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Research Article

COMPARISION OF SEDATIVE EFFECT OF DEXMEDETOMIDINE/ XYLAZINE IN COMBINATION WITH BUTORPHANOL-MIDAZOLAM AS PREANAESTHETIC TO KETAMINE ANAESTHESIA FOR OVARIOHYSTERECTOMY IN DOGS

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ABSTRACT: The research was conducted in 12 female dogs undergoing elective ovariohysterectomy. They were divided into two groups of six animals each to evaluate and compare sedative effect in Group-I atropine- meloxicam - dexmedetomidine - butorphanol - midazolam - ketamine and Group-II atropine- meloxicam - xylazine - butorphanol - midazolam - ketamine anaesthetic combination. Maintenance of anaesthesia was done by ketamine in both the groups. Anaesthetic combinations were evaluated by clinical and physiological observations. Adequate muscle relaxation, sedation and analgesia necessary for surgical intervention were achieved along with smooth and uneventful recovery of the patients. Onset of sedation and induction time were quicker in Group-I. Physiological parameters fluctuated within the normal limits. Both anaesthetic protocols in the present study provided satisfactory surgical plane of anaesthesia in dogs. But dexmedetomidine may be preferred over xylazine in the anaesthetic regimen of atropine-meloxicam-butorphanol-midazolam-ketamine for elective ovariohysterectomy in dogs.

Key words: Sedative effect, Dexmedetomidine, Xylazine, Butorphanol, Midazolam, Ketamine, Dog.

INTRODUCTION

Injectable anaesthetics produce rapid induction of anaesthesia and are useful in situations where inhalational techniques are not readily available. Injectable anaesthetics are also suitable for maintenance of anaesthesia for short duration surgical procedures. A good preanaesthetic sedation facilitates smooth induction and has anaesthetic sparing effects during maintenance (Laredo 2015).

Ketamine is a centrally acting dissociative general anaesthetic that provides amnesia, analgesia and immobility with longer duration of effect (20 - 45minutes) (Reves *et al.* 2010) Because of potential adverse effect, dissociative anaesthetic should not be used alone. Ketamine is routinely employed in combination with sedatives (benzodiazepines and alpha-2 agonists) and analgesics to improve muscle relaxation, antinociception and quality of recovery (Barletta *et al.* 2011). Combination with xylazine is popular mainly due to its supplemental effects i.e. analgesic properties, muscle relaxation and sedation. Dexmedetomidine is newer and 40 times more potent than xylazine (Alvaides *et al.* 2008). Combination with ketamine produces predictable, rapid and smooth induction for anaesthesia in surgical procedures.

Alpha-2 adrenoreceptor agonists (α_2- agonists) are commonly used in small animal anaesthesia for their potent sedative and analgestic properties (Murrell and Hellebrekers 2005). Xylazine and dexmedetomidine, being two α_2 adrenergic receptor agonists, mediate sedative, anxiolytic and analgesic effects (Clark *et al.* 2014). The α_2/α_1-receptor binding selectivity indicates that the medetomidine is more selective and specific α_2-

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adrenergic receptor agonist than xylazine (Dewangan *et al.* 2010). Dexmedetomidine is a potent and selective α_2-adrenergic agonist, the dextro-isomer of medetomidine (Genccelep *et al.* 2004).

The present study was undertaken to evaluate the sedative effects of dexmedetomidine @10 µg/kg b.wt. i.m. and xylazine @2mg/kg b.wt.i.m. when administered in the anaesthetic regimen of atropine-meloxicam-midazolam-butorphanol-ketamine for elective ovariohysterectomy in dogs.

MATERIALS AND METHODS

Animals

The present clinical study was carried out in 12 adult female dogs undergoing elective ovariohysterectomy. Animals selected were clinically healthy, aged between 1 to 4 years and weighing between 15-20 kgs. The dogs were randomly assigned to 2 groups of 6 each as group – I and group-II based on the preanaesthetic regimen given. All the animals were fasted for 12 hours prior to the start of the procedure.

Anaesthetic protocols

Atropine @ 0.04 mg/kg b.wt. i.m. and meloxicam @ 0.1mg/kg b.wt. s.c. was administered. After 5 min, animals of group-I received dexmedetomidine @ 10µg/kg. b.wt. i.m., midazolam @ 2mg/kg. b.wt. i.m. and butorphanol @ 0.2 mg/kg. b.wt. i.m. Animals of group-II received xylazine @ 2mg/kg. b.wt. i.m. along with midazolam @ 2mg/kg. b.wt. i.m. and butorphanol @ 0.2 mg/kg. b.wt. i.m. Anaesthesia was achieved by administration of ketamine @ 5 mg/kg b.wt. i.m. after 10 minutes of preanaesthetic medication. Maintenance of anaesthesia was done by incremental doses of ketamine as and when needed during surgery.

All the animals underwent ovariohysterectomy through right lower flank approach by experienced surgeons. Oxygen saturation of haemoglobin was continuously monitored using pulse oxymeter.

Table 1. Clinical parameters related with anaesthesia at different intervals in dogs of group I and group II (Mean±SD).

Parameters	Group I	Group II
Onset of sedation (min.)	3.00±0.89[a]	9.17±1.47 [b]
Induction time (min.)	1.50±0.55 [a]	1.50±0.55 [a]
Duration of anaesthesia (min.)	28.50±1.22 [a]	32.50±2.66 [b]
Recovery time (min.)	17.50±1.64 [a]	34.67±3.89 [b]

Values bearing common superscript in columns and in rows do not differ significantly from each other (p≥0.05).

Evaluation of clinico-physiological parameters

Clinical and physiological parameters were recorded 0 min and then at 10, 15, 30, 45, 60 and 90 min after injection of drugs. The parameters recorded were onset of sedation (noted with onset of symptoms like head down, drooping of eyelids, sleepiness and ataxia in standing animals), induction time (time taken for induction of general anaesthesia after administration of ketamine i.m.), duration of anaesthesia (time between the abolition and reappearance of pedal reflex), recovery time (time taken for animal to stand voluntarily from the time of last administration of ketamine), palpebral reflex (blink in response to tap on the medial canthus of eye, graded from 0-3), pedal reflex (withdrawal of limb in response to pedal pinch, graded from 0-3), jaw tone (resistance to open the jaw, graded from 0-3), muscle relaxation (relaxation of abdominal muscles and reduced resistance to passive flexion of the limb, graded from 0-3), heart rate, rectal temperature and respiratory rate.

Statistical analysis

The mean and standard deviation of all parameters were computed as per Snedecor and Cochran (1994). The variance in clinical and physiological parameters recorded at different time intervals within the group and between the group were analyzed with Paired T test using SPSS software.

RESULTS AND DISCUSSION

All the 12 dogs in this study were apparently healthy on clinical examination before the induction of anaesthesia. The mean ± SD of body weight of animals was 17.25±1.37 and 16.93±1.34 in group-I and II respectively. The mean± SD of values of different clinical parameters and physiological parameters were given in Table 1, Table 2, Table 3 and Table 4.

Clinical parameters

The animals of group-I had quicker onset of sedation and quicker induction time when compared to group-II animals. Dexmedetomidine had rapid onset of action owing to its lipophilic properties (Amarpal *et al.* 1996). The fast onset of sedation recorded in the present study confirmed to the observations made in earlier studies following the administration of medetomidine/dexmedetomidine (Amarpal *et al.* 1996, Ahmad *et al.* 2011). Group-I animals administered with dexmedetomidine went into smooth head down and sleepiness state in sternal recumbency without any signs of ataxia and nausea. Group-II animals showed ataxia and uncoordinated head movement for 2-3 minutes before going to sleepiness. Nausea was observed in one of the animal of xylazine group after 5 minutes of administration of xylazine combination. Colby *et al.* (1981) reported

Table 2. Clinical parameters at different interval in dogs of group I and group II (Mean±SD).

Parameter	Groups	0 min	10 min	15 min	30 min	45 min	60 min	90 min
Pedal reflex	I	3.00±0.00^{a}	1.00±0.00^{b}	0.00±0.00^{b}	0.00±0.00^{b}	0.00±0.00^{b}	1.50±0.55^{b}	3.00±0.00^{b}
	II	3.00±0.00^{a}	1.50±0.55^{b}	0.00±0.00^{b}	0.00±0.00^{b}	0.00±0.00^{b}	1.50±0.55^{b}	3.00±0.00^{b}
Palpebral reflex	I	3.00±0.00^{a}	1.00±0.00^{b}	0.00±0.00^{b}	0.00±0.00^{b}	0.00±0.00^{b}	1.50±0.55^{b}	3.00±0.00^{b}
	II	3.00±0.00^{a}	1.00±0.00^{b}	0.00±0.00^{b}	0.00±0.00^{b}	0.00±0.00^{b}	1.50±0.55^{b}	3.00±0.00^{b}
Jaw tone	I	3.00±0.00^{a}	1.00±0.00^{b}	0.00±0.00^{b}	0.00±0.00^{b}	0.00±0.00^{b}	1.50±0.55^{b}	3.00±0.00^{b}
	II	3.00±0.00^{a}	1.00±0.00^{b}	0.00±0.00^{b}	0.00±0.00^{b}	0.00±0.00^{b}	1.67±0.52^{b}	3.00±0.00^{b}
Muscle relaxation	I	0.00±0.00^{a}	1.33±0.52^{b}	2.33±0.82^{b}	2.43±0.41^{b}	2.17±0.41^{b}	1.17±0.41^{b}	0.00±0.00^{b}
	II	0.00±0.00^{a}	1.50±0.55^{b}	2.17±0.75^{b}	2.37±0.52^{b}	2.17±0.41^{b}	1.33±0.52^{b}	0.00±0.00^{a}

*Parameters reading graded from 0 to 3 wherein 0 is absence, 1 is mild, 2 is moderate and 3 is good response/relaxation. Values bearing common superscript in columns and in rows do not differ significantly from each other ($p \geq 0.05$).

Table 3. Physiological parameters at different interval in dogs of group I and group II (Mean±SD).

Parameter	Gr. No.	0 min	10 min	15 min	30 min	45 min	60 min	90 min
Rectal temp. (^{0}F)	I	101.55±0.61^{a}	101.42±0.72^{a}	101.32±0.68^{a}	101.37±0.68^{a}	101.47±0.63^{a}	101.47±0.52^{a}	101.55±0.61^{a}
	II	101.65±0.30^{a}	101.85±0.46^{a}	101.70±0.37^{a}	101.75±0.44^{a}	101.90±0.54^{a}	101.90±0.59^{a}	101.97±0.55^{a}
Heart rate (min)	I	97.00±5.58^{a}	96.42±6.01^{a}	96.20±6.05^{a}	95.72±6.28^{a}	95.50±6.23^{a}	94.98±6.50^{a}	94.68±6.70^{a}
	II	96.85±5.81^{a}	96.15±6.39^{a}	96.15±6.12^{a}	95.65±6.37^{a}	95.43±6.32^{a}	94.85±6.66^{a}	94.47±6.95^{a}
Resp. rate (min)	I	17.18±1.17^{a}	17.42±1.16^{a}	17.23±1.35^{a}	17.00±1.22^{a}	16.71±1.07^{a}	16.48±1.05^{a}	16.40±1.03^{a}
	II	19.23±1.13^{a}	18.97±1.09^{a}	18.73±1.31^{a}	18.53±1.29^{a}	18.28±1.30^{a}	18.12±1.23^{a}	17.83±1.36^{a}

*Values bearing common superscript in columns and in rows do not differ significantly from each other ($p \geq 0.05$).

vomiting in cats caused by xylazine is due to stimulation of receptors in the chemoreceptor trigger zone in the brain.

Duration of anaesthesia was depended on the length and need of the surgery. Duration of surgery was 28.50 ± 1.22 minutes in Group-I animals and 32.50±2.66 minutes in Group-II animals. Except one animal in group-II incremental dose of ketamine was not required in surgical procedure during this study. Incremental dose of ketamine was administered once @ 1/3rd of induction dose after 10 minutes of induction in one animal in group-II. Jena *et al.* (2014) reported duration of anaesthesia and recovery time 72.50±3.35 and 11.17±1.14 minutes respectively under xylazine-propofol anaesthesia in dogs.

Group-I animals recovered faster and smoother when compared to group-II animals. Sharma *et al.* (2014) observed significantly lesser recovery time and superior quality of recovery in dexmedetomidine in preanaesthetic combination when compared to xylazine in dogs and similar observation was recorded in this study. However, Kuusela *et al.* (2000) reported longer recovery time in dogs in dexmedetomidine combination administered in dogs compared to xylazine due to rapid biotransformation of xylazine with elimination half life of 47 minutes and 30.1 minutes respectively.

Analgesia was good with complete loss of pedal reflex in both groups. Lemke (2004) opined that analgesic effects of $\propto_2$-agonists mediated by activation of heteroceptor ($\propto_2$- receptor located on noradrenergic neuron) located in the dorsal horn of the spinal cord. Stimulation of the $\propto_2$- adrenoceptors in this area terminates the propagation of pain signals leading to analgesia (Vanda and Marie 2006). Analgesic action of dexmedetomidine is mainly through spinally at the spinal cord, stimulation of the $\propto_2$-receptors at the substansia gelatinosa of the dorsal horn leads to inhibition of the firing of nociceptive neurons (Kuraishi *et al.* 1985).

Palpebral reflex and pedal reflex was completely abolished during surgical plane of anaesthesia in both groups. Similar findings were reported by Gupta (2010) under dexmedetomdine - butorphanol - propofol

Table 4. Blood pressure in dogs of different groups (Mean ± SE).

Category of Blood Pressure (mm/Hg)	Hrs Group	0 min	10 min	15 min	30 min	45 min	60 min	90 min
Systolic	A-1	124.17± 2.52^{ax}	131.17± 2.80^{ax}	135.83± 2.50^{bx}	140.17± 1.40^{bx}	136.67± 1.31^{bx}	130.67± 1.89^{ax}	128.00± 1.63^{ax}
	C-1	123.00± 2.25^{ax}	128.00± 2.49^{ax}	132.33± 1.94^{bx}	136.67± 1.05^{bx}	134.50± 0.96^{bx}	129.67± 1.63^{bx}	125.83± 1.66^{ax}
Diastolic	A-1	85.67± 1.50^{ax}	88.67± 1.61^{ax}	92.67± 1.67^{bx}	96.83± 1.89^{bx}	95.67± 2.63^{bx}	91.50± 1.34^{bx}	89.50± 1.34^{ax}
	C-1	86.17± 1.19^{ax}	88.67± 1.45^{ax}	92.67± 1.67^{bx}	96.83± 1.89^{bx}	95.83± 2.68^{bx}	91.33± 1.28^{bx}	89.33± 1.20^{ax}
Arterial (Mean)	A-1	98.50± 1.40^{ax}	102.83± 1.48^{ax}	107.06± 1.58^{bx}	111.28± 1.42^{bx}	109.33± 2.05^{bx}	104.56± 1.30^{bx}	102.33± 1.13^{ax}
	C-1	98.44± 1.12^{ax}	101.78± 1.33^{ax}	105.89± 1.34^{bx}	110.11± 1.09^{bx}	108.72± 1.78^{bx}	104.11± 1.17^{bx}	101.50± 1.01^{ax}

*Values bearing common superscript in columns and in rows do not differ significantly with each other ($p \leq 0.05$).

anaesthesia in dogs. Muscle relaxation was good in all the animals of both groups. However faster muscle relaxation was noticed in group-I as compared to group-II. Xylazine group caused a moderate decrease in all the reflexes whereas dexmedetomidine group scored higher with moderate loss of all the reflexes due to high potency owing to the specificity of medetomidine for $\propto_2$-adrenoreceptors than xylazine. The cumulative effect of dexmedetomidine/xylazine and ketamine might have caused attenuation of all the reflexes. Resistance to open the mouth fully is lost in moderate anaesthesia, hence jaw tone is considered to be a useful indicator of anaesthesia. Jaw tone became sluggish after the administration of dexmedetomidine/xylazine in both the groups due to inhibition of ∝2 adrenoceptors in the interneuron level of spinal cord. But the jaw tone score was more in the dexmedetomidine group than the xylazine group due to the higher potency of dexmedetomidine. Xylazine produces muscle relaxation mainly by inhibition of intraneural transmission within the central nervous system (Brikas *et al.* 1987).

Physiological parameters

Physiological parameters *viz.*, rectal temperature, heart rate and respiratory rate were slightly decreased from the base line at different time interval of study period in both groups. However the values were within normal range without statistically significant variation within and between the groups. Decrease in the values of physiological parameters was attributed due to decreased metabolic rate, muscle relaxation and direct depressant action on central nervous system (Kandpal *et al.* 2005). Similar non-significant physiological parameters findings were observed by Bloor *et al.* (1992) and Pagel *et al.* (1998) after dexmedetomidine administration. However, bradycardia induced by dexmedetomidine was modurated by atropine which was stated by Hogue *et al.* (2002). Bradycardia induced by xylazine was prevented by prior administration of atropine sulphate opined by Klide *et al.* (1975) and Hsu *et al.* (1985).

The mean ± SE of systolic blood pressure, diastolic blood pressure and mean arterial blood pressure in all the groups were higher than baseline throughout the study period. In all the groups values gradually increased reaching maximum by 30 min followed by gradual decrease towards baseline and non-significant ($p \leq 0.05$) by 90 min. However the values were within the normal range throughout the study period. The comparison between the groups at different time interval was not significant ($p \leq 0.05$) within the study period. Rafee *et al.* (2015) have also reported the increase in systolic blood pressure (in dogs administered with atropine-dexmedetomidine-butorphanol-midazolam-ketamine) initially followed by a decrease in its values possibly due to the effect of atropine which increased the systolic blood pressure and later on when dexmedetomidine was metabolized the systolic blood pressure values showed a

decrease. Santosh *et al.* (2013) have reported that in dogs anaesthetized with midazolam-dexmedetomidine-ketamine, the mean arterial pressure values first increased and then decreased with the passage of time but remained within the normal physiological range.

CONCLUSION

In the present study, both dexmedetomidine and xylazine in the anaesthetic regimen provided good analgesia and muscle relaxation without significant variation in the physiological parameters. However, onset of sedation, induction of anaesthesia and recovery were quicker and smoother with administration of dexmedetomidine providing better degree of basal anaesthesia than xylazine. Xylazine also caused nausea and ataxia in some of the animals. Hence dexmedetomidine may be preferred over xylazine for in the anaesthetic regimen of atropine-meloxicam-midazolam-butorphanol-ketamine for elective ovariohysterectomy in dogs.

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