Comparison of Most Common Anesthetic Protocols Used in Dogs in Kosovo

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Cite this article as: Robaj, A., Mazreku, N., Sylejmani, D., Hamidi, A., Alishani, M., 2020. Comparison of Most Common Anesthetic Protocols Used in Dogs in Kosovo. Acta Vet Eurasia 2020; 46: 81-86.

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Abstract

The goal of this study was to investigate the difference in the physiological parameters through sedative and anesthetic effects by comparing three most common protocols of anesthesia used in dogs in Kosovo. For this purpose, from June 2018 to February 2019, 30 clinical cases of stray dogs have been examined. Animals were distributed randomly into three different anesthetic groups. The group xylazine and ketamine (XK; n=10), containing the combination of 5 mg/kg xylazine and 10 mg/kg ketamine, was administered intramuscularly. The group medetomidine and ketamine (MK; n=10), containing 0.04 mg/kg medetomidine and 10 mg/kg ketamine, was given intravenously, whereas in the group acepromazine and ketamine (n=10), by using intramuscular route, 0.01 mg/kg of acepromazine and 10 mg/kg ketamine was given to the dogs. The recorded duration and onset of action, including the recovery time of the three different anesthetic combinations, produced statistically significant differences within the groups, with an exception of XK-MK groups. The clinical changes associated with anesthetic combinations also registered the statistically significant differences of the physiological parameters of heart rate and rectal temperature but not of respiratory rate between the three groups of anesthetics. These results indicate that combined administration of a group XK is considered satisfactory for anesthesia in healthy dogs with minimal postoperative effects and is also suitable for using in ambulatory conditions in Kosovo.

Keywords: Acepromazine, anesthesia, dog, ketamine, medetomidine, xylazine

Introduction

The stray dog population remains one of the ongoing challenges all around the country of Kosovo. The dog population continues to be unregistered not only in Kosovo but also in some of the neighboring Balkan countries; these should be considered as a potential reservoir of infectious diseases, especially zoonotic diseases (Alishani et al., 2017). The increasing number of dogs may arise because of the lack of official programs to control the population of dogs (Acosta-Jamett et al., 2010). In Kosovo, xylazine, medetomidine, acepromazine, and ketamine in different combinations are widely used by veterinary surgeons because of the limited number of other anesthetics present in the market. Ketamine has a very quick distribution within the tissues because of the high liposolubility (Kurdi et al., 2014). Preventing the postoperative pains by applying ketamine alone showed ineffectiveness (Chaparro et al., 2013; Dualé et al., 2009; Ryu et al., 2011). The selectivity to adrenergic receptors is higher in medetomidine and dexmedetomidine than in xylazine (Güzel, 2018a; Lamont et al., 2012; Quiros-Carmona et al., 2017). Nevertheless, to prevent the negative effects such as muscle rigidity, hallucination, and excitation, xylazine is routinely combined with adrenoceptor agonists (Belda et al., 2009). Besides showing the myorelaxant effect when used as a premedicant, xylazine is also used to initate the general anesthesia (Camkerten et al., 2013). An easy induction with a cataleptic state of recovery may be produced by combining xylazine hydrochloride with ketamine hydrochloride (Durrani et al.,

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Received Date: 02.12.2019 • **Accepted Date:** 04.03.2020 • **Available Online Date:** 23.07.2020 • DOI: 10.5152/actavet.2020.19031

Available online at actaveteurasia.istanbulc.edu.tr

2009). Regarding the effect of sedation, analgesia, and muscle tranquility, alpha-2 (α2)-adrenoceptor agonists are in advantage compared with others (Sinclair, 2012). Acepromazine as a neuroleptic agent with a low toxicity induces mild to moderate muscle relaxation and tranquilization (Vesal et al., 2011). Acepromazine, besides being hypotensive and hypothermic, can also have other properties such as being anticonvulsant, antispasmodic, and antiemetic (Khalaf et al., 2014). Furthermore, its administration brings muscle relaxation and has no analgesic effect (Tranquilli, 2007). The risk of death must be considered in every induced anesthesia by balancing the physiological parameters of the patients before anesthesia, which may reduce the risk of deaths related to anesthesia (Bille et al., 2012; Itami et al., 2017). The recovery time from anesthesia up to the recuperation state of the patient is also strongly related to the quietness of the environment where the patients are hospitalized (Brodeur et al., 2017; Quandt, 2013). The aim of this study was to evaluate which of the most common anesthetic protocols used in small animal surgery in Kosovo on healthy male dogs is safer or has a lower risk in the crucial functions, determined by physiological parameters.

Materials and Methods

The study was carried out between June 2018 and February 2019. In total, 30 (n=30) male stray dogs (weight range 20-35 kg and age range 2-5 years) were used in this investigation. Animals being processed by the Catch, Neuter, Vaccinate, and Release project implemented by Kosovo Food and Veterinary Agency (KFVA) were assigned randomly to different treatment groups (premedication/anesthetic protocol). All the clinical cases of stray dogs have been examined at the Clinic of the Faculty of Agriculture and Veterinary, University of Prishtina. All animals were allowed free access to water and food before sedation; access to food and water was stopped 12 and 4 hours, respectively, before the sedation. Furthermore, small areas of the front leg of all investigated animals were shaved and an intravenous (i.v.) catheter was placed for administering fluids. All dogs involved in this study received intraoperative infusion of 0.9% NaCl i.v., 10 mL/kg/h.

The clinical parameters evaluated in this investigation were as follows: 1) the nutritive conditions, by counting: a) normal state, b) an overfeed state, and c) an underfeed state; 2) animal behavior states, by counting: a) normal state, b) quiet state, and c) an excited state; and 3) the mucosal color, by appearance: a) pink, b) pale, and c) congestive. Assignment of physical status was based on the patient's overall signalment, physical examination, diagnostics, and anesthetic urgency (Shelby and McKune, 2014). The physical status classification system was based on categories designed by the American Society of Anesthesiologists (ASA). However, during the anesthesia of the patients categorized in ASA 4 and ASA 5, by combination of propofol with isoflurane, the rate of mortality related to the anesthesia was reduced (Bille et al., 2014).

Physiological parameters such as respiratory rate (RR), by recording the diaphragmatic excursion; rectal temperature (RT), by using a digital thermometer; and heart rate (HR), by placing the stethoscope on the patient's left side/lateral aspect at the left thorax, were recorded by an investigator before the administration of sedative agents and during anesthesia. All recorded variables such as relative data of respiratory and cardiac rate as well as the RT were registered and compared from the moment of induction every 5 min, respectively, every 5, 10, 15, 20, 30, 40, 45, 50, and 55 min before waking. Furthermore, dogs included in the study were divided in three different groups. Each group of dogs (consisting 10 dogs per group, n=10) was administered combinations of xylazine (Xylazed, Bioveta, a.s. akciová společnost / joint-stock company, Ivanovice na Hané, Czech Republic), ketamine (Ketamin, Bremer Pharma Gmbh, Bremerhaven, Germany), medetomidine (Domitor, Vetoquinol Ltd, Towcester, UK), and acepromazine (PromAce Injectable, Boehringer Ingelheim, Ingelheim am Rhein, Germany) (Kapica et al., 2018). The groups were categorized namely xylazine and ketamine (XK), medetomidine and ketamine (MK), and acepromazine and ketamine (AK). Animals in the first group XK (n=10) first received a premedication of 5 mg/kg of xylazine, followed by intramuscular (i.m.) administration of 10 mg/kg of ketamine. Animals in the second group MK (n=10) first received a premedication of 0.04 mg/kg medetomidine, followed by intravenous administration of 10 mg/kg of ketamine. The third group AK (n=10), was first given 0.01 mg/kg of acepromazine, followed by i.m. administration of 10 mg/kg of ketamine. In the second group, drugs were given intravenously through cephalic veins, whereas in the first and third groups, drugs were intramuscularly administered into either the left or right epaxial muscle (Time 0, Basal). The entire drug combinations mentioned in the three different groups, namely XK, MK, and AK, present the most common anesthetic protocols performed routinely in most of the veterinary ambulatory condition in Kosovo. It is also worth pointing out that to prevent hypothermia, the investigation was conducted at room temperature with minimum 25°C to maximum 27°C, and all investigated animals were placed on heated pads (in dimensions 15″× 40″× 1″) at 38°C.

Statistical analyses

Asymmetric Wilson score confidence intervals (CIs) taking into account the sample size and the total population (sampling fraction) were calculated for prevalence estimates using the online statistical toolbox at OpenEpi.com (http://openepi.com/Menu/OE_Menu.htm).

The method mentioned above was used to provide an exact and asymmetrical CI for estimates based on simple random samples that are strong as well as small in size having prevalence near 0% or 100% (Cana et al., 2019; Wallis, 2013; Wilson, 1927). Descriptive statistics such as mean and standard deviation (SD) were used to describe the distribution of the estimated parameters. The analysis of variance was performed to test the difference between the three groups (XK, MK, and AK); Fisher's test and pairwise comparison using *t*-test was estimated to find out if there are differences between these three groups.

Table 1. The evaluation of the clinical parameters in dogs before the anesthesia

The clinical feature	The clinical state	n=30 (%), (95% CI*)
Nutritive condition	Normal	20 (66.67%), (48.78–80.77)
	Underfed	06 (20%), (20.51–37.3)
	Overfed	04 (13.33%), (5.31–29.68)
Behavior	Quite	10 (33.33%), (19.23–51.22)
	Excited	09 (30%), (16.67–47.87)
	Normal	11 (36.66%), (21.87–54.49)
Color of mucosa	Pink	25 (83.33%), (66.44–92.66)
	Pale	03 (10%), (3.46–25.62)
	Congestive	02 (6.66%), (1.85–21.32)
ASA Physical Status 1	(20 of 30 or 66.7%), (20.51–37.3)	
ASA Physical Status 2	(10 of 30 or 33.7%), (19.23–51.22)	
	Values	
Age (years)	2–5	
Weight (kg)	20–35	

*The 95% CI are Wilson score 95% CI given for a simple number of samples based on clinical state of dogs before the anesthesia.
ASA: American Society of Anesthesiologists; CI: confidence interval.

Results

In this study, only ASA Physical Status 1 (20 of 30 or 66.7%, 95% CI [20.51–37.3]) and ASA Physical Status 2 (10 of 30 or 33.33%, 95% CI [19.23–51.22]) of dogs were included, as shown in Table 1. The sedative effect of anesthesia was first registered in the group of MK just after 6±1.52 min of intramuscularly injecting the drugs; second, the effect was registered in XK group after 6±3.12 min; and the latest effect of anesthesia was registered in the AK group, which was reached after 10±3.16 min of intramuscularly injecting the drugs. Data were reported as mean±SD or a range, as appropriate. Moreover, the mean±SD time of anesthesia duration was different in each group of anesthetic combinations, as described in Table 2. The recorded data of onset and duration actions included the recovery time in three different administered groups of anesthetic combinations, namely XK, MK, and AK, which showed statistically significant differences within the groups, with the exception of XK-MK groups where the significant differences were not registered, as shown in Table 2. These three anesthetic protocols were correlated with some of the clinical changes such as changes in the heart and respiratory frequencies and the body temperatures, as described in Table 3. In terms of HR, the estimated t-value shows that there is significant difference between the HR2 and HR1 (t=3.84; p=0.001) and HR3 with HR2 (t=–5.04; p=0.000), but not between HR3 and HR1 (t=–1.20; p=0.239). The estimated t-value shows that there is no significant difference between

Table 2. Effects of XK, MK, and AK combination on onset of action, duration, and recovery time

Anesthetic groups	XK (n=10), i.m.	MK (n=10), i.v.	AK (n=10), i.m.
Doses (mg/kg)	5 mg/kg +10 mg/kg	0.04 mg/kg + 10 mg/kg	0.01 mg/kg + 10 mg/kg
Onset of action (min)	6±3.12	6±1.52	10±3.16
Duration of action (min)	52.7±7.4	32.3±3.2	66.2±2.19
Recovery time (min)	63.6±4.13	45.9±3.15	76.8±2.15
Onset of action (min)			
Two-sample t-test differences	**XK-MK**	**XK-AK**	**MK-AK**
	6±3.12; 6±1.52	6±3.12; 10±3.16	6±1.52; 10±3.16**
	t-value=0.00, p-value=1.000, DF=13	t-value=-2.85, p-value=0.011*, DF=17	t-value=-3.61, p-value=0.004**, DF=12
Duration of action (min)			
Two-sample t-test differences	**XK-MK**	**XK-AK**	**MK-AK**
	52.7+7.4; 32.3±3.2	52.7±7.4; 66.2±2.19	32.3±3.2; 66.2±2.19
	t-value=8.00, p-value=0.000***, DF=12	t-value=-5.53, p-value=0.000***, DF=10	t-value=-27.65, p-value=0.000***, DF=15
Recovery time (min)			
Two-sample t-test differences	**XK-MK**	**XK-AK**	**MK-AK**
	63.6±4.13; 45.9±3.15	63.6±4.13; 76.8±2.15	45.9±3.15; 76.8±2.15
	t-value=10.78 p-value=0.000***, DF=16	t-value=-8.97 p-value=0.000***, DF=13	t-value=-25.62 p-value=0.000***, DF=15

*p<0.05, **p<0.01, ***p<0.001
XK: Xylazine + Ketamine; MK: Medetomidine + Ketamine; AK: Acepromazine + Ketamine; i.m.: intramuscular; i/v: intravenous

the RR2 and RR1 (t=3.84; p=0.263) and RR3 with RR1 (t=-0.10; p=0.924) and RR3 with RR2 (t=–1.24; p=0.225). In terms of RT, the estimated t-value shows that there is significant difference between the RT2 and RT1 (t=8.79; p=0.000) and RT3 with RT2 (t=–8.88; p=0.000), but not between RT3 and RT1 (t=–0.09; p=0.926; Table 4).

Discussion

A government designed, comprehensive strategy to reduce the number of the stray dogs started to be implemented in 2018 and would last over a 4-year period. The strategy entitled "Controlling and managing of the stray dogs," conducted by KFVA, through licensed PVP's (Private Veterinary Practices), was

Table 3. The changes and comparison of the physiological parameters on HR, RR, and RT, by effects of XK group (xylazine + ketamine), MK group (medetomidine + ketamine), and AK group (acepromazine + ketamine)

	XK (n=10)			MK (n=10)			AK (n=10)		
Time (minutes)	HR1 (beam/min)	RR1 (breath/min)	RT1 (°C)	HR2 (beam/min)	RR2 (breath/min)	RT2 (°C)	HR3 (beam/min)	RR3 (breath/min)	RT3 (°C)
Basal	80.4 ±1.22	23.5 ±0.75	38.22 ±0.24	88.6 ±11.7	29.6 ±2.5	38.81 ±0.35	83.1 ±1.22	23.9 ±0.56	37.51±0.47
5	79.2±2.11	23.2±0.41	37.87±0.36	91.3±15.4	21.8±6.2	38.67±67	79.9±1.23	23.6±0.78	37.66±0.58
10	79.1±2.24	19.1±0.84	37.58±0.12	83±14.9	19.4±11.1	39.58±0.6	79.2±2.13	19.5±0.35	37.51±0.36
15	78.3±2.12	17.7±0.87	37.84±0.25	83.8±14.0	16.2±3.5	38.14±0.9	78.9±2.26	18.4±0.98	37.2±6.87
20	77.9±2.35	17.9±0.75	37.26±0.65	79.4±11.6	17.4±3.3	39.18±0.33	74.4±2.39	18.3±0.95	37.24±0.98
25	77.8±3.26	16.8±0.83	37.32±0.32	79.1±11.6	18.4±2.9	39.34±0.44	74.8±1.18	16.9±0.99	37.22±0.75
30	77.7±1.46	16.9±0.98	37.4±0.12	78.9±11.8	20.4±2.4	39.14±0.14	73.9±2.31	15.8±0.15	37.40±0.87
35	76.9±2.12	16.2±0.91	37.5±0.36	76.1±10.1	20.2±1.1	39.24±0.22	72.9±2.22	15.6±1.24	37.65±0.23
40	76.7±2.41	17.9±1.1	37.4±0.78	84.9±11.8	20.7±1.1	39.34±0.44	72.7±2.41	15.6±1.32	37.79±0.65
45	77.4±2.47	18.9±1.3	37.42±0.63	85.6±12.3	21.4±2.1	39.4±0.44	74.2±1.49	18.9±0.98	37.82±0.45
50	78.2±2.47	23.1±0.84	37.42±0.21	86.3±14.9	24.2±1.2	37.8±0.27	78.2±2.35	22.9±0.85	37.57±0.69
55	79.2±2.11	22.9±0.59	38.1±0.34	92.7±12.3	25.9±5.2	39.28±0.25	79.7±1.23	23.8±0.59	37.88±0.54

XK: Xylazine + Ketamine; MK: Medetomidine + Ketamine; AK: Acepromazine + Ketamine; HR: heart rate; RR: respiratory rate; RT: rectal temperature

Table 4. Test of differences between HR, RR, and RT between the three groups of anesthetics XK, MK, and AK

Difference of Levels	Difference of Means	SE of Difference	95% CI	t	p
HR2-HR1[a]	5.70	1.48	(2.67–8.73)	3.84	0.001***
HR3-HR1[a]	–1.78	1.48	(-4.81 to 1.25)	–1.20	0.239
HR3-HR2[a]	–7.48	1.48	(-10.51, -4.45)	–5.04	0.000**
RR2-RR1[b]	1.40	1.23	(–1.10 to 3.90)	3.84	0.263
RR3-RR1[b]	–0.12	1.23	(–2.62, 2.39)	–0.10	0.924
RR3-RR2[b]	–1.52	1.23	(–4.01, –0.99)	–1.24	0.225
RT2-RT1[c]	1.45	1.16	(1.11, 1.79)	8.79	0.000**
RT3-RT1[c]	–0.01	1.16	(–0.35, 0.32)	–0.09	0.926
RT3-RT2[c]	–1.47	1.16	(–1.80, –1.13)	–8.88	0.000**

[a]The overall Fisher's test was 13.89 with the p-value of 0.000 which indicates that there is statistically significant difference between the three groups XK, MK, AK in terms of HR. The estimated t-value shows that there is significant difference between the HR2 and HR1 (t=3.84; p=0.001) and HR3 with HR2 (t=–5.04; p=0.000), but not between HR3 and HR1 (t=–1.20; p=0.239).
[b]The overall Fisher's test was 0.95 with the p-value of 0.399 which indicates that there is no statistically significant difference between the three groups XK, MK, AK in terms of RR. The estimated t-value shows that there is no significant difference between the RR2 and RR1 (t=3.84; p=0.263) and RR3 with RR1 (t=–0.10; p=0.924) and RR3 with RR2 (t=–1.24; p=0.225).
[c]The overall Fisher's test was 52.00 with the p-value of 0.000 which indicates that there is statistically significant difference between the three groups XK, MK, AK in terms of RT. The estimated t-value shows that there is significant difference between the RT2 and RT1 (t=8.79; p=0.000) and RT3 with RT2 (t=–8.88; p=0.000), but not between RT3 and RT1 (t=–0.09; p=0.926).
*p<0.05, **p<0.01, ***p<0.001.
RR: Respiratory rate; HR: Heart rate; RT: Rectal temperature; XK: Xylazine + Ketamine; MK: Medetomidine + Ketamine; AK: Acepromazine + Ketamine

applied under the Catch, Sterilization or Castration/Vaccination and Release (CSVL) techniques.

This study was designed to assess the comparison of three most common anesthetic protocols used in dogs in veterinary ambulatory condition all around the country of Kosovo during the implementation of the CSVL project. The combination of α2-adrenergic receptor (or adrenoceptor) agonist with ketamine is considered to be one of the most popular injectable anesthetics used in small animal surgery. Furthermore, the combination between xylazine as a sedative and ketamine as an anesthetic is very commonly used by vets in animal practices (Demirkan et al., 2002). Furthermore, the small sample size of this investigation must be considered as a limitation. Some of the results presented in this paper may be matching to the results of combinations between MK in dogs as described by Moens and Fargetton, (1990). The combination of MK i.m. injection has given the earliest or first sedative effect of anesthesia, followed by the combination of XK i.m. injection, whereas the latest effect of anesthesia was recorded in the combination of AK i.m. injection. The duration of action of anesthesia in this study was registered as longer in the AK group and shorter in the MK group; the shortest onset of action was registered in the MK group, whereas the longest duration of action and recovery time were registered in the anesthetic combination of the AK group. The cardiovascular stability and minimal depression were classified as one of the major goals during the anesthesia of healthy dogs. Reduced heart frequencies were remarked in the three groups but principally was showed in the first and third groups (XK and AK) after 25–40 min of anesthetics and less in the second group (MK). In addition, the vital role of the drugs and endotracheal intubation on the pulmonary and cardiovascular system was described by Güzel et al. (2013).

Meanwhile, reduced respiratory frequencies were remarked in the first group (XK) between 15 and 40 min after the narcosis, in the second group (MK) after 15-25 min, and 25-40 min in the third group (AK). Similarly, lower hypothermia was registered in XK and AK groups after 20-30 min, whereas MK was registered with a bit higher values. Moreover, according to the effects of the three tested anesthetic protocol combinations on cardiopulmonary system including body temperature, it can be concluded that combining ketamine with xylazine has a significant effect on HR and body temperature, which improves the quality of anesthesia. Intravenous administration of MK in dogs produced rapid onset of sedation and anesthesia, which persisted for 32.3±3.2 min. According to the similar studies conducted previously, it was concluded that to have better properties, the anesthetic drugs have to be combined with other anesthetics. There are no superior properties between xylazine and medetomidine, apart from carefully using medetomidine owing to its property of decreasing HR rapidly as described by Güzel (2018b). The three common protocols included in this study should be recommended to the PVP's in the healthy dogs in Kosovo. According to the results of this paper, we can conclude that the combination made led to superior properties in the first group, namely, XK, which assured safety and healthier a environment.

Ethics Committee Approval: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.R.; Design – A.R., M.A.; Supervision – M.A.; Materials – N.M., D.S., A.H.; Data Collection and/or Processing – N.M.; Analysis and/or Interpretation – A.R., M.A. Literature Search – D.S., A.H.; Writing Manuscript – A.R., M.A.; Critical Review – D.S., A.H.; Other – A.R., N.M., D.S., A.H., M.A.

Acknowledgements: We greatly acknowledge the colleagues for technical assistance and support during this research. We especially thank Dr. Nick Taylor and Dr. Iliriana Miftari for reading and commenting on a draft of the manuscript.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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