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Comparative evaluation of physiological and cardiopulmonary effects of diazepam-ketamine and Zolazepam-tiletamine for abdominal surgeries in dogs

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Abstract
The present study was undertaken to compare the physiological and cardiopulmonary effects in dogs after induction of anaesthesia with diazepam-ketamine and Zolazepam-tiletamine for abdominal surgeries**.** Twelve dogs presented to Small Animal Surgery Unit, VCRI, Namakwa were selected and divided into two groups comprising six animals in each group. Group I dogs were induced with ketamine-diazepam and Group II dogs with tiletamine-zolazepam. Both the groups were premedicated with atropine, dexmedetomidine and butorphanol and maintained with isoflurane. The physiological parameters such as heart rate, respiratory rate and rectal temperature were recorded preoperatively and during maintenance at 0, 15, 30, 45 and 60 minutes, whereas cardiopulmonary parameters such as saturation of peripheral oxygen (SpO_2), mean arterial pressure, tidal volume and minute volume were recorded during maintenance of anaesthesia at 0, 15, 30, 45 and 60 minutes in both the groups. There is no significant difference in physiological and cardiopulmonary parameters between the groups. Heart rate was found to be increased in both the groups after induction, but it was less increase in group II compared to group I. Respiration rate and rectal temperature were decreased in both the groups during different intervals of anaesthesia. However, the changes in physiological parameters studied were within the physiological limits throughout the surgery in both the groups. The cardiopulmonary parameters such as SpO_2, mean arterial pressure, tidal volume and minute volume were assessed during different time intervals of maintenance did not vary significantly. It can be concluded that based on the parameters studied both the anaesthetic protocols are found to be suitable and safe for abdominal surgeries in dogs. Further, studies are warranted to determine the anaesthetic efficacy of these protocols.

Keywords: Abdominal surgery, dogs, Zolazepam-tiletamine, diazepam-ketamine, physiological and cardiopulmonary parameters

Introduction

Abdominal surgery is one of the generally performed surgical procedures in dogs and many patients require anaesthesia either for diagnostic procedures or to adopt surgical procedures. Currently there are no controlled veterinary studies that quantify the risk benefit ratio of abdominal surgery in companion animals (Osborne and Lulich, 2000) [18]. Dogs are frequently subjected to general anaesthesia with the combination of anaesthetic drugs for the performance of abdominal surgeries. Balanced anaesthesia is being widely used in small animal practice for to compensate the side effects of one individual agent (Demirkan *et al*., 2002) [4].

Atropine is a commonly used premedicating agent in usually with alpha-2-agonists, like dexmedetomidine to prevent vagal effects and potential muscle spasm, gastrointestinal motility and secretion, salivation and respiratory secretion during anaesthesia (Liga and Edite, 2011). The advantages of combining dexmedetomidine and an opioid butorphanol will facilitate a rapid and smooth induction. Ketamine is a dissociative anaesthetic agent and Diazepam belongs to the benzodiazepine group, acts as central muscle relaxant and it reduces the muscle tone associated with the ketamine (Lin, 2007) [17].

Zolazepam-tiletamine combination has been found to be safe and versatile injectable anaesthetic indicated for canine patients. The pharmacological action of these two drugs is complementary with tiletamine providing analgesia and immobilization: zolazepam providing muscle relaxation and tranquilization. However, there are limited research on the use of Zolazepam-tiletamine combination for induction and its comparison with diazepam-ketamine for abdominal surgeries in dogs.

Therefore, the purpose of the study here was to compare the physiological and cardiopulmonary effects in dogs after induction with diazepam-ketamine and Zolazepam-tiletamine for abdominal surgeries in dogs.
Diazepam-ketamine combination is used for induction of anaesthesia in dogs as a routine anaesthetic protocol. As an alternative to this combination, Zolazepam-tiletamine could be used for induction of anaesthesia.

Materials and Methods

The study was conducted at the Department of Veterinary Surgery and Radiology, Veterinary College and Research Institute, Namakwa on clinical cases presented for abdominal surgeries in dogs. Twelve dogs were selected irrespective of breed, age and sex and randomly divided into two groups with six animals in each group. Food and water were withheld for 12 h and 6 h, respectively before the conduct of anaesthetic trial in all the dogs selected for the study.
The premedicates *viz*. atropine sulphate were administered @ 0.02 mg per kg body weight subcutaneously, followed by administration of dexmedetomidine @ 5 µg per kg body weight and butorphanol @ 0.2 mg per kg body weight intravenously and kept as a standard protocol in both the groups. Anaesthetic induction was done in Group I animals with intravenous administration of diazepam@ 0.5 mg per kg body weight followed by ketamine @ 5 mg per kg body weight whereas group II animals were induced with Zolazepam-tiletamine @ 2 mg per kg body weight intravenously. Maintenance of anaesthesia was carried out with isoflurane.
The physiological parameters such as heart rate, respiratory rate and rectal temperature were recorded preoperatively (before and after premedication as well as after induction) and during maintenance at 0, 15, 30, 45 and 60 minutesin all the dogs.
Cardiopulmonary parameters such as saturation of peripheral oxygen (SpO_2), mean arterial pressure, tidal volume and minute volume were recorded during maintenance of anaesthesia at 0, 15, 30, 45 and 60 minutes in both the groups.
The data were statistically analysed in SPSS (version 20) by Students'' test and One-way ANOVA with repeated measures (General Linear Model)

Results and Discussion

Heart rate, respiratory rate and rectal temperature were recorded during different stages of anaesthesia, after employing the respective anaesthetic protocol in both groups (Table 1).

Table 1: Mean (±SE) heart rate per minute, respiratory rate per minute and rectal temperature (°C) recorded during different stages of anesthesia.

Parameters	Group	Before Premedication	After Premedication	After Induction	Maintenance				
					0 min	15 min	30 min	45 min	60 min
Heart rate (Beats per minute)	I	115.17 ± 3.54^{a}	89.17 ± 7.04^{b}	117.17 ± 5.76^{a}	118.17 ± 4.28^{a}	121.50 ± 4.13^{a}	118.50 ± 3.79^{a}	$114.17\pm4.30^{a, x}$	$105.50\pm2.49^{a, b, x}$
	II	$115.83\pm2.07^{a, b}$	93.00 ± 2.9^{c}	105.00 ± 3.6^{b}	$112.17\pm3.54^{a, b}$	$116.67\pm2.87^{a, b}$	120.50 ± 2.13^{a}	$104.83\pm1.76^{b, c, y}$	$108.67\pm1.15^{a, b, y}$
	p-value	0.045	0.079	0.123	0.513	0.370	0.115	0.000	0.000
Respiratory rate (Breaths per minute)	I	31.17 ± 2.04^{a}	$23.67\pm1.41^{a, b}$	$20.33\pm0.61^{b, c}$	$17.67\pm0.58^{b, c}$	15.67 ± 1.74^{c}	$14.67\pm1.76^{c, x}$	15.50 ± 2.39^{c}	$15.50\pm1.31^{c, x}$
	II	33.00 ± 1.13^{a}	24.17 ± 2.46^{b}	13.50 ± 1.41^{c}	13.33 ± 1.15^{c}	13.50 ± 0.92^{c}	$14.00\pm0.77^{c,y}$	14.33 ± 1.41^{c}	$14.00\pm0.58^{c, y}$
	p-value	0.099	0.347	0.255	0.805	0.286	0.035	0.360	0.029
Rectal temperature (°C)	I	38.03 ± 0.34^{a}	$37.72\pm0.43^{a, b}$	$37.55\pm0.36^{a, b}$	$37.05\pm0.37^{a, b}$	$37.10\pm0.42^{a, b}$	$36.80\pm0.49^{a, b, x}$	$36.47\pm0.51^{a, b, x}$	$36.00\pm0.50^{b, x}$
	II	38.42 ± 0.36^{a}	37.87 ± 0.38^{a}	37.37 ± 0.40^{b}	37.03 ± 0.34^{c}	36.82 ± 0.22^{c}	$36.57\pm0.23^{c, y}$	$36.23\pm0.23^{c, y}$	$35.88\pm0.16^{c, y}$
	p-value	0.954	0.959	0.766	0.950	0.092	0.030	0.003	0.000

Means bearing different superscripts (a, b, c) within the rows differ significantly ($p\leq0.05$)
Means bearing different superscripts (x, y) within the columns differ significantly ($p\leq0.05$)

The heart rate recorded during anaesthetic procedure in the study did not produce any significant difference between the groups except during 45 and 60 min of maintenance but within physiological limits. However, a non-significant decrease in the heart rate was noticed after administration of premedicates in all the animals whereas a non-significant increase in heart rate was observed after administration of diazepam-ketamine in group I animals and zolazepam-tiletamine in group II animals, respectively.
Heart rate was reduced in all the animals after administration of premedicates in the present study concurred with the findings of Bayan *et al.* (2021) [2]. It could be attributed to the synergistic effect of dexmedetomidine-butorphanol that leads to decrease in sympathetic tone, reflex response from peripheral hypertension, activation of parasympathetic tone or combination of these (Krimins *et al.*, 2012) [14]. However, administration of atropine moderated the dexmedetomidine induced bradycardia. (Hogue *et al.*, 2002) [11].
Heart rate was increased in all the animals of group I after administration of diazepam-ketamine which resembles the findings of Gebremedhin *et al.* (2018) [5]. The initial non-significant increase in heart rate might be due to cardiovascular stimulant property of ketamine that causes increase in central release of catecholamine resulting in tachycardia (Hardie and Lukasik, 2007) [9] and gradually decrease might be due to the suppression of limbic system in the brain by diazepam (Yohannes *et al.*, 2018) [22]. However, in group II animals, the non-significant increase in heart rate resembles the findings of Koli *et al.* (2021) [13] and Ratnu *et al.* (2021) [19] who stated that heart rate increased due to sympathomimetic activity of tiletamine that leads to rise in the catecholamine concentration due to the blockade of norepinephrine reuptake and stimulation of sinus node caused elevation of heart rate, a well-documented feature of dissociative drugs.
Statistically there was no significant difference noticed in respiratory rate in the anaesthetic study except during 30 and 60 min of maintenance, between two groups. Within group I, significant decrease in respiratory rate noticed after premedication and induction resembles the findings of and Bayan *et al.* (2020) [1] who reported that respiratory rate was decreased non significantly from 10 minutes up to 40 minutes following administration of the anaesthetic combination of diazepam and ketamine. Further, Sabbe *et al.* (1994) [20]

observed that dexmedetomidine produce respiratory depression in dose dependent manner. Lascelles and Robertson (2004) [15] stated that butorphanol produce dose dependant respiratory ceiling effect. The respiratory depression with ketamine anaesthesia might also be due to airway relaxation by acting on various receptors, inflammatory cascades and bronchial smooth muscles as reported by Goel and Agrawal (2013) [7]. In the present study, the decrease in respiratory rate could be attributed to the combined use of dexmedetomidine, butorphanol and diazepam -ketamine.

Significant decrease in respiratory rate noticed in group II animals could be due to administration of premedicates. A non-significant decrease in respiratory rate after induction with Zolazepam-tiletamine is in concordance with the findings of, Krimins *et al.* (2012) [14], and Koli *et al.* (2021) [13].

There was no significant difference in rectal temperature noticed between groups except at 30, 45 and 60 min of maintenance when compared to other studies which might be due to difference in breed and physiological status of the dogs (Gebremedhin *et al.*, 2018) [5]. But a non-significant decrease in temperature noticed in group I in all the stages of anaesthesia except at 60 min is concurred with the findings of Yohannes *et al.* (2018) [22]. Gebremedhin *et al.* (2018) [5] reported that decrease in body temperature after administration of diazepam-ketamine could be explained by blocking of the hypothalamic thermoregulatory centre. However, in group II animals, significant reduction in rectal temperature was noticed after induction and during maintenance which is in accordance with the findings of Ratnu *et al.* (2021) [19] who stated that the decrease in rectal temperature might be related to reduction in metabolic rate due to generalized sedation and muscle relaxation.

The saturation of peripheral oxygen (SpO_2), mean arterial pressure, tidal volume and minute volume were recorded during maintenance with isoflurane in all the animals of Group I and II (Table 2).

Table 2: Mean (±SE) saturation of peripheral oxygen, mean arterial pressure, tidal volume and minute volume recorded during maintenance of anesthesia.

Parameters	Group	Maintenance				
		0 min	**15 min**	**30 min**	**45 min**	**60 min**
SpO_2 (%)	I	99.33±0.42	99.50±0.22	99.50±0.22	99.33±0.33	99.33±0.49
	II	99.67±0.33	99.50±0.34	99.33±0.33	99.33±0.42	99.00±0.37
	p-value	0.234	0.341	0.29	0.304	0.553
Mean arterial pressure. (mmHg)	I	110.50±1.89^{a}	106.33±4.34$^{a, b}$	101.33±4.03$^{a, b}$	95.17±3.70^{b}	93.66±3.47^{b}
	II	119.33±5.03	123.66±4.33	127.83±3.61	117.33±3.02	112.66±1.68
	p-value	0.053	0.881	0.744	0.71	0.209
Tidal volume (ml/kg)	I	296.33±70.03	281.50±69.41	272.17±67.99	264.83±68.49	252.67±67.69
	II	250.50±47.65	239.17±47.75	226.00±44.81	217.67±43.61	206.67±42.09
	p-value	0.816	0.818	0.747	0.704	0.679
Minute volume (l/kg)	I	5.33±1.34	4.78±1.31	3.77±0.83	3.84±0.88	3.85±0.95
	II	3.16±0.51	3.15±0.64	3.06±0.56	2.98±0.62	2.94±0.66
	p-value	0.140	0.242	0.337	0.254	0.661

Means bearing different superscripts (a, b) within the rows differ significantly ($p \leq 0.05$)

There was no significant difference in saturation of peripheral oxygen during different intervals of maintenance of anaesthesia with isoflurane among the groups. In the present study, high SpO_2 values throughout the maintenance and varied from 96.6 to 99% was noticed is indicative of good ventilation during the long-term anaesthesia in the anaesthetic protocols. These findings are in concordance with Koli *et al.* (2021) [13] and Ghareeb *et al.* (2022) [6].

There was no significant difference in mean arterial pressure during different intervals of maintenance of anaesthesia with isoflurane between the groups, which is in concordance with White *et al.* (2001) [21] who stated that there is absence of significant difference in mean arterial pressure while comparing the induction characteristics between diazepam-ketamine and thiopentone in dogs which could be attributed to the concurrent administration of diazepam (Jackson *et al.*, 1978) [12] or maintenance of anaesthesia with inhalational agent (Bidwai *et al.*, 1975) [3].

However, in group I, significant decrease in mean arterial pressure was observed at 45 and 60 min. Decreased mean arterial pressure might be due to arterial and venous vasodilatation and decreased contractility of the heart due to effect of isoflurane or due to peri-operative sympatholytic and stimulation of central alpha 2 adrenergic receptors. This was in corroboration with the findings of (Bayan *et al.*, 2021) [2]. However, in group II, a non-significant increase in MAP up to 30 min then a gradually decrease was observed which is in accordance with Krimins *et al.* (2012) [14] who stated that the increased MAP could be due to the vasoconstriction induced by dexmedetomidine and the increase in heart rate and positive ionotropic effects attributable to the dissociative drugs, which is a hemodynamic response.

The tidal volume and minute volume recorded during maintenance of anaesthesia was not significant among the groups. However, there was a non-significant decrease in tidal and minute volume during maintenance in both the groups and this could be attributed to the lower respiratory rate. This was in accordance with the findings of Grimm *et al.* (2015) [8] who stated that there is a strong correlation between decrease in respiratory rate and tidal volume. Further, Hellyer *et al.* (1989) [10] also stated that administration of zolazepam-tiletamine to conscious dogs caused decreases in minute volume without any significant change in respiratory rate.

Conclusion

From the present study, it can be concluded that induction of anaesthesia with diazepam-ketamine and zolazepam-tiletamine did not produce any alterations in the physiological and cardiopulmonary parameters. The changes that occurred were within the physiological limits. However, the heart rate was found to be increased in both the groups after induction, but that increase was less with zolazepam- tiletamine. Based on the parameters studied both the anaesthetic protocols are found to be suitable and safe for abdominal surgeries in dogs.

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