

**ATROPINE – MEDETOMIDINE – KETAMINE AS  
BALANCED ANAESTHESIA FOR NEONATAL  
CALVES**

**THESIS**

**By**

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**Submitted to**



**CHAUDHARY SARWAN KUMAR HIMACHAL PRADESH KRISHI  
VISHVA VIDYALAYA PALAMPUR - 176 062 (H.P.) INDIA**

**IN**

**Partial fulfilment of the requirements for the degree**

**OF**

**MASTER OF VETERINARY SCIENCE  
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*Is there anything I can say  
anything I can give  
or do for you?  
Because all that I'm  
all that I have  
I owe to you.....*

**AFFECTIONATELY  
DEDICATED TO MY WIFE AND  
CHILDREN**

*Who sacrificed their present  
to make my future better*

**Dr S.K. Sharma**  
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## **CERTIFICATE I**

This is to certify that the thesis entitled "Atropine – medetomidine – ketamine as balanced anaesthesia for neonatal calves" submitted in partial fulfilment of the requirements for the award of the degree of Master of Veterinary Science (Veterinary Surgery and Radiology) of Choudhary Sarwan Kumar Krishi Vishvavidyalaya, Palampur, is a bonafide research work carried out by Shri Ajay Kumar Singh son of Shri Prabhat Singh under my supervision and that no part of this thesis has been submitted for any other degree or diploma.

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




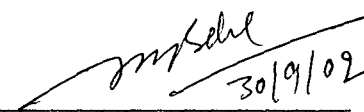
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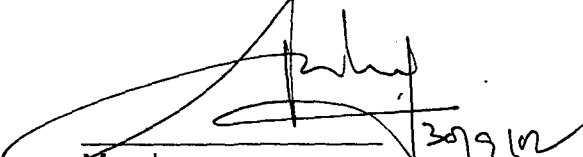
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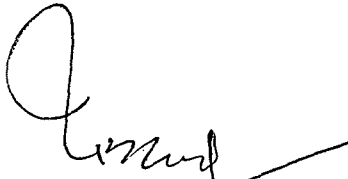
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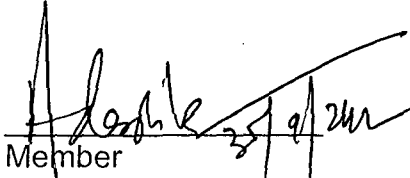
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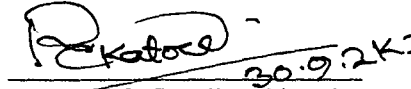
  
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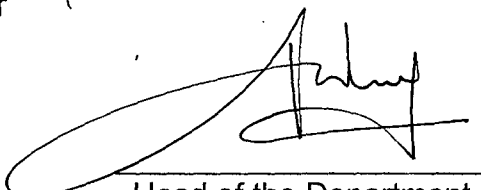
  
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*Place ; Palampur*

*Dated : the 5<sup>th</sup> September, 2002*

  
(A.K Singh)

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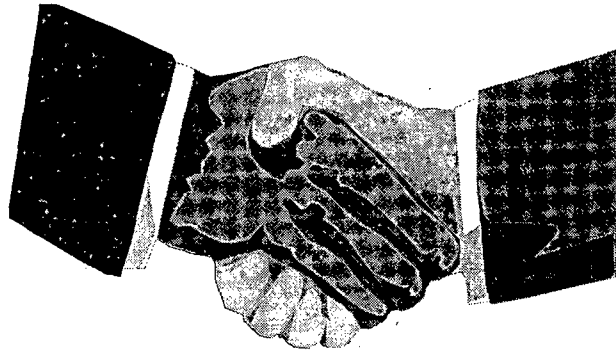
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## ABBREVIATIONS

ALT	Alanine amino transferase
AST	Aspartate amino transferase
AV	Atrio ventricular
BUN	Blood urea nitrogen
bw	Body weight
cm	Centimeter
DP	Diastolic pressure
ECG	Electrocardiography/Electrocardiogram
EEG	Electroencephalography
(F)	Fahrenheit
g/dl	Gram per deciliter
Hb	Haemoglobin
I/M or IM	Intramuscular
I/V or IV	Intravenous
kg	Kilogram
MAP	Mean arterial pressure
meq/L	milliequivalent per litre
mg	milligram
mg/dl	milligram per deciliter
mm	millimeter
min	minute
mV	milli volt
n	Number
PCV	Packed cell volume
PP	Pulse pressure
Resp.rate	Respiration rate
SA	Sinoatrial
S.E	Standard error
SP	Systolic pressure
TC	Time constant
Temp.	Temperature
TEC	Total erythrocyte count
TLC	Total leukocyte count
µg	microgram
U/L	Units per litre



# INTRODUCTION

## Chapter – 1

### INTRODUCTION

Anaesthesia, as understood today is a state in which one is insensible to the trauma of surgery. Many ailments, congenital or acquired, do require surgical intervention to be carried out under proper surgical anaesthesia. Since neonates are riskier candidates for anaesthesia as compared to adults, the need for safe and effective anaesthetic regimen has gained increasing importance in neonatal patients. Because all the anaesthetic agents have some undesirable effects when used alone, modern anaesthetic practice increasingly involves the use of combinations of drugs. This technique is well known as balanced anaesthesia.

Neonate patients of any species carry the risk of anaesthetic accidents as compared to adults due to absence or reduced hepatic microsomal enzyme system and vulnerability to vital body functions (Kaneko and Cornelius, 1970). From pharmacological and physiological point of view neonates differ a lot in comparison to adults, which must be taken into consideration while planing an anaesthetic regimen for them (Elizabeth and Martinez, 1995). The newborn and young animals are more sensitive to toxic effects of drugs in comparison to adults (Done, 1964). Due to difference in distribution and elimination mechanisms in neonates, adverse reactions to the drugs have been noted in them when administered in adult doses (Baggot and Short; 1984). The anaesthetic protocol for such patients should, therefore, be different from the adults.

The economics of dairy industry is largely dependent on bovines and any loss of young one directly affects the farmer and the dairy industry as a whole.

Neonate calves are often presented to the veterinarian for the treatment of ailment or anomaly, which can be acquired or congenital. Since neonate calves are as good as monogastric animals, general anaesthesia can safely be induced facilitating adequate physical restraint during the course of surgery or physical examination. Little work has been done with regard to anaesthesia in bovine neonates (Blaze *et al.*, 1988; Peshin *et al.*, 1991; Sharma, 1995; Sharma *et al.*, 1998a&b; Lester *et al.*, 1999 and Shakuntla, 2000).

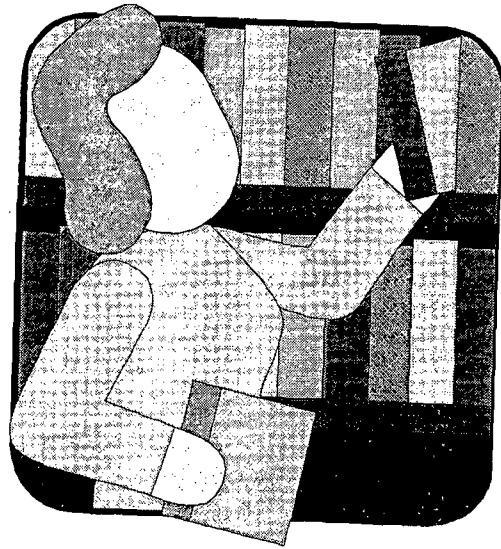
Medetomidine an imidazole derivative is highly selective and specific  $\alpha_2$  adrenoceptor agonist and is finding increased use in combination with other drugs in recent times for producing analgesia and anaesthesia in bovines. The actions of medetomidine are generally similar to those of xylazine, but it is more specific and potent in its activity. Decreased motor activity and analgesia are readily seen following medetomidine injection in small and lab animals (Savola *et al.*, 1986). However, the use of  $\alpha_2$  agonists have been tempered by the potential of cardiopulmonary depression (Eisenach and Tong, 1991). To overcome the side effects of these drugs, the drugs from different pharmacological classes have been used in combination with  $\alpha_2$  agonists. Ketamine has been used most extensively in combination with  $\alpha_2$  – agonists for systemic use because it is not only a good analgesic but also counter balance the majority of side effects of  $\alpha_2$  – agonists.

Since ketamine hydrochloride is a potent dissociative anaesthetic and has less musculoskeletal and convulsive seizure activity, it finds its use in most of the anaesthetic regimen. Since it produces a state of cataleptoid analgesia without hypnosis, its combination with xylazine (Singh *et al.*, 1985) is preferred. The duration, depth and extent of analgesia are adequate to perform surgical procedures

and the xylazine – ketamine combination is safe to use in calves (Kinjavdekar *et al.*, 1999) whereas the combination of ketamine with medetomidine has been shown to produce better analgesia in comparison to medetomidine alone in buffalo calves (Pratap *et al.*, 2000). Ketamine has also been used in combination with detomidine hydrochloride for balanced anaesthesia in neonate calves (Shakuntla *et al.*, 2001).

Taking into account the importance of balanced anaesthesia in neonates and considering the utility of medetomidine and ketamine in bovines, the present study was planned with the following objectives;

- I. To evaluate the sedative, analgo - clinical and biochemical effects of Atropine - Medetomidine + Ketamine anaesthesia in neonate calves.
- II. To evaluate the cardiovascular and electroencephalographic effects of Atropine - Medetomidine + Ketamine anaesthesia in neonate calves.



# REVIEW OF LITERATURE

## Chapter -2

### REVIEW OF LITERATURE

There are limited reports regarding the systematic detailed investigations related to suitability of various central nervous system depressant drugs including anaesthetics in bovine neonates. Therefore the available literature has been reviewed under the following heads: -

- 2.1 Anaesthesia in neonate animals
- 2.2 Medetomidine hydrochloride in adult bovines
- 2.3 Ketamine hydrochloride in adult bovines

#### 2.1 ANAESTHESIA IN NEONATE ANIMALS

There are instances where neonate animals upto 15 days of age are presented to a veterinarian for diagnostic and surgical procedures. Leaving aside few minor procedures, general anaesthesia is often required to overcome the resistance exhibited by neonates. Neonates have unique pharmacological and physiological differences as compared to adults, which must be considered while planning an anaesthetic regimen (Elizabeth and Martineze, 1995).

##### 2.1.1 Sedative studies

Xylazine has been described to produce good sedation in neonate calves (Stephens and Sharman, 1988). In bovine neonates surgical anaesthesia was achieved by using the combination of xylazine - ketamine (Kumar and Singh, 1979; Waterman, 1981 and Sharma *et al.*, 1998a). The combination of diazepam - xylazine - ketamine has also been shown to produce surgical anaesthesia in neonate calves (More *et al.*, 1998). Injection of thiopentone sodium in paediatric

calves premedicated with diazepam produced good surgical anaesthesia (Kandpal and Kumar, 1998). The surgical anaesthesia was successfully induced in neonate calves when ketamine was used in combination with xylazine (Sharma *et al.*, 1998a) or detomidine (Shakuntla *et al.*, 2001). Medetomidine reliably induced sedation and recumbency in goat kids, and the animals recovered from the sedative effect of medetomidine without any apparent adverse effect (Mohammad *et al.*, 1991). Xylazine produces good sedation in foals (Carter *et al.*, 1990) where as the combination of xylazine - ketamine (Schmidt – Oechtering, 1989) and propofol - xylazine (Matthews *et al.*, 1995) induced surgical anaesthesia in equine neonates. In neonate pups, intravenous chloralose (Grad *et al.*, 1988) and diazepam – ketamine, intranasally (Amarpal *et al.*, 1997) have been used for surgical anaesthesia.

The induction of surgical anaesthesia was rapid and smooth following the use of atropine - promazine – halothane in neonate calves (Sarma *et al.*, 1993). The combination produced good muscle relaxation and the recovery was smooth. The combination of xylazine - ketamine or diazepam - xylazine - ketamine produced good muscle relaxation with smooth recovery in neonate calves (Waterman, 1981; More *et al.*, 1998 and Sharma *et al.*, 1998a). Detomidine produced good muscle relaxation in foals (Oijala and Katila, 1988) and neonate calves (Peshin *et al.*, 1991). Excellent sedation was achieved by using detomidine hydrochloride in neonate calves but it failed to produce analgesia whereas the combination of detomidine and ketamine successfully induced surgical anaesthesia suggesting their use in clinical practice (Shakuntla, 2000). The combination of intravenous naloxone and local anaesthesia has been used to eliminate behavioural changes and response to acute pain following castration and tail docking in newborn lambs (Wood *et al.*, 1991).

### 2.1.2 Clinical studies

Bradycardia was noticed following xylazine - ketamine (Kumar and Singh, 1979; Blaze *et al.*, 1988 and Sharma *et al.*, 1998a) or detomidine – ketamine (Shakuntla *et al.*, 2001) anaesthesia in neonate calves and following xylazine – ketamine anaesthesia in foals. However, no change in heart rate was observed following the use of nitrous oxide/halothane anaesthesia in newborn piglets (Crane *et al.*, 1975 and Buckley *et al.*, 1976). Halothane also causes bradycardia in neonate rabbits (Wear *et al.*, 1982) and in children (Lerman *et al.*, 1983). Bradycardia has also been recorded following the use of xylazine or detomidine in neonate foals (Oijala and katila, 1988, and Carter *et al.*, 1990) and calves (Peshin *et al.*, 1991 and Sharma, 1995). Contrarily tachycardia was observed following acepromazine/promazine - halothane (Sarma *et al.*, 1993) and ketamine or diazepam/detomidine - ketamine (Kandpal and Kumar, 1998) anaesthesia in bovine paediatrics and chloral hydrate narcosis in neonate calves (Sharma *et al.*, 1998b). In another study significant increase in heart rate was observed with diazepam – thiopentone sodium combination in paediatric calves (Kandpal and Kumar, 1998).

In bovine neonates, following the use of xylazine - ketamine (Blaze *et al.*, 1988 and Sharma *et al.*, 1998a), xylazine and chloral hydrate (Sharma, 1995) and diazepam - detomidine – ketamine, diazepam - thiopentone (Kandpal and Kumar, 1998), an increase in respiration was observed. Interestingly the combination of xylazine - ketamine produced a decrease in respiration rate in neonate calves (Kumar and Singh 1979 and Waterman *et al.*, 1981). Xylazine and propofol - xylazine combination also produced oligopnea in neonate foals (Carter *et al.*, 1990 and Matthews *et al.*, 1995) whereas a transient apnea to hyperapnea was

observed following diazepam - xylazine - ketamine anaesthesia in neonate calves (More *et al.*, 1998). Detomidine caused no significant change in respiration rate and rectal temperature in neonate calves (Peshin *et al.*, 1991). A significant increase in respiration rate along with rectal temperature have been reported following detomidine hydrochloride administration in neonate calves (Shakuntla, 2000). Hypothermia has been observed in neonate/paediatric calves following the use of xylazine - ketamine (Sharma *et al.*, 1998a), acepromazine/promazine – halothane (Kumar and Singh, 1979; Sarma *et al.*, 1993), chloral - mag / chloral - mag - thiopental (Sharma, 1995) anaesthetic combinations. Rectal temperature decreased significantly in paediatric calves following the administration of diazepam – thiopentone sodium (Kandpal and Kumar, 1998). Also there was terminal hypothermia along with initial tachypnea following detomidine – ketamine anaesthesia in neonate calves (Shakuntla *et al.*, 2001)

### **2.1.3 Haematological studies**

Non-significant changes have been noticed in different haematological parameters like haemoglobin, PCV, TLC and TEC following different anaesthetic(s) administration in neonate calves (Kumar and Singh, 1979; Sharma, 1995; Kandpal and Kumar, 1998 and Sharma *et al.*, 1998a&b; Shakuntla, 2000). The combination of glyceryl guaiacolate - halothane anaesthesia caused a significant decrease in haemoglobin and PCV and a significant increase in TLC in kids (Balagopalan *et al.*, 1992). All the haematological parameters like Hb, PCV, TEC and TLC remained within normal range following detomidine – ketamine anaesthesia in neonate calves (Shakuntla, 2000).

#### **2.1.4 Biochemical studies**

Hyperglycemia was a constant feature following different anaesthetic administration, alone or in combination in neonate calves (Peshin *et al.*, 1991 and Sharma, 1995) and kids (Balagopalan *et al.*, 1992) where as a decrease in blood glucose and insulin level was observed following xylazine administration in foals (Robertson *et al.*, 1990). Significant to highly significant increase in blood glucose was observed after administration of detomidine alone or in combination with ketamine in neonate calves (Shakuntla, 2000). Insignificant decrease in sodium and increase in potassium were noticed after administration of diazepam – thiopentone combination in paediatric calves (Kandpal and Kumar, 1998). A significant increase in blood urea nitrogen has been reported following chloral hydrate anaesthesia in neonate calves (Sharma, 1995). In general, the other biochemical parameters like sodium, potassium, chloride, total protein, creatinine, ALT, AST and LDH remained unaltered following different anaesthetic administration in neonate animals.

#### **2.1.5 Cardiovascular studies**

Varied changes have been reported in the blood pressure of different neonate animals following variety of anaesthetic regimen. Hypotension was observed following xylazine - ketamine anaesthesia in neonate calves (Blaze *et al.*, 1988) and foals (Robertson *et al.*, 1990) and following the administration of detomidine hydrochloride in neonate calves (Shakuntla, 2000). A nonsignificant increase in blood pressure has been reported following detomidine + ketamine anaesthesia in neonate calves (Shakuntla *et al.*, 2001). Propofol and xylazine anaesthesia caused an increase in blood pressure in 3 -10 days old foals (Matthews *et al.*, 1995). Similar changes in blood pressure were noted after isoflurane and

pentobarbital administration in newborn piglets (Eisenhour *et al.*, 1994). In paediatric calves a significant decrease in MAP was noted following diazepam – thiopentone sodium anaesthesia (Kandpal and Kumar, 1998). Anaesthesia induced by halothane in nitrous oxide and oxygen mixture depressed mean arterial pressure and increased carotid, femoral and renal resistance in newborn piglets and the effects increased with increase in halothane concentration from 0.25 to 1.5 % (Crane *et al.*, 1975).

There was a decrease in the slope of P-R interval in baby rabbits than in adults after halothane anaesthesia (Wear *et al.*, 1982). Sporadic ECG changes like elevation of ST-segment, downward PR- segment, bifid P- wave, increase in T-wave amplitude and transient SA block were noticed following chloral hydrate, chloral - mag thiopental and xylazine administration in neonate calves (Sharma, 1995). Similarly highly significant increase in the components of ECG was observed in another study on neonate calves following xylazine - ketamine anaesthesia (Sharma *et al.*, 1998). Contrarily no significant changes in ECG components were noticed following ketamine anaesthesia (with or without diazepam or detomidine premedication) in bovine pediatrics (Kandpal and Kumar, 1998).

#### **2.1.6 Miscellaneous studies.**

Blood gases and pH remained within normal physiological limits when halothane anaesthesia was given to piglets aged 7hrs to 25 days (Crane *et al.*, 1975). Thiopentone anaesthesia was observed to cause severe hypercarbia in neonate lambs which delayed the onset of respiration with minimum drug disposition (Coopland, 1977). Increased arterial CO<sub>2</sub> tension was noticed following xylazine - ketamine anaesthesia in newborn calves (Blaze *et al.*, 1988). Xylazine alone caused

no significant change in blood gas tensions and pH in 10-28 day old foals (Carter *et al.*, 1990). Following isoflurane anaesthesia time related increase in end tidal CO<sub>2</sub> tension and PaCO<sub>2</sub> was observed in spontaneously breathing equine neonates (Geiser and Rohrback, 1992). Nitrous oxide was found to be a potent, selective vasodilator of the pulmonary circulation in healthy newborn foals (Lester *et al.*, 1999). It was suggested to take care while using repeated doses of diazepam in neonatal foals as its terminal half life remained unchanged during first 21 days of life (Norman *et al.*, 1997). One should avoid using single mixture of chloral - mag - thiopental because of precipitation (Sharma, 1995).

## **2.2 MEDETOMIDINE HYDROCHLORIDE IN ADULT BOVINES**

Medetomidine hydrochloride [(+)-4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole hydrochloride], is a potent, selective and specific full agonist of both pre- and postsynaptic  $\alpha_2$  -adrenoceptors (Savola *et al.*, 1986 and Virtanen, 1989). Medetomidine is a racemic mixture, the active isomer being predominantly the d - enantiomer (dexmedetomidine). Medetomidine acts by modulating noradrenaline release on adrenergic nerve terminals and is reported to be essentially devoid of affinity for other receptors (Savola 1989; Virtanen, 1989).

### **2.2.1 Sedative studies**

Medetomidine has been shown to have antinociceptive effects by stimulating  $\alpha_2$  - adrenoceptors at various sites in the pain pathways at the spinal and supraspinal level (Ossipov *et al.*, 1990; Pertovaara, 1993). Medetomidine (0.039  $\pm$  0.10 mg/kg) induced complete immobilization after single darting with sternal or lateral recumbency in free ranging cattle (Arnemo and Soli, 1993). Deep sedation with analgesia has been reported for about 60 min following medetomidine (0.03

mg/kg, IM) administration in calves (Sharma *et al.*, 1996). Atipamezole successfully reversed the sedation induced by a combination of ketamine and medetomidine (Raekallio *et al.*, 1991) or medetomidine alone (Sharma *et al.*, 1996) in calves

### **2.2.2 Clinical studies**

In vitro studies on cattle tracheal smooth muscle after administration of medetomidine indicated inhibition of smooth muscle contraction at all frequencies to electrical field stimulation of 0.1 to 10 Hz (Manning and Broadstone, 1995). A constant bradycardia and hyperpnea were observed following medetomidine administration in cow calves (Sharma *et al.*, 1996). Following epidural administration of medetomidine a decrease in heart rate and respiration rate along with an increase in salivation were noticed in cows (Lin-Hui Chu *et al.*, 1998). The analgesia lasted for  $412 \pm 156$  min. Epidurally administered  $\alpha_2$  – agonists including medetomidine have been reported to cause reduction in respiratory rate in different animal species (Skarda and Muir, 1996; Aithal *et al.*, 1996; Kinjavdekar, 1998). Intravenous injection of medetomidine significantly reduced heart rate and increased rectal temperature for 45 minutes in lactating dairy cows (Ranheim *et al.*, 1999). The combination of medetomidine and ketamine was found to produce better analgesia than medetomidine alone in buffalo calves when administered in the lumbosacral epidural space (Pratap *et al.*, 2000).

### **2.2.3 Cardiovascular studies**

Alpha-2 adrenoreceptor agonists cause decrease in cardiac output as a result of bradycardia and increased peripheral resistance (Wagner *et al.*, 1991). In spite of the considerable advantages of the alpha-2 agents, undesirable side effects, particularly those on the cardiovascular unit have limited their use and also there is

particularly those on the cardiovascular unit have limited their use and also there is dose dependent cardiovascular depression, with bradycardia due to sinus bradycardia, first and second degree AV block and transient increase in arterial blood pressure followed by return to normal or moderate hypotension (Taylor, 2001). Medetomidine administered epidurally in calves produced an increase in arterial pressure by a direct effect on the postsynaptic  $\alpha_2$  – adrenoceptors in the vascular smooth muscles (Vesal *et al.*, 1996). An initial hypertension with subsequent hypotension has been reported following medetomidine administration in calves (Sharma *et al.*, 1996).

#### **2.2.4 Biochemical studies**

Plasma glucose level was found to be elevated in free ranging cattle after intramuscular injection (darting) of medetomidine (Arnemo *et al.*, 1993). Increase in aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine kinase (CK), plasma glucose and serum fatty acids (FFA) where as decrease in  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$  were observed after administration of medetomidine in semi domesticated reindeer (Soveri *et al.*, 2000). Medetomidine when administered intravenously induced a marked hyperglycemia and also the cortisol levels were increased significantly in cows where as levels of nor-adrenaline decreased reflecting the inhibition of sympathetic activity (Ranheim *et al.*, 2000).

#### **2.2.5 Miscellaneous studies**

Medetomidine concentration increased on intravenous administration of antagonist atipamezole in dairy calves and animals relapsed into sedation on average 80 min after reversal (Ranheim *et al.*, 1998). The same type of effect was also reported later on in dairy cows.

## 2.3 KETAMINE HYDROCHLORIDE IN ADULT BOVINES

Ketamine hydrochloride [2(O-chlorophenyl)-2-methylamine cyclohexamine hydrochloride] is classified as a dissociative anaesthetic. It has a molecular weight of 238 and pKa of 7.5 and is water soluble (Cohen and Trevor, 1974). It contains two resolvable optical isomers or enantiomers. The (+) isomer produces hypnosis lasting nearly twice as long (-) isomer. Analgesia with (+) isomer is more profound and there is less locomotor activity after anaesthesia (Lumb and Jones, 1984). Ketamine has been used either alone or in combination with other drugs in bovines.

### 2.3.1 Sedative and behavioural studies

Ketamine produced effective and satisfactory surgical anaesthesia in bovines either alone (Fuentes *et al.*, 1973; Mottelib, 1980 and Ramakrishna *et al.*, 1981) or in combination with xylazine (Aouad *et al.*, 1981 and Rings and Muir, 1982), thiopentone (William, 1995) or promazine (Mates *et al.*, 1991). Dissociative anaesthesia achieved by using ketamine was found to be ideal for surgery on foot, horn, management of wounds, and other minor operations of shorter duration in cows (Fuentes and Tellez, 1974). Surgical anaesthesia achieved following xylazine - ketamine combination in calves was better, economical and safer (Gorgul *et al.*, 1991). In cattle onset of dissociative anaesthesia following ketamine administration was rapid but without loss of palpebral, anal and swallowing reflexes (Fuentes and Tellez, 1974 and Mbiuki, 1982). The endotracheal intubation was easily achieved in cattle following the administration of ketamine alone or in combination with xylazine (Tadmor *et al.*, 1979 and Mbiuki, 1982). Duration of anaesthesia following ketamine varied with route of administration and part of the body to be tested for anaesthesia

as analgesia ranged from 8.3 min at coronet to 60 min at paralumbar fossa (Mbiuki, 1982) and in general persisted for 10 min in cattle (Koike *et al.*, 1974 a&b). Holstein calves became sternally recumbent in  $23 \pm 14$  seconds for a duration of  $94 \pm 25$  min after administration of medetomidine + ketamine mixture suggesting that the combination can effectively be used to induce anaesthesia in dairy calves (Lin-Hui Chu *et al.*, 1998).

Muscle relaxation was excellent following diazepam - glyceryl guaiacolate - ketamine anaesthesia in cow calves (Singh *et al.*, 1990) and atropine/ triflupromazine - sedivet - ketamine anaesthesia in buffalo calves (Sharma *et al.*, 1999). Adequate to good muscular relaxation has also been reported following diazepam - ketamine (Singh *et al.*, 1991), glyceryl guaiacolate - xylazine or ketamine - thiopentone (William *et al.*, 1992) and atropine - diazepam - ketamine with or without guaifenesin in calves (Sarma and kumar, 1998). Muscle tremors seen with ketamine were abolished by thiopentone and recovery was smooth in young calves (William, 1995). Epidural administration of the combination ketamine and xylazine is safe and effective for surgery involving the hindquarters in ruminants (Aithal *et al.*, 1997). Duration, depth and extent of analgesia caused by spinal xylazine - ketamine was adequate to perform surgical procedures like rumenotomy, repair of femur fracture, umbilical hernia, cystoplasty, urethrotomy, neurorrhaphy and tarsorrhaphy in clinical cases (Kinjavdekar *et al.*, 1999). Epidural injection of ketamine in cows produced dose related analgesia of the tail, anus, perineum and vulva but not of the hind limb area (Marsico *et al.*, 1999). The combination of detomidine - diazepam - ketamine used intravenously is safe and suitable for 15 min of anaesthesia with excellent muscle relaxation and had only limited cardio respiratory effects in

buffaloes (Pawde *et al.*, 2000). Excellent anaesthesia was achieved when detomidine was used with ketamine as single injection in neonate calves (Shakuntla, 2000).

### 2.3.2 Clinical studies

Majority of the clinical parameters remained within normal range following ketamine (Aouad *et al.*, 1981), xylazine - ketamine (Gorgul *et al.*, 1991) or ketamine - thiopentone anaesthesia (William *et al.*, 1992) in calves. An initial rise followed by drop in heart and respiration rates were noticed following ketamine (Mottelib, 1980) or ketamine - xylazine (Aouad *et al.*, 1981) administration in calves where as no change in heart rate was observed by Rings and Muir (1982), although an increase in respiratory frequency was seen. In buffalo calves, heart rate remained within normal range following xylazine - ketamine anaesthesia but respiration and rectal temperature varied (Mbiuki *et al.*, 1982). Significant tachycardia has also been reported following ketamine anaesthesia alone or with chlorpromazine in buffalo calves (Pathak *et al.*, 1982a) and following diazepam - glyceryl guaiacolate - ketamine (Singh *et al.*, 1992), diazepam - ketamine, diazepam - glyceryl guaiacolate - ketamine (Amarpal *et al.*, 1994), ketamine - glyceryl guaiacolate (William, 1995) and atropine - diazepam - ketamine anaesthesia in calves (Sarma and Kumar 1998). In contrast, bradycardia was observed after medetomidine - ketamine anaesthesia (Rae-kallio *et al.*, 1991) in calves and following atropine/triflupromazine - sedivet - ketamine anaesthesia in buffalo calves (Sharma *et al.*, 1999). Spinal xylazine - ketamine anaesthesia in ruminants (Kinjavdekar *et al.*, 1999) has also been reported to cause bradycardia.

Following intravenous administration of medetomidine + ketamine mixture in calves, PaCO<sub>2</sub> increased whereas pH and PaO<sub>2</sub> decreased (Raekallio *et al.*, 1991). Significant decrease in tidal volume and minute volume and non significant decrease in respiration rate were noticed following diazepam - ketamine or diazepam - glyceryl guaiacolate - ketamine anaesthesia in calves (Amarpal *et al.*, 1994) and following atropine/triflupromazine anesthesia in buffalo calves (Sharma *et al.*, 1999). Respiratory acidosis and hypoxemia were observed in cows following the intravenous administration of guaifenesin – ketamine – xylazine combination (Yamashita *et al.*, 1996). Respiratory rate and PaCO<sub>2</sub> were significantly reduced while values of PaO<sub>2</sub> showed significant decrease after the administration of medetomidine + ketamine mixture in dairy calves (Lin-Hui Chu *et al.*, 1998). A nonsignificant decrease in respiration has also been reported following spinal xylazine - ketamine anaesthesia in ruminants (Kinjavdekar *et al.*, 1999). Hypothermia was recorded following sedivet - ketamine anaesthesia in atropine/triflupromazine premedicated calves (Sharma *et al.*, 1999) and following spinal xylazine and ketamine anaesthesia in ruminants (Kinjavdekar *et al.*, 1999).

### **2.3.3 Haematological studies**

TEC, TLC, Hb and PCV showed significant drop after sedivet - ketamine anaesthesia with or without atropine/triflupromazine in buffalo calves (Sharma *et al.*, 1999). These changes were transient and minimum following glyceryl guaiacolate - xylazine - ketamine anaesthesia (William, 1995). There was no significant change in haematological parameters following diazepam - glyceryl guaiacolate - ketamine (Singh *et al.*, 1990), xylazine - ketamine (Gorgul *et al.*, 1991 and William *et al.*, 1992) or ketamine - thiopentone anaesthesia (William, 1995) in calves. Blood analysis

diazepam - ketamine with or without guaifenesin in calves suffering from acute renal failure (Sarma and Kumar, 1999).

#### **2.3.4 Cardiovascular studies**

Administration of ketamine hydrochloride in buffalo calves resulted in an increase in mean arterial pressure, cardiac output and peripheral vascular resistance during maximum depth of anaesthesia (Pathak *et al.*, 1982b), where as when ketamine was used in combination with xylazine both initial increase (Aouad *et al.*, 1981) or decrease (Rings and Muir, 1982) in blood pressure was recorded in calves. But the central venous and mean arterial pressure remained unchanged when the calves were observed for 24 hours (Rings and Muir, 1982). When ketamine was used in combination with glyceryl – guaiacolate in calves an increase in blood pressure was recorded (William, 1995). Total intravenous anaesthesia in cows using a combination of guaifenesin - ketamine - xylazine kept the heart rate and blood pressure within reasonable limits (Yamashita *et al.*, 1996). An increase in blood pressure has also been reported when ketamine was used in combination with diazepam with or without guaifenesin (Sarma and Kumar, 1998). On contrary significant hypotension and decrease in central venous pressure were noticed following diazepam - glyceryl guaiacolate - ketamine anaesthesia in calves (Singh *et al.*, 1992).

Cardiopulmonary stimulation was noticed after rapid intravenous induction of ketamine anaesthesia in buffaloes (Ramakrishna *et al.*, 1981). The

cardiopulmonary depressant effect of xylazine have been reported to be moderated by cardiostimulatory action of ketamine and the combination was found suitable alternative for other non inhalant techniques in buffaloes (Singh *et al.*, 1985).

ECG changes like wandering pace maker and depressed ST segment were noticed following ketamine anaesthesia in buffalo calves (Pathak *et al.*, 1982a& b) and xylazine - ketamine anaesthesia in cow calves (Kumar and Singh, 1977). Various other changes recorded were slight changes in P-wave, and QRS complex and amplitude, biphasic T-wave, elevation followed by depression of ST-segment, T-wave changes and sinus tachycardia. A significant increase in QRS amplitude and decrease in PR and QT intervals and PR segments were observed when ketamine was used along with diazepam and glyceryl guaiacolate in calves ( Singh *et al.*, 1992). No changes in ECG components were recorded following atropine - diazepam - ketamine with or without guaifenesin in buffalo calves (Sarma and Kumar, 1998).

#### **2.3.4 Biochemical studies**

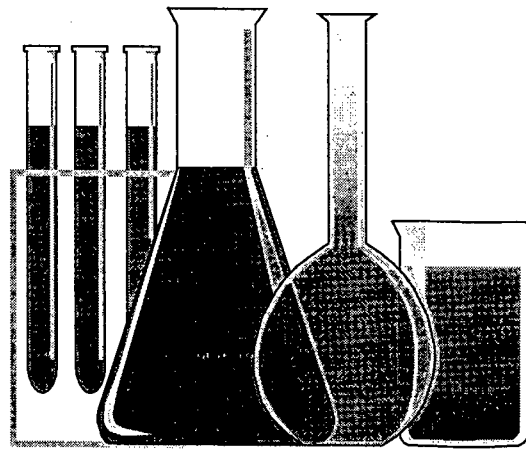
Ketamine anaesthesia in bovines produced hyperglycemia, when the drug was used alone (Rings and Muir, 1982, and Pathak *et al.*, 1982b) or in combination with other drugs (William, 1995). Combination of chlorpromazine and ketamine anaesthesia caused an increase in the serum alkaline phosphatase (ALKP) and lactate dehydrogenase (LDH) in buffalo calves (Pathak *et al.*, 1982b) where as in combination with xylazine it produced mild hyperkalemia and hypernatraemia in cow calves (Rings and Muir, 1982). Ketamine has also been shown to cause significant increase in plasma ascorbic acid, decrease in serum alkaline phosphatase and cholesterol (Mottelib, 1980), significant increase in ALT

and AST (Mottelib, 1980 and Pathak *et al.*, 1982b) and ALKP and LDH (Pathak *et al.*, 1982b) in buffalo calves. However, significant hypokalaemia was noticed following I/V diazepam -glyceryl guaiacolate - ketamine anaesthesia in calves (Singh *et al.*, 1991), ketamine - thiopentone (William *et al.*, 1992) and atropine diazepam - ketamine anaesthesia with or without guaifenesin in calves (Sarma and kumar, 1999). Sodium and chloride levels remained unchanged after intravenous diazepam - glyceryl guaiacolate - ketamine in cow calves (Singh *et al.*, 1990) and sedivet - ketamine in buffalo calves (Kinjavdekar *et al.*, 1999). Changes in plasma calcium, phosphorus, chloride, potassium and sodium were nonsignificant, whereas there was significant increase in creatinine level after the administration of atropine - diazepam - ketamine combination in calves suffering from acute renal failure (Sarma and kumar, 1999).

### **2.3.6 Miscellaneous studies**

While using ketamine as dissociative anaesthesia in bovines, fasting for 24 hrs is recommended (Fuentes *et al.*, 1973). Death due to regurgitation of ingesta was noticed during the study. Ketamine produced very little effect on blood gases in cattle (Mbiuki, 1982) where as in another study in calves, an increase in PCO<sub>2</sub>, standard bicarbonate and decrease in blood pH were noticed (Waterman, 1983). A combination of xylazine - ketamine produced mild bloat and regurgitation along with increased salivation (Mbiuki, 1982) and decrease in arterial partial pressure of oxygen (Rings and Muir, 1982) where as in combination with medetomidine (Rae, kallio *et al.*, 1991) or glyceryl guaiacolate/xylazine (William, 1995) hypercarbia and hypoxemia with drop in blood pH was observed. Respiratory acidosis along with

significant hypoxia has been reported following diazepam - glyceryl guaiacolate - ketamine combination in calves (Amarpal *et al.*, 1994).



# MATERIALS AND METHODS

## Chapter-3

### MATERIALS AND METHODS

The present study was conducted on 19 apparently healthy neonatal male calves aged 10 to 15 days and weighing 13 to 30 kg ( $20.47 \pm 1.14$ ) (Mean  $\pm$  SE). All the animals were kept under same managemental conditions and were fed on milk. Water and milk were withheld for 3 to 6 hrs prior to the experimentation work and each animal was weighed on the day of experiment.

#### 3.1 PILOT TRIALS:

Seven calves were used for pilot trials to standardize the dose of medetomidine hydrochloride<sup>a</sup> in combination with ketamine hydrochloride<sup>b</sup>. During pilot trials the dose rate of medetomidine hydrochloride used were 0.010 mg/kg and 0.015 mg/kg body weight. The dose rates of ketamine hydrochloride used in combination with computed dose of medetomidine were 5 mg/kg, 7.5 mg/kg and 10 mg/kg body weight. The different dose combination of the drugs medetomidine hydrochloride and ketamine hydrochloride in a single syringe were administered intramuscularly. The different dose combinations used during the pilot trials were as follows:

Pilot trial	Dose rate per kg body weight (I/M)	
	Medetomidine hydrochloride	Ketamine hydrochloride
I	0.010 mg	5.0 mg
II	0.010 mg	7.5 mg
III	0.010 mg	7.5 mg
IV	0.010 mg	10.0 mg
V	0.010 mg	10.0 mg
VI	0.015 mg	10.0 mg
VII	0.015 mg	10.0 mg

a. Domitor (10mg/ml). Orion Farma Ltd., Finland.

b. Ketamil (100mg/ml). Troy Laboratories PTY. Ltd. Australia.

Subjective analysis was adopted to standardize the dose of the drug combination. Based on the adequate extent of sedation, muscle relaxation and analgesia produced, the standardized dose rate of medetomidine hydrochloride and ketamine hydrochloride were 0.015 mg/kg body weight and 10.0 mg/kg body weight, respectively. There after the standardized combination was evaluated in two groups (Group 1 and 2), of six animals each.

### **3.2 METHOD OF EXPERIMENTATION**

The method of experimentation was divided into two groups.

**Group 1** : Evaluation of various sedative, analgo-clinical, haematological and biochemical parameters were carried out following intramuscular medetomidine + ketamine (single syringe) administration.

**Group 2** : Evaluation of various cardiovascular and electroencephalographic parameters were done following medetomidine + ketamine administration.

**3.2.1 GROUP 1:** Following atropinization, the animals were administered the standardized dose of medetomidine and ketamine combination in a single syringe intramuscularly. There after the animals were let loose and various sedative, analgo-clinical, haematological and biochemical parameters were recorded. The recordings wherever applicable, were done at 0 hr (Base line value, before administration of any drug), 15 min after atropinization and there after at 5, 15, 30, 45, 60, and 75 min intervals following administration of medetomidine + ketamine.

#### **3.2.1.1 Sedative studies**

For sedative studies, after the administration of medetomidine + ketamine, following time parameters were recorded:

**I) Onset time**

The time lapsed between administration of drugs (medetomidine + ketamine) and development of incoordination.

**II) Down time**

I) Sternal: The time lapsed between administration of drugs (medetomidine + ketamine) and the animal going into sternal recumbency.

II) Lateral: The time lapsed between the administration of the drugs (medetomidine + ketamine) and the animal going into lateral recumbency.

**III) Recovery time**

I) Sternal: The time lapsed between administration of drugs (medetomidine + ketamine) and the animal coming back to sternal recumbency.

II) Standing ataxia: The time lapsed between administration of drugs (medetomidine + ketamine) and the animal regaining its feet but ataxic.

III) Normal gait: The time lapsed between administration of drugs (medetomidine + ketamine) and the animal regaining its normal gait.

In addition to the above time parameters, any behavioural change (ear shaking, urination etc.) in the animals were also recorded during the study.

**3.2.1.2 Analgo-clinical studies**

The depth of sedation was assessed by monitoring various reflexes like palpebral, corneal, photopupillary, pin prick reflexes of neck, trunk and interdigital space, relaxation of neck, jaws, tail and anal sphincter, extent of salivation, and lacrimation at the above mentioned time intervals following the administration of medetomidine plus ketamine. The analgesic depth was evaluated by observing the physical response to the cutaneous hypodermic needle pricks in neck, trunk

(including scratching of periosteum of rib) and interdigital space. The judgment of analgesic effect was qualitative and subjective. The rectal temperature, heart rate and respiration rate were also recorded.

### **3.2.1.3 Haematological studies**

At the mentioned time intervals the venous blood (0.5 – 1 ml) from the jugular vein was collected in vials containing EDTA (10 mg/ml) for estimation of various haematological parameters like haemoglobin (Sahli's method), packed cell volume (micro haematocrit method), total leukocyte count (neubaur chamber) and total erythrocyte count (neubaur chamber) before and after atropine – medetomidine + ketamine administration.

### **3.2.1.4 Biochemical studies**

The blood was collected from the jugular vein approximately 5 ml in the heparinized centrifuge tubes at the mentioned time intervals before and after the administration of atropine - medetomidine + ketamine. The blood was centrifuged at 2500 rpm for 15 min and plasma was separated out which was collected in sample vials. The blood glucose was estimated immediately on computerized autoanalyzer<sup>c</sup>. The sample vials were then stored at  $-20^{\circ}\text{C}$  for analysis of the rest of the biochemical parameters. The various plasma attributes estimated on computerized autoanalyzer were viz., plasma glucose, total proteins, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine amino transferase (ALT) and chloride. Plasma sodium and potassium were estimated by Flame photometry (Oser, 1965).

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c. RA-50 Chemistry Analyzer. Bayer Diagnostics, Baroda, Gujarat, India.

**3.2.2 GROUP 2:** The animals of this group were used for cardiovascular and electroencephalographic studies (Plate A). Prior to the start of the experiment, the animals were secured in lateral recumbency. Various needle electrodes were placed in position for recording of electrocardiogram (ECG) and electroencephalogram (EEG). Under local infiltration analgesia using 2 % lignocaine hydrochloride<sup>d</sup>, the carotid artery was exteriorized and cannulated with a plastic catheter filled with heparinized normal saline, which was connected to sphygmomanometer for recording the blood pressure. There after an interval of 30 to 40 minutes was given as 'stabilizing time' before recording of all the parameters (ECG, EEG and blood pressure) to form base (0, hour) values. There after each animal was administered atropine sulphate @ 0.04 mg/kg body weight subcutaneously. At post atropine administration, ECG, EEG and blood pressure were recorded again. Thereafter the anaesthetic combination (medetomidine + ketamine) was administered intramuscularly and recordings of ECG, EEG and blood pressure were made at 5, 15, 30, 45, 60, and 75 minutes time interval.

### **3.2.2.1 Cardiovascular studies**

**I) Blood pressure:** The following pressures were recorded at different time intervals.

- a) Systolic Pressure (SP)
- b) Diastolic Pressure (DP)
- c) Mean Arterial Pressure (MAP) =  $(SP + 2DP)/3$

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d. Xylocaine 2% AstraZeneca Pharma, India Ltd.



**Plate A : Comprehensive experimentation unit, showing monitoring of A: ECG; B: EEG and C: blood pressure in a neonate calf, following atropine - medetomidine + ketamine administration.**

d) Pulse Pressure (PP) = SP - DP

## II) **Electrocardiographic studies:**

Electrocardiograms (ECG) were recorded by a bipolar base apex lead system with positive needle electrode placed subcutaneously at the centre of the sternal pad, negative electrode at posterior border of scapula and the neutral at the anterior side of the head of humerus, connected to the polyphysiograph<sup>e</sup>. The electrocardiograms were analyzed for various conduction and duration parameters. The calibrations made were 1 mv = 1 cm, paper speed of 25 mm/sec and 0.03 TC.

The time function components of ECG were recorded from tracings as follows:

- I) P-interval i.e. origin of P-wave and end of P-wave.
- II) PR-interval i.e. origin of P-wave and origin of QRS complex.
- III) QRS-complex i.e. origin of QRS-complex and end of QRS-complex
- IV) Q<sub>0</sub>T-interval i.e. origin of QRS-complex and origin of T-wave.
- V) QT-interval i.e. origin of QRS-complex and end of T-wave.
- VI) T-interval i.e. origin of T-wave and end of T-wave.
- VII) ST-segment i.e. end of QRS-complex and origin of T-wave.

The other voltage functions viz. P-wave, QRS-complex (whole) and T-wave were also calculated from ECG tracings.

### 3.2.2.2 **Electroencephalographic studies**

A bipolar transfrontal lead with positive and negative electrode inserted subcutaneously about 2 cm lateral to the frontal line on left and right

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e. Polyrite, Recorder and Medicare System, Chandigarh, India Ltd.

side respectively. EEGs were obtained using the signal output of amplifier 50  $\mu\text{V}/\text{cm}$ , 0.1 TC and paper speed of 25 mm/sec.

### **3.3 STATISTICAL ANALYSIS**

Statistical analysis of the data was done by Dunett's test at 1% and 5% level of significance using instat software<sup>f</sup>.

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f. Graphpad Instat tm, Graphpad software, 1990-1994.



RESULTS

## Chapter-4

# RESULTS

Based on the pilot trials conducted on seven neonate calves, the standardized dose rates of medetomidine hydrochloride and ketamine hydrochloride taken as a mixture in a single syringe for producing surgical anaesthesia were 15µg/kg and 10 mg/kg body weight respectively.

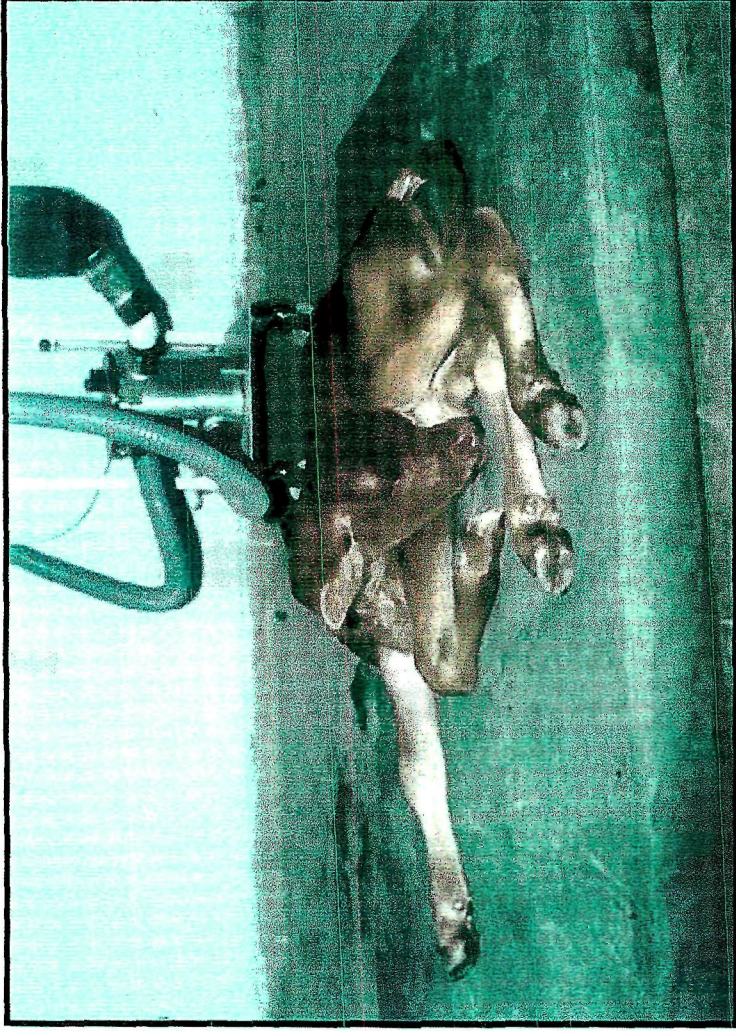
### **4.1 GROUP-1: SEDATIVE, ANALGO-CLINICAL, HAEMATOLOGICAL AND BIOCHEMICAL STUDIES.**

#### **4.1.1 Sedative studies**

The onset time recorded was  $1.16 \pm 0.166$  min (Mean  $\pm$  SE) and down time recorded for sternal and lateral recumbency (Plate B) were  $3 \pm 0.73$  min and  $4.5 \pm 0.50$  min respectively following medetomidine + ketamine administration in neonate calves. Recovery time recorded were  $79.33 \pm 1.05$  min (sternal),  $108.16 \pm 2.18$  min (standing ataxia) and  $128.5 \pm 1.33$  min (normal gait). Winking of eyes and flapping of ears were observed 15-18 min after medetomidine + ketamine administration. Head shaking was noticed in all the animals. The relaxation of neck and anal sphincter were last to return to normal during recovery from anaesthesia. There was urination in three animals during recovery period. In four animals typical reoccurrence of deep sedation was observed, generally after 60 min of drug administration.

#### **4.1.2 Analgo-clinical studies**

Following medetomidine + ketamine administration there was complete



**Plate B: Atropine - Medetomidine + Ketamine anaesthesia in a neonate calf showing lateral recumbency.**

loss of corneal reflex at 5 , 15 and 30 min intervals in three animals, whereas in other three animals mild to moderate depression was observed upto 45 min intervals. In three animals, complete relaxation of neck, tail, jaws and anal sphincter was observed at 5, 15, 30 and 45 min intervals, following medetomidine + ketamine administration. The relaxation of anal sphincter was last to come to normal during recovery period. In five animals there was complete analgesia at 5 min interval, which persisted uptill 45 minutes, whereas in one animal moderate to complete analgesia remained uptill 60 min interval. There was complete depression of swallowing reflex upto 45 min through out the period of study following medetomidine + ketamine administration in four neonate calves. Lacrimation and salivation remained absent in all the animals.

There was indication of terminal hypothermia (Fig.1) and bradycardia (Fig.1) following medetomidine + ketamine administration in neonate calves but the changes were statistically nonsignificant (Table 1). However increase in respiratory rate was highly significant ( $P < 0.01$ ) at 5, 15, and 30 min interval (Table1). Thereafter there was an increase in respiratory rate of the animals, which came to near normal at 60 and 75 min interval (Fig 1).

#### **4.1.3 Haematological studies**

All the haematological parameters like Hb, PCV, TLC and TEC remained within normal range following medetomidine + ketamine administration in neonatal calves (Table 1).

#### **4.1.4 Biochemical studies**

The effect of medetomidine + ketamine combination on different biochemical parameters in neonate calves are shown in Table 2.

**Table 1: Effect of atropine - medetomidine + ketamine hydrochloride on clinical and haematological parameters in neonate calves (n=6)  
Mean  $\pm$  SE**

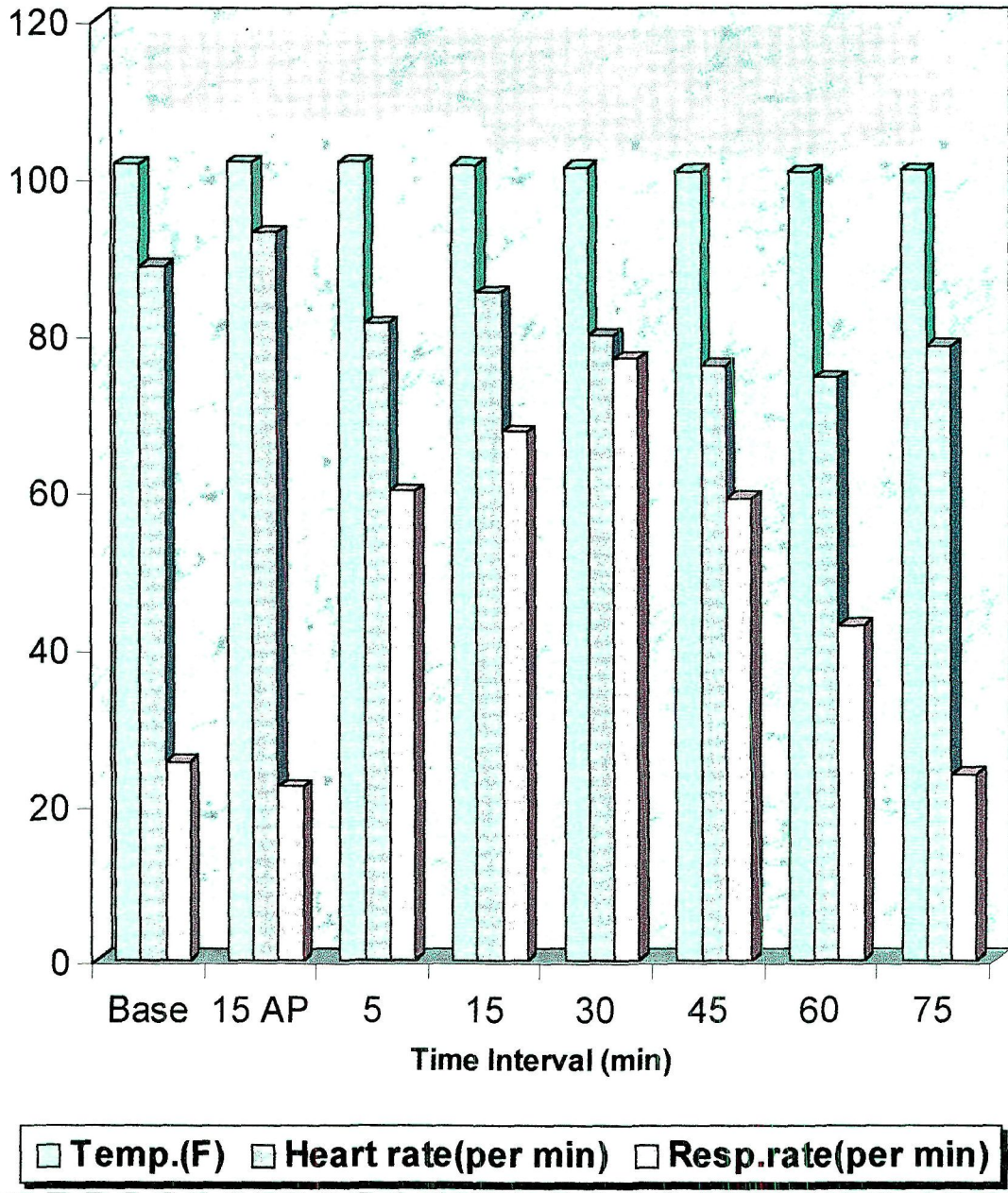
Parameters (unit)	Base	Minutes after medetomidine + ketamine						
		15 min aft.↓ atropine	5	15	30	45	60	75
Temp ( $^{\circ}$ F)	101.50 $\pm$ 0.39	101.80 $\pm$ 0.50	101.80 $\pm$ 0.62	101.40 $\pm$ 0.45	101.16 $\pm$ 0.51	100.70 $\pm$ 0.60	100.53 $\pm$ 0.53	100.83 $\pm$ 0.44
Heart rate (per min)	88.66 $\pm$ 4.52	93.00 $\pm$ 7.79	81.33 $\pm$ 7.01	85.33 $\pm$ 4.06	79.83 $\pm$ 5.71	76.00 $\pm$ 6.30	74.50 $\pm$ 6.38	78.50 $\pm$ 7.88
Resp.rate (per min)	25.50 $\pm$ 1.31	22.33 $\pm$ 2.17	59.83** $\pm$ 7.14	67.50** $\pm$ 10.80	76.83** $\pm$ 5.07	59.00** $\pm$ 4.50	43.00 $\pm$ 4.05	24.00 $\pm$ 2.45
Hb (g%)	09.00 $\pm$ 0.32	09.63 $\pm$ 0.33	10.23 $\pm$ 0.48	09.50 $\pm$ 0.35	09.36 $\pm$ 0.42	09.30 $\pm$ 0.58	09.43 $\pm$ 0.47	09.50 $\pm$ 0.56
PCV (%)	37.00 $\pm$ 2.11	38.33 $\pm$ 2.27	38.33 $\pm$ 2.09	37.33 $\pm$ 2.34	40.00 $\pm$ 2.12	39.00 $\pm$ 2.62	39.33 $\pm$ 2.10	39.66 $\pm$ 2.15
TEC (mill/mm <sup>3</sup> )	8.48 $\pm$ 0.33	9.08 $\pm$ 0.23	9.14 $\pm$ 0.23	9.83 $\pm$ 0.36	10.05 $\pm$ 0.41	10.20 $\pm$ 0.34	9.14 $\pm$ 0.23	8.99 $\pm$ 0.24
TLC (thou./mm <sup>3</sup> )	12.28 $\pm$ 1.01	13.30 $\pm$ 0.69	13.44 $\pm$ 1.10	12.32 $\pm$ 0.68	11.91 $\pm$ 0.95	12.49 $\pm$ 0.42	13.52 $\pm$ 0.62	12.93 $\pm$ 1.02

\*\* P < 0.01

↓ When medetomidine + ketamine administered intramuscularly.

Highly significant (P < 0.01) hyperglycemia was observed almost through out the period of study (Fig.2). The plasma concentration of BUN increased following the administration of the drugs but the changes were statistically non significant (Table 2). The rest of the biochemical constituents viz. total proteins, creatinine, AST, ALT, sodium, potassium and chloride remained within normal range following medetomidine + ketamine administration in neonate calves.

**Fig 1 : Effect of atropine - medetomidine + ketamine on clinical parameters in neonate calves (n=6)**



AP: After atropine

**Table 2: Effect of atropine - medetomidine + ketamine hydrochloride on biochemical parameters in neonate calves (n=6) Mean  $\pm$  SE**

Parameters (unit)	Base	15 min af.↓ atropine	Minutes after - medetomidine + Ketamine					
			5	15	30	45	60	75
Glucose (mg/dl)	64.83 $\pm$ 5.12	81.33 $\pm$ 4.63	114.16 $\pm$ 10.14	140.66** $\pm$ 18.52	155.33** $\pm$ 20.11	141.83** $\pm$ 16.34	149.50** $\pm$ 8.01	151.83** $\pm$ 16.01
TP 's (g/dl)	4.76 $\pm$ 0.43	4.81 $\pm$ 0.43	4.55 $\pm$ 0.54	5.21 $\pm$ 0.55	4.73 $\pm$ 0.37	4.43 $\pm$ 0.48	4.93 $\pm$ 0.36	4.50 $\pm$ 0.37
BUN (mg/dl)	12.91 $\pm$ 1.63	16.38 $\pm$ 1.12	16.30 $\pm$ 1.48	16.13 $\pm$ 0.92	16.88 $\pm$ 1.14	16.65 $\pm$ 0.92	16.50 $\pm$ 1.04	16.46 $\pm$ 1.02
Creatinine (mg/dl)	1.52 $\pm$ 0.13	1.77 $\pm$ 0.12	1.63 $\pm$ 0.20	1.58 $\pm$ 0.22	1.59 $\pm$ 0.19	1.62 $\pm$ 0.15	1.59 $\pm$ 0.16	1.49 $\pm$ 0.15
AST (U/L)	34.83 $\pm$ 3.32	44.16 $\pm$ 5.04	34.33 $\pm$ 1.76	36.00 $\pm$ 3.30	34.66 $\pm$ 1.68	36.83 $\pm$ 2.62	37.83 $\pm$ 0.70	36.50 $\pm$ 1.33
ALT (U/L)	13.00 $\pm$ 0.51	11.33 $\pm$ 0.20	11.83 $\pm$ 0.74	11.16 $\pm$ 0.30	10.50 $\pm$ 0.50	10.33 $\pm$ 0.49	10.83 $\pm$ 0.48	12.00 $\pm$ 1.63
Sodium (meq/l)	124.66 $\pm$ 3.33	122.66 $\pm$ 3.88	121.33 $\pm$ 2.45	115.66 $\pm$ 7.23	119.67 $\pm$ 7.57	118.50 $\pm$ 5.01	121.50 $\pm$ 4.51	122.50 $\pm$ 4.42
Potassium (meq/l)	3.53 $\pm$ 0.24	3.43 $\pm$ 0.23	2.33 $\pm$ 0.21	3.35 $\pm$ 0.18	3.45 $\pm$ 0.14	3.35 $\pm$ 0.14	3.48 $\pm$ 0.21	3.60 $\pm$ 0.15
Chloride (meq/l)	93.25 $\pm$ 5.82	97.88 $\pm$ 3.28	95.08 $\pm$ 2.85	96.71 $\pm$ 4.00	97.10 $\pm$ 3.70	97.55 $\pm$ 4.79	100.86 $\pm$ 4.05	99.55 $\pm$ 3.80

\*\* P < 0.01

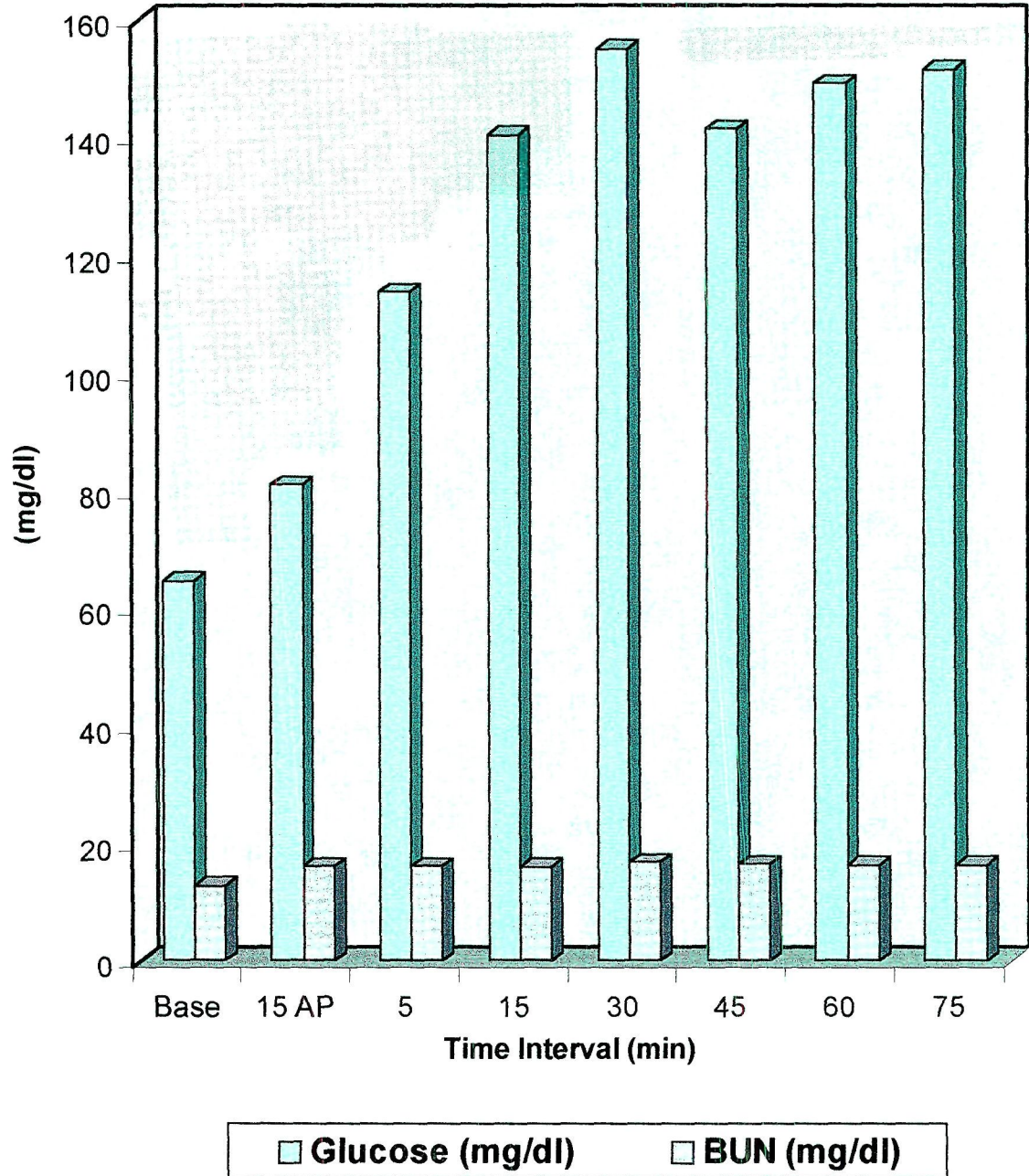
↓ when medetomidine + ketamine administered intramuscularly.

## 4.2 GROUP 2: CARDIOVASCULAR AND ELECTROENCEPHALOGRAPHIC STUDIES

### 4.2.1 Cardiovascular studies

There was hypotension (Fig 3) after the administration of the anaesthetic combination of medetomidine and ketamine hydrochloride in neonate calves, as indicated by significant ( $P < 0.05$ ) to highly significant ( $P < 0.01$ ) decrease in SP, DP

**Fig 2: Effect of atropine - medetomidine + ketamine on plasma glucose and BUN in neonate calves (n=6)**



AP: After atropine

**Table 3: Effect of atropine - medetomidine + ketamine on blood pressure in neonate calves (n=6) Mean  $\pm$  SE**

Parameters (unit)	Base	15 min af.↓ atropine	Minutes after medetomidine + ketamine					
			5	15	30	45	60	75
SP (mm Hg)	116.25 $\pm$ 5.54	123.75 $\pm$ 4.73	98.75 $\pm$ 10.87	69.50** $\pm$ 3.68	70.75** $\pm$ 1.70	78.00** $\pm$ 8.20	81.75** $\pm$ 4.80	87.75 $\pm$ 7.53
DP (mm Hg)	101.25 $\pm$ 7.73	108.75 $\pm$ 5.15	81.25 $\pm$ 12.64	54.50** $\pm$ 4.94	51.25** $\pm$ 4.53	59.50** $\pm$ 7.32	62.00** $\pm$ 5.22	67.50** $\pm$ 6.61
MAP (mm Hg)	106.24 $\pm$ 6.95	113.74 $\pm$ 4.73	87.07 $\pm$ 12.02	61.58** $\pm$ 4.99	57.74** $\pm$ 3.56	65.66** $\pm$ 7.59	68.58** $\pm$ 5.01	74.24* $\pm$ 6.74
PP (mm Hg)	15.00 $\pm$ 2.88	15.00 $\pm$ 3.53	17.50 $\pm$ 2.50	15.00 $\pm$ 2.04	17.00 $\pm$ 4.74	18.50 $\pm$ 1.50	19.75 $\pm$ 1.84	20.25 $\pm$ 3.42

SP = Systolic pressure ; DP = Diastolic pressure; MAP = Mean arterial pressure

PP = Pulse pressure

\*\* P < 0.01

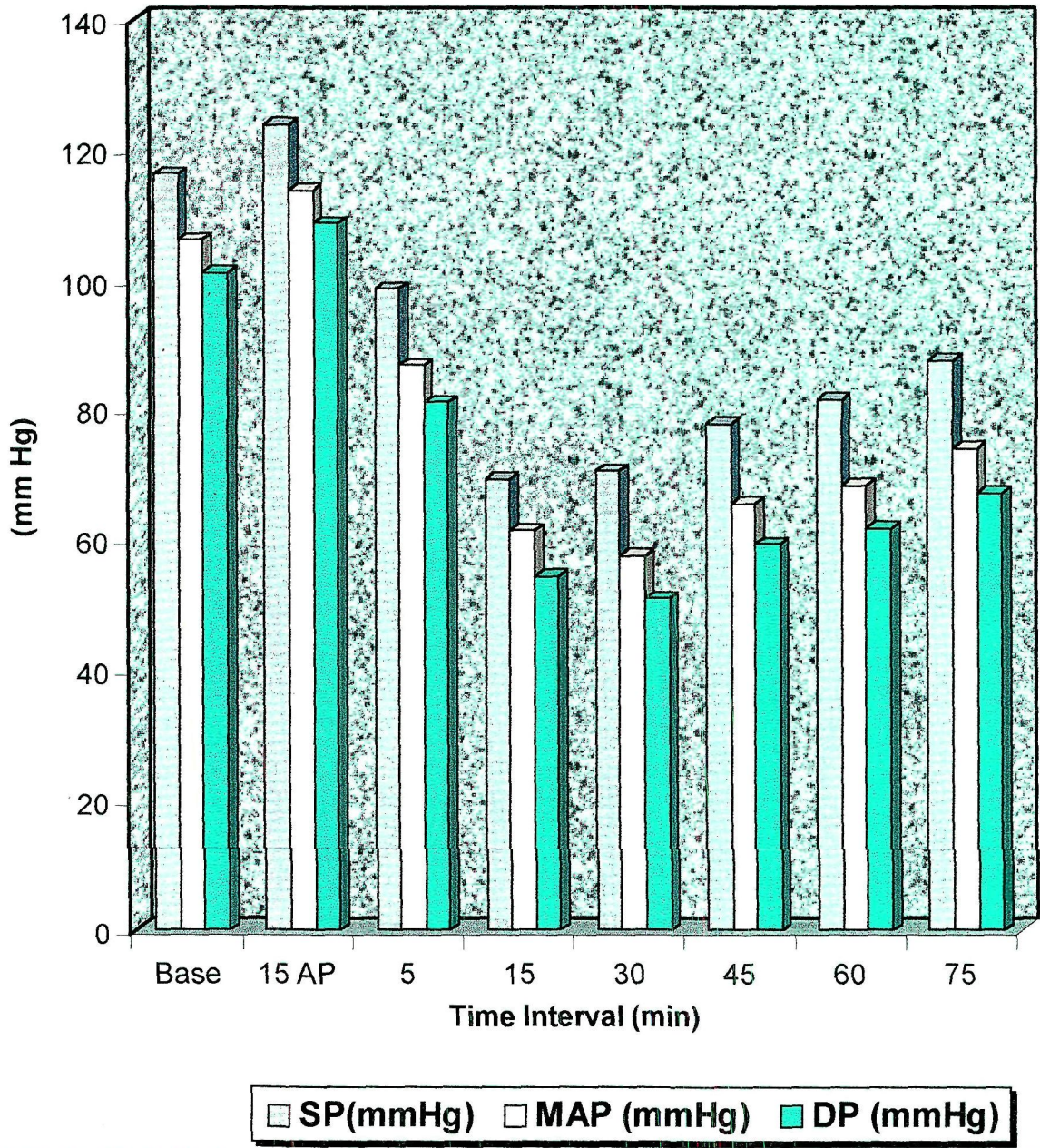
\* P < 0.05

↓ when medetomidine + ketamine administered intramuscularly.

and MAP values at 15, 30, 45 and 60 min intervals in comparison to the base (0hr) values (Table 3). The fall in blood pressure was also recorded at 75 min interval but it was statistically non-significant (Table 3). A slight but non-significant ( $P > 0.05$ ) increase in pulse pressure was also recorded at 30, 45, 60 and 75 min intervals following medetomidine + ketamine administration in neonate calves (Table 3).

The effect of medetomidine + ketamine combination on various ECG parameters in neonatal calves are presented in Table 4. There was an overall increase in different time interval parameters of ECG. However these changes were statistically nonsignificant. The P - wave and QRS - complex remained almost constant through out the period of study. The T - wave showed a decrease in amplitude from 5 min interval till 75 min interval following medetomidine + ketamine

**Fig 3: Effect of atropine - medetomidine + ketamine on blood pressure in neonate calves (n=6)**



AP: After atropine

administration but it was statistically nonsignificant.

**Table 4: Effect of atropine - medetomidine + ketamine on ECG parameters in neonate calves (n=6) Mean  $\pm$  SE**

Parameters (unit)	Base	15 min af.↓ atropine	Minutes after medetomidine + ketamine					
			5	15	30	45	60	75
P-interval (sec)	0.059 $\pm$ 0.009	0.058 $\pm$ 0.008	0.053 $\pm$ 0.008	0.041 $\pm$ 0.010	0.046 $\pm$ 0.008	0.047 $\pm$ 0.008	0.053 $\pm$ 0.005	0.051 $\pm$ 0.009
PR-interval (sec)	0.130 $\pm$ 0.012	0.117 $\pm$ 0.010	0.131 $\pm$ 0.024	0.128 $\pm$ 0.022	0.135 $\pm$ 0.024	0.122 $\pm$ 0.016	0.134 $\pm$ 0.015	0.123 $\pm$ 0.013
QRS int. (sec)	0.124 $\pm$ 0.006	0.108 $\pm$ 0.010	0.126 $\pm$ 0.011	0.120 $\pm$ 0.017	0.116 $\pm$ 0.020	0.126 $\pm$ 0.013	0.129 $\pm$ 0.026	0.126 $\pm$ 0.015
Q <sub>0</sub> T-interval (sec)	0.236 $\pm$ 0.029	0.186 $\pm$ 0.029	0.238 $\pm$ 0.028	0.238 $\pm$ 0.028	0.260 $\pm$ 0.032	0.256 $\pm$ 0.033	0.243 $\pm$ 0.033	0.256 $\pm$ 0.035
T-interval (sec)	0.190 $\pm$ 0.020	0.172 $\pm$ 0.026	0.202 $\pm$ 0.012	0.216 $\pm$ 0.036	0.214 $\pm$ 0.036	0.166 $\pm$ 0.019	0.252 $\pm$ 0.047	0.220 $\pm$ 0.050
QT-interval (sec)	0.426 $\pm$ 0.047	0.353 $\pm$ 0.028	0.441 $\pm$ 0.034	0.455 $\pm$ 0.060	0.474 $\pm$ 0.067	0.422 $\pm$ 0.047	0.495 $\pm$ 0.072	0.476 $\pm$ 0.077
ST-segment (sec)	0.112 $\pm$ 0.023	0.089 $\pm$ 0.033	0.112 $\pm$ 0.019	0.118 $\pm$ 0.018	0.147 $\pm$ 0.026	0.129 $\pm$ 0.020	0.113 $\pm$ 0.016	0.130 $\pm$ 0.024
P-wave (mv)	0.190 $\pm$ 0.020	0.172 $\pm$ 0.026	0.202 $\pm$ 0.012	0.216 $\pm$ 0.036	0.214 $\pm$ 0.036	0.166 $\pm$ 0.019	0.252 $\pm$ 0.047	0.220 $\pm$ 0.050
QRS Comp.(mv)	-1.166 $\pm$ 0.084	-1.066 $\pm$ 0.066	-1.150 $\pm$ 0.102	-1.083 $\pm$ 0.087	-1.150 $\pm$ 0.099	-1.100 $\pm$ 0.100	-1.200 $\pm$ 0.089	-1.183 $\pm$ 0.087
T-wave (mv)	0.096 $\pm$ 0.052	0.816 $\pm$ 0.012	0.050 $\pm$ 0.012	0.075 $\pm$ 0.024	0.058 $\pm$ 0.036	0.090 $\pm$ 0.036	0.088 $\pm$ 0.008	0.071 $\pm$ 0.017

↓ when medetomidine + ketamine administered intramuscularly.

In all the animals there was ST-segment elevation and biphasic T-wave before and after the administration of drugs/anaesthetics (Fig 5). In one animal atrial flutter was recorded at 75 min interval (Fig 5).

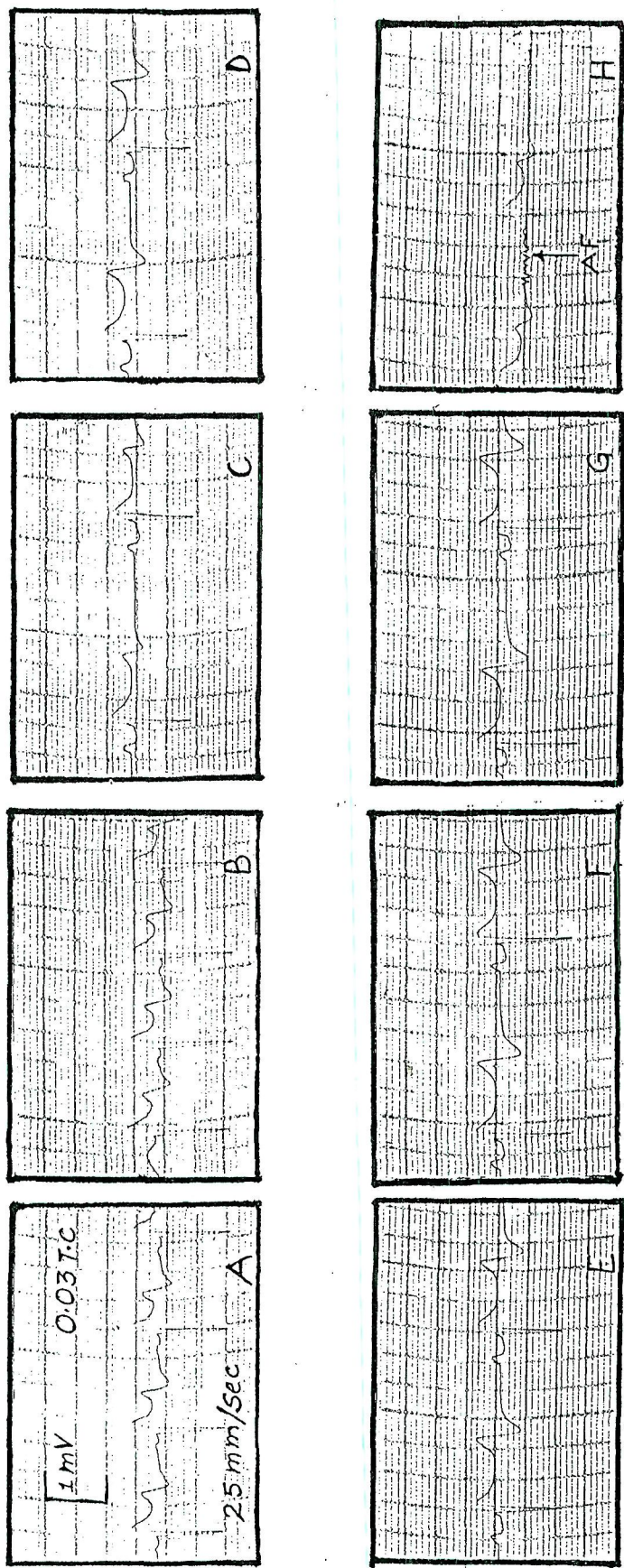


Fig 5: Electrocardiogram (ECG) of a neonatal calf showing biphasic T-wave and ST- segment elevation before and after the administration of atropine – medetomidine + ketamine anaesthesia.

A – Base (0hr); B – 15 min after atropinization; C, D, E, F, G, H – 5, 15, 30, 45, 60 and 75 min interval respectively.

AF – Atrial flutter at 75 min interval.

#### **4.2.2 Electroencephalographic studies**

Following medetomidine + ketamine administration in neonate calves electroencephalographic studies revealed the base (0hr) low voltage high frequency waves changing to low voltage low frequency / high voltage low frequency waves at different time intervals (Fig 6), with burst suppressions recorded between 5 to 60 min intervals (2 animals), 5 to 45 min (2 animals), 5 to 30 min (1 animal) and at 5 and 15 min intervals (1 animal).

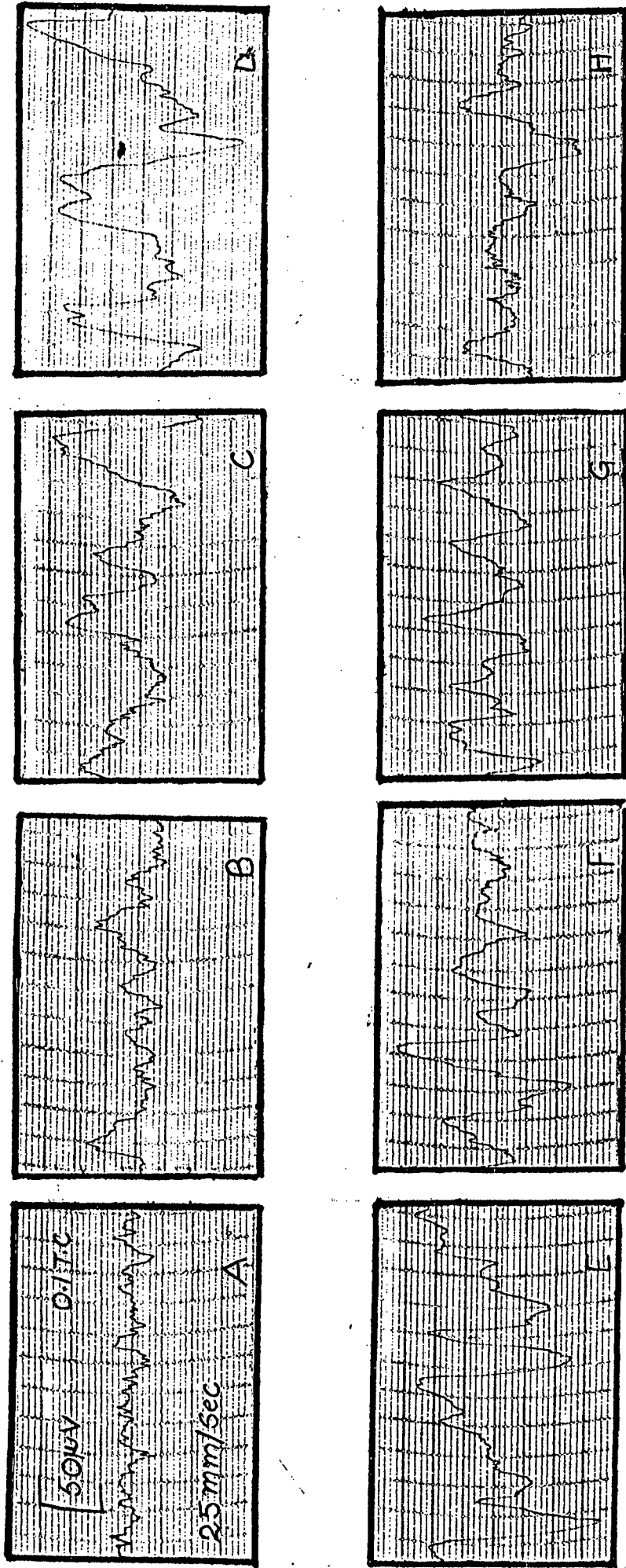


Fig 6: Electroencephalograph (EEG) of a neonatal calf following atropine – medetomidine + ketamine administration showing high voltage low frequency activity against the background of low voltage high frequency waves with intermittent burst suppression; C, D, E, F, G, H – 5, 15, 30, 45, 60 and 75 min interval respectively.



# DISCUSSION

## DISCUSSION

Neonates carry the risk of anaesthetic accidents more in comparison to adults owing to their immature physiological system. It thus becomes necessary to plan such a suitable anaesthetic regimen that it should not lead to any immediate or future risk to the life of the patient. It is only through scientific study that the choice of drug for induction of anaesthesia, can be made. Review of literature has revealed a scanty work on neonatal anaesthesia in animals especially in bovines. Medetomidine hydrochloride is becoming increasingly popular pre-anaesthetic in cattle and horses and the results indicate that its combination with ketamine hydrochloride produces good level of surgical anaesthesia, which also moderates the majority of side effects of medetomidine.

### 5.1 SEDATIVE, ANALGO-CLINICAL, HAEMATOLOGICAL AND BIOCHEMICAL STUDIES

Medetomidine, an imidazole derivative is highly selective and specific  $\alpha_2$  - adrenoceptor agonist. Decreased motor activity and analgesia are readily seen following medetomidine injection in small and lab animals (Savola *et al.*, 1986). Since medetomidine hydrochloride is highly potent and specific for  $\alpha_2$  receptors it has found increased use in cattle (Ranheim *et al.*, 2000), neonatal calves (Sharma *et al.*, 1996), goat kids (Mohammad *et al.*, 1991) and sheep (Ranheim *et al.*, 2000). The dose rate of medetomidine (15  $\mu\text{g}/\text{kg}$ , I/M) in combination with ketamine computed was less than what has been used with the similar combination in adult dairy calves (Lin-Hui Chu *et al.*, 1998a). In adult cattle medetomidine has been

injected intravenously at the dose rate of 40 µg/kg body weight (Ranheim *et al.*, 1999) and epidurally at the dose rate of 15 µg/kg body weight (Lin-HuiChu *et al.*, 1998b). Intramuscular route was used to produce anaesthesia in the present study. Ketamine is a good analgesic and also moderates the majority of side effects of  $\alpha_2$  agonists and hence finds extensive use with them for systemic use (Kinjavdekar *et al.*, 1999). Dose rate of ketamine hydrochloride (10 mg/kg I/M), used in the present study in combination with medetomidine as a single injection was less than reported in paediatric calves (Kandpal and Kumar, 1988) but higher than reported in cows (Fuentes and Tellez, 1974), heifers (Tadmor *et al.*, 1979) and neonatal calves (Sharma *et al.*, 1998a). However ketamine has been administered by I/V route in adult bovines.

In the present study the onset of effect was noticed within  $1.16 \pm 0.166$  min after the administration of the anaesthetic combination and the peak effect remained for 28-45 min. Surgical anaesthesia remained for  $24.75 \pm 2.39$  min in bovine paediatrics (Kandpal and kumar, 1998) and for, 28-75 min in neonate calves (Shakuntla, 2000) following the use of detomidine and ketamine combination. There was rapid and smooth induction with good muscle relaxation following detomidine - ketamine administration in paediatric/neonate calves (Kandpal and Kumar, 1998; Shakuntla, 2000). The present study also revealed complete loss of ocular and swallowing reflexes with complete muscle relaxation following medetomidine + ketamine administration. Good muscle relaxation has also been reported following administration of xylazine - ketamine or diazepam – xylazine - ketamine anaesthesia in calves (More *et al.*, 1998 and Sharma *et al.*, 1998a). There was complete analgesia up to 45 min, in the present study, which may be attributed to ketamine

complete analgesia up to 45 min, in the present study, which may be attributed to ketamine induced block of conduction of pain impulses to the thalamic and cortical areas (Booth, 1977).

Medetomidine + ketamine produced no significant change in rectal temperature in the present study. However there was evidence of hypothermia following onset of surgical anaesthesia. Decrease in rectal temperature has also been reported following detomidine – ketamine anaesthesia in neonatal calves (Shakuntla, 2000) and bovine paediatrics (Kandpal and Kumar, 1998). This decrease in rectal temperature was probably because of generalized sedation, decrease in basal metabolic rate and heat loss by vasodilation and muscle relaxation (Sarma, 1998). Also as there was significant to highly significant hypotension in the present study, this might also have contributed to a nonsignificant fall in the rectal temperature. Medetomidine induced CNS depression along with depressed hypothalamic noradrenergic  $\alpha_2$ -receptors might also have led to hypothermia in the present study.

There was initial tachycardia following atropine sulphate administration but thereafter bradycardia was noticed subsequent to medetomidine + ketamine administration. These changes were, however, non-significant. Detomidine - ketamine anaesthesia produced highly significant bradycardia in neonate calves (Shakuntla, 2000), whereas the same anaesthetic combination, when was used along with atropine sulphate, produced tachycardia in bovine paediatrics (Kandpal and Kumar, 1998). Bradycardia has also been reported in pediatric/neonate calves following xylazine ketamine anaesthesia (Kumar and Singh, 1979; Blaže *et al.*, 1988 and Sharma *et al.*, 1998a). The underlying mechanism responsible for bradycardia

could be the decreased sympathetic outflow from the CNS, direct depression of cardiac pacemaker and conduction tissue and increased vagal tone due to activation of baroreflex.

A significant increase in respiratory rate was observed following medetomidine + ketamine administration in the present study, which persisted up to 30 min interval as has also been reported in neonate calves following detomidine – ketamine anaesthesia (Shakuntla, 2000). Contrarily a decrease in respiratory rate was observed following detomidine - ketamine anaesthesia in bovine pediatrics (Kandpal and Kumar, 1998), following diazepam-ketamine or diazepam - glyceryl guaiacolate - ketamine anaesthesia in calves (Amarpal *et al.*, 1994) and following sedivet - ketamine anesthesia in buffalo calves (Sharma *et al.*, 1999). The increase in respiratory rate is probably because of decrease in tidal volume thus increasing respiration to maintain lung compliance as compensatory mechanism.

All the haematological parameters like Hb, PCV, TEC, and TLC remained within normal range following medetomidine + ketamine administration in neonatal calves where as transient and non-significant changes in haematological parameters have been reported following detomidine – ketamine (Kandpal and Kumar, 1998), xylazine - ketamine (Kumar and Singh, 1979 and Sharma *et al.*, 1998a), and detomidine - ketamine (Shakuntla, 2000) anaesthesia in pediatric and neonate calves.

Highly significant hyperglycemia was observed from 15 min interval uptill 75 min interval in the present study, after the administration of medetomidine + ketamine combination. Similar increase has also been reported following detomidine – ketamine anaesthesia in neonatal/paediatric calves (Kandpal and Kumar 1998;

an  $\alpha_2$  adrenergic inhibition of insulin release by stimulation of  $\alpha_2$  receptors in the pancreatic  $\beta$  - cells (Angel and Langer, 1988). Medetomidine when administered intravenously induced a marked hyperglycemia in cows (Ranheim *et al.*, 2000). Ketamine increases the nor – adrenaline blood levels and turnover. Since nor – adrenaline affects gluconeogenesis and glycogenolysis and also decrease insulin production, enhanced hyperglycemic effects after ketamine administration is obvious. There was a nonsignificant increase in BUN levels in the present study but all the values were within normal range. So no clinical significance could be attributed to this change. The increased hepatic urea production from amino acid degradation could account for the increase in urea nitrogen values (Eichner *et al.*, 1979). Renal blood flow may have decreased subsequent to hypotension, renal vasoconstriction or a combination of both thus decreasing the GFR. Decrease in GFR increases the absorption of urea due to slow movement of filtrate through renal tubules. Elevated BUN level noted in the present study could also be due to hyperglycemia which in turn increased the osmolarity of the blood. Increased osmolarity of the blood flowing through the kidneys and direct  $\alpha_2$  -receptor stimulation caused increase in urine production thus putting the kidney under stress which ultimately could have resulted in increased BUN level. The changes in plasma total proteins, AST, ALT, creatinine, sodium, potassium and chloride were statistically nonsignificant reflecting absence of any hepatic or renal toxicity in the present study. Clinically nonsignificant changes in body electrolytes can be attributed to body's homeostatic mechanism operating due to increased urine production. A significant decrease in ALT concentration was observed following detomidine - ketamine anaesthesia in neonate calves (Shakuntla, 2000).

production. A significant decrease in ALT concentration was observed following detomidine - ketamine anaesthesia in neonate calves (Shakuntla, 2000).

## 5.2 CARDIOVASCULAR AND ELECTROENCEPHALOGRAPHIC STUDIES

In the present study there was evidence of fall in blood pressure after the administration of the anaesthetic combination of medetomidine and ketamine hydrochloride which was quite marked up to 30 min interval and there after there was gradual rise in blood pressure as recorded at 45, 60 and 75 min intervals. This hypotensive effect could probably be due to medetomidine used in the present study as alpha-2 adrenoreceptor agonists inhibit nor – adrenaline from peripheral presynaptic nerve endings and have a direct action on the haemodynamic control areas in the ventrolateral medulla thus resulting in bradycardia and hypotension. When ketamine was used in combination with medetomidine in neonate calves in the present study it had a beneficial effect as the combination induced a moderate decrease in heart rate and blood pressure thus avoiding the undesirable and adverse effects of alpha<sub>2</sub> agonists when used alone. Alpha<sub>2</sub> agonists decrease the cardiac output as a result of bradycardia (noticed in the present study also) and increased peripheral resistance (Wagner *et al.*, 1991). Also, alpha-2 agonists cause a dose dependent cardiovascular depression, with bradycardia due to sinus bradycardia and first and second degree AV block and transient increase in arterial blood pressure followed by return to normal or moderate hypotension (Taylor, 2001). In contrast a non-significant increase in blood pressure was observed in neonate calves (Blaze *et al.*, 1988) and in foals (Robertson *et al.*, 1990) following the use of xylazine - ketamine anaesthesia. An initial increase (Aouad *et al.*, 1982) or decrease (Rings and Muir, 1982) in blood pressure have also been recorded following xylazine

ketamine anaesthesia in young calves. In buffalo calves cardiopulmonary depressant effect of xylazine are moderated by cardiostimulatory action of ketamine (Singh *et al.*, 1985), which was not noticed in the present study.

There was no significant change in different time interval parameters of the ECG, though there was an increase in Q<sub>o</sub>T interval, QT interval and ST segment, which could be attributed to bradycardia noticed in the present study. The P-wave showed a slight and gradual increase through out the period of study where as QRS-complex increased intermittently during the period of study. The increase in QRS complex amplitude reflects positive inotropic effect of ketamine on heart (Singh *et al.*, 1992). The T-wave showed a decrease in amplitude from 5 min interval till 75 min interval following medetomidine + ketamine administration but it was statistically non-significant.

Following medetomidine + ketamine administration in neonate calves, the EEG showed high voltage activity against the background of low voltage in comparison to low voltage high frequency activity seen before administration of the drugs, indicating surgical state of anaesthesia. Whenever such waves are seen or high voltage low frequency patterns are observed, the anaesthesia is appropriate for surgical intervention (Nigam and Peshin, 1993). During sedative studies, this state of surgical anaesthesia was characterized by the absence of physical response to deep pinpricks in different parts of body.



# SUMMARY

## Chapter- 6

### SUMMARY

The present study was conducted on 19 clinically healthy neonate male calves aged 10 -15 days and weighing 13 to 30 kg ( $20.47 \pm 1.14$ ). All the animals were kept under identical managemental conditions and were fed on milk during the course of experimental work. The animals were kept off feed and water for 3 - 6 hrs prior to the experimentation and each animal was weighed to calculate the dose of atropine, medetomidine and ketamine. Seven calves were used during the pilot trials to standardize the dose of medetomidine hydrochloride and ketamine hydrochloride for I/M use as a single injection. During pilot trials the dose rate of medetomidine hydrochloride used were 10  $\mu\text{g}/\text{kg}$  and 15  $\mu\text{g}/\text{kg}$  body weight, intramuscularly. The dose rates of ketamine hydrochloride used in combination with computed dose of medetomidine were 5 mg/kg, 7.5 mg/kg and 10 mg/kg body weight. On subjective analysis, based on the extent of sedation, muscle relaxation, analgesia produced and smooth recovery the dose rates of medetomidine and ketamine standardized were, 15  $\mu\text{g}/\text{kg}$  and 10  $\mu\text{g}/\text{kg}$  body weight, respectively. After computation of dose the remaining 12 animals were divided into two groups (Group 1 and Group 2) of 6 animals each. In Group 1, sedative, analgo – clinical, haematological and biochemical effects were evaluated and in Group 2, cardiovascular and electroencephalographic effects were evaluated, following atropine - medetomidine + ketamine anaesthesia. The statistical analysis of the data was done with Dunett's test at 1% and 5% level of significance.

Surgical anaesthesia was induced within  $4.5 \pm 0.50$  min following medetomidine + ketamine administration. The peak effect remained for 28 to 45 min. Winking of eyes, flapping of ears 15-18 min after medetomidine + ketamine administration and head shaking was observed in all the animals. There was complete loss of corneal reflexes upto 45 min interval in three animals whereas in other three animals mild to moderate depression was observed through out the period of study. Complete muscle relaxation was observed upto 45 min interval following medetomidine - ketamine administration. In five animals analgesia persisted uptill 45 min interval whereas in one animal it was moderate to complete to 60 min interval. There was complete depression of swallowing reflex upto 45 min in all the animals. Lacrimation and salivation were absent in all the animals. Following medetomidine + ketamine administration in neonate calves there was no significant change in rectal temperature and heart rate at different intervals of time. However, increase in respiratory rate was highly significant at 5, 15, and 30 min interval. All the haematological parameters remained within normal range in the present study.

Highly significant hyperglycemia was observed 15 min onwards till 75 min. A nonsignificant increase in BUN was noticed upto 75 min post administration of medetomidine + ketamine. Other biochemical attributes viz. ALT, AST, total proteins, creatinine, chloride, sodium and potassium were not affected in the present study.

There was initial rise of blood pressure after the administration of atropine and thereafter significant to highly significant hypotension was recorded following the injection of the anaesthetic combination of medetomidine + ketamine. There was an overall increase in different time interval parameters of ECG. The P-interval showed

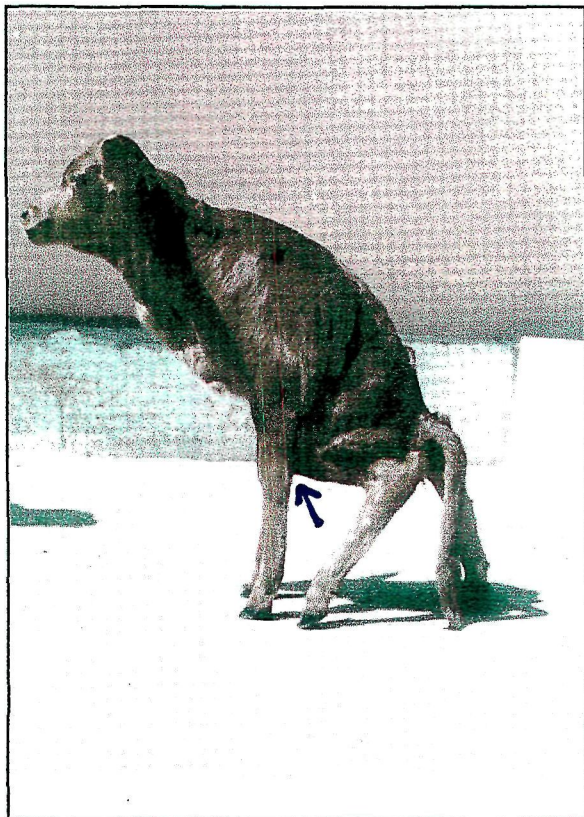
a gradual decrease through out the period of study, whereas P-wave showed a slight and gradual increase. The QRS-complex increased intermittently till 75 min time interval. The T-wave showed a decrease in amplitude but it was statistically non-significant. There was ST-segment elevation and biphasic T-wave observed in all the animals. One animal showed atrial flutter at 75 min interval. EEG studies revealed low voltage high frequency waves changing to low voltage low frequency waves with burst suppressions indicating surgical state of anaesthesia.

## CONCLUSIONS

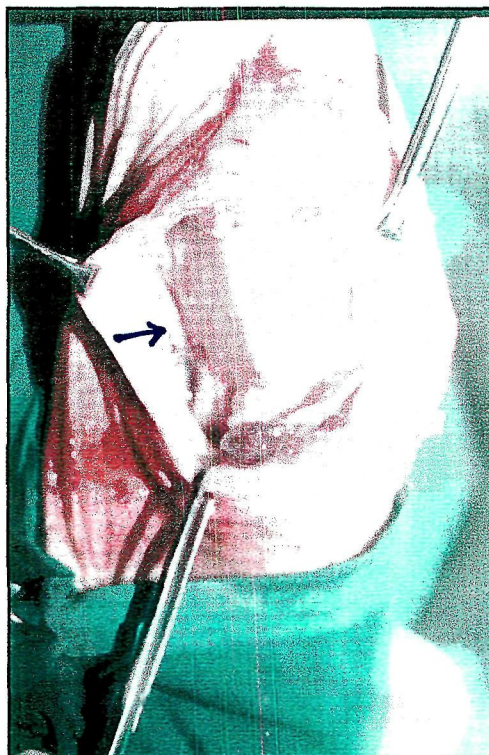
1. Medetomidine hydrochloride (15  $\mu$ g/kg) plus ketamine hydrochloride (10 mg/kg) intramuscularly as a single injection induced surgical anaesthesia within  $4.5 \pm 0.50$  min in <sup>atropinised</sup> neonate calves with peak effect of 28 to 45 min.
2. Medetomidine + ketamine anaesthesia produced a highly significant increase in respiratory rate and nonsignificant bradycardia in neonate calves with evidence of terminal hypothermia.
3. All the haematological parameters viz. Hb, PCV, TLC and TEC remained within normal range following medetomidine + ketamine anaesthesia in neonate calves.
4. There was highly significant hyperglycemia after the administration of medetomidine + ketamine anaesthesia in neonate calves.
5. There was no indication of renal or hepatic toxicity following medetomidine + ketamine anaesthesia in neonate calves.
6. Medetomidine + ketamine can safely be used in bovine neonates for achieving surgical anaesthesia in clinical practice (Annexure – I and II ).

## ANNEXURE I

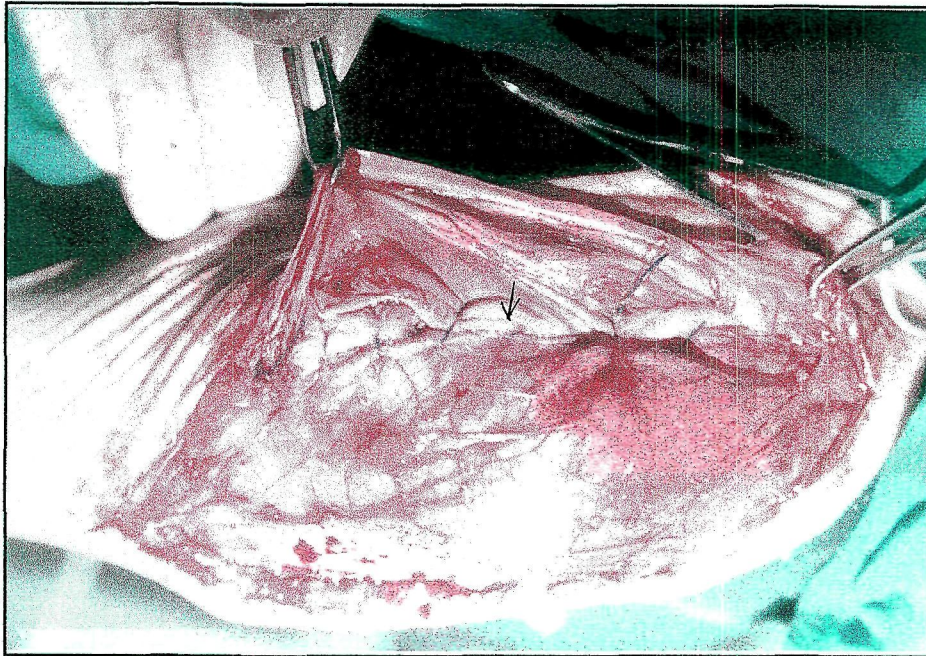
**Atropine - medetomidine + ketamine anaesthesia in a 14 day female calf suffering from Congenital Grade III Bilateral Medial Patellar Luxation.**



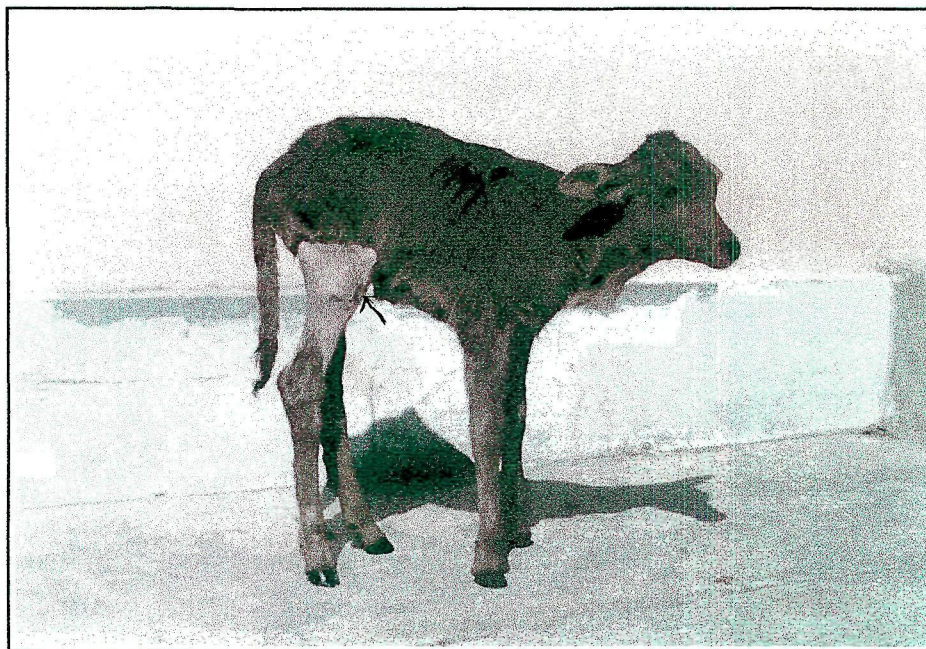
**Plate 1 : Crouched Posture due to Congenital Grade III Bilateral Medial Patellar Luxation in a 14 day female calf. (Before the administration of medetomidine + ketamine anaesthetic combination)**



**Plate 2 : Medially Luxated Patella. (Intraoperative)**



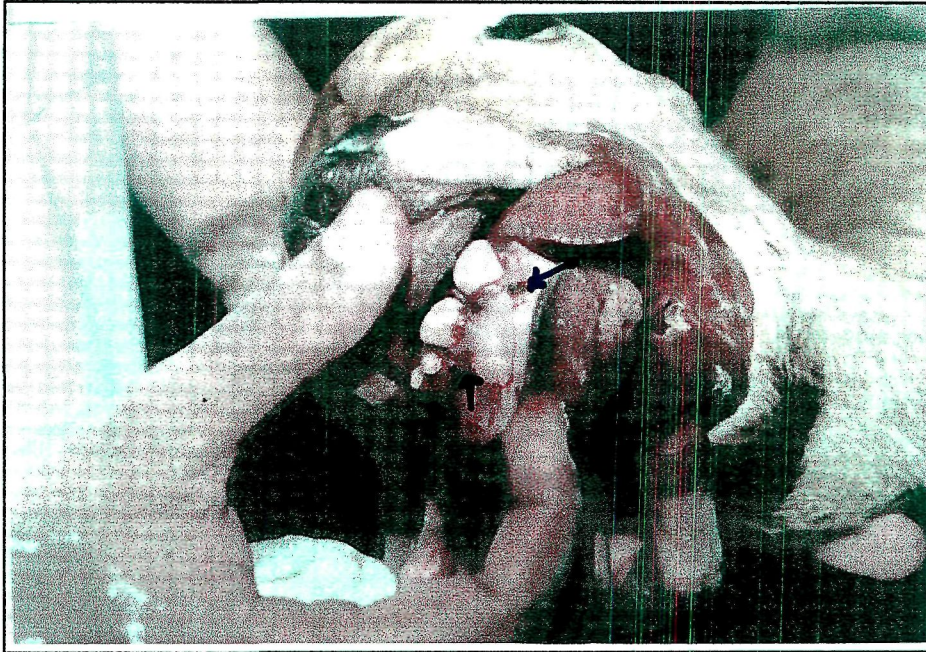
**Plate 3 : Lateral Imbrication of joint Capsule  
(Intraoperative)**



**Plate 4 : Normal posture of the animal after  
surgical correction, after recovery from anaesthesia.  
(medetomidine + ketamine combination)**

## ANNEXURE II

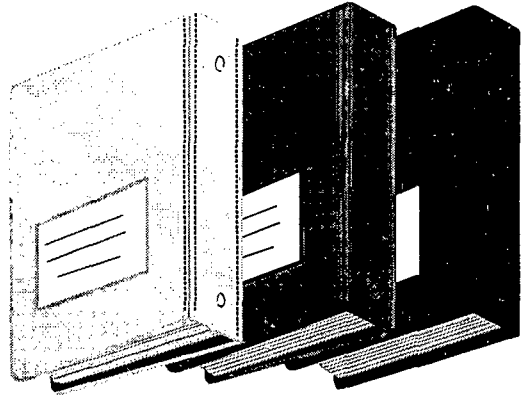
**Atropine - medetomidine + ketamine anaesthesia in a 12 day female calf suffering from Mandibular fracture.**



**Plate 5 : Mandibular fracture stabilization using two steinmein pins in a 12 day female calf using the anaesthetic combination of medetomidine + ketamine.**



**Plate 6 : Fracture Healing after 45 days.**



# LITERATURE CITED

## LITERATURE CITED

- Aithal, H.P., Amarpal, Pratap, K. and Singh, G.R. 1996. Clinical effects of epidurally administered ketamine and xylazine in goats. *Small Ruminant Research* **24**: 55-64
- Aithal, H.P., Amarpal, Singh, G.R., Mogha, I.V., Gupta, O.P., Naveen, K., Hoque, M. and Kumar, N. 1997. Epidural ketamine and xylazine for hind quarter surgery in ruminants: a study on 35 clinical cases. *Indian Veterinary Journal* **74**: 7, 625-626.
- Amarpal, Kumar, A. and Singh, H. 1994. Clinico-physiological effects of ketamine with or without glyceryl guaiacolate – thiopentone mixture in hepatotoxic calves. *Indian Journal of Veterinary Surgery* **15(2)** : 70-73.
- Amarpal, Aithal, H.P., Singh, G.R. and Pratap, K. 1997. Intranasal diazepam and ketamine for reduction and analgesia in pups. *Indian Veterinary Journal* **74(12)**: 1056-1057.
- Angel, I. and Langer, S.Z. 1988. Adrenergic induced hyperglycemia in anaesthetized rats: involvement of peripheral  $\alpha_2$  – adrenoceptor. *Eur. J.Pharmacol.* **154**: 191-196.
- Aouad, J.I., Wright, E.M. Jr., Shaner, T.W. 1981. Anaesthetic evaluation of ketamine and xylazine in calves. *Bovine Practice* **2(2)** : 22-31.
- Arnemo, J.M. and Soli, N.E. 1993. Chemical capture of free ranging cattle: immobilization with xylazine or medetomidine, and reversal with atipamezole. *Veterinary Research Communications* **17**: 6, 469-477.
- Baggot, J.D. and Short, C.R. 1984. Drug disposition in neonatal animals with particular reference to the foal. *Equine Veterinary Journal* **16**: 364-367.
- Balagopalan, T.P., Nayar, K.N.M., Nayar, S.R. and Varkey, C.A. 1992. Certain physiological and biochemical effects of glyceryl guaiacolate-ether along with triflupromazine hydrochloride in kids. *Indian Journal of Veterinary Surgery* **13(2)**: 56-60.
- Blaze, C.A., Holland, R.E. and Grant, A.L., 1988. Gas exchange during xylazine ketamine anaesthesia in neonatal calves. *Veterinary Surgery* **17(3)** : 155-159.
- Booth, N.H. 1977. Intravenous and other parenteral anaesthetics. In: *Veterinary pharmacology and therapeutics* by Jones, Booth and MacDonald (Eds) 4<sup>th</sup> Edition. The Iowa State University Press, Iowa. 241-306 pp.

- Buckley, U.M., Gootman, P.M., Gootman, N., Reddy, G.D., Weaver, L.C. and Crene, L.A. 1976. Age dependent cardiovascular effects of afferent stimulation in neonatal pigs. *Biology of the neonate* **56**: 268-279.
- Carter, S.W., Robertson, S.A., Steel, C.J. and Jourdenias, D.A. 1990. Cardiopulmonary effects of xylazine sedation in the foal. *Equine Veterinary Journal* **22(6)** : 384-388.
- Cohen, M.L. and Trevor, A.J. 1974. Study on the cerebral accumulation of ketamine and relationship between the metabolism of the drug and its pharmacological effects. *Journal of Pharmacology and Experimental Therapeutics* **189**: 351-358.
- Coopland, M.D. 1977. The effects of CT-1341, thiopentone and induction delivery time on the blood gas and acid base status of lambs delivered by caesarean section and on onset of respiration. *Australian Veterinary Journal* **53(9)** : 436-439.
- Crane, L., Gootman, N. and Gootman, P.M. 1975. Age dependent cardiovascular effects of halothane anaesthesia in neonatal pigs. *Archives International-de-pharmacodynamic-et-de-therapie* **214(2)** : 180-187.
- Done, A.D. 1964. Developmental pharmacology. *Clinical pharmacology and Therapeutics* (5): 432-479.
- Eichner, R.D., Proir, R.L., and Kvasenieka, W.G. 1979. Xylazine induced hyperglycemia in beef cattle. *American Journal of Veterinary Research* **40**: 127-129.
- Eisenach, J.C. and Tong, C. 1991. Site of haemodynamic effects of intrathecal alpha2-adrenergic agonists. *Anaesthesiol* **74**: 766
- Eisenhaur, C.I., Matsuda, L.S. and Vyebara, C.E. 1994. Normal physiologic values of neonatal pigs and the effect of isoflurane and pentobarbital anaesthesia. *Laboratory Animal Sciences* **44(3)** : 245-252.
- Elizabeth, A. and Martinez. 1995. Anaesthetizing neonatal foals. *Veterinary Medicine* **90(9)** : 879-884.
- Fuentes, V.O., Montefort, R.R., Tellez, E. and Zamora, F.M. 1973. Ketamine dissociative anaesthesia in cattle. *Veterinaria Mexico* **4(4)** : 247-250.
- Fuentes, V.O. and Tellez, E. 1974. Ketamine dissociative anaesthesia in the cow. *Veterinary Record* **94**: 482.

- Geiser, D.R. and Rohrback, B.W. 1992. Use of endtidal CO<sub>2</sub> tension to predict arterial CO<sub>2</sub> values in isoflurane anaesthetized equine neonates. *American Journal of Veterinary Research* **53(9)** : 1617-1621.
- Gorgul, S., Pekbilir, A., Comoglu, A. and Atasoy, N. 1991. Clinical application of the use of the combination of thiazine hydrochloride (Xylazine – Rompun) and ketamine hydrochloride (Ketalar) in calves. *Journal of Veterinary Anaesthesiology Special Supplement*. 181-182 pp.
- Grad, R., Witen, M.L., Cruen, S.F., McKelvey, D.H. and Lemon, R.J. 1988. Intravenous chloralose as a safe anaesthetic for longitudinal use in Beagle puppies. *Laboratory Animal Sciences* **38(4)** : 422-425.
- Kaneko, J.J. and Cornelius, C.E. 1970. *Clinical Biochemistry of Domestic Animals*, edn 2. Academic Press Network, p 22.
- Kandpal, M. and Kumar, A. 1998. Ketamine with or without diazepam or detomidine pre-medication in bovine paediatric patients. *Indian Journal of Veterinary Science* **68(9)** : 901-906.
- Kinjavdekar, P. 1998. Spinal analgesia with  $\alpha_2$  – agonists and their combination with ketamine and lignocaine in goats. Ph.D. thesis submitted to IVRI Deemed University, Izatnagar (U.P) India.
- Kinjavdekar, P., Singh, G.R., Amarpal and Aithal, H.P. 1999. Clinical use of spinal xylazine and ketamine in ruminants. *Indian Veterinary Journal* **76**: 1101-1103.
- Koike, J., Too, K. Abe, I., Maturba, K. and Sakai, T. 1974a. III. Clinical observation on the cow injected I/V with 1 mg/kg body weight of Ketalar. *Veterinary Medicine* **613**: 83-87.
- Koike, T., Too, K., Hoda, H., Kurosava, T., Kumabara, M. and Tazaki, T. 1974b. IV. Clinical observation on Japanese cattle injected I/V with 2-mg/kg body weight of Ketalar. *Journal of Veterinary Medicine* **613**: 413-416.
- Kumar, A. and Singh, H. 1977. Ketamine with xylazine pre-medication in bovine paediatric surgery. *Ist Symposium, Indian Society for Veterinary Surgery, Hisar*.
- Kumar, A. and Singh, H. 1979. Ketamine and xylazine anaesthesia in bovine paediatric surgery. *Indian Veterinary Journal* : 219-222.
- Lerman, J., Robinson, S., Willis, M.M. and Gregory, G.A. 1983. Anaesthetic requirement for halothane in young children, 0-1 M and 1-6 M of age. *Anaesthesiology* **59**: 421-424.

- Lester, G.D., DeMarco, V.G., Norman, W.M. 1999. Effect of inhaled nitric oxide on experimentally induced pulmonary hypertension in neonatal foals. *American Journal of Veterinary Research* **60**: 10, 1207-1212.
- Lin-HuiChu, Riddell, M.G., DeGraves, F.J. 1998a. Comparison of three alpha2-antagonists, yohimbine, tolazoline, or atipamezole for reversing the anaesthetic effects of medetomidine and ketamine. *Bovine Practitioner* **32**: 2, 21-28.
- Lin-HuiChu, Trachte, E.A., DeGraves, F.J., Rodgeron, D.H., Steiss, J.E. and Carson, R.L. 1998b. Evaluation of analgesia induced by epidural administration of medetomidine to cows. *American Journal of Veterinary Research* **59**: 2, 162-167.
- Lumb, W.V. and Jones, E.W. 1984. *Veterinary Anaesthesia*. 2<sup>nd</sup> ed. Lea and Febiger, Philadelphia, 307-329.
- Manning, M.M. and Broadstone, R.V. 1995. Effects of alpha2-adrenergic receptor agonists and antagonist drugs on cholinergic contraction in bovine tracheal smooth muscle in vitro. *American Journal of Veterinary Research* **56**: 7, 930-935.
- Marsico, F., Nascimento, P.R.L., Paula, A.C.de., Nascimento, A.J., Tendillo, F.J., Criado, A. and Segura, I.A.G.de. 1999. Epidural injection of ketamine for caudal analgesia in the cow. *Journal of Veterinary Anaesthesia* **26**: 27-31.
- Mates, N., Oana, L., Cosmo, C. and Grabovschi 1991. Use of "Ursotamin" to potentiate anaesthesia in farm animals. *Seriza Zootehnie si Medicina Veterinara* **456**: 119-124.
- Matthews, N.S., Chaffin, M.K., Erickson, S.W. and Overhulse, W.A. 1995. Propofol anaesthesia for non-surgical procedures of neonatal foals. *Equine Practice* **17(3)** : 15-20.
- Mbiuki, S.M. 1982. Xylazine and ketamine anaesthesia in cattle. *Vety. – Medicine – and small animal clinician* **77(2)** : 251-253.
- Mohammad, F.K., Zangana, I.K., Al-Kassim, N.A. 1991. Clinical observations in Shami goat kids sedated with medetomidine. 1991. *Small Ruminant Research* **5**: 1-2, 149-153.
- More, D.B., Bhokre, A.P., Sarkate, C.B. and Panchbhai, U.S. 1998. Diazepam-xylazine-ketamine anaesthesia in bovines; a clinical study. *Intas Polyvet* **1(1)** : 58-60.

- Mottelib, A.A. 1980. Clinical and serum biochemical studies on the effect of ketamine in buffalo calves. *Zentralblatt fur Veterinarmedizin* **27 A(7)** : 596-599.
- Nigam, J.M., and Peshin, P.K. 1993. General Anaesthesia. : Ruminant Surgery by R.P.S. Tyagi and Jit Singh. 1<sup>st</sup> edition, CBS Publishers, Delhi. 120-136 pp.
- Norman, W.M., Court, M.H. and Greenblatt, D.J. 1997. Age selected changes in pharmacokinetic disposition of diazepam in foals. *American Journal of Veterinary Research* **58(8)** : 878-880.
- Oijala, M. and Katila, J. 1988. Detomidine in foals: sedative and analgesic effects. *Equine Veterinary Journal* **20(5)** : 327-330.
- Oser, B.L. 1965. *Hawk's Physiological Chemistry*, 14<sup>th</sup> ed. McGraw Hill Book Co., New York.
- Ossipov, M.H., Harris, S., Lloyd, P., Messineo, E., Lin, B.S. and Bagley, J. 1990. Antinociceptive interaction between opioids and medetomidine: systemic additivity and spinal synergy. *Anesthesiol* **73**: 1227-1235.
- Pathak, S.C., Nigam, J.M., Peshin, P.K. and Singh, A.P. 1982a. Anaesthetic and haemodynamic effects of ketamine hydrochloride in buffalo calves. (*Bubalus bubalis*). *American Journal of Veterinary Research* **43**: 875.
- Pathak, S.C., Nigam, J.M., Peshin, P.K. and Singh, A.P. 1982b. Ketamine anaesthesia in buffalo calves: Haematological and biochemical studies. *Indian Journal of Animal Sciences* **52**: 319-324.
- Pawde, A.M., Amarpal, Kinjavdekar, P., Aithal, H.P., Pratap, K. and Bisht, G.S. 2000. Detomidine – diazepam – ketamine anaesthesia in buffalo (*Bubalus bubalis*) calves. *Journal of Veterinary Medicine* **47**: 3, 175-179.
- Peshin, P.K., Singh, A.P., Patil, D.B. and Sharifi, D.C. 1991. Sedative effects of detomidine in infant calves. *Acta Veterinaria Hungarica* **39(3-4)**: 103-107.
- Pertovaara, A.1993. Antinociception induced by alpha<sub>2</sub> – adrenoceptor agonists, with special emphasis on medetomidine studies. *Prog. Neurobiol.* **40**: 691-709.
- Pratap, K., Amarpal, Kinjavdekar, P. 2000. Clinico-physiological studies on xylazine and medetomidine for lumbosacral epidural anaesthesia in buffalo calves. *Indian Journal of Animal Sciences* **70**: **9**, 929-930.

- Raekallio, M., Kivalo, M., Jalanka, H. and Vainio, O. 1991. Medetomidine ketamine sedation in calves and its reversal with atipamezole. *Journal of Veterinary Anaesthesia* **18**: 45-47.
- Ramakrishana, O., Murthy, D.K. and Nigam, J.M. 1981. Ketamine anaesthesia in buffalo calves. *Indian Veterinary Journal* **58(6)**: 503-505.
- Ranheim, B., Arnemo, J.M., Ryeng, K.A., Soli, N.E. and Horsberg, T.E. 1998. Pharmacokinetics of medetomidine and atipamezole in dairy calves : an agonist-antagonist interaction. *Journal of Veterinary Pharmacology and Therapeutics* **21**: 6, 428-432.
- Ranheim, B., Arnemo, J.M., Ryeng, K.A., Soli, N.E. and Horsberg, T.E. 1999. A pharmacokinetic study including some relevant clinical effects of medetomidine and atipamezole in lactating dairy cows. *Journal of Veterinary Pharmacology and Therapeutics* **22**: 6, 368-373.
- Ranheim, B., Horsberg, T.E., Soli, N.E., Ryeng, K.A. and Arnemo, J.M. 2000. The effects of medetomidine and its reversal with atipamezole on plasma glucose, cortisol and noradrenaline in cattle and sheep. *Journal of Veterinary Pharmacology and Therapeutics* **23**: 6, 379-387.
- Rings, D.M. and Muir, W.W. 1982. Cardiopulmonary effects of intramuscular xylazine-ketamine in calves. *Canadian Journal of Comparative Medicine* **46(40)** : 386-389.
- Robertson, S.A., Carter, S.W., Donovan, M. and Steele, L. 1990. Effect of I/V xylazine hydrochloride on blood glucose, plasma insulin and rectal temperature in neonatal foals. *Equine Veterinary Journal* **22(1)** : 43-47.
- Sarma, K.K., Pathak, S.C. and Saika, J. 1993. A note of general anaesthesia with halothane in bovine paediatrics: certain clinical and respiratory effects. *Indian Journal of Veterinary Surgery* **14(1)** : 23-24.
- Sarma, B. and Kumar, A. 1998. Clinical and cardiopulmonary effects of atropine-diazepam-ketamine with or without guaifenesin in calves suffering from acute renal failure. *Indian Journal of Animal Sciences* **68(9)** : 901-903.
- Sarma, B. and Kumar, A. 1999. Haematological and biochemical effects of atropine-diazepam-ketamine with or without guaifenesin in calves suffering from acute renal failure. *Indian Veterinary Journal* **76**: 421-423.

- Savola, J.M., Ruskoaho, H., Puurunen, J., Salonen, J.S. and Karki, N.T. 1986. Evidence for medetomidine as a selective and potent agonist at  $\alpha_2$  – adrenoceptors. *J. Auton. Pharmacol.* **5**: 275-284.
- Schmidt and Oechtering, G.U. 1989. Anaesthesia of horses with xylazine and ketamine. I. Anaesthesia of foals. *Tierarztliche-Praxis* **17(3)** : 388-393.
- Shakuntla. 2000. Evaluation of detomidine as sedative to ketamine anaesthesia in neonatal calves. M.V.Sc thesis submitted to C.S.K.K.V., Palampur (H.P).
- Shakuntla, Sharma, S.K. and Kumar, A. 2001. Clinico-sedative, cardiovascular and electroencephalographic studies following detomidine-ketamine anaesthesia in neonatal calves. *Proceeding 25<sup>th</sup> Annual Congress, Indian Society for Veterinary Surgery.* w.e.f Dec. 5-7, CCSHAU, Hisar.
- Sharma, S.K. 1995. Studies on neonatal anaesthesia in bovines. Ph.D. thesis submitted to C.S. Azad University of Agri. and Tech., Kanpur.
- Sharma, S.K., Nigam, J.M., Kumar, A., Varshney, A.C. and Singh, M. 1996. Reversal of sedative and clinico-physiological effects of medetomidine by atipamezole in calves. *Indian journal of Veterinary Surgery* **17(1)**: 24-27.
- Sharma, S.K., Mishra, S.S. and Nigam, J.M. 1998a. Clinicobiochemical and electrocardiographic studies following xylazine ketamine anaesthesia in neonatal calves. *Proc. 2<sup>nd</sup> Pan Commonwealth Veterinary Conference, Bangalore.* Vol. II: 1125-1129.
- Sharma, S.K., Mishra, S.S. and Varshney, A.C. 1998b. Evaluation of chloral hydrate anaesthesia in neonatal calves. *Indian Veterinary Medical Journal* **22**: 69-72
- Sharma, K., Kumar, N., Hoque, M., Gupta, O.P. and Maiti, S.K.. 1999. Clinical, physiological and haematobiochemical effects of sedivet ketamine anaesthesia in atropine and trifluproinazine premedicated buffalo calves. *23<sup>rd</sup> Symposium, Indian Society for Veterinary Surgery, Chennai.*
- Singh, A.P., Singh, J., Peshin, P.K., Gahlawat, J.S., Singh, P. and Nigam, J.M. 1985. Evaluation of xylazine-ketamine anaesthesia in buffaloes (*Bubalus bubalis*) *Veterinary Medicine* **32**: 54-58.
- Singh, K.I., Sharma, S.N. and Sobti, V.K. 1990. Clinical evaluation of diazepam-glyceryl guaiacolate-ketamine anaesthesia for bone surgery in calves. *Indian Journal of Veterinary Surgery* **11(1)** : 1-5.
- Singh, K.I., Sharma, S.N., Mirakhur, K.K. and Singh, S. 1991. Clinical and biochemical effects of diazepam-ketamine combination anaesthesia in calves. *Indian Veterinary Journal* **68**: 258-256.

- Singh, K.I., Sharma, S.N., Mirakhur, K.K. and Sobti, V.K. 1992. Cardiovascular and respiratory effect of diazepam glyceryl-guaiacolate induced ketamine anaesthesia in calves. *Indian Veterinary Journal* **68**: 256-258.
- Skarda, R.T. and Muir, W.W. 1996. Comparison of antinociceptive, cardiovascular and respiratory effects, head ptosis and position of pelvic limbs in mares after caudal epidural administration of xylazine and detomidine hydrochloride solution. *American journal of veterinary research* **57**: 1338-1345.
- Soveri, T., Sankari, S., Salonen, J.S. and Nieminen, M. 2000. Effects of immobilization with medetomidine and reversal with atipamazole on blood chemistry of semi-domesticated reindeer (*Rangifer tarandus tarandus* L.) in autumn and late winter. *Acta Veterinaria Scandinavica* **41**: 4, 335-349.
- Stephens, D.B. and Sharman, D.F. 1988. Observations on the effect of xylazine in naturally and artificially reared calves. *Journal of Association of Veterinary Anesthetists* **15**: 91-95.
- Tadmor, A., Mareus, S. and Eting, E. 1979. The use of ketamine hydrochloride for endotracheal intubation in cattle. *Australian Veterinary Journal* **55**: 537-538.
- Taylor, P.M. 2001. Proceedings Association of Veterinary Anaesthetists. Uppsala, Sweden. p 17-21.
- Tiwari, S.K., Kumar, A., Jadon, N.S. and Parikh, P.V. 1999. Epidural xylazine and detomidine with or without local anaesthesia in buffaloes: Haematological and biochemical changes. *Indian Journal of Animal Sciences* **69(2)** : 85-87.
- Vesal, N., and Cribb, P.H. Cardiopulmonary effects in dogs of oxymorphone administered epidurally and intramuscularly and medetomidine administered epidurally : A comparative clinical study. *Veterinary Surgery* **25**: 361-369.
- Viratanen, R. 1989. Pharmacological profiles of medetomidine and its antagonist, atipamezole. *Acta Vet. Scand. Suppl.* 85:29-37.
- Wagner, A.E., Muir, W.W. and Hinchcliff, K.W. 1991. Cardiovascular effects of xylazine and detomidine in horses. *American Journal of veterinary Research* **52**: 651-657.
- Waterman, A.E. 1981. Preliminary observation in use of combination of xylazine and ketamine hydrochloride in calves. *Veterinary Record* **109(21)** : 464-467.
- Waterman, A.E. 1983. Effect of combination of ketamine and xylazine on respiratory gas tensions and acid-base status in calves. *Veterinary Record* **109(21)** : 464-467.

- Wear, R., Robinson, S. and Gregory, G.A. 1982. The effect of halothane on the baroreponse of adult and baby rabbits. *Anaesthesiology* **56**: 188-191.
- William, B.J., Ragevender, K.B.P., Rao, G.D. and George, R.S. 1992. Ketamine-thiopentone anaesthesia in calves. *Cherion* **21(5-6)** : 142-146.
- William, B.J. 1995. Studies on efficacy of glyceryl guaiacolate as adjunct to ketamine, xylazine and ketamine-xylazine continuous intravenous anaesthesia in calves. *Indian Journal of Veterinary Surgery* **16(1)** : 70.
- Wood, G.M., Molony, V., Fleetwood-Walker, S.M., Hodgson, J.C. and Mellor, D.J. 1991. Effect of local anaesthesia and I/V naloxone on the changes in behaviour and plasma concentration of control produced by castration and tail docking with light rubber rings in young lambs. *Research in Veterinary Sciences* **51(2)** : 193-199.
- Yamashita, K., Sasa, Y., Ikeda, H., Izumisawa, Y. and Kotani, T. 1996. Total (general) intravenous anaesthesia in cows using a combination of guaifenesin, ketamine and xylazine. *Journal of the Japan Veterinary Medical Association* **49**: 10, 709-713.