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Clinical Evaluation of Detomidine-Butorphanol-Guaifenesin-Ketamine as Short Term TIVA in Spiti Ponies

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Abstract: Veterinarians working under remote field conditions are routinely presented with variety of surgical interventions in equines like castrations, management of wound, traumatic and congenital hernias and musculoskeletal disorders thus necessitating the use of general anaesthesia for management of these conditions. The present study was carried out to evaluate and recommend the suitable short term anaesthetic technique for Spiti ponies under field conditions. Seven clinically healthy male Spiti ponies presented for castration were evaluated for short term Total Intravenous Anaesthesia (TIVA) using detomidine (0.02 mg kg^{-1}), butorphanol (0.01 mg kg^{-1}), 5% guaifenesin (20 mg kg^{-1}) and ketamine (2.0 mg kg^{-1}). The studies conducted were open label trials and all the animals received same treatment. After proper tetanus prophylaxis and preanesthetic fasting, detomidine was administered intravenously. Subsequently at head down position the animals received butorphanol intravenously. Thereafter, guaifenesin was administered intravenously. As soon as the signs of ataxia developed, the induction of surgical anaesthesia was achieved by intravenous administration of ketamine hydrochloride. The onset of sedation was observed in 2.43±0.53 min following detomidine administration and the animals were ataxic in 1.43±0.43 min after butorphanol and guaifenesin administration when ketamine was injected. The ponies were in surgical plane of anaesthesia within 2.28±0.42 min following ketamine administration. During recovery the limb/head movement and sternal recumbency were attained in 18.71±1.98 and 26.14±1.62 min, respectively whereas standing ataxia and normal gait were seen at 29.42±3.21 and 71.14±4.74 min, respectively. There was excellent to good muscle relaxation. The surgical anaesthesia remained for 22.57±1.48 min. The recovery was smooth. Moderate to good suppression of palpebral and corneal reflexes were observed immediately after induction and during anaesthesia. The analgesia was excellent. A highly significant ($p<0.01$) to significant ($p<0.05$) decrease in respiration rate was observed after induction, during anaesthesia and after recovery. The mean SpO_2 value in equines of this group was 76.50±4.14 and 83.33±4.18% after induction and during anaesthesia, respectively. Some of the blood biochemical parameters like plasma alanine amino transferase (ALT), total proteins and glucose showed significant increase without clinical consequence. It was concluded that detomidine (0.02 mg kg^{-1}), butorphanol (0.01 mg kg^{-1}), guaifenesin 5% (20 mg kg^{-1}) and ketamine (2.0 mg kg^{-1}) combination can safely be used for short term total intravenous anaesthesia in equines under field conditions where the monitoring facilities are meager.

Key words: Equine anaesthesia, total intravenous anaesthesia, detomidine, guaifenesin, ketamine, butorphanol

INTRODUCTION

High altitude equines form the backbone of the economy of people of tribal areas of Himachal Pradesh with tremendous potential for tourism industry (Chauhan and Dogra, 2005), in spite of modernization, people have adopted equine rearing as their major avocation for employment and income generation. It has been reported that intravenous anaesthesia is associated with lower incidence of perioperative cardiovascular emergencies and lower anesthetic risk (Johnston *et al*., 2002). Therefore, it can be successfully used as an alternative to inhalation anaesthesia in animals (Bettschart-Wolfensberger *et al*., 1996; Nolan *et al*., 1996; Flaherty *et al*., 1997; Taylor *et al*., 1995, 1998). 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

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anaesthesia is a constraint. Spiti ponies, the high altitude equines, thrive under cold arid conditions, where extreme cold temperature and low atmospheric oxygen are considerable factors from anaesthesia point of view (Thakur *et al*., 2011).

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". 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 alpha 2 agonist drugs are better, ever over that of opioids. Detomidine effects are more pronounced than those of Xylazine due to its higher affinity to alpha-2 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.

The use of Total Intravenous Anaesthesia (TIVA) helps in reducing a variety of preanaesthetic, anaesthetic and post anaesthetic problems such as arrhythmias, hypotension, respiratory or ventilatory insufficiency etc. (Garcia *et al*., 2002). Good sedation with optimal muscle relaxation has been reported following xylazine (Singh *et al*., 1996), chloral hydrate (Singh *et al*., 1997) or detomidine (Singh *et al*., 2000) administration in Spiti ponies. Sharma *et al*. (1999) reported reversal of detomidine induced sedative effects by atipamezole in spiti ponies. Therefore, the present study was carried out to evaluate analgo-clinical, cardiovascular and haemato-biochemical changes of detomidine-butorphanol-guaifenesin-ketamine combination as TIVA for castration in Spiti ponies.

MATERIALS AND METHODS

The present study was carried out in 7 clinically healthy male Spiti ponies from different parts of Himachal Pradesh, India, 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 Himachal Pradesh, India during the period from February to May, 2010. After proper tetanus prophylaxis, the ponies were fasted overnight and water was withheld for 6-8 h. The horses anaesthetized were 4.27±1.63 years of age and weighing 150 to 222 kg with the mean of 181.66±32.26 kg. Detomidine (Domitor, Orion Farma Ltd., Finland) at 0.02 mg kg^{-1} was administered intravenously in all the animals. Subsequently at head down position the animals received butorphanol (Butrum (2 mg mL^{-1}) Aristo Pharmaceuticals Pvt. Ltd; Mumbai.) at the dose rate of 0.01 mg kg^{-1}, intravenously. Thereafter, 5% guaifenesin (Guaifenesin IP Prudential Pharmaceuticals Ltd; Andhra Pradesh, India) at 20 mg kg^{-1} was administered intravenously in the horses. As soon as the signs of ataxia developed, the induction of surgical anaesthesia was achieved by intravenous administration of ketamine hydrochloride (Ketamil-100™ injection (100 mg mL^{-1}), ILIUM, Troy Laboratories, Australia) at the rate of 2.0 mg kg^{-1}. During induction the horses were properly restrained to prevent forward fall. After induction, the horses were left undisturbed for one minute 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.

The anaesthetic parameters recorded during each experiment were, time for sedation/ataxia, time for induction, duration of anaesthesia and recovery time. The depth of anaesthesia (light or deep) was analyzed by recording different reflexes (palpebral, corneal, photopupillary and swallowing), extent of muscle relaxation (relaxation of neck, jaws, tail and anal sphincter) and analgesia (using pin prick method to test the response to noxious stimuli on the coronary band of the front and hind limbs, the shoulders and the gaskin). 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. A score ranging from 1 to 5, as per method of Ringer *et al*. (2007), was used for assessment of quality of recovery from anaesthesia. The clinical parameters like heart rate, respiratory rate and rectal temperature Respiration rate was recorded by observing costo-abdominal movements manually and by vital signs monitor (Multi Para Monitor-Execello BPL, Bangalore, India), heart rate by auscultation and vital sign monitor, gingival perfusion time and SpO_2 by tongue transducer attached to vital sign monitor. Electrocardiograms (ECG) were also recorded using bipolar base apex lead system. The calibrations made were conduction 1 mV = 1 cm and paper speed of 25 mm sec^{-1}. The electrocardiograms were analyzed for various conduction abnormalities if any. All the observations were made Before Induction (BI), After Induction (AI), during anaesthesia (Dan-15 min after induction) and After Recovery (AR).

The venous blood from jugular vein was collected at different time intervals as mentioned above for monitoring of haemoglobin, packed cell volume and total leukocyte count using blood cell counter (BC-2800 vet-Auto hematology analyzer-Mindray, China) and various biochemical parameters namely blood glucose, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, chloride, total proteins, blood urea nitrogen and creatinine using commercially available kits on computerized semi automatic blood analyzer (RA-50 Chemistry Analyzer, Bayer Diagnostics, Baroda, Gujarat, India). Estimation of sodium and potassium was done by flame photometry.

Statistical analysis: Data was expressed as Mean±SEM and statistical analysis was carried out by one-way ANOVA with post hoc Dunnett's test performed using GraphPad InStat. The p-value was considered significant when $p<0.05$ and highly significant when $p<0.01$.

RESULTS

In the present study the combination of detomidine (0.02 mg kg^{-1} IV), butorphanol (0.01 mg kg^{-1} IV), guaifenesin 5% (20 mg kg^{-1} IV) and ketamine (2 mg kg^{-1} IV) were used for Total Intravenous Anaesthesia (TIVA) to carry out castration in Spiti ponies. The onset of sedation was observed in 2.43±0.53 min following detomidine administration. The ponies were ataxic in 1.43±0.43 min after the administration of butorphanol and guaifenesin when ketamine was administered to achieve surgical anaesthesia. All the horses were in surgical plane of anaesthesia within 2.28±0.42 min. During recovery the limb/head movement and sternal recumbency were attained in 18.71±1.98 and 26.14±1.62 min, respectively whereas standing ataxia and normal gait were seen at 29.42±3.21 and 71.14±4.74 min, respectively.

In the present study all of the Spiti ponies had excellent recoveries. Neighing was a constant feature during recovery period except in two horses. The dribbling of urine and lacrimation were noticed in one horse each.

There was moderate to good suppression of palpebral and corneal reflexes immediately after induction and during anaesthesia in Spiti ponies. 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. The TIVA combination used in the present study produced excellent to good muscle relaxation in all the Spiti ponies as evidenced by relaxation of jaw, neck, tail and anal sphincter. The loss of anal tone was noticed initially after induction and was last to return to normal during recovery. There was excellent analgesia for 22.57±1.48 min in the present study and the surgery was facile.

There was a 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 (15.57±1.60), during anaesthesia (19.71±1.14) and after recovery (19.57±2.18) (Table 1).

Capillary Refill Time (CRT) remained normal throughout the period of anaesthesia in Spiti ponies. The mean SpO2 value in ponies recorded were 76.50±4.14 and 83.33±4.18 percent after induction and during anaesthesia.

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 1).

In general biphasic T wave and biphasic P wave were observed in all the ponies before and during anaesthesia (Fig. 1). PR segment depression (Fig. 1) and notched P wave Fig. 2) 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 (Fig. 2) was recorded.

All the pre induction plasma samples of Spiti ponies, evaluated for various biochemical parameters, were within normal range.

There was highly significant ($p<0.01$; 18.64±0.70) increase in the plasma ALT concentration during anesthesia. Significant ($p<0.05$) to highly significant ($p<0.01$) increase in total proteins ($p<0.01$) was observed after induction (10.83±0.45) and in post anaesthetic period (11.88±1.06), respectively. The plasma glucose was increased throughout the period of study but the changes were statistically non significant ($p>0.05$) (Table 2).

A non significant decrease in chloride, potassium, creatinine, AST and BUN concentration was also noticed during the anaesthetic period. However, all the biochemical changes observed in the present study were of temporary nature as they returned to normal during post anaesthetic period.

Table 1: Clinical and haematological effects following detomidine-butorphanol-guaifenesin-ketamine anaesthesia in Spiti ponies (n = 7)

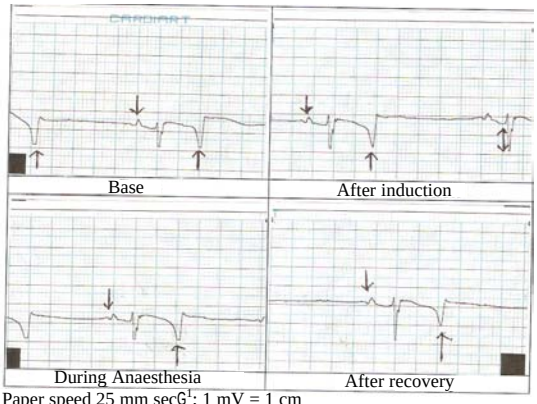
Parameters (unit)	Before induction (BI)	After induction (AI)	During anaesthesia (Dan)	After recovery (AR)
Rectal temp (°F)	100.00±0.31	99.55±0.25	99.37±0.26	98.90±0.27
Heart rate (per min)	49.71±2.44	40.85±6.37	47.42±7.07	44.71±4.24
Respiratory rate (per min)	28.57±3.31	15.57±1.60**	19.71±1.14*	19.57±2.18*
Hb (g dL^{-1})	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

*$p<0.05$; **$p<0.01$

Table 2: Biochemical effects following Detomidine-butorphanol-Guaifenesin-Ketamine anaesthesia in Spiti ponies (n = 7)

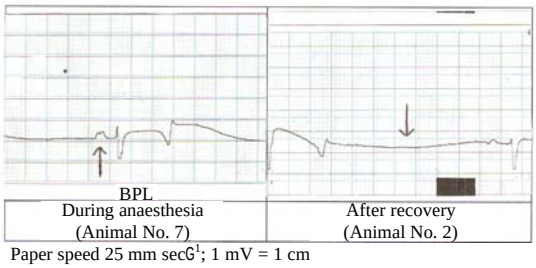
Parameters (unit)	Before induction (BI)	After induction (AI)	During anaesthesia (DAn)	After recovery (AR)
Sodium (mEq L^{-1})	108.47±8.75	105.15±4.45	119.25±8.62	107.09±4.53
Potassium (mEq L^{-1})	3.12±0.23	3.84±0.32	3.71±0.31	3.14±0.37
Chloride (mEq L^{-1})	80.41±4.85	76.49±2.97	77.16±3.70	74.33±2.42
Glucose (mg dL^{-1})	88.00±8.78	90.85±5.63	101.14±5.73	100.85±8.35
Total proteins (g dL^{-1})	8.25±0.44	10.83±0.45*	10.12±0.40	11.88±1.06**
AST (U L^{-1})	223.00±26.14	194.71±20.67	173.71±23.63	163.71±23.75
ALT (U L^{-1})	11.40±0.58	17.84±1.18**	18.64±0.70**	14.47±1.26
ALKP (U L^{-1})	187.00±6.06	195.86±8.28	176.28±4.99	200.14±11.58
BUN (mg dL^{-1})	30.87±3.40	26.04±2.46	23.40±1.91	24.45±2.47
Creatinine (mg dL^{-1})	0.81±0.05	0.70±0.04	0.71±0.07	0.86±0.14

*p<0.05; **p<0.01



Paper speed 25 mm $secG^{1}$; 1 mV = 1 cm
↑Biphasic T wave; ↓Biphasic P wave: ↕ PR segment depression

Fig. 1: Electrocardiogram of a Spiti pony following detomidine-butorphanol-guaifenesin-ketamine anaesthesia showing different wave changes



Paper speed 25 mm $secG^{1}$; 1 mV = 1 cm

Fig. 2: ECG of Spiti ponies following detomidine-butorphanol-guaifenesin-ketamine anaesthesia showing notched P wave (↑) and Sinus block (↓)

DISCUSSION

The dosages of detomidine used in the present study are well documented in literature (Taylor *et al*., 1995; Taylor *et al*., 1998). Detomidine plus ketamine and detomidine plus guaifenesin and ketamine have been used for induction and maintenance of anaesthesia in ponies. The blood pressure and cardiac index are well maintained during this anaesthetic combination in comparison to inhalant anaesthesia (Mama, 2000). Detomidine is used as it is more potent than xylazine in both behavioral and neurochemical effects (Atasoy *et al*., 2009). Addition of guaifenesin helps to achieve desirable effects (analgesia, unconsciousness and muscle relaxation) associated with general anaesthesia (Muir *et al*., 1977). Butorphanol, an agonist-antagonist opioid, was used for profound sedation and surgical analgesia because the use of only agonist opioid induces different excitement states during anaesthesia in horses (Garcia *et al*., 2002).

There was optimal sedation in the present study and duration of surgical anaesthesia was good enough to carry out castration in Spiti ponies. Sedation is conceivably the result of activation of central alpha-2 adrenoreceptors which causes a decrease in release and turnover of norepinephrine in CNS (Kinjavdekar *et al*., 1999). Ketamine hydrochloride exerts its effect on CNS during induction and produces functional and electrophysiological dissociation of thalamocortical areas from limbic and other subcortical structures in the brain; as a result consciousness is lost (Staffieri and Driessen, 2007). In the present study all of the Spiti ponies had excellent recoveries. In general, horses induced anaesthesia with xylazine and ketamine experience smooth recoveries characterized by a roll to sternal recumbency and a single attempt to stand (Aubin and Mama, 2002). The dribbling of urine in one horse can be attributed to the combination used which has been reported to induce diuresis in equines (Garcia *et al*., 2002) as a result of alpha-2 adrenoreceptor agonism in kidneys.

Eye evaluation, which is usually used to judge the depth of anaesthesia, is of limited value following administration of ketamine because of the responses like voluntary blinking, nystagmus (Bertone and Horspool, 2004) and lacrimation. Therefore different changes in ocular reflexes observed in the present study are of little clinical significance.

The muscle relaxation observed in the current study is largely 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 excellent analgesia observed could be attributed to the detomidine induced stimulation of alpha-2 adrenoreceptors in CNS which inhibits release of neurotransmitter and decrease neuronal activity resulting in loss of pain reflexes (Kinjavdekar *et al*., 1999). Also, the analgesia produced can also be due to ketamine induced block of conduction of pain impulses to the thalamic and cortical areas (Booth, 1977).

The decrease in respiration rate could be due to direct depressant effect alpha-2 agonist on CNS in general and respiratory centre in particular (Kinjavdekar *et al*., 1999). The low SpO_2 values could be due to some drop in oxygenation commonly seen in horses under general anaesthesia and recumbent position. Assumption of lateral recumbency is associated with the development of ventilation-perfusion mismatches and the shunting of blood through the lungs resulting in less than optimal oxygenation (Hubbell, 1999). Also, it could be due to the low atmospheric oxygen since the anaesthetic trials were conducted at high altitude.

Non significant change in rectal temperature indicates that this drug combination does not induce depression of thermoregulatory centers and does not reduces BMR and muscle activity. Robertson and Muir (1983) reported no significant effect of this combination on heart rate whereas marked bradyarrhythmia with decreased heart rate were recorded by Wagner *et al*. (1991) and Taylor *et al*. (1995). Similar findings were observed in the present study.

All the ECG changes recorded in this study represent normal impulse conduction and hence are of no clinical relevance. Occasional conduction abnormalities seen during anaesthesia in different Spiti ponies are likely a consequence of detomidine used in the present study. 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).

As regards the alteration in the concentration of plasma ALT, it is pertinent to mention that as the values returned to the pre administration baseline values, the possibilities of pathological changes in the liver could therefore, be ruled out. It corroborates with the findings of Koichdev *et al*. (1988) and Kilic (2008). Significant hyperglycemia has also been observed by Taylor *et al*. (1995) and Zager (1984) 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. Contrarily Kilic (2008) reported a significant increase in plasma creatinine and BUN and therefore, were of no clinical importance.

CONCLUSIONS

It was concluded that detomidine (0.02 mg kg^{-1}), butorphanol (0.01 mg kg^{-1}), guaifenesin 5% (20 mg kg^{-1}) and ketamine (2.0 mg kg^{-1}) combination can safely be used for short term total intravenous anaesthesia in equines under field conditions where the monitoring facilities are meager. The respiration rate decreased with sporadic ECG conduction abnormalities but the observations were of no clinical importance since such findings are usually present in equines. The combination produces minimal side effects without any hepatic or renal toxicity.

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