Statistical Evaluation of Acepromazine and Midazolam as Preanaesthetics to Ketamine in Yak

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KEY WORDS: Acepromazine, Midazolam, Preanaesthetics, Ketamine, Yak

ABSTRACT

The study was conducted to study the anaesthetic effects of acepromazine, midazolam, and ketamine in yak. Twelve clinically healthy yaks of either sex and below 2 years of age from yak farm of ICAR- National Research Centre on Yak, Dirang, Arunachal Pradesh were selected for the study. Yak were randomly divided into two groups, Group AK and Group MK, i.e., six animals in each group. The animals in Group AK received acepromazine @0.1mg/kg body weight IM followed by ketamine @2.5mg/kg body weight IM after 15 minute and the animals in Group MK received midazolam @0.5mg/kg body weight IM followed by ketamine @2.5mg/kg body weight IM after 15 minutes. The weak time, duration of analgesia, and recovery times were recorded in all of the animals after administration of anaesthetic agents. Venous blood samples were collected and the physiological, cardiopulmonary, and haemato-biochemical parameters were monitored at 0 (baseline) and at 15, 30, 60, and 90 minutes after the administration of anaesthetic agents. In AK group and MK group, the weak times were 5.33±1.25 and 7.83±1.70 minutes, duration of analgesia 45.00±0.12 and 22.00±0.17 minutes, and recovery times were 84.83±9.19 and 46.16±1.83 minutes respectively. The duration and recovery times were significantly shorter in the MK group, although there were no significant differences in weak time between the groups. There was a significant decrease in heart rate, systolic pressure, and diastolic pressure in AK group. However, the values remained within normal physiological limit. The changes in heart rate, systolic pressure, and diastolic pressure were not significant in MK group. The changes in haemato-biochemical parameters remained within the normal physiological

limit in both the groups. Based on the findings, both the anaesthetic combinations were found safe to be used in yak.

INTRODUCTION

Yak (Poephagus grunniens) is a unique bovine species of economic importance in hill and snow bound areas, and had originated from the cold region of Tibet. Yak is the only hairy multipurpose bovid and a unique genetic resource with amazing ability to survive, reproduce, and provide marketable products to the highlanders. Traditionally, yaks are reared under free-ranged system in the high hills where the air, water, and pasture are free from pollution, and their products are organic and natural. In India, yak is mostly reared in Jammu & Kashmir, Himachal Pradesh, Sikkim, west Bengal, Uttarakhand, and Arunachal Pradesh. In Arunachal Pradesh, though the population of yak is very less in comparison to total livestock population, it still commands importance in life of the nomadic people in the mountainous regions of Tawang and West Kameng districts.

Many diseases are encountered requiring treatment or surgical intervention in yak. Keeping in view of the economic losses to farmers, it is essential to restore the structural and functional continuity of the animal (Kumar et al., 2004). Hence, anaesthetising a large ruminant is a challenge and a wide scope of research exists with a quest to search for more safe and effective general anaesthetic techniques for ruminants (Malik et al., 2011).So, keeping in view of these, the present study was done to investigate the safety of using the combination and statistical evaluation of acepromazine, midazolam, and ketamine in yak.

Acepromazine (2-acetyl-10-(3-dimethylaminopropyl) phenothiazine) is a tranquilizer and anaesthetic premedication used in veterinary anaesthesia while Midazolam(8-chloro-6(2-flurophenol)-1-methyl-4H imidazo (1,5-a) (1,4)) is a medication used for anesthesia, procedural sedation, trouble sleeping, and severe agitation. Moreover Ketamin is usually used for starting and maintaining anesthesia.

MATERIALS AND METHODS

The study was conducted at yak farm of ICAR-National Research Centre on Yak, situated at Nyukmadung, Dirang, Arunachal Pradesh at an altitude of 2,800 m above msl during February-March, 2016. The ambient temperature during study ranged between -2 ^{0}C to 15^{0}C, with an average of 8-11 ^{0}C during the day time. Twelve clinically healthy yaks of either sex and below 2 years of age were selected and randomly divided into two groups, Group AK and group MK with six animals each. The yaks were randomly divided into two groups viz. Group AK and Group MK comprising six yaks in each group. Group AK was treated with acepromazine @ 0.1mg per kg body weight IM followed by ketamine @ 2.5mg per kg bodyweight after 15 minutes. Group MK was treated with midazolam @ 0.5mg per kg body weight IM followed by ketamine @2.5mg per kg bodyweight after 15 minutes. Blood samples were collected from the jugular vein in sterilized vials prior to injection of preanaesthetic at 0 minute (baseline) and at 15, 30, 60, and 90 minutes after administration of the anaesthetic agent.

All animals were evaluated for physiological parameters before and after the administration of the anaesthetic agents. Recording of the cardiopulmonary parameters were done by non-invasive method using an automatic multiparameter monitor (Omron Healthcare BP monitor). The haematological parameters were estimated as per the standard methods. The estimation of haemoglobin was done by Sahli's Acid Haematin method and was expressed in gm percentage. The PCV was estimated by microhaematocrit method and expressed in percentage. The TEC was estimated under a haemocytometer and was expressed in million/mm.^{3} The TLC was estimated under a hemocytometer and was expressed in thousand/mm.^{3} The biochemical estimations were done in Spectrophotometer, Model No-Tcc-2404. The data was analysed by using t-test between the groups.

Table 1. *Effects of Anaesthetic Treatments on Weak Time, Inductions Behaviour, Duration of Analgesia and Recovery Time at Different Time Intervals in Yaks*

Group	Weak time (min)	Induction behaviour		Duration of analgesia (min)	Recovery Time (min)
		Staggering (min)	Grunting (min)		
AK	5.33±1.25	7.00±5.88	7.20±4.78	45.00±0.12	84.83±9.19A
MK	7.83±1.70	8.00±3.54	8.13±2.07	22.00±0.17	46.16±1.83B
Significance	NS	NS	NS	NS	**

NS,Non-significant,
**, Significant at 0.05 level of probability*
***, Significant at 0.01 level of probability*

RESULT AND DISCUSION

Clinical Parameters

Weak Time

The weak time recorded in Table 1 showed a non-significant variation between the groups. The signs of sedation were exhibited by yaks within 5 to 7 minutes regardless of the sedative used in both the groups. The signs observed during weak time were head drooping, heavy upper eyelid, ataxia, and reduced tail movement with a marked decrease in spontaneous activity in both the groups. However, the signs were more pronounced in Group AK. Similar observations were observed by Ahmed et al. (2010) in deer where calming effect shortly occurred 8.5 minutes with acepromazine-ketamine administration and by Stegmann (1998) in goat within 5 minutes with midazolam-ketamine.

Induction Behaviour

Non significant variations in induction behaviour between the groups were observed in Table 1. Induction behaviour such as grunting and staggering were recorded among the animals in both the groups, salivation and urination were not observed in all the animals except in one in Group AK. In both the groups, the animal atained sternal recumbency following induction with ketamine. Similar observations were also reported by Sharma et al. (2001) and Baishya (2010).

Duration of Analgesia

The duration of analgesia was significantly longer ($P<0.01$) in AK group than in MK group. In group AK, the analgesia was moderate as compared to the MK group. The findings of the study concurred with the observations reported by Ahmed et al. (2010), Kumar et al. (2014), and Al-Redah et al., (2011). Shorter duration of analgesia in Group MK might be due to the rapid recovery seen in the animals owing to shorter half-life of midazolam (Vree et al. 1981). Ketamine exerts its action on N-methyl-D-aspartate (NMDA) receptor. NMDA has been found to mediate central sensitization, which appears to be an important factor in chronic pain and might possibly explain ketamine's analgesic properties (Adeola, 2007). Kohrs and Durieux (1998) also reported that the analgesia was mediated by anatagonistic effects of ketamine on N-methyl-D-aspartate receptors. The mean±SE values of duration of analgesia have been shown in Table 1 and scoring of quality of analgesia in Table 2.

Depth of Anaesthesia

In Group AK, the pedal, palpebral, corneal, and auditory reflexes were absent till 45 minutes after induction with ketamine. In Group MK, the reflexes were absent up to 22 minutes, and the reflexes regained towards the end of observation in both the groups (Table 3).The findings were similar to the observations reported by Ahmed et al. (2010) and Kumar etal., (2014).

Recovery Time

Table 1 it shows that the animals in Group MK showed significantly shorter recovery time than in Group AK. The shorter recovery time in MK group might be due to the

Table 2. *Scoring of Quality of Analgesia*

Score	Quality	Quality of analgesia							
		AK				MK			
		Time (minutes)				Time (minutes)			
		15	30	60	90	15	30	60	90
0	Excellent	0	0	0	0	0	6*	0	0
1	Good	0	0	0	0	2*	0	0	0
2	Moderate	6*	6*	6*	0	4*	0	0	0
3	Poor	0	0	0	0	0	0	0	0

**number of animals*

action of midazolam. Midazolam has shorter duration of action with rapid elimination half-life and total body clearance (Greene, 2002). Kaur and Singh (2004) also observed early restoration of vital reflexes and quick recovery after midazolam followed by ketamine and thiopentone in bovines. In Group AK, longer recovery time could be attributed to its excellent sedative property that persists for several hours, as opined by Lemke (2007). It was also reported by Baniadam et al. (2007) that acepromazine increases the degree and duration of muscle relaxation and prevents reflex movements of the limbs.

PHYSIOLOGICAL PARAMETERS

Heart Rate (HR)

From Table 4 it was depicted that, in Group AK, the heart rate decreased significantly ($p<0.05$) up to 30 minute (63.66±3.80) and increased gradually towards pre- induction levels at 90 minutes. In Group MK, there was a non-significant decrease in heart rate at 15 minutes, which returned gradually towards the pre-induction level till the end of study period. However, the changes were statistically non-significant between the groups, and the values were within the physiological limit. Decreased heart rate was also reported by Kumaret al. (2014), with midazolam and ketamine in buffalo calves. The decrease in heart rate in Group AK could be attributed to direct adrenergic blocking effect of acepromazine in the heart or some sort of centrally mediated action. While decrease in heart rate in Group MK might be due to midazolam as it decreases, myocardial contractibility by direct action and by attenuating the catecholamine response to hypotensive state (Glisson et al. 1982).

Respiratory Rate (RR)In Group MK, the

Table 3. *Scoring of Reflexes*

Reflexes	Groups	0 min	15 min	30 min	60 min	90 min
Corneal	AK	+	-	-	-	+
	MK	+	-	-	+	+
Palpebral	AK	+	-	-	-	+
	MK	+	-	-	+	+
Pedal	AK	+	-	-	-	+
	MK	+	-	-	+	+
Auditory	AK	+	-	-	-	+
	MK	+	-	-	+	+

Absent= - , Present= +

respiratory rate increased at 15 minutes (23.50±2.44). Thereafter, it gradually decreased with minor changes towards the end of study period. However, the changes were statistically non-significant, and the values were within the physiological limit. The slight reduction in respiratory rate during the peak period of sedation might be attributed to the reason that sedated animals may breathe slowly, although clinical doses of acepromazine have little effect on respiration (Parry et al. 1982). There was an initial non-significant increase in respiratory rate followed by gradual decrease in MK group. The initial increase in respiratory rate in Group MK may be due to the mild respiratory depression caused by ketamine which is manifested by an increased rate that does not compensate for a decreased tidal volume (Hall et al., 2001), as midazolam causes respiratory depression (Greene, 2002).

Rectal Temperature (RT)

In Group AK, the rectal temperature decreased non-significantly untill 60 minute mark. In Group MK, there was no change in the rectal temperature. However, all the values were within the physiological limit. The slight decrease in the rectal temperature in Group AK might be due to depression of the thermoregulatory centre in the hypothalamus coupled with dilation of cutaneous blood vessels by acepromazine. All of the phenothiazine derivatives caused dialatation of cutaneous vessels and affected thermoregulatory mechanisms. Moreover, there was no change in rectal temperature in the MK group. Similar observation was made by Al- Redah (2011) after administration of midazolam in sheep.

Table 4. *Effects of Anaesthetic Treatmentson Heart Rate (HR), Respiratory Rate (RR) and Rectal Temperature (RT) at Different Time Intervals in Yaks*

Parameter	Heart Rate(beats/min)		Sig	Respiratory rate (breaths/min)		Sig	Rectal Temperature (^{0}c)		Sig
Group	AK	MK		AK	MK		AK	MK	
0 min Mean± SE	76.66^a±2.33	74.13±4.94	NS	21.33±3.36	19.33±1.74	NS	39.11±0.13	39.05±0.14	NS
15 min Mean± SE	68.50^b±9.12	69.84±7.81	NS	19.66±3.11	23.50±2.44	NS	38.97±0.12	39.04±0.29	NS
30 min Mean± SE	63.66^c±3.80	71.50±8.99	NS	17.83±5.14	22.66±5.38	NS	38.80±0.11	39.02±0.14	NS
60 min Mean± SE	67.33^b±3.07	73.16±16.72	NS	20.34±4.57	20.16±2.41	NS	38.42±0.19	39.02±2.24	NS
90 min Mean± SE	73.16^a±8.42	72.33±5.97	NS	20.33±3.42	21.50±1.45	NS	38.53±0.22	39.01±0.35	NS
Significance	*			NS	NS		NS	NS	

NS,Non-significant,
**, Significant at 0.05 level of probability*
***, Significant at 0.01 level of probability*

CARDIOPULMONARY PARAMETERS

Systolic Pressure

Table 5 revealed that there was significant decrease in systolic pressure untill 30 minutes in the AK group. A non-significant decrease in systolic pressure was also observed in MK group at 15 minutes. The decrease in systolic pressure might be attributed to a negative inotropic effect or adecrease in preload and arterial vasodilatation (Nain et al., 1988). Kumar et al. (2004) reported

Table 5. Effects of Anaesthetic Treatments on Systolic Pressure, Diastolic Pressure and Saturation of Peripheral Oxygen (SPO2) at Different Time Intervals in Yaks

Parameter	Systolic pressure (mmHg)		Sig	Diastolic pressure (mmHg)		Sig	SpO_2 (%)		Sig
Group	AK	MK		AK	MK		AK	MK	
0 min Mean± SE	128.17^{a}±10.23	124.00±8.19	NS	76.00^{ab}±8.78	77.33±4.63	NS	97.16±4.40	96.33±1.52	NS
15 min Mean ± SE	114.83^{b}±9.28	116.33±16.17	NS	62.16^{cB}±5.55	73.16^{A}±20.15	*	91.00±1.63	92.16±2.77	NS
30 min Mean ± SE	104.16^{BC}±4.46	121.50^{A}±8.29	*	64.16^{cB}±7.24	75.00^{A}±9.79	*	94.33±2.34	95.16±2.15	NS
60 min Mean ± SE	116.50^{Bb}±10.35	123.16A±3.47	*	72.50^{b}±4.82	76.66±5.61	NS	95.66±3.73	96.12±0.74	NS
90 min Mean ± SE	121.83ª±4.05	125.33±8.78	NS	74.16^{ab}±10.70	76.50±9.50	NS	96.83±2.90	97.50±1.31	NS
Significance	*	NS		*	NS		NS	NS	

NS, Non-significant,
**, Significant at 0.05 level of probability*
***, Significant at 0.01 level of probability*

significant decrease in the systolic pressure in yak during acepromazine and chloromag anaesthesia. Baishya (2010). It was also reported that midazolam, even in low dose, caused significant hypotension and a decrease in systolic pressure following medetomidine-ketamine and atropine-medetomidine-ketamine administration in yaks.

Diastolic Pressure

The diastolic pressure decreased in both groups at 15 minutes. However, the changes were significant only in AK group. Phenothiazine derivatives block α1 adrenergic receptors, which lead to hypotension primarily due to peripheral vasodialatation. This might lead to fall in the blood pressure .When acepromazine was administered as premedication, its vasodilator effect potentially interferes with blood pressure control during perioperative period (Monterio et al., 2011).

Saturation of Peripheral Oxygen

The SpO_2 level decreased at 15 minute in both the groups. A non significant decrease in oxygen saturation in both the groups might be due to fall in the blood haemoglobin level in the circulatory blood volume during the period of anaesthesia. Baishya (2010) also reported decrease in SpO_2 level during xylazine-ketamine, atropine-xylazine-ketamine, medetomidine-ketamine and atropine- medetomidine-ketamine administration in yaks.

HAEMATOLOGICAL PARAMETERS

HaemoglobinA perusal of the data presented in Table 6 indicated that there was a non-significant decrease in haemoglobin level in both the groups. The decrease in haemoglobin level in both the groups might be due to the pooling of circulatory blood cells in the spleen and other reservoirs

Table 6. *Effects of Aanaesthetic Treatments on Hb, PCV, TEC, and TLC t Different Time Intervals in Yaks*

Parameter	Haemoglobin (g/dl)		Sig			Sig			Sig			Sig
Group	AK	MK		AK	MK		AK	MK		AK	MK	
0 min Mean± SE	11.73±0.55	11.12±0.37	NS	34.33±2.83	32.75±2.58	NS	5.28±0.36	5.05±0.41	NS	4.51±0.32	4.41±0.69	NS
15 min Mean ± SE	10.68±0.31	10.93±0.45	NS	33.16±3.15	30.00±1.20	NS	4.92±0.20	4.88±0.38	NS	4.10±0.16	4.30±0.58	NS
30 min Mean ± SE	10.52±0.51	11.10±0.51	NS	29.83±1.75	31.08±1.52	NS	4.83±0.35	4.98±0.38	NS	4.28±0.16	4.43±0.49	NS
60 min Mean ± SE	11.22±0.47	11.29±0.69	NS	32.16±3.63	31.25±1.28	NS	5.18±0.25	5.38±0.36	NS	4.33±0.11	4.52±0.45	NS
90 min Mean ± SE	11.34±0.52	11.16±0.75	NS	33.83±4.05	32.41±0.85	NS	5.51±0.46	5.16±0.40	NS	4.48±0.30	4.45±0.56	NS
Significance	NS	NS		NS	NS		NS	NS		NS	NS	

NS,Non-significant,
**, Significant at 0.05 level of probability*
***, Significant at 0.01 level of probability*

Table 7. *Effects of Anaesthetic Treatments on Total SERUM PROTEIN, BLOOD UREA NITROGEN, SERUM CREATININE AND SERUM GLUCOSE AT Different Time Intervals in Yaks*

Parameter	Total serum protein (g/dl)		Sig	Blood urea nitrogen (g/dl)		Sig	Serum creatinine (mg/dl)		Sig	Serum glucose (mg/dl)		Sig
Group	AK	MK		AK	MK		AK	MK		AK	MK	
0 min Mean± SE	6.94±0.45	7.39±1.64	NS	34.29±1.28	36.33±1.89	NS	0.21±0.20	0.20±0.01	NS	76.97±4.24	74.31±3.40	NS
15 min Mean ± SE	6.59±0.49	7.10±0.44	NS	34.38±1.62	35.91±0.96	NS	0.23±0.14	0.23±0.01	NS	79.65±5.04	77.38±4.06	NS
30 min Mean ± SE	6.23±0.52	7.13±0.49	NS	35.43±1.34	36.44±1.52	NS	0.26±0.02	0.21±0.48	NS	86.52±7.11	82.72±3.43	NS
60 min Mean ± SE	6.52±0.44	7.24±0.53	NS	34.47±1.70	36.23±2.22	NS	0.24±0.02	0.24±0.01	NS	87.26±9.16	84.10±5.61	NS
90 min Mean ± SE	6.48±0.30	6.93±0.44	NS	33.81±3.16	36.58±2.58	NS	0.24±0.28	0.22±0.01	NS	83.14±9.79	78.40±5.36	NS
Significance	NS	NS		NS	NS		NS	NS		NS	NS	

NS,Non-significant,
**, Significant at 0.05 level of probability*
***, Significant at 0.01 level of probability*

secondary to decreased sympathetic activity and shifting of fluid from extra-vascular compartment to intravascular compartment in order to maintain normal cardiac output in animals (Al-Redah, 2011).

Packed Cell Volume

The packed cell volume showed a non-significant decrease initially in both the groups. The decrease in PCV in both groups might be due to splenic pooling of blood and inter-compartmental fluid shift during anaesthesia. Alpha adrenergic blocking effect of acepromazine might induce relaxation to the spleen and consequently caused splenic sequestration of erythrocytes. Similar observations were also reported during midazolam-ketamine anaesthesia in buffaloes by Malik (2011).

Total Erythrocyte Count

In both groups there was an initial non-significant fall in TEC. However, the changes were of no clinical importance. The changes in the TEC values could be attributed to the spleenic pooling of blood and shifting of fluid from extravascular compartment to intravascular compartment to maintain normal cardiac output. Kilic (2011) also reported the same during medetomidine-midazolam-ketamine anaesthesia in calves.

Total Leukocyte Count

In both the groups, no significant change was observed in TLC. Montane et al., (2003) also observed similar observation while studying the effects of acepromazine and Sharma et al., (2001) during detomidine sedation in yak.

BIOCHEMICAL PARAMETERS

Total Serum Protein

From the findings in Table 7, it was found that there is no significant change in the serum total protein level in both the groups after the administration of the anaesthetics. Similar findings were reported by Montane et al. (2003), Sharma et al. (2001), and Baishya (2010).

Blood Urea Nitrogen

No significant change was observed in the BUN level in both the groups. This finding was in conformity with that of Malik et al. (2011) and Baisya (2010).

Serum Creatinine

No significant change was observed in the creatine level in both groups, indicating little or no effect of the anaesthetic agents on the body functions and supports the findings of Montane et al.,(2003), Malik et al. (2011), and Singh et al. (2014).

Serum Glucose

The glucose level increased non-significantly during the period of anaesthesia in both groups. This might be due to the release of catecholamine in a stressful condition during anaesthesia, resulting in glycogenolysis, or due to decreased glucose utilization, impaired insulin activity, or increased adrenocortical hormone. During the period of anaesthesia, there was a decrease in basal metabolic rate, with negligible muscular activity, leading to decreased utilization of glucose. Kandpal and Kumar (1998) also reported non-significant increase in glucose level after atropine-diazepam-ketamine anaesthesia in bovine. Similar observations were recorded by Kumar et al. (2004) in yak during acepromazine and chloromag anaesthesia.

CONCLUSION

- Acepromazine and midazolam were found to be safe and effective as pre-anaestheticsto ketamine anaesthesia in yak.
- The clinicophysiological, cardiopulmonary and haematobiochemical parameters remained within the normal physiological limit with both the combination.
- Midazolam and ketamine combination produced shorter duration of anaesthesia with shorter and smoother recovery.
- Acepromazine and ketamine combination produced longer duration of anaesthesia with moderate analgesia and longer recovery time.

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