CLINICAL EVALUATION OF XYLAZINE OR DETOMIDINE IN COMBINATION WITH BUTORPHANOL, GUAIFENESIN AND KETAMINE FOR TOTAL INTRAVENOUS ANAESTHESIA IN EQUINES

THESIS

BY

BHANU PRATAP SINGH THAKUR
(V-08-30-33)

Submitted to

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

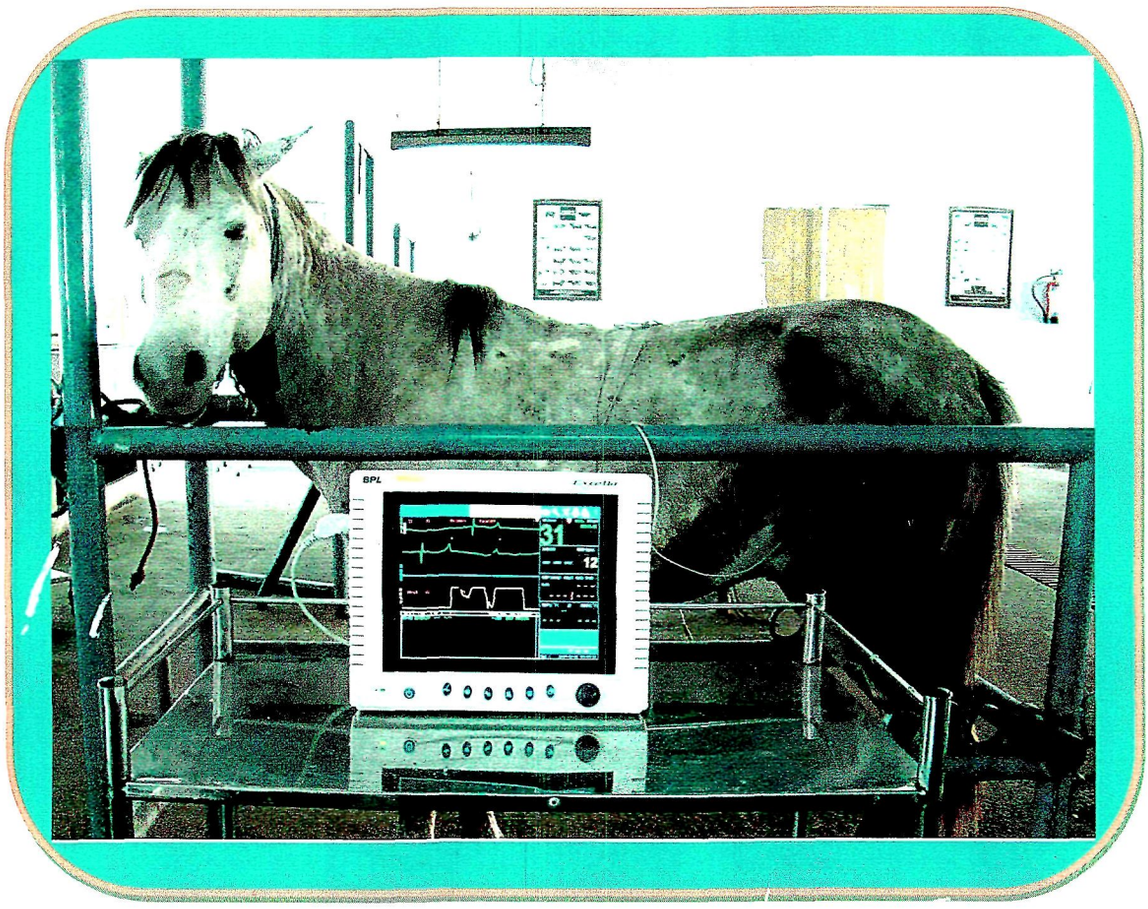
IN

partial fulfillment of the requirements for the degree

OF

MASTER OF VETERINARY SCIENCE
(VETERINARY SURGERY AND RADIOLOGY)

2010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Dedicated to

My

respected

Major Advisor

Dr. S. K. Sharma

Professor (Dr) SK Sharma

Department of Surgery & Radiology
DGCN College of Veterinary and Animal Sciences
CSK Himachal Pradesh Krishi Vishvavidyalaya
Palampur-176 062 (H.P.) India

CERTIFICATE - I

This is to certify that the thesis entitled "**Clinical evaluation of xylazine or detomidine in combination with butorphanol, guaifenesin and ketamine for total intravenous anaesthesia in equines**" submitted in partial fulfillment of the requirements for the award of the degree of **Master of Veterinary Science** in the discipline of **Veterinary Surgery and Radiology** of CSK Himachal Pradesh Krishi Vishvavidyalaya, Palampur is a bonafide research work carried out by **Bhanu Pratap Singh Thakur (V-08-30-33)** son of Shri Manohar Lal Thakur 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 duly acknowledged.

(S. K. Sharma)
Major Advisor

Place: Palampur
Date: 28th June, 2010

CERTIFICATE – II

This is to certify that the thesis entitled "**Clinical evaluation of xylazine or detomidine in combination with butorphanol, guaifenesin and ketamine for total intravenous anaesthesia in equines**" submitted by **Bhanu Pratap Singh Thakur (V-08-30-33)** son of Shri Manohar Lal Thakur to the CSK Himachal Pradesh Krishi Vishvavidyalaya, Palampur in partial fulfillment of the requirements for the degree of **Master of Veterinary Science** in the discipline of **Veterinary Surgery and Radiology** has been approved by the Advisory Committee after an oral examination of the student in collaboration with an External Examiner.

20/8/10
(Dr. S. K. Sharma)
Chairperson
Advisory Committee

20.8.10
(Dr. Rishi Tayal)
External Examiner

20/8/10
(Dr. S. P. Tyagi)
Member

20/08/2010
(Dr. Arvind Sharma)
Member

20/8/10
(Dr. R Kumar)
Member

20/8/10
(Dr. MS Kanwar)
Dean's Nominee

20/8/10
Head of the Department

21/8
Dean, Postgraduate Studies

ACKNOWLEDGEMENTS

With abyssal prerogative, I would like to offer my deep sense of gratitude and indebtedness to my revered major advisor Dr. S.K. Sharma for his impeccable guidance, careful supervision, devotion, immaculate suggestions, scholarly guidance and swift execution during the study and completion of this work. I owe to him more than I could care to admit.

I avail myself to this rare opportunity to express my special thanks to Dr. Adarsh Kumar who never left me unattended and continued to motivate me telephonically as I unfortunately lost his valuable guidance in the middle of my research work due to his visit to Libia. His continuous encouragement, valuable advice, unceasing support and generosity are the foundation stone of this manuscript.

I feel highly honored and equally proud of being guided by an expert surgeon Dr. Arvind Sharma. His painstaking efforts, ever available help, technical acumen, erudition and guidance will always be remembered.

I owe my heartiest thanks to other esteemed and competent members of the advisory committee Dr. M.S. Kanwar, Dr. S.P. Tyagi and Dr. R.Kumar for their kind help, constructive suggestions and insuring efforts during the study and finalization of this manuscript.

My sincere thanks are due to Dr. Amit Singla for his cordial and prompt support, friendly nature and able stewardship whenever needed.

Esteemed thanks are also extended to Dr. A.C. Varshney, Dean DGCNCOVAS.Also the support extended by entire teaching fraternity of this college is worth mentioning.

My earnest thanks are also due to field veterinarians Dr. Sujay Sharma (Veterinary officer), Dr. Atul Puri (Veterinary officer), Dr. Amitabh Thakur (Veterinary officer), Dr. Ajay Raj Singh Katwal (Veterinary officer,) Dr. B.N. Sharma (Senior veterinary officer), Dr. Anil Kumar Gupta(Deputy Director, Department of Animal Husbandary.)

The plausible encouragement, unconditional support during my post graduation and caring acts of Dr. Richa and Dr. Arun have become a treasure of precious memories which will be with

me throughout my life. I would fail in my duty if I do not articulate my appreciation to these two beloved juniors.

My vocabulary fails to express thanks to Dr. V. S. Nanda, Dr. Mohit Mahajan, Dr. R.S. Jaswal, Saurabh, Ruthwal, K.D. Imran, Shivali, Manisha, Mridu, Brijesh, Ranaut, Rajta, J.P, Vikrant, Vijay, Negi, Nikhil, Subu, Shama and all the Monalians of 18th "G" for their tremendous help in combating the stress and strain of research work.

I am also thankful to Mr. Anoop and laboratory staff of Department of Veterinary Physiology for their help during analysis of my samples.

I endure the help and cooperation rendered by the laboratory and ministerial staff of Department of Veterinary Surgery and Radiology specially Kishan and Prem ji.

Although it is not customary to acknowledge inanimate objects but I would like to mention my car HP 33-A-0195 which helped me in making up with my trials.

Final thanks with my prime heartfelt salutation at the lotus feet of my parents, Big B and Bharti Bhabhi.

Needless to mention errors and omissions are mine

Place: Palampur
Date: 28/6/10.

Bhanu

(Bhanu Thakur)

CONTENTS

LIST OF ABBREVATIONS USED AND THEIR MEANING

Abbrevation	Meaning
@	At the rate of
°F	Degree Fahrenheit
°C	Degree centigrade
%	Percent
/	Per
µL	Microlitre
&	And
i.e.	*id est* (that is)
>	Greater than
<	Less than
µ	Mu
α	Alpha
β	Beta
κ	Kappa
δ	Delta
AI	After induction
ALKP	Alkaline phosphatase
ALT	Alanine amino transferase
AR	After recovery
AST.	Aspartate amino transferase
BI	Before induction
BMR	Basal metabolic rate
BUN	blood urea nitrogen
BW	Body weight
Cl	Chloride
CNS	Central nervous system
cm	Centimeter
CRT	Capillary refill time
CRTN	Creatinine

DAn	During anaesthesia
ECG	Electrocardiography/electrocardiogram
e.g.	For example
EMG	Electromyelography/electromyelogram
et al.	et alii (and others)
etc.	Et cetera
Fig.	Figure
GKX	Guaifenesin, ketamine, xylazine
g/dL	Gram per deciliter
Gluc	Glucose
gp	Group
Hb	Haemoglobin
H or hr	Hour
HR	Heart rate
IM	Intramuscular
Na	Sodium
Ng/ml	Nanograms per milliliter
O2	Oxygen
P	Phosphorus
P<0.01	Statistically significant at 1% level
P <0.05	Statistically significant at 5% level
paO2	Partial pressure of oxygen
PaCO2	Partial pressure of carbondioxide
PCV	Packed cell volume
Pg/kg	Picograms per kilogram
Ph	Potential hydrogen
PmVO2	Microvascular O2 pressure
RBC	Red blood cell
RR	Respiration rate
RT	Rectal temperature
S.E.	Standard error
sec	Second

SpO2	Oxygen saturation
TIVA	Total intravenous anaesthesia
TLC	Total leukocyte count
TPR	Total protein
U/L	Units per litre
VA/Q	Ventilation perfusion ratio
viz.	*videlicet* (namely)

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Department of Surgery and Radiology
CSK Himachal Pradesh Krishi Vishvavidyalaya
Palampur (H.P.) 176062

Title of the thesis	: Clinical evaluation of xylazine or detomidine in combination with butorphanol, guaifenesin and ketamine for total intravenous anaesthesia in equines.
Name of the student	: Bhanu Pratap Singh Thakur
Admission No.	: V-2008-30-33
Major discipline	: Veterinary Surgery and Radiology
Minor discipline	: Veterinary Physiology
Date of thesis submission	: June 28, 2010
Total pages in thesis	: 61
Major Advisor	: Dr. S.K. Sharma

Abstract

The present study was conducted in 13 clinical cases of adult male spiti ponies presented for castration. Tetanus prophylaxis was given. In Group I (n=6) xylazine (1.1 mg/kg), butorphanol (0.02 mg/kg), guaifenesin 5% (20 mg/kg) and ketamine (2.2 mg/kg) and Group II (n=7) detomidine (0.02mg/Kg), butorphanol (0.01 mg/kg), guaifenesin 5% (20 mg/kg) and ketamine (2.0 mg/kg) combinations were used for TIVA. Dunett's "t" test. was employed for statistical analysis.

In Group I onset of sedation was recorded as 2.5±0.85min with ataxia at 1.0±0min and surgical anaesthesia at 2.66±0.66min. The limb/head movement and sternal recumbency was attained in 18.0±3.21min and 28.56±2.23min, respectively. Standing ataxia and normal gait were seen at 32.16±3.20min and 48.83±3.99min. Excellent to good muscle relaxation was observed. Surgical anaesthesia remained for 23.33±2.57min. Urination and neighing were observed. The ocular reflexes and swallowing reflex were suppressed. The rectal temperature remained unaffected with non significant decreases in heart rate and respiration rate. Capillary refill time (CRT) was normal and the mean SpO2 values were 82.18±5.33 and 87±2.94% during anaesthesia. Hemoglobin, PCV and TLC remained within normal range. Biphasic T wave was a constant observation before administration of any drug. After induction biphasic P wave, biphasic T wave, shortening of QRS segment and slight elevation of ST segment were recorded. There was highly significant increase in the plasma ALT values and a significant increase in plasma ALKP values along with non significant hyperglycemia.

In Group II onset of sedation was observed in 2.43±0.53mins with ataxia at 1.43±0.43min. Surgical anaesthesia was induced in 2.28±0.42min. The recovery was smooth and limb/head movement and sternal recumbency were attained in 18.71±1.98min and 26.14±1.62min. Standing ataxia and normal gait were seen at 29.42±3.21min and 71.14±4.74min. Excellent to good muscle relaxation was noticed and the surgical anaesthesia remained for 22.57±1.48min. Neighing was a constant feature during recovery period. Moderate to good suppression of ocular reflexes were observed with markedly depressed swallowing reflex. There was non significant decrease in rectal temperature and heart rate with a highly significant ($P<0.01$) to significant ($P<0.05$) decrease in respiration rate. Capillary refill time (CRT) remained normal. The mean SpO2 values were 76.50±4.14 and 83.33±4.18% during anaesthesia. No significant changes were observed in various hematological parameters. In general biphasic T wave and biphasic P wave were observed before anaesthesia. Following induction biphasic T wave, biphasic P wave and ST segment elevation were recorded. A highly significant ($P<0.01$) increase in the plasma ALT activity along with significant ($P<0.05$) to highly significant ($P<0.01$) increase in total proteins concentrations were noticed with non significant increase in plasma glucose level. It is concluded that the anaesthetic combinations xylazine-butorphanol-guaifenesin-ketamine and detomidine-butorphanol-guaifenesin-ketamine can safely be used for TIVA in equines under field conditions.

Bhanu 28/6/10
(Signature of the student with date)

28/06/10
(Signature of the Major Advisor)

28/6/10
(Signature of Head of Department)

INTRODUCTION

Chapter 1

INTRODUCTION

High altitude equines form the backbone of the economy of people of tribal areas of Himachal Pradesh. Although rigorous mechanization has taken place in the transportation means, the working equines continue to play a substantial role especially to the marginal farmers of this hilly state. In the event of tremendous potential for tourism industry (Chauhan and Dogra, 2005) and in spite of modernization, people have adopted equine rearing as their major avocation for employment and income generation. Therefore, equines are routinely presented to veterinary hospitals for variety of surgical interventions like castrations, management of wound, traumatic hernias and musculoskeletal disorders thus necessitating the use of general anaesthesia for management of these conditions.

High altitude equines differ from other breeds of horses in relation to the cardiovascular dynamics and handling of horse itself entails an inherent risk of injury to the handlers due to the larger size. The temperament of equinesoften precludes the use of local analgesia without heavy sedation (Hall and Clarke, 1991). Since all the anaesthetic agents have some undesirable effects, it is important to have in mind that the result of any anaesthetic procedure should not unify any morbidity or mortality in the patient. The use of gaseous anaesthesia in horses offers great safety in these regards, but the non-availability of sophisticated anaesthetic machines and necessary equipments to administer inhalant anaesthesia in the field makes its use practically unfeasible for the field veterinarians. Therefore, in the recent times the anaesthetic investigations have been aimed to develop safe total intravenous anaesthesia (TIVA) protocols in horses to manage a large number of surgical interventions and medical procedures. The use of TIVA helps in reducing a variety of preanaesthetic, anaesthetic and post anaesthetic problems such as arrhythmias, hypotension, respiratory or ventilator insufficiency, motor excitement, anxiety or post anaesthetic myopathy etc (Garcia *et al.* 2002).

The concept of balanced anaesthesia is not new. Specific anaesthetic drugs are used to produce specific effects which compromise the anaesthetic state namely hypnosis, ostentation of autonomic reflexes and muscular relaxation. No

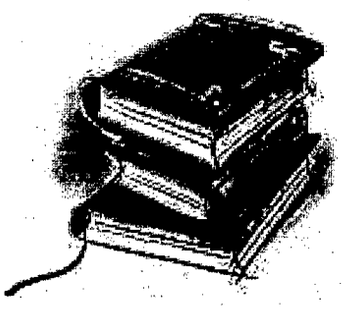
single agent exists which can provide all these components with an acceptable margin of safety. In field conditions intravenous anaesthesia is usually the method of choice, as it can be performed with limited facilities at hand in animal hospitals. TIVA is widely used for short period of anaesthesia in horses, so called "field anaesthesia". Moreover, many investigators have demonstrated that severe cardiovascular depression caused by the volatile agents, in particular halothane, contributes to the high anaesthetic mortality in horses (Steffey and Howland 1978).

Sedation with alpha2 adrenoreceptor agonist (alpha2 agonist) has been found useful in equine practice. The risk of injury is reduced and the ability to perform surgery is improved if the horse is suitably anaesthetized. The analgesic effects of α2 agonist drugs are better, ever over that of opioids. Detomidine effects are more pronounced than those of Xylazine due to its higher affinity to α2 adrenoreceptor. Butorphanol and other opioids have been effectively used in horses with varying degree of effects (Garcia *et al.* 2002) and also for modification of commonly used anaesthetic techniques.

Guaifenesin is a centrally acting muscle relaxant, which augments alpha$_2$ agonist induced sedation and improves the quality of surgery. Xylazine or detomidine, ketamine and butorphanol have been successfully used to produce short term TIVA in horses. This combination is more advantageous as in this combination the hassle of maintaining continuous drip has altogether ended. The common use of these drugs in clinical veterinary practice for induction of anaesthesia has not been fully investigated in high altitude equine, especially in Spiti ponies. The overall aim of this investigation was to study the effects of xylazine or detomidine with Butorphanol, Guaifenesin and Ketamine for total intravenous anaesthesia (TIVA) in Spiti ponies and to examine the suitability of these drugs in clinical cases needing short term surgical interventions like castration under field conditions.

Therefore, the present study was carried out to evaluate analgo-clinical, cardiovascular and haemato-biochemical changes of various anaesthetic combinations for castration in Spiti ponies presented in the teaching veterinary clinical complex and at different places of Himachal Pradesh with the following objectives:

1. To evaluate the anaesthetic effects of Xylazine or Detomidine with Butorphanol, Guaifenesin and ketamine for total intravenous anaesthesia (TIVA) in equines.
2. To record the cardiopulmonary and haemato-biochemical alterations during above mentioned anaesthetic regimens in equines.
3. To explore the suitability of above anaesthetic protocols for total intravenous anaesthesia (TIVA) in equines under field conditions.



REVIEW OF LITERATURE

Chapter 2

REVIEW OF LITERATURE

The evaluation of equine anaesthesia has been slow primarily because of traditional reliance upon various methods of physical restraint. Total intravenous anaesthesia (TIVA) for short term surgeries in horses is normally considered as a unique event, but must be assessed and monitored individually. In the present day scenario three groups of anaesthetic agents are commonly used in horses namely sedatives/hypnotics (Phenothiazine, diazepam etc), non opioids (xylazine, detomidine etc) and opioids. Therefore, Keeping in view the objectives of the present study, the available literature has been reviewed under the following heads:-

2.1 EQUINE ANAESTHESIA

The term "Balanced anaesthesia" was first introduced by Lundy in 1926 who advocated to use a balance of agents and techniques like premedication, regional anesthesia and general anesthesia to achieve the different desired objectives of muscle relaxation, analgesia, amnesia and elimination or reduction of autonomic reflexes during anesthesia without disturbing the homeostasis.

2.1.1 TOTAL INTRAVENOUS ANAESTHESIA (TIVA) IN EQUINES

Sir Federic Hobday, a British veterinary surgeon was the first person credited for advancing the art and science of equine anaesthesia (Hubbell 2004). He advocated the use of cocaine, chloral hydrate and chloroform as the safest anaesthetics for horses.

Diazepam (0.22mg/Kg IM), xylazine (1.1mg/Kg IV) and ketamine (2.2mg/Kg IV) combination has been used for short term anaesthesia in the horses (Butera *et al.* 1978). The horses were successfully anaesthetized.

With recent developments in new drugs, a new term total intravenous anaesthesia (TIVA) emerged in the field of anaesthesia. Muir and co-workers (1979) suggested that TIVA can also be used in conjunction with inhalant anaesthesia. The use of TIVA as an alternate to inhalant anaesthesia to produce the ideal anaesthetic state in adult horses has been well documented (Greene *et al.* 1986 and Hubbell *et al.* 1989). TIVA was defined in 1997 by Robertson as a technique which utilizes intravenous administered drugs to produce and maintain unconsciousness, analgesia, and muscle relaxation without concurrent use of inhalant agents. It may consist of a single bolus, repeated bolus, or continuous infusion of intravenous drugs.

Advantage of TIVA over inhalant anaesthesia was attributed to modifying or limiting the stress response due to maintenance of higher arterial blood pressure during maintenance phase of anaesthesia (Taylor 1992 and Taylor *et al.*1998). The use of intravenous anaesthesia over the inhalant anaesthesia on the basis of better cardiopulmonary findings has been reported by Luna *et al.* (1996).

Steffey and Howland (1978) suggested that most profound negative effects of anesthesia are caused by inhalant anesthetics. The mortality rate was higher with inhalation anaesthesia when compared with TIVA Johnston *et al.* (2002).

Under field conditions, TIVA has been used for many years and is preferred over inhalant anaesthesia because it can be administered without the sophisticated, costly and bulky equipments required during inhalation anaesthesia (Muir[a] 1991). TIVA today represents the most common anesthetic technique used for surgical procedures in the field (Taylor and Clarke, 1999). Spadavecchia *et al.* (1999) used TIVA in 20 horses with ketamine, guaifenesin and xylazine using computerized pump infusion. One hour anaesthesia with uneventful recovery comparable to inhalation anaesthesia was observed. Heess and Schatzmann (2003) reported total intravenous anaesthesia (TIVA) of more than hour duration in 101 horses under clinical conditions. The horses were routinely given a sedative premedication of xylazine and diazepam and anaesthesia was induced with xylazine-ketamine.

2.1.2 ANAESTHESIA IN SPITI PONIES

A number of anaesthetic combinations have been used in horses intravenously for undertaking various clinical procedures (Hoffman 1974). However, a very meager literature is available on anaesthesia in spiti ponies. Good sedation with optimal muscle relaxation but without surgical analgesia has been reported following xylazine administration in spiti ponies (Singh *et al.* 1996).

Singh *et al.* (1997) concluded that chloral hydrate in spiti ponies produced good muscle relaxation, adequate narcosis and sedation but local analgesia was needed at operation site.

Sharma *et al.* (1999) reported reversal of detomidine induced sedative effects by atipamazole in spiti ponies. Detomidine hydrochloride (60 µg/kg IV) was able to produce satisfactory sedation in spiti ponies and atipamazole at the rate of 60 µg/kg IV was able to reverse the effect.

Singh *et. al.* (2000) concluded that detomidine hydrochloride (60 µg/Kg IV) produced satisfactory sedation and analgesia with fair muscle relaxation in five spiti ponies presented for castration. Constant bradycardia and transient apnea were observed in two ponies.

Nanda (2009) suggested that the continuous rate infusion anaesthesia using guaifenesin- ketamine-xylazine triple drip provided consistent and reliable total intravenous anaesthesia in spiti ponies. The quality of surgical anaesthesia coupled with manageable recoveries suggested that this combination was good even for prolonged anaesthesia under field conditions.

2.2 GUAIFENESIN

2.2.1 INTRODUCTION

Guaifenesin is also known as Glyceryl guaiacolate or Guaiacol glycerol ether (GGE) or Guaiphenesin. Its chemically 3 – (o-methoxy-phenoxy) -1, 2-propanediol and is closely related to mephenesin (Davis and Wolff 1970). Guaifenesin has been used since 1949 as a general anaesthetic in Europe and United states respectively (Lindley 1976). Guaifenesin is a central acting anxiolytic and muscle relaxant. Apart from complete muscle relaxation it has sedative and analgesic properties when used alone. The unique advantage of guaifenesin is that it produces muscle relaxation with little effect on respiration (Robert 1968). It selectively depresses the nerve impulse transmission at the internuncial neurons

of the spinal cord, brainstem and subcortical regions of the brain (Davis and Wolff 1970).

Guaifenesin is physically compatible with sterile water or 5% DNS, it's also compatible with ketamine, xylazine, thiamylal and thiopental. Apart from its use in guaifenesin has also been used as muscle relaxant in various animals such as sheep (Gehring 1957), swine (Gehring and Lukanc 1962; Moon and Smith 1996), cattle (Westhues and Fritsch 1965; Garner *et al.* 1975) and in buffalo (Takarkhede *et al.* 1973; Singh *et al.* 1981).

2.2.2 GUAIFENESIN IN EQUINES

Guaifenesin has been extensively used in horses, either as muscle relaxant (Kraft 1962; Schebitz 1965; Westhues and Fritsch 1965; Davis and Wolf 1970) or to induce anaesthesia with ketamine or barbiturates (Gertsen and Tillotson 1968; Roberts 1968; Tavernor 1970). It helps to reduce the dose of drugs such as thiopental or thiamylal (Jackson and Lundvall 1972). Concentration of 10 to 12.5% or more of Guaifenesin has been found to cause haemolysis (Westhues and Fritsch 1965) or venous thrombosis and haemoglobinuria (Hall *et al.* 2001) in horses.

Tavernor (1970) reported that recumbency in horse was obtained by IV administration of guaifenesin at the dose rate of 160 mg/kg. A plasma concentration of 331µg/ml in horses and 238 µg/ml in ponies were capable of producing complete muscle relaxation when guaifenesin was used alone, which was lowered to 277µg/ml in horses premedicated with xylazine (Hubbell *et al.* 1980; Brouwer 1985; Young *et al.* 1993). These plasma concentrations were achieved when a rapid dose of guaifenesin at the dose rate of 88 – 140 mg/kg BW (10% solution) was given IV (Young *et al.*1993). Intravenous preanaesthetic medication with xylazine (1.1mg/kg) significantly decreased the amount of guaifenesin needed to produce lateral recumbency without affecting the plasma half life (Hubbell *et al.* 1980).

The signs of toxicity due to over dosage following guaifenesin administration were tetany, convulsions, hypotension, deep coma, apnea and death (Fritsch 1965). The lethal dose of guaifenesin in a horse was at least three times the calculated dose (Gertsen and Tillotson 1968).

Hubbell *et al.* (1980) reported that geldings required significantly more guaifenesin (163 ± 31 mg/kg) than the mares (111± 23 mg/kg). They also

observed that guaifenesin crossed the placental barrier in pregnant mares but caused minimal fetal depression of transient duration.

Luna *et al.* (1996) used 1-2 % halothane in oxygen or detomidine-ketamine-guaifenesin for maintenance of anaesthesia in 6 Welsh gelding ponies. The ponies were premedicated with acepromazine (0.03 mg/kg IV), and detomidine (0.02 mg/kg IV) and surgical anesthesia was induced with ketamine (2 mg/kg IV). It was concluded that cardio respiratory depression was more marked with increase in lactate, arginine, vasopressin and cortisol during halothane anesthesia as compared to TIVA.

The dose of guaifenesin required to produce recumbency in donkeys was 131 ± 27 mg/kg which was much lesser when compared to the dose of 211 ± 8 mg/kg in horses (Mathews *et al.* 1997). Recovery time was also lesser in donkeys than horses. They also reported significant difference in clearance which was 546 ± 73 ml/h/kg in donkeys and 313 ± 62 ml/h/kg for horses.

2.3 BUTORPHANOL

2.3.1 INTRODUCTION

Butorphanol is a potent, mixed agonist/antagonist that belongs to opioid family (Monkovic *et al.* 1973). Its predominant action is agonism at kappa receptors (Gear *et al.* 1996) with competitive agonist and antagonist activity at μ and δ opioid receptors (Horan and Ho 1989).

Laffey and Kay (1984) suggested that butorphanol parenterally administered exerts an analgesic effect with the potency approximately 5-7 times greater than that of morphine, the prototypical opioid analgesic. Butorphanol is widely used because of its safety and relative lack of side-effects as it does not depress cardiovascular function but it is expensive as compared to morphine (Muir 1998).

2.3.2 BUTORPHANOL IN EQUINES

Butorphanol produces sedation and analgesia via agonism at μ and κ opioid receptors. However the addition of low doses of alpha2 agonists has been reported to enhance sedation and analgesia while minimizing cardiopulmonary depression (Taylor *et al.* 1988 and Thurmon *et al.*1996).

Addition of butorphanol in premedication caused a significant reduction of EEG and EMG values during ketamine and halothane induced anaesthesia in equines (Kruljc and Cestnik 2003).

Garcia *et al.* (2005) observed that there were no significant butorphanol dose related differences on physiology, anaesthetic induction, recovery quality scores or recovery time in horses anaesthetized with xylazine, butorphanol and propofol. Also with the addition of butorphanol in acepromazine, romifidine and zolazepam combination the median score for quality of anaesthesia increased from 1 to 2 and time spent in lateral recumbency increased from 52 to 61 minutes in colts under dissociative anaesthesia at field and hospital conditions for castration (Marntell *et al.* 2006).

Butorphanol, at the dose rate of 0.025 to 0.05 mg/kg intraoperatively, provide additional analgesia and prolongs down time, however when butorphanol was administered in addition to 1mg/kg of xylazine there was risk of encountering significant ataxia (Caulkett 2007).

The quality of sedation and anaesthesia as well as maintenance of anaesthesia was significantly better in butorphanol when compared with morphine. The quality of induction of anaesthesia and recovery were not significantly different, between the two, nor are the surgical conditions, recovery time and the number of repeated anaesthetic doses required subsequently.

Butorphanol @ 50 µg/kg IV reduced the response to imposed stimuli in horses sedated with romifidine (Clarke *et al.* 2008). Butorphanol in combination with α2 adrenoreceptor agonist produces no cardiovascular changes induced by with α2 adrenoreceptor agonist alone but did increase the degree of respiratory depression.

Nolan *et al.* (2008) reported that both morphine (0.02- 0.05 mg /kg IV) and butorphanol (0.05 mg /kg IV) caused no adverse effect on cardiovascular and respiratory systems of detomidine, ketamine-halothane anesthetized horses.

DeRossi *et al.* (2009) observed a better sedation and analgesia following the use of romifidine and butorphanol combination than the administration of romifidine or butorphanol alone. There was decrease in heart rate with little interference in arterial blood pressure.

Caure *et al.* (2010) found that addition of butorphanol 0.05 mg/kg IV in balanced anesthesia (romifidine, halothane and ketamine) decreased the mean dose of vaporized halothane from 6.5±1 to 4.8±1.3 and dobutamine from 0.16 to 0.07. However, the mean arterial pressure significantly increased after addition of butorphanol.

2.4 XYLAZINE

2.4.1 INTRODUCTION

Code named BayVa 1470, xylazine was synthesized in 1962 and was first used in various domestic and exotic animals in Germany (Sanger *et al.* 1968) It is chemically 2-(2,6-Dimethylphenylamino)-5,6-dihydro-4H-thiazine.

Xylazine, an alpha-2 adrenergic agonist, produces excellent non narcotic sedation and analgesia as well as muscle relaxation, primarily due to central nervous system depression mediated by stimulation of α-2 receptors (Hsu 1981).

Garcia-Villar *et al.* (1981) observed that the peak plasma concentration of xylazine in horses was attained within 12 to 14 min after IM injection where as its systemic half life was found to be 50 min. There was marked difference in doses and effects among various species of animals. Horses required 10 times more dose for sedation as compared to cattle (Hall *et al.* 2001).

2.4.2 XYLAZINE IN EQUINES

Hoffman (1974) administered xylazine IV, in horses and found that 1.1 mg/kg was an optimal dose required for restraint, sedation or analgesia prior to any clinical procedure. Minimal sedation occurred within 3 minutes of administration and lasted for 30 to 40 minutes. Also at the same dose rate there was significant decrease in heart rate, cardiac output and respiratory frequency and increased arterial pressure initially followed by a decrease (Muir *et al.* 1979; Lavoie *et al.* 1992). Sudden death in horses after xylazine administration has been reported by Clarke and Hall (1969); Fuentes (1978). Violent seizers followed by collapse have been recorded if xylazine is injected in to carotid artery inadvertently.

Taylor *et al.* (2008) anaesthetized five adult standard donkeys previously sedated with xylazine @ 1.1 mg/kg BW, IV, with different combinations of guaifenesin, ketamine and xylazine (GKX) under field conditions.

2.5 KETAMINE

2.5.1 INTRODUCTION

Ketamine is a cyclohexylamine anaesthetic, which produces a dissociative state in humans. It was introduced in veterinary practice in 1970 for anaesthesia of cats. It's chemically (2-(*o*-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride. *The molecule of ketamine has two isomers, in animals (+) isomer* produced hypnosis lasting nearly twice as long as the (-) isomer (Marietta *et al.* 1977; Ryder *et al.* 1978). The racemic mixture had intermediate effect.

Ketamine's low ability to cause cardio respiratory depression was unequaled by other general anaesthetics (Lanning and Harmel 1975).

2.5.2 KETAMINE IN EQUINES

In horses 60% of ketamine is metabolized in liver while remaining is excreted in the urine unchanged. Ketamine should not be used as a mono anaesthetic in horses because it causes uncontrollable behavior and muscle incoordination. Ketamine produces muscular relaxation; it in fact increases the muscular tone and produces a state similar to a convulsive phase (Waterman *et al.* 1987). When used alone, the horses first raised their heads within 10 to 30 min after ketamine injection and stood up in 5 to 6 min thereafter (Muir[b] 1991).

In donkeys ketamine has been used @ 2.0 -3.0 mg/kg, IV following sedation with xylazine @ 1.6 mg/kg, IV. The half life of ketamine was shorter in donkey as compared to horses (Matthews *et al.* 1994). Rough recoveries are associated in donkeys if ketamine is increased above 3.3 mg/kg (Trawford 2000).

Low dose intravenous infusions or repetitive boluses of racemic ketamine or S-ketamine might be beneficial when administered in conjunction with other anaesthetic agents and could be used in horses requiring additional analgesia and/or improve haemodynamic functions (Regula and Larenza 2007).

2.6 DETOMIDINE

2.6.1 INTRODUCTION

Detomidine is an imidazole derivative and α adrenergic agonist, used as a large animal sedative. Detomidine is chemically 4-[(2, 3-dimethylphenyl) methyl]-3H-imidazole.Detomidine has a half life of 30 min. Detomidine is a novel sedative with analgesic properties and is more selective α2 agonist than Xylazine. It produces dose dependent sedative and analgesic effect, mediated by activation of α2 catecholamine receptors thus inducing a negative feedback response, reducing production of excitatory neurotransmitter due to inhibition of sympathetic nervous system. It has also cardiac and respiratory effects and an antidiuretic action. It is commonly combined with butorphanol for increased analgesia and depth of sedation. If conjugated with ketamine it may also be used for IV anesthesia.

2.6.2 DETOMIDINE IN EQUINES

Dyson *et al.* (1987) reported a significantly greater frequency of sinus block and second degree A.V block following detomidine administration in comparison to xylazine. Detomidine sedated horses were significantly more depressed.

Peak concentration of detomidine (51.3 µg/ml) is achieved in horse in 0.5 hr. The apparent volume of distribution is higher after IM dosing (1.56l/kg) than after IV dosing (074 l/kg). Elimination half life is 1.19 hr for IV dose and 1.78 hr for IM dose. Total clearance is 6.7 ml\min\kg and renal clearance is less than 1% of total clearance (Salonen *et al.* 1989).

Wagner *et al.* (1991) had reported a significant decrease in heart rate, increased incidence of A.V block and decreased cardiac output following detomidine administration. There was marked decrease in cardiac output and cardiac index @0.02 mg/kg as compared to doses 0.01mg/kg and 0.04 mg/kg of detomidine and doses 1.1 mg/kg and 2.2 mg/kg of xylazine. Detomidine (0.02 mg/kg) initially caused hypertension followed by significant decrease in mean arterial pressure, packed cell volume and respiration rate.

Muir and Mason (1993) reported that there was decreased cardiac output, respiration rate and increased blood pressure when detomidine (0.01 mg\kg IV) was administered prior to thiamylal and this effect was similar to xylazine (0.5 mg/kg or 1.0 mg\kg, IV).

Although atropine administration has been reported to prevent bradyarrythymia and bradycardia following detomidine, there was no significant effect on heart rate, respiration rate, borborygmia, distance from lower lip to ground, systolic blood pressure and response to needle insertion when detomidine was used without atropine in equines (Diana 1993).

Detomidine (0.015 mg/kg IV) in combination with propofol (2mg/kg IV) produced little cardiovascular depression, but with hypoxemia and respiratory depression and some excitement in horses in dorsal recumbency (Matthews *et al.* 1999). Therefore, the combination was not recommended for surgical procedures in horses if dorsal recumbency is necessary and supplemental O2 is not available.

Varshney and Singh (2001) found that epidural administration of detomidine and lignocaine combination in horses produced analgesia of longer duration than detomidine alone. There was long acting caudal analgesia, marked sedation, mild ataxia, less cardiovascular depression and renal diuresis. Similar observations have been reported by Skarda and Muir (1994).

Detomidine (0.02 mg/kg IV) has been reported as satisfactory premedicant, before ketamine and halothane anaesthesia for maintenance of blood pressure as there was less severe hypotension when compared to other alpha2 adrenoreceptor

agonists like Romifidine (0.1 mg/kg IV) . The requirement of dobutamine was more in romifidine treated horses as compared to detomidine treated horses (Taylor *et al.* 2001).

Steffey and Pascoe (2002) reported that detomidine reduces isoflurane anaesthetic requirement (MAC) in horses by 42.8% and 44.8% at 83 and 125 min respectively, following 0.03 and 0.06mg/kg. The MAC reduction was dose dependent time dependent. There was a tendency for mild cardiovascular and respiratory depression, especially following the higher detomidine dose. Detomidine also increased both blood glucose and urine flow; the magnitude of these changes was found to be time and dose dependent.

Moens *et al.* (2003) demonstrated the analgesic potential of detomidine in the horses for somatic pain by measuring nociceptive threshold using an electric stimulus applied to the coronary band and a pneumatically operated pin pressing on the cannon bone. There was 3.4 times greater increase in threshold using electric current testing as compared to use of mechanical pressure testing.

Buhl *et al.* (2007) studied the effects of detomidine on cardiographic measurements and cardiac function in normal horses and indicated that the sedation of horses with detomidine had a significant effect on heart function, echocardiographic measurements of heart dimensions and the occurrence of valvular regurgitation.

There was a delay in transmission of pain impulses to the CNS following detomidine administration along with increased blood glucose concentration, increased blood pressure, decreased pulse rate and increased respiration rate (Zager 2008). Also the use of detomidine was not harmful in pregnant mares.

Plasma drug concentration of detomidine and its measured effects (behavioral, e.g. head position and physiological, e.g. heart rate) were correlated positively and varied with the route of administration following a single dose of Detomidine (Mama *et al.* 2009). When a longer duration of plasma concentration was warranted, the intramuscular route should be considered (Grimsrud *et al.* 2010).

The dose of Detomidine to produce an equivalent effect may be higher in horses after exercise than in resting horses (Hubbell *et al.* 2009).

2.7 XYLAZINE, BUTORPHANOL, GUAIFENESIN, AND KETAMINE COMBINATION

The addition of guaifenesin to xylazine and ketamine anaesthesia was first described for short time equine anaesthetic maintenance by Muir *et al.* (1978). This combination produced optimal analgesia, unconsciousness, muscle relaxation and predictable recovery, thus making it an ideal anaesthetic combination. Hypotension which was commonly observed during inhalation anaesthesia was rarely seen with this combination when horses breathed air.

Adding guaifenesin to the induction protocol also reduces the dose of induction agents needed and therefore, helped to minimize drug related side-effects (Hubbell *et al.* 1998).

Guaifenesin-ketamine-xylazine combination has been used to anaesthetize animals undergoing various surgeries like plating, pinning, penile surgery, hernia repair, cesarean section and celiotomy (Thurmon 1986).

Muir and Robertson (1985) studied the visceral analgesic, cardio respiratory and behavioral effects induced by xylazine. Butorphanol, meperidine and pentazocine in colic, artificially produced by inflating a balloon in horse caecum. Xylazine and butorphanol decreased the haemodynamic response to caecal balloon inflation. Xylazine produced the most pronounced and longest visceral analgesia (90 min) followed by butorphanol (60 min).

Brunson and Majors (1987) compared the analgesic effect of xylazine, xylazine/morphine, xylazine/butorphanol and xylazine/nalbuphine in horses using dental dolorimetry and reported that xylazine and xylazine/butorphanol were better analgesics. Xylazine resulted peak analgesia faster than with butorphanol or combination of xylazine/butorphanol.

Prolongation of anaesthesia with xylazine, ketamine and guaifenesin with or without butorphanol has been reported in 64 horses (McCarty *et al.* 1990). Anaesthesia was prolonged for upto 70 min by administration of 1-9 supplemental IV injection of xylazine and ketamine at approximately 1/3 the initial dose. Respiratory and heart rates and coccygeal artery pressure remained consistent .The average interval between the last injection of ketamine and assumption of sternal position was approximately 30 minutes.

Merritt *et al.* (1998) reported profound suppressive effect of routine dose of detomidine or xylazine and butorphanol combination on equine duodenal motility.

Wooldridge *et al.* (2002) compared the effect of oxytocin, xylazine, butorphanol, guaifenesin, acepromazine and detomidine on oesophageal manometric pressure in horses. They reported that detomidine, acepromazine and combination of xylazine and butorphanol had the greatest effect on oesophageal motility.

Olson (2002) reported that the draft horses require lower doses of many sedatives and anaesthetics compared to the thoroughbreds (on mg/kg basis) but when doses are adjusted for metabolic size it was true only for guaifenesin.

Garcia *et al.* (2002) reported that anaesthesia induction with xylazine (0.5 mg/kg), ketamine (2.2 mg/kg) and butorphanol (0.04 mg/kg) is rapid and smooth; recovery is smooth with fair muscle relaxation. Recumbency lasts for 10-30 min and good analgesia is ensured due to the addition of butorphanol.

When the dose of xylazine was increased the side effects were also increased. But the frequency and severity of the rapid effects were reduced when butorphanol was administered 3-5 minutes after xylazine. The onset of xylazine sedation occurred after 2-5 minutes and analgesia from butorphanol after 5-10 minutes. The duration of good analgesia and sedation was 30-35 minutes. The combination of xylazine and butorphanol allowed reduction in the dose of butorphanol and also some of the CNS signs produced by butorphanol were reduced (Geiser and Henton 2006).

The influence of butorphanol dose on characteristics of xylazine (0.5 mg/kg IV), butorphanol (0.025 –0.05mg/kg IV) and propofol (2 mg/kg IV) anaesthesia were studied in horses (Garcia *et al.*2005) and it was observed that dose of butorphanol did not markedly influenced study results. The low PaO2 values related to geographic location of study and general anaesthesia indicated narrow margin of error for hypoxemia related complications in anaesthetized horses breathing un-supplemented air.

Lin *et al.* (1993) studied guaifenesin 5% (50 mg/ml), ketamine 1mg/ml (group I) or 2mg/ml (group II) and xylazine (1.1 mg/ml) anaesthesia for castration in ponies. Total mean guaifenesin, ketamine, xylazine dose required for induction and maintenance of anaesthesia for 50 min with guaifenesin, ketamine, xylazine 1 and 45 min with guaifenesin, ketamine, xylazine was 4.5±0.3 ml/kg /hr and 4.3±0.2ml/kg/hr respectively. Respiration rate decreased in both the groups and heart rate was unchanged following induction. However the heart rate was

decreased at 40-50 min intervals in group I and 30-50 min for group II reflecting bradicardiac action of xylazine somewhat more than the stimulating effect of ketamine. Stability of anaesthesia, degree of analgesia and muscle relaxation were found to be better in group I than in group II.

Malik and Singh (2008) evaluated the effect of midazolam supplementation on ketamine anaesthesia in horses premedicated with butorphanol and xylazine. It was observed that midazolam supplementation increased the dose of anaesthesia, slightly improved the duration of anaesthesia and significantly improved the quality of analgesia, muscular relaxation and depth of anaesthesia without producing any adverse effect on cardio respiratory system.

Taylor and Watkin (2008) reported that a combination of 2.0 mg/ml ketamine, 0.5 mg/ml xylazine and 50 mg/ml guaifenesin produced satisfactory anaesthesia without significant respiratory depression and produced safe and effective anaesthesia in donkeys under field conditions. It was also noticed that donkeys required higher amount of ketamine to achieve satisfactory anaesthetic levels without producing excessive depression with guaifenesin.

It has been reported that xylazine requirement for constant standing sedation was reduced by addition of butorphanol at constant rate infusion (Ringer *et al.* 2009).

Nanda (2009) reported that guaifenesin(25 g),ketamine(2.2 mg/kg IV) and xylazine(1.1 mg/kg IV) combination produced longer duration of anaesthesia with better muscle relaxation , analgesia ,uniform plane of anaesthesia in tandem with continuous rate of infusion and excellent recovery than diazepam(25 mg/kg), ketamine (2.2 mg/kg) and xylazine (1.1 mg/kg) infusion anaesthesia.

2.9 DETOMIDINE, BUTORPHANOL, GUAIFENESIN AND KETAMINE COMBINATION

It has been reported that the effects on the cardiovascular system were minimum following the use of detomidine, butorphanol, guaifenesin and ketamine anaesthesia (Robertson and Muir 1983). The circulatory changes were within normal range in comparison to different changes induced by the alpha2 agonist alone. Although there might be slight respiratory depression (Clarke *et al.*1991; Clarke and Paton 1988), the decrease in ventilation and increase in PaO2 was probably an effect of butorphanol.

Taylor *et al.* (1988) reported that in 92% horses necessary procedures were carried out under excellent conditions with detomidine (13µg/kg) and butorphanol (26 µg/kg) combination. Bradycardia and ataxia were the major side effects.

Dijk (1994) studied the effect of TIVA with intravenous infusion of the combination of guaifenesin (100mg\ml), ketamine (2mg\ml) and detomidine (0.02mg\ml) at the infusion rate of 1ml/kg/hr and reported significant hyperglycemia whereas the plasma concentration of AST decreased significantly. During anaesthesia pulse rate, mean arterial pressure, arterial blood gases, pH, lactate, LDH and creatinine did not show any significant change and remained within the normal ranges.

Guaifenesin (100mg/kg), detomidine (0.02mg/kg) and ketamine (2 mg/kg) combination produced minimal cardio respiratory depression and hyperglycemia. The recovery was satisfactory and did not occur as promptly as after halothane (Taylor and Luna 1995).

Lavoie *et al.* (1996) suggested that combination of detomidine and butorphanol in healthy horses as well as horses with pre-existing respiratory depression affected the respiratory function.

Freeman *et al.* (2002) reported that during anaesthesia produced by romifidine (120µg/kg) and detomidine (20µg /kg) when used as premedicant for ketamine (2.2 mg/kg)-halothane (expired concentration 1%) combination, the arterial blood pressure, cardiac index, Pao2 and Pmv02 decreased and systemic vascular resistance and Paco2 increased.

It has been observed that anaesthesia produced by detomidine (0.04 mg/ml), ketamine (4mg/kg) and guaifenesin (100 mg/kg) following pre anaesthetic medication with butorphanol (20mg/ml) was suitable for maintenance of anaesthesia in pregnant equidae as it was smooth with minimal cardiovascular effects (Taylor *et al.* 2001).

Garcia *et al.* (2002) reported that detomidine (0.005 mg/kg) caused dose dependent bradycardia and also increased the possibility of first and second degree atrio-ventricular blocks. Xylazine and detomidine depressed respiration, induced hyperglycemia and diuresis without glycosuria. But on addition of ketamine (2.2 mg/kg IV) more balanced anaesthesia was produced. Induction and recovery were smooth and satisfactory.

Yamashita *et al.* (2002) studied the cardiovascular effects of infusion of guaifenesin, ketamine and medetomidine in combination with inhalation of sevoflurane versus inhalation of sevoflurane alone for anaesthesia of horses. It was suggested that the combination of guaifenesin, ketamine and medetomidine infusion and inhalation of sevoflurane result in better transition and maintenance phases while improving cardiovascular function and reducing the number of attempts to stand after the completion of anaesthesia compared with inhalation of sevoflurane alone.

Lin and Riddell (2003) studied the sedative effect induced by administering detomidine hydrochloride (0.01mg\kg) or xylazine (0.02 mg\kg with or without butorphanol tartarate (0.05mg\kg). Heart rate, respiration rate were recorded and found to be significantly decreased. Duration of sedation was 43.0 min whereas sedation was for 36 min in xylazine and butorphanol combination. Ptosis and salivation was observed in all the animals. The degree of sedation seemed to be most profound in cows receiving detomidine and least profound in cows receiving xylazine.

Khan *et al.* (2003) reported that premedication with detomidine (50 µg/kg) in chloral hydrate (60 mg/kg) induced anaesthesia exhibited very smooth induction and none of the animal showed staggering and incoordination. Recovery was rapid and smooth in all the cases. This study provided evidence that chloral hydrate at reduced doses with detomidine premedication can be used for minor surgical interventions of short duration.

Also it was suggested that guaifenesin, ketamine and detomidine combination produced slight cardio-respiratory depression, hyperglycemia and a reduction in haematocrit (Taylor *et al.* 2004). A decrease in plasma cortisol concentration and increase in plasma 11-deoxycorticol indicated a suppression of steroidogenesis were observed.

Kruljc and Nemec (2005) confirmed that detomidine and butorphanol combination was safe and more appropriate for painless and non painless procedures in standing horses. Detomidine alone or detomidine-Butorphanol combination significantly reduced EEG and EMG and caused change in individual brain wave fraction during sedation and particularly during analgo-sedation. Detomidine-butorphanol combination provided greater and longer muscle relaxation.

Guaifenesin (50 mg/kg); ketamine (2 mg/kg) and detomidine (0.01 mg/kg) combination appeared as a potential total intravenous technique for maintenance of anaesthesia in horses (Taylor and Watkin 2008).

Kilic (2008) reported that the combination of detomidine (100 µg/kg), midazolam (0.5 mg/kg) and ketamine (10 mg/kg) resulted in anaesthesia lasting about 45min and produced satisfactory immobilization for umbilical surgery. Hypoxaemia and respiratory acidosis were observed. The body temperature, hemoglobin, PCV and RBC decreased significantly whereas values of plasma glucose, creatinine and ALT increased significantly. Muscle relaxation was found to be good without any complication.

Nyman (2009) reported that addition of butorphanol during the detomidine sedation resulted in a significant decrease in respiration rate and a small but significant increase in PaCo2 as compared to detomidine sedation alone. Minute ventilation decreased significantly compared to that in un-sedated horses. The cardiovascular changes persisted but the vascular resistance in both the pulmonary and systemic circulation decreased compared to detomidine sedation alone. VA/Q distribution improved and dead space ventilation decreased as compared to detomidine sedation.

MATERIALS AND METHODS

Chapter 3

MATERIALS AND METHODS

The present study was carried out from January 2010 to March 2010 on 13 clinically healthy male spiti ponies presented for castration in the Teaching Veterinary Clinical Complex of Dr. G. C. Negi College of Veterinary and Animal Sciences, Palampur and at various field Veterinary hospitals of department of Animal Husbandry, Himachal Pradesh. Tetanus prophylaxis was given to all the horses two weeks prior to the date of elective surgery. Animals were fasted overnight and water was withheld for 6- 8 hours.

The animals were randomly divided into two groups *viz.* Group I (6 horses) and Group II (7 horses). The anaesthetic protocols adopted for TIVA in both the groups were as follows:

Group	Pre-anaesthesia	Induction	Maintenance (if required)
I	Xylazine, Butorphanol and 5% Guaifenesin, all IV	Ketamine IV	Ketamine
II	Detomidine, Butorphanol and 5% Guaifenesin, all IV	Ketamine IV	Ketamine

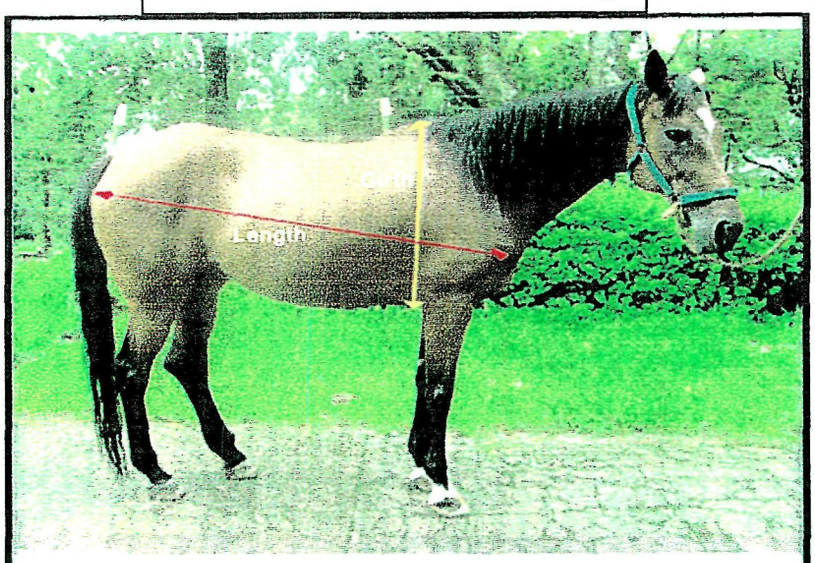
The dose regimens used for different drugs were standardized as per reference available in the literature based on subjective analysis.

3.1 EXPERIMENTAL DESIGN

3.1.1 Preanaesthetic management

The fasted animals were brought to a calm isolated area and site for jugular vein puncture was prepared for aseptic administration of drugs and blood collection. Estimation of body weight was ascertained by measuring the length and the girth of the horse as per the formula described by Ellis and Hollands (1998; Plate 1). Before induction of anaesthesia a pad of cotton wool was placed in horses ears to reduce external stimuli.

Plate 1: Measurement of Body



$$\text{Body weight (Kg)} = \frac{(\text{Length) in cm} \times (\text{Girth})^2 \text{ in cm}}{11{,}877}$$

3.1.2 Preanaesthesia

Xylazine[a] (1.1mg/Kg) and detomidine[b] (0.02mg/Kg) were administered intravenously in group I and group II animals, respectively. Subsequently at head down position the animals of both the groups received butorphanol[c] at the dose rate of 0.2mg/Kg in (group I) and 0.1mg/Kg (group II), intravenously. Thereafter 5% guaifenesin[d] (20mg/Kg) was administered intravenously in horses of both the Groups.

3.1.3 Induction of anaesthesia

Following guaifenesin administration, as soon as the signs of ataxia developed, induction of surgical anaesthesia was achieved by intravenous administration of ketamine hydrochloride[e] at the rate of 2.2mg/Kg (group I) and 2.0 mg/Kg (group II), respectively. During induction the horses were properly

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a- Xylazine – XYLAZIL - 100™ injection (100mg/ml), ILIUM, Troy Laboratories, Australia.
b- Domosedan (10mg/ml) Orion pharma limited; Finland.
c- Butrum (2mg/ml) Aristo pharmaceuticals Pvt. Ltd; Mumbai.
d- Guaifenesin IP Prudential Pharmaceuticals Ltd; Andhra Pradesh. India.
e- Ketamine- KETAMIL- 100™ injection (100mg/ml), ILIUM, Troy Laboratories, Australia.

restrained to prevent forward fall. After induction, the horses were left undisturbed for one minute and head and neck were extended to maintain a patent airway. Neosporin ophthalmic ointment was applied in both the eyes and eyes were protected by a piece of cloth.

3.1.4 Maintenance of anaesthesia

Wherever required, the maintenance of anaesthesia was achieved by ketamine hydrochloride intravenously, 'to effect'.

3.2 ANAESTHETIC PARAMETERS

The following anaesthetic parameters were recorded during each experiment.

3.2.1 Time for sedation/ataxia

The time lapse between the intraveneous administration of xylazine or detomidine, butorphanol and guaifenesin and development of signs of ataxia/head down position.

3.2.2 Time for induction

The time interval between the intravenous administration of ketamine and attainment of lateral recumbency and loss of response to cutaneous pin pricks.

3.2.3 Quality of anaesthesia

The quality was analyzed by recording different reflexes, extent of muscle relaxation and analgesia before induction (BI), after induction (AI), during anaesthesia (DAn) / 12-15 min after induction and after recovery (AR) as follows:

a. Reflex status

Presence or absence of palpebral reflexes (lash reflex), corneal reflex, effect on photopupillary reflex and swallowing reflex.

b. Muscle relaxation

Muscle relaxation of neck, jaws, tail and anal sphincter were examined and the quality was recorded as follows:

Score card for quality of muscle relaxation

Quality of muscle relaxation		
Score	Quality	Character
4	Excellent	Complete relaxation
3	Good	Adequate muscle relaxation for surgical procedure
2	Moderate	Partial relaxation of head, neck and limb muscles
1	Poor	Rigidity in muscles of neck, head and limbs

c. Analgesic quality:

The quality of analgesia was recorded using pin prick method to test the response to noxious stimuli on the coronary band of the front and hind neck, the shoulders and the gaskin (the part of hind leg between the stifle and the hock). Purposeful skeletal muscle movement, observed at any of the four test sites, was interpreted as a response and score was given ranging from 0 to 3 (Nanda, 2009).

Score card for quality of analgesia

Quality of Analgesia		
Score	**Quality**	**Character**
0	Excellent	No response
1	Good	Response to stimuli, Nystagmus created, a blood pressure response or a local muscle response (nerve stimulator) observed
2	Moderate	Purposeful movement of limbs, head, or neck produced
3	Poor	Horse moved into sternal position or stood

3.2.4 Recovery time

The time interval between inductions of anaesthesia, start of the limb/head movements, standing ataxia and the time of browsing and normal gait were recorded. The following score ranging from 1 to 5 was given as per method of *Ringer et al.* (2007).

Score card for Quality of Recovery

Quality of Recovery		
Score	**Quality**	**Character**
1	Excellent	Horse capable of standing at first attempt
2	Very good	Horse remained calm and needed two attempts to stand
3	Good	Horse remained calm but needed more than two attempts to stand
4	Poor	Excitement during recovery with danger of injury and needed more than one attempts to stand
5	Very poor	Severe excitement during recovery with injury

3.2.5 Complications

Complications if any during anaesthesia, recovery and post recovery were recorded.

3.3 CLINICAL PARAMETERS

Following clinical parameters were recorded before induction (BI), after induction (AI), during anaesthesia (DAn-12 to 15 minutes after induction) and after recovery (AR):

a. Rectal temperature (RT)

b. Cardiopulmonary parameters

Respiration rate (RR) was recorded by observing costo-abdominal movements manually and by vital signs monitor[f], heart rate (HR) by auscultation and vital sign monitor, capillary refill time (CRT) and SpO_2 by tongue transducer were recorded. Electrocardiograms (ECG) were recorded on vital sign monitor using bipolar base apex lead system with positive electrode placed at the centre of the sternal pads, negative electrodes at the posterior border of the scapula and the neutral at the anterior side of the head of the humerus on the neck, before induction (BI), after induction (AI), during anaesthesia (DAn) and after recovery (AR). The calibrations made were conduction 1mV=1cm and paper speed of 25mm/sec. the elector cardiograms were analyzed for various conduction abnormalities if any.

3.4 Haematological parameters

Venous blood (2ml-2.5ml) from jugular vein was collected in EDTA vials at different time intervals as mentioned above for estimation of haemoglobin (Hb), packed cell volume (PCV) and Total leukocyte count (TLC). The samples were analyzed using blood cell counter[g].

3.5 Biochemical parameters

Five ml of venous blood was collected in heparinized vials for the analysis of various blood biochemical parameters. The plasma was separated by centrifugation. Blood glucose was estimated immediately on computerized semi automatic blood analyzer[h]. The plasma was stored at -20^{0}C for further analysis of

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f - Multi Para Monitor --- Execello BPL, Bangalore, India
g - BC- 2800 vet- Auto hematology analyzer
h - RA- 50 Chemistry Analyzer, Bayer Diagnostics, Baroda, Gujarat, India.

other biochemical parameters namely aspartate aminotransferase (AST), Alanine aminotransferase (ALT), alkaline phosphatase (AKLP), chloride (Cl), total proteins (TPR), blood urea nitrogen (BUN) and creatinine (CTRN) using commercially available kits on semi automatic blood analyzer. Estimation of sodium and potassium was done by flame photometry

3.6 Statistical analysis

The data recoded, wherever applicable, was statistically analyzed using Dunett's 't' test at 1% and 5 % level of significance.

RESULTS AND DISCUSSION

Chapter 4

RESULTS AND DISCUSSION

Knowledge of available data related to various cardiopulmonary effects of different anesthetics/anaesthetic combinations enables the veterinarians in handling each case more authoritatively, especially under field conditions where sophisticated gadgets for monitoring are not available. Therefore, various physiological alterations a patient undergoes during anaesthesia must be evaluated clinically to form a data base of safe anaesthetic techniques to be used readily by field veterinarians. Such data base is very important in spiti ponies, the high altitude equines, as they have a different cardiopulmonary physiology in comparison to thorough bred horses. The ultimate aim should be to choose the safest and most balanced anaesthetic technique for TIVA in horses. This formed the basis of present work so as to recommend the safe TIVA for short surgical procedures like castration in spiti ponies.

Total intravenous anaesthesia (TIVA) trials were conducted in 13 spiti ponies (Group I – 6 animals and Group II – 7 animals) during January to March with the ambient temperature of $18.63^0C \pm 0.72^0C$ ranging from16.2^0C to 21.4^0C.

4.1 EVALUATION OF XYLAZINE, BUTORPHANOL, GUAIFENESIN AND KETAMINE COMBINATION (GROUP –I)

Based on the data available in literature and as per clinical response during pilot trials the dose of different drugs used were 1.1 mg/kg IV for xylazine, 0.02 mg/kg IV (butorphanol), 20 mg/kg IV (guaifenesin 5%) and 2.2 mg/kg IV (ketamine) for total intravenous anaesthesia in spiti ponies presented for castration. The dosages used are well documented in literature (Kerr *et al.* 1996; Muir *et al.* 1977; Butera *et al.* 1978; Kaka *et al.* 1979). One of the most studied and familiar TIVA technique in horses is using a combination of ketamine, alpha$_2$ agonist and guaifenesin (Greene *et al.* 1986; McCarty *et al.* 1990;. Taylor 1992; Taylor *et al.* 1998; Young *et al.* 1993). Xylazine and ketamine combination is commonly used for induction and maintenance of anaesthesia in horses (Muir *et al.* 1977) whereas, addition of guaifenesin helps to achieve desirable effects (analgesia, unconsciousness and muscle relaxation) associated with general anaesthesia (Muir *et al.* 1978). Butorphanol,

an agonist-antagonist opioid, was used in the present study for profound sedation and surgical analgesia because the use of only agonist opioids induces different excitement states during anaesthesia in horses (Garcia *et al.* 2002).

4.1.1 Pre-induction recording

The horses (n=6) anaesthetized were 4.27±1.63 years of age, which ranged from 1.5 years to 12 years. The body weight ranged from 150 to 222 kg with the mean of 181.66±32.26kg.

4.1.2 Sedative and behavioral studies

The onset of sedation (head down) following xylazine administration recorded was 2.5±0.85 min. These findings were attributed to significant muscle relaxation by xylazine (Hubbell *et al.* 1999). The sedative and analgesic property of xylazine is due to CNS depression mediated by stimulation of α2 receptors (Hsu 1981). The animals were ataxic at 1.0±0 min following butorphanol and guaifenesin. Although there is risk of encountering significant ataxia when butorphanol is administered in addition to xylazine (Caulkett 2007), no such observation was recorded in the present study. The induction of surgical anaesthesia was achieved in 2.66±0.66min. During recovery limb/head movement and sternal recumbency was attained in 18.0±3.21min and 28.56±2.23min respectively. Almost similar observations were reported by McCarty *et al.* (1990) and Baetage *et al.* (2007) who recorded the sternal recumbency in 30min and in 15±6min, respectively. On the contrary Garcia (2005) reported that there was non significant butorphanol dose related difference in anaesthetic induction, recovery score and recovery time. Standing ataxia and normal gait were seen at 32.16±3.20min and 48.83±3.99min, respectively after induction of anaesthesia with ketamine. Ketamine hydrochloride exerts its effect on CNS during induction and produces functional and electrophysiological dissociation of thalamoneocortical areas from limbic and other subcortical structures in the brain; as a result consciousness is lost. The neuronal activity in other brain centers such as limbic system, including the hippocampus is maintained (Staffieri and Driessen 2007). Maintenance of anaesthesia was required in two horses which was obtained with ketamine at the dose rate of 1.0 mg/kg, IV "to effect". Head shaking was observed during induction in two horses which is of no clinical importance. Urination and neighing was a constant feature

during recovery period except in one horse. Defecation following xylazine administration was also seen in one horse. The lacrimation was observed in three horses indicating light plane of anaesthesia.

4.1.3 Clinical studies

Ocular reflexes like palpebral and corneal were suppressed after induction and during anaesthesia. Eye evaluation is of limited value following administration of ketamine because of the responses like voluntary blinking, lateral nystagmus and lacrimation. This effect may be attributed to ketamine which is often referred to as cateleptoid anaesthesia, which differ markedly from the classical signs of anaesthesia. Ketamine appears to alter the reactivity of the CNS to various sensory impulses without blocking the sensory inputs at spinal or brain stem levels. The input may reach the cortical receiving areas, but fails to be perceived because of depression or disorganization of the associated areas during the period of anaesthesia (Spark *et al.* 1973; Wright 1982). The swallowing reflex was depressed in all the operated horses.

The TIVA combination used in the present group produced excellent to good muscle relaxation during anaesthesia in all the animals as evidenced by relaxation of jaw, neck, tail and anal sphincter. This finding is in agreement with Malik and Singh (2008) and Lin (1993) who reported that muscle relaxation is better with ketamine @ 1 mg/kg than 2mg/kg when used in conjunction with guaifenesin and xylazine. This effect is also attributed to guaifenesin which acts centrally by depressing or blocking nerve impulse transmission at subcortical areas of brain, brainstem and spinal cord (Cullen 1996). The relaxation of anal sphincter was first to be noticed and last to come to normal during recovery. There was complete to moderate analgesia during anaesthesia in all the animals which remained for 23.33±2.57min following induction of anaesthesia as had also demonstrated by Geiser and Henton (2006) where analgesia in horses remained for 30-35min. Surgical plane of anaesthesia following guaifenesin-xylazine-ketamine administration has also been observed in horses (McCarty *et al.* 1990 and Young *et al.*. 1993). Visceral analgesia was observed for 90min following xylazine administration in colic horses (Muir and Robertson 1985). Interestingly Brunson and Majors(1987) reported better analgesia with xylazine or combination of xylazine and butorphanol in comparison to butorphanol alone. The analgesia in the present study could be attributed to xylazine and ketamine used in the

combination as the electric activity of the brain slows down following xylazine administration and subsequently an increase in high voltage activity of the brain is seen following ketamine administration (Purohit *et al.* 1981). Whenever high voltage low frequency patterns are observed in EEG the anaesthesia is appropriate for surgical intervention (Nigam and Peshin 1993). Whether guaifenesin alone has mild analgesic properties in horses is still debatable (Regula and Larenza 2007). In one animal there was mild analgesia during recovery period. In two animals in which surgical anaesthesia was observed for only 17 and 18 minutes, respectively, the maintenance of anaesthesia was achieved with ketamine hydrochloride "to effect".

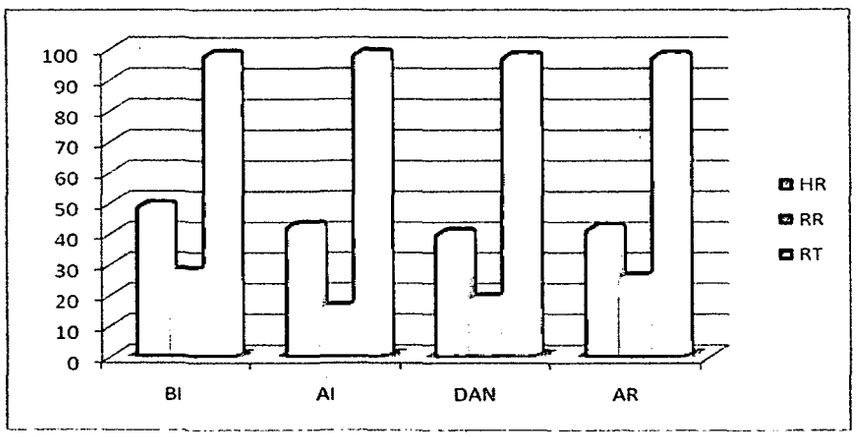
Malik and Singh (2008) have reported a significant decrease in respiration rate, heart rate and rectal temperature following xylazine-butorphanol administration in horses. However in the animals of group I in the present study, the rectal temperature remained unaffected during the period of study whereas non significant decrease in heart rate and respiration rate was observed after induction and during anaesthesia (Table 1; Fig 1).

Table1: Clinical and haematological effects following Xylazine-butorphanol-Guaifenesin-Ketamine anaesthesia in Spiti ponies (n=6)

Parameters (unit)	Before induction (BI)	After induction (AI)	During anaesthesia (DAn)	After recovery (AR)
Rectal Temp(°F)	98.65 ±0.29	98.88 ±0.41	98.03 ±0.53	98.13 ±0.42
Heart rate (per min)	49.50 ±3.93	43.00 ±3.44	40.66 ±4.03	42.00 ±2.63
Respiratory Rate (per min)	28.00 ±4.93	16.33 ±1.48	19.33 ±3.30	26.17 ±3.06
Hb (g/dl)	10.03 ±0.43	9.92 ±0.71	9.60 ±0.36	10.93 ±1.22
PCV (%)	26.43 ±1.17	27.52 ±1.57	25.45 ±1.04	26.60 ±0.96
TLC (thous./mm^3)	8.87 ±2.16	8.17 ±1.87	8.75 ±0.70	8.29 ±0.75

However, the changes recorded were within normal range. A similar trend was observed by Nanda (2009) following continuous intravenous triple drip of xylazine-ketamine guaifenesin. The decrease in respiration rate was related to direct depression of respiratory centres by xylazine (Rings and Muir 1982). Butorphanol is also a potential respiratory depressant drug, although no serious effect was observed by Robertson *et al.* (1981) when it was injected in healthy horses. Though ketamine stimulates respiratory centre but decrease in respiratory rate even after the administration of ketamine may probably be due to the depressant effect of xylazine and butorphanol which might have balanced the stimulatory effect of ketamine (Malik and Singh 2008). The decrease in the heart rate is attributed to xylazine-induced vagal stimulation. A significant bradycardia has also been reported following xylazine-guaifenesin-ketamine anaesthesia in calves (Kerr *et al.* 2008).

Fig 1. Clinical effects following Xylazine-butorphanol-Guaifenesin-Ketamine anaesthesia in Spiti ponies (n=6).



HR=Heart rate/min; RR= Respiratory rate/min; RT=Rectal Temperature (°C); BI-Before induction; AI-After induction; DAN-During anaesthesia; AR- After recovery

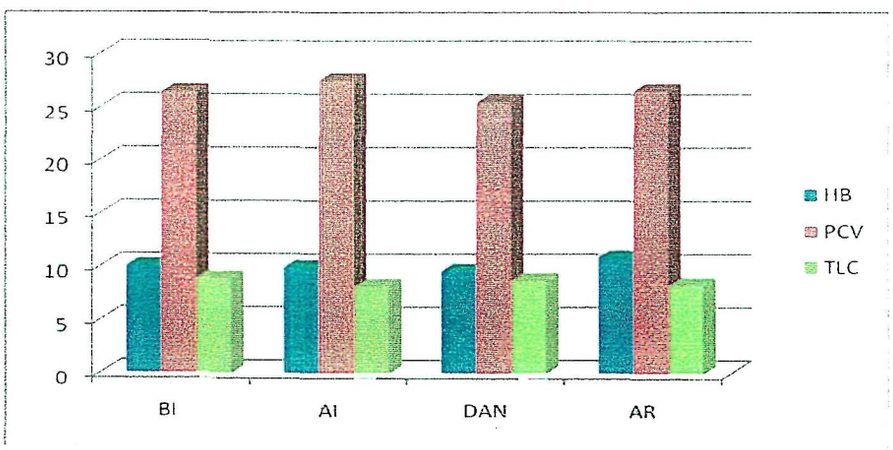
Capillary refill time (CRT) remained normal throughout the period of anaesthesia which was less than 1min indicating normal circulation in the animals. The mean SpO2 value in equines of this group was 82.18±5.33 and 87±2.94% after induction and during anaesthesia, respectively. Pulse oximetry allows continuous calculation of oxygen (O_2) saturation using non invasive technology. It measures the Hb saturation and thus gives indirect evaluation of

PaO_2. Since the equines in the present study were on spontaneous respiration and cyanosis is not always detectable in hypoxemic horses, estimation of oxygen saturation becomes important in horses when oxygen enrichment is not provided to anaesthetize recumbent horses. The SpO_2 level decreased in this group as the duration of anaesthetic period progressed as the normal Hb saturation varies between 95 to 100%. Baetge *et al.* (2007) observed increased partial pressure of CO_2 and decreased partial pressure of O_2 in arterial blood of horses when this combination was administered. Hypoventilation could be one of the causes for hypoxemia (Muir 1991[b]) as the respiration rate decreased in the present study. Ventilation perfusion mismatch is more possible cause of these changes. During anaesthesia ventilation is directed preferentially to the uppermost region of the lungs while perfusion is concentrated caudodorsally (Dobson *et al.*. 1985). In other words the uppermost regions of the lungs containing oxygen do not have perfusion to transport this oxygen to the tissues and the caudodorsal areas of the lungs with perfusion do not have adequate oxygen supply, thus creating hypoxemia. Guaifenesin is known to produce hypoventilation, but the resultant hypoxia is often effectively counteracted by oxygen administration (Jackson and Lundvall 1972).

4.1.4 HAEMATOLOGICAL STUDIES

All the hematological parameters namely hemoglobin, PCV and TLC remained within normal range following the use of xylazine-butorphanol-guaifenesin-Ketamine combination for TIVA in spiti ponies (Table 1; Fig 2).

Fig 2. Haematological effects following Xylazine-butorphanol-Guaifenesin-Ketamine anaesthesia in Spiti ponies (n=6)



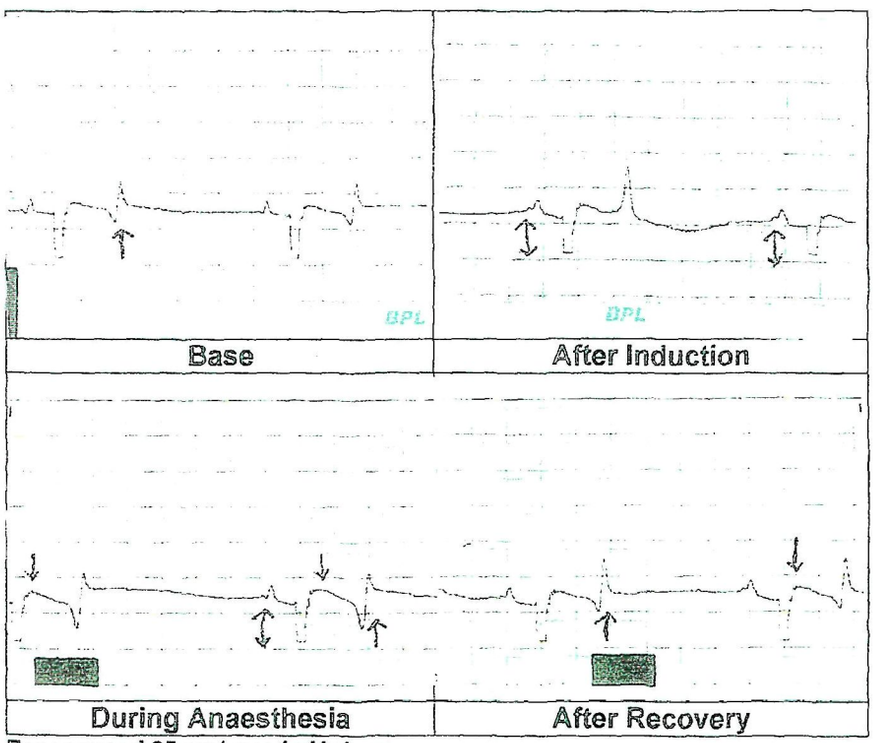
Hb= g/dl; PCV= %; TLC= thous./mm^3; BI-Before induction; AI-After induction; DAN-During anaesthesia; AR-After recovery

The values observed during anaesthesia and in post anaesthetic period were comparable to the base values. A significant decrease in PCV and TLC and a non significant decrease in Hb have been reported following continuous intravenous triple drip of xylazine-ketamine-guaifenesin in spiti ponies (Nanda 2009).

4.1.5 CARDIOVASCULAR STUDIES

The ECG changes recorded before, during and after anaesthesia are shown in (Fig 3, 4 and 5).

Fig 3 Electrocardiogram of a Spiti Pony following xylazine-butorphanol-guaifenesin-ketamine anaesthesia showing different wave changes

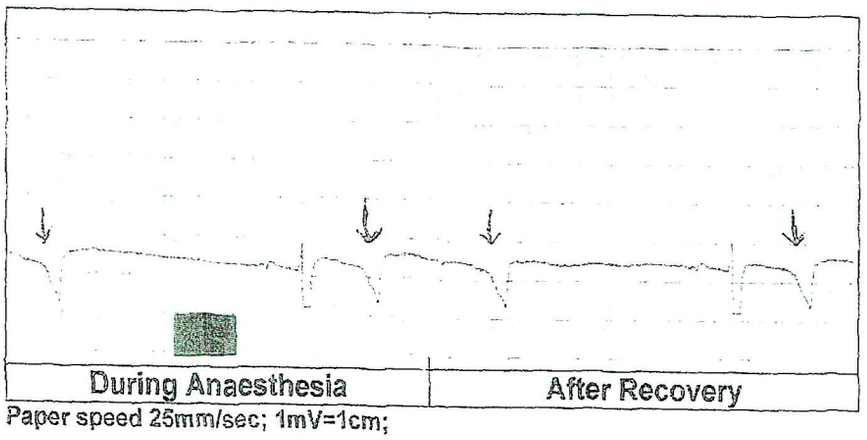


Paper speed 25mm/sec; 1mV=1cm;
↑Biphasic T wave; ↕Biphasic P wave; ↓ST segment Elevation

Biphasic T wave was a constant observation in all the horses before administration of any drug. In one horse PR segment was depressed whereas ST segment elevation was noticed in another two horses at base. After induction of anaesthesia biphasic P wave, biphasic T wave, shortening of QRS segment and slight elevation of ST segment were recorded in all the animals. In one horse where PR segment was depressed at base continued to remain so throughout the period of study. Negative T wave was also recorded during

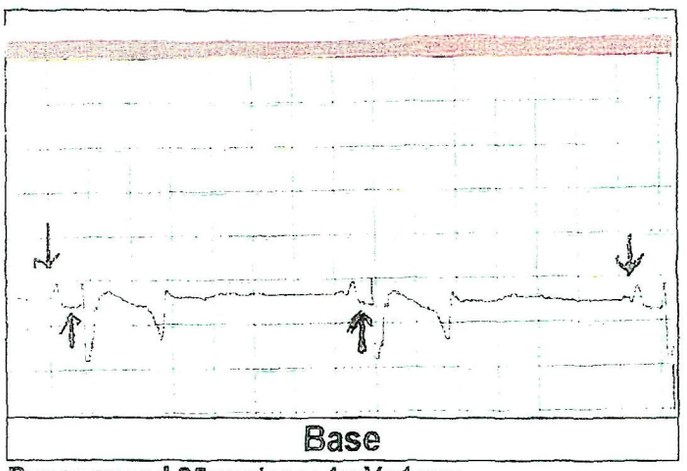
surgical anaesthesia and after recovery in one animal. There was no indication of any type of heart block. All the ECG changes recorded in this group represent normal impulse conduction and hence are of no clinical relevance. Occasional conduction abnormalities seen during anaesthesia in different spiti ponies were possibly due to myocardial hypoxemia as the respiration rate was decreased in the present group.

Fig 4 Electrocardiogram of a Spiti Pony following xylazine-butorphanol-guaifenesin-ketamine anaesthesia showing negative T wave (↓) during anaesthesia and after recovery



Paper speed 25mm/sec; 1mV=1cm;

Fig 5 Electrocardiogram of a Spiti Pony following xylazine-butorphanol-guaifenesin-ketamine anaesthesia showing biphasic P wave (↓) and depressed PR segment (↑) at base



Paper speed 25mm/sec; 1mV=1cm;

4.1.6 BIOCHEMICAL STUDIES

The alterations in various biochemical parameters following xylazine-butorphanol-guaifenesin-ketamine anaesthesia in spiti ponies of Group I are shown in Table 2 and Fig 6 and 7.

Table 2: Biochemical effects following Xylazine-butorphanol-Guaifenesin-Ketamine anaesthesia in Spiti ponies (n=6)

Parameters (unit)	Before induction (BI)	After induction (AI)	During anaesthesia (DAn)	After recovery (AR)
Sodium (mEq/L)	128.05 ±11.70	122.80 ±11.16	113.93 ±5.32	109.80 ± 5.72
Potassium (mEq/L)	4.17 ±0.39	3.93 ±0.29	4.12 ±0.69	3.29 ± 0.31
Chloride (mEq/L)	79.15 ±12.44	81.30 ±7.50	84.39 ±9.47	77.41 ± 5.43
Glucose (mg/dl)	75.50 ±11.03	119.17 ±14.77	125.66 ±13.66	120.83 ± 13.42
Total proteins (g/dl)	8.60 ±0.49	10.60 ±0.49	10.83 ±0.61	10.36 ± 1.06
AST (U/L)	241.00 ±29.24	200.33 ±25.39	176.83 ±29.37	169.16 ± 29.78
ALT (U/L)	13.60 ±0.63	18.92** ±0.60	18.44** ±0.62	13.18 ± 0.71
ALKP(U/L)	123.00 ±4.12	138.00* ±3.54	111.17 ±2.48	118.50 ±3.56
BUN (mg/dl)	25.70 ±2.97	24.33 ±2.18	23.28 ±1.66	22.05 ± 1.98
Creatinine (mg/dl)	0.81 ±0.05	0.74 ±0.05	0.78 ±0.06	0.84 ± 0.14

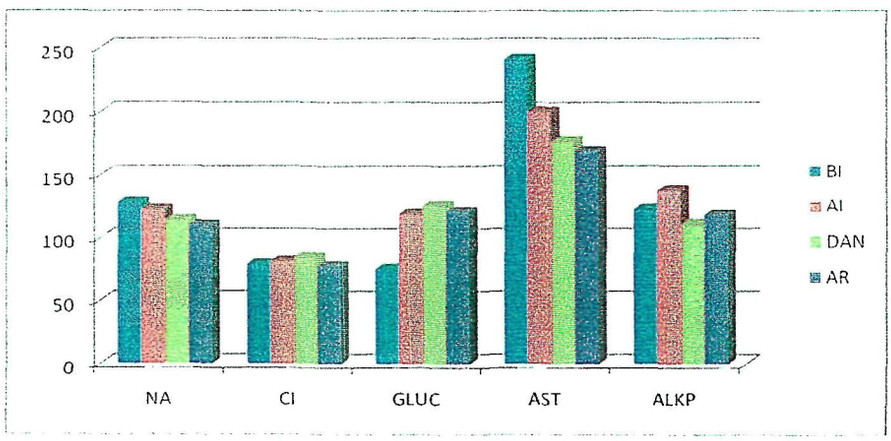
***P<0.05;**P<0.01**

All the pre-induction plasma samples of spiti ponies evaluated for various biochemical parameters were within normal range. There was highly significant (P< 0.01) increase in the plasma ALT values during anaesthesia.

The increase in ALT values could probably be due to alteration in cell membrane permeability which might permit these enzymes to leak from cells with intact membrane (Tiwari *et al.* 1999). Also a significant ($P<0.05$) increase in plasma ALKP values was noticed immediately after induction of anaesthesia. Since the range of ALKP values in horses is wide so a change in its value is of no clinical relevance. There was evidence of non significant ($P>0.05$) hyperglycemia throughout the period of study following induction of anaesthesia. The increase in plasma glucose level was probably due to an alpha$_2$ adrenergic inhibition of insulin release by stimulation of alpha$_2$ receptors in the pancreatic β - cells (Angel and Langer, 1988) and to the increased glucose production in the liver (Hsu and Hammel, 1981). Ketamine hydrochloride generally increases nor– epinephrine blood levels and turnover. Since nor–epinephrine affects gluconeogenesis and glycogenolysis and also decrease insulin production, enhanced hyperglycemic effects after ketamine administration are obvious. A significant hyperglycemia following general anesthesia has been reported in horses (Young *et al.* 1993; Singh *et al.* 1996). The hyperglycemic response in horses varies with anaesthetic regimen (Snow 1979) along with an increase in chloride and total protein concentrations.

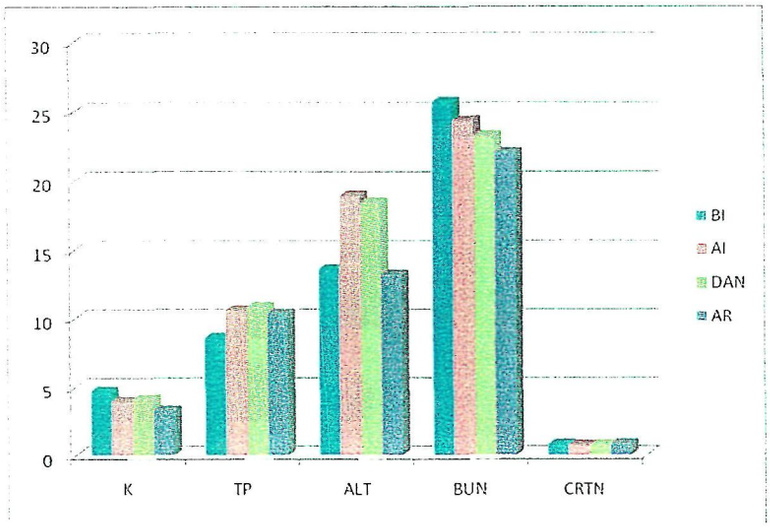
However since these changes were statistically non significant therefore, reflecting no effect on renal blood flow in the present study.

Fig 6. Biochemical effects following Xylazine-butorphanol-Guaifenesin-Ketamine anaesthesia in Spiti ponies (n=6)



NA-sodium (mEq/L); Cl-Chloride (mEq/L); GLUC -Glucose (mg/dl); AST (U/L); ALKP (U/L); BI-Before induction; AI-After induction; DAN-During anaesthesia; AR-After recovery

Fig 7. Biochemical effects following Xylazine-butorphanol-Guaifenesin-Ketamine anaesthesia in Spiti ponies (n=6)



K-potassium (mEq/L); TP-Total proteins (g/dl); ALT (U/L); BUN-blood urea nitrogen (mg/dl); CRTN-Creatinine (mg/dl); BI-Before induction; AI-After induction; DAN-During anaesthesia; AR-After recovery

Non significant decreases in sodium, potassium, AST and BUN concentration were recorded during the anaesthetic period reflecting no alterations in body electrolyte balance as well as absence of any hepatic or renal toxicity in the present study. The changes were comparable to base values after recovery.

4.2 EVALUATION OF DETOMIDINE, BUTORPHANOL, GUAIFENESIN AND KETAMINE COMBINATION (GROUP –II)

Detomidine plus ketamine and detomidine plus guaifenesin and ketamine have been studied for induction and maintenance of anaesthesia in ponies and to a limited degree in horses (Mama 2000). Blood pressure and cardiac index are also well maintained during this anaesthetic protocol in horses in comparison to inhalant anaesthesia. In spiti ponies of this group the combination of detomidine (0.02 mg/kg IV), butorphanol (0.01 mg/kg IV), guaifenesin 5% (20 mg/kg IV) and ketamine (2 mg/kg IV) were used for total intravenous anaesthesia (TIVA) to carry out castration. Detomidine was used in the present group animals as it is more specific α2 agonist compared to xylazine and also it is more potent than xylazine in both behavioral and neurochemical effects (Atasoy *et al.* 2009). The dosages used in the present

group are well documented in literature (Matthew *et al.* 1991; Taylor 1992;Taylor and Luna 1995; Taylor *et al.*1988;). When used alone detomidine has been used @ 60 µg/Kg IV for sedation in spiti ponies (Sharma *et al.* 1999; Singh *et al.* 2000).

4.2.1 Pre-induction recording

The horses anaesthetized were 3.12±0.56 years of age, which ranged from 1 year to 4 years. The body weight ranged from 130 to 220 kg with the mean of 170±11.34 kg.

4.2.2 Sedative and behavioral studies

The onset of sedation was observed in 2.43±0.53min following detomidine administration which was comparable to group I. Sedation is conceivably the result of activation of central α2 adrenoreceptors which causes a decrease in release and turnover of norepinephrine in CNS (Kinjavdekar *et al.* 1999). Lin and Riddell (2003) reported that detomidine @ 0.01 mg/kg alone actually induces a greater degree of sedation than xylazine. Levine *et al.* (1992) observed a decrease in the level of sedation with a higher dose of butorphanol (0.07 mg/kg). The horses were ataxic in 1.43±0.43min after the administration of butorphenol and guaifenesin when ketamine was injected intravenously to achieve surgical anaesthesia. Interestingly the time taken by the horses of this group to become ataxic was more than group I animals although it is well known fact that detomidine is more potent than xylazine. Although it is difficult to explain but one of the possible reason could be the lower dose of butorphanol used in the present group (0.01mg/kg) in comparison to group I animals (0.02 mg/kg). All the horses were in surgical plane of anaesthesia within 2.28±0.42min following ketamine administration which was comparable to group I. During recovery the limb/head movement and sternal recumbency were attained in 18.71±1.98min and 26.14±1.62min, respectively whereas standing ataxia and normal gait were seen at 29.42±3.21min and 71.14±4.74min, respectively, after administration of ketamine. The longer duration of sedation observed in the present group in comparison to group I was obvious because of the sedative effect of more potent drug detomidine. Garcia *et al.* (2002) reported attaining of sternal recumbency after 25 minutes. Recovery was smooth in the present group animals as has also been reported in earlier studies (Taylor and Luna 1995; Garcia *et al.* 2002). Maintenance of anaesthesia was not required in any of the present group spiti ponies. Head

shaking was observed during induction in two horses. Neighing was a constant feature during recovery period except in two horses. The combination has been reported to induce diuresis in equines (Garcia *et al.* 2002) as a result of α2 adrenoreceptor agonism in kidneys but in the present study dribbling of urine was noticed only in one horse. Lacrimation, an indication of light plane of anaesthesia was noticed only in one horse in comparison to 3 horses of group I.

4.2.3 Clinical studies

There was moderate to good suppression of palpebral and corneal reflexes immediately after induction and during anaesthesia following detomidine, butorphanol, guaifenesin and ketamine anaesthesia in spiti ponies. The observations were comparable to the horses of group I. As discussed earlier in group I, these effects can be attributed to ketamine used in the combination. The swallowing reflex was markedly depressed in all the operated horses during the surgical plane of anaesthesia except in one horse where the depression was moderate during anaesthesia.

The combination of detomidine, butorphanol, guaifenesin and ketamine produced excellent to good muscle relaxation in all the spiti ponies as evidenced by relaxation of jaw, neck, tail and anal sphincter. This finding is in conjunction with observations of Kruljic and Nemec (2005) and Taylor and Watkin (2008). Muscle relaxant effect is due to inhibition of inter neuronal transmission of impulses (Kumar and Singh 1977). The relaxation of anal sphincter was first to be noticed and last to come to normal during recovery. There was excellent analgesia in the present group and the surgery was facile. Similar observations have been made by Moens *et al.* (2003). The combination of guaifenesin, ketamine, and detomidine was found to be a potential total intravenous technique for maintenance of anaesthesia in horses (Taylor and Watkin 2008) whereas detomidine and butorphanol combination was safe and more appropriate for painless and non painless procedures on standing horses (Krulje and Nemec 2005). The analgesia in the present study could be attributed to detomidine, butorphanol and ketamine used in the combination. The analgesic activity can also be related to the stimulation of α2 adrenoreceptors in CNS, which inhibits release of neurotransmitter and decrease neuronal activity resulting in loss of pain reflexes (Kinjavdekar *et al.* 1999) and ketamine induced block of conduction of pain impulses to the thalamic and cortical areas

(Booth 1977). However, in one horse only moderate analgesia was observed. In all the animals analgesia was observed for 22.57±1.48min following induction of anaesthesia. Sedative and analgesic role of detomidine for minor work of short duration has also been reported (Jochle *et al.* 1991; Klein 1975).

The effect of detomidine, butorphanol, guaifenesin and ketamine combination on rectal temperature, respiration rate and heart rate are shown in Table 3.

Table 3: Clinical and haematological effects following detomidine-butorphanol-guaifenesin-ketamine anaesthesia in Spiti ponies (n=7)

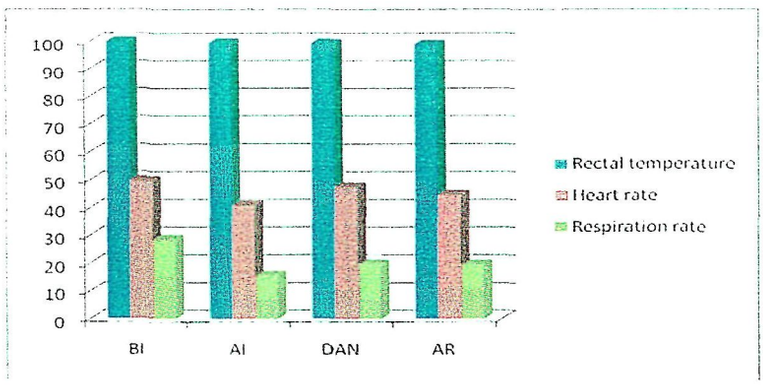
Parameters (unit)	Before induction (BI)	After induction (AI)	During anaesthesia (DAn)	After recovery (AR)
Rectal Temp(°F)	100.00 ±0.31	99.55 ±0.25	99.37 ±0.26	98.90 ±0.27
Heart rate (per min)	49.71 ±2.44	40.85 ±6.37	47.42 ±7.07	44.71 ±4.24
Respiratory Rate (per min)	28.57 ±3.31	**15.57** ±1.60**	**19.71* ±1.14**	**19.57* ±2.18**
Hb (g/dl)	10.81 ±0.62	10.92 ±0.62	10.00 ±0.66	10.34 ±0.54
PCV (%)	28.97 ±1.35	29.12 ±1.56	27.10 ±1.69	27.54 ±1.15
TLC (thous./mm^3)	7.75 ±0.37	7.27 ±1.18	6.95 ±0.65	8.42 ±0.94

***P<0.05; **P<0.01**

There was non significant decrease in rectal temperature and heart rate during the period of study whereas a highly significant (P<0.01) to significant (p<0.05) decrease in respiration rate was observed after induction, during anaesthesia and after recovery (Fig 8.). Decrease in respiration rate could be due to direct depressant effect of α2 agonist on CNS in general and respiratory centre in particular (Tiwari and Kumar 1998; Kinjavdekar *et al.* 1999). This finding is in agreement with earlier observations using different anaesthetic

protocols in horses (Wagner *et al.* 1991; Muir and Mason 1993; Lavoie *et al.* 1996; Clarke and Paton 1988; Nyman *et al.* 2009). Contrarily Zager (2008) reported a significant increase in respiration rate when detomidine alone was used in pregnant mares. Robertson and Muir (1983) reported no significant effect of this combination on heart whereas marked bradyarrythymia and decreased heart rate were recorded by Wagner *et al.* (1991), Taylor and Luna (1995) and Taylor *et al.* (2004). Non significant change in rectal temperature indicates that this drug combination does not induce depression of thermoregulatory centers and does not reduce BMR and muscle activity. However, this finding was contrary to the observations of Kilic (2008) who reported a significant decrease in rectal temperature following the use of combination of detomidine, midazolam and ketamine in horses. Capillary refill time (CRT) remained normal throughout the period of anaesthesia following the use of detomidine, butorphanol, guaifenesin and ketamine combination of TIVA in spiti ponies. The mean SpO2 value in equines of this group was 76.50±4.14 and 83.33±4.18 percent after induction and during anaesthesia, respectively, possibly due to significant decrease in the respiratory rate observed in group II.

Fig 8. Clinical effects following Detomidine-butorphanol-Guaifenesin-Ketamine anaesthesia in Spiti ponies (n=7)



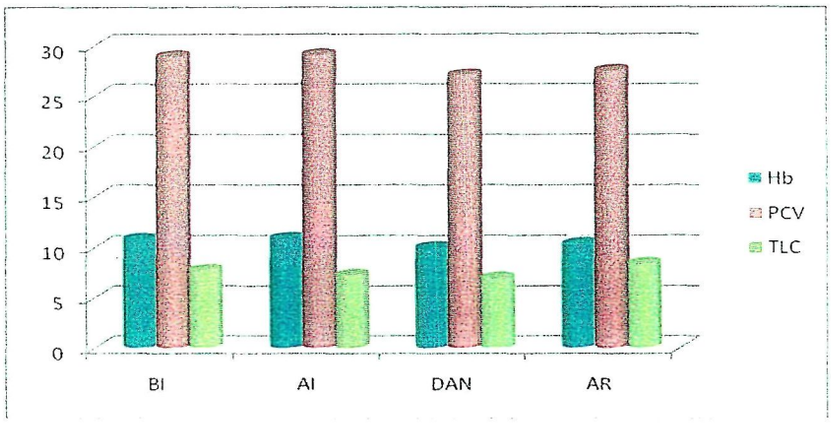
Heart rate/min; Respiratory rate/min; Rectal Temperature (°C); BI-Before induction; AI-After induction; DAN-During anaesthesia; AR-After recovery

4.2.4 HAEMATOLOGICAL STUDIES

The combination of detomidine, butorphanol, guaifenesin and ketamine for TIVA in horses failed to produce any significant change in various hematological parameters in horses during the period of study (Table 3 and Fig

9). The values recorded throughout the period of study were within normal range and were comparable to base values. On the contrary Wagner *et al.* (1991) and Taylor *et al.* (2004) reported a significant decrease in haematocrit. Kilic (2008) also reported a significant decrease in Hb and PCV after administration of combination of detomidine, midazolam and ketamine in horses.

Fig 9. Haematological effects following detomidine-butorphanol-Guaifenesin-Ketamine anaesthesia in Spiti ponies (n=7)



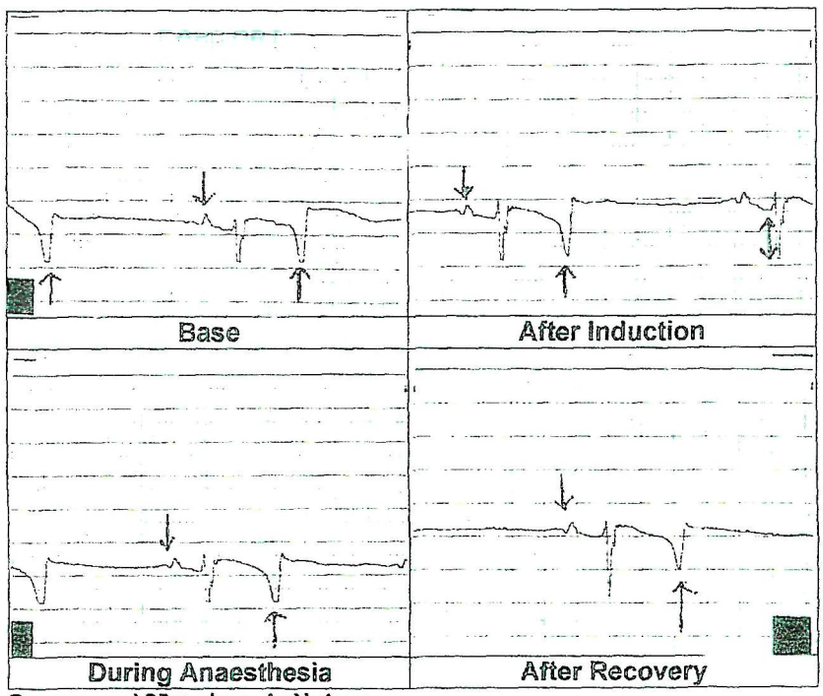
Hb= g/dl; PCV= %; TLC= thous./mm^3; BI-Before induction; AI-After induction; DAN-During anaesthesia; AR-After recovery

4.2.5 CARDIOVASCULAR STUDIES

The electrocardiograms (ECG) of spiti ponies recorded before anaesthesia and following the use of detomidine, butorphanol, guaifenesin and ketamine combination during anaesthesia and in post anesthetic period are shown in figures 10 to 13. In general, biphasic T wave and biphasic P wave were observed in all the horses before anaesthesia with slight elevation of ST segment recorded only in one horse. Following induction of anaesthesia the ECG recordings depicted biphasic T wave, biphasic P wave, and slight elevation of ST segment in all the horses. PR segment depression and notched P wave were also observed in one horse each, respectively. In almost all the spiti ponies the ECG observations recorded before and during anaesthesia, remained so in the post anaesthetic period also except in one horse where sinus block was recorded. Sinus blockade may be attributed to myocardial hypoxia since there was decrease in respiration rate. Dyson *et al.* (1987) also demonstrated that frequency of sinus blockade, arrest and 2^0 AV block is higher with detomidine than xylazine. A dose dependent bradycardia and possibility of

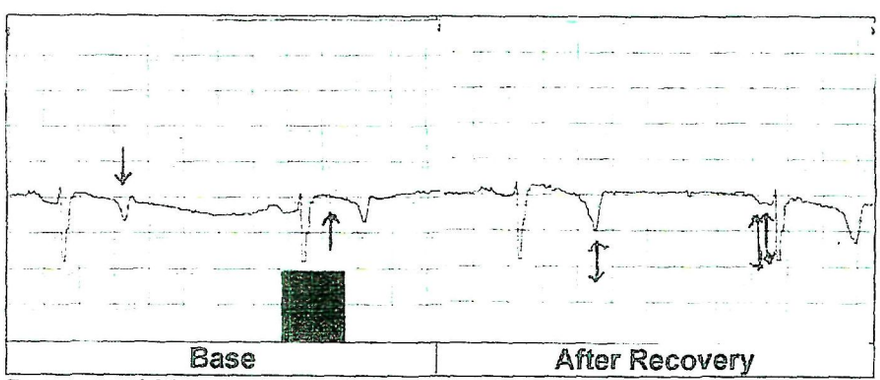
first and second degree atrio-ventricular block have been reported following detomidine or xylazine in horses Garcia et al. (2002). Sporadic ECG changes recorded in the present group are of no clinical relevance.

Fig 10 **Electrocardiogram of a Spiti Pony following detomidine-butorphanol-guaifenesin-ketamine anaesthesia showing different wave changes**



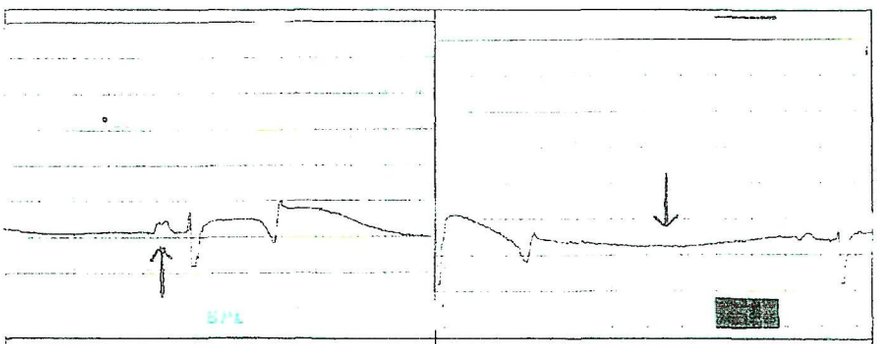
Paper speed 25mm/sec; 1mV=1cm;
↑Biphasic T wave; ↓Biphasic P wave: ↕PR segment depression

Fig 11 **Electrocardiogram of a Spiti Pony following detomidine-butorphanol-guaifenesin-ketamine anaesthesia showing biphasic T wave (↓) and ST segment elevation (↑) at base and and negative T wave (↕) and PR segment depression (↕↕)after recovery**



Paper speed 25mm/sec; 1mV=1cm;

Fig 12 Electrocardiogram of Spiti Ponies following detomidine-butorphanol-guaifenesin-ketamine anaesthesia showing Sinus block (↓) after recovery and notched P wave (↑) during anaesthesia



Paper speed 25mm/sec; 1mV=1cm;

4.2.6 BIOCHEMICAL STUDIES

The observations on different biochemical parameters following detomidine-butorphanol-guaifenesin-ketamine anaesthesia in spiti ponies are presented in Table 4 and figures 14 and 15. All the pre induction plasma samples of spiti ponies, evaluated for various biochemical parameters, were within normal range. There was highly significant ($P<0.01$) increase in the plasma ALT concentration during anaesthesia. As the values returned to the pre administration values, the possibilities of pathological changes in the liver could therefore, be ruled out. It corroborates with the findings of Koichev *et al.* (1988) and Kilic (2008). Significant ($p<0.05$) to highly significant ($p<0.01$) increase in total proteins was observed during anaesthesia and in post anaesthetic period, respectively, which might be attributed to the temporary inhibitory effect of these drugs on the renal blood flow. The plasma glucose was increased throughout the period of study following detomidine-butorphanol-guaifenesin-ketamine anaesthesia in spiti ponies but the changes were statistically non significant ($P>0.05$). Significant hyperglycemia has also been observed by Taylor *et al.* (2004) and Zager (2008) following the use of different anaesthetic protocols in equines. The hyperglycaemic observation was obvious in the present group because of presence of detomidine, an alpha$_2$ agonist sedative drug used in the combination. A non significant decrease in chloride, potassium, creatinine, AST and BUN concentration was also noticed during the anaesthetic

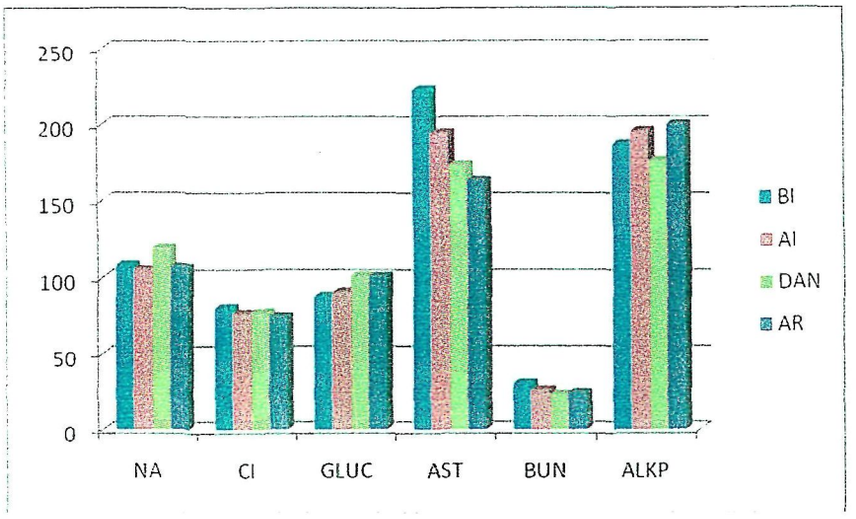
period. Contrarily Kilic (2008) reported a significant increase in plasma creatinine and BUN. However, all the biochemical changes observed in the present study were of temporary nature as they returned to normal levels during post anaesthetic period and therefore, were of no clinical importance.

Table 4: Biochemical effects following Detomidine-butorphanol-Guaifenesin-Ketamine anaesthesia in Spiti ponies (n=7)

Parameters (unit)	Before induction (BI)	After induction (AI)	During anaesthesia (DAn)	After recovery (AR)
Sodium (mEq/L)	108.47 ±8.75	105.15 ±4.45	119.25 ±8.62	107.09 ± 4.53
Potassium (mEq/L)	3.12 ±0.23	3.84 ±0.32	3.71 ±0.31	3.14 ± 0.37
Chloride (mEq/L)	80.41 ±4.85	76.49 ±2.97	77.16 ±3.70	74.33 ± 2.42
Glucose (mg/dl)	88.00 ±8.78	90.85 ±5.63	101.14 ±5.73	100.85 ± 8.35
Total proteins (g/dl)	8.25 ±0.44	**10.83* ±0.45**	10.12 ±0.40	**11.88** ± 1.06**
AST (U/L)	223.00 ±26.14	194.71 ±20.67	173.71 ±23.63	163.71 ± 23.75
ALT (U/L)	11.40 ±0.58	**17.84** ±1.18**	**18.64** ±0.70**	14.47 ± 1.26
ALKP(U/L)	187.00 ±6.06	195.86 ±8.28	176.28 ±4.99	200.14 ±11.58
BUN (mg/dl)	30.87 ±3.40	26.04 ±2.46	23.40 ±1.91	24.45 ± 2.47
Creatinine (mg/dl)	0.81 ±0.05	0.70 ±0.04	0.71 ±0.07	0.86 ± 0.14

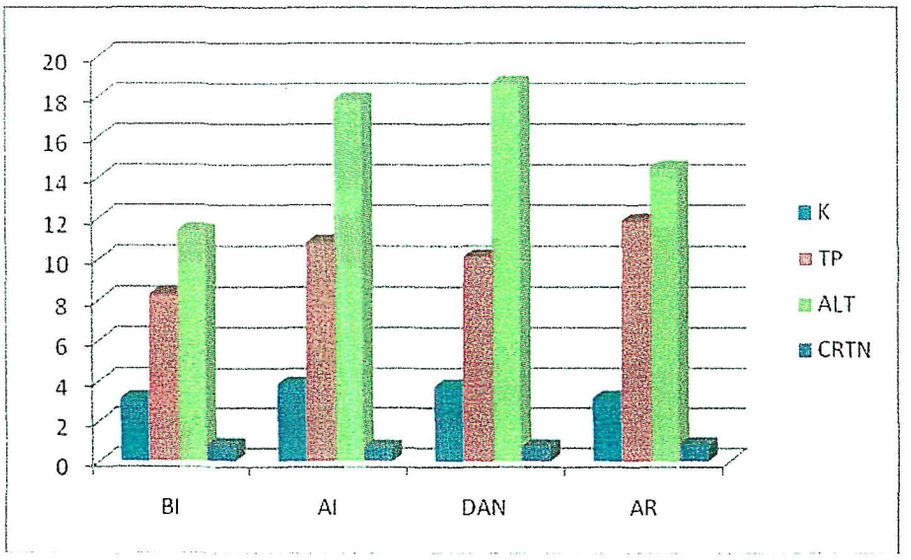
***P<0.05; **P<0.01**

Fig 14. Biochemical effects following Detomidine-butorphanol-Guaifenesin-Ketamine anaesthesia in Spiti ponies (n=7)

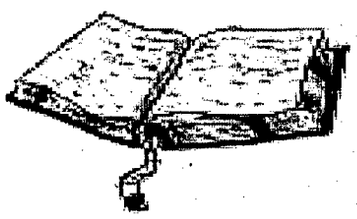


NA-sodium (mEq/L); Cl-Chloride (mEq/L); GLUC -Glucose (mg/dl); AST (U/L); BUN-blood urea nitrogen (mg/dl); ALKP (U/L); BI-Before induction; AI-After induction; DAN-During anaesthesia; AR- After recovery

Fig 15. Biochemical effects following Detomidine-butorphanol-Guaifenesin-Ketamine anaesthesia in Spiti ponies (n=7)



K-potassium (mEq/L); TP-Total proteins (g/dl); ALT (U/L); CRTN-Creatinine (mg/dl); BI-Before induction; AI-After induction; DAN-During anaesthesia; AR-After recovery



SUMMARY AND CONCLUSIONS

CHAPTER 5

SUMMARY AND CONCLUSIONS

Equines are presented to veterinary hospitals for variety of surgical interventions necessitating the use of general anaesthesia for management of these conditions. Total intravenous anaesthesia (TIVA) for short term surgeries in horses appears to be most practical solution for field conditions where availability of equipments for inhalant anaesthesia is a constraint.

The present study was conducted in 13 clinical cases of spiti ponies presented in the clinics of Dr. G.C. Negi College of Veterinary and Animal Sciences, Palampur and various field veterinary hospitals of Department of Animal Husbandry, Himachal Pradesh for castration. The ponies were randomly divided into two groups namely Group I (n=6; 4.27±1.63 years old; weighing 181.66±32.26kg) and Group II (n=7; 3.12±0.56 years old; weighing 170±11.34 kg). Tetanus prophylaxis was given. Animals were fasted overnight and water was withheld for 6- 8 hours. In Group I xylazine (1.1 mg/kg), butorphanol (0.02 mg/kg), guaifenesin 5% (20 mg/kg) and ketamine (2.2 mg/kg) and Group II detomidine (0.02mg/Kg), butorphanol (0.01 mg/kg), guaifenesin 5% (20 mg/kg) and ketamine (2.0 mg/kg) combinations were used for TIVA. Evaluation of anaesthesia was based on sedative, behavioral, clinical, hematological, cardiovascular and biochemical studies. The statistical analysis of data was done with Dunett's "t" test at 1 % and 5% level of significance.

In the animals of Group I onset of sedation following xylazine administration was recorded as 2.5±0.85min. The animals were ataxic at 1.0±0min following butorphanol and guaifenesin administration. The induction of surgical anaesthesia following ketamine administration was achieved in 2.66±0.66min. During recovery limb/head movement and sternal recumbency was attained in 18.0±3.21min and 28.56±2.23min, respectively. Standing ataxia and normal gait were seen at 32.16±3.20min and 48.83±3.99min, respectively. The TIVA combination used in the present group produced excellent to good muscle relaxation during anaesthesia. The surgical anaesthesia remained for 23.33±2.57min. Head shaking was observed during induction in two horses. Urination and neighing were a constant features during recovery period except in one horse. Defecation (one horse) and lacrimation (three horses) were observed.

The palpebral and corneal reflexes as well as swallowing reflex were suppressed after induction and during anaesthesia. The rectal temperature remained unaffected during the period of study whereas non significant decreases in heart rate and respiration rate was observed after induction and during anaesthesia. Capillary refill time (CRT) remained normal throughout the period of anaesthesia. The mean SpO2 value in equines of this group was 82.18±5.33 and 87±2.94% after induction and during anaesthesia, respectively. All the hematological parameters namely hemoglobin, PCV and TLC remained within normal range following the use of xylazine-butorphanol-guaifenesin-Ketamine combination for TIVA in spiti ponies. Biphasic T wave was a constant observation in all the horses before administration of any drug. After induction of anaesthesia, biphasic P wave, biphasic T wave, shortening of QRS segment and slight elevation of ST segment were recorded in all the animals. There was no indication of any type of heart block. There was highly significant ($P< 0.01$) increase in the plasma ALT values during anaesthesia. A significant ($P<0.05$) increase in plasma ALKP values was also noticed immediately after induction of anaesthesia. There was also an evidence of non significant ($P>0.05$) hyperglycemia throughout the period of study following induction of anaesthesia.

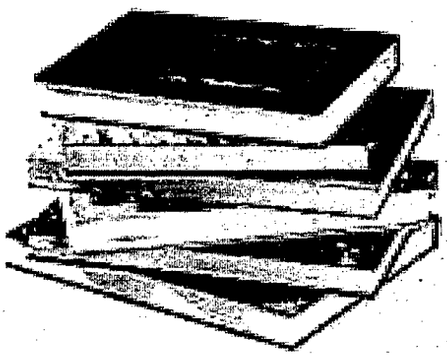
In Group II spiti ponies the onset of sedation was observed in 2.43±0.53min following detomidine administration. The horses were ataxic in 1.43±0.43min after the administration of butorphenol and guaifenesin when ketamine was injected intravenously to achieve surgical anaesthesia. All the horses were in surgical plane of anaesthesia within 2.28±0.42min following ketamine administration. During recovery the limb/head movement and sternal recumbency were attained in 18.71±1.98min and 26.14±1.62min, respectively whereas ataxia and normal gait were seen at 29.42±3.21min and 71.14±4.74min, respectively. Excellent to good muscle relaxation was noticed in all the spiti ponies throughout the period of study. The surgical anaesthesia remained for 22.57±1.48min following induction of anaesthesia. In all the animals recovery was smooth. Head shaking was observed during induction in two horses. Neighing was a constant feature during recovery period except in two horses. Dribbling of urine and lacrimation were seen in one horse each. Moderate to good suppression of palpebral and corneal reflexes were observed immediately after

induction and during anaesthesia. The swallowing reflex was markedly depressed in all the operated horses during the surgical plane of anaesthesia. The analgesia was excellent in all the animals of group II except in one pony where it was moderate. There was non significant decrease in rectal temperature and heart rate during the period of study whereas a highly significant ($P<0.01$) to significant ($P<0.05$) decrease in respiration rate was observed after induction, during anaesthesia and after recovery. Capillary refill time (CRT) remained normal throughout the period of anaesthesia. The mean SpO2 value in equines of this group was 76.50±4.14 and 83.33±4.18% after induction and during anaesthesia, respectively. The combination of detomidine, butorphanol, guaifenesin and ketamine for TIVA in horses did not produce any significant change in various hematological parameters during the period of study. In general biphasic T wave and biphasic P wave were observed in all the ponies before anaesthesia. Following induction of anaesthesia the ECG recordings depicted biphasic T wave, biphasic P wave, and slight elevation of ST segment in all the horses. PR segment depression and notched P wave were also observed in one horse each, respectively which remained so in the post anaesthetic period. Sinus block was recorded in one horse during recovery period. A highly significant ($P<0.01$) increase in the plasma ALT activity was noticed during anaesthesia along with significant ($P<0.05$) to highly significant ($P<0.01$) increase in total proteins concentrations, observed during anaesthesia and in post anaesthetic period, respectively. The plasma glucose level increased throughout the period of study but the changes were statistically non significant ($P>0.05$).

CONCLUSIONS

1. Xylazine (1.1mg/kg), butorphanol (0.02mg/kg), guaifenesin 5% (20mg/kg) and ketamine (2.2mg/kg) combination in ***Group I*** as well as detomidine (0.02mg/kg), butorphanol (0.01mg/kg), guaifenesin 5% (20mg/kg) and ketamine (2.0mg/kg) combination in ***Group II*** were able to induce short term surgical anaesthesia for 23.33±2.57min and 22.57±1.48min, respectively, in spiti ponies. Maintenance of anaesthesia was required only in 2 ponies of group I.
2. The quality of anaesthesia was better in group II with prolonged sedation, excellent muscle relaxation and analgesia.

3. The respiration rate decreased in both the groups but was significant only in Group II animals which resulted in simultaneous fall in SpO2 values.
4. Biochemical attributes were within physiological limits in both the groups except a significant increase in ALT (both groups) and total proteins (Group II) values during anaesthesia. The values returned to normal during recovery ruling out any renal or hepatic toxicity.
5. Biphasic P wave, biphasic T wave and depressed PR segment were common electrocardiographic findings in both the groups. Occasionally, negative T wave, notched P wave and sinus block were noticed. The observations were of no clinical importance since such ECG findings are usually present in equines.
6. It is recommended that the anaesthetic combinations xylazine-butorphanol-guaifenesin-ketamine and detomidine-butorphanol-guaifenesin-ketamine can safely be used for short term total intravenous anaesthesia (TIVA) in equines under field conditions.



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Brief Biodata of the Student

Name: Bhanu Pratap Singh Thakur
Father's Name: Sh. Manohar Thakur
Mother's Name: Smt Sarojana Thakur
Date of Birth: 16.04.1982
Permanent Address: V.P.O. Jahal, Tehsil Chachiot, Distt. Mandi, H.P 175039
Academic Qualifications: (Starting with 10th class)

Qualification	Month	Year	School/Board/University	Marks (%)	Division
10th Class	March	1998	H.P.B.S.E	72.14	First
12th Class	March	2000	H.P.B.S.E	64.25	First
B.V.Sc.	July	2008	CSKHPKV, Palampur	62.80	First
M.V.Sc.	July	2010	CSKHPKV, Palampur	72.70	First

Fellowships/Scholarships/Gold Medals/Awards/Any Other Distinction: Nil

Publications:

Total: Nil

Research papers (in peered journals): - Nil
Scientific Popular Articles: - Nil
Others: Nil

Visits abroad along with duration and purpose of visit: Nil