. Reduction in AP was attributed to stimulation of central α_2-adrenoceptors at brain stem and spinal cord sites (Drew, 1976). However, in this study, instead of a biphasic curve a consistent decrease was recorded throughout probably due to smaller doses of xylazine. At small doses, the primary effect of α_2-agonists is reported at spinal and or supraspinal α_2-adrenergic receptors inhibiting sympathetic outflow (Eisenach and Tong, 1991) and producing decreased AP. Spinal route of these drugs probably made it readily available to CNS. However, medetomidine administered epidurally in another study produced an increase in AP by a direct effect on the post-synaptic α_2-adrenoceptors in the vascular smooth muscles (Vesal *et al.,* 1996).

MAP in calves with combined xylazine-guaiphenesin-ketamine infusion and extradural (intercococygeal lidocaine) anaesthesia, was reported to show a significant decrease (Picavet *et al.,* 2004); and also with xylazine-ketamine in dogs (Jang-Hwangsoo *et al.,* 2002). Decrease in arterial pressure in group D animals might be attributed to the paralysis of cardiac sympathetic fibres or a generalised decrease in sympathetic activity by local anaesthetic (Lumb and Jones, 1984). A significant drop in catecholamines could be explained by a change in sympathetic control of the adrenal medulla due to bupvacaine which epidurally anaesthetizes the sympathetic nerves (Bonath *et al.,* 1987). As in the group F animals, the decrease in MAP recorded is in accordance with the findings of Jacobson *et al.* (1994) where MAP decreased significantly after buprenorphine injection. A decrease in MAP was recorded with buprenorphine-acepromazine and etomidate mixture in cats (Akkerdaas *et al.,* 2001). Buprenorphine i.v. or i.m. didn't produce alterations in MAP in dogs anaesthetised with desflurane (Souza *et al.,* 2004). The decrease in MAP in group F animals could be due to th fact that endogenous opioids may inhibit ACTH secretion in ponies (Luna and Taylor, 2001). In the present study group D produced a least depression of arterial pressure which could also be due to additive effects of ketamine, which is a cardiostimulatory drug. However, in other groups xylazine and buprenorphine might have dominated the cardiostimulatory effects of ketamine.

CVP didnot change significantly in any of the groups which indicated that none of the drugs produced alteration in myocardial contractility and an increase in after load (Serteyn *et al.,* 1993). Group D and group E showed a non-significant decrease in CVP. However, a non-significant increase in CVP was exhibited by group F as compared to its respective base line and also as comapred to all other groups ($P<0.05$). The results of the present study confirmed to the observation of earlier workers. No significant cange in CVP with or without epidural xylazine was found in the dogs anaesthetized with isoflurane (Greene *et al.,* 1995). A significantly lower CVP was recorded in horses after xylazine administration i.v. as a sedative (Singh *et al.,* 1997). No significant change in CVP was recorded with buprenorphine administered i.v. or i.m. in dogs (Souza *et al.,* 2004).

Electrocardiogram showed bradycardia in the group E (ketamine - xylazine) throughout the period of observation and a non-significant decrease in HR in group D followed by the return of values to normal. Animals of group F showed, a non-significant variation and values returned to normal at 150 min post-injection. Significantly higher amount of bradycardia was recorded in group E as compared to the other groups. Animals of group D produced a least depression of heart rate. Several mechanisms contribute to the α_2-agonists induced bradycardia, such as an increase in vagal tone leading to decrease in the sinus depolarization of rythm, decreased sympathetic outflow from the CNS, direct depression of the cardiac pacemaker and conduction tissue (Campbell *et al.,* 1979), increased vagal and barorceptor activity (Antonaccio *et al.,* 1973). Significant bradycardia has also been reported with epidural xylazine (Jean *et al.,* 1990; Skarda *et al.,* 1990; Rehage *et al.,* 1994; Prado *et al.,* 1999; Lewis *et al.,* 1999; Ozba *et al.,* 2003), with epidural xylazine and ketamine (Aithal *et al.,* 1997a; Amarpal *et al.,* 1997; Singh, 1999; Kinjavdekar *et al.,* 2000; De Rossie *et al.,* 2003; Pathak *et al.,* 2003). The non-significant decrease in HR in group D is in accordance with obsrvations of DeRossi *et al.* (2004) and Adetunji *et al.* (2002) who remained non-significant change in HR after epidural bupivacaine in horses. Group F produced no significant alterations, which's in accordance with the studies of Souza *et al.* (2004); Umbricht *et al.* (2004) where buprenorphine was regarded to have a ceiling on cardiorespiratory changes. Moreover, buprenorphine being more lipophillic gets less absorbed into circulation vascular/lymphatic, from subarachnoid space (Negus *et al.,* 2002), which could also be responsible for minimal systemic effects of buprenorphine. The spinal drugs did not produce any significant change in the duration of wave except for group D where a non-significant increase was recorded and values did not return to the baseline till the end. This is in accordance with the studies of Lacombe *et al.* (1991) where an increase in P-wave duration was found with bupivacaine infused into isolated rabbit hearts. In group E and group F, a non-significant decrease in duration of P-wave was recorded. However, group F showed significantly longer P-wave duration at 15-30 min than other groups and group D showed a significantly longer P-wave duration at 180 min than group E.

This suggests that atrial depolarization was affected only slightly in group D. The increased P-wave duration might be due to delayed conduction impulse from sinoatrial (SA) node to atrioventricular (AV) node. Vagal stimulation markedly reduces the rate of impulse genetration from SA node and rate of cardiac impulse propagation (Keele and Neele, 1971). Group E however, showed no significant change in P-wave duration, except for a transient decrease was recorded. This is in accordance with the findings of Tiwari *et al.* (1999) where epidural xylazine was used in goats and a transient decrease in P-wave duration was recorded. A positive P-wave was recorded in all the animals. P-wave amplitude decreased in all the groups but the decrease was non-signficant except group E where a significant decrease was noticed at 30 min and amplitude of P-wave became zero in one of the animals of group E from 5 min to 30 min. Comparison between the groups revealed no significant variation in the amplitudes of P-wave. In the animals of group E, a non-significantly ($P>0.05$) lesser amplitude than other groups was recorded at 180 min. These findings indicated that atrial depolarization/ conductive area decreased in group E and remained so upto a longer duration as comapred to groups D and F.

QRS amplitude increased in all the groups non-significantly but in group E significant increase ($P<0.001$) at 10-60 min was recorded which remained higher than the base line value. Group F showed a non-signfiicant increase in QRS amplitude. In one animal, missing of QRS was noticed at 75 min. QRS duration also showed a non-significant increase in all the groups. This shows that ventricular depolarization time increased and area depolarized increased more with group E animals than other groups. Decrease in conduction velocity in AV node due to vagal activity after xylazine has been reported in buffaloes by Peshin and Kumar (1979). However, Dilip Kumar and Hugar (1993) reported increases or decreases in ventricular depolarization time and area after administration of α_2-agonists and ketamine in goats. The significant increase in QRS amplitude ($P<0.05$) and duration ($P>0.05$) in group E of the present study is in accordance with the studies of Tiwari *et al.* (1999) where QRS duration and amplitude increased upon epidural administration of xylazine in buffalo calves.

PR-interval increased non-significantly in group E at a few intervals and in group F throughout the period of observation and decreased non significantly in group D from 90-180 min post injection. Group F showed a significantly ($P<0.05$) longer PR-interval than group D and non-significantly longer than group E. P-R interval is the time required for the transmission of cardiac impulse from SA node to AV node. It usually varies inversely with the heart rate and is generally longer when the heart rate is slow. The changes like shortening and lengthening in PR-interval are correlated to faster or delayed conduction from SA node to AV node. Because PR interval changes are dependent an conduction velocity between SA node and AV conduction system, prolonged PR interval would indicate that these drugs might have caused a decrease in conduction velocity within the atrial muscle, the SA conduction system or both (Venugopalen *et al.*, 1994). The increase in P-R interval might be due to corresponding increase in oxygen requirement of the heart (Peshin and Kumar, 1979). Bradycardia produced by these drugs in the present study was a consistent finding which is related to increase the P-R interval. Similar findings were oberved by (Kinjavdekar, 1998) and Dilip Kumar and Hugar (1993) in goats.

A non-significant increase in QT interval was observed in all the groups except in group E where the increase in QT interval was significant. The values of QT-interval in all the groups remained elevated and never returned to the base line. Group E, showed higher QT-interval as compared to group F. QT interval is the summation of ventricular depolarization and repolarization which represents ventricular systole (Tilley, 1985). It varies inversely with heart rate. In the present study, bradycardia and increased QT-interval were the consistent observations following the administration of drugs. Higher QT-intervals in group E animals suggested slow depolarization of ventricles in group E. However, it was also suggested in another study that heart rate and QT-interval are governed separately by sympathetic neurons and these may or may not activate together (Tilley, 1985). The changes like shortening or lengthening of Q-T interval are correlated to faster or delayed time interval of ventricular systole. The increased Q-T interval might

be due to corresponding increase in oxygen requirement of the heart (Peshin and Kumar, 1979) and spinal administration of xylazine, medetomidine, xylazine ketamine and medetomidine-ketamine in goats (Kinjavdekar, 1998).

A positive T wave was seen in most of the animals. Changes in the polarity of T-wave due to anaesthetic induced hypoxia are quite common (Tilley, 1985). No significant change in T-wave amplitude was recorded in all the treatment groups except group F, where a significant decrease in T-wave amplitude occured at 60, 75 and 90 min and values remained decreased even at the end of the observation period. Out of the three animals of group F two animals showed an inverted T-wave at 60 minutes and 45 minutes respectively with associated bradycardia. This reflected a detrimental effect of buprenorphine and ketamine (group F) on heart because change in polarity of the T-wave is probably due to myocardial hypoxia (Tilley, 1985). Biphasic T-wave might be due to transient electrolyte imbalances such as hypokalaemia (Kinjavdekar, 1998). No significant change in amplitude in group D and E is in accordance with the findings of Kinjavdekar (1998) in goats. However, decrease in T-wave amplitude after medetomidine and its increase after ketamine and medetomidine has been reported in goats (Hugar, 1993).

The duration of T-wave didnot show any significant change in group D (one animal showed an increase in ampitude and duration) but increased significantly in group E and decreased significantly in group F. Comparison between the groups revealed that group D and group E showed longer duration of T-wave than group F. The deviation and inconsistency of T-wave might be due to transient changes in acid base balance on account of retention of CO_2 (Peshin and Kumar, 1979). Increase in T-wave duration is due to slow repolarization of ventricles (Tilley, 1985). Similar changes were noted in buffaloes (Peshin and Kumar, 1979), during xylazine anaesthesia in goats (Hugar, 1993; Dilip Kumar, 1993; Kinjavdekar, 1998). Sinoatrial block was observed in one animal of group E and one animal of group F ectopic beat was seen. Xylazine-ketamine and buprenorphine-ketamine induced arrythmias observed in the present study might be

due to vagal stimulation and vasopressor effects of these drugs. Bradycardia and AV blocks probably occur from increased vagal activity caused by the vasopressor effects of xylazine (Knight, 1980).

The haemodyanamic effects recorded in the present study can be summated as follows.

More amount of bradycardia and arrythmia was recorded in group E and F. Significant increase in amplitude of QRS was seen in the animals of group E and increase in PR interval was recorded in group E and F. Significant decrease in the amplitude of P wave and T-wave was recorded in the animals of group E. Higher QT interval was recorded in group E. Significantly lesser MAP and higher CVP were recorded in group E and F than group D. This reflected more deleterious effects of xylazine-ketamine (group E) and buprenorphine-ketamine (group F) and relative safety of bupivacaine - ketamine (group D).

There was no significant change in PO_2, PCO_2, pH and BE-ECF in all the groups all the combinations were safe as per the arterial gases measurements except group F, where PO_2 concentration decreased significantly at 90 and 180 min post-injection as compared to base-line value. PCO_2 increased non-significantly at the same time intervals. The values never returned to the base line even at the end. These parameters were taken during haemodyanamic studies (i.e. carotid and jugular catheterization) and the animal tied in lateral recumbency, which could be responsible for decreased Pa O_2 and increased $PaCO_2$. The signifciant decrease in group F might be contributed to less profund analgesia in group F due to which animal was continuously struggling. Due to this struggle, the muscle cells utilized oxygen at a rapid rate, which causes the interstitial fluid (blood here) PO_2 to fall significantly (Guyton, 1991).

Group E animals showed significantly higher PO_2 than groups D and F, which reflects a lesser amount of respiratory depression or lesser hypoventillation with ketamine-bupivacaine combination as compared to other groups. Group E showed

significantly lower PO_2 values than group D and F which reflected more amount of respiratory depression as compared to other groups. There was a non-significant increase in PCO_2 in group E as compared to the base line, which reflected relatively more hypoventillation in group E animals.

The pH values fluctuated within normal limits and remained near the base line throughout the period of observation which is in accordance with the study of Boitquin *et al.* (2004) with epidural bupivacaine and Skarda and Muir, (1982) with xylazine. Significant decrease in arterial PO_2 and pH (Hara *et al.*, 2002) and significant increase in PCO_2 were reported after epidural xylazine administration in cows (Jean *et al.*, 1990; Picavet *et al.*, 2004). The cause of which was attributed to hypoventilation and decreased cardiac output (Campbell *et al.*, 1979; Rings and Muir, 1982). Xylazine depressed respiratory centres in calves and goats (Kumar and Thurmon, 1979; Rings and Muir, 1982; Peshin *et al.*, 1985), cattle (Skarda and Muir, 1990) and effect was reversed by tolazoline administration.

Group D had significantly higher base excess values than group F but non-significantly higher than group E which reflected more amount of respiratory acidosis in F and least amount of respiratory depression or acidosis in group D. However, a significant increase in base excess has been reported after administration of xylazine in some studies (Jean *et al.*, 1990; Raidurg *et al.*, 1995). However, decrease in PO_2 with epidural bupivacaine in pulmonary edema during a caessarean section in human being has been reported by Rodriguez *et al.* (2004) and PO_2 remained unchanged with thoracic epidural anaesthesia in rats (Freise *et al.*, 2005).

No significant variation in arterial blood gas tensions and pH has been reported by Souza *et al.* (2004), with buprenorphine in dogs with transdermal fentanyl in dogs (Welch *et al.*, 2002), but PCO_2 was significantly lower with buprenorphine in dogs (Welch *et al.*, 2002), increase in PCO_2 and PO_2 in cats with buprenorphine was also reported (Akkerdaas *et al.*, 2001).

Blood electrolytes like Na,K, Cl^-, bicarbonates, calcium remained unaltered throughout the period of the study in all the groups. A transient rise in bicarbonates at 30 and 60 min was recorded in all the combination groups (D, E and F) but values remained decreased even at the end in all the groups. An increase in bicarbonate in all the groups throughout the observation period might be explained by the fact that in response to depression of respiratory rate, respiratory acidosis develops and then kidney will secrete an excess of hydrogen ions, resulting in an increase in sodium bicarbonate in the extracellular fluids (Guyton, 1991). Increased bicarbonate after epidural xylazine in cows has been reported. (Jean *et al.,* 1990). However, a significant decrease in arterial bicarbonate concentration has been reported in calves by Picavet *et al.* (2004) in goats with xylazine and no change in bicarbonate was recordd in dogs with xylazine-ketamine (LZuna *et al.,* 2003). A decrease in serum electrolytes (Na, Cl^-) and increase in pottassium has been reported by Kumar and Singh (1979) in cows calves and buffalo calves with xylazine and ketamine anaesthesia. Increase in bicarbonates has been reported in calves with xylazine-guaiphenesin-ketamine infusion and extradural lidocaine (Picavet, *et al.,* 2004). Plasma potassium concentration in the animals of group D and group E decreased non-significantly but increased non-significantly in the animals of group F. A decrease in potassium has also been reported after spinal administration of lignocaine, ketamine and their combinations in goats (Kinjavdekar, 1998; Singh, 1999), which might be due to the entry of potassium into cells or increased level of mineral corticoids or increased copious secretion of saliva leading to loss of pottassium ions (Burgeon and Seeman, 1958).

Blood calcium levels were found to have no change in any of the groups except group E where slight decrease in calcium levels was noticed at 180 minutes post-injection. It was also significantly lower as compared to other groups. Blood chloride was found to show a non-significant change in any of the groups except group E where a significant decrease in plasma chloride concentration from 30 min to end of the observation period was recorded. The significant decrease of plasma chloride in group

E might be attributed to depressed respiration in response to epidural α_2-adrenergic agonist as chloride levels are affected due to changes in respiratory activity (Hussain and Kumar, 1988). Epidural xylazine induced metabolic alkalosis might have caused a decrease in plasma chloride level as also reported by Benjamin (1985). Blood sodium values also showed no significant change in any groups except group E where it had a non-significant decrease from 90-180 min.

The non-significant changes to electrolyte imbalances reflected that these drugs didnot incite electrolyte imbalances in calves. However, decrease in calcium, pottasium, sodium and chloride in group E might be due to fluid shifts caused by water or electrolyte retention and in other groups, by the increased temporary migration of interstitial fluid to the vascular system. Similar observation with Na, K and Cl^- was reported by after detomidine and ketamine administration in goats (Dilip kumar, 1993). No change in serum electrolytes was observed after administration of xylazine (Kumar and Thurmon, 1979; Peshin and Kumar, 1983 and medetomidine (Hugar, 1993) Lima *et al.*, 2001). However, plasma sodium, potassium, chloride and calcium are reported to increase after ketamine-Diazepam and xylazine-ketamine in New Zealand white (NZW) rabbits (Gonzalez *et al.*, 2004).

Phase III

CLINICAL STUDIES

Xylzaine and ketamine in the animals of group H produced significantly ($P<0.05$) earliest onset as compared to all the groups where as bupivacaine and ketamine in the animals of group G produced signifiantly ($P<0.05$) the slowest onset as compared to all the groups. Group I animals, showed a significantly ($P<0.05$) earlier onset than group G and significantly ($P<0.05$) slower onset than group H.

Comparitively a slower onset in the animals of group G, in uremic animals might have been due to a reduced hydrolysis of the drug in acidotic uremic animals and

consequently, a less release of active alkaloidal base which is responsible for the anaesthetic action. This could be the probable reason of slower onset of analgesia in the animals of group G. This might have also been due to increased spinal hyperexcitability due to outlasting nociceptive afferent inputs during pain (Woolf, 1983; Cook *et al.*, 1987) in the clinical cases of obstructive urolithiasis. So this might hae caused an increase in the pain threshold of animal which could be a reason for less action of the analgesia caused by group G animals. This finding is in accordance with the findings of Obbossier and Biscoping, (2004).

On the contrary an early onset of xylazine-ketamine might have been due to the less absorption of dung from the site of injection as xylazine brings about bradycardia (Booth, 1988) in uraemic animals. This might have reduced the tissue perfusion and allowed the whole drug to be at the site of injection without getting absorbed. In the animals of group G, a complete analgesia of perineum, inguinal and tail was recorded for 15-30 min and complete analgesia of digits was recorded for 20-45 min. Only moderate analgesia of hind limbs, flank and abdomen and mild analgesia of thorax was recorded.

At many regions the depth of analgesia in animals of group G was lower as compared to that observed in experimental animals of group D. Lesser depth of analgesia delayed onset of complete analgesia and shorter duration of analgesia in uremic cases as compared to healthy calves (group D) is in accordance with the findings of Obboussier and Biscoping (1998) who have recorded reduced action of bupivacaine following supra clavicular plexus block in patients with chronic kidney insufficiency. Various reasons have been discussed as possible explanation for this phenomenon such as 1) uremia-induced changes in acid base status of blood and tissue 2) alternations in protein binding and 3) changes in haemodynamic parameters (Obbousier and Biscoping, 1998). Local anaesthetics are generally water soluble acid salts. When these salts are injected into tissues that normally are slightly alkaline, the acid salt formed of the local anaesthetic is neutralised. This releases the free amino or alkaloidal base through hydrolysis, which is necessary before the drug can penetrate the lipid barrier of the cell membrane to induce

anaesthetic action (Booth, 1988). It is generally thought that the base in primarily responsible for the onset of action, because the uncharged form (base) diffuses more readily across the nerve sheath (Booth and McDonald, 1982). But in cases of uremia and more especially with the prolonged cases with rupture of urinary bladder (as with the most of the clinical cases in the present study), the animals may become hyperkalemic, hyponatremic, hypochloraemic and acidotic (Finco, 1980). The pH of blood becomes acidic due to a continuous positive balance (retention) of hydrogen ions due to a decrease in tubular ammonia production to excrete hydrogens retained anions such as SO_4 and PO_4 also contribute to acidosis. This acidosis is the result of the balance between the acidifying effect of increased unmeasured anions and hyperphosphatemia and the lesser alkalinizing effect of hypoalbuminemia (Dubose, 1997; Rockaeschel *et al.*, 2003). The resultant acidosis might have prevented the hydrolysis of the bupivacaine and subsequent release of active alkaloidal base. Clinically also it is found that local anaesthetic when injected into tissue having an acid reaction from accumulation of pus failed to produce the effects. Slightly acidic pH prevents the hydrolysis of the acid salt and freeing of the potent alkaloidal base (Booth and McDonald, 1982). Further, protein binding is believed to be a primarily determinant of the duration of local anaesthetic. Presumably, because the site of action of local anaesthetic involves the protein within the axonal membrane. The greater the binding affinity to axonal protein, the longer anaesthetic activity persists (Lumb and Jones, 1996).

As the animals of group G were uraemic with long standing problem of urinary bladder rupture, a state of acidosis could be present in these animals. The acidotic nature of the tissues might have prevented the hydrolysis of bupivacaine which could be responsible for lesser depth and shorter duration of regional analgesia in animals of group G compared to group D. The hyperexcitable state of spinal cord in cases of uremia might also contribute to the reduced effect of bupivacaine in uraemic animals. Since it is reported that pain is much harder to control once the spinal hyperexcitability is set up (Hardie, 1996). In contrast to group G, in the animals of group H, a complete

analgesia of all the regions was recorded, which remained so for a longer duration (60-120 min) as compared to the respective regions of experimental animals of the same drug combination (group E). More deeper and longer duration of analgesia in animals of group H as compared to the animals of group E might be due to a direct cardiac depressant action of xylazine (Mcdonald and Virtanen, 1992). The uremic-subjects are already in the state of extreme dehydration, hypotension, toxemia, bradycardia and in a depressed state (Simeonova *et al.*, 2001; Guyton, 1991). In such condition, xylazine might be thought to aggravate the hypotension and might reduce the tissue perfusion further. This causes a reduced renal clearance and slow elimination of drug. As a result of reduced tissue perfusion in the uremic animals, the absorption of xylazine and ketamine from the site of action could be reduced drastically, which in turn may prolong the depth and duration of analgesia. Decreased proteins binding might have also contriuted to more drug available for specific action with consequent apparent sensitivity to a normal dose (Baggot, 1977).

In uraemic animals due to hypoproteinemia xylazine and ketamine after absorption from the site of action remain available in greater quality, which could be responsible for deeper sedation and analgesia in uremic animals. This might be due to the manifestation of control effect of α_2-agonist. The drug after absorption from the subarachnoid space was distributed to the brain (Skarda *et al.*, 1989b). This might have caused the activation of central α_2-adrenoceptors, which causes decreas in the release and turnover of norepinephrine in the CNS (Lee *et al.*, 2001a). In the animals of group I, a moderate analgesia of perineum, inguinal region, tail, hind limbs, digits, flank, abdomen and thorax was recorded which was otherwise recorded as only mild in respective experimental animals (group F). In experimental animals (group F), mild analgesia of flank, abdomen and thorax was recorded.

This might have been due to the reduced tissue perfusion in uremic animals due to dehydration and hypotension (Sharma *et al.*, 1994; Guyton, 1991). As a result of this the absorption of buprenorphine from the site of action could be reduced drastically

which in turn may increase the depth of analgesia. Decreased protein binding might have led to the greater availability of drug for its specific actions (Baggot, 1977). Buprenorphine is reported to raise the pain threshold or decrease the perception of pain by interfering with nociceptive neural transmission centrally. Opioids produce analgesia by action at several sites, but a major mechanism involves the activation of bulbospinal inhibitory , primarily serotonergic, pathways (Yaksh and Tyce, 1979; Mason, 1999) and noradrenergic pathways (Tyce and Yaksh, 1981; Zemin-Xu *et al.*, 1997) which exerts an inhibitory control over the dorsal horn, where the primary sensory neurons involved in pain sensation by releasing predominantly substance P and glutamate (Nollet *et al.*, 2003).

In the animals of group G, very less sedation as evidenced by tired appearance and slight ptosis of eye lids was recorded. Moreover the animals were alert towards the end of the observation period. Drugs in this group when compared to its respective experimental group (Group D) produced lesser sedation and early recovery to normal. Whereas in experimental group, the animals never returned to normal (Zero score of sedation) throughout the observation period. This was probably due to the lesser release of active alkaloid base in acidotic animals as explained earlier and the excitatory state of CNS due to prolonged barrage of noxious stimuli caused by urinary retention and rupture of urinary bladder (Hardie, 1996) animals of group H showed lateral recumbency at 5 min and couldnot sit without support from 45 to 75 min post-injection. Thereafter animals were recumbent throughout the observation period. On the other hand in the respective experimental animals of the same drugs combination (group E), a lesser degree and duration of sedation was recorded and animals could walk with slight staggering at 130 min post-injection. More severe and protracted sedation in animals of group H could be due to prolonged availability of greater quantity of xylazine in circulation due to hypoproteinemia and reduced tissue reperfusion which might have retarded the redistribution of drug. The sedation produced in this group might be due to the manifestation of central effects of α_2-agonist. The drug after absorption from the

subarachnoid space was distributed to the brain (Skarda *et al.*, 1989). This might have caused the activation of central α_2-adrenoceptors, which causes decrease in the release and turnover of norepinephrine in the CNS.

Group I animals showed mild sedation with slight ptosis of eyelids from 15 to 60 min post-injection in contrast to the experimental animals of the same drugs combination where the animals remained alert throughout the observation. The reasons for this in also explained earlier.

In the animals of group G, sternal recumbency was recorded within 5 min which continued upto 30 min. From 45 min, animals showed extreme incoordination but could walk normally after 60 min. In contrast, the animals of group D respective group of healthy animals attained higher scores of motor incoordination at most of the intervals. This difference might have been due to the basic reason explained i.e., less hydrolysis of drug in the acidic pH of uraemic animals and less release of the active alkaloidal base for action as compared to the healthy animals. This finding is in accordance with the findings of Obbousier and Biscoping (1998) where a decreased amount of action of bupivacaine was found in uremic patients.

In the animals of group H, Sternal recumbency was attained immediately after the injection of the drugs (i.e. within 5 min). However, animals aquired lateral recumbency at 5 min of injection and remained so till 60 min post-injection. Thereafter, animals attained sternal recumbency again upto 130 min. Even after 130 min animals showed extreme in-coordination of walk till the end of the observation period. In the healthy animals of respective group (Group E), lesser scores of MI were recorded at different intervals and the animals could walk normally by 180 min post-injection. More motor incoordination in uraemic animals (group H) as compared to healthy calves (group E) might be due to prolonged availability of the drugs at the site of injection as a result of decreased rate of absorption in the circulation. In uraemic animals already in the state of extreme dehydration, hypotension, toxemia, bradycardia etc. (Simeonova *et al.*, 2001;

Guyton, 1991) xylazine might have further aggravated the hypotension and reduced the tissue perfusion. As a result of reduced perfusion in uraemic animals, the absorption of drugs from the site of action is reduced and which in turn might have caused more intense action at the site for the reasons explained earlier. On the other hand hypoprotenemia - as recorded in uraemic animals might have made (after absorption from the site of action into the circulation) greater availability of xylazine in circulation for central action (Baggot, 1977). This might have been responsible for second episode of recumbency in uraemic animals due to central effects (Segura *et al.,* 1998)

In the animals of group I, sternal recumbency was recorded as soon as 5 min of the spinal injection and continued upto 30-45 min post-injection. This was followed by extreme incoordination from 60-75 min. Animals couldnot walk normally even at the end of the observation period. Contrarily the healthy animals of the same drug combination (group F) showed comparitively lower scores of motor incoordination for relatively shorter duration. Increased MI in uraemic animals (group I) might be due to the reasons explained earlier for deeper analgesia i.e. reduced perfusion at the site of action and hence increased depth of effects of the drug combination as compared to healthy animals.

Among the animals of clinical cases of obstructive urolithiasis/uremia, the duration of analgesia of group G was less as compared to its respective experimental group (Group D). This difference might have been due to the fact that the uremic animals are acidotic after the rupture of bladder (Finco, 1969). The local anaesthetics are acidic salts and when they are injected and get into contact with the tissues which are slightly alkaline, hydrolysis of local anaesthetics occur where they release the active alkaloidal base which can actually penetrate the lipid barrier of the cell membrane to induce anaesthesia (Booth 1988). However, the uremic subjects which are acidotic after rupture of the bladder might render less hydrolysis of the local anaesthetic and hence shorter duration due to early elimination of undissociated drug from the site of action. On the contrary, xylazine and ketamine combination produced the longest duration of action as compared to all the groups of uremic animals and also longer than its respective experimental animals of group E.

This was attributed to the fact that xylazine is a cardio depressant drug and causes aggravated bradycardia (Kumar and Thurmon, 1979; Rings and Muir, 1982) in the uremic animals, which are already in a state of dehydration, hypovolemia and hypotension (Guyton, 1991). The systemic absorption of drugs from the site of action will be reduced due to a longer stay of drugs can be assumed at the site of the action, due to less absorption resulting from diminished perfusion. This might have resulted in a prolonged anaesthetic duration.

Similarly, group I animals were also having a longer duration of action as compared to group F (Buprenorphine alone). This might have been due to the simple reason that in uremic animals less perfusion to the site of injection might have resulted in a longer stay of drug at the side of injection.

Recovery of the clinical cases took place in the following order.

Group I animals recovered earlier than group G. Group G animals recovered earlier than group H. The earliest recovery from anaesthesia in the animals of group I might have been due to the less anaesthetic effect exerted by buprenorphine due to its ceiling effect (Sporer, 2004). However, as compared to the respective experimental animals (group F), the recovery was prolonged in uremic animals of group I. This was probably due to the fact that uremic animals are dehydrated and hypovalemic. The cardiac output is reduced and hence the perfusion to tissues is less (Guyton, 1991). This caused a lesser absorption of drugs from the site of action which thereby, rendered a longer stay of drug at the site of action as compared to the healthy animals. On the contrary, group G animals showed an early recovery as compared to experimental animals of the respective group (group D). This might have been due to the fact that lesser hydrolysis of local anaesthetics in the acidotic uremic animals with rupture of bladder (Finco, 1980) might have led to a reduced release of the active alkaloidal base which's responsible for the anaesthetic action of the drug (Booth, 1988) and hence lesser depth and duration of action as compared to healthy animals. Group H animals

showed prolonged recovery as compared to all the groups and also in comparison to its respective group of healthy animals. It could be attributed to depression of cardiac functions (Kumar and Thurmon, 1979; Rings and Muir, 1982), by xylazine which might have aggravated the reduced tissue perfusion in already dehydrated uremic animals. This might have caused a reduced absorption of drugs from the site of injection and hence a prolonged recovery from regional anaesthesia.

In the clinical cases of group G, an increase in the HR from 5-45 min was recorded followed by a decrease from 60-105 min. There after the values remained nonsignificantly higher than the baseline values. In contrast in the respective experimental animals (group D), a significant decrease in HR was recorded and values remained below the base line even at the end of the observation period. This might have been due to lesser action of bupivacaine in acidotic animals as described earlier and concurrent excitation of animals by handling and restraining. HR in the animals of group H (ketamine + xylazine) decreased significantly during 30-90 min and 150-180 min interval. The values remained decreased throughout the observation period. Whereas in the healthy animals of the same group (group E), a less amount of decrease in HR was recorded and HR showed a gradual increase after 75 min post-injection as compared to group H. This might have been due to the hypotensive and cardiodepressant effects of xylazine (McDonald and Virtanen, 1992) that might have led to aggravation of hypotension in uraemic animals that are already dehydrated, hypotensive and bradycardiac (Simeonova *et al.*, 2001). This might be responsible for an intense effect of the drug at central α_2 receptors and consequently increased depression of HR. In the clinical cases of group I, a steady significant reduction in the HR was recorded throughout the observation period. Whereas, the healthy animals of same group (Group F), showed no significant change in HR throughout the observation period. The systemic absorption might have contributed to the decrease in HR because buprenorphine is reported to have a depressant effect on the myocardium (Coltart and Malcom, 1979), and relaxation of muscle of vascular wall or vasomotor relaxation is seen (Vickers *et al.*, 1984). Due to reduced blood volume from dehydration might have

been responsible for more circulation to the vital organs, which might have led to the more quantity of drug available for CNS action. PR also showed a similar trend as HR.

There was a significant decrease in the respiration rate of all the groups. There was an initial rise in RR for 5-20 min in the animals of group G and then it decreased from 30 min. till the end of obsrvation. The decrease was however more significant at 30 minutes. In contrast, the experimental animals of the same drug combination (group D), showed an early and prolonged decrease in RR i.e. at 5 to 10 min and 60-75 min and thereafter remained non-signfiicantly different from base values. Higher RR in uraemic animals could be attributed to more excitable state of CNS and lesser effect of bupivacaine in uraemic animals due to lesser hydrolysis of bupivacaine in acidotic animals and lesser release of the active alkaloidal base.

Group H, animals showed a decrease in the respiration rate from 5 min post-injection till the end of observation with the fall in RR more significantly ($P<0.01$) from 75 min till the end of observation. In contrast, in the healthy animals of same drug combination, the RR after a transient rise at 5-10 min, decreased, but again increased from 75 min and fluctuated near the base line. More decreased RR in uraemic animals of group H might have been due to aggravation of hypotensive state of the dehydrated uremic animals by the cardio pulmonary depressant effect of xylazine (Simeonova *et al.*, 2001).

Similarly, in the animals of group I, RR showed a significant decrease at 30 min and increased thereafter but remained lesser than the baseline throughout the observation period. Whereas in the experimental / healthy animals of the same drugs combination (group F), there was comparatively lesser decrease in RR and early return to normal values. This difference might have been due to dehydration and hypovolemia in uraemic animals which might have led to an increased concentration of drug in the circulation for the action at CNS and consequently a more intense effect of the drugs.

Epidural opioids or spinal opioids are reported to produce respiratory depression but doesn't change in cardiovascular or CNS function (Cousins and Mather, 1984). This

is due to the sedative ability of opioids through reduction in release of excitatory neurotransmitters from C-fibres as well as decrease the excitability of dorsal horn neurons (Livingston *et al.*, 1992). The decrease may have been attributable to depression of the respiratory centre (Aminovkov and Hubbenon, 1977).

In the animals of group G, a significant decrease in rectal temperature was recorded, the values started to increase at 150 min but remained significantly below the base line whereas in the experimental animals of same drugs (group D), comparitvely more amount of decrease in RT was recorded throughout the observation period as compared to group G animals. But the difference was less between the two groups.

The rectal temperature doesn't change much in uraemic animals if there is no infection. However, in later stages, the temperature, falls to below normal (Radostits, 1995). All the clinical cases were in different stages of uraemia with ruptured urinary bladder and having a wide variation of base line rectal temperature. However, in the animals of group G, there was no much difference as compared to group D except for a less decrease in RT by the animals of group G. This might have been probably due to lesser effect of bupivacaine in acidotic animals as decribed earlier. Maximum amount of decrease of RT was seen in group H animals where a decrease in RT from 20 min till the end of observation was recorded. The decrease was significant, and values never improved and always remained significantly below the base line. On the contrary, the RT of the respective experimental / healthy animals (group E), showed a lesser amount of decrease in rectal temperature and the values started to improve at 120 min post-inection. Xylazine can induce hypothermia by cardiodepressant effect (Simeonva *et al.*, 1992) and a consequent decrease in rectal temperature due to inadequate perfusion of tissues. Further xylazine is reported to induce depression of therox regulation (Ponder and Clarke, 1980) and depression of hypothalamic nor-adrenergic α_2-receptors to cause hypothermia (MacDonald *et al.*, 1988). Reduced BMR and muscle activity and depression

of thermo-regulation additively result in hypothermia (Ponder and Clarke, 1980). More hypothermia in uraemic animals than the healthy animals could be attributed to more intense systemic effects of xylazine in these animals.

In the animals of group I, RT decreased from 10 min till the end of observation period. The values didnot improve even at the end of the observation period. Similarly, in the experimental animals also, a significant reduction in RT was recorded for upto 90 min. Buprenorphine has less bearing on the rectal temperature since it has less sympatholytic activity due to more tightly bound to receptors. The difference in rectal temperature of the two groups might have been due to circulatory effect of uraemia than due to the basic action of these drugs.

A significant decrease in PCV and Hb was recorded invariably in all the three clinical grcups at 30 min to 180 min. The values remained below the base line till the end of observation period. there was no significant difference between the PCV and Hb of any of the groups. In the experimental animals also a non-significant change in PCV was recorded for throughout the observation period in group D E and F. Total leucocyte count also showed similar trend in animals of all the groups of experimental animals and clinical cases. Initially the Hb, PCV and TLC values were elevated in all the clincial cases of urolithiasis. This increase could be attributed to dehydration and consequent Haemoconcentration (Guyton, 1991). Increase in haemoglobin, PCV; total erythrocyte count and total leucocyte count has been reported in cases of clinical and experimetnal urolithiosis (Gera and Nigam, 1981; Peshin *et al.,* 1985; Jadon *et al.,* 1989; Joshi *et al.,* 1989; Gangwar *et al.,* 1990; Reddy, 1992).

A slight decrease in Hb and PCV and TLC might have been due to the supplemental intravenous therapy. Due to this reason, the PCV and Hb at the end of the observation period remained below the base line values. The neutrophil in all the groups decreased throughout the period of observation and this decrease was significant in group I at 120 minutes. There was a concomitant non-significant increse in the lymphocyte count in all the groups, throughout the observation period.

In uraemia, due to the oxidative stress which directly linked to acute phase reactions there could be neutrophilia accompanied with lymphocytopaenia (Himmelfarb *et al.*, 2003). The acute phase of the uraemic animals, leads to adrenocortical stimulation and subsequently the glucocorticoids are released, which have a direct effect on the circulating neutrophils and lymphocytes to cause neutrophillia and lymphocytopenia (Benjamin, 1985). In the clinical cases due to anaesthesia pain and stress response declined gradually and also due to evacution of urine from the body cavity / urinary bladder by surgical interventions. The animals were relieved of pain and looked much comfortable as compared to the initial restless and stress full condition. This might have thought to bring down the stimulation of adrenocortical axis and a consequent decrease in the neutrophil count and relative increase in lymphocyte count. There was no change in monocyte, eosinophils and basophils count throughout the observation period.

In the animals of group G, decrease in plasma glucose was recorded at 30 min of injection. Thereafter the values increased and remained elevated till the end of the observation period. Respective group of experimental animals (group D) also showed a non-significant change in plasma glucose throughout the period of observation. The initial fall in plasma glucose in animals of group G could be attributed temporary inhibition of stress response by regional analgesia by spinal bupivacaine. Further, evacuation of urine from abdomenal cavity and urinary bladder, the animals looked relieved and comfortable. This might have also caused a reduction in a adrenocorticoid stimulation and hence less glucose concentration at 30 min. The increase in glucose values thereafter might have been due to the post-operative stress after recovery from anaesthesia. The decrease in glucose levels corresponded with the decrease in plasma cortisol.

Similarly in the animals of group H also a significant decrease ($P<0.01$) in plasma glucose was recorded at 30 and 60 min post-injection. Thereafter the values increased and remained elevated non-significantly from the base line. In the animals of group E,

as compared to group H, showed no significant variation in the plasma glucose. In the animals of group H, a significant decrease was recorded due to the same reason as mentioned about group G i.e., reduction in the stress and discomfort of animals might have led to the reduction in the hyperglycaemic stress response and also partially due to haemodilution by fluid-therapy. The increase in plasma glucose thereafter might have been due to reduced analgesia scores (since the score of analgesia decreased after 120 min). The increase in glucose concentration corresponded to the decrease in analgesia scores. The cortisol level increase also corresponded to the same time intervals.

Plasma glucose in the animals of group I showed a non-significant change throughout the observation period and the values always fluctuated near the base line. On the contrary, plasma glucose of respective healthy animals of group F, showed a significant ($P<0.05$) incrase at 60 and 75 min post-injection. No significant change in plasma glucose levels in the animals of group I and a significant increase in the respective healthy group (Group F) suggested that the combination failed to produce the stress response in the uraemic animals. As the values were already high at base level, and the analgesic scores did not suggest adequate analgesia, animals of this group remained hyperglycaemic though out the period of observation. In the animals of group G plasma urea nitrogen decreased at non-significantly at 30 min and started increasing upto 120 min followed by a decrease at 180 min. There was no significant change in the experimental animals (group D). The initial decrease in animals of group G in plasma urea nitrogen might have been due to the effect of evacuation of urine collected in the body cavity/organs and consequently decrease in uremia and also due to fluid therapy. The increase in the later intervals might have been due to a longer time required for the animals for normalization. Plasma urea nitrogen of group H decreased significantly at 30 min and 180 min post-injection and it fluctuated near the base line at rest of the intervals. In the respective experimental group there was no significant variation throughout the observation period. Plasma urea nitrogen decrease in this group was probably due to the reason, that the urine collected in the body cavities/organ was evacuated by surgical interventions combined with the effect of the fluid therepy which

was given to monitor dehydration. The increase in plasma urea nitrogen did not go beyond the base levels, which ruled out the possible effect of anaesthetic on renal blood flow and instead reflects that animals required more time for stabilization. Plasma urea nitrogen of group I showed no significant change throughout the period of observation and always flucuated near the base line. Same was the case with experimental animals (group F). No significant change in plasma urea of group I reflected that the drugs had no effect on urea excretion.

A gradual decrease in creatinine was recorded in animals of group D and E. similarly plasma creatinine levels decreased significantly in group G and H at most of the intervals. The decrease in plasma creatinine might have been due to the effect of fluid therapy and haemodilution. The decrease in creatinine levels also reflected that epidural drugs (ketamine and bupivacaine) xylazine-ketamine had no adverse effects on renal blood flow and creatinine excretion. However, plasma creatinine showed no change in the animals of group F (experimental) and I (clinical). Since the level of analgesia was least in group F and I, as compared to the respective groups given other drugs, the haemodynamic changes and intercompartmental fluid shift could be considered minimal in the group.

In the animals of group D (healthy animals) a stready rise in plasma cortisol was recorded upto 180 min post-injection. But the values returned to base line at 24 hrs. Contrarily plasma cortisol in the animals ofgroup G, decreased at 30 min post-injection as compared to base line. It increased again upto 90 minutes and then decreased again to remain below the base levels.

The reduction in plasma cortisol in group G at 30 min might have been due to reduction in the stress response of patients due to regional blockade and fluid therapy. Thereafter the increase might have been due to deminished effect of analgesia and concomitant surgical stress.

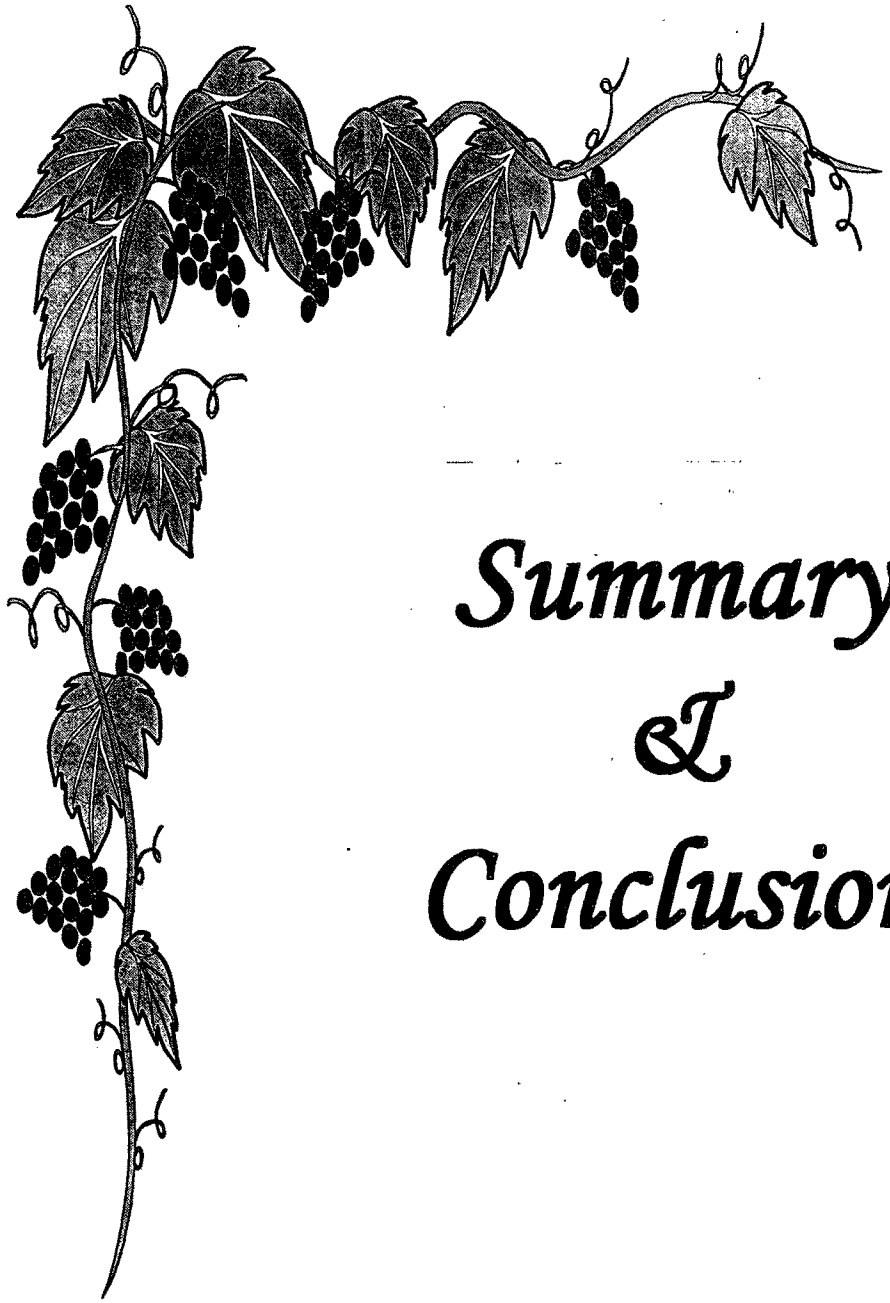
Tsuji *et al.* (1983) have shown that increase in plasma cortisol concentration due gastrectomy was significantly less in patients recieving epidural blockade than those

recieving general anaesthesia. Plasma cortisol in the animals of group H showed a significant increase at 120 min and the values at 180 min remained elevated than the base line. In the animals of group E, the plasma cortisol fluctuated near the base line throughout the period of observation. The significant increase of plasma cortisol in group H might have been due to the surgical stress in the animal after the surgery and concomitant decrease in analgesia scores of the anaesthetics. Gordon *et al.* (1973) reported that epidural blockade which lasted only for intraoperative period modified adrenocortical response to abdominal hysterectomy in human females during surgery but a rise in corticosteroid concentration was noticed after surgery.

Plasma cortisol levels in the animals of group I showed a non-significant decrease upto 90 min. Thereafter the values started to increase and reached near the base line at the end of the observation period. This was in accordance with the group F animals where a non-significant decrease was recorded upto 60 min and then the values started to rise but fluctuated near the base line at the end of the observation period. A decrease in the cortisol levels might have been due to the reduced stress after induction of anaesthesia. The values of cortisol in animals of group I (clinical) and F (experimental) did not show any trend and fluctuated around the base line during entire period of observation. It could be attributed to in complete analgesia and only partial blockade pain stimuli in clinical cases.

In all the animals of group G and H, GGT decreased non-significantly throughtout the observation period as same as their respctive experimental groups (group D and E, respectively) but in the animals of group I, a significant increase was recorded from120-180 min post-injection. This might be related to the drug induced metabolic disturbances of liver (Baxter and Miert, 1983). This reflected that group G and H drugs were compartively safer from the hepatic functions point of view and Buprenorphine+ketamine in group I could not be considered free from side effects on liver function.

□□□



Summary & Conclusion

SUMMARY & CONCLUSIONS

The present study was conducted to evaluate the effects of bupivacaine, xylazine, buprenorphine, and their respective combinations with ketamine for lumbosacral spinal analgesia in buffalo calves and also to evaluate the combination groups in order to create a balanced spinal analgesia in the clinical cases of obstructive urolithiasis with uremia in buffalo calves. The study was broadly divided into three phases.

The experimental study was carried out using nine male buffalo calves in two phases for the case of proper recording of different parameters. In phase I of the study, clinical, haematological and biochemical studies were carried out in six animals used in a latin square method with each treatment (or group) having six animals.

In phase II, three animals were used in the latin square method in the combination groups only, with three animals in each group. Phase II, of the study included the recording of haemodynamic parameters.

In phase I of the study, the animals were randomly divided into five groups A, B,C,D, E and F of six animals each. The treatments were group A bupivacaine (@ 0.25 mg/kg), group B xylazine (@ 0.05 mg/kg), group C buprenorphine (@ 20 µg/kg), group D bupivacaine + ketamine (@ 0.25 mg/kg + 2.5 mg/kg respectively) group E xylazine + ketamine (@ 0.05 mg/kg + 2.5 mg/kg respectively) and group F buprenorphine + ketamine (@ 20 µg/kg + 2.5 mg/kg respectively).

A total volume of 6 ml of the drug(s) injected was injected at the lumbosacral space intraspinally under aseptic conditions.

The onset of analgesia (min), duration of analgesia (min) and standing recovery from the effects of the drugs were recorded in all the animals. The depth and extent of analgesia at perineum, inguinal region, tail, flank, abdomen, thorax, upper part of hind limbs and digits, motor incoordination and sedation were recorded before the injection of drugs and at 5, 10, 15, 20, 30, 45, 60, 75, 90, 105, 120, 130, 150 and 180 min intervals post-injection. Physiological observation HR, RR and RT were recorded before and at 5, 10, 15, 20, 30, 45, 60, 75, 90, 105, 120, 130, 150 and 180 min post-injection. Levels of haemoglobin PCV, TLC, DLC and plasma glucose, blood urea nitrogen, creatinine, plasma cortisol and gamma glutamyl transferase (GGT) were estimated before and at 30, 60, 90, 120, 180 minutes and 24 hrs of post-injection using standard procedures.

In the second phase of the study haemodyanamic parameters were recorded after catheterization of carotid artery and jugular vein for recording the changes in mean arterial pressure (MAP) and central venous pressure (CVP) respectively at the same time intervals upto 180 minutes. In this phase all the combination groups were evaluated. ECG recordings were also made by using a lead II ECG at 1 mV and 25 mm/sec paper speed by placing negative electrode subcutaneously at caudal border of scapula and positive electrode at 5th costochondral junction (bage-apex lead) using ECG machine. These observations were also made at before and 5, 10, 15, 20, 30, 45, 60, 75, 90, 105, 120, 150 and 180 min of the injection of drugs.

The fresh heparinized arterial blood collected during the phase II was utilized for the estimation of pH, PO_2, PCO_2, BE, HCO^-_3, Na^+, K^+, Cl^- and calcium using blood gas analyzer (stat profile M Nava Biomedicals, USA). This was recorded before and at 30, 60, 90, 120 and 180 min post-injection.

In the last phase, phase III all the combination groups of ketamine, tried and evaluated on healthy experimental animals were utilized in the clinical cases of obstructive urolithiasis with uremia. In this phase thirty six animals having obstructive urolithiasis,

rupture of bladder and uremia were randomly divided in to 3 groups (G, H and I) with twelve animals in each group. The doses were kept similar to those used in the healthy experimental animals.

The observations made in the phase were clinical, physiolgical, haematological and biochemical as done in phase I of the study.

Depth and extent of analgesia, sedation and motor incoordination were measured at 0, 5 min of the drug administration. Surgery was performed, which included catheterization of bladder with foleys catheter and repair of the rupture of bladder. In all the animals time of surgery from the start did not take more than 25 minutes. So animal was taken off the operation table and rest of the recordings of the above parameters were made at 30, 45, 60, 75, 90, 105, 120, 130, 150 and 180 minutes post-injection. The rest of the observations were made at the similar intervals as for phase 1 of the study. Animals were also observed for their response to skin incision and to any other stimuli during surgery. Additional dose of drug required or use of local anaesthetics as infiltration analgesia was also recorded.

Among all the experimental groups of animals, the earliest onset of analgesia was observed with xylazine with ketamine (group E), followed by bupivacaine with ketamine (group D), buprenorphine with ketamine (group F), bupivacaine alone (group A), xylazine alone (group B) and buprenorphine alone (group C). Bupivacaine in animals of group A produced a maximum of moderate analgesia of perineum, inguinal and tail and mild analgesia of hind limbs, flank and thorax whereas the bupivacaine-ketamine combination (group D) produced moderate analgesia of thorax, abdomen and flank and complete analgesia of tail, perineum, inguinal region, hind limbs and digits. Xylazine alone (group B) produced no analgesia of thorax and flank, mild analgesia of digits and abdomen, and a moderate analgesia of tail, perineum, inguinal region and hind limbs. Xylazine-ketamine combination (group E) produced moderate analgesia of thorax, abdomen and flank and complete analgesia of digits, perineum, inguinal region, hind limbs and tail. Bupivacaine alone (group A) and bupivacaine-ketamine (group D) produced

least sedation among all the groups. Xylazine (group B) produced gradually extreme sedation but the animals could sit without support throughout the observation period. Xylazine-ketamine (group E) produced maximum sedation with lateral recumbency from 5 to 75 min and animals could not sit without support 30-60 min post-injection. Buprenorphine in group C and buprenorphine-ketamine (group F) produced mildest degree of sedation as compared to all the groups. Motor incoordination was higher in group D and group E as compared to all the groups where animals of both of groups attained lateral recumbecy and thereafter extreme incoordination of limb persisted upto 120-150 min. Animals of group A,B,C and F showed only very mild to moderate degree of motor incoordination. The duration of analgesia was longest in group D. But group D was non-significantly more than duration in group E. Group C and group F had significantly lower duration of analgesia.

All the groups showed a significant or non-significant decrease in HR except group C and F where the HR was not changed much. The groups D and E had significantly higher depression of HR. Groups D and E had significant decrease in RR, whereas groups A, B, C and F remained non-significant in the change of RR. The RT was significantly lower in groups E and D as compared to A, B, C and F which did not differ significantly from one another. Haematological studies revealed a decrease in Hb and PCV in groups A, B, C, D and E with no much significant change in group F. TLC increased in groups A, C, D, E and F except group B where it decreased from 30 min to 60 min post-injection. At 24 hrs. the values in groups A, B, C, D and E were non significantly higher than baseline and in group F it was significantly higher than base line value. There was a non-signifcant consistent neutrophillia and concomitant lymphocytopaenia in all the groups with the neutrophil count elevated than base level in all the groups at 24 hr. Monocytes and eosinophils did not show any change is the post injection period. pH values fluctuated within normal limits and remained near the base line throughout the observation period. Group D and E showed significantly higher PO_2 values than group F and group E had higher PCO_2 value than groups D and F. Group D

had E had higher base excess value than group F and group D had significantly lower base excess value than group E. The bicarbonate concentration showed a transient non-significant rise in all the groups at 30-60 min post-injection. However, there was no significant variation in the levels of sodium, potassium, chloride and calcium except for a significant decrease in plasma chloride concentration in group E animals throughout the observation period.

The plasma glucose was found to have an increase in groups A, B, C, E and F and significant decrease in group D. Plasma urea nitrogen values decreased in group A, B, C, D and F throughout the period of observation and increased in group E animals. Plasma creatinine concentration increased in group A whereas decreased in groups B, D and E. In group C, the values fluctuated near the baseline with a non-significant rise. Plasma cortisol showed a non-significant rise in group A and B followed by a decrease later. Whereas in groups D, E and F there was a rise in plasma cortisol throughout the observation period. Group F animals showed significantly higher values of GGT than all the groups. There was a non-significant decrease in GGT in all the animals. ECG showed bradycardia in all the groups.

Group F animals showed significantly higher CVP and lower values of MAP as compared to other groups. Maximum arrythmia between 5-10 min, 45-75 min and also at the end i.e. at 180 min was seen in group F animals. Group E animals showed lowest P-wave amplitude and group F animals showed significantly higher P-wave duration and QRS amplitude as compared to all the groups. Groups E and F had higher PR and QT intervals. Group F animals showed presence of inverted T-waves. T-wave duration was longer in groups D and E than group F.

The onset of analgesia was quickest in group H followed by group I followed by group G. Group I animals did not show complete analgesia of any regions and only group G animals achieved a complete analgesia of perineum, inguinal, digits and tail and rest of the regions achieved moderate analgesia only. Whereas group H animals

achieved a complete analgesia of all the regions recorded. Sedation, MI, duration and recovery was comparitively longer in group H followed by group I followed by group G. HR, RR, RT was significantly lower in group H compared to all the clinical groups. PCV, Hb, TLC decreased significantly in all the groups. Neutrophil count was decreased and lymphocyte count was increased in all the groups. Plasma glucose decreased significantly in group G, H and increased non-significantly in group I. PUN values a significant decrease in group H by remained non-significant in group G and I. Plasma creatinine decreased in group G and H and remained non-significant in group I. Plasma cortisol showed a decrease in group G and I followed by an increase after 60 and 120 min respectively whereas it increased significantly in group H.

The GGT values decreased in all the groups except group I where only a non-significant change was recorded.

From the results of the study it could be concluded that :

CONCLUSIONS

On the basis of the results of the study it was concluded that

1. Bupivacaine and xylazine have almost similar analgesic potency. Buprenorphine is a poor analgesic agent when used spinally in buffalo calves.
2. Spinal analgesia produced by bupivacaine, xylazine and buprenorphine can be enhanced significantly by addition of ketamine without further worsening the side effects of these drugs.
3. Spinal bupivacaine and xylazine with or without ketamine produced only transient alterations in haematobiochemical, haemodyanamic and ECG parameters and therefore, could be considered safe in healthy buffalo calves.

4. The combination of ketamine and buprenorphine should be used with caution in cases with compromised cardiac functions as it induced, irregular ECG pattern.

5. The combination ketamine and bupivacaine was considered safe for uremic buffalo calves suffering from obstructive urolithiasis. However, the onset was delayed and duration of analgesia was shorter in uremic animals as compared to healthy ones.

6. Combination of ketamine with xylazine was not considered safe in uremic buffalo calves owing to its serious depressant action on cardiopulmonary function in uremic buffalo calves.

❑❑❑

Mini Abstract

MINI-ABSTRACT

Effects of intraspinal and lumbosacral bupivacaine @ 0.25 mg/kg, (group A), xylazine @ 0.05 mg/kg (group B), buprenorphine @ 20 µg/kg (group C) and their respectiive combinations with ketamine @ 2.5 mg/kg, were evaluated in healthy (groups D, E and F respectively) with six animals in each group and uremic buffalo calves in 36 clinical cases of obstructive urolithiasis with uremia in buffalo calves (group G, H and I respectively) with 12 animals in each group. Analysis of clinical and haematobiochemical studies revealed that groups D and E had among all the groups increased depth and extent of analgesia, higher sedation, higher MI, decrease in HR, RR, RT, decrease in PCV, Hb, non-significant leucocytosis, neutrophillia and lymphocytopaenia. Plasma glucose increased in groups A, B, C, E and F but decreased in group D. Creatinine concentrations increased in group A and decreased in all the groups. PUN was recorded as significantly higher in groups D, E and F than A, B, and C. Group F animals showed an increased irregular ECG pattern and hemodyanamic changes with arrythmias, increased CVP, reduced MAP, increased PR and QT intervals inverted T-waves than all combination groups. In the uremic animals, the effect of drugs in group H was intensified as compared to its respective healthy experimental group E with many associated side effects. On the contrary, the effect of drugs in group G were diluted as compared to its respective healthy group (group D). Group I animals showed comparitively an increased analgesia as compared to its respective healthy group (group F). It was concluded from this study that xylazine-ketamine and ketamine-bupivacaine can be safely used in healthy animals without any detrimental effect to vital organs at the above said dose rate but ketamine-buprenorphine combination produces more of adverse haemodyanamic changes in buffalo calves. Whereas in case of uremic buffalo calves. Xylazine-ketamine combination is highly unsafe and ketamine-bupivacaine is very safe.

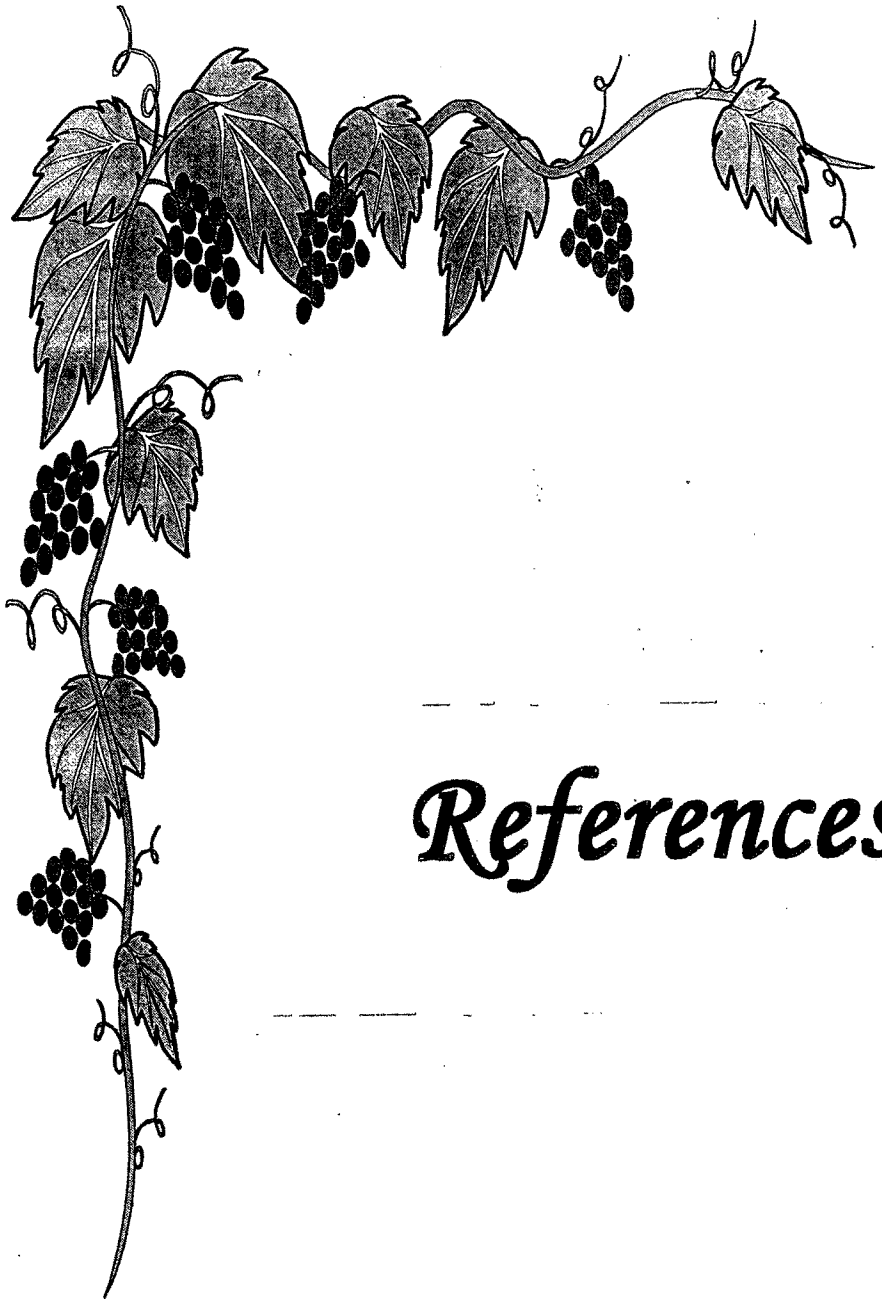
□□□

लघु सारांश

लघु सारांश

प्रस्तुत अध्ययन क्रमशः प्रायोगिक एवं शयनिक, दो भागों में विभाजित कर दिया गया है। प्रायोगिक के अन्तर्गत प्रथम चरण में 36 विजातीय भैंस के नर बछड़ों 6 से 9 माह आयु तथा 60 से 75 किलो (शरीर के भार) का प्रयोग किया गया। इन बछड़ों को छह समूहों में विभाजित किया गया। प्रत्येक समूह में छहः बछड़ों को संलग्न किया गया। समूह अ, बुपिवाकेन (0.25 मिग्रा०/किग्रा०), समूह ब जाइलेजिन (0.05 मिग्रा०/किग्रा०), समूह स बुपरीनॉरफीन (20 माइक्रोग्राम/किग्रा०), समूह द किटामिन तथा बुपिवाकेन (2.5 मिग्रा०/किग्रा० तथा 0.25 मिग्रा०/किग्रा०), समूह ई में किटामिन तथा जाइलेजिन (2.5 मिग्रा०/किग्रा० तथा 0.05 मिग्रा०/किग्रा०), समूह फ किटामिन तथा बुपरीनॉरफीन (2.5 मिग्रा०/किग्रा० तथा 20 माइक्रोग्रा०/किग्रा०) को सामान्य लवणीय घोल के साथ मिलाकर कुल आयतन 6 मिग्ली० कटिन्त्रिक अवजालतानिका अवकाश में दी गई। इसी प्रकार शयनिक बछड़े जिनमें मूत्राशय फटा हुआ था तथा यूरेमिया थी ठीक समूह द, ई, फ की भांति तीन समूहों में विभाजित किया तथा कुल 36 बछड़ों में प्रति समूह दर 12 बछड़े प्रयोग किये गये। उपचार प्रणाली की तुलना शयनोदैहिक, रूधिर विज्ञान तथा जैवरासायनिक प्राचलों के आधार पर की गई। द्वितीय चरण में (रूधिर गतिकी अध्ययन) 9 बछड़ों में समूह द, ई, एवं फ की औषधियों की तुलना रूधिर गतिकी प्राचल जैसे धमनी चाप, केन्द्रीय शिरा चाप तथा विद्युत हृदय लेख के आधार पर की गयी। तृतीय चरण में 36 शयनिक बछड़ों में कथित समूह ज, ह व आई मय 12 बछड़े प्रत्येक समूह में प्रयोग किए गये। प्रथम चरण में द और ई समूह में दूसरे समूहों की अपेक्षा अधिक व सम्पूर्ण पीड़ाहरण, गतिविभ्रम व शमन तथा हृदय फुफ्फुस अवनमन पाया गया। रूधिकीय जैव रासायनिक प्राचालों में पैक्ड कोशिका आयतन व हिमोग्लोबिन की मात्रा में गिरावट आयी व श्वेत कोशिकाओं में सभी समूहों में वृद्धि पायी गई। समूह अ, ब, स, ई व फ में रक्त शर्करा में वृद्धि हुई जबकि समूह द में गिरावट आयी। क्रियेटनीन की वृद्धि केवल समूह अ में व अन्य समूहों में गिरावट आयी। रक्त यूरिया नत्रजन समूह द, ई, और फ में अपेक्षाकृत बढ़ा। समूह फ में अधिक रूधिर गतिकी अस्थिरता पाई गई जिसमें केन्द्रीय शिराचाप, पी०आर० व क्यू०टी० मध्यान्तर में वृद्धि पाई गई व औसत धमनी चाप में गिरावट आयी। इसमें विपरीत पी० वेव भी पायी गयी। यूरेमिक शयनियक बछड़ों में, समूह ज में समूह द की अपेक्षा मंद प्रभाव रहा जबकि समूह द में समूह ई की अपेक्षा औषधियों का प्रभाव काफी अधिक प्रभावशाली रहा जिसमें अवांछित अतिरिक्त प्रभाव की भी वृद्धि हुई। समूह "आई" में भी समूह ह की भांति क्रमशः प्रायोगिक बछड़ों का समूह (समूह फ) की अपेक्षा प्रभाव अधिक रहा। इस अध्ययन से यह प्रतिलक्षित होता है कि किटामीन–जाइलेजिन यूरिमिया में कथित मात्रा में अवांछित प्रभाव डालता है असुरक्षित व हानिकारक सिद्ध होता है व किटामिन–बुपिवाकेन कथित मात्रा में सुरक्षित रूप से प्रयोग किया जा सकता है।

❑❑❑



References

REFERENCES

Abbound, T.K., Zhu, J., Gangolly, J. (1988). Transnasal analgesics : A new method for pain relief in post-cesarean patients. *Anaesthesiology.* **69:** A657.

Acalovschi, I., and Cristea, T. (1995). Intravenous regional anaesthesia with meperidine. *Anaesth. Analg.* **81:** 539-543.

Adentunji, A., Adewonge, Co., Ajadi, R.A. (2002a). Comparison of epidural anaesthesia with lignocaine or xylazine in cats. *Vet. J.,* **163(3):** 335-336.

Adetunji, A., Ajadi, R.A., Opia, R.E. (2002b). A comparison of epidural anaesthesia with xylazine, bupivacaine and bupivacaine/xylazine mixture in West aprican Dwarf goats. *Israel J. Vet. Med.,* **57(2):** 76-81.

Adjarov, D., Popov, S. and Ivanov, E. (1976). Studies on the mechanism of the changes in serum and liver gamma-glutamyl transpeptidase activity I. experimental extranepatic clolestatsis in rabbits enzyme. **21:** 1-7.

Aithal, H.P., Amarpal, Kinjavdekar, P. and Singh, G.R. (1999). Epidural anaesthesia with ketamine in dogs with poor risk surgical patients. *Indian Vet. J.,* **74:** 625-626.

Aithal, H.P., Amarpal, Pratap, K. and Singh, G.R. (1996). Clinical effects of epidurally administered ketamine and xylazine in goat. *Small Ruminant Res.,* **24:** 55-64.

Aithal, H.P., Amarpal, Singh, G.R., Mogha, I.V., Gupta, O.P., Naveen Kumar and Hoque, M. (1997b). Epidural ketamine and xylazine for hind quarter surgery in ruminants. *Indian Vety. J.,***74(7):** 625-626.

Aithal, H.P., Singh, G.R., Hoque, M., Maiti, S.K., Kinjavdekar, P., Amarpal, Pawde, A.M., Sethia, H.C. (2004). The use of a circular external skeletal muscle fixation device for the management of long bone osteotomies in lare ruminants : an experimetnal study. *Journal of Vet. Med.* Series-A **51(6):** 284-293.

Akkerdaas, L.C., Mioch, P., Sap, R., Hellebrekers, L.J. (2001). Cardiopulmonary effects of three different anaesthesia protocols in cats. *Vet.* **23(4):** 182-186.

Albert, Z. (1967). GGT in man and other mammals. *Enzyme histochemistry Simpooslo Antonio Baselli. Milan.*

Althura, B.M., Altura, B.R. and Corella, A. (1980). Effects of ketamine on vascular smooth muscle function. *Br. J. Pharmacol.*, **70:** 257.

Amarpal, Aithal, H.P., Kinjavdekar, P., Singh, G.R. (2003). Interaction between epidurally administered ketamine and pethidine in dogs. *J. Vet. Med. A. Physiol. Pathol. Clin. Med.* **50(5):** 254-258.

Amarpal, Aithal, H.P., Singh, G.R. and Bisht, G.S. (1999). Preemptive effects of epidural ketamine for analgesia in dgs. *Ind. Vet. J.* **76(4):** 300-303.

Amarpal, Aithal, H.P., Singh, G.R., Pawde, A.M. and Sharma, A.K. (1997). Epidural xylazine and ketamine for hind quarter analgesia in cow calves. *Indian J. Anim. Sci.*, **67(7):** 587-588.

Amarpal, Kinjavdekar, P., Aithal, H.P., Pawde, A.M., Pratap, K. (2002). Analgesia sedative and hemodyanamic effects of spinally administered romifive in female goats. *J. Vet. Med. A. Physiol. Pathol. Clin. Med.* **49(1):** 3-8.

Ambrisko, T.D., Kikasa, Y. (2002). Neurohormonal and metabolic effects of medetomidine compared with xylazine in begle dogs. *Can. J. Vet. Res.* **66(1):** 42-49.

Aminkov, B.Y., and Hubenon, H.D. (1995). The effect of xylazine epidural anaesthesia on blood gas acid-base parameters in rams. *Br. Vet. J.*, **151:** 579-585.

Amione, L.D. and Yaksh, T.L. (1989). Opioid modulation of capsacicin-evoked release of substance P from rat spinal cord *in vivo. Peptides,* **10:** 1127-1131.

Angel, I. and Langer, S.Z. (1988). Adrenergic induced hyperglycaemia in anaesthetised rats : involvement of peripheral α_2-adrenoceptors. *Eur. J. Pharmacol.*, **154:** 191-196.

Antonaccio, M.J., Robson, R.D. and Kerwin, L. (1973). Evidence for increased vagal tone and enhancement of baroreceptor reflex activity after xylazine in anaesthetised dogs. *Eur. J. Pharmacol.*, **23:** 311-315.

Arras, M., Autenried, P., Rettich, A., Spaeni, D., Rulicke, T. (2001). Optimization of intraperitoneal injection anaesthesia in mice : drugs, dosages, adverse effects, and anaesthesia depth. *Comparative Medicine,* **51(5):** 443-456.

Aziz, M.A. and Martin, G.J. (1978). Alpha agonist and local anaesthetic properties of xylazine. *Zentralbl Veterinarimed (A).* **25:** 181-188.

Baggot, J.D., Ludden, T.M. Powers, T.E. (1976). The bioavailability disposition pinetics and dosage of sulphadimethoxine in dogs. *Can. J. Comp. Med.* **40(3):** 310-317.

Baha, F. and Malbert, C.H. (1991). Effect of ketamine given by the intrathecal route in dogs. *Rev. Med. Vet.,* **142:** 283-285.

Baxter, J.T. and Miert, A.S.J.P. (1983). Gamma glutamyl transferase in domestic animals. *Vet. Res. Communicat.* **6:** 77-90.

Bengtsson, M., Malmquist, C.A. and Edstrom, H.H. (1984). Spinal analgesia with glucose free bupivacaine effects of volume and concentration. *Acta Anaesthesiol Scand.,* **28:** 583-586.

Benjamin, M.M. (1985). Outline of veterinary clinical pathology, IOWA State University Press.

Benson, G.J. and Tranquilli, Q.J. (1992). Advantages and guidelines for using agonist-antagonst analgesics *Vet. Clin. North Am. Small. Anim. Pract.* **22(2):** 363-365.

Bernards, C.M. and Hill, H.f. (1992). Physical and chemical properties of drug molecules governing their diffusion through the spinal meninges. *Anesthesiol.,* **77:** 750-756.

Besson, I.M. and Chaouch, A. (1987). Peripheral and spinal mechanisms of nociaption. *Physiol. Rev.* **67:** 67.

Bion, J.F. (1984). Intrathecal ketamine for war surgery : A Preliminary study under field conditions. *Anaesthesia,* **39:** 1023-1028.

Birnbaumer, L., Codina, J., Yatani, A., Mattera, R., Graf, R., Olate, J. (1989). Molecular basis of regulation of ionic channels by G-proteins. *Recent Prog. Horm. Res.* **45(2):** 206-208.

Bishoff, U., Brau, M.e., Vogel, W., Hemplemann, G. and Olschewski, A. (2003). Local anaesthetics block hyperpolarization activated increased current in rat small dorsal root ganglian neurones. *British J. Pharmacol.,* **139:** 1273-1280.

Blass, C.E. and Shires, P.K. (1986). Respiratory paralysis secondary to epidural anaesthesia in a dog. *J. Am. Vet. Med. Assoc.* **189:** 315-316.

Bliesener, N., Albercht, S., Schwager, A. (2005). Plasma testosterone and sexual function oin men recieving buprenorphine maintainence for opioid dependence. *J. Clin. Endocrinol. Metab.* **90(1):** 203-206.

Blood, D.C. and Radostitis, O.M. (1989). Veterinary medicine. A Text book of the diseases of cattle, pigs, goat and horses. 7th Edn., Bailliere Tindall, London.

Boitquin, L.P., Heeq, J.D., Vanbecklergen, D.F., Jamart, J., Galanti, L.M. (2004). Stability of sufentanil citrate with levbupivacaine HCL in NaCl 0.9% infusion after microwave freeze thaw treatment. *Ann. Pharmacol.* **38(11):** 1836-1839.

Bonath, K.H. and Saleh, A.J. (1985). Long term pain treatment in dogs by peridural morphines. In: proceedings of the Second International Veterinary Anaesthesiology Symposium, Santa Barbara, CA, Veterinary Practice Publishing Co., p. 161.

Booth, N.H. and Macdonald, L.E. (1982). Text Book of Vety. Pharmacology.

Booth, N.H. (1984). Intravenous and other parenteral anaesthetics. *In* : John's Veterinary Pharmacology and therapeutics, 5th edn. Booth N.H. and L.E. McDonald (eds), Kalyani Publishers, New Delhi, pp. 203-254.

Booth, N.H. (1988). Intrathecal and epidural anaesthesia. In: Veterinary pharmacology and therapeutics 6th edn. IOWA State University Press, Ames, IOWA, pp. 424.

Bramage, P.R., Shibata, H.R. and Willoughby, H.W. (1971). Influence of prolonged epidural blockade on blood sugar and cortisol responses to operations upon upper part of the abdomen and thorax. *Surg. Gynecol. Obstet.,* **132:** 1051-1056.

Brand, S. and Livingston, A. (1990). Receptor changes in the spinal cord of sheep associated with exposure to chronic pain. *Pain* **42:** 323.

Brikas, P., Tsiamitas, C. and Ayiannidis, A. (1987). Xylazine-induced hyperglycaemia and α-adrenergic receptors in sheep. *J. Vet. Med. (A).* **34:** 58-60.

Brockman, R.P. (1981). Effect of xylazine on plasma glucose, glucagon and insulin concentration in sheep. *Res. Vet. Sci.,* **30:** 383-384.

Bromage, P.R. (1962). Spread of analgesic solutions in the epidural space and their site of action. *Br. J. Anesth.* **34:** 161-178.

Bromage, P.R. (1967). Physiology and pharmacology of epidural analgesia : a review. *Anesthesiol.,* **28(3):** 592-622.

Bromage, P.R., Shibata, H.R. and Willoughby, H.W. (1971). Influence of prolonged epidural blockade on blood sugar and cortisol responses to operations upon upper part of the abdomen and thorax. *Surg. Gynecol. Obstet.,* **132:** 1051-1056.

Bromage, P.R., Comporesi, E. and Chestnul, D. (1980). Epidural narcotics foro postoperative analgesia. *Anaesth. Analg.* **59:** 473-480.

Bromage, P.R., Joyal, A.C. and Binney, J.C. (1963). Local anesthetic drugs : Penetration from the spinal extradual space into the neuraxis. *Science.* **140:** 392-394.

Buchholz, H.W. and Koerner, K.F. (1952). Die durchlaessigketi der dura fuer pantocainloesungen bei den vershiendenen methoden der periduralanesthesie. *Anaesthesist.* **1:** 73-75.

Buckler, K.J., William, B.A. and Honore, E. (2000). An oxygen acid and anaesthetic sensitive task - like background potassium channel a rat arterial chemo receptor cells. *J. Physiol.*, **525:** 135-142.

Bugedo, G.J., Carcamo, C.R. and Mertens, R.A. (1990). Preoperative percutaneous ilionguiinal and iliohypogastric pain management in adults. *Reg. Anaesth.* **15:** 130-133.

Bulka, A., Kouya, P.F., Boftiger, Y., Svensson, J.O., *et al.* (2004). Comparison of the antinociceptive effect of morphine, methadone, buprenorphine and codiene in two substrains of spraque-Dawley-rats. *Eur. J. Pharmacol.*, **492(1):** 27-34.

Busoni, P. and Andreuccetti, T. (1986). The spread of caudal analgesia in children : A mathematical model. *Anesth. Intens Care,* **14:** 140-144.

Butterworth, J.F. and Strichartz, G.R. (1990). Molecular mechanisms of local anaesthesia : a review. *Anaesthesiology,* **72:** 711-734.

Calguner, E., Gozil, R., Erdogan, D., Kurt, I., Keskil, S., Elmas, C., Sabuncuogla, H. (2003). Atropic and regenerative changes in rabbit mimic muscles after lidocaine and bupivacaine application. *Andomia-Hlstologia. Embryotogia,* **32:** 11, 54-59.

Campbell, B., Klavano, P.A., Richardon, P. *et al.,* (1979). Haemodynamic effects of xylazine in the calf. *Am. J. Vet. Res.* **40:** 1177-1180.

Campbell, W.I. and Kendrick, R. (1990). Intravenous diclofenac sodium. Does its administration before operation suppress postoperative pain? *Anaesthesia,* **45:** 763-766.

Carli, F., Webster, J., Pearsen, M., Pearson, J., Bartlett, S., Bannister, P., Halliday, D. (1991). Protein metabolism after abdominal surgery : effect of 24 hr extradural block with local anaesthetic.*Br. J. Anaesth.*, **67(6):** 729-34.

Caron, J.P. and LeBanc, P.H. (1989). Caudal epidural analgesia in cattle using xylazine. *Can J. Vet. Res.*, **53:** 486-489.

Carpenter, R.E., Wilson, D.V., Evans, A.T. (2004). Evaluation of intraperitoneal and incisional lidocaine or bupivacaine for analgesia following ovariohysterectomy in the dog. *Vet. Anaesthesia and Analgesia,* **31(1):** 46-52.

Carpenter, R.L., Caplan, R.A., Brawn, D.L. *et al.* (1992). Incidence and risk factors for side effects of spinal anaesthesia. *Anaesthesiology,* **76:** 906-16.

Carter, K.K., Chakraborty, P.K., Bush, M. and Wildt, D.E. (1984). Effects of electroejaculation and ketamine HCl on serum cortisol, progesterone and testosterone in the male cat. *J. of Andrology.* **5(6):** 431-437.

Caulkett, N.A., MacDonald, D.G., Janzen, E.P., Cribb, P.N. and Fretz, P.B. (1993). Xylazine hydrochloride epidural analgesia – a method of providing sedation and analgesia to fascilitate castration of mature bulls. *Compendium on Conf. Edu. Prac. Vet.*, **15(8):** 1155-1159.

Celerier, E., Rivat, C., Jun, Y., Laulin, J.P., Larcher, A., Rejnier, P., Simonnet, G. (2000). Long lasting hyperalgesia induced by fentanyl in rats : Preventve effect of ketamine. *Anesthesiology.* **92(2):** 465-72.

Chastain, G.B., Faranklin, R.T., Ganjam, V.K. and Madsen, R.W. (1986). Evaluation of hypothalamic-pituitary-adrenal axis in clinically stressed dogs. *J. Am. Anim. Hosp. Assoc.*, **22:** 435-442.

Chavelier, H.M., Provest, P.J. and Karas, A.Z. (2004). Effect of caudal epidural xylazine on intraoperative distress and post-operative pain in Holstein heifers. *Vet. Anaes. and Analg.*, **31(1):** 1-10.

Chestnut, D.H., Owen, C.L. and Bates, J.N. *et al.* (1988). Continuous infusion of epidural analgesia during labor : a randomized, double blind comparison of 0.0625% bupivacaine/0.0002% fentanyl versus 0.125% bupivacaine. *Anaesthesiol.*, **68:** 754-759.

Cohen, E.N. (1968). Distribution of local anaesthetic agents in the neuraxis of the dog. *Anesthesiol.*, **29:** 1002-1005.

Collette, W.L. and Meriwether, W.F. (1965). Some changes in the peripheral blood of dogs after administration of certain tranquilizers and narcotics. *Vet. Med. Small Anim. Clin.* **60:** 1223.

Coltart, D.J., Malcolm, A.D. (1979). Pharmacological and clinical importance of narcotic antagonists and mixed antagonists - use in cardiology. *Br. J. Clin. Pharmacol.* **3:** 3098-3115.

Conzemius, M.G., Sammarco, J.L., Perkowski, S.Z. (1994). Analgesic effect of intraarticular, bupivacaine, morphine or saline after cranial cruciate repair : a randomized; prospective, double blind study. *Vet. Surg.*, **23:** 398.

Cook, A.J., Woolf, C.J. and Wall, P.D. (1987). Dynamic receptive field plasticity in rat spinal cord dorsal horm following C-primary afferent inputs. *Nature.* **325:** 151-153.

Coombes, D.W., Jensen, L.B. and MUrphy, C. (1987). Microdose intrathecal clonidine and morphine for post-operative analgesia. *Anesthesiol.*, **67:** A238.

Coombes, D.W., Saunders, R.L., Lachance, D. *et al.* (1985). Intrathecal morphine tolerance : use of intrathecal clonidine, DADLE, and intraventricular morphine. *Anesthesiol.* **62:** 358-363.

Cousins, M.J. and Mather, L.E. (1984). Intrathecal and epidural administration of opioids. *Anesthesiol.,* **61(3):** 276-310.

Covino, B.G. and Vassallo, H.G. (1976). Local anaesthetics – mechanisms of action and clinical use. First Edn. Grune and Stratten, New York pp. 58-59; 95-114.

Crisp, T., Perrotti, J.M., Smith, D.L., Stafinsky, J.L. and Smith, D.J. (1991). The local monoaminergic dependency of spinal ketamine. *Eur. J. Pharmacol.,* **194:** 167-172.

Crisp, T., PErrotti, J.M., Smith, D.L., Stafinsky, J.L. and Smith, D.J. (1991). The local monoaminergic dependency of spinal ketamine. *Eur. J. Pharmacol.* **194:** 167-172.

Cucchiaro, G., Markowitz, S.D., Kaye, R., Adzick, N.S., Litman, R.S., Stanley, C.A., Watcha, M.F. (2004). Blood glucose control during selective arterial stimulation and venous sampling for localization of focal hyperinsulinism lesion in anaesthetized children. *Anesth. Analg.* **99(4):** 1044-1048.

Cullen, LK. (1996). Medetomidine sedation in dogs and cats : A review of its pharmacology, antagonism and dose. *Br. Vet. J.* **152:** 519-535.

Curatolo, M., Orlando, A., Zbinden, A.M. *et al.* (1994). A multifactorial analysis of the spread of epidural analgesia. *Acta Anesthesiol Scand.,* **38:** 646-652.

Dahl, J.B., Rosenberg, J., Dirkes, W.E., Mogensen, T. and Kehlet, H. (1990). Prevention of postoperative pain by balanced analgesia. *Br. J. Anaesth.,* **64:** 518-520.

Daugirdas, J.T. (1994). Handbook of dialysis, Second Edition, 472, 545-553.

De Rossi, R., Junqueira, Al, Beretta, M.P., Gaspar, E.B., Chares, L.L. (2003). Evaluation of the antinociceptive and motor blocking action of subarachnoid injection of 0.5% hyperbasic bupivacaine in goats. *Revista-Brasileria-de-Ciencia-Veterinaria,* **10(1),** 10-15.

Dekock, M., Wiederkher, P., Laghmiche, A. and Scholtes, J.L. (1997). Epidural clamidine used as a sole analgesic agent during and after abdominal surgery. A dose respons study. *Anaesthesiology,* **86(2):** 285-92.

Denns, P.M., Heard, D.J. (2002). Cardiopulmonary effects of a medetomidine-ketamine combination administered intravenously in gopher toroises. *JAVMA.* **220:** 1516-1519.

DeRossi, R., Jungueira, A.L., Beretta, M.P. (2003). Analgesic and systemic effects of ketamine, xylazine and lidocaine after subarachnoid administration in goats. *Am. J. Vet. Res.*, **64(1):** 51-56.

DeRossi, R., Sampaio, B.F.B. , Varela, J.V., Janqueira, Al (2004). Perineal analgesia and haemodyanamic effects of the epidural administration of meperidine or hyperboric bupivacaine in carcious horses. *Canadian Vet. Journal,* **45(1):** 42-47.

Deshmukh, S.P., Bhokre, A.P. (2002). A comparative study of cystorrhaphy in experimental male buffalo calves. *Indian Veterinary Journal,* **79(2):** 131-133.

Dhokarikar, P., Caywood, D.D., Stobie, D., Raffe, M.R. *et al.* (1996). Effects of intramuscular or interpleural administration of morphine and interpleural administration of bupivacaine on pulmonary function in dogs that have undergone median sternotomy. *Am. J. Vet. Res.* **57(3):** 375-380.

Dijk, P.-Van, Lankvel, D.P.K., Rijkenhuizen, A.B.M., Jonker, F.H. (2003). Hormonal, metabolic and physiolgoical effects of laparoscopic surgery using a detomidine burenorphine combination in standing horses. *Vet. Anaes. Analg.*, **30(2):** 72-80.

Dilip Kumar, D. (1993). Studies on detomidine hydrochloride (Domoseda) as a preanaesthetic in ketamine anaesthesia in goats. M.V.Sc. thesis, submitted to Deemed University, IVRI, Izatnagar, India.

Dickenson, A.H. (1995). Spinal cord pharmacology of pain. *Br. J. Anaesth.* **75:** 193-200.

Dobbins, S., Brown, N.O., Shofer, F.S. (2002). Comparison of the effects of buprenorphine, oxymorphone hydrochloride and ketoprofen for post-operative analgesia after oxychectomy and sterilization in cats. *J. Am. Anim. Hosp. Assoc.*, **38(6):** 507-514.

Dobbins, S., Brown, N.O., Shofer, F.S. (2002). Comparison of the effects of buprenorphine, oxyneorphanehydrochloride and ketoprofen for postoperative analgesia after onychectomy and stertization in cats. *J. Am. Anim. Hosp. Assoc.*, **38(6):** 507-514.

Doiphode, P.V., Aher, V.D. (2003). Clinical and physiological effects of neuroleptanalgesia with xylazine and pentazocine in bovine. *Indian Vet. Journal,* **80(8):** 772-774.

Dollery, C.T. (1991). Therapeutic drugs : A clinical pharmacopocia Vols. 1 and 2. Edinburgh, Churchill Livingstone.

Domzal, T., Szczudlik, A., Kwasucki, J., Zalcoka, B. and Lypka, A. (1983). Plasma cortisol concentrations in patients with different circadian pain rhythm. *Pain,* **17:** 67-70.

Dowdy, E.G. and Kaya, K. (1968). Studies of the mechanism of cardiovascular responses to CI-581. *Anaesthesiol.*, **29:** 931-943.

Drenger, B., Magora, F. (1989). Urodyanamic studies after intrathecal Fentanyl and Buprenorphine in the dog. *Anaesthesia and Analgesia,* **69:** 348-353.

Drew, G.M. (1976). Effects of alpha-adrennoceptor agonist and antagonist on pre- and post synaptically located alpha-adrenoceptors. *Eur. J. Pharmacol.* **36:** 313-320.

DuBois, W.R., Prado, T.M., Kojch, Mandsager, R.E., Morghan, G.L. (2004). A comparison of two intramuscular doses of xylazine-ketamine combination and tolazoline reversal in llamas. *Veterinary Anaesthesia and Analgesia* **31(2):** 90-96.

Dubose, T.D. Jr. (1997). Hyperkalemic hyperchloremic metabolic acidosis. Pathophysiology insights. *Kidney Int.* **51(2):** 591-602.

Duke, T., Cox, A.K., Remedios, A.M., Cribb, P.H. and Komulainen-Cox, A.M. (1994). The analgesic effects of administering fentanyl or medetomidine in the lumbosacral epidural space of cats. *Vet. Surg.* **23(2):** 143-148.

Ebert, J. and Varner, P.D. (1980). The effect of use of epidural morphine sulfate for postoperative orthopaedic pain. *Anaesthesiology.* **53:** 257-258.

Edderai, D., Aran, A., Woringer, E. and Houben, P. (2001). Preliminary results on the chemical immobilization of African rodents. The brush tailed porcupine (Atherurus africanus, Gray, 1842) and giant rat. *Study on four protocols Revue-d' Elevage-et-de-Medicine-Veterinarie-des-Pays-Tropicaux* **54(2):** 169-174.

Eichner, R.D., Proir, R.L. and Kvascnicka, W.G. (1979). Xylazine-induced hyperglycaemia in beef cattle. *Am. J. Vet. Res.* **40:** 127-129.

Eisenach, J.C. (1992). Intraspinal α_2 -adrenogic analgesia in sheep. In: Short, CE and Poznak, AV eds. Animal pain, Churchill, Livingstone, New York, 277-280.

Eisenach, J.C. and Tong, C. (1991). Site of haemodynamic effects of intrthecal alpha-2-adrenergric agonists. *Anaesthesiol.,* **74:** 766.

Eisenach, J.C., Dewan, D.M., Rose, J.C. and Angelo, J.M. (1987). Epidural clonidine produces antinociception, but not hypotension in sheep. *Anaesthesiol.,* **60:** 496-501.

Ekblom, A., Westmnan, L., and Soderland, A. (1993). Is intra-articular pethidine an alternative to local anaesthetics in arthroscopy? A double-blind study comparing prilocaine with pethidine. Knee-surg-spoorts. *Traumatol-arthros.* **1(3-4):** 189-1974.

Ekenstam, B., Enger, B. and Pettersson, G. (1957). N-alkyl pyrolidine and N-alkyl piperidine carbomglic acid amides. *Acta Chem. Scand.*, **11:** 1183.

Fields, H.L., Emson, P.C., Leigh, B.K., Gilbert, R.F.T. and Iverses, L.L. (1980). Multiple opiate receptor sites on primary afferent fibres. *Nature,* **284:** 351-353.

Fikes, L.W., Lin, H.C. and Thurmon, J.C. (1989). A preliminary comparison of lidocaine and xylazine as epidural analgesics in ponies. *Vet. Surg.*, **18(1):** 85-86.

Finco, D.R. (1980). Kidney function. In Kaneko J.J., ed. Clinical biochemistry of domestic animals, 3rd ed. New York :Academic Press.

Fleetwood-Walker, S.M., Mitchelli, R. and Hope, P.J. (1985). An α_2 -adrenoreceptor mediates the selective inhibition by noradrenaline of nociceptive responses of identified dorsal horn neurons. *Brain Res.*, **334:** 243-254.

Ford, D.J., Raj, P.P. and Singh, P. *et al.* (1984). Differential peripheral nerve block by local anesthetics in the cat. *Anesthesiol.* **60(1):** 28-33.

Fox, S.M., Mellor, D.J. Firth, E.C., Hodge, H. and Lawoko, C.R.O. (1994). Changes in plasma cortisol concentrations before, during and after analgesia, anaesthesia and anaesthesia plus ovariohysterectomy in bitches. *Res. Vet. Sci.* **57:** 110-118.

Foye, W.O., T.L. Lemke and Wiliam, D.A. (1995). Principles of medicinal chemistry. Wiliams and Wilkins. Fourth Edition.

Freise, H., Anthonsen, S., Fischer, L.G., Van Aken, H.K. and Sieben, Kamper (2005). Continuous thoracic epidural anesthesia induces segmental block in the awake rat. *Anesth. Analg.* **100(1):** 255-262.

Freitas, P.M.C., Lima, Cap, Mota, F.C.D., Goulart, M.R., Shimizu, B.J., Eurides, D., Melo, M.S. (2002). Comparison betweenthe use of 0.25% and 0.75% bupivacaine solutions for the bractial plexus blockade in cats. **18:** 3, 218-222.

Frey, H.H. and Soehring, K. (1954). Intersuchungen ueber die durch laessigkeit der dura mater des hundes fuer procain. II Mitteilung : Procainnachweisim rueckenmark waehrend der epiduralanesthesie. *Arch. Exp. Veterinaermed.* **8:** 803-806.

Frumin, M.J., Schwartz, H. and Burns, J.J. *et al.* (1953). The appearance of procaine in the spinal fluid during epidural block in man. *J. Pharmacol. Exp. Ther.* **109:** 102-105.

Futema, F., Fantoni, D.T., Auler-Junior, J.O.C., Cortopassi, S.R.G., Acaui, A., Stopiglia, A.J. (2002). A new brachial plexusblock technique in dogs. *Vety. Anaesthesia and Analgesia,* **29(3):** 133-139.

Gangwar, S.D., Pandey, N.N. and Celly, C.S. (1990). Clinico haematological profile of calves in experimental uraemia of post-renal origin. *Ind. Vet. J.* **67:** 645-648.

Ganti, A.S. 6th Edition A text book of Veterinary Pathology.

Gebhardt, B. (1994). Pharmacology and clinical results with peridural and intrathecal administration of ketamine. *Anaesthetist.*, **43(2):** S34-40.

Gera, K.L. and Nigam, J.M. (1981). Biochemical and haematological studies following retension of urine due to urolithiasis in buffaloes. *Ind. Vet. J.* **58:** 403-406.

Gerlach, K., Bonath, K., Ristić, D.J.Z. and Knorr, S. (1983). Possibilities for prolonged anaesthesia with bupivacaine and prolonged analgesia with morphine in dogs by means of an extradural permanent catheter. *Fort. Der. Veterinars Medizin*, **37:** 231-236.

Gill, G.V., Prudhoe, K., Cook, D.B. and Latner, A.L. (1975). Effect of surgical trauma on plasma concentrations of cyclic AMP and cortisol. *Br. J. Surg.*, **62:** 441-443.

Glynn, C.J., Mather, L.E. and Cousins, M.J. (1981). Peridural meperidine in humans : Analgesic response, pharmacokinelics and transmission into CSF. *Anaesthesiology.* **55:** 520-526.

Gonzalez-Arrieta, M.L., Martinez, H.M.A., Ramirez, M.L. (2004). Analgesic alternatives for the control of post-operatory pain in radical mastectomy. *Cir. Cir. Oct.*, **72(5):** 363-8.

Gordon, N.H., Scott, D.B., Percy Robb, I.W. (1973). Modification of plasma corticosteroid concentrations during and after surgery by epidural blockage. *Br. Med. J.* **5853:** 581-583.

Graham, M.J., Kent, J.E., Molony, V. (1997). Effects of four analgesic treatments on the behavioural and cortisol responses of 3-week old lambs to tail ducking. *Vet. J.* **153(1):** 87-97.

Greene, N.M. (1983). Uptake and elimination of local anesthetics during spinal anesthesia . *Anesth. Analg.* **62:** 1013-1024.

Greene, N.M. (1985). Distribution of local anaesthetic solutions within the subarachnoid space. *Anesth. Analg.*, **62:** 1013-1024.

Greene, S.A. and Thurmon, J.C. (1985). *Equine Pract.*, **7:** 14.

Greene, S.A., Keegan, R.D. and Weil, A.B. (1995). Cardiovascular effects after epidural infection of xylazine in isoflurane-anaesthetized dogs. *Vet. Surg.*, **24(3):** 283-289.

Greene, S.A., Thurmon, J.C., Tranquilli, W.J. and Benson, G.J. (1986). Decreased antidiurectic hormone concentration is associated with xylazine-induced diuresis in mares (Abstr.). *Vet. Surg.* **15:** 459.

Grubb, T.L., Reibold, T.W. and Huber, M.J. (1993). Evaluation of lidocaine, xylazine and a combination of lidocaine and xylaziine for epidural analgesia in Llamas. *J. Am. Vet. Med. Assoc.* **203(10):** 1441-1444.

Grubb, T.L., Riebold, T.W. and Huber, M.J. (1992). Comparison of lidocaine, xylazine and xylazine/ lidocaine for caudal epidural analgesia in horses. *J. Am. Vet. Med. Assoc.*, **201(8):** 1187-1190.

Grubb, T.L., Riebold, T.W., Crisman, R.O. and Lamb, L.D. (2002). Comparison of tidocaine, xylazine and lidocaine-xlazine for caudal epidural analgesia in cattle. *Vet. Anaesth Anaglesia,* **29(2):** 64-68.

Guyton, A.C. (1991). Textbook of medical physiology, 8th edn. Prisum Books (Pvtl.) Ltd.

Halder, S., Bose, P.K. (2001). Preemptive analgesic studies of xylazine and buprenorphine combination via epidural route in dog. *Indian J. Anim. Health,* **40(1):** 28-30.

Hall, L.W. and Clarke, K.W. (1983). Veterinary Anesthesia. 8th ed. ELBS and Bailleire Tindall, London.

Hall, L.W., Clark, K.W. (2001). Anesthesia of cattle In : Veterinary anaesthesia 10th edn. W.B. Saunders, pp. 315-338.

Hall, L.W., Clark, K.W. and Trim, C.M. (2001). Veterinary anaesthesia 10th edition, W.B. Saunders London, pp. 3, 226.

Hansen, B., Hendrix, P.K. Critical Care,acute pain management. (2002). In: Dhupa, N. Murtaugh, R.J., Bonangura, J.D., eds. Kirks current Veterinary therapy XIII. Philadelphia. W.B. Saunders. Co., 57-61.

Hansraj, Amarapal, Singh, G.R. and Aithal, H.P. (2000). *Indian J. Anim. Sci.*, **70:** 362.

Hansraj, Amarpal, Singh, G.R. and Aithal, H.P. (2002). Comparison of preemptive analgesia with epidrual pethidine and ketamine for the management of post-operative pain in dogs. *Indian Vet. J.*, **79:** 1059-1062.

Hara, S., Takahashi, K., Tomizawa, N., Nagashima, Y., Sasaki, N., Jorgensen, R.J. (2002). Effects of fasting and xylazine sedative on digestive tract mobility, rumen VFA and certain blood components in ruminants. **19:** 5-14.

Hardie, E.M. (1996). Recognization and management of pain in small animals. *Small Anim. Med. Digest.* **2(2):** 89-96.

Harper, A.A. and Lawson, S.N. (2000). Electrical properties of rat dorsal root ganglian neurones with different peripheral nerve conduction velocities. *J. Physiol.*, **359:** 47-63.

Harper, A.A., Lawson, S.N. (1985). Conduction velocity is related morphological cell type in rat dorsal root ganglion neurons. *J. Physiol.* **359:** 31-46.

Haskins, S.C. (1987). *J. Am. Vet. Med. Assoc.* **191:** 1266 (cited by Kaneko 1989).

Hawkey, C.M. (1985). Changes in blood count during sedation and anaesthesia. *Br. Vet. Zool. Soc. Newsl.* **19:** 27-31.

Heim, K.E., Morrell, J.S., Ronan, A.M. and Tagliaferro, A.R. (2002). Effects of ketamine-xylazine and isoflurane on insulin sensitivity in dehydroepiandrosterone sulfate treated minipigs. *Comparative Med.*, **52(3):** 233-237.

Hendrickson, D.A., Kruse-Elliot, K.T. and Broadstone R.V. (1996). A comparison of epidural saline, morphine and bupivacaine for pain relief after abdominal surgery in goats. *Vet. Surg.* **25:** 83-87.

Hensen, B.D. (1994). Analgesic therapy. *Compend Cont. Educ. Pract. Vet.* **16:** 868-875.

Himmelfarb, J., Hakim, R.M. (2003). Oxidative stress in uremia. *Curr. Opin. Nephrol. Hypertens.* **12(6):** 593-598.

Howe, J.R., Yaksh, T.L. and Go, V.L.W. (1987). The effect of unilateral dorsal root ganglionectomies or ventral rhizotomies on α_2-adrenoceptor binding to, and the substance, P, enkephalin and neurotensin content of the cat lumbar spinal cord. *Neuroscience,* **21:** 385-394.

Hsu, W.H. and Hummel, S.K. (1981). Xylazine induced hyperglycaemia in cattle : A possible involvement of α_2 -adrenergic receptors regulating insulin release. *Endocrinol.* **109:** 825-829.

Hugar, B. (1993). Studies on medetomidine as a preanaesthetic to ketamine anaeesthesia in goats. M.V.Sc. thesis submitted to Deemed University, IVRI, Izatnagar, India.

Hughes, H.C. and Lang, M.C. (1983). Control in pain in dogs and cats. In : Animal pain, preception and alleviation, Kitchell R.L., Erickson, H.H. ed. Bethesda, Md : Americal Physiological Society. pp. 207-291.

Humphreys, C.F. and Kay, H. (1976). The control of post operative wound pain with the use of bupivacaine infections.

Humphreys, C.F. and Kay, Harold (1976). The control of post-operative wound pain with the use of bupivacaine injections. *J. Urol.* **116 (5):** 618-619.

Hussain, S.S. and Amresh, K. (1988). Bupivacaine HCl for epidural anaesthesia in buffalo calves. *Ind. J. Vet. Surg.* **9:** 2-17.

Hylden, J.L.K. and Wilcox, G.L. (1983). Pharmacological characterization of substance P induced nociception in mice. Modulation by opioid and noradrenorgnic agonists at the spinal level. *J. Pharmacol. Exp. Ther.*, **226:** 398-404.

Illera, J.C. Gonzalez, Gil,A. Silvan, G., Illera, M. (2000). The effects of different anaesthetic treatments as the adrenocortical functions and glucose levels in NZW rabbits.

Ilson, B.E., Bland, P.S., Jorkasky, D.K. (1992). Intraoperative versus routine hemodialysis in end stage renal disease in patients undergoing open heart surgery. *Nephron.* **61:** 170-175.

Islas, J.A., Astorga, J. and Laredo, M. (1985). Epidural ketamine for control of postoperative pain. *Anesth. Analg.* **64:** 1161-1162.

Jackson, R., Reid, J.A., Thorburn, J. (1995). Volume predoading is not essential to prevent spinal-epidural anaesthesia for caessarean delivery. *Br. J. Anesth.*, **75:** 262-5.

Jadon, N.S., Joshi, H.C., Singh, B. and Kumar, A. (1989). Urological and biochemical changes in urethral obstruction in buffaloes. *Ind. J. Vet. Med.* **9:** 29-30.

Jain, N.C. (1986). Schalm's Veterinary Haematology, 4th Edn. Lea. and Febiger, Philadelphia.

Jang-Hwangsoo, Lee Mangee, Jan, I.H. (2002). Effects of yohiobine and atipamezole in dogs anaesthetized with xylazine-ketamine combination on EEG. **19(2):** 174-185.

Jean, G. St., Skarda, R.T., Muir, W.W. and Hoffsis, G.F. (1990). Caudal epidural analgesia induced by xylazine administration in cows. *Am. J. Vet. Res.*, **51(8):** 1232-1236.

Jlson, B.E., Bland, P.S., Jorkasky, D.K. *et al.* (1992). Intraoperative verus routine hemodialysis in end stage renal disease patients undergoing open heart surgery. *Nephron,* **61:** 170-175.

Johnson, R.E., Fudala, P.J. andPayne, R. (2005). Buprenorphine : considerations for pain management. *J. Pain Symptom Manage.* **29(3):** 297-326.

Joshi, H.C., Zangana, I.K. and Saleem, A.N. (1989). Haematobiochemical and electrocardiographic changes in uraemia in sheep. *Ind. J. Vet. Med.* **9:** 95-99.

Katz, J. and Nelson, W. (1992). Effects of intrathecal morphine injected with bupivacaine on pain after orthopaedic surgery. *Br. J. Anaesth.* **55:** 415-422.

Keele, A.C. and Neele, E. (1971). Samson Wright's Applied Physiology. 12th edn. Oxford University Press, London.

Kelawala, N.H., Amresh Kumar, Chaudhary, S., Singh, H.N. and Singh, H.P. (1996). Effect of epidural xylazine with diazepam premedication in dogs. *Indian Vet. J.* **73:** 552-557.

Kim, J.K., Jeong, S.M., Yi, N.Y., Jeong, M.B., Lee, E.S., Nam, t.C., Seo, K.M. (2004). Effect of intratesticular injection of xylazine-ketamine combination on canine castration. *Journal of Vet. Sci.,* **5(2):** 151-155.

Kinjavdekar, P. (1998). Spinal analgesia with alpha-2 agonists and their combinations with ketamine and lignocaine in goats. Ph.D. thesis submitted in Vety. Surg. IVRI, Izatnagar.

Kinjavdekar, P., Singh, G.R., Amarpal; and Aithal, H.P. (1999). Clinical use of spinal xylazine and ketamine in ruminants. *Ind. Vet. J.* **76:** 1101-1103.

Kiss. I. and Killian, M. (1992). Does opiate premedication influence postoperative analgesia? A prospective study. *Pain.* **48:** 157-158.

Kissin, I., Bright, C.A., Bradley, E.L. Jr. (2000). The effect of ketamine on opioid induced acute tolerance can it explain reduction of opoid consumption with ketamine-opoid analgesic combinations. *Anesth. Analg.* **91(6):** 1483-1488.

Kitahata, L.M., Taub, A. and Koska, Y. (1973). Lamina-specific suppression of dorsal horn unit activity by ketamine hydrochloride. *Anesthesiol.* **38:** 4-11.

Klasen, J., Junger, A., Hartmann, B., Benson-M, Jost, A., BAnzhaf, A., Kwapisz, M., Hempelmnn, G. (2003) Differing incidences of relevant hypotention with combined spinal epidural anaesthesia and spinal anaesthesia. *Anesth. Analg.* **96(5):** 1491-1495.

Klide, A.M. (1984). Anaesthesia for urogenital surgery. *Vet. Clin. North. Am. Small Anim. Pract.,* 14.

Knight, A.P. (1980). Xylazine. *J.Am. Vet. Med. Assoc.,* **176:** 454-455.

Ko, J.C.H., Thurman, J.C., Benson, J.G. *et al.* (1992). Evaluation of analgesia induced by epidural injection of determidine or xylazine in swine. *J. Vet. Anaesth.,* **19:** 56-60.

Kolwas, J. (1979). Drugs Today. **15:** 357.

Komai, H. and McDewell, T.S. (2001). Local anaesthetic inhibition of voltage-activated potassium currents in rat dorsal root ganglian neurons. *Anaesthesiology,* **94:** 1089-1095.

Krishna, M.R., Kumar, R.V.S., Ramakrishna, O. (2001). A note on the effect of glucose on bupivacaine anaesthesia in buffalo calves. *Cheiron.* **30:** 1-2, 54-55.

Kristensen, O., Espegren, O., Asland, R., Jakobsen, E., Lie, O., Seiler, S. (2005). Buprenorphine and methalone to opiate addicts a randomized trial. *Tidsskr. Nor. Laegeforen,* **125(2):** 148-151.

Kruskal, W.H. and Wallis, W.A. (1952). Use of ranks in one criterion variance analysis. *J. Amer. Statist. Asso.*, **47:** 583-621.

Kuchinka, G.D. and Riedesel, D.H. (1995). Management of acute post operative pain in dogs and cats. *IOWA State Veterinarians.* **56:** 2, 71.

Kumar, A. and Thurmon, J.C. (1979). Cardiopulmonary, haematolgoical and biochyemical effects of xylazine. *Lab. Animal Sci.*, **29:** 4.

Kuraishi, Y., Hirota, N., Sato, Y., Kaneko, S., Satoh, M. and Takagi, H. (1985). Noradrenergic inhibition of the release of substance P from the primary afferents in the rabbit spinal dorsal horn. *Brain Res.* **359:** 177-182.

Lacombe, P., Blaise, G., Hollmann, C., Tanguay, M., Loulmet, D. (1991). Isoproterenool corrects the effects of bupivacaine on the eletrophysiologic properties of the isolated rabbit heart. *Anesth. Analg.* **72(1):** 70-74.

Lanz, E., Thesis, D., Riess and Somme, V. (1982). Epidural morphine for postoperative analgesia. A double blind study. *Anaesth. Analg.*, **61:** 230-240.

Lawhead, R.G., Blaxau, H.S. and Bylund, D.B. (1992). α_{2A} is the predominant a_2 adrenergic receptor subtype in human spinal cord. *Anaesthesiol.*, **77:** 983-991.

Lebeux, M. (1975). Sheep a model for testing spinal and epidural anaesthetic agents. *Lab. Anim. Sci.*, **1975:** 25: 629-633.

LeBlanc, P.H. and Caron, J.P. (1990). Clinical use of epidural xylazine in the horse. *Equine Vet. J.* **22(3):** 180-181.

LeBlanc, P.H. and Eberhart, S.W. (1990). Cardiopulmonary effects of epidurally administered xylazine in horse. *Equine Vet. J.*, **22:** 389-391.

LeBlanc, P.H., Caron, J.P., Patterson, J.S., Brown, M. and Matta, M.A. (1988). Epidural injection of xylazine for perineal analgesia in horses. *J. Am. Vet. Med. Assoc.*, **193:** 1405-1408.

Lee Danghee, Bae-Chunsik (2001). Effect of xylazine in cattle under rope restrained conditions. *Journal of Veterinary Clinics,* **18(3):** 189-194.

Lee, A.G. (1976). Model for action of local anesthetics. *Nature.* **262:** 545.

Lee, I., Yamagish, N., Oboshi, K., Ayukaw, Y., Sasaki, N., Yamada, H. (2004). Comparison of xylazine, lidocaine and the two drugs combined for modified dorsolumbar epidural anaesthesia in cattle. *Veterinary Rec.*, **155(25):** 797-799.

Lee, I., Yausagishi, N., Oboshi, K., Yamada, H. (2003). Effect of epidural fat on xylazine-induced dorsolumbar epidural analgesia in cattle. *Vet. J.*, **165(3):** 330-332.

Lewis, C.A., Coustable, P.D., Huhn, J.C. and Morin, D.E. (1999). Sedation with xylazine and lembosacral epidural administration of lidocaine and xylazine for umblical surgery in calves. *J. Am. Vet. Med. Assoc.* **214(1):** 89-95.

Lewis, M.J., Swan, S.K. (1997). A pofpourri of drug Idiosyncracies in ESRD, Seminars in Dialysis, **10:** 278-287.

Lima, M.S., Malta, M., Lamas, L. (2001). Comparison of the effects of xylazine on the increase of blood glucose in Friesan and Mertolenga heifers. *Revista Portuguesa de-Ciencias Veterinarias.* **96:** 149-152.

Lin-Hiichu, Trachte, E.A., Steiss, J.E., Carson, R.L. (1998). Evaluation of analgesia induced by epidural administration of medetomidine to cows. *Am. J. Vet. Res.* 59: 162-167.

Livingston, A., Low, J. and Morris, B. (1984). Effects of clonidine and xylazine on body temperature in the rat. *Br. J. Pharmacol.* **81:** 189-195.

Livingston, A., Waterman, A.E., Bouchenafa, O. and Kyles, A. (1992). Antinociceptive effects of intrathecal opioids and α_2 -agonists in sheep. In: Short, CE and Poznak, AV eds. Animal pain Churchill Livingstone, New York, pp. 281-291.

Lucky, N.S., Haque, M.A., Alam, M.R. and Hashim, M.A. (2001). Effects of different anaesthetic agents on various clinical parameters in chickens (*Gallus gallus*) Bangladesh. *Veterinary* **18(2):** 89-94.

Luginbuhl, M., Gerber, A., Schnider, T.W., Petersen, Felix, S, Arendt-Nielsen, L., Curatolo, M. (2003). Modulation of renifentanil induced analgesia, hyperalgesia and tolerance by small dose ketamine in humans. *Anesth. Analg.* **96(3):** 726-732.

Lumb, W.V. and Jones, E.W. (1984). Spinal anesthesia. In: Veterinary Anaesthesia. 9th Edn. Lea and Febiger, Phliadelphia, pp. 393-412.

Lumb, W.V. and Jones, E.W. (2001). Other methods of general anaesthesia. In: Veterinary anaesthesia : 9th edn. Lea and Febiger, Philadelphia, pp. 238-244.

Luna, S.P., Cassu, R.N., Castro, G.B., Teixerira, Neto, F.J., Silva, Juniiior, J.R., Lopes, M.D. (2004). Effects of four anaesthetc protocols on the neurological and cardiorespiratory variables of puppies born by caesarean section. *Vet. Rec.* **154(13):** 387-389.

Luna, S.P., Taylor, P.M. (2001). Cardiorespiratory and endocrine effects of endogenous opioid antagonism by malaxone in ponies anaesthetized with halothane. *Res. Vet. Sci.* **70(2):** 95-100.

Luna, S.P.L., Cruz, M.L., Carregaro, A.B.,Margues, J.E. (2003). *Revista Brasleira de Ciencia Veterinaria.* **10(1):** 34-38.

MacDonald, E. and Virtanen, R. (1992). Review of the pharmacology of m edetomidine and detomidine : Two chemically similar α_2-adreconceptor agonists used as veterinary sedatives. In : Short, C.E. and Poznak, A.V. eds. Animal Pain, Churchill Livingstone, New York. pp. 181-191.

MacDonald, E.J., Cavan, K.R. and Smith, T.K. (1988). Effect of acute oral doses of T-2 toxin on tissue concentrations of biogenic amines in the rat. *J. Anim. Sci.*, **66:** 434-441.

Madsen, S.N., Brandt, M.R., Engquist, A., Badawi, I. and Kehlet, H. (1977). Inhibition of plasma cyclic AMP, glucose and cortisol response to surgery by epidural analgesia. *Br. J. Surg.*, **64:** 669-671.

Makady, F.M., Ahmed, I.H. and Seleim, S.M. (1990). Epidural anesthesia in goats using lignocaine HCl with and the without hyaluronidase. *Assiut Vet. Med. J.* **22(44):** 164-166.

Malinovsky, J.M., Cozian, A., Lepage, J.Y. *et al.*, (1991). Ketamine and midzolam neurotoxicity in the rabbit. *Anaesthesiol.*, **75:** 91-97.

Maru, A. and Pachauri, S.P. (1995). Evaluation of multiple serum enzymes as indicators of liver pathology in domestic buffaloes. *Ind. J. Anim. Sci.* **55(7):** 549-550.

Mason, P. (1999). Central mechanisms of pain modulation. *Curr. Opin. Neurobiol.* **9(4):** 436-441.

Mathews, K.A., Doherty, T., Dyson, D.H., Wilcock, B. and Valliant, A. (1990). *Canadian Vety. J.*, **31:** 766-771.

Mayer, M.L. and Westbrook, G.L. (1983). A voltage clamp analysis of in ward (anomalous) rectification in mouse spinal sensory ganglian neurones. *J. Physiol.*, **340:** 19-45.

McEvoy, G.K. (1995). American hospital formulatory service drug information. Bethesda, Maryland, American Society of Health System Pharmacist.

McGorum, B.C., Murphy, S. and Love E.M. Milne (1999). Clinicopathological features of equine primary hepatic disease. *Vety. Record.* **145:** 734-739.

McMeekan, C.M., Stafford, K.J., Mellor, D.J., Bruce, R.A., Ward, R.N., Gregory, N.G. (1998a). Effects of regional analgesia and or a non-steroidal anti-inflammatory analgesic on the acute cortisol response to dehorning in calves. *Research in Veterinary Science.* **64:** 147-150.

McQuay, H.J., Carroll, D. and Moore, R.A. (1988). Postoperative orthopaedic pain. The effect of opiate premedication and local anaesthetic blocks. *Pain.* **33:** 291-295.

Meadows, H.J. and Randall, A.D. (2001). Functional characterisation of human TASK-3, an acid sensitive two pore domain potassium channel. *Neuropharmacology,* **40:** 551-559.

Mirakhur, K.K., Sobti, V.K. and Nigam, J.M. (1984). Effect of thiopentone anaesthesia on plasma catecholamine and cortisol in buffalo calves (*Bubalus bubalis*). *Ind. J. Vet. Surg.* **3:** 86.

Mishra, A.K., Amresh Kumar and Harpal Singh (1993). Physiological and clinical effects of unilateral and bilateral segmental epidural and subarachnoid anesthesia with bupivacaine hydrochloride in buffaloes. *Ind. Vet. J.* **70:** 1146-1149.

Miyamoto, H., Saitoy, Kirihara, Y., Hara, K., Sakura, S., Kosoaka, Y. (2000). Spinal co-administration of ketamine reduces the development to tolerance to viseceral as well as somatic antinociception during spinal morphine infusion. *Anesth. Analg.* **90(1):** 136-141.

Mogensen, T. and Bartholdy, L. (1992). Pre-operative infiltration of incisional area enhances post-operative analgesia to a combined low dose epidural bupivacaine and morphine regime after upper abdominal surgery. *Reg. Anaesth.,* **17:** 74.

Monzaly, M.E.L.M., Amrousi, S.E.L. and Gindi, M.H.E.L. (1972). Some aspects of tranquilization and anaesthetization in the goat. *J. Vet. Med.* **19A:** 219.

Moore, D.C., Bridenbaugh, L.D., Bridenbaugh, P.D. and Tucker, G.T. (1970). Bupivacaine : A review of 2,077 cases. *Indian J. Med. Assoc.,* **214:** 713.

Morimoto, K., Nishimura, R., Matsunaga, S., Mochizuki, M. and Sasaki, N. (2001). Epidural analgesia with a combination of bupivacaine and buprenorphine in rats. *J. Vet. Med.* Series, A, **48(5):** 303-312.

Murata, K., Nakagawa, I. and Kumeta, Y. (1989). Intrathecal clonidine suppresses noxiously evoked activity of spinal wide dyanamic range neurons in cats. *Anaesth. Analg.,* **69:** 185-191.

Naguib, M., Adu-Gyamfi, Y. and Absood, G.H. (1986). Epidural ketamine for post operative analgesia. *Can Anaesth. Soc. J.,* **33:** 16-21.

Nau, C., Vogel, w., Hemplemann, G. and Brau, M.E. (1999). Stereoselectivity of bupivacaine in loal anaesthetic sensitive ion channels of peripheral nerve. *Anaesthesiology,* **91:** 786-795.

Negus, S.S., Bidlack, J.M., Medlo, N.K., Furness, M.., Rice, K.C., Brandt, M.T. (2002). Delta opioid antagonist effects of buprenorphine is rhesus monkeys. *Behav. Pharmacol.* **13(7):** 557-570.

Neilan, C.L., Husbands, S.M., Breeden, S., Ko, M.C., Auto, M.D. *et al.* (2004). Characterization of the complex morphinan derivative BV72 as a high efficasy long lasting mu-opioid receptor agonist. *Eur. J. Pharmacol.* **499(1-2):** 107-16.

Nolan, A., Livingston, A. and Waterman, A. (1987). Antinociceptive action of intravenous α_2-adrenoceptor agonist in sheep. *J. Vet. Pharmacol. Ther.* **110:** 202-209.

Nolan, A., Livingston, A., Waterman, A.E. (1987). Investigation of the antinococeptive activity of buprenorphine in sheep. *Br. J. Pharmacol.* **92(3):** 527-533.

Nolan, A.M. and Erhardt, W. (1990). The cardiorespiratory effects of intrathecal xylazine in the conscious rabbit. *J. Vet. Pharmacol. Ther.,* **13:** 29-35.

Nollet, H., Deprez, P., Van Ham, L., Gasthuys, F., Dewulf, J., Vanderstraeten, G. (2003). Influence of detomidine and buprenorphine on motor-evooked potentials in horses. *Vet. Rec.* **152:** 534-537.

Oboussier, W., Biscoping, J. (1988). The action of bupivacaine HCl following supraclavicular plexus block is patients with chronic kidney insufficiency. *Red. Anaesth.* **11(3):** 65-70.

Olschewski, A., Hempleman, G., Vogel, W. and Safronov, B.V. (1998). Blockade of Na^+ and K^+ currents by local anaesthetics in the dorsal horn neurons of the spinal cord. *Anesthesiology,* **88:** 172-179.

Ossipov, M.N., Suarez, L.J. and Spaulding, T.C. (1988). A comparison of the antinocicetive and behavioural effects of intrathecally administered opiates, α_2-adrenergic agonists and local anesthetics in mice and rats. *Anesth. Analg.* **67:** 616-624.

Otto, K.A., Gerich, T. and Volmert, C. (2000). Haemodynamic and electroencephalographic effects of epidural buprenorphine during orthopaedic hindlimb surgery in sheep a comparison with intramscular buprenorphine and epidural saline. *Journal of Experimental Animal Science,* **41(3):** 121-132.

Ozaydin, I., Kilic, E. (2003). Lumbosacral intrathecal anaesthesia with isoboric bupivacaine in cattle. *Indian Vety. Journal,* **80(6):** 540-542.

Ozba, B., Ozaydin, I., Kilic, E., Atalan, G. and Baran, V. (2003). Xylazine and zolezepam – Tiletamine anaesthesia in calves for uneblical operation. *Indian Vet. J.,* **80:** 46-48.

Pascoe, P.J. (1992). Advantages and Guidelines for using epidural drugs for Analgesia. *J. Small Anim. Pract.* **22:** 421-423.

Pascoe, P.J. and Dyson, D.H. (1993). Analgesia after lateral thoracotomy in dogs : Epidural morphine vs intracostal bupivacaine. *Vet. Surg.* **22:** 141-147.

Pathak, R. (1999). Post-traumatic pain and stress management in goats : Preemptive analgesia with epidural bupivacine hydrochloride and xylazine-ketamine. M.V.Sc. thesis submitted in Vety. Surg. IVRI, Izatnagar.

Pathak, R., Amasrpal, Kingavdekar, P., Pratap, K. and Singh, G.R. (2002). Reduction of pain by neuroxial blocade with bupivacaine. *Indian J. Anim. Sci.,* **72(7):** 535-538.

Pereira, M.T.C., Carvahlo, S.F.M. (2003). Brachial plexusblock in dogs using bupivacaine. *Archives of Vet. Sci.,* **8(2):** 15-18.

Pernow (1983). Substance P. Pharmacol. Rev, **35:** 85-141.

Peshin, P.K. and Kumar, A. (1983). Haemocytological and Biochemical. Effects of xylazine in buffaloes. *Ind. Vet. J.* **60:** 981-986.

Peshin, P.K. and Kumar, A. (1979). Physiological and sedative effects of xylazine in buffaloes. *Ind. Vet. J.* **56:** 864-871.

Peshin, P.K., Singh, A.P., Singh, J., Singh, P. and Singh, M. (1985). Acid base, blood gas and biochemical changes following urethral ligation in buffalo calves (*Bubalus Bubalis). Acta Veterinaria Yogoslavia.* **35:** 143-148.

Pflug, A., Aashein, G. and Beck, H. (1976). Spinal anaesthesia : bupivacaine versus tetracaine. *Anesth. Analg.,* **55:** 489-492.

Picavet, M.T.J.E., Gasthuys, F.M.R., Leavens, H.H. and Watts, S.A. (2004). Cardiopulmonary effects of combined xylazine-gauphenesin-ketamine infusion and extradural intercoccygeal lidocaine anaesthesia in calves. *Vet. Anaesthesia and Analgesia,* **31(1):** 11-19.

Pitman, D.L., Natelson, B.H., Otten Weller, J.E., McCarty, R., Pritzel, T., Tapp, W.N. (1995). Effects of exposure to stressors of varying predictability on adrenal function in rats. **109(4):** 767-776.

Pockett, S., Spinal Cord (1995). Synaptic plasticity and chronic pain. *Anesth. Analg.,* **80:** 173-9.

Ponder, S.W. and Clarke, W.G. (1980). Prolonged depression of thermoregulation after xylazine administration to cats. *J. Vet. Pharmacol. Ther.* **3:** 203-207.

Prado, M.E., Streeter, R.N., Mandsager, R.N., Shawley, R. V. and Clapool, P.L. (1999). Pharmacologic effects of epidural versus intramuscular administration of detomidine in cattle. *American J. Vet. Res.* **60(10):** 1242-1247.

Priston, M.J., Hughes, J.M., Santillo, M., Christies, I.W. (2004). Stability of an epidural analgesic mixture containing epinephrine, fentanyl and bupivacaine. *Anaesthesia.* **59(10):** 979-983.

Raffee, M.R. (1984). Use of anaesthetic in cats with obstructive uropathy. *Vet. Clin. North. Am.,* **14:** 691-702.

Raidurg, R., Ranganath, B.N., Jayadevappa and Srinavas, C.L. (1995). Study of xylazine as an epidural analgesia in experimental calves. *Indian Vet. J.,* **72:** 894-895.

Reddy, S.V.R. and Yaksh, T.L. (1980). Spinal noradrenergic terminal system mediates antinociception. *Brain Res.,* **189:** 391-401.

Reddy, T.K.K., Rao, T.M., Chandrasekhar, E.L., Haragopal, V. (2003). Effects of haloperiodol on barbiturate anaesthesia in dogs. **24(1):** 46.

Reddy, Y.K. (1992). A comparative study on peritoneal and pleural dialysis in the management of uraemia following urinary bladder rupture in goats. M.V.Sc. thesis submitted in Surgery to the Deemed University, I.V.R.I., Izatnagar (U.P.).

Rehage, J., Kehler, W. and Scholz, H. (1994). Use of xylazine for epidural anaesthesia in cattle. Deutsche-Tierarztliche-Wochenschrift **101(1):** 14-16.

Rekha Pathak, Amarpal, Kinjavdekar, P., Pratap, K. and Singh, G.R. (2004). Evaluation of epidural xylazine and ketamine for premptive analgesia in goats. *Ind. J. Anim. Sci.* **74:** 501-503.

Rings, D.M. and Miur, W.W. (1982). Cardiopulmonary effects of intramuscular xylazine-ketamine in calves. *Can. J. Comp. Med.,* **46:** 386-389.

Robertson, S.A., Taylor, P.M., Lascelles, B.D., Dixon, M.J. (2003). Changes in thermal threshold response in eight cats after administration of buprenorphine, butorphenol and morphine. *Vet. Rec.* **153(15):** 462-465.

Rocktaeschel, J. Morimatus, H., Uchinos, Gold Smith, D., Poustie, S. Story, D., Gutteridge, G., Belpmoo, R. (2003). Acid-base status of critically ill patients with acute renal failure analysis based on stewart. *Figge Methodology Crit Care.* **7(4):** 60.

Rodriguezcde-la-Torre-M.R., Gallego Alonso, J.., Gil-Fernandez, M. (2004). Pulmonary edema related to administration of 15-methyl-prostaglandin F_2 alpha during a caessarean section. *Rev-Esp-Anesteriol-Reamim.* **51(2):** 104-107.

Roerig, S.C., Fujinoto, J.M. (1989). Multiplicative interaction between intratherally and intracerebroventricularly administered mu opioid agonists but limited interactions between delta and kappa agonists foro antinociception in mice. *J. Pharmacol. Exp. Therapeut.* **249(3):** 762-768.

Roscow, C.E., (1985). Sufentanyl. In : Anaesthesiology : Stanley, T.H., Pretty, W.C. (eds.) Today and Tommorow. Martinus Nipjhoff Dordrecht p. 29.

Rouot, B., Quennedey, M.C. and Schwartz, J. (1982). Characteristics of EHT-Yohimbine binding on rat brain alpha-2 adrenoceptors. *Nau-Schmiedebergs Archives of Pharmacology,* **321:** 253-259.

Roy, S.D. and Flynn, G.L. (1989). Transdermal delivery of narcotic analgesics : Comparitive permeabilities of narcotic analgesics through human cadaver skin. *Pharmacol. Res.* **6:** 825.

Ruckebuch, Y. and Allal, C. (1987). Depression of reticulo-ruminal motor function through the stimulation of alpha-2 adrenoceptors. *J. Vet. Pharmacol. Ther.,* **10:** 1-10.

Ryder, S.,Way, W.L. and Trevor, A.J. (1978). Comparative pharmacology of the optical isomers of ketamine in mice. *Eur. J. Pharmacol.* **49:** 15-23.

Sabbe, M.B., Penning, J.P., Ozoki, G.T. and Yaksh, T.L. (1994). Spinal and systemic action of the alpha-2- receptor agonist dexmedetomidine in dogs. *Anaesthesiol.* **80(5):** 1057-1072.

Saeker, G. and Gaida, A. (1955). Grundlagefragen der periduralanaesthesie. II. Gewebsinnendruck,m windkessel funktion and abflussverhaeltnise des periduralgewebes. *Anaesthesist.* **3:** 270-273.

Sao, P.C., Sahay, P.N., Dass, L.L. (2002). Epidural analgesia induced by varying doses of xylazine ketamine and their combination in goats. *J. of Res-Birsa-Agricultural-University.* **14(2):** 259-263.

Sarafzadeh, R.F. (1999). Ketamine HCL epiduralanalgesia in the dog. *J. Faculty Vet. Med. Univ.* Tehran, **54(3):** 7-10.

Sawyer, D.C. and Rech, R.H. (1987). Analgesia and behavioural effects of butorphanol, nalbuphine, pentazocine in cat. *J. Am. Anim. Hosp. Assoc.***23:** 438-446.

Schalm, O.W., Jain, N.C. and Carroli, E.J. (1975). Veterinary Haematology 3rd edn. Philadelphia, Lea and Febiger.

Schricker, T., Klubien, K., Wykes, L., Carlif (2000). Effect of epidural blockage in protein, glucose and lipid metaboolism in the fasted state and during dextrose infusion in volunteers Anaesthesiology. **92(1):** 62-69.

Scull, T.J., Hemmings, G.T., Carli, F., Weeks, S.K., Mazza, L., Zingg, H.H. (1998). Epidural analgesia in early labour blocks the stress response but uterine contractions remain unchanged. *Can. J. Anaesth.* **45(7):** 626-630.

Sebel, P.S., Barret, C.W. and Kirkc, J.C. (1987). Transdermal absorption of fentanyl and sufentanyl ,in main. *Eur. J. Clin. Pharmacol.* **32:** 529.

Seeman, P. (1972). The membrane actions of anesthetics and tranquilizers. *Pharmacol. Rev.* **24(4):** 583.

Segura, A.J., Metodiewa, D., Welch, C.J. (1998). Metabolic activation of dopamine O-quinones to 0 semiquinones by NADPH cytochrome P450 redurase may play an important role in oxidative stress and adoptotic effects. *Biochim Biophs Acta.* **138(1):** 1-6.

Serteyn, D., Coppens, P., Jones, R., Verstegen, J., Philippart, C. and Lamy, M. (1993). Circulatory and respiratory effects of the combination medetomidine-ketamine in beagles. *J. Vet. Pharmacol. Ther.* **16(2):** 199-206.

Shapiro, L.A., Hoffman, S., Jedeikin, R. and Kaplan, R. (1981). Single injection epidural anaesthesia with bupivacaine and morphine for prostatectomy. *Anaesth. Analg.* **60:** 818-820.

Sharda, R., Kumar, A., Jadon, N.S. (2001). Effect of epidural blockage on then management of nephritis in buffloes. *Ind. J. Anim. Sci.* **71(4):** 312-315.

Sharma, S.D., Gahlot, T.K., Purohit, N.R., Sharma, C.K., Chouhan, D.S. and Chaudhary, R.J. (1994). Haematological and biochemical alterations following epidural administration of xylazine in camels (Camelus dromedarius). *J. Camel Pract. Res.* **1(1):** 26-29.

Shesky, M.C., Rocco, A.G., Bizzarri-Schmid, M., Francis, D.M., Edstram, H. and Covino, B.G. (1983). A dose response study of bupivacaine for spinal anaesthesia. *Anesth. Analg.,* **62:** 931-935.

Short, C.E., Hoppingardner, J. and Bendick, F. (1971). Comparative responses of pentazocine and meperidine for control of postoperative pain in dogs. *Vet. Med. Small. Anim. Clin.* **166:** 586-588.

Simeonova, G., Dimov, D., Dinev, D., Zlateva, N. (2001). Feline urologic syndrome II. Changes in some clinical and Laboratory indices. *Bulgarian J. Vet. Med.,* **4(3):** 183-188.

Simonnet, N., Marcantoni, N., Simmonet, L., Gritton, C. *et al.,* (2004). Puffy hand in long term intravenous drug users. *J. Mal. Vasc.* **29(4):** 201-4.

Singh, A.A., Singh, J., Peshin, P.K., Gahlawat, J.S., Singh, P. and Nigam, J.M. (1985). Evaluation of xylazine-ketamine anaesthesia in buffaloeos. *Zentral blatt fur veterinar medicin.* **32:** 54-58.

Singh, J., Singh, A.P., Peshin, P.K. and Sharma, D.K. (1983). Ureaemia in camel and effects of xylazine administration. *Haryana Vet.* **22:** 105.

Singh, K. (2003). Evaluation of epidural bupivacaine, ropivacaine and xylazine-ketamine for anaesthetic management of goats suffering from urolithiasis. M.V.Sc. thesis submitted to Deemed University, IVRI, Izatnagar.

Singh, N.K., Kinjavdekar, P., Amarpal, Singh, G.R., Pratap, K. (2002). Influence of epidural analgesics on plasma glucose and insulin in arthritic goats. *Indian J. Vety. Surgery,* **23(1):** 37-38.

Singh, P. (1999). Xylazine, ketamine, lignocaine and their combinations for lumbar epidural analgesia in buffalo calves. M.VSc. Thesis submitted to Deemed University, IVRI, Izatnagar.

Singh, S., Young, S.S., Mc Donell, W.M., O'Grady, M. (1997). Modification of cardiopulmonary and intestinal mobility effects of xylazine with glycoopyrroolate in horses. *Can. J. Vet. Res.* **61(2):** 99-107.

Singh, V. Amarpal, Kinjavdekar, P., Aithal, H.P., Pratap, K. (2005). Medetomidine with ketamine and bupivacaine for epidermal analgesia in buffaloes. *Vet. Res. Commun.* **29(1):** 1-18.

Singh, V., Amarpal, Kijavdekar, P., Pratap, K. (2004). Epidural analgesia with xylazine, medetomidine, ketamine and bupivacaine in buffaloes : a comparison. *Indian Journal of Animal Sci.,* **74(2):** 172-174.

Skaer, T.L. (2004). Practice guidelines for transdermal opioids in malignant pain. *Drugs,* **64(23):** 2629-98.

Skarda, R.T., Yeary, R.A., Muir, W.W. and Burt, J.K. (1981). Appearance of procaine in spinal fluid during segmental epidural analgesia in cows. *Am. J. Vet. Res.* **42(4):** 639-646.

Skarda, R.T. and Muir, W.W. (1979a). Segmental lumbar epidural analgesia in cattle. *Am. J. Vet. Res.* **40(1):** 52-57.

Skarda, R.T. and Muir, W.W. (1982a). Haemodynamic and respiratory effect of segmental subarachnoid analgesia in adult Holstein cows. *Am. J. Vet. Res.* **43(8):** 1343-1348.

Skarda, R.T. and Muir, W.W. (1983a). Segmental epidural and subarachnoid analgesia in conscious horse : A comparative study. *Am. J. Vet. Res.* **44(10):** 1870-1876.

Skarda, R.T. and Muir, W.W. (1983b). Continuous caudal epidural and subarchnoid analgesia in conscious horse: A comparative study. *Am. J. Vet. Res.* **44(12):** 2290-2298.

Skarda, R.T. and Muir, W.W. (1992). Physiologic responses after caudal epidural administration of detomidine in horses and xylazine in cattle. *Animal Pain,* 1st edn., pp. 292-302. (eds) Short CE-and Poznak, V.A.V., Churchill Livingstone, London.

Skarda, R.T. and Muir, W.W. (1994). Caudal analgesia induced by epidural or subarachnoid administration of detomidine hydrochloride solution in mares. *Am. J. Vet. Res.* **55(5):** 670-680.

Skarda, R.T. and Muir, W.W. (1996). Analgesic, haemodynamic and respiratory effects of caudal epidurally administered xylazine hydrochloride solution in mares. *Am. J. Vet. Res.,* **57(2):** 193-200.

Skarda, R.T., Hubbe, Il-Jae, Muir, W.W., Bednarski, K.M., Madson, D.E. (1996). Sedation and anaesthesia in dogs and cats with cardiovascular disease. Part III: Ventillation, monitoring of respiration and post-operative analgesia. *Schweizer-Archiv-Fur-Tierheilkunde,* **138(6):** 312-318.

Skarda, R.T., St. Jean, G. and Muir, W.W. (1989). Influence of caudal epidural xylazine on central nervous, respiratory, cardiovascular and reticuloruminal motor function in cows. *Vet. Surg.* 249.

Skarda, R.T., St. Jean, G. and Muir, W.W. (1990). Influence of tolazoline on caudal epidural administration of xylazine in cattle. *Am. J. Vet. Res.* **51(4):** 556-560.

Skarda, R.T., St. Jean, G. and Muir, W.W. (1990). Influence of tolazoline on caudal epidural administration of xylazine in cattle. *Am. J. Vet. Res.,* **51(4):** 556-560.

Slearda, R.T. and Muir, W.W. (1994). Caudal analgesia induced by epidural or subarachnoid administration of detoxidin hydrochloride solution in mares. *Am. J. Vet. Res.,* **55(5):** 670-680.

Smith, A.C., Perrotti, J.M., Mansell, A.L. and Manroe, P.J. (1985). Ketamine analgesia is not related to an opiate action in the periaqueductal gray region of the rat brain. *Pain,* **21:** 253.

Smith, L.J., Yu-Kwang An - [Yu-KAJ] and Yu-KAJ (2001). A comparison of epidural buprenorphine with epidural morphine for postoperative analgesia following stifle surgery in dogs. *Veterinary Anaesthesia and Analgesia,* **28(2):** 87-96.

Sobbe, M.B., Penning, J.P., Ozaki, T.G. and Yaksh, T.L> (1994). Spinal and systemic action of the alpha-2 receptor agonist dexmedetomidine in dogs. *Anesthesiol.,* **80(5):** 1057-1072.

Solimon, M.K., Amrousi, S.E. and Khamis, M.Y. (1965). The influence of tranquilizers and barbiturate anaesthesia on the blood picture and electrolytes of dogs. *Vet. Rec.* **77:** 1256.

Solomon, R.E. and Gebhart, G.F. (194). Synergistic antinociceptive interactions among drugs administered to the spinal cord. *Anesth. Analg.,* **78:** 1164-1172.

Soontornvipart, K., Rauser, P., Kecova, H., Lexamaulora, L. (2003). Effect of anaethetic premedication with medetomidine buprenophine on the aqueous tear production in dogs. *Acta Veterinaria Brno,* **72(2):** 267-272.

Souza, A.P.-de; Rezende, M.L.-de; Nunes, N., Nishimori, C.T. *et al.* (2004). Buprenorphine cardiovascular and intracranial alterations in dogs anaesthetized with desfluorare. *Ciencia Rural,* **34(3):** 815-820.

Sporer, K.A. (2004). Buprenorphine : a primer for emergency physicians. *Ann. Emerg. Med.,* **43(5):** 580-4.

Srettici, G., Genfilini, A., Eichenberger, U., Zanderigo, E., Sarteri, V., Luginbuh, M., Curatolo, M. (2004). Combinations of bupivacaine, fentanyl and clonidine for lumbar epidural post operative analgesia : a novel optimization procedure. *Anaesthesia,* **59(10):** 979-83.

Stanway, G.W., Taylor, P.M., Brodbell, D.C. (2002). A preliminary investigation comparing pre-operative morphine and buprenorphine for post-operative analgesia and sedation in cats. *Vet. Anaesth Analgesia* **29(1):** 29-35.

Stein, C., Comisel, K. and Haimerl, E. (1991). Efficacy of intra-articular morphine after arthroscopic knee surgery. *N. Engl. J. Med.* **325:** 1123-1126.

Stevens, C.W., Lacey, C.B., Miller, K.E., Elde, R.F. and Saybold, V.S. (1991). Biochemical characterization and region quantification of mu, delta and kappa, opioid binding sites in rat spinal cord. *Brain Res.,* **550:** 77-85.

Stewart, L.S.A., Martin, W.J. (2003). Influence of post-operative analgesics on the development of neuropathic pain in rats. *Comparative Medicine,* **53(1):** 29-36.

Stone, E.A., Rawlings, C.A., Finco, D.R. and Crowell, W.A. (1981). *Am. J. Vet. Res.,* **42:** 1675-1680.

Tamsen, A., Sjostram, S., Hartvig, P., Persson, P., Gabrielsson, J. and Paalzaw, L. (1983). CSF and plasma kinetics of morphine and meperidine after epidural administration. *Anaesthesiol.,* **59:** A1196.

Tarkkila, P., Jsola, J. (1992). A regression model for identifying patents at high risk of hypotension, bradycardia and nausea during spinal anaesthesia. *Acta Anaesthesiol. Scand.*, **36:** 554-8.

Taylor, P.M. (1987). β-endrophin immunoreactivity during anaesthesia in equidae-*Vety-Anaesth. and Analg.* **27:** 27.

Tendillo, F.J., Pera, A.M., Mascias, A., Santos, M., Gomez de Sagura, I.A., Roman, F.S. and Castillo-Olivares, J.L. (1995). Cardiopulmonary and analgesic effects of epidural lidocaine, alfentanil and xylazine in pigs anaesthetizedwith isoflurane. *Vet. Surg.*, **24:** 73-77.

Thurmon, J.C., Nelson, R.D., Harsfield, S.M. and Rumore, R.A. (1978). Effects of xylazine hydroochloride on urine in cattle. *Australian Vet. J.* **54:** 178.

Tibirica, E., Feldman, J., Mermet, C. *et al.* (1991). An imidazoline specific mechanism for the hypotensive effect of clonidine : a study with yohimbine and idazoxan. *J. Pharmacol. Exp. Ther.* **256:** 600-613.

Tilley, L.P. (1985). Essentials of canine and feline electrocardiography. 2nd Edn. Lea & Febiger, Philadelphia.

Tiwari, S.K., Amresh-Kumar and Vainio, O. (1999). Cardiopulmonary effects of epidural xylazine or defomidine with and without local anaesthetics in recumbent buffaloes. *Indian J. of Anim. Sci.*, **69(11):** 918-920.

Tiwari, S.K. and Kumar, A. (1998). Clinicophysiological effects of epidural xylazine and detomidine with or without local anaesthetic in buffaloes. *Ind. J. Vet. Surg.*, **19(1):** 37.

Torda, T.A. and Pybus, D.A. (1981). Clinical experience with epidural morphine. *Anaesth. Intensive Care.* **9:** 129-134.

Torneke, K., Bergstrom, U., Neil, A. (2003). Interactions of xylazine and detomidine with alpha-2 adrenoceptors in brain tissue from cattle, swine and rats. *J. Vet. Pharmacol. Therap.*, **26:** 205-211.

Trim, C.M. (1981). Epidural analgesia with 0.75% bupivacaine for laparotomy in goats. *J. Am. Vet. Med. Assoc.*, **194:** 1292-1296.

Troncy, E., Junof, S., Keroack, S., Sammut, V., Pibarot, P., Genevois, J.P., Cuvelliez, S. (2002). Results of preemptive epidural administration of morphine with or without bupivacaine in dogs and cats undergoing surgery : 265 cases (1997-1999). *J. Vet. Med. Assoc.*, **221(5):** 666-672.

Trujillo, K.A. (2000). Are NMDA receptors involved in opiate induced neural behaviour plasticity ? A review of preclinical studies psychophacology (Beri), **151(2-3):** 121-41.

Tsuji, H., Asoh, T., Takeuchi, Y. and Shirasaka, C. (1983). Attenuation of adrenocortical response to upper abdominal surgery with epidural blockage. *Br. J. Surg.* **70:** 122-124.

Tung, A.S. and Yaksh, T.L. (1981). Analgesic effect of intrathecal ketamine in the rat. *Reg. Anesth.* **6:** 91.

Tyce, G.M., Yaksh, T.L. (1981). Monoamine release from cat spinal cord by somatic stimuli : an intrinsic modulatory system. *J. Physiol.* **314:** 513-529.

Umbricht, A. Herestis, M.A., Cone, E.T., Preston, K.L. (2004). Effects of high dose intravenous buprenorphine in experienced opioid abugers. *J. Clin. Psychopharmacol.*, **24(5):** 479-487.

Unnerstall, J.R., Kopajtic, T.A. and Kuhar, M.J. (1984). Distribution of α_2 -agonist binding site in the rat and human central nervous system, analysis of some function, anatomic correlates of the pharmacologic effects of clonidine and related odrenergic agonist. *Brain. Res. Rev.*, **7:** 69-101.

Vainio, O., Bloor, B.C. and Kim, C. (1992). Cardiovascular effects of a ketamine medetomidine combination that produces deep sedation in Yucatan miniswine. *Lab. Anim. Sci.* **42(6):** 582-588.

Venugopalen, C.S., Holmes, E.P., Fucci, V., Keefe, T.J. and Crawford, M.P. (1994). Cardiopulmonary effects of medetomidine in heart worm infected and non-infected dogs. *Am. J. Vet. Res.* **55(8):** 1148-1152.

Vesal, N., Cribb, P.H. and Frketic, M. (1996). Poostoperative analgesic and cardiopulmonary effects in dogs of oxymorphone administered epidurally and intramuscularly, and medetomidine administered epidurally : A comparative clinical study. *Vet. Surg.* **25:** 361-369.

Vesal, N., Sajedianfard, J. and Dehghani, S. (1998). Epidural xylazine HCL as an analgesic and sedative for teat surgery in cows. *Indian J. Anim. Hlth.*, **37(1):** 59-60.

Vickes, M.D., Schnieden, H., Woodsmith, F.G. (1984). Drugs in anaesthetic practice, 6th edn. Bufferworth and Co. Ltd.

Virtanen, R. (1986). Pharmacology of detomidine and other α_2-adrenoceptors agonists in the brani. *Acta. Vet. Scand.* **82:** 35-46.

Virtanen, R., Ruskoaho, H. and Nyman, L. (1985). Pharmacological evidence for the involvement of α_2-adreoceptors in the sedative effect of detomidine, a novel sedative-analgesic. *J. Vet. Pharmacol. Ther.* **8:** 30-37.

Wagner, A.E., Muir, W.W. III and Hinchcliff, K.W. (1991). Cardiovascular effects of xylazine and detomidine in horses. *Am. J. Vet. Res.* **52:** 651-657.

Wald-Oboussier, G., Viell, B., Biscoping, J. (1988). The action of bupivacaine-HCl following supra-clavicular plexus block in patients with chronic kidney in sufficiency Reg. *Anaesth.* **11(3):** 65-70.

Waterman, A.E., Livingston, A., Bouchenafa, O. and Dash, A. (1988). Analgesic actions of α_2-adrenergic agonist drugs administered intrathecally in conscious sheep. (Abstr.). In Proceedings. Third international Congress of Vet. Anesth. Brisbane, Australia.

Waterman, A.E, Livingstone, A. and Benchenafa, O. (1987a). Analgesic effects of intrathecally applied α_2-adrenoceptor agonists in cancious, inrestrained sheep. *Neuropharmacol.*, **27:** 213-216.

Welch, J.A., Wohl, J.S., Wright, J.C. (2002). Evaluation of postoperative respiratory function by serial blood gas analysis in dogs treated with transdermal fentanyl. *J. Vet. Emergency Critical Care,* **12(2):** 81.

Westhues, W.G. and Fritsch, R. (1964). Animal anaesthesia. Oliver and Bajd – Edinburgh and London, p. 153.

White, P.F., Ham, J., Way, W.L. and Trevor, A.J. (1980). Pharmacology and ketamine isomers in surgcal patients. *Anesthesiol.* **52:** 231.

White, P.F., Way, W.L. and Trevor, A.J. (1982). Ketamine-Its Pharmacology and Therapeutic uses. *Anesthesiol.* **56(2):** 119-136.

Wilcox, G.L., Carlsson, K.H., Jochim, A. and Jurna, I. (1987). Mutual potentiation of antinociceptive effects of morphine and clonidine on motor and sensory responses in rat spinal cord. *Brain Res.* **405:** 84-93.

Woolf, C.J. (1983). Evidence for a central component of post-injury pain hypersensitivity. *Nature.* **308:** 686-688.

Woolf, C.J. and Thompson, S.W.N. (1991). The induction and maintenance of central sensitizastion is dependent on N-methyl-D-aspartic acid receptor activation : Implications for the treatment of post injury pain hypersensitivity states. *Pain.* **44:** 293-299.

Yaksh, T.L. (1981). Spinal opiate analgesia : Characteristics and principles of action. *Pain.* **11:** 293-346.

Yaksh, T.L. and Reddy, S.V.R. (1981). Studies on the primate on the analgesic effects associated with intrathecal actions of opiates, alpha-adrenergic agonists and baclogen. *Anesthesiol.*, **54:** 451-467.

Yaksh, T.L. and Rudy, T.A. (1976). Chronic catheterization of the spinal subarachnoid space. *Physiol. Behav.*, **17:** 1031.

Yaksh, T.L., Tyce, G.M. (1979). Micro injection of morphine into the periaqueductal gray evokes the release of serotonin from spinal cord. *Brain Res.* **171(1):** 176-181.

Yamamura, T., Harada, K., Okamura, A. and Kemmotsu, O. (1990). It the site of ketamine anaesthesia the N-methyl-D-asparate receptor ? *Anaesthesiol.*, **72:** 704-710.

Yamashit, A., Mastumeto, M., Matsumoto, S. etc. (2003). A comparison of the neurotoxic effects on the spinal cord of Tetracaine, lidocaine, bupivacaine and ropivacaine administered intrathecally in rabbits. *Anesth. Analg.*, **97:** 512-519.

Yamashita, K., Muir, W.W. (3rd), Tsubakishita, S., Abrahamsen, E., Lerch, P., Hubbel, J.A., Bednarski, R.M., Skarda, R.T., Izumisawa Y., Kotani, T. (2002). Clinical comparison of xylazine and medetamidine for premedication of horses. *J. Am. Vet. Med. Assoc.* **221(5):** 1144-1149.

Young, L.E. and Jones, R.S. (1990). Clinical observations on medetomidine/ketamine anaesthesia and its antogonism by atipamezole in the cat. *J. Small. Anim. Pract.* **31(5):** 221-224.

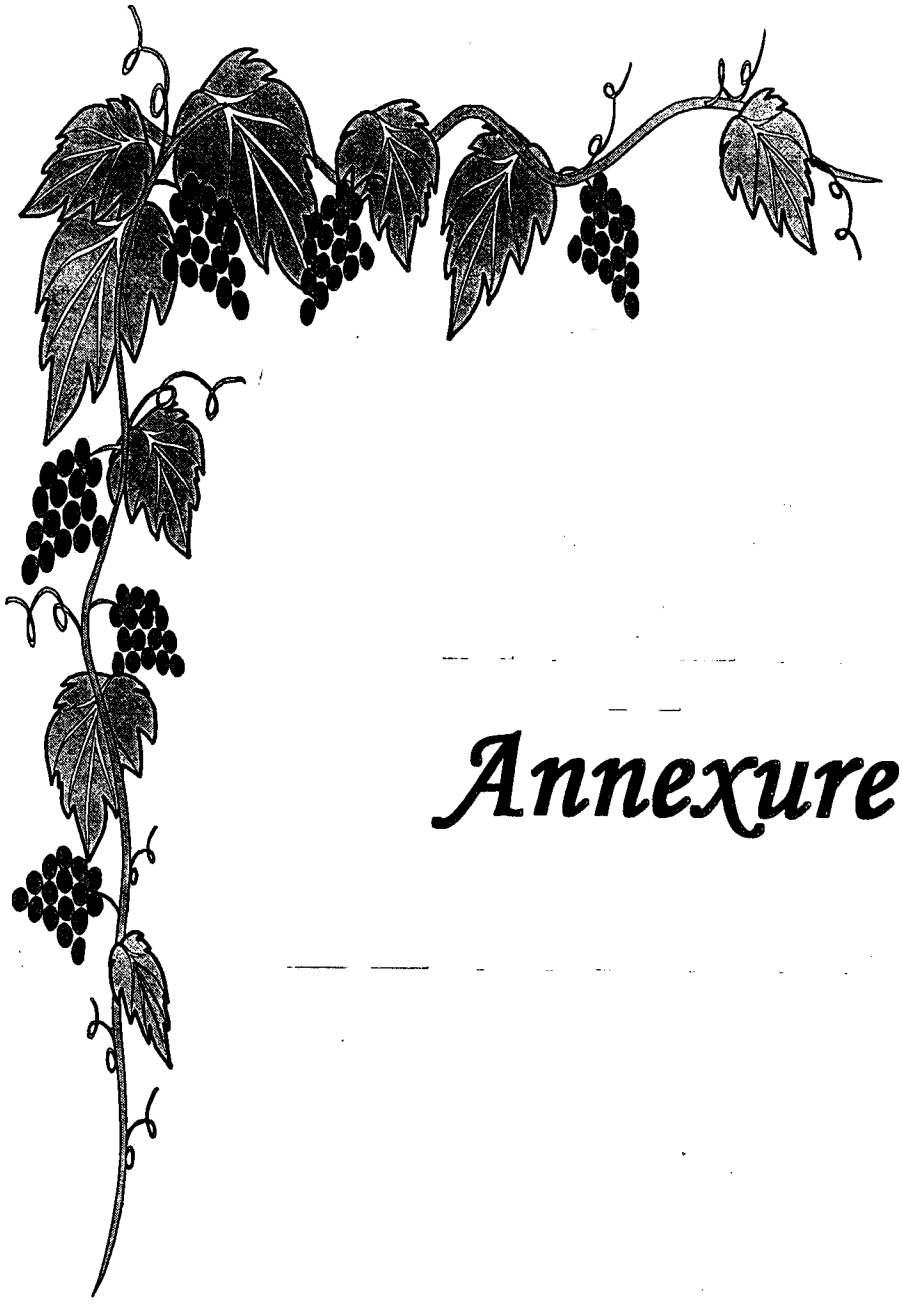
Youssef, H.A. (1992). Rompun in comparison with lidocaine for epidural analgesia in rabbits. *Assint. Vet. Med. J.*, **26(52):** 220-225.

Zemin, Xu, Chuanyao Tong, Hui-Liu Pan, Sergi, D.E., Cerda and James, C. Eisenach. (1997). Intraveous morphine increase release of nitric oxide from spinal cord byan-adrenergic and cholinergic mechanism. *J. Neurophysio.* **78:** 2072-2078.

Zieglgansberger, W. and Bayerl, H. (1976). The mechanism of inhibition of neuronal activity by opiates in the spinal cord of cat. *Brain Res.*, **115:** 111-128.

Zink, W., Graf, B.M. (2004). Benefit-risk assessment of bopivacaine in the management of post-operative pain. *Drug Surg.*, **27(14):** 1093-114.

□□□



Annexure

Table no. 4.1: Mean±SE of onset of analgesia in the animals of different groups

Group	Onset time (min)
A	6.6 ± 1.02^{c}
B	16.0 ± 1.86^{b}
C	29.0 ± 5.5^{a}
D	3.0 ± 0.3^{c}
E	2.6 ± 0.4^{c}
F	4.0 ± 0.4^{c}

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine

Means bearing different superscripts differ significantly at corresponding intervals ($P<0.05$)

Table no. 4.2 : Mean±SE of score of analgesia at perineum recorded in the animals of different groups

Group	Time Interval (min)														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
A	0.00 ±0.00	2.10^{ab} ±0.30	2.00^{ab} ±0.20	2.00^{ab} ±0.20	2.50^{ab} ±0.20	2.50^{ab} ±0.20	2.50^{ab} ±0.20	2.00^{ab} ±0.20	1.60^{ab} ±0.30	1.30^{ab} ±0.30	1.00^{ab} ±0.30	0.60^{ab} ±0.20	0.60^{ab} ±0.20	0.60^{ab} ±0.20	0.60^{ab} ±0.20
B	0.00 ±0.00	0.10^{a} ±0.10	0.30^{a} ±0.20	0.60^{a} ±0.20	1.10^{a} ±0.30	1.80^{ab} ±0.40	2.10^{ab} ±0.40	2.30^{ab} ±0.40	2.60^{b} ±0.30	2.50^{ab} ±0.30	1.80^{ab} ±0.40	1.50^{ab} ±0.40	1.10^{ab} ±0.30	0.60^{ab} ±0.20	0.60^{ab} ±0.20
C	0.00 ±0.00	0.00^{a} ±0.00	0.30^{a} ±0.30	0.50^{a} ±0.30	0.50^{a} ±0.30	0.80^{a} ±0.30	1.30^{a} ±0.30	1.50^{a} ±0.30	0.80^{a} ±0.30	0.30^{a} ±0.30	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00
D	0.00 ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	2.60^{b} ±0.20	2.60^{b} ±0.20	2.00^{b} ±0.00	2.00^{b} ±0.00	2.00^{b} ±0.00
E	0.00 ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	2.30^{b} ±0.20	1.60^{ab} 0.30	1.10^{ab} ±0.30	0.00^{a} ±0.00	0.00^{a} ±0.00
F	0.00 ±0.00	2.60^{b} ±0.20	2.80^{b} ±0.10	2.80^{b} ±0.10	2.80^{b} ±0.10	2.60^{ab} ±0.30	2.30^{ab} ±0.40	2.30^{ab} ±0.40	1.60^{ab} ±0.30	0.30^{a} ±0.30	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

Table no. 4.3 : Mean±SE of score of analgesia at Inguinal region recorded in the animals of different groups

Group	Time Interval (min)														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
A	0.00 ±0.00	1.50^{ab} 0.22	1.50^{ab} 0.22	1.80^{ab} 0.16	2.10^{ab} 0.30	2.30^{ab} 0.21	2.30^{ab} 0.21	2.10^{ab} 0.30	1.50^{a} 0.22	1.10^{ab} 0.16	0.50^{a} 0.22	0.50^{ab} 0.22	0.50^{ab} 0.22	0.30^{ab} 0.21	0.30^{ab} 0.21
B	0.00 ±0.00	0.30^{a} 0.30	0.60^{a} 0.40	0.80^{a} 0.40	1.10^{a} 0.40	1.30^{a} 0.40	1.80^{ab} 0.40	1.80^{ab} 0.40	2.10^{ab} 0.40	2.10^{ab} 0.40	1.50^{ab} 0.50	1.00^{ab} 0.30	0.80^{ab} 0.30	0.30^{ab} 0.20	0.30^{ab} 0.20
C	0.00 ±0.00	0.00^{a} ±0.00	0.10^{a} 0.10	0.30^{a} 0.30	0.60^{a} 0.30	0.60^{a} 0.30	1.10^{a} 0.40	0.80^{a} 0.40	0.60^{a} 0.30	0.30^{a} 0.30	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00
D	0.00 ±0.00	0.00^{a} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	1.60^{b} 0.21	1.50^{b} 0.22	1.00^{b} ±0.00	1.00^{b} ±0.00
E	0.00 ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	2.80^{b} 0.16	2.80^{b} 0.16	2.60^{b} 0.21	2.00^{b} ±0.00	1.00^{ab} 0.44	0.30^{ab} 0.21	0.00^{a} ±0.00	0.00^{a} ±0.00
F	0.00 ±0.00	2.10^{ab} ±0.47	2.10^{ab} 0.47	2.10^{ab} 0.47	2.80^{b} 0.16	2.30^{ab} 0.33	2.00^{ab} 0.44	2.00^{ab} 0.44	1.50^{a} 0.34	0.30^{a} 0.33	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals ($P<0.05$)

Table no 4.4 : Mean±SE of score of analgesia at tail recorded in the animals of different groups

Group	Time Interval (min)														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
A	0.00 ±0.00	2.10^{ab} ±0.40	2.60^{ab} ±0.30	2.60^{ab} ±0.30	2.80^{ab} ±0.10	2.80^{ab} ±0.10	2.80^{ab} ±0.10	2.60 ±0.40	1.60 ±0.20	1.00^{ab} ±0.20	0.50^{ab} ±0.20	0.50 ±0.20	0.30 ±0.20	0.30 ±0.20	0.10 ±0.10
B	0.00 ±0.00	0.10^{a} ±0.10	0.60^{a} ±0.30	1.00^{a} ±0.20	1.30^{ab} ±0.30	1.60^{ab} ±0.30	2.10^{ab} ±0.40	2.10 ±0.40	2.50 ±0.30	2.30^{ab} ±0.30	2.00 ±0.40	1.50 ±0.50	1.00 ±0.30	0.80 ±0.40	0.80 ±0.40
C	0.00 ±0.00	0.10^{a} ±0.10	0.50^{a} ±0.20	0.80^{a} ±0.10	0.80^{a} ±0.10	1.00^{a} ±0.00	1.30^{a} ±0.20	1.50 ±0.40	1.50 ±0.40	0.30^{a} ±0.30	0.30^{a} ±0.30	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00
D	0.00 ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00 ±0.00	3.00 ±0.00	3.00^{ab} ±0.00	1.00 ±0.00	1.00 ±0.00	1.00 ±0.00	1.00 ±0.00	1.00 ±0.00
E	0.00 ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00 ±0.00	2.80 ±0.10	2.60^{a} ±0.20	2.10^{b} ±0.10	1.50 ±0.30	1.00 ±0.40	0.10 ±0.10	0.00 ±0.00
F	0.00 ±0.00	2.60^{ab} ±0.20	2.80^{ab} ±0.10	2.80^{ab} ±0.10	2.80^{ab} ±0.10	2.50^{ab} ±0.30	2.30^{ab} ±0.40	2.30 ±0.40	2.00 ±0.40	0.80^{ab} ±0.50	0.50 ±0.50	0.50 ±0.50	0.50 ±0.50	0.50 ±0.50	0.50 ±0.50

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

Table no. 4.7 : Mean±SE of score of analgesia at throax recorded in the animals of different groups

Group	Time Interval (min)														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
A	0.00 ±0.00	0.00 ±0.00	0.50 ±0.30	0.50 ±0.30	0.80 ±0.50	0.80 ±0.50	0.80 ±0.50	1.10 ±0.40	0.80 ±0.30	0.80^{ab} ±0.30	0.80^{ab} ±0.30	0.40^{ab} ±0.20	0.20^{ab} ±0.10	0.20^{ab} ±0.10	0.20^{ab} ±0.10
B	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^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00
C	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^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00
D	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.30 ±0.30	1.00 ±0.40	1.30 ±0.40	2.50^{b} ±0.20	2.60^{b} ±0.20	2.30^{b} ±0.20	2.00^{b} ±0.20	1.80^{b} ±0.10	1.80^{b} ±0.10
E	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.30 ±0.20	0.60 ±0.20	1.30 ±0.40	1.30 ±0.40	1.60 ±0.50	2.00 ±0.60	1.60^{ab} ±0.50	1.30^{ab} ±0.40	1.30^{ab} ±0.40	0.50^{ab} ±0.20	0.00^{a} ±0.00	0.00^{a} ±0.00
F	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.30 ±0.30	0.60 ±0.40	0.30 ±0.30	0.30 ±0.30	0.10 ±0.10	0.00 ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

Table no. 4.8 : Mean±SE of score of analgesia at hind limb recorded in the animals of different groups

Group	Time Interval (min)														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
A	0.00 ±0.00	0.80^{ab} ±0.40	1.00^{ab} ±0.40	1.00^{ab} ±0.50	0.80^{ab} ±0.40	0.80^{ab} ±0.40	0.60^{ab} ±0.30	0.80^{a} ±0.40	0.50^{a} ±0.30	0.50^{a} ±0.30	0.50^{ab} ±0.30	0.50^{a} ±0.30	0.30 ±0.20	0.30 ±0.20	0.30 ±0.20
B	0.00 ±0.00	0.00^{a} ±0.00	0.00^{b} ±0.00	0.10^{a} ±0.10	0.50^{a} ±0.30	0.80^{ab} ±0.40	1.80^{ab} ±0.40	1.80^{ab} ±0.40	1.60^{ab} ±0.30	2.00^{ab} ±0.30	1.00^{ab} ±0.30	0.80^{ab} ±0.30	0.50 ±0.30	0.30 ±0.20	0.30 ±0.20
C	0.00 ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00
D	0.00 ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{a} ±0.00	2.60^{b} ±0.20	2.00^{ab} ±0.00	2.00^{b} ±0.00	2.00^{ab} ±0.00	2.00^{b} ±0.00	1.60^{b} ±0.20	1.50 ±0.20	0.50 ±0.20	0.20 ±0.10
E	0.00 ±0.00	2.80^{b} ±0.10	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	2.80^{b} ±0.10	2.60^{b} ±0.20	2.10^{b} ±0.10	1.60^{ab} ±0.30	1.60 ±0.30	0.30 ±0.30	0.00 ±0.00
F	0.00 ±0.00	1.50^{ab} ±0.50	2.00^{ab} ±0.40	2.10^{ab} ±0.40	2.30^{ab} ±0.30	1.80^{ab} ±0.40	2.00^{ab} ±0.40	1.80^{ab} ±0.40	1.10^{ab} ±0.40	0.60^{ab} ±0.40	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

Table 4.10 : Complete analgesia (score 3) of different regions produced by different anaesthetics and their duration

Sl. No.	Regions	Groups duration								
		A	B	C	D	E	F	G	H	I
1.	Perineum	x	x	x	5-90 min.	5-90 min.	x	15-20 min	10-60 min	x
2.	Inguinal	x	x	x	10-105 min	5-45 min	x	15-30 min	10-90 min	x
3.	Tail	x	x	x	5-90 min	5-60 min	x	20-30 min	10-90 min	x
4.	Thorax	x	x	x	x	x	x	x	60-75 min	x
5.	Digits	x	x	x	5-30 min	5-45 min	x	20-45 min	60-75 min	x
6.	Abdomen	x	x	x	60-75 min	x	x	x	only at 60 min	x
7.	Hind limbs	x	x	x	5-30 min	10-60 min	x	x	60-90 min	x
8.	Flank	x	x	x	15-90 min	x	x	x	60-75 min	x

Table no. 4.11 : Mean±SE of score of sedation recorded in the animals of different groups

Group	Time Interval (min)														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
A	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.30^{a} ±0.21	0.10^{a} ±0.16	0.10^{a} ±0.16	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00
B	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00^{a} ±0.00	0.30^{a} ±0.33	0.60^{a} ±0.42	1.60^{ab} ±0.49	1.60^{ab} ±0.42	3.00^{b} ±0.36	3.00^{b} ±0.36	3.00^{b} ±0.36	2.50^{b} ±0.22	2.10^{b} ±0.16	2.10^{b} ±0.16	2.10^{b} ±0.16
C	0.00 ±0.00	0.30 ±0.21	0.60 ±0.16	0.80^{ab} $\pm0.16^{ab}$	0.80^{ab} ±0.16	0.80^{a} ±0.16	0.80^{a} ±0.30	0.80^{a} ±0.30	0.60^{a} ±0.33	0.60^{ab} ±0.33	0.60^{ab} ±0.33	0.60^{ab} ±0.33	0.60^{ab} ±0.33	0.60^{ab} ±0.33	0.50^{a} ±0.22
D	0.00 ±0.00	0.00 ±0.00	0.30 ±0.33	1.10^{ab} ±0.40	1.30^{ab} ±0.33	1.50^{ab} ±0.42	2.00^{ab} ±0.25	2.50^{b} ±0.22	2.50^{ab} ±0.22	2.80^{b} ±0.16	2.80^{b} ±0.16	2.60^{b} ±0.21	2.00^{b} ±0.00	1.80^{b} ±0.16	1.50^{b} ±0.22
E	0.00 ±0.00	0.10 ±0.16	1.30 ±0.61	2.10^{ab} ±0.83	3.60^{ab} ±0.21	4.00^{b} ±0.00	4.00^{b} ±0.16	4.00^{b} ±0.16	3.30^{b} ±0.21	3.30^{b} ±0.21	2.80^{b} ±0.47	2.30^{b} ±0.55	1.60^{ab} ±0.33	1.50^{ab} ±0.34	1.30^{ab} ±0.21
F	0.00 ±0.00	0.00 ±0.00	1.30 ±0.42	1.50^{b} ±0.22	1.10^{b} ±0.16	0.80^{a} ±0.30	0.50^{a} ±0.34	0.10^{a} ±0.16	0.10^{a} ±0.16	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals ($P<0.05$)

Table no. 4.12 : Mean±SE of score of motor incoordination of hind limbs recorded in the animals of different groups

Group	Time Interval (min)														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
A	0.00 ±0.00	3.60^{ab} ±0.21	3.60^{ab} ±0.21	3.60^{ab} ±0.21	3.10^{ab} ±0.16	3.10^{ab} ±0.16	3.00^{ab} ±0.00	2.80^{ab} ±0.16	2.60^{ab} ±0.33	2.50^{ab} ±0.34	1.50^{ab} ±0.22	0.50^{a} ±0.22	0.50^{ab} ±0.22	0.50^{ab} ±0.22	0.50^{ab} ±0.22
B	0.00 ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.60^{a} ±0.33	1.10^{a} ±0.47	2.30^{a} ±0.21	2.30^{a} ±0.21	2.30^{ab} ±0.21	2.30^{ab} ±0.21	2.60^{ab} ±0.21	2.50^{ab} ±0.22	2.30^{ab} ±0.21	2.10^{b} ±0.30	2.10^{b} ±0.30	2.10^{b} ±0.30
C	0.00 ±0.00	1.60^{ab} ±0.33	1.60^{ab} ±0.33	1.60^{ab} ±0.33	1.80^{a} ±0.40	1.60^{a} ±0.55	1.60^{a} ±0.55	1.60^{a} ±0.55	1.30^{a} ±0.61	1.60^{ab} ±0.76	2.00^{ab} ±0.89	2.00^{ab} ±0.89	2.00^{ab} ±0.89	1.60^{ab} ±0.76	1.60^{ab} ±0.76
D	0.00 ±0.00	3.80^{b} ±0.00	3.80^{b} ±0.00	3.80^{b} ±0.00	4.00^{b} ±0.00	4.00^{b} ±0.00	4.00^{b} ±0.00	3.50^{ab} ±0.20	3.30^{ab} ±0.30	3.00^{b} ±0.20	2.80^{b} ±0.10	2.80^{b} ±0.10	2.10^{b} ±0.10	2.00^{b} ±0.00	2.00^{ab} ±0.00
E	0.00 ±0.00	3.80^{b} ±0.00	4.00^{b} ±0.00	4.00^{b} ±0.00	4.00^{b} ±0.00	4.00^{b} ±0.00	4.00^{b} ±0.00	4.00^{b} ±0.00	3.80^{b} ±0.16	2.00^{ab} ±0.00	2.00^{ab} ±0.00	1.50^{ab} ±0.22	0.80^{ab} ±0.16	0.50^{ab} ±0.22	0.00^{a} ±0.00
F	0.00 ±0.00	3.80^{b} ±0.00	3.80^{b} ±0.00	4.00^{b} ±0.00	3.30^{ab} ±0.42	3.10^{ab} ±0.40	2.50^{ab} ±0.56	1.60^{a} ±0.55	1.10^{a} ±0.54	0.50^{b} ±0.50	0.30^{a} ±0.30	0.10^{a} ±0.16	0.10^{a} ±0.16	0.00^{a} ±0.00	0.00^{a} ±0.00

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0 05)

Table no. 4.13 : Duration of analgesia in the animals of different groups

Group	Duration time (min)
A	180
B	180
C	105
D	180
E	180
F	180

A : Bupivacaine, B : Xylazine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine

Table no. 4.14 : Mean±SE of score of heart rate (per minute) recorded in the animals of different groups

Group	Time Interval (min)														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
A	46.50 ±2.12	42.00^{b} ±2.38	45.33 ±4.08	39.50* ±1.25	41.33 ±0.84	21.00 ±1.77	39.16^{b*} ±1.10	42.00 0.73	41.50* ±1.25	41.83 ±1.79	44.00 ±2.06	42.00 ±2.00	41.50 ±1.50	41.33 ±1.33	41.50 ±1.50
B	48.00 ±2.30	55.33^{a} ±4.05	50.00 ±3.54	49.33 ±4.80	47.33 ±4.78	49.66 ±4.91	48.66^{ab} ±5.20	46.00 ±3.96	45.33 ±4.08	44.66 ±4.43	44.00 ±4.61	40.00* ±1.03	39.33** ±1.60	40.66* ±1.60	40.00 ±1.03
C	45.25 ±3.81	50.50^{abc} ±4.32	44.75 ±3.46	44.37 ±3.37	44.37 ±4.20	45.62 ±3.35	43.25 ±3.70	41.25 ±3.94	41.75 ±4.09	45.50 ±4.11	44.25 ±4.00	44.75 ±4.30	44.50 4.25	44.25 ±4.21	44.75 ±4.03
D	58.00 ±4.16	30.00^{c} ±4.16	50.00 ±4.16	63.33 ±10.7	45.33 ±1.33	49.33** ±4.80	60.00^{a} ±6.11	35.33** ±2.90	35.66** ±2.96	33.66* ±1.85	36.00** ±3.05	36.00* ±3.05	42.00 ±4.16	42.00 ±4.16	42.00 ±4.16
E	52.25 ±8.61	41.00^{b} ±3.41	39.50* ±4.78	39.50* ±5.31	39.75* ±5.63	34.00* ±4.76	36.00^{b*} ±4.89	40.00* ±5.88	40.50 ±3.68	43.50 ±5.31	43.00 ±5.06	43.50 ±4.64	44.25 ±4.04	46.00 ±3.46	46.00 ±3.46
F	50.40 ±3.70	53.60^{ab} ±2.99	50.40 ±6.27	50.40 ±6.76	49.60 ±3.25	48.80 ±2.72	51.20^{ab} ±5.98	51.20 ±5.98	50.40 ±1.60	56.00 ±4.38	54.80 ±5.20	53.60 ±5.26	52.40 ±2.04	52.40 ±2.04	51.60 ±2.22

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)
** Significantly different from the base value within group (P<0.05)*
*** Significantly different from the base value within group (P<0.01)*
**** Significantly different from the base value within group (P<0.001)*

Table no. 4.15 : Mean±SE of score of respiration rate/min recorded in the animals of different groups

Group	Time Interval (min)														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
A	14.00 ±1.71	17.33 ±6.16	19.33 ±3.73	17.50 ±2.82	14.66 ±2.86	16.33 ±2.55	14.83 ±2.37	15.83 ±3.44	15.00 ±2.91	15.50 ±2.91	16.50 ±3.34	16.33 ±2.55	15.83 ±2.76	15.83 ±2.68	16.00 ±2.68
B	21.33 ±1.97	21.33 ±1.97	20.66 ±3.49	21.33 ±3.04	22.00 ±2.47	22.00 ±3.83	24.00 ±5.36	20.66 ±4.18	19.33 ±4.66	21.33 ±5.71	21.33 ±3.81	21.33 ±3.81	19.33 ±2.81	20.00 ±4.13	20.00 ±4.13
C	15.25 ±1.68	16.62 ±1.53	17.00 ±1.68	17.37 ±1.79	16.75 ±0.69	13.62 ±0.75	12.25 ±1.09	14.62 ±1.01	14.25 ±1.03	13.00 ±0.65	14.50 ±1.84	13.50 ±0.73	13.25 ±1.13	13.25 ±1.13	13.25 ±1.13
D	13.33 ±0.42	9.33 ±0.42	9.00*** ±0.44	15.66 ±1.20	13.00 ±0.44	12.33 ±0.33	15.00 ±1.00	8.33*** ±0.33	8.33*** ±0.33	12.33 ±0.33	12.33 ±0.33	12.33 ±0.33	14.33 ±1.08	14.33 ±1.08	14.33 ±1.08
E	12.00 ±0.73	13.33 ±2.17	13.50 ±2.30	11.83 ±1.04	10.50 ±1.08	12.00 ±0.51	10.66 ±1.22	11.50 ±2.02	12.00 ±1.55	13.33 ±2.40	12.33 ±1.96	10.83 ±1.10	11.83 ±1.04	12.50 ±0.71	12.50 ±0.71
F	18.66 ±1.68	17.33 ±1.33	14.00 ±1.71	17.33 ±1.08	24.50 ±11.36	21.50 ±8.00	23.50 ±7.57	22.83 ±7.73	22.83 ±7.73	24.00 ±7.30	26.66 ±10.71	26.00 ±10.82	25.83 ±11.05	16.66 ±1.35	16.66 ±1.22

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)
** Significantly different from the base value within group (P<0.05)*
*** Significantly different from the base value within group (P<0.01)*
**** Significantly different from the base value within group (P<0.001)*

Table no. 4.17 : Mean±SE of values of haemoglobin (g/dl) in the animals of different groups

Group	Time Interval						
	0	30	60	90	120	180	24 hrs.
A	10.56[a] ±0.13	10.43 ±0.29	9.90*** ±0.10	9.80* ±0.10	10.56 ±0.13	10.56[a] ±0.13	10.56[a] ±0.13
B	9.86[a] ±0.29	9.23** ±0.29	8.76 ±0.39	9.00 ±0.51	9.10 ±0.58	8.86*[c] ±0.43	9.76[ab] ±0.39
C	10.10[a] ±0.10	10.23 ±0.23	9.53 ±0.23	9.66 ±0.20	9.86 ±0.29	10.20[ab] ±0.10	10.00[a] ±0.39
D	10.36[a] ±0.26	10.10* ±0.30	10.03** ±0.23	10.43 ±0.13	10.70 ±0.45	9.70[b] ±0.10	10.26[a] ±0.26
E	10.10[a] ±0.34	9.80 ±0.20	8.93 ±0.91	8.60 ±0.66	9.43 ±1.33	9.93 ±0.17	10.06[a] ±0.06
F	9.90[b] ±0.95	10.63 ±0.49	10.46 ±0.46	10.80 ±0.43	10.93 ±0.43	10.40[b] ±0.50	10.00[b] ±0.57

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine

Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

** Significantly different from the base value within group (P<0.05)*

*** Significantly different from the base value within group (P<0.01)*

**** Significantly different from the base value within group (P<0.001)*

Table no. 4.18 : Mean±SE of values of PCV (%) in the animals of different groups

Group	Time Interval						
	0	30	60	90	120	180	24 hrs.
A	31.66 ±0.33	31.33 ±0.88	29.66* ±0.33	29.33 ±0.33	31.66 ±0.33	31.66[a] ±0.33	31.33[a] ±0.33
B	29.66 ±0.88	27.67 ±0.88	26.33** ±1.20	27.00* ±1.52	27.34 ±1.76	26.66*[b] ±1.33	27.00*[c] ±1.00
C	30.33 ±0.33	30.66 ±0.66	28.66* ±0.66	29.00* ±0.57	29.66 ±0.88	30.66[a] ±0.33	30.66[a] ±0.33
D	31.00 ±1.00	30.33 ±0.88	30.66 ±0.66	30.33 ±1.20	33.66 ±1.33	30.00[a] ±1.00	30.33 ±0.88
E	31.33 ±1.70	30.66 ±1.70	28.00 ±3.70	28.66 ±3.70	27.66 ±3.70	31.00[a] ±1.50	29.66[ab] ±0.33
F	29.66 ±0.31	30.66 ±1.40	30.66 ±0.88	32.00 ±1.15	31.66 ±1.20	29.66[b] ±0.33	29.33[b] ±0.33

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine

Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

* *Significantly different from the base value within group (P<0.05)*

** *Significantly different from the base value within group (P<0.01)*

*** *Significantly different from the base value within group (P<0.001)*

Table no. 4.19 : Mean±SE of values of total leucocyte count (thousand/ µl) in the animals of different groups

Group	Time Interval						
	0	30	60	90	120	180	24 hrs.
A	5.76 ±0.36	5.94 ±0.38	5.99 ±0.40	6.11 ±0.46	6.04 ±0.43	5.94 ±0.38	5.83 ±0.39
B	4.90 ±0.11	4.79 ±0.15	4.54 ±0.10	4.52 ±0.02	4.56 ±0.05	4.46 ±0.03	5.29 ±0.15
C	6.07 ±0.43	5.82 ±0.38	6.13 ±0.41	6.23 ±0.47	6.41 ±0.49	6.30 ±0.46	6.42 ±0.38
D	4.72 ±0.07	4.76 ±0.09	4.79 ±0.09	4.81 ±0.02	4.89 ±0.02	4.97 ±0.08	4.78 ±0.12
E	4.83 ±0.21	4.74 ±0.20	4.37 ±0.13	5.08 ±0.16	5.21 ±0.22	5.33 ±0.31	5.38 ±0.30
F	4.62 ±0.12	4.70 ±0.08	4.72 ±0.18	4.86 ±0.06	4.73 ±0.19	4.84 ±0.10	5.13 ±0.11

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine

Table no. 4.20 : Mean±SE of values of neutrophil (%) in the animals of different groups

Group	Time Interval						
	0	30	60	90	120	180	24 hrs.
A	32.50 ±0.51	33.50 ±0.45	33.00 ±0.00	34.00 ±0.00	33.50^{b} ±0.51	33.50 ±0.50	33.50^{c} ±0.50
B	35.00 ±0.55	36.00 ±0.58	37.00 ±0.00	37.00 ±0.00	37.00^{a} ±0.52	38.00 ±0.50	38.00^{a} ±0.50
C	33.50 ±0.50	34.50 ±0.50	35.00 ±1.00	35.00 ±0.00	35.50^{a} ±0.50	37.50 ±0.50	37.00^{b} ±1.00
D	34.50 ±0.50	35.00 ±1.00	35.50 ±0.50	35.50 ±0.50	36.00^{a} ±1.00	35.50 ±0.50	35.00^{c} ±1.00
E	35.50 ±0.50	36.50 ±1.50	36.50 ±1.50	36.00 ±1.00	36.50^{a} ±0.50	37.00 ±1.00	36.00^{b} ±1.00
F	34.50 ±0.50	35.00 ±1.50	35.50 ±0.50	37.70 ±1.00	37.00^{a} ±0.50	38.00 ±1.00	37.00^{ab} ±1.00

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine

Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

Table no. 4.21 : Mean±SE of values of lymphocytes (%) in the animals of different groups

Group	Time Interval						
	0	30	60	90	120	180	24 hrs.
A	61.50 ±0.50	60.50 ±0.50	61.00 ±0.00	60.00 ±0.00	60.00 ±0.00	59.50 ±0.50	60.00 ±1.00
B	60.00 ±2.00	58.00 ±2.00	58.00 ±1.50	58.00 ±2.00	57.00 ±1.00	61.50 ±0.50	61.00 ±6.00
C	59.00 ±2.00	57.00 ±2.00	57.00 ±1.00	57.00 ±1.00	56.50 ±0.50	57.00 ±1.00	57.00 ±1.00
D	59.50 ±0.50	59.50 ±0.50	59.00 ±1.00	58.50 ±0.50	58.00 ±1.00	59.00 ±1.00	59.50 ±0.50
E	58.50 ±0.50	56.50 ±1.50	56.50 ±0.50	56.00 ±1.00	58.00 ±1.00	57.50 ±1.50	57.00 ±1.00
F	58.50 ±0.50	58.00 ±1.00	58.50 ±0.50	57.00 ±1.00	56.50 ±0.50	56.00 ±1.00	56.00 ±1.00

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine

Table no. 4.22 : Mean±SE of values of eosinophils (%) in the animals of different groups

Group	Time Interval						
	0	30	60	90	120	180	24 hrs.
A	3.50 ±0.54	3.50 ±0.52	3.50 ±0.54	3.50 ±0.51	4.00 ±0.00	4.50 ±0.45	4.00 ±0.00
B	3.50 ±0.48	4.50 ±0.58	4.00 ±0.58	3.50 ±0.52	4.00 ±0.00	4.00 ±0.50	4.00 ±0.00
C	4.00 ±0.56	4.50 ±0.58	4.50 ±0.58	4.50 ±0.56	4.50 ±0.50	4.00 ±0.51	4.50 ±0.48
D	3.50 ±0.45	3.50 ±0.35	3.50 ±0.45	3.50 ±0.45	4.00 ±0.35	3.50 ±0.35	3.50 ±0.25
E	4.00 ±1.00	4.00 ±0.50	4.00 ±0.50	4.50 ±0.50	4.50 ±0.50	4.50 ±0.50	4.00 ±0.50
F	4.50 ±0.55	4.50 ±0.58	4.00 ±0.56	4.50 ±0.52	4.50 ±0.45	4.50 ±0.35	4.00 ±0.35

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine

Table no. 4.23 : Mean±SE of values of monocytes (%) in the animals of different groups

Group	Time Interval						
	0	30	60	90	120	180	24 hrs.
A	2.51 ±0.54	2.52 ±0.52	2.57 ±0.50	2.51 ±0.50	2.51 ±0.50	2.55 ±0.50	2.57 ±0.50
B	2.35 ±0.50	2.25 ±0.50	2.10 ±0.50	2.50 ±0.50	3.00 ±0.50	2.50 ±0.50	2.50 ±0.50
C	2.46 ±0.50	3.00 ±0.50	2.51 ±0.50	2.52 ±0.50	2.54 ±0.50	2.51 ±0.50	2.45 ±0.50
D	2.15 ±0.50	2.25 ±0.50	2.35 ±0.50	2.45 ±0.50	2.50 ±0.50	2.50 ±0.50	2.50 ±0.50
E	2.50 ±0.50	3.00 ±0.50	2.50 ±0.50	2.50 ±0.50	2.00 ±1.00	2.50 ±0.50	2.50 ±0.50
F	2.50 ±0.50	2.50 ±0.50	3.00 ±0.50	2.50 ±0.50	2.50 ±0.50	2.50 ±0.50	3.00 ±0.50

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine

Table no. 4.24 : Mean±SE of values of plasma glucose (mg/100ml) in the animals of different groups

Group	Time Interval						
	0	30	60	90	120	180	24 hrs.
A	46.99^{b} ±3.3	61.95* ±2.8	58.61^{bc} ±9.8	64.79^{ab} ±10.8	68.01 ±10.2	61.20^{ab*} ±4.1	46.52^{bc} ±1.9
B	39.89^{c} ±4.4	59.05* ±2.6	68.75^{ab*} ±7.9	81.99^{a***} ±8.2	88.86 ±20.0	81.67^{a*} ±13.5	44.90^{c} ±8.23
C	38.72^{c} ±4.4	32.75 ±3.6	42.25^{c} ±3.6	42.84^{b} ±3.8	40.21 ±2.7	40.54^{b} ±2.7	38.51^{c} ±4.2
D	100.45^{a} ±15.1	39.94 ±25.2	53.60^{ac} ±1.5	40.92^{b} ±2.8	50.68 ±6.4	43.62^{b} ±28.5	87.98 ±7.9
E	59.48^{b} ±5.3	57.69 ±6.9	63.61^{abc} ±6.3	62.99^{ab} ±6.4	58.39 ±5.9	64.04^{ab} ±4.8	60.79^{b} ±4.9
F	61.35^{b} ±4.7	45.87 ±14.6	83.58^{a*} ±7.1	76.42^{a*} ±6.8	61.50 ±2.9	60.10^{ab} ±3.8	60.82^{bc} ±3.4

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)
** Significantly different from the base value within group (P<0.05)*
**** Significantly different from the base value within group (P<0.001)*

Table no. 4.25 : Mean±SE of values of plasma urea (g/l) in the animals of different groups

Group	Time Interval						
	0	30	60	90	120	180	24 hrs.
A	41.84^{ab} ±5.7	42.43^{a} ±4.1	49.58^{a} ±6.1	39.10 ±1.9	25.46* ±3.5	34.39 ±4.7	35.32^{b} ±4.1
B	32.82^{b} ±3.2	42.82^{a} ±7.8	41.65^{ab} ±7.2	44.67* ±8.0	54.81 ±14.2	49.59* ±9.4	36.07^{b*} ±3.3
C	40.43^{ab} ±3.8	25.13^{c*} ±1.9	27.55^{bc*} ±2.0	33.44 ±0.94	30.43* ±0.85	28.54* ±1.8	38.90^{ab} ±3.0
D	55.75^{a} ±10.3	45.77^{abc} ±2.5	39.81^{abc} ±3.5	36.89 ±6.8	63.72 ±1.2	47.57 ±2.7	51.00^{a} ±11.0
E	22.90^{b} ±1.7	25.20^{bc} ±2.1	26.06^{c} ±3.9	36.25 ±10.9	35.31 ±11.0	30.89 ±6.9	22.5^{c} ±1.7
F	32.04^{b} ±4.2	28.38^{bc} ±4.7	31.10^{bc} ±3.9	29.49 ±4.3	31.48 ±4.3	35.30 ±4.6	29.90^{bc} ±3.8

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine

Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

** Significantly different from the base value within group (P<0.05)*

Table no. 4.26 : Mean±SE of values of plasma creatinine (mg/100 ml) in the animals of different groups

Group	Time Interval						
	0	30	60	90	120	180	24 hrs.
A	2.01^{b} ±0.23	1.76 ±0.34	2.08 ±0.44	2.71** ±0.15	1.73^{ab} ±0.34	1.27* ±0.10	2.09 ±0.20
B	3.18^{a} ±0.46	2.56 ±0.56	2.28* ±0.48	3.38 ±0.89	3.35^{a} ±0.83	3.22 ±0.76	3.09 ±0.37
C	0.872 ±0.31	1.48 ±0.65	0.58 ±0.07	0.652 ±0.14	1.42^{b} ±0.28	1.30 ±0.13	0.894 ±0.283
D	2.82^{ab} ±0.53	2.38 ±0.38	1.35* ±0.47	2.11 ±0.64	2.47^{ab} ±0.47	3.76 ±0.76	2.62 ±0.62
E	1.98^{b} ±0.37	1.58 ±0.19	1.54 ±0.22	1.41 ±0.26	1.33^{b*} ±0.22	1.33* ±0.22	1.28* ±0.21
F	2.52^{ab} ±0.15	3.68 ±1.11	2.76 ±0.55	2.95 ±0.46	2.74^{a} ±0.55	3.14 ±0.44	2.72 ±0.24

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine

Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

** Significantly different from the base value within group (P<0.05)*

*** Significantly different from the base value within group (P<0.01)*

Table no. 4.27 : Mean±SE of values of plasma cortisol (n mol/L) in the animals of different groups

Group	Time Interval						
	0	30	60	90	120	180	24 hrs.
A	18.95 ±8.8	30.38 ±6.6	37.34^{ab} ±3.0	35.85 ±3.3	17.49 ±0.41	8.40^{b} ±0.92	9.25^{bc} ±0.96
B	13.07 ±3.0	11.67 ±2.8	22.72^{b} ±12.6	6.62* ±1.6	8.84 ±1.6	5.91^{c} ±1.4	11.23^{c} ±2.3
C	8.66 ±1.8	16.38 ±5.6	16.95^{a} ±4.4	18.69* ±3.8	31.99* ±6.4	18.17^{ab} ±3.4	40.35^{bc} ±10.0
D	125.2 ±92.7	149.91 ±120	144.75^{a} ±85.7	215.35** ±94.1	222.8 ±112	334.20^{abc*} ±102	115.11^{a} ±84.8
E	48.71 ±21.5	26.79 ±7.4	55.28^{b} ±21.1	41.30 ±16.1	77.62 ±29.1	49.97^{ab} ±10.1	74.93^{bc} ±10.0
F	85.37 ±28.8	72.39 ±13.8	59.41^{b} ±15.3	100.29 ±22.5	127.56 ±15.3	69.11^{a} ±25.3	94.11^{b} ±8.25

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine

Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

** Significantly different from the base value within group (P<0.05)*

*** Significantly different from the base value within group (P<0.01)*

Table no. 4.28 : Mean±SE of values of GGT (U/L) in the animals of different groups

Group	Time Interval						
	0	30	60	90	120	180	24 hrs.
A	17.85[b] ±5.50	11.34[b] ±2.21	14.59[b] ±4.05	14.79 ±3.93	14.56 ±3.86	14.36 ±2.15	19.43[b] ±4.53
B	23.04[b] ±6.77	24.12[b] ±7.63	24.11[b] ±7.61	18.43 ±3.33	18.37 ±3.33	25.65 ±6.21	23.60[b] ±6.64
C	20.26[b] ±3.85	15.92[b] ±3.79	15.92[b] ±3.79	15.05 ±1.25	15.05 ±1.25	31.26 ±20.53	18.03[b] ±2.97
D	45.69[b] ±0.54	16.74[b] ±3.78	16.80[b] ±3.84	18.17 ±12.38	21.75 ±8.80	30.90* ±0.36	42.73[a] ±2.51
E	12.11[b] ±5.24	9.05[b] ±2.68	9.05[b] ±2.68	23.90 ±11.23	44.07 ±27.84	93.05 ±81.46	12.57[b] ±4.67
F	46.89[a] ±13.01	44.02[a] ±15.31	50.44[a] ±19.98	31.54 ±4.29	36.21 ±3.88	45.16 ±11.36	46.72[a] ±12.83

A : Bupivacaine, B : Xylzine; C : Buprenorphine; D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine

Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

** Significantly different from the base value within group (P<0.05)*

Table no. 4.29 : Mean±SE of mean arterial pressure (mm Hg) recorded in the animals of different groups

Group	Time Interval (min)														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
D	173.33 ±21.27	163.33 ±12.01	156.66 ±18.55	151.66 ±19.22	146.66 ±14.53	138.33 ±16.93	133.66 ±23.33	133.66 ±37.23	138.66 ±24.36	141.00 ±13.45	147.00** ±23.07	140.66* ±15.72	145.00* ±27.53	151.66* ±23.15	157.33 ±25.43
E	156.33 ±14.49	160.00 ±5.77	154.66 ±5.33	142.33* ±13.29	141.66 ±17.36	145.66 ±25.18	135.33 ±23.95	132.66* ±20.82	142.33 ±22.39	145.66 ±19.09	137.66* ±16.49	151.66 ±21.27	150.66 ±20.34	149.00 ±19.60	141.66* ±16.41
F	164.33 ±11.05	146.66* ±15.89	140.00* ±16.07	129.33 ±11.05	120.00* ±21.79	133.33* ±17.40	150.00 ±16.07	138.66 ±5.92	161.66 ±9.28	200.66 ±44.80	144.66* ±7.86	139.66* ±4.84	138.33* ±4.41	145.00* ±10.40	148.33** ±10.13

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)
** Significantly different from the base value within group (P<0.05)*
*** Significantly different from the base value within group (P<0.01)*

Table no. 4.30 : Mean±SE of central venous pressue (cm H_2O) recorded in the animals of different groups

Group	Time Interval (min)														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
D	11.00 ±3.21	10.83 ±3.19	7.83^{ab} ±1.92	8.16 ±1.62	8.76 ±1.65	6.83^{b} ±1.09	6.40 ±0.83	3.90^{b} ±1.80	5.33 ±1.59	7.26 ±1.89	4.00 ±1.52	3.50 ±0.57	2.83^{b} ±0.92	3.83 ±0.44	3.33^{b} ±0.72
E	11.50 ±5.26	12.00 ±5.00	9.00^{a} ±1.50	7.76 ±0.26	8.00 ±1.04S	8.00^{ab} ±1.04	10.83 ±2.77	9.66^{a} ±1.74	9.66 ±1.74	7.33 ±1.09	10.16 ±6.05	7.66 ±3.72	8.83^{a} ±1.48	8.83 ±1.48	8.83^{a} ±1.48
F	6.66 ±4.70	9.66 ±5.06	10.16^{b} ±5.63	10.83 ±6.22	13.00 ±2.75	11.83^{a} ±2.31	10.46 ±1.81	12.00^{a} ±1.60	12.00 ±2.78	10.66 ±2.83	10.16 ±3.58	10.66 ±4.10	9.53^{a} ±2.55	10.70 ±1.35	9.86^{a} ±2.18

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

Table no. 4.31 : Mean±SE of heart rate of ECG recorded in the animals of different groups

Group	Time Interval (min)														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
D	49.33 ±5.81	42.67 6.36	46.67 3.33	45.00 2.89	46.67 3.33	41.67 6.01	41.67 1.67	45.00 2.89	49.33[a] 0.67	50.00[a] 5.77	50.00[a] 0.00	53.33[a] 3.33	46.67[a] 3.33	50.00 5.77	48.33 6.01
E	48.33 ±6.01	51.67 4.41	43.33 3.33	33.33* 3.33	36.67** 6.67	43.33 13.33	36.67** 6.67	33.33 3.33	33.33[b*] 3.33	31.67[b*] 1.67	30.00[b*] 0.00	30.00[b*] 3.33	30.00[b*] 3.33	33.33 3.33	36.67 3.33
F	46.67 ±6.67	52.67 3.71	52.67 10.48	45.00 8.66	41.00 5.57	42.67 2.67	43.33 3.33	40.00 5.77	43.33[a] 3.33	43.33[a] 8.82	46.67[a] 3.33	46.67[a] 3.33	48.33[a] 1.67	46.67[a] 3.33	46.00 2.89

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)
** Significantly different from the base value within group (P<0.05)*
*** Significantly different from the base value within group (P<0.01)*

Table no. 4.32 : Mean±SE of amplitude of P-wave (mV) recorded in the animals of different groups

Group	Time Interval (min)														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
D	0.083 ±0.017	0.067 ±0.017	0.067 ±0.017	0.050 ±0.029	0.033 ±0.017	0.050 ±0.00	0.067 ±0.017	0.067 ±0.017	0.067 ±0.017	0.083 ±0.017	0.083 ±0.017	0.083 ±0.017	0.067 ±0.017	0.067 ±0.017	0.067 ±0.017
E	0.117 ±0.044	0.100 ±0.058	0.100 ±0.058	0.100 ±0.058	0.083 ±0.060	0.050* ±0.029	0.100 ±0.050	0.100 ±0.050	0.100 ±0.050	0.067 ±0.017	0.067 ±0.017	0.067 ±0.033	0.067 ±0.033	0.067 ±0.033	0.050 ±0.029
F	0.083 ±0.017	0.067 ±0.017	0.067 ±0.01	0.033 ±0.01	0.033 ±0.017	0.050 ±0.029	0.050 ±0.050	0.067 ±0.017	0.083 ±0.017	0.067 ±0.017	0.083 ±0.017	0.067 ±0.033	0.067 ±0.017	0.067 ±0.017	0.067 ±0.017

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)
** Significantly different from the base value within group (P<0.05)*

Table no. 4.33 : Mean±SE of P-wave duration (mV) recorded in the animals of different groups

Group	Time Interval (min)														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
D	0.053 ±0.01	0.080 ±0.00	0.067 ±0.01	0.040^{b} ±0.00	0.053 ±0.01	0.040^{b} ±0.00	0.080 ±0.00	0.053 ±0.01	0.053 ±0.01	0.067 ±0.01	0.080 ±0.00	0.067 ±0.01	0.080 ±0.00	0.080 ±0.00	0.080^{a} ±0.00
E	0.067 ±0.01	0.067 ±0.01	0.067 ±0.01	0.067^{ab} ±0.01	0.053 ±0.02	0.053^{b} ±0.01	0.053 ±0.01	0.067 ±0.01	0.067 ±0.01	0.053 ±0.03	0.053 ±0.03	0.053 ±0.03	0.040 ±0.02	0.040 ±0.02	0.027^{b} ±0.01
F	0.093 ±0.01	0.093 ±0.01	0.080 ±0.01	0.093^{a} ±0.01	0.067 ±0.01	0.080^{a} ±0.01	0.067 ±0.01	0.067 ±0.01	0.067 ±0.01	0.080 ±0.03	0.080 ±0.03	0.080 ±0.03	0.067 ±0.01	0.067 ±0.01	0.080^{ab} ±0.01

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

Table no. 4.34 : Mean±SE of QRS amplitude (mV) recorded in the animals of different groups

Group	Time Interval (min)														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
D	0.37 ±0.03	0.40 ±0.06	0.37 ±0.03	0.33 ±0.03	0.37 ±0.07	0.40 ±0.06	0.43 ±0.03	0.43 ±0.03	0.43 ±0.03	0.43 ±0.03	0.43 ±0.03	0.43 ±0.03	0.33 ±0.12	0.33 ±0.12	0.30 ±0.12
E	0.37 ±0.07	0.43 ±0.07	0.40 ±0.10	0.53 ±0.20	0.53 ±0.19	0.50 ±0.12	0.50 ±0.12	0.47 ±0.15	0.47 ±0.18	0.50 ±0.17	0.53 ±0.15	0.57* ±0.12	0.43 ±0.12	0.43 ±0.12	0.43 ±0.12
F	0.33 ±0.03	0.40 ±0.07	0.43*** ±0.03	0.40 ±0.06	0.40 ±0.06	0.40 ±0.06	0.37 ±0.03	0.43*** ±0.03	0.40 ±0.18	0.40 ±0.17	0.37 ±0.03	0.37 ±0.03	0.37 ±0.03	0.37 ±0.03	0.40 ±0.12

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
** Significantly different from the base value within group (P<0.05)*
**** Significantly different from the base value within group (P<0.001)*

Table no. 4.36 : Mean±SE of P-R interval (sec) recorded in the animals of different groups

Group	Time Interval (min)														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
D	0.093 ±0.01	0.093 ±0.01	0.080 ±0.02	0.060 ±0.02	0.080 ±0.02	0.100 ±0.01	0.093[b] ±0.01	0.087 ±0.01	0.093 ±0.01	0.080 ±0.00	0.080 ±0.00	0.067 ±0.01	0.067 ±0.01	0.067 ±0.02	0.067 ±0.02
E	0.11 ±0.01	0.11 ±0.01	0.11 ±0.01	0.11 ±0.01	0.12 ±0.00	0.12 ±0.00	0.12[ab] ±0.00	0.11 ±0.03	0.11 ±0.01	0.12 ±0.02	0.12 ±0.00	0.11 ±0.01	0.11 ±0.01	0.11 ±0.01	0.11 ±0.01
F	0.10 ±0.02	0.10 ±0.02	0.12 ±0.00	0.12 ±0.01	0.09 ±0.01	0.10 ±0.02	0.13[a] ±0.01	0.12 ±0.02	0.11 ±0.01	0.11 ±0.02	0.10 ±0.02	0.11 ±0.03	0.11 ±0.03	0.11 ±0.03	0.11 ±0.03

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

Table no. 4.35 : Mean±SE of QRS duration (sec) recorded in the animals of different groups

Group	Time Interval (min)													
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
D	0.053 ±0.01	0.04 ±0.00	0.080 ±0.00	0.067 ±0.01	0.067 ±0.01	0.053 ±0.01	0.053 ±0.01	0.067 0.01	0.053 ±0.01	0.053 ±0.01	0.067 ±0.01	0.053 ±0.01	0.067 ±0.01	0.053 ±0.01	0.080 ±0.00
E	0.053 ±0.01	0.067 ±0.00	0.80 ±0.01	0.067 ±0.01	0.080 ±0.01	0.067 ±0.01	0.067 ±0.02	0.067 ±0.02	0.067 ±0.01	0.053 ±0.01	0.067 ±0.02	0.080 ±0.02	0.080 ±0.02	0.080 ±0.02	0.080 ±0.02
F	0.080 ±0.01	0.080 ±0.02	0.080 ±0.02	0.067 ±0.02	0.067 ±0.01	0.067 ±0.01	0.067 ±0.01	0.067 ±0.01	0.067 ±0.01	0.067 ±0.01	0.067 ±0.01	0.080 ±0.02	0.080 ±0.02	0.080 ±0.02	0.080 ±0.02

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine

Table no. 4.37 : Mean±SE of QT interval (sec) recorded in the animals of different groups

Group	Time Interval (min)													
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
D	0.51 ±0.03	0.56 ±0.06	0.57 ±0.04	0.57 ±0.04	0.57 ±0.06	0.59 ±0.05	0.59 ±0.05	0.55 ±0.03	0.57 ±0.04	0.57 ±0.04	0.57 ±0.04	0.57 ±0.06	0.59^{ab} ±0.05	0.59 ±0.05	0.57 ±0.04
E	0.44 ±0.02	0.50* ±0.03	0.50* ±0.03	0.58 ±0.07	0.58 ±0.08	0.58 ±0.09	0.62 ±0.05	0.62 ±0.05	0.62 ±0.05	0.66 ±0.08	0.68 ±0.06	0.70* ±0.07	0.69^{a*} ±0.06	0.58 ±0.09	0.68 ±0.09
F	0.50 ±0.05	0.57 ±0.05	0.53 ±0.03	0.54 ±0.01	0.54 ±0.01	0.53 ±0.03	0.57 ±0.01	0.48 ±0.02	0.48 ±0.02	0.50 ±0.01	0.46 ±0.01	0.45 ±0.01	0.45^{b} ±0.01	0.46 ±0.01	0.46 ±0.01

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)
** Significantly different from the base value within group (P<0.05)*

Table no. 4.38 : Mean±SE of T-wave amplitude (mV) recorded in the animals of different groups

Group	Time Interval (min)														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
D	0.21 ±0.06	0.23 ±0.06	0.25 ±0.07	0.26 ±0.08	0.26 ±0.08	0.25 ±0.07	0.26 ±0.08	0.28 ±0.07	0.28 ±0.07	0.25 ±0.07	0.23 ±0.06	0.23 ±0.06	0.20 ±0.05	0.20 ±0.05	0.20 ±0.05
E	0.10 ±0.06	0.10 ±0.06	0.10 ±0.07	0.10 ±0.08	0.10 ±0.08	0.07 ±0.02	0.10 ±0.08	0.10 ±0.07	0.10 ±0.07	0.10 ±0.07	0.10 ±0.06	0.10 ±0.06	0.10 ±0.05	0.22 ±0.17	0.17 ±0.12
F	0.20 ±0.10	0.27 ±0.02	0.20 ±0.10	0.30 ±0.08	0.30 ±0.08	0.30 ±0.02	0.17 ±0.07	0.15*** ±0.10	0.10* ±0.05	0.10* ±0.05	0.12 ±0.02	0.10 ±0.05	0.10 ±0.05	0.10 ±0.05	0.17 ±0.07

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
** Significantly different from the base value within group (P<0.05)*
**** Significantly different from the base value within group (P<0.001)*

Table no. 4.39 : Mean±SE of T-wave duration (sec) recorded in the animals of different groups

Group	Time Interval (min)														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
D	0.14 ±0.01	0.16 ±0.00	0.16 ±0.02	0.14 ±0.01	0.14 ±0.01	0.15 ±0.01	0.16 ±0.02	0.14 ±0.01	0.14 ±0.01	0.14 ±0.02	0.14^{a} ±0.01	0.12 ±0.02	0.14 ±0.02	0.14 ±0.02	0.13 ±0.01
E	0.10 ±0.02	0.14 ±0.26	0.14 ±0.02	0.14 ±0.02	0.15 ±0.05	0.11 ±0.05	0.14 ±0.02	0.12 ±0.02	0.14 ±0.04	0.14 ±0.02	0.18^{a**} ±0.02	0.12 ±0.04	0.16 ±0.02	0.18^{**} ±0.02	0.16 ±0.08
F	0.14 ±0.01	0.13 ±0.01	0.11 ±0.00	0.13 ±0.01	0.13 ±0.01	0.12 ±0.00	0.12 ±0.01	0.16 ±0.04	0.10 ±0.03	0.10 ±0.00	0.09^{b*} ±0.01	0.10 ±0.01	0.09^{*} ±0.01	0.10 ±0.01	0.11^{*} ±0.00

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)
** Significantly different from the base value within group (P<0.05)*
*** Significantly different from the base value within group (P<0.01)*

Table no. 4.40 : Mean±SE of values of pH in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
D	7.49 ±0.01	7.51 ±0.03	7.49 ±0.02	7.51 ±0.01	7.49 ±0.01	7.48 ±0.01
E	7.49 ±0.03	7.48 ±0.01	7.54 ±0.05	7.55 ±0.04	7.52 ±0.05	7.51 ±0.06
F	7.47 ±0.01	7.48 ±0.00	7.49 ±0.00	7.49 ±0.01	7.50 ±0.00	7.49 ±0.01

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine

Table no. 4.41: Mean±SE of values of PO_2 (mm Hg) in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
D	64.33^{a} ±6.47	64.90 ±15.31	63.26 ±11.2	66.56^{a} ±7.06	71.43 ±5.75	71.20^{b} ±6.17
E	78.83^{ab} ±5.60	80.86 ±6.33	86.03 ±11.6	93.56^{b} ±10.3	92.56 ±9.68	87.23^{b} ±10.2
F	82.83^{b} ±4.92	65.86 ±6.30	83.23 ±7.80	60.33^{*a} ±2.30	71.40 ±10.4	50.23^{*a} ±1.20

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)
** Significantly different from the base value within group (P<0.05)*

Table no. 4.42 : Mean±SE of values of PCO_2 (mm Hg) in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
D	39.13[ab] ±1.57	37.86 ±1.56	40.13 ±1.69	36.06 ±4.15	37.76 ±3.25	38.20 ±2.30
E	39.90[a] ±2.70	40.23 ±3.29	40.60 ±2.90	33.06 ±4.91	41.40 ±1.70	44.20 ±1.70
F	37.93[b] ±5.29	41.03 ±0.73	38.36 ±2.04	39.76 ±1.53	30.53 ±7.78	36.83 ±3.14

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

Table no. 4.43 : Mean±SE of values of BE-ECF (millimole/litre) in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
D	6.83 ±2.51	7.66[a] ±1.82	8.76 ±2.90	5.93[b] ±4.02	6.30 ±3.42	4.86 ±2.59
E	7.10 ±1.10	7.20[ab] ±1.03	6.60 ±0.70	7.10[a] ±0.75	6.10 ±1.57	7.06 ±1.60
F	7.46 ±3.06	6.93 ±0.88	7.30 ±0.20	6.50[ab] ±0.60	6.86 ±1.46	4.73 ±0.93

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

Table no. 4.44 : Mean±SE of values of BE-B (millimole/litre) in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
D	7.20 ±2.20	7.93 ±1.60	8.90 ±2.50	6.43 ±3.50	6.80 ±2.90	6.16 ±3.00
E	7.40 ±1.10	7.46 ±0.80	7.86 ±0.80	7.60 ±0.50	6.50 ±1.30	7.23 ±1.40
F	6.80 ±3.10	7.46 ±0.60	6.76 ±0.80	7.60 ±0.60	8.60 ±1.30	5.06 ±0.90

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine

Table no. 4.45 : Mean±SE of values of bicarbonate concentration (millimole/litre) in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
D	30.36 ±2.28	30.83 ±1.33	31.90 ±2.63	29.13 ±3.91	29.73 ±3.26	29.13 ±2.90
E	30.63 ±0.81	30.73 ±1.33	31.16 ±1.17	29.56 ±1.38	29.00 ±1.65	30.03 ±1.73
F	28.43 ±4.85	30.90 ±0.68	29.76 ±1.20	30.70 ±0.76	24.60 ±6.31	27.73 ±1.43

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine

Table no. 4.46 : Mean±SE of values of sodium (millimole/litre) in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
D	138.3 ±1.20	137.0 1.10	136.6 1.20	138.0 0.50	138.0 0.50	137.0 0.50
E	140.0 ±2.50	140.6 2.70	140.0 2.00	135.3 1.40	135.6 1.40	135.6 1.40
F	140.3 ±0.80	137.6 0.80	138.0 1.10	138.6 1.40	141.6 2.10	137.0 1.00

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine

Table no. 4.47 : Mean±SE of values of potassium concentration (millimole/ litre) in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
D	3.70 ±0.25	3.53 ±0.31	3.50 ±0.35	3.63 ±0.41	3.40 ±0.32	3.56 ±0.28
E	3.83 ±0.35	3.76 ±0.29	3.40 ±0.40	4.06 ±0.14	4.06 ±0.14	4.06 ±0.18
F	3.33 ±0.40	3.36 ±0.03	3.36 ±0.18	3.80 ±0.32	3.46 ±0.24	3.60 ±0.30

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine

Table no. 4.48 : Mean±SE of values of chloride concentration (millimole/ litre) in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
D	96.33 ±2.45	96.33 ±1.66	95.66 ±1.85	97.33 ±3.18	96.00 ±2.51	97.00 ±2.51
E	94.00 ±2.40	94.93** ±0.07	95.93** ±0.07	95.93** ±0.07	94.93** ±0.07	95.93** ±0.07
F	101.0 ±4.72	95.33 ±1.45	96.66 ±0.88	95.33 ±0.88	107.3 ±11.34	97.00 ±1.15

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
*** Significantly different from the base value within group (P<0.01)*

Table no. 4.49 : Mean±SE of values of calcium (millimole/litre) in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
D	1.09 ±0.03	1.10[a] ±0.03	1.08 ±0.03	1.11 ±0.03	1.11 ±0.02	1.11 ±0.02
E	1.07 ±0.05	1.09[ab] ±0.04	1.11 ±0.03	1.06 ±0.05	1.04 ±0.04	0.98 ±0.07
F	1.02 ±0.12	1.07[b] ±0.03	1.05 ±0.06	1.12 ±0.03	1.11 ±0.03	1.01 ±0.04

D : Ketamine + Bupivacaine; E : Xylazine + Ketamine; F : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

Table no. 4.50 : Mean±SE of onset of analgesia in the animals of different groups

Group	Onset time (min)
G	5.0±0.00[a]
H	1.75±0.47[c]
I	3.5±0.6[b]

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
** Significantly different from the base value within group (P<0.05)*

Table no. 4.51 : Mean±SE of score of analgesia at perineum recorded in the animals of different groups

Group	Time Interval											
	0	5	30	45	60	75	90	105	120	130	150	180
G	0.00 ±0.00	2.50 ±0.33	2.80 ±0.11	2.30^{ab} ±0.33	2.00^{ab} ±0.33	1.30^{ab} ±0.37	1.10^{ab} ±0.42	0.40^{a} ±0.29	0.20^{a} ±0.22	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00
H	0.00 ±0.00	2.50 ±0.50	3.00 ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	2.80^{b} ±0.16	2.60^{b} ±0.21	2.60^{b} ±0.21	2.50^{b} ±0.34	2.50^{b} ±0.34	2.10^{b} ±0.30	2.10^{b} ±0.30
I	0.00 ±0.00	2.20 ±0.28	2.40 ±0.42	1.10^{a} ±0.34	0.50^{a} ±0.42	0.40^{a} ±0.42	0.20^{a} ±0.28	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

Table no. 4.52 : Mean±SE of score of analgesia at inguinal region recorded in the animals of different groups

Group	Time Interval											
	0	5	30	45	60	75	90	105	120	130	150	180
G	0.00 ±0.00	2.50 ±0.24	2.60 ±0.16	2.30^{ab} ±0.33	1.50^{a} ±0.37	1.10^{a} ±0.42	1.00^{a} ±0.44	0.60^{ab} ±0.33	0.60^{ab} ±0.33	0.20^{a} ±0.14	0.00^{a} ±0.00	0.00^{a} ±0.00
H	0.00 ±0.00	2.50 ±0.34	3.00 ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	2.50^{b} ±0.22	2.00^{b} ±0.51	1.80^{b} ±0.47	1.50^{b} ±0.56	1.30^{b} ±0.49
I	0.00 ±0.00	2.00 ±0.43	2.40 ±0.42	1.10^{a} ±0.34	1.00^{a} ±0.37	0.50^{a} ±0.42	0.20^{a} ±0.28	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

Table no. 4.53 : Mean±SE of score of analgesia at tail recorded in the animals of different groups

Group	Time Interval											
	0	5	30	45	60	75	90	105	120	130	150	180
G	0.00 ±0.00	2.50 ±0.33	3.00 ±0.00	2.80^{ab} ±0.11	2.20^{ab} ±0.27	1.50^{ab} ±0.37	1.40^{a} ±0.41	0.70^{a} ±0.32	0.60^{a} ±0.28	0.10^{a} ±0.11	0.00^{a} ±0.00	0.00^{a} ±0.00
H	0.00 ±0.00	2.60 0.33	3.00 ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	2.80^{b} ±0.16	2.60^{b} ±0.21	2.60^{b} ±0.21	2.50^{b} ±0.22	2.50^{b} ±0.22
I	0.00 ±0.00	2.70 ±0.18	2.40 ±0.42	1.40^{a} ±0.42	1.10^{a} ±0.34	0.40^{a} ±0.42	0.20^{a} ±0.28	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

Table no. 4.54 : Mean±SE of score of analgesia at flank recorded in the animals of different groups

Group	Time Interval											
	0	5	30	45	60	75	90	105	120	130	150	180
G	0.00 ±0.00	2.10 ±0.38	2.70 ±0.22	2.60 ±0.23	2.00^{ab} ±0.37	1.10^{a} ±0.42	0.70^{a} ±0.36	0.30^{a} ±0.33	0.30^{a} ±0.33	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00
H	0.00 ±0.00	1.00 ±0.51	2.60 ±0.33	2.60 ±0.33	3.00^{b} ±0.00	3.00^{b} ±0.00	2.80^{b} ±0.16	2.30^{b} ±0.21	2.10^{b} ±0.16	2.10^{b} ±0.16	2.10^{b} ±0.16	2.10^{b} ±0.16
I	0.00 ±0.00	1.80 ±0.40	2.30 ±0.49	1.30 ±0.42	0.80^{a} ±0.47	0.30^{a} ±0.33	0.30^{a} ±0.33	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

Table no. 4.55 : Mean±SE of score of analgesia at abdomen recorded in the animals of different groups

Group	Time Interval											
	0	5	30	45	60	75	90	105	120	130	150	180
G	0.00 ±0.00	1.70 ±0.49	2.10 ±0.44	1.70 ±0.49	1.30^{ab} ±0.49	0.60^{a} ±0.37	0.30^{a} ±0.37	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00
H	0.00 ±0.00	1.00 ±0.51	2.60 ±0.33	2.60 ±0.33	3.00^{b} ±0.00	2.80^{b} ±0.16	2.60^{b} ±0.33	2.60^{b} ±0.33	2.10^{b} ±0.40	2.00^{b} ±0.36	1.80^{b} ±0.30	1.80^{b} ±0.30
I	0.00 ±0.00	1.40 ±0.42	1.70 ±0.52	1.00 ±0.37	0.50^{a} ±0.42	0.40^{a} ±0.42	0.20^{a} ±0.28	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

xxxxx

Table no. 4.56 : Mean±SE of score of analgesia at throax recorded in the animals of different groups

Group	Time Interval											
	0	5	30	45	60	75	90	105	120	130	150	180
G	0.00 ±0.00	1.10 ±0.42	1.40 ±0.37	1.40 ±0.37	1.40^{ab} ±0.37	0.70^{a} ±0.36	0.60^{a} ±0.41	0.30^{a} ±0.33	0.30^{a} ±0.33	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00
H	0.00 ±0.00	0.80 ±0.47	2.50 ±0.34	2.50 ±0.34	3.00^{b} ±0.00	3.00^{b} ±0.16	2.30^{b} ±0.33	2.10^{b} ±0.30	2.10^{b} ±0.30	2.00^{b} ±0.25	1.80^{b} ±0.30	1.80^{b} ±0.30
I	0.00 ±0.00	0.57 ±0.36	1.40 ±0.48	1.00 ±0.37	0.50^{a} ±0.42	0.40^{a} ±0.42	0.20^{a} ±0.28	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

Table no. 4.58 : Mean±SE of score of analgesia at digits recorded in the animals of different groups

Group	Time Interval											
	0	5	30	45	60	75	90	105	120	130	150	180
G	0.00 ±0.00	2.60 ±0.33	3.00 ±0.00	3.00^{b} ±0.00	2.20^{ab} ±0.32	2.00^{ab} ±0.44	1.60^{ab} ±0.40	1.00^{a} ±0.40	1.00^{a} ±0.40	0.60^{a} ±0.33	0.40^{a} ±0.29	0.00^{a} ±0.00
H	0.00 ±0.00	2.50 ±0.50	2.80 ±0.16	2.80^{b} ±0.16	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	3.00^{b} ±0.00	2.80^{b} ±0.16	2.60^{b} ±0.21	2.50^{b} ±0.22
I	0.00 ±0.00	2.40 ±0.36	2.20 ±0.47	1.00^{a} ±0.37	0.50^{a} ±0.42	0.40^{a} ±0.42	0.20^{a} ±0.28	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals ($P<0.05$)

Table 4.59 : Complete analgesia (score 3) of different regions produced by different anaesthetics and their duration

Sl. No.	Regions	Groups duration								
		A	B	C	D	E	F	G	H	I
1.	Perineum	x	x	x	5-90 min.	5-90 min.	x	15-20 min	10-60 min	x
2.	Inguinal	x	x	x	10-105 min	5-45 min	x	15-30 min	10-90 min	x
3.	Tail	x	x	x	5-90 min	5-60 min	x	20-30 min	10-90 min	x
4.	Thorax	x	x	x	x	x	x	x	60-75 min	x
5.	Digits	x	x	x	5-30 min	5-45 min	x	20-45 min	60-75 min	x
6.	Abdomen	x	x	x	60-75 min	x	x	x	only at 60 min	x
7.	Hind limbs	x	x	x	5-30 min	10-60 min	x	x	60-90 min	x
8.	Flank	x	x	x	15-90 min	x	x	x	60-75 min	x

Table no. 4.57 : Mean±SE of score of analgesia at hind limbs recorded in the animals of different groups

Group	Time Interval											
	0	5	30	45	60	75	90	105	120	130	150	180
G	0.00 ±0.00	2.60 ±0.33	2.80 ±0.11	2.70^{a} ±0.22	2.00^{ab} ±0.37	1.30^{ab} ±0.47	1.00^{ab} ±0.44	0.50^{b} ±0.37	0.30^{b} ±0.33	0.20^{b} ±0.22	0.00^{b} ±0.00	0.00^{b} ±0.00
H	0.00 ±0.00	2.50 ±0.50	2.80 ±0.16	2.80^{a} ±0.16	3.00^{a} ±0.00	3.00^{a} ±0.00	3.00^{a} ±0.00	2.80^{a} ±0.16	2.30^{a} ±0.33	2.10^{a} ±0.47	2.00^{a} ±0.44	2.00^{a} ±0.40
I	0.00 ±0.00	2.10 ±0.40	1.70 ±0.52	1.00^{b} ±0.37	0.40^{b} ±0.42	0.40^{b} ±0.42	0.20^{b} ±0.28	0.00^{b} ±0.00	0.00^{b} ±0.00	0.00^{b} ±0.00	0.00^{b} ±0.00	0.00^{b} ±0.00

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

Table no. 4.60 : Mean±SE of score of analgesia at sedation recorded in the animals of different groups

Group	Time Interval											
	0	5	30	45	60	75	90	105	120	130	150	180
G	0.00 ±0.00	0.60 ±0.42	1.50^{a} ±0.22	1.30^{a} ±0.33	1.10^{a} ±0.30	0.80^{ab} ±0.16	0.80^{ab} ±0.16	0.10^{ab} ±0.16	0.10^{ab} ±0.16	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00
H	0.00 ±0.00	0.80 ±0.54	2.80^{b} ±0.16	4.00^{b} ±0.16	4.00^{b} ±0.16	4.0 0^{b} ±0.33	3.10^{b} ±0.65	3.30^{b} ±0.66	3.10^{b} ±0.65	3.00^{b} ±0.68	2.50^{b} ±0.56	2.30^{b} ±0.55
I	0.00 ±0.00	0.00 ±0.00	1.50^{a} ±0.34	1.30^{a} ±0.21	1.10^{a} ±0.30	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

Table no. 4.61 : Mean±SE of score of analgesia at motor incoordination recorded in the animals of different groups

Group	Time Interval											
	0	5	30	45	60	75	90	105	120	130	150	180
G	0.00 ±0.00	3.70 ±0.16	3.10^{a} ±0.12	2.50^{a} ±0.42	1.20^{a} ±0.55	0.80^{a} ±0.58	0.30^{a} ±0.37	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00	0.00^{a} ±0.00
H	0.00 ±0.00	4.00 ±0.00	4.00^{b} ±0.00	4.00^{b} ±0.00	4.00^{b} ±0.00	3.60^{b} ±0.21	3.60^{b} ±0.21	3.60^{b} ±0.20	3.50^{b} ±0.34	3.50^{b} ±0.34	2.80^{b} ±0.40	2.80^{b} ±0.40
I	0.00 ±0.00	3.40 ±0.36	3.50^{ab} ±0.29	3.00^{a} ±0.29	2.40^{a} ±0.00	2.00^{a} ±0.42	1.70^{ab} ±0.43	1.70^{ab} ±0.47	1.10^{ab} ±0.34	0.70^{ab} ±0.18	0.70^{a} ±0.18	0.50^{a} ±0.20

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)

Table no. 4.63 : Mean±SE values of heart rate (per minute) recorded in the animals of different groups

Group	Time Interval														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
G	63.7^{b} ±4.90	72.0 ±4.80	79.5** ±6.30	67.6 ±6.50	69.1 ±7.30	67.6 ±6.80	70.2 ±7.40	62.6 ±3.50	62.6^{a} ±4.20	63.1^{a} ±3.70	61.5^{a} ±4.40	64.2^{a} ±3.40	64.2^{a} ±3.40	64.2^{a} ±3.40	64.2^{a} ±3.40
H	74.5^{ab} ±6.10	67.6 ±7.00	64.3 ±7.60	62.6 ±7.80	59.3 ±7.80	50.6* ±6.90	46.0* ±6.60	49.6* ±7.90	41.8^{b*} ±6.40	43.0^{b*} ±6.90	35.0^{b} ±10.2	34.0^{b} ±10.1	36.0^{b} ±9.40	33.3^{b*} ±5.60	33.3^{b*} ±5.60
I	84.1^{a} ±8.40	76.5 ±6.80	69.7 ±5.50	63.1* ±4.00	61.1* ±3.40	56.0** ±4.50	57.7* ±6.90	51.4*** ±6.10	54.2^{ab**} ±5.50	54.5^{ab**} ±5.80	58.2^{a**} ±2.10	56.2^{a**} ±3.10	56.2 ±3.30	66.5 ±2.90	56.5 ±2.90

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)
** Significantiy different from the base value within group (P<0.05)*
*** Significantly different from the base value within group (P<0.01)*
**** Significantly different from the base value within group (P<0.001)*

Table no. 4.64 : Mean±SE values of respiration rate (per minute) recorded in the animals of different groups

Group	Time Interval														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
G	28.0 ±5.00	29.0 ±5.00	28.0 ±6.10	28.2 ±6.80	28.6 ±6.80	23.3* ±4.70	19.3 ±2.90	23.3 ±3.80	24.8 ±5.70	22.2 ±4.30	20.8 ±4.30	20.4 ±4.40	21.3^{a} ±3.40	21.7^{a} ±3.30	22.0^{a} ±3.30
H	20.6 ±2.80	19.6 ±2.70	20.0 ±3.40	19.6 ±2.70	20.6 ±3.20	17.6 ±3.80	19.0 ±3.00	15.3 ±2.60	11.6* ±2.70	9.30** ±3.40	10.0** ±3.50	10.3* ±3.50	9.30^{b**} ±3.40	9.00^{b**} ±3.40	9.60^{b**} ±3.50
I	29.7 ±7.00	24.5 ±6.70	23.4 ±6.90	17.7 ±3.90	18.2 ±3.70	14.8* ±3.30	16.5 ±2.60	18.0 ±3.70	16.2 ±3.30	16.8 ±8.40	19.1 ±3.40	17.4 ±2.40	17.1^{ab} ±2.20	17.1^{ab} ±2.00	17.1^{ab} ±2.00

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)
** Significantly different from the base value within group (P<0.05)*
*** Significantly different from the base value within group (P<0.01)*

Table no. 4.65 : Mean±SE values of rectal temperature (°F) recorded in the animals of different groups

Group	Time Interval														
	0	5	10	15	20	30	45	60	75	90	105	120	130	150	180
G	101.06 ±0.42	101.0 ±0.42	101.0 ±0.42	101.0 ±0.42	100.3 ±0.30	99.9* ±0.49	99.4* ±0.69	99.4ab* ±0.69	99.6ab* ±0.86	99.3ab* ±0.92	99.6ab* ±0.84	99.9ab* ±0.66	99.9ab* ±0.66	100.1ab* ±0.58	100.1ab* ±0.58
H	100.4 ±0.78	100.4 ±0.77	100.4 ±0.75	100.3 ±0.74	99.8 ±1.00	99.4 ±0.97	99.3* ±0.92	98.1ab** ±00.6	97.0b*** ±0.6	97.8b*** ±00.5	96.7b*** ±00.5	96.2b*** ±00.4	96.2b*** ±10.4	96.2b*** ±10.4	96.1b*** ±10.4
I	101.3 ±0.35	101.4 ±0.25	100.9 ±0.29	100.9 ±0.30	100.9 ±0.36	100.8 ±0.28	100.8 ±0.28	100.7a ±0.31	100.3a ±0.47	100.4a ±0.45	100.6a ±0.45	100.7a ±0.35	100.8a ±0.26	100.8a ±0.26	100.8a ±0.26

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)
** Significantly different from the base value within group (P<0.05)*
*** Significantly different from the base value within group (P<0.01)*
**** Significantly different from the base value within group (P<0.001)*

xxxxxx

Table no. 4.66 : Mean±SE values of haemoglobin (g/dl) recorded in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
G	13.40 ±0.30	10.33*** ±0.33	10.10** ±0.49	10.23** ±0.50	10.03[ab]** ±0.43	10.26*** ±0.26
H	12.00 ±0.57	9.56* ±0.86	9.33** ±0.81	9.03[b]** ±0.57	8.50[b]** ±0.86	10.48* ±0.41
I	13.70** ±1.06	9.70* ±0.66	9.63 ±0.63	11.53[a] ±0.53	11.03[a] ±0.14	10.70 ±0.35

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)
** Significantly different from the base value within group (P<0.05)*
*** Significantly different from the base value within group (P<0.01)*
**** Significantly different from the base value within group (P<0.001)*

Table no. 4.67 : Mean±SE values of clinical PCV (%) recorded in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
G	40.66 ±1.20	30.33** ±0.88	30.33* ±1.20	29.33** ±0.66	29.33** ±0.66	30.66** ±0.88
H	36.66 ±2.60	28.00** ±2.30	28.00** ±2.64	26.33*** ±2.60	26.00** ±3.21	31.66 ±1.20
I	41.00 ±3.05	28.66** ±1.76	28.66* ±1.66	32.66* ±1.76	32.00* ±1.15	31.00* ±1.00

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
** Significantly different from the base value within group (P<0.05)*
*** Significantly different from the base value within group (P<0.01)*
**** Significantly different from the base value within group (P<0.001)*

Table no. 4.68 : Mean±SE values of total leucocyte count (thousand/µl) recorded in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
G	7.99 ±0.74	6.71 ±0.27	6.23 ±0.19	6.11 ±0.10	5.83 ±0.19	5.36 ±0.12
H	7.48 ±0.54	7.04 ±0.80	6.69 ±0.75	6.49 ±0.85	6.55 ±0.85	6.55 ±0.81
I	7.04 ±0.50	6.59 ±0.55	6.04 ±0.40	6.28 ±0.36	6.48 ±0.44	6.51 ±0.47

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine

Table no. 4.69 : Mean±SE values of neutrophil (%) recorded in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
G	49.50 ±1.50	46.00 ±2.00	43.00 ±1.00	42.50 ±0.50	41.50 ±0.50	40.00 ±0.00
H	54.50 ±4.50	51.00 ±3.00	48.00 ±2.00	46.00 ±2.00	44.50 ±1.50	45.50 ±0.50
I	51.50 ±2.50	47.00 ±2.00	45.50 ±2.50	41.50 ±2.50	42.00* ±3.00	41.00 ±4.00

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
** Significantly different from the base value within group (P<0.05)*

Table no. 4.70 : Mean±SE values of lymphocyte (%) recorded in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
G	44.50 ±2.50	48.00 ±2.00	51.00 ±1.00	51.00 ±1.00	52.00 ±1.00	53.50 ±0.50
H	44.50 ±0.50	43.00 ±3.00	46.00 ±2.00	47.50 ±2.50	54.00 ±3.00	48.50 ±0.50
I	46.50 ±2.50	46.50 ±1.50	48.50 ±2.50	52.00 ±2.00	52.00 ±4.00	52.50 ±4.50

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine

Table no. 4.71 : Mean±SE values of Eosinophils (%) recorded in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
G	3.50 ±0.50	4.00 ±0.00	3.50 ±0.50	4.00 ±0.00	4.00 ±0.00	4.00 ±0.00
H	3.50 ±0.50	3.50 ±0.50	3.50 ±0.50	4.00 ±0.00	4.00 ±0.00	3.50 ±0.50
I	4.00 ±1.00	4.00 ±1.00	4.00 ±1.00	4.00 ±0.00	4.00 ±0.00	4.00 ±0.50

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine

Table no. 4.72 : Mean±SE values of monocytes (%) recorded in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
G	2.50 ±0.45	2.50 ±0.45	2.50 ±0.45	2.50 ±0.55	2.50 ±0.51	2.50 ±0.52
H	2.50 ±0.35	2.50 ±0.25	2.50 ±0.25	2.50 ±0.28	2.50 ±0.14	2.50 ±0.38
I	2.50 ±0.50	2.50 ±0.50	2.50 ±1.00	2.50 ±0.50	2.50 ±0.50	2.50 ±0.50

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine

Table no. 4.73 : Mean±SE of plasma glucose (mg/100ml) in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
G	40.58 ±11.86	27.94* ±8.8	70.12 ±15.9	71.55 ±17.6	102.53 ±36.2	109.76 ±34.8
H	122.53 ±55	90.78** ±53	86.17* ±47	108.17 ±40	128.97 ±33	128.90 ±33
I	48.85 ±13.7	43.40 ±17.4	51.05 ±14.8	45.43 ±10.5	56.28 ±9.7	66.12 ±12.2

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
** Significantly different from the base value within group (P<0.05)*
*** Significantly different from the base value within group (P<0.01)*

Table no. 4.74 : Mean±SE of plasma urea (g/l) in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
G	83.63 ±19.5	89.27 ±23.9	91.65 ±17.6	123.28 ±18.0	101.91 ±20.8	66.20 ±11.7
H	107.92 ±20.3	91.50* ±17.2	104.96 ±17.8	110.48 ±17.1	106.40 ±14.7	69.42* ±13.9
I	86.09 ±25.7	91.57 ±28.0	80.96 ±20.8	86.78 ±32.4	95.16 ±25.1	87.55 ±25.3

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
** Significantly different from the base value within group (P<0.05)*

Table no. 4.75 : Mean±SE of plasma creatinine (mg/100 ml) in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
G	24.75[a] ±4.1	19.03** ±3.4	18.26* ±2.7	19.12[a] ±2.0	19.33[a*] ±2.2	19.85 ±4.8
H	11.0[b] ±4.1	9.25 ±2.6	8.94 ±2.6	8.95[b] ±3.2	8.79[b] ±3.1	7.14 ±2.1
I	11.89[ab] ±2.2	11.52 ±2.5	13.45 ±2.8	13.43[ab] ±2.6	12.88[ab] ±2.7	14.48 ±2.9

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)
** Significantly different from the base value within group (P<0.05)*
*** Significantly different from the base value within group (P<0.01)*

Table no. 4.76 : Mean±SE of plasma cortisol (n mol/L) in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
G	121.89 ±58.0	73.7 ±27.6	138.7[a] ±30.1	158.6** ±53	96.24 ±26.8	54.14 ±15.6
H	11.50 ±4.8	11.02 ±7.0	10.07[b] ±0.07	81.42 ±54.7	70.20* ±15.2	67.54 ±14.5
I	70.05 ±36.2	34.50 ±14.4	16.57[b] ±5.6	26.79 ±63	76.53 ±15.6	70.34 ±17.2

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)
** Significantly different from the base value within group (P<0.05)*
*** Significantly different from the base value within group (P<0.01)*

Table no. 4.77 : Mean±SE of GGT (U/L) in the animals of different groups

Group	Time Interval (min)					
	0	30	60	90	120	180
G	94.08[a] ±48.15	76.73[a] ±40.44	80.77[a] ±41.08	70.35[a] ±29.93	64.56[a] ±19.77	51.24[a] ±20.39
H	18.06[b] ±7.63	8.56[b] ±1.66	8.56[b] ±1.66	10.19[b] ±2.27	10.42[b] ±2.07	10.42[b] ±2.07
I	21.42[a] ±5.76	18.45[a] ±7.08	18.45[a] 7.08	47.06[a] 25.81	42.84[a*] 10.90	42.84[a*] 10.90

G: Bupivacaine + ketanine; H : Xylazine + Ketamine; I : Buprenorphine + Ketamine
Means bearing different superscripts differ significantly at corresponding intervals (P<0.05)
** Significantly different from the base value within group (P<0.05)*

VITAE

Name	:	**Rekha Pathak**
Father's Name	:	Shri L.N. Pathak
Date of birth	:	06.12.1972
Husband's Name	:	Dr. Pankaj
Educational Qualification	:	☞ Completed B.V.Sc. in 1997 from College of Veterinary Science and Animal Husbandry, Rajendranagar, ANGRAU, Hyderabad, (A.P.) (OGPA - 8.6/10) ☞ Completed M.V.Sc. programme at Indian Veterinary Research Institute, Izatnagar in 1999 (OGPA - 8.4/10) ☞ Joined Ph.D. programme at IVRI, Izatnagar in 1999 (OGPA - 8.6/10) ☞ Joined U.P. Govt. as Veterinary Officer in 2001
Fellowship awarded	:	☞ ICAR JRF (M.V.Sc.) in Veterinary Surgery. ☞ ICAR SRF (Ph.D.) in Veterinary Surgery ☞ Qualified NET eligibility test in the year 1999
Membership	:	☞ Life membership of Indian Society of Veterinary Surgery ☞ Life membership of MOBILIZATION
Current Status	:	Veterinary Officer
Medals	:	A Gold medal in subject Dairy Science & Technology in B.V.Sc. & A.H.

Permanent Address:

Dr. Rekha Pathak
C/O - Shri Surendra Pal Singh Katiyar (Advocate)
Vill. -Chandpur
Post - Maceni
Distt. - Farrukhabad
Ph. No. 05692-240425
Mob. : 9412645231