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Effects of Medetomidine-Ketofol Anaesthesia on Clinico-Physiological and Haemato-Biochemical Parameters in Goats

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A B S T R A C T

The study was conducted on six healthy non-descript goats of either sex weighing between 20-25 kg by administrating atropine sulphate (0.04 mg/kg I/M) followed by medetomidine (10 µg/kg I/M) and 15 min. later followed by induction of anaesthesia with ketofol (5mg/kg I/V). After medetomidine administration, lowering of head was observed in all the animals within 4.20±0.33 min. After ketofol injection, there was rapid and smooth onset of anaesthesia (0.55±0.15 min). There was marked sedation with protrusion of tongue from buccal cavity, profuse salivation was noticed. Eyes remained partially closed throughout anaesthesia. The corneal and palpebral reflexes were abolished within 3 min. The anal pinch reflex was abolished completely. Muscle relaxation was excellent. The duration of anaesthesia was 85.42 ± 2.31 min. and lasted by raising of head. The recovery was smooth, free from excitement which occurs within 132.85 ± 3.24 min. A significant ($P<0.05$) decrease in heart rate and respiration rate was observed up to 20 min. and 60 min. respectively whereas rectal temperature showed slight variation. There was non-significant decrease in Hb, PCV and TLC. Neutrophils showed significant ($P>0.05$) increase with significant ($P<0.05$) decrease in lymphocyte count at 60 min. There was significant ($P>0.05$) increase serum glucose level upto 60 min. with non-significant variation in serum urea nitrogen, creatinine AST and ALT. All the physio-haemato-biochemical parameters changes remained within physiological range. Therefore, it is concluded that medetomidine-ketofol provides adequate anaesthesia with smooth and rapid recovery without any deleterious effects on vital organs. Hence, Ketofol can be safely used as general anaesthesia in goats for longer duration.

Introduction

India with 135.173 million goats population (19th livestock census 2012) is one of the largest goats owning country in the world and playing a significant role in the livelihood and nutritional security as well as providing supplementary income to nearly 70 million farmers of over 5,00,000 remote villages. A variety of major and minor surgical procedures like urolithiasis, dystocia, ruptured bladder, volvulus, rumenotomy, strangulation etc. are routinely performed in small ruminants practice that requires short term

sedation, analgesia or anaesthesia. Anaesthesia of the small ruminants is challenging but can be accomplished safely if the anaesthetist considers all of the special attributes of goats when making his/her anaesthetic plan. Today is an era of balanced anaesthesia where two or more drugs are combined to achieve optimum hypnosis, analgesia and muscle relaxation. However, there is no available anaesthetic drug which can provide proper anaesthesia alone at present. Therefore, combinations of tranquilizer and anaesthetics have been widely used in animal practice. Atropine, the most important of the alkaloids obtained from Atropa belladonna is used in premedication as an antisialogogue and to antagonize the unwanted muscarinic effects of anticholinesterase when these are required for their nicotinic effects at the motor end-plates of striated muscles. Medetomidine is a highly selective alpha2-adrenoceptor agonist which stimulates receptors centrally to produce dose-dependent sedation and analgesia and to cause marked bradycardia and decrease in cardiac output (Sinclair, 2003). It provides excellent immobilization and muscle relaxation in a wide range of species of animals (Hall *et al.,* 2001).

Ketamine is a non-competitive N-methyl-d-aspartate receptor antagonist which provides sedation, amnesia and analgesia and has anticonvulsive and neuroprotective properties (Sartoon *et al.,* 2001). Afshar *et al.,* (2005) assessed the effect of xylazine-ketamine on physiological parameters in goats and reported that heart rate decreased at 15 to 60 min but respiratory rate did not change significantly. Similarly, Umar and Wakil (2013) also observed the effect of medetomidine-ketamine anaesthesia in Sahel goats and concluded that this combination produced satisfactory anaesthesia in goats but there was decrease in PCV, HB and neutrophils. Ketamine possibly increases muscle tone and it induces spontaneous movement and occasionally convulsions. To reduce these undesirable effects, it is often used in conjunction with propofol, benzodiazepines, acepromazine and alpha 2 agonist (Saikia *et al.,* 2016).

Propofol is a non-opioid, non-barbiturate intravenous sedative hypnotic agent has a rapid onset and short duration as well as a smooth induction and uneventful recovery. Propofol induces depression by increasing the effects of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and decreasing the brain's metabolic activity (Rankin, 2015). Propofol following medetomidine premedication has been reported to produce good muscle relaxation and analgesia in goats (Carroll *et al.,* 1998). Medetomidine-propofol combination produces bradycardia in goats which was pronounced after premedication with medetomidine (Amarpal *et al.,* 2002). Ketamine and propofol are two completely different sedative which mitigate each other's deficits due to their opposing physiological effects (Green *et al.,* 2011).

The combination of propofol and ketamine in predetermined ratio is called ketofol. A combination of ketamine and propofol can be mixed in the same syringe or administered independently in two separate syringes. Ketofol can be administered as bolus or as a continuous infusion for longer procedures. Ketofol appears to be the ideal anaesthetic agent theoretically as the disadvantages of one agent are easily offset by the other. Whereas, propofol is known to cause pain on injection, hypotension, respiratory depression and no analgesia (thus requiring co-administration of opioids), ketamine maintains blood pressure and respiration and possesses excellent analgesic properties. The opposing haemodynamic and respiratory effects of each drug may enhance the utility

of this drug combination, increasing both safety and efficacy and allowing reduction in the dose of propofol required to achieve sedation (Daabiss *et al.,* 2009). The combination of both these agents in a single polypropylene syringe has been found to be chemically stable and physically compatible. These theoretical advantages have led to ketofol being increasingly used for short surgical procedures and sedation (Moezzi *et al.,* 2014). Data on the effects of ketofol with medetomidine in goats is scanty, therefore the present study was designed to assess the effects of medetomidine-ketofol anaesthesia on clinico-physiological and haemato-biochemical parameters in goats.

Materials and Methods

The study was conducted on six healthy non-descript goats of either sex weighing between 20-25 kg by administrating atropine sulphate (0.04 mg/kg I/M) followed by medetomidine (10 µg/kg I/M) and 15 min. later followed by induction of anaesthesia with ketofol (5 mg/kg I/V). The ketofol mixture was prepared in the ratio of 5:1 with the five part of propofol (10 mg/ml conc.) and one part ketamine (50 mg/ml conc.) mixed in one syringe. The following clinical parameters were studied are onset of sedation / anaesthesia, lowering of head, salivation, onset of sternal or lateral recumbency and duration of anaesthesia. Depth of anaesthesia was judged by monitoring the loss of swallowing reflex, corneal, palpebral reflexes, relaxation of anal sphincter anal pinch, pedal reflexes and extent of muscle relaxation. Recovery from anaesthesia was monitored raising of head, trying to stand with ataxia and complete recovery i.e. standing without ataxia. Physiological parameters like Rectal temperature, heart rate and respiratory rate which were recorded before and 10 minutes after premedication and 10, 20, 40, 60, 90, 120 and 180 minutes after ketofol anaesthesia. After administration of ketofol, the blood / serum samples were collected from goats before (0 min.), 30, 60, 120 minutes and 6 hrs. post ketofol anaesthesia for estimation of haematological and biochemical parameters which includes haemoglobin (Hb), packed cell volume (PCV), total leucocyte count (TLC) and differential leucocyte count (DLC), serum glucose (mg/dl), serum urea nitrogen (mg/dl), creatinine (mg/dl) aspartate aminotransferase (AST) (U/L) and alanine aminotransferase (ALT) (U/L). All the data were expressed as mean±Standard Error which was analyzed as per the standard procedure outlined by Snedecor and Cochran (1994). One way analysis of variance (ANOVA) was used to compare the means at different intervals with base values.

Results and Discussion

Clinical parameters

The effects on clinical parameters following administration of atropine-medetomidine-ketofol in goats are shown in Table 1. There was marked sedation with lowering of head and neck after medetomidine administration within 4.20±0.33 min. All the animals went to lateral recumbency, remained conscious but unable to stand when disturbed. The sedative/hypnotic effects of medetomidine are mediated through pertussis-sensitive inhibitory G protein in locus coeruleus neurons resulting in hyperpolarization and reduced nerve conduction (Kuusela *et al.,* 2000). After administration of ketofol, induction of anaesthesia (0.55±0.15 min) was smooth and no sign of excitement was observed. Marked sedation with protrusion of tongue from buccal cavity and profuse salivation was noticed after onset of anaesthesia. After ketofol anaesthesia, consciousness was lost in all the goats with eyeballs rotated downward. Eyes remained partially closed throughout anaesthesia.

Absence of corneal and palpebral reflexes was observed at 3 min. post medetomidine-ketofol anaesthesia which was an indication of sufficient CNS depression in goats. The anal pinch reflex was abolished completely. The muscle relaxation was excellent as there was complete relaxation of all muscles of jaw, tail, anus, prepuce, neck and limb. Laryngeal and pharyngeal reflexes were also depressed. Regurgitation nor bloat was not observed in any of the animals. There was complete analgesia at fetlock, base of tail, abdomen, rib, peritoneum and base of horn. Salivation after induction with either propofol or ketamine in the present study might be due delayed effect of alpha 2 agonist medetomidine or due to decreased swallowing reflex. Urination and defecation in three animals was observed after medetomidine-ketofol administration. Urination is a means of elimination of drugs by the kidney and it is a response of healthy kidney to eliminate these drugs from the body. The duration of anaesthesia was 85.42 ± 2.31 min. and lasted by raising of head. Longer duration of anaesthesia in animals might be due to synergistic action of medetomidine with ketofol as the analgesic properties of ketamine and medetomine produced a lack of arousal which might resulted in longer duration of anaesthesia. Contrary to present study, Amarpal *et al.,* (2002) reported that propofol (5.65±0.39 mg/kgIV)-medetomidine (10µg/kg IV) combination produces anaesthesia for 6.25±1.25 min in goats and the animals are able to walk with assistance in 14.75±1.55 min. The clinical efficacy of ketofol in dog was assessed by Shinde *et al.,* (2018) and reported that ketofol in xylazine combination produces duration of anaesthesia of 109.17±16.11 min. alongwith quick and smooth recovery. Medetomidine has been widely used in combination with ketamine and other drugs to prolong recumbency (Hall *et al.,* 2001). In the present study, animals returned to sternal recumbency at 110±3.80 min. and tried to stand with ataxia at 122.60 ±4.20 min. The complete recovery was smooth, free from excitement took 132.85±3.24 min. and prolonged which might be attributed due to medetomidine-ketamine ability to depress the thermoregulartory centre and muscle relaxation. Propofol has been associated with smooth recovery from anaesthesia and especially when combined with an alpha2 adrenergic. Similarly, Canpolat *et al.,* (2016) reported recovery time 90-150 min after medetomidine-ketamine anaesthesia in goats and Maravi *et al.,* (2018) observed duration of anaesthesia of 52.50 ±8.44 min. and complete recovery took 91.66±14.24 min. in goats after after detomidine-propofol anaesthesia. This might be due to prior administration of medetomidine, which activates alpha 2 adrenoceptors present in the spinal cord.

Physiological parameters

The effects of atropine-medetomidine-ketofol anaesthesia on physiological parameters in goats at various time intervals are shown in Table 2. The rectal temperature showed non significant decrease as compared to base value. The hypotensive effect caused by propofol is cancelled by ketamine component in ketofol which cause stimulatory action on cardiovascular system thus resulting in maintenance of body temperature throughout ketofol anaesthesia (Shinde *et al.,* 2018). A reduction in body temperature as observed by some authors might be due to the peripheral vasoconstriction and central redistribution of blood due to the action of alpha-2 agonist as documented by Sinclair (2003). Heart rate significantly ($P<0.01$) decreased up to 30 min. (from 76.85 ± 2.62 to 54.42±2.74 beats/min.) after atropine-medetomidine-ketofol anaesthesia which might be attributed to vasoconstriction due to alpha-2 agonist administration leading to reflex bradycardia (Lemke, 2004) and thereafter returned to

normalcy by 180 mins. Results of the present study are in conformity with Amarpal *et al.*, (2002) as xylazine-propofol and medetomidine-propofol combination produces bradycardia in goats which was pronounced after premedication with medetomidine. Contrary to present study, Shinde *et al.*, (2018) reported that ketofol provides cardiopulmonary stability to anaesthetized dogs without altering its haemodynamic and respiratory profile. A significant (P< 0.05) decrease in respiration rate at 10 mins. post medetomidine which became highly significant (P< 0.01) up to 60 mins. after ketofol anaesthesia (from 24.57±1.79 to 11.14±1.07 per min.). Then respiration rate gradually increased to return to near normalcy by 180 mins. Similarly, Maravi *et al.*, (2018) also reported significant (<0.05) decrease in respiration rate in goats after detomidine-propofol anaesthesia. Decrease in respiration rate might be due to direct depressant action of alpha-2 agonist (medetomidine) on central nervous system in general and respiratory centre in particular (Kim *et al.*, 1999). In the present study, decrease in respiration rate following ketofol might be due to predominant effect of ketamine in the initial stages and then its respiratory stimulant effect might have been counteracted by the depressant effect of propofol. Depression in respiratory rate in the later stages might be due to the depressant effects of medetomidine as by that time the effect of ketamine would have weaned off owing to its shorter duration of action.

Haematological parameters

The effects of atropine-medetomidine-ketofol anaesthesia on haematological parameters in goats at various time intervals are shown in Table 3. A non significant decrease in haemoglobin, PCV and TLC were noted at 60 min after atropine-medetomidine-ketofol anaesthesia. However, the values fluctuated to near normalcy in 6 hrs. The reason for decrease in Hb, PCV and TLC might be due to pooling of blood in the spleen or other reservoirs secondary to decreased sympathetic activity. During anaesthesia, decrease in haemoglobin and PCV can also be attributed to shifting of fluid from extravascular compartment to intravascular compartment in order to maintain normal cardiac output in animals (Umar and Wakil, 2013). Neutrophils count showed a significant (P<0.05) increase whereas lymphocyte count also showed significant (P<0.05) upto 60 min after ketofol anaesthesia respectively. The rise in neutrophils count and decrease in lymphocyte count might be due to adrenocortical stimulation and subsequent effect of gluocoticoids on circulating neutrophils and lymphocytes (Maravi *et al.*, 2017). There was a non significant variation in monocyte and eosinophil count after atropine-medetomidine-ketofol anaesthesia at various intervals. In the present study, haemoglobin, PCV and TLC decreased non-significantly during ketofol anaesthesia in goats. Umar and Wakil (2013) also observed significant (P<0.05) decrease in Hb, PCV and neutrophils while lymphocytes, monocytes and eosinophils showed non-significant difference during ketamine-medetomidine anaesthesia in Sahel goats. Similarly, non-significant decrease in Hb PCV and TLC while significant (P<0.05) increase in neutrophils with significant (P<0.05) decrease in lymphocytes were also reported by Maravi *et al.*, (2017) in atropinized goats after detomidine-propofol anaesthesia.

Biochemical parameters

The effects of atropine-medetomidine-ketofol anaesthesia on biochemical parameters in goats at various time intervals are shown in Table 4. In the present study, there was non-significant variation in all biochemical parameters during medetomidine-ketofol

anaesthesia except serum glucose level which highly significant (P<0.01) increased (from 79.60±2.88 to 93.51±2.52 mg/dl) up to 60 min. which after decreased and returned to normalcy by 6 hrs. Similar finding have been documented by Maravi *et al.*, (2017) in goats after detomidine-propofol anaesthesia. Increased serum glucose level is probably an indication of stress. Hyperglycaemia observed in the present study might be attributed to increased hepatic glucose production, decreased glucose utilization, decreased membrane transport and reduced plasma concentrations which are mediated by activation of α_2-adrenoceptors present in the β-cells of pancreatic islets exerting a negative control of basal insulin release (Burton *et al.*, 1997).

Table.1 The effects of atropine-medetomidine-ketofol anaesthesia on clinical parameters in goats at various time intervals (Mean ± SE)

Clinical Parameters	Mean±S.E. (Time in minutes)
Onset of sedation after medetomidine (Lowering of head)	4.20±0.33 min.
Onset of anaesthesia	0.55±0.15 min
Duration of anaesthesia	85.42±2.31 min.
Time for raising of head up	85.42±2.31 min.
Time for sternal recumbency	110.50±3.80 min.
Time for stand with ataxia	122.60±4.20 min.
Time for complete recovery (Standing without ataxia)	132.85±3.24 min.

Table.2 The effects of atropine-medetomidine-ketofol anaesthesia on physiological parameters in goats at various time intervals (Mean ± SE)

Time Period (Minutes)	Parameters		
	Rectal Temperature (^{0}F)	Heart Rate (Beats/min.)	Respiration Rate (breaths/min.)
0 min.	103.38±0.19	76.85±2.62	24.57±1.79
10 min. after premedication	103.22±0.19	67.14* ±3.48	18.28*±1.14
Post –Anaesthesia (min.)			
10 min.	103.00±0.19	61.42** ±3.05	15.28**±1.39
20 min.	102.98±0.22	56.14**±3.20	13.14**±1.22
30 min.	102.87±0.19	54.42**±2.74	11.42**±1.08
60 min.	102.74±0.18	58.00**±2.94	11.14**±1.07
90 min.	102.70±0.20	64.42**±3.27	17.57**±1.19
120min.	102.82±0.21	72.71±2.89	20.00*±1.53
180 min	102.95±0.21	78.42±3.38	23.57±0.81

* P < 0.05 = Significant at 5% level when compared to base value
** P < 0.01 = Significant at 1% level when compared to base value

Table.3 The effects of atropine-medetomidine-ketofol anaesthesia on haematological parameters in goats at various time intervals (Mean ± SE)

Parameters	Post -Anaesthesia (Min.)				
	0	30	60	120	6hr
Hb (g%)	8.28±0.24	7.90±0.21	7.62±0.29	7.85±0.25	8.10±0.21
PCV (%)	25.11±0.96	23.45±1.04	22.68±1.99	23.87±1.01	24.67±1.00
TLC (x 10^3 $cumm^{-1}$)	32.52±0.65	31.82±1.51	30.72±0.89	31.42±0.95	31.98±1.12
DLC (%)					
Neutrophils	36.28±0.56	38.71±0.42	41.14±0.45*	40.28±0.71	37.14±0.63
Lymphocytes	60.71±0.42	57.85±0.45	55.42±0.48*	56.57±0.52	60.00±0.69
Monocytes	2.08±0.18	2.14±0.26	2.44±0.26	2.51±0.18	2.42±0.20
Eosinophils	1.11±0.18	1.18±0.34	1.26±0.28	1.14±0.34	1.42±0.20

* P < 0.05 = Significant at 5% level when compared to base value

Table.4 The effects of atropine-medetomidine-ketofol anaesthesia on biochemical parameters in goats at various time intervals (Mean ± SE)

Parameters	Post -Anaesthesia (Min.)				
	0	30	60	120	6hr
Serum Glucose(g/dl)	79.60±2.88	89.84±3.18**	93.51±2.52**	90.12±1.82**	79.85±1.98
Serum Urea Nitrogen(mg/dl)	17.25±1.18	22.91±1.59	24.95±1.54	21.11±0.93	17.52±1.17
Serum Creatinine (mg/dl)	0.92±0.09	1.25±0.10	1.50±0.09	1.35±0.09	0.95±0.06
AST (U/L)	94.85±6.27	98.92±6.40	100.57±5.93	99.07±4.06	95.64±5.33
ALT (U/L)	23.07±1.84	27.72±2.50	29.55±2.48	25.52±2.50	22.65±1.16

* P < 0.05 = Significant at 5% level when compared to base value
** P < 0.01 = Significant at 1% level when compared to base value

Moreover, during the period of anaesthesia, there is decrease in basal metabolic rate of the animal and muscular activity is negligible, so utilization of glucose by muscles is also decreased probably causing slight increase in glucose concentration. However, since hyperglycaemia produced was transient in nature and within the normal physiological limit, therefore, a clinical significance cannot be fixed. In the present study, there was no significant increase in serum urea nitrogen, serum creatinine, AST and ALT at 60 min after medetomidine-ketofol anaesthesia respectively. It corroborate with findings of Shinde *et al.*, (2018) following ketofol anaesthesia in dogs. However, Dewangan *et al.*, (2016) reported significant (P>0.05) increase in all biochemical parameters (serum glucose, serum urea nitrogen, serum creatinine, AST and ALT) after xylazine-propofol anaesthesia in dogs which appeared within normal physiological limit and returned to normalcy within observation period. Anaesthetics may indirectly alter the renal function via change in cardiovascular and neuroendocrine activity (Stephen, 1996), but this did not happen in the present study as suggested by non significant changes. The

transient increase in the level of creatinine might be attributed to the temporary inhibitory effect of drugs on the renal blood flow in both groups and consequent decrease in glomerular filtration rate which in turn might also have caused a rise in serum creatinine values.

The increase in the AST and ALT activities might be due to alterations in cell membrane permeability in response to haemodynamic changes by the anaesthetic agent which might be due to the immediate response to cardiac insufficiency (Lehninger, 1990). This might also be due to the hypoxia induced by respiratory centre depression due to systemic absorption of alpha-2 agonists like medetomidine which are potent CNS depressant agents. All the haemato-biochemical changes induced by these combinations were compensated within 6 hrs and remained within physiological range, the possibility of pathological changes in liver couldn't be ruled out. Our study suggests that, ketofol a combination of ketamine and propofol results in excellent sedation, analgesia, muscle relaxation alongwith smooth induction, adequate anaesthesia with smooth and rapid recovery. Therefore, it is concluded that medetomidine-ketofol anaesthesia in goats provides adequate anaesthesia with smooth and rapid recovery without any deleterious effects on vital organs. Hence, ketofol can be safely used as general anaesthesia in goats for longer duration.

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