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Research Article

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Evaluation of the Physiological and Anaesthetic Efficacy of Atropine-Xylazine-Diazepam-Ketamine Anesthesia in Non-Descriptive Dogs

J.D Parrah[1], Hakim Athar[2], Khadim Hussain Dar*[3], Bashir Ahmad Moulvi[4], Waseem-ul-Firdous[5] and Anwar Hussain Nagoo[6]

[1]Associate Professor, Division of Veterinary Surgery and Radiology, Sher-e-Kashmir University of Agricultural Sciences and Technology.

[2,3]Ph.D Research Scholar, Division of Veterinary Surgery and Radiology, Sher-e-Kashmir University of Agricultural Sciences and Technology.

[4]Professors, Division of Veterinary Surgery and Radiology, Sher-e-Kashmir University of Agricultural Sciences and Technology.

[5,6]M.V.Sc scholars, Division of Veterinary Surgery and Radiology, Sher-e-Kashmir University of Agricultural Sciences and Technology.

***Corresponding author**

Khadim Hussain Dar, Veterinary Clinical Services Complex, Faculty of Veterinary Sciences and Animal Husbandry, Sher-e-Kashmir University of Agricultural Sciences and Technology, Shuhama, Alusteng, Srinagar-190 006, Jammu & Kashmir, India. E-mail: drkhadim23@gmail.com.

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Abstract

The study was conducted on 12 healthy adult mongrel bitches (aged 2.50 ± 0.9 years and weighing 31.5 ± 2.8 kg), presented for elective ovariohysterectomy (OVH); to clinically evaluate atropine and xylazine premedication for diazepam-ketamine anaesthesia. The mean±SE value of sedation score on descriptive scale was 1.70±0.23. All the bitches were ataxic at 4.96±0.23 minutes and onset of sedation was characterized by signs of depression at 6.10±0.23 minutes following xylazine administration. There was complete to moderate analgesia during anaesthesia which remained for 15.26±0.64 minutes following the attainment of lateral recumbency after ketamine administration. Palpebral, corneal, swallowing reflexes and response to noise were either absent or mild at 5 and 15 minutes, respectively and at 30 and 60 minutes these reflexes was moderate to nearly normal. The anaesthetic combination produced muscle relaxation ranging from nearly complete to absent as evidenced by relaxation of neck, tail, jaw and tail. The mean±SE values of the rectal temperature ranged between 101.04±0.23 to 102.00±0.28 oF throughout the period of anaesthesia. Heart rate saw a decrease from 74.00±7.11 beats/minutes at 0 minutes to 73.00±6.30 at 60 minutes. After an initial static value, the respiration rate increased non-significantly (P>0.05) above the base value at 30 minutes, returning to near base value at the end of 60 minute interval. The color of conjunctival mucous membrane was pink and remained so during whole period of observation. The mean±SE values of the capillary refill time (CRT) ranged between 0.82±0.30 to 0.86±0.18 throughout the period of study. The mean±SE values of the oxygen saturation of haemoglobin (SPo2%) showed slight non-significant (P>0.05) changes during the entire period of observation. Therefore anaesthetic combination can safely and effectively be used for various short term surgical interventions in canines under field conditions.

Keywords: Bitches, Premedication, Anaesthesia, Ovariohysterectomy.

Introduction

Companion animals especially dogs bring many well documented benefits to individuals and to society as a whole. The stray/wandering dogs particularly in the developing countries like India, work day and night as scavengers complimenting the efforts of the local municipalities in keeping the cities and the towns clean. However on occasions when coordinated and persistent efforts are not undertaken to control their overpopulation, they become a nuisance while exhibiting socially unacceptable or dangerous behaviours [1]. Anaesthesia is dynamic and many anesthetic combinations are available whose proper use is of paramount importance for human animal care. An ideal anaesthetic produces sleep, amnesia, analgesia and muscle relaxation but no drug alone can provide all components of anaesthesia without depressing the vital organ functions [2]. Therefore, a combination of drugs is used and this technique is referred to as "balanced anaesthesia [3]. Although induction with short acting intravenous anaesthestics agents and maintenance with inhalant anaesthetics is the preferred method of general anaesthesia in most species of animals, but it is not practicable under field conditions especially in India where the costly equipment required for administration of inhalant anaesthetics is not available [4].

In clinical practice barbiturate intravenous anaesthesia became very popular in small animal surgery due to its rapid onset, smooth induction and pleasant anaesthetic action [5]. But it is commonly associated with undesirable side effect like cardiac and respiratory depression, cumulative effect, excitable and prolonged recovery phase, tissue irritation on accidental perivascular injection, transplacental transfer leading to foetal depression even foetal death [6]. Though inhalation anaesthesia could be other alternative but the need of costly anaesthetics equipments and specialized persons to monitor it makes this technique less popular at field level [7]. Still there is a dire need to tailor some injectable anaesthetic combination which can provide all components of anaesthesia with minimal side effects and can be easily applied at field level.

Atropine, an anticholinergic agent, blocks muscarinic receptors at the postganglionic terminations of cholinergic fibers in the autonomic nervous system. Atropine increases the incidence of cardiac dysrhythmia and sinus tachycardia in dogs [8]. Anticholinergics have been used to prevent bradycardia caused by administration of α2- agonists in dogs [9]. Different levels of sedation and analgesia may be obtained by the use of a number of drugs, including alpha-2 agonists [10]. The α-2–adrenoceptor agonists like xylazine are frequently used as sedative drugs and preanesthetic analgesics [4]. When these agents are given in combination with opioids or dissociative agents, the sedative and analgesic effects of α-2 adrenoceptor agonists get enhanced [11]. The combination of diazepam and ketamine, at a dose range of 0.2-0.5 mg/kg and 5-10 mg/kg respectively, has generally been associated with excitement free induction of anaesthesia in dogs [12].Various other combinations are cited in literature but their efficacy still needs to be evaluated clinically. Keeping all these facts in view, the present study was designed to evaluate the clinical efficacy and safety of atropine-xylazine-diazepam-ketamine anaesthesia in non descriptive dogs.

Material and methods

The study was conducted in the Division of Veterinary Surgery and Radiology, Sher-e-Kashmir University of Agricultural Sciences and Technology, Kashmir-190006, INDIA.

Animals

The anaesthetic trial was conducted on 12 healthy adult mongrel bitches (aged 2.50 ± 0.9 years and weighing 31.5 ± 2.8 kg), presented for elective ovariohysterectomy (OVH).

Study design

All the animals were fasted for 12 hours and were kept off water for 6 hours. The fasted animals were brought to a calm, isolated area and prepared for surgery after recording their body weight. The site for cephalic vein-puncture was carefully prepared for aseptic administration of various anaesthetic drugs. After recording baseline parameters such as rectal temperature, respiratory rate and heart rate. Atropine sulphate (0.04 mg kg-1; Atrapar, Biomedica, India) was administered intramuscularly (IM). 15 minutes after the atropine administration xylazine (2 mg kg-1 Xylaxin, Indian Immunologicals, India) was administered IM. Approximately 10 minutes after xylazine administration, when sedation was achieved, the anaesthesia was induced by IV administration of ketamine hydrochloride (10 mg kg-1; Aneket, Neon laboratories Limited, India). After induction, the bitches were left undisturbed and head and neck were extended to maintain a patent airway. The ovariohysterectomy was performed through ventral midline incision in all the animals after attaining the surgical plane of anaesthesia. The anaesthesia was maintained by using intermittent bolus of ketamine hydrochloride and diazepam hydrochloride (0.2 mg kg-1; Lori, Neon laboratories Limited, India) mixture combined in the same syringe in the ratio of 1:1. A balanced crystalloid (Ringer's Lactate, Alberts David, India) was administered intra-operatively at a rate of 10 ml/kg/hour for the duration of the anaesthesia.

Clinical Observations

For recording and observing the clinical observations the animals after the administration of xylazine hydrochloride were left undisturbed to allow the onset of the sedation. Once the sedation was achieved the animals were administered ketamine hydrochloride and placed on operation table for OVH. The various parameters were observed and recorded at different time intervals by independent observers.

Sedation time and recumbency time

Onset of sedation time was determined as the time elapsed from time of administration of the xylazine hydrochloride to the time of onset of drowsiness. A person unaware of the treatment was responsible for assessing objective and subjective data throughout the study. The degree of sedation was assessed on a simple descriptive scale of 0-3 (**Table 1**). Onset of recumbency time was recorded as the time elapsed from the time of injection of the ketamine hydrochloride to the time when the animal became recumbent.

Table 1. Scoring system used for description of sedation following xylazine-diazepam-ketamine anaesthesia in dogs (n=12)

Category	Description
0	Not sedated. No signs of depression, drowsiness or ataxia
1	Slightly sedated. Mild signs of depression, drowsiness or ataxia. Decreased reaction to stimuli
2	Moderate sedation. Sever ataxia, reluctant to move, may attain sternal recumbency
3	Deep sedation. Depressed, drowsy and sleepy, no resistance to positioning on lateral recumbency

Quality and depth of anaesthesia

The quality and depth of anaesthesia was analyzed by recording different reflexes, extent of muscle relaxation and analgesia at 5, 15, 30 and 60 minutes after the administration of diazepam-ketamine hydrochloride.

Reflex status

Presence or absence of palpebral reflex, corneal reflex, swallowing reflex, and response to noise were recorded. These reflexes of the animals were graded as 0, 1, 2 and 3 depending on response. Where '0' represents absence of reflexes, 1=mild, 2=moderate and 3=normal reflexes, respectively.

Muscle relaxation

Muscle relaxation of neck, jaws, tail and anal sphincter were examined and score from 0 to 3 was awarded. The extent of muscle relaxation was graded from 0 to 3 depending upon the extent of relaxation. Where '0' represents complete muscle relaxation,

1=moderate, 2= mild and 3= absence of muscle relaxation, respectively.

Surgery and Recovery time

Surgery time was recorded on completion of the OVH, and canines moved to a designated recovery area to recover from general anaesthesia. A quality of recovery score was then allocated by the independent observer. Score ranging from 1 to 5 was given. Where 1= excellent, 2= very good, 3= good, 4=poor and 5=very poor quality of recovery.

TABLE 2: Scoring system used for quality of recovery following xylazine-diazepam-ketamine anaesthesia in dogs (n=12)

Category	Description
1	Calm transition to alertness, coordinated movement, calm
2	Fairly calm transition, holds head up, no body movement Attempted
3	Unremarkable transition, , some incoordination, does not startle, generally quiet
4	Unremarkable transition, limited muscle control, startles, may paddle or whine
5	Struggling during transition, with chewing and coughing elicited, uncoordinated whole body movements, startles, vocalises

Physiological parameters

The physiological parameters were recorded at 0, 5, 15, 30 and 60 minutes after administration of various drugs. Heart rate (beats min-1) was determined by auscultation using a stethoscope, respiratory rate (RR) (breaths min-1) was evaluated by counting thoracic wall movements for 1 minute, rectal temperature (OF) was recorded with a digital thermometer, capillary refill time (CRT) was determined by pressing a figure against the upper gums for 2 seconds, Oxygen saturation of haemoglobin (SpO2) was determined by using the pulse oximeter applied to tongue of animal and color of conjunctival mucous membrane was also recorded.

Statistical analyses

A statistical analysis was performed using repeated measures with 2 factor Complete Randomized Design and Duncan's Multiple Range Test. All analyses were performed using the Statistical Software Package (SPSS Version 11.5). Significance was set at $p < 0.05$. Data were reported as mean ± standard error (SE).

Results

Clinical observations

The mean±SE value of sedation score was 1.70±0.23. All the bitches were ataxic at 4.96±0.23 minutes following xylazine hydrochloride administration. The onset of sedation was characterized by signs of depression at 6.10±0.23 minutes. Urination occurred in two animals only at 7.10±0.29 minutes after xylazine hydrochloride administration, but no urination or defecation was seen in other animals throughout the period of study. Vomiting was also recorded in two bitches at 5.10±0.18 minutes after xylazine hydrochloride administration. All the animals were down in sternal recumbency after 6.47±0.40 minutes of after xylazine hydrochloride administration and went to lateral recumbency 0.14±0.16 at minutes, with hypertonicity of hind limbs after ketamine hydrochloride administration. The mean±SE of the various reflexes are shown in (**Table 3**).

Table 3: Reflex status at different time intervals following xylazine-diazepam-ketamine anaesthesia in dogs (n=12)

Reflexes	0 minutes	5 minutes	15 minutes	30 minutes	1 hour
Palpebral	3.00 ± 0.00^{D}	0.00 ± 0.00^{A}	0.80 ± 0.13^{B}	1.80 ± 0.13^{C}	2.70 ± 0.15^{D}
Corneal	3.00 ± 0.00^{D}	1.00 ± 0.10^{A}	1.00 ± 0.10^{B}	1.90 ± 0.17^{C}	2.75 ± 0.15^{D}
Swallowing	3.00 ± 0.00^{D}	0.00 ± 0.00^{A}	1.00 ± 0.00^{B}	2.20 ± 0.13^{C}	2.72 ± 0.15^{D}
Response to noise	3.00 ± 0.00^{D}	0.00 ± 0.00^{A}	0.90 ± 0.10^{B}	1.80 ± 0.13^{C}	2.77 ± 0.15^{D}
Where 0 represents absence of reflexes, 1 mild, 2 moderate and 3 normal reflexes					

Means bearing different superscripts in a row differ significantly (P<0.05).
Means bearing different superscripts in a row differ non-significantly (P>0.05).

Palpebral, corneal, swallowing and response to noise reflexes was either absent or mild at 5 and 15 minutes, respectively and at 30 and 60 minutes these reflexes was moderate to nearly normal with mean±SE score of 2.70±0.15. Lacrimation was observed in three animals at 15.10±0.24 minutes and there corneal reflexes were mild to moderate up to the 30 minute interval. By the one hour interval all of these reflexes were almost normal in these three animals. The extent of muscle relaxation at various time intervals observed during the anaesthesia is presented in (**Table 4**).

Table 4: Mean±SE values extent of muscle relaxation at different time intervals following xylazine-diazepam-ketamine anaesthesia in dogs (n=12)

Muscle relaxation	0 minutes	5 minutes	15 minutes	30minutes	1 hour
Jaw	NR	0.30 ± 0.15^{B}	0.80 ± 0.20^{C}	1.80 ± 0.20^{D}	2.70 ± 1.50^{A}
Tongue	NR	0.30 ± 0.16^{B}	0.30 ± 0.16^{C}	0.30 ± 0.15^{D}	0.90 ± 0.15^{A}
Limbs	NR	0.30 ± 0.15^{B}	0.30 ± 0.15^{C}	0.90 ± 0.17^{D}	2.70 ± 0.15^{A}
Tail	NR	0.90 ± 0.99^{B}	1.00 ± 0.00^{B}	2.00 ± 0.00^{C}	3.00 ± 0.00^{A}
Where 0 represents complete muscle relaxation, 1 moderate, 2 mild and 3 absence of muscle relaxation					

Means bearing different superscripts in a row differ significantly (P<0.05).
Means bearing different superscripts in a row differ non-significantly (P>0.05).

The anaesthetic combination used in the bitches produced muscle relaxation ranging from nearly complete to absent during the study as evidenced by relaxation of neck, tail, jaw and tail. The relaxation of jaws was nearly complete at 5 minutes, moderate at 15 minutes and mild at 30 minutes. The relaxation of tongue was complete to moderate throughout the period of study. The relaxation of limbs was nearly complete to moderate between 5 and 30 minutes, respectively. The relaxation of tail was complete to moderate at 5 and 15 minutes with the scores of 0.90±0.99 & 1.00±0.00, respectively and the relaxation of tail was mild to absent with the scores of 2.00±0.00 and 3.00±0.00 at 30 and 60 minutes respectively. There was complete to moderate analgesia during anaesthesia in bitches which remained for 15.26±0.64 minutes following the attainment of lateral recumbency after anaesthetic administration. During recovery limb & head movements, and sternal recumbency without any stimulus were attained in 15.00±0. 42 minutes and 23.30±1.23 minutes, respectively, from the time of diazepam-ketamine administration. Thus the duration of anaesthesia was 15.26±0.64 minutes, though muscle relaxation was good to poor. Standing ataxia and normal gait were seen at 28.00±0.89 minutes and 39.75±3.25 minutes, respectively, from diazepam-ketamine mixture administration. In spite of the return

of swallowing reflex, the tongue protrusion was a constant feature during recovery. The mean±SE value of recovery score was 2.70±0.21. The recovery was quiet and smooth, with fairly calm transition from initial incoordination to complete coordination. The OVH was done through ventral midline approach with a mean±SE value of 37.70±0.41minutes for each surgery. The results of the physiological observations are shown (**Table 5**).

Table 5: Mean±SE values of Physiological parameters following xylazine-diazepam-ketamine anaesthesia in canines (n= 12)

Parameter (unit)	0 minutes	5 minutes	15 minutes	30 minutes	1 hour
Rectal Temperature (^oF)	$101.58±0.23^B$	$101.56±0.28^B$	$101.04±0.23^A$	$101.00±0.29^A$	$102.00±0.28^B$
Heart rate beats/minute	$74.00±7.11^A$	$67.30±6.91^A$	$71.20±6.56^A$	$65.80±5.50^A$	$73.00±6.30^A$
Respiration rate/minute	$19.70±2.33^A$	$19.60±2.02^A$	$18.10±1.99^A$	$20.10±1.99^A$	$19.80±1.11^A$
CRT (Seconds)	$0.82±0.30^A$	$1.16±0.84^B$	$1.09±0.56^B$	$1.08±0.59^B$	$0.86±0.18^A$
SPO_2 %	$91.80±1.24^A$	$89.50±1.10^A$	$88.50±1.68^A$	$89.20±1.03^A$	$91.10±1.00^A$

Means bearing different superscripts in a row differ significantly (P<0.05).
Means bearing same superscripts in a row differ non-significantly (P>0.05).

The mean±SE values of the rectal temperature ranged between 101.04±0.23 to 102.00±0.28 oF throughout the period of anaesthesia and the changes recorded were significant (P<0.05) at 0, 5 and one hour interval. In the present study, animals showed a steady decrease in the heart rate from 74.00±7.11 beats/minutes at 0 minutes to 73.00±6.30 at 60 minutes after diazepam-ketamine mixture administration. However, changes were within normal physiological range for canines and non-significant (P>0.05). After an initial static value, the respiration rate increased above the base value at 30 minutes, returning to near base value at the end of 60 minute interval, however the changes were non-significant (P>0.05). The changes in physiological parameters were within normal range for canines. The color of conjunctival mucous membrane was pink and remained so during whole period of observation form start of anaesthesia to complete recovery. The mean±SE values of the capillary refill time (CRT) ranged between 0.82±0.30 to 0.86±0.18 throughout the period of anaesthesia. Although, after initial significant (P<0.05) increase to 1.16±0.84, 1.09±0.56 and 1.08±0.59 at 5, 15 and 30 minutes there was non-significant (P>0.05) decrease in capillary refill time (CRT) to 0.86±0.18 at 60 minutes. The mean±SE values of the oxygen saturation of haemoglobin (SPo2%) in the arterial blood of the animals in present study showed only a slight non-significant (P>0.05) changes and remained slightly below the base value of 91.80±1.24% during the entire period of study.

Discussion

Atropine, xylazine, and ketamine were chosen for administration along with diazepam with consideration of their synergism and their minimal side effects. The aim of administering multiple drugs was to achieve variable levels of sedation, muscle relaxation, analgesia and anaesthesia that would meet clinical demands in a variety of diagnostic and therapeutic procedures without major side effects. The doses used in the current study were based on the results of earlier reports [10,12,13]. Xylazine induces a dose dependent sedation but increasing the dose beyond a certain level does not cause a further increase in sedation [13,14]. Ketamine alone induced moderate muscle relaxation, which was increased further by alpha-2 agonists, including xylazine are known to induce good muscle relaxation through the inhibition of intraneuronal transmission of impulses at the level of the CNS [3]. Better muscle relaxation could be attributed to the addition of diazepam [10]. The high quality of induction score recorded in the present study supports current literature, which describes excitement-free dissociative anaesthesia with sufficient muscle relaxation in dogs [15]. Atropine-xylazine-ketamine combination effectively reduced some of the undesirable effects of ketamine, such as muscle rigidity, insufficient suppression of reflexes and tachycardia [16]. Urination observed in two bitches after xylazine hydrochloride administration might be due to the decreased urethral closure pressure [3]. Vomiting was recorded in two animals. Vomiting after administration of alpha-2 agonists is mainly attributed to activation of the chemoreceptor trigger zone (CTZ). It has been recorded that alpha-2 adrenoreceptors are involved in the mediation of emetic action in CTZ and this does not involve beta adrenergic, cholinergic, dopaminergic, serotonergic and opioid receptors in the emetic pathway [10]. The complete anaesthesia for 15.26±0.64 minutes can be explained by the action of ketamine, mediated through the interruption of ascending transmission from those parts of the brain responsible for unconscious and conscious functions [4]. Recovery was smooth and shorter in accordance with the previous findings [12]. The initial increase in the heart rate might be due to the stimulatory effects of ketamine on the heart rate [17]. Ketamine has been reported to oppose the bradycardiac effects of alpha-2-agonists [4]. Bradycardia was almost completely prevented prior administration of atropine. Atropine inhibits the action of acetylcholine on the muscarinic cholinergic receptors and would be a drug of choice when severe bradycardia is presented secondary to increased vagal tone [13,18]. However, excessive doses of atropine may cause sinus tachycardia. It has been reported that prior administration of atropine only partially reverses xylazine-induced bradycardia [19].The decrease in respiratory rate in was in agreement with the observations of that alpha-2-agonists induce a dose-dependent depression in the respiratory rate [14]. The decrease in rectal temperature recorded after the onset of effects in all might be attributed to a possible decrease in heat production due to sedation and decreased muscular activity. Activation of alpha-2 receptors might have also contributed to hypothermia [10]. The critical analysis of results indicates that administration of xylazine-diazepam-ketamine anaesthesia resulted in quick induction. The quality of anaesthesia remains good to moderate with prolonged sedation, excellent to good analgesia and excellent to very good recovery. However muscle relaxation remains good to poor [20].

Conclusion

The combination of diazepam-ketamine anesthesia after premedication with atropine and xylazine administration can safely and effectively be used for various short term surgical interventions in canines under field conditions. However, additional dose would be required for prolonging the period of anesthesia and dose of xylazine and/ or diazepam may have to be increased for better muscle relaxation.

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