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Comparison of cardiorespiratory effects and perioperative analgesia efficacy of dexmedetomidine or fentanyl continuous infusion during ovariohysterectomy in propofol-anesthetized dogs

Comparação dos efeitos cardiorrespiratórios e eficácia analgésica perioperatória da infusão contínua de dexmedetomidina ou fentanil durante a ovariohisterectomia de cadelas anestesiadas com propofol

Comparación de los efectos cardiorrespiratorios y la eficacia analgésica perioperatoria de la infusión continua de dexmedetomidina o fentanilo durante la ovariohisterectomía en perras anestesiadas con propofol

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Abstract
The present study aimed to compare the cardiorespiratory, perioperative analgesic and blood gas analysis of the constant rate infusion of dexmedetomidine or fentanyl in 16 female dogs undergoing to elective ovariohysterectomy. The dogs were premedicated with morphine (0.5 mg/kg) and dexmedetomidine (5 µg/kg) or acepromazine (0.05 mg/kg), both intramuscularly (IM), in GDEX or GFEN, respectively. After anesthesia induction with propofol intravenously (IV), animals of GFEN received bolus of fentanyl (2.5 µg/kg) IV followed by continuous rate infusion (CRI) (10 µg/kg/h) and the GDEX received bolus of saline solution 0.9% (corresponding volume of fentanyl) followed by CRI of dexmedetomidine (1 µg/kg/h) and anesthesia was maintained with propofol (0.22 mg/kg/min). In the end of surgery all animals were evaluated using the Glasgow composite measure pain scale (GCPS) and a visual analogue scale (VAS). Data was compared with a statistical p value > 0,05. The mean heart rate was statistically lower in GDEX when compared to GFEN ($p = 0.0498$): 54.25 ± 3.919 and 88.38 ± 8.766 beats per minute, respectively. Opposed, the average mean blood pressure was statistically higher in GDEX when compared to GFEN ($p = 0.0021$): 99.38 ± 8.551 and 80.75 ± 11.12 mmHg, respectively. The GDEX and GFEN, in the firsts 4 and 2 postoperative hours, respectively, presented values significantly higher than baseline in the GCPS, occurring analgesic rescues for both groups. It is concluded that both drugs in the proposed rates were safe and efficient for nociceptive control during intraoperative, however, failed to promote efficient postoperative analgesia.
Keywords: Dexmedetomidine; Fentanyl; Dogs; Propofol; Total intravenous anesthesia.

Resumo

O estudo objetivou comparar os efeitos cardiorrespiratórios, analgésicos perioperativos e hemogasométricos de 16 cadelas submetidas a ovariohisterectomia eletiva sob infusão contínua de dexmedetomidina ou fentanil. Os cães foram pré-medicados com morfina (0,5 mg/kg) e dexmedemidina (5 µg/kg) ou acepromazina (0,05 mg/kg), ambos intramuscular (IM), no GDEX ou GFEN, respectivamente. Depois na indução anestésica com propofol intravenoso (IV), os animais do GFEN receberam *bolus* de fentanil (2,5 µg/kg) IV seguido de infusão contínua (IC) (10 µg/kg/h) e o GDEX recebeu *bolus* de solução salina 0,9% (volume correspondente de fentanil) seguido de IC de dexmedetomidina (1 µg/kg/h) e a anestesia foi mantida com propofol (0,22 mg/kg/min). Ao final do procedimento todos os animais foram avaliados usando a Escala composta de dor de Glasgow (GCPS) e a Escala analógica visual (VAS). Os dados foram comparados com um valor estatística de $p > 0,05$. A média da frequência cardíaca foi estatisticamente menor no GDEX quando comparado ao GFEN ($p = 0,0498$): 54,25 ± 3,919 e 88,38 ± 8,766 batimentos por minuto, respectivamente. Em oposição, a média final da pressão arterial média foi estatisticamente maior no GDEX quando comparado ao GFEN ($p = 0,0021$): 99,38 ± 8,551 e 80,75 ± 11,12 mmHg, respectivamente. O GDEX e GFEN, nas primeiras 4 e 2 horas de pós-operatório, respectivamente, apresentaram escores estatisticamente maiores que o basal pela GCPS, ocorrendo resgate analgésico em ambos os grupos. Conclui-se que ambos os fármacos nas taxas propostas foram seguros e eficientes no controle nociceptivo intraoperatório, no entanto, falharam em promover analgesia pós-operatória.

Palavras-chave: Anestesia total intravenosa; Cachorro; Dexmedetomidina; Fentanil; Propofol.

Resumen

El objetivo del estudio era comparar los efectos cardiorrespiratorios, analgésicos perioperatorios y hemogasométricos de 16 perras sometidas a ovariohisterectomía electiva bajo infusión continua de dexmedetomidina o fentanilo. Las perras fueron premedicadas con morfina (0,5 mg/kg) y dexmedemidina (5 µg/kg) o acepromacina (0,05 mg/kg), intramuscular (IM), en GDEX o GFEN, respectivamente. Tras la inducción anestésica con propofol intravenoso (IV), los animales de GFEN recibieron un bolo de fentanilo (2,5 µg/kg) IV seguido de infusión continua (IC) (10 µg/kg/h) y los de GDEX recibieron un bolo de solución salina al 0,9% (volumen correspondiente de fentanilo) seguido de dexmedetomidina IC (1 µg/kg/h) y la anestesia se mantuvo con propofol (0,22 mg/kg/min). Al final del procedimiento, todos los animales fueron evaluados mediante la *Glasgow Composite Pain Scale* (GCPS) y la *Visual Analogue Scale* (VAS). Los datos se compararon con un valor estadístico de $p > 0,05$. La frecuencia cardiaca media fue estadísticamente inferior en GDEX en comparación con GFEN ($p = 0,0498$): 54,25 ± 3,919 y 88,38 ± 8,766 latidos por minuto, respectivamente. Por el contrario, la presión arterial media final fue significativamente mayor en GDEX que en GFEN ($p = 0,0021$): 99,38 ± 8,551 y 80,75 ± 11,12 mmHg, respectivamente. GDEX y GFEN, en las primeras 4 y 2 horas del postoperatorio, respectivamente, presentaron puntuaciones estadísticamente superiores a las basales por GCPS, produciéndose rescate analgésico en ambos grupos. Concluimos que ambos fármacos en las dosis propuestas fueron seguros y eficaces en el control nociceptivo intraoperatorio; sin embargo, no consiguieron promover la analgesia postoperatoria.

Palabras clave: Anestesia intravenosa total; Dexmedetomidina; Fentanilo; Perro; Propofol.

1. Introduction

Ovariohysterectomy is a routine procedure capable of generating acute pain in dogs (Gaynor & Muir, 2015), which consequently can cause negative postoperative effects, such as delayed wound healing and anxiety. To minimize deleterious physiological effects of pain, analgesia is an essential tool, moreover ethical considerations (Hansen, 2005).

A great number of techniques and analgesic drugs are available for pain control in veterinary medicine (Wagner & Hellyer, 2002). Pain control drugs in continuous rate infusion (CRI) have the potential to be applied in perioperative, demonstrating advantages to keep a better steady level of analgesia and less deleterious effects compared to intermittent technique (Dyson, 2008).

Fentanyl is characterized as a fast-acting drug (Pascoe, 2000) and is the most popular opioid for CRI (Dyson, 2008). The CRI of fentanyl was reported reducing the minimum alveolar concentration (MAC) of volatile anesthetics in humans (Mcewan et al., 1993) and dogs (Williamson et al., 2017), furthermore, reduced CRI of propofol in cats (Mendes & Selmi, 2003) and dogs (Davis et al., 2017). The drug is characterized for its short duration of action (Yaksh et al., 1986) and its side effects when administered in high doses (3 mg/kg, almost 600 times more than recommended) in awake dogs were cardiac output and arterial pressure reduction (Liu et al., 1976).

The antinociception obtained by opioids can be reached with multimodal administration of nonopioid drugs like α_2 agonists (Hwang et al., 2015). Dexmedetomidine is a potent α_2-adrenoreceptor agonist used for sedation and analgesia in dogs and cats (Murrell & Hellebrekers, 2005; Pascoe et al., 2006). Furthermore, CRI of dexmedetomidine promotes analgesia at lower doses than those capable to produce hemodynamic changes, providing perioperative hemodynamic stability (Simon et al., 2018) and postoperative analgesia equally as morphine, with no significant adverse reactions in dogs (Valtolina et al., 2009). Total intravenous anesthesia (TIVA) protocols with dexmedetomidine significantly decreased the minimum infusion rate of propofol preventing movement (Smith et al., 2017).

Therefore, the current study was performed to compare the intraoperative cardiorespiratory effects and the perioperative analgesic efficacy of fentanyl or dexmedetomidine associated with propofol in CRI for elective ovariohysterectomy in dogs. We hypothesized that dexmedetomidine would promote a higher arterial blood pressure and lower heart rate when compared to fentanyl. Also, both drugs would be efficient on pain control and would promote similar postoperative analgesia as well as similar sedation score.

2. Methodology

The study was designed as a prospective, blind, controlled clinical trial and was approved by the Animal Research and Ethical Committee of the Santa Catarina State University (Universidade do Estado de Santa Catarina – number 01.17.14). Female dog owners from hospital routine were contacted for elective ovariohysterectomy procedure during the study. After a clinical, hematological and serum biochemical evaluation, 16 ASA I female dogs were enrolled in the study with a prior owner written consent form.

The animals were allocated in a different room from the hospital routine 24 hours before the start of the study for acclimation. Food and water were withheld for up to 12 and 6 hours, respectively, before premedication. For the experimental procedure, except for two operators who administered the drugs (FC and NO) all the other operators were blind for treatments and the animals were randomly allocated to one of two study groups: in dexmedetomidine group (GDEX, n = 8) dogs were premedicated with dexmedetomidine (5 µg/kg; Dexdomitor; Zoetis Ltda., São Paulo, SP, Brazil) and morphine (0,5 mg/kg; Dimorf; Cristália Produtos Químicos e Farmacêuticos Ltda., São Paulo, SP, Brazil); In fentanyl group (GFEN, n = 8) dogs received acepromazine (0,05 mg/kg; Acepran; Vetnil Indústria e Comércio de Produtos Ltda., Louveira, SP, Brazil) and morphine (0.5 mg/kg; Dimorf; Cristália Produtos Químicos e Farmacêuticos Ltda., São Paulo, SP, Brazil). Both groups received premedication intramuscularly (IM).

Approximately 15 minutes after application, a catheter was placed and fixed in cephalic vein and unconsciousness was induced with intravenous (IV) propofol (1 mg/kg every 30 seconds; Propovan; Cristália Produtos Químicos e Farmacêuticos Ltda., São Paulo, SP, Brazil) for loss of swallowing reflex in a dose response rate. Lidocaine (0,1 mL, 10%; Xylestesin; Cristália Produtos Químicos e Farmacêuticos Ltda., São Paulo, SP, Brazil) was instilled in the larynx and the trachea was intubated using a cuffed endotracheal tube with appropriately size. Continuous infusion of propofol started immediately after induction at a fixed rate of 0,22 mg/kg/min in a syringe infusion pump (ST 670, Samtronic, São Paulo, SP, Brasil). Simultaneously, the animals were mated in a circle system (Ventilador Pulmonar Oximag Agile; Magnamed, São Paulo, SP, Brazil) in pressure control ventilation mode of 10 cmH_2O, adjusted during procedure for normocapnia maintenance (End-tidal CO_2 (EtCO2) between 35-45 mmHg), with a fresh gas flow of compressed air with 40% oxygen (10 ml/kg/minute). To supply temperature control during the procedure, all animals were positioned in dorsal recumbency above an electric heating blanket (Colchão Térmico Digital Grande; Prevtech Equipamentos Veterinários, SP, Brazil).

After induction, treatment bolus application occurred IV over 5 minutes with fentanyl (2.5 µg/kg; Fentanest; Cristália Produtos Químicos e Farmacêuticos Ltda., São Paulo, SP, Brazil) in GFEN and Saline Solution 0.9% (corresponding volume of fentanyl; Laboratório Sanobiol, Pouso Alegre, MG, Brazil) in GDEX. Continuous infusions started immediately after bolus application for 1 hour long: fentanyl (10 µg/kg/h) in GFEN or dexmedetomidine (1 µg/kg/h) in GDEX. The CRIs were adjusted to equivalent volumes for both groups for the same operator to maintain the blindness of the study for the rest of the operators. Immediately after bolus application, the dorsal pedal artery was accessed with a venous catheter and connected with a blood pressure transducer for measurement of systolic (SAP), diastolic (DAP) and mean (MAP) blood pressures.

The other variables were also measured with a multiparameter monitor (Carescape Monitor B650; GE Healthcare, São Paulo, SP, Brazil): heart rate (HR), with an electrocardiogram (ECG), peripheral hemoglobin oxygen saturation (SpO_2) and esophageal temperature (T ºC). Respiratory rate (*f*) and $EtCO_2$ were measured with capnography in a sidestream sensor attached to the endotracheal tube (the sensor was automatically calibrated at the beginning of each animal).

Physiological variables were recorded after performing arterial access (T0); 10 and 15 minutes (min) after CRI's beginning (T1 and T2, respectively); after alba line incision (T3); after clamping the first and second ovarian pedicle (T4 and T5, respectively); after clamping cervix (T6); immediately after the end of surgery (T7). Blood gas variables were also recorded (T0, T1, T2, T4, T6 and T7) by arterial blood analysis (cobas b 121; Roche Diagnóstica Brasil Ltda.; SP, Brazil). At the end of surgery, all animals received IV meloxicam (0.2 mg/kg; Maxicam 0.2%, Ourofino Saúde Animal, Vinhedo, SP, Brasil). All the process during anesthesia and the variables register was performed by the same operators that were blind to the study treatment and the surgery was performed by the same operator during the study process.

All animals were evaluated using the Visual Analogue Scale for Sedation (VAS) and the Glasgow Composite Measure Pain Scale (GCPS) 24 hours before the study start, called moment 0 (M0), and hourly from the second to the sixth postoperative hour after extubation (M2, M3, M4, M5 and M6). Using the VAS, animals were evaluated using a scale from 0 to 100 points, scoring subjectively in which 30 points would result in analgesic rescue. Also, the GCPS evaluates behavior, reaction to palpation around surgical wound, walking, vocalization, posture, activity and attitude. The analgesic rescue occurred when animals scored 30 (VAS) and/or six (GCPS) points during evaluation and morphine (0,5 mg/kg) IM was administered. The same experienced operator performed all sedation and pain scores evaluation. The dogs were observed continuously throughout the recovery period until their discharge with home prescription treatment.

All statistical analyses were performed using GraphPad Prism Version 8.0.0 (Windows Software, San Diego, CA, USA) by the operators GBC, FC and NO. Values were reported as mean ± standard deviation (SD). Data normality was analyzed by Shapiro Wilk test. Nonparametric data were analyzed using Friedman test followed by the Tukey test for moments comparison within the same group and Wilcoxin Signed Rank Test for comparison between groups. Physiological data were analyzed using Student T test for comparison between groups and Mann-Whitney Rank test for comparison between moments within the same group. Diferences were statistically significant when $p < 0.05$.

3. Results

There was no statistical difference of age or weight between enrolled animals ($p > 0.05$). Dogs were 16 ± 10 months old and weighed 17.3 ± 6.04 kg. Also, the propofol doses for induction of anesthesia were similar between groups, 3.38 ± 0.64 mg/kg in GFEN and 3.1 ± 0.64 mg/kg in GDEX, with no statistical difference ($p > 0.05$).

In physiological measurements (Table 1), regular heart rhythm was observed throughout anesthesia by ECG. The HR was different between groups, it was statistically lower in GDEX than GFEN ($p < 0.05$) from T0 to T7 (Table 1). When all the moments from the study were compared as a set mean, the HR was statistically lower ($p = 0.0498$) in GDEX compared do

GFEN (54.25 ± 3.91 and 88.38 ± 8.76 beats minute, respectively). When HR from before surgery (T0, T1 and T2) was compared to the set mean of surgical moments (T3 to T7) there was no statistical difference in both groups: HR mean was 56.33 ± 1.52 and 53.00 ± 4.52 beats minute, respectively, in GDEX ($p = 0.275$) and 94.33 ± 8.5 and 84.80 ± 7.46 beats minute, respectively, in GFEN ($p = 0.1463$). The SAP was statistically higher in GDEX from T0 to T3, while DAP and MAP were higher from T0 to T6 when compared to GFEN ($p < 0.05$). The SAP, DAP and MAP were higher in T4 and T5 in GFEN when compared to baseline whilst only DAP was higher in GDEX in the same moments ($p < 0.05$). Also, comparing all the moments as a set mean, all the pressures were statistically higher in GDEX when compared to GFEN: SAP was 134 ± 11.14 and 113.3 ± 13.46 mmHg ($p = 0.0047$), respectively; DAP was 85.38 ± 9.33 and 69.88 ± 9.31 mmHg ($p = 0.005$), respectively; MAP was 99.38 ± 8.55 and 80.75 ± 11.12 mmHg ($p = 0.0021$). Moreover, when the baseline (T0) was compared with the set mean of surgical moments, there was no statistical difference in both groups for all the pressures: MAP was 94.0 and 103.4 mmHg, respectively, in GDEX ($p = 0.367$) and 77.0 and 86.4 mmHg, respectively, in GFEN ($p = 0.4279$).

Table 1 – Physiological parameters (HR, SAP, MAP, DAP, SpO_2 and $EtCO_2$) recorded during anaesthesia with propofol in CRI (0.22 mg/kg/min) associated with CRI of dexmedetomidine (1 µg/kg/h) in GDEX or fentanyl (10 µg/kg/h) in GFEN, in dogs undergoing ovariohysterectomy. Physiological variables were recorded after performing arterial access (T0); 10 and 15 minutes (min) after CRI's beginning (T1 and T2, respectively); after alba line incision (T3); after clamping the first and second ovarian pedicle (T4 and T5, respectively); after clamping cervix (T6); immediately after the end of surgery (T7).

Variable	**Group**	**Time points**							
		(T0)	**(T1)**	**(T2)**	**(T3)**	**(T4)**	**(T5)**	**(T6)**	**(T7)**
HR (beats/min)	GDEX	56 ± 14a	55 ± 15a	58 ± 16a	55 ± 18a	49 ± 10a	51 ± 13a	50 ± 15a	60 ± 12a
	GFEN	103 ± 29a	94 ± 30a	86 ± 22a	92 ± 29a	83 ± 35a	80 ± 22a	76 ± 22 Aa	93 ± 26a
T (ºC)	GDEX	37.1 ± 0.6	37.2 ± 0.7	37.2 ± 0.8	37.2 ± 0.7	37,2 ± 0,6	37 ± 0.6	37 ± 0.6	36.9 ± 0.8
	GFEN	36.8 ± 0.9	36.6 ± 1.1	36.6 ± 1.3	36.5 ± 1.3	36,3 ± 1,2	36.4 ± 1.3	36.3 ± 1.3	36.2 ± 1.4
SAP (mmHg)	GDEX	130 ± 10a	124 ± 17a	125 ± 14a	129 ± 12a	154 ± 31	148 ± 20	135 ± 24	127 ± 15
	GFEN	107 ± 13a	99 ± 12a	95 ± 10a	110 ± 15a	132 ± 13A	131 ± 16a	116 ± 21	116 ± 17
MAP (mmHg)	GDEX	94 ± 12a	94 ± 13a	90 ± 12a	92 ± 11a	110 ± 20a	111 ± 10a	107 ± 11a	97 ± 20
	GFEN	77 ± 12a	71 ± 10a	66 ± 10a	75 ± 5a	98 ± 6aA	95 ± 9aA	81 ± 12a	83 ± 13
DAP (mmHg)	GDEX	82 ± 11a	81 ± 11a	77 ± 14a	79 ± 11a	101 ± 17aA	95 ± 8aA	92 ± 9a	76 ± 9
	GFEN	67 ± 12a	61 ± 10a	59 ± 6a	65 ± 5a	85 ± 7aA	82 ± 9a	69 ± 10a	71 ± 12
SpO_2 (%)	GDEX	94 ± 3	94 ± 2a	95 ± 3	95 ± 3	94 ± 3	93 ± 6	94 ± 3	93 ± 7
	GFEN	96 ± 2	97 ± 3a	96 ± 3	96 ± 2	94 ± 4	93 ± 4	96 ± 2	96 ± 2
$EtCO_2$ (mmHg)	GDEX	37 ± 7	37 ± 6	37 ± 7	37 ± 5	38 ± 5	39 ± 4	39 ± 5	40 ± 5
	GFEN	31 ± 5	32 ± 5	33 ± 4	32 ± 4	34 ± 4A	35 ± 4A	35 ± 4	37 ± 4

(A): significant difference ($p < 0.05$) from baseline (T0). (a): significant difference ($p < 0.05$) between groups at the same period. Source: Authors.

Body temperature and SpO_2 were similar between groups, despite that the SpO_2 was statistically lower ($p < 0.05$) in GDEX compared to GFEN during T1 (94 ± 2 and 97 ± 3 %, respectively). Also, the $EtCO_2$ was lower ($p < 0.05$) in T4 and T5 compared to baseline in GFEN (Table 1). For blood gas analyses (Table 2), there was statistically difference between groups in pH ($p < 0.05$) during T1 (7.38 ± 0.05 and 7.44 ± 0.03 in GDEX and GFEN, respectively), however, all the variables were close to physiological values for the specie ($p < 0.05$).

Table 2 - Arterial blood gas variables (pH, PCO2, base excess, HCO3, Na, Cl, Ca, K, SO_2, AG) recorded during anaesthesia with propofol in CRI (0.22 mg/kg/min) associated with CRI of dexmedetomidine (1 µg/kg/h) or fentanyl (10 µg/kg/h), in dogs undergoing ovariohysterectomy. Arterial blood gas variables were recorded after performing arterial access (T0); 10 and 15 minutes (min) after CRI's beginning (T1 and T2, respectively); after clamping the first ovarian pedicle (T4); after clamping cervix (T6); immediately after the end of surgery (T7).

Variable	Group	Time points					
		T0	T1	T2	T4	T6	T7
PO_2 (mmHg)	GDEX	203 ± 28	220 ± 17	170 ± 66	226 ± 31	222 ± 29	227 ± 27
	GFEN	218 ± 31	227 ± 30	220 ± 12	219 ± 19	207 ± 23	194 ± 41
PCO_2 (mmHg)	GDEX	32 ± 8	31 ± 8	32 ± 6	34 ± 3	36 ± 5	40 ± 7
	GFEN	28 ± 5	27 ± 2	28 ± 2	31 ± 3	34 ± 5	39 ± 5
pH	GDEX	7.39 ± 0.06	7.38 ± 0.05a	7.37 ± 0.05	7.36 ± 0.03	7.33 ± 0.05	7.32 ± 0.06
	GFEN	7.45 ± 0.06	7.44 ± 0.03a	7.42 ± 0.02	7.39 ± 0.05	7.38 ± 0.04	7.34 ± 0.04
tHb (g/dL)	GDEX	15 ± 2	15 ± 1	14 ± 2	15 ± 2	15 ± 3	14 ± 3
	GFEN	13 ± 2	13 ± 3	12 ± 3	13 ± 2	13 ± 2	12 ± 2
Na (mmol/L)	GDEX	152 ± 3	152 ± 4	152 ± 3	151 ± 2	151 ± 3	151 ± 3
	GFEN	150 ± 1	152 ± 0.1	152 ± 2	148 ± 6	150 ± 4	151 ± 3
Cl (mmol/L)	GDEX	316 ± 448	119 ± 5	117 ± 3	115 ± 2	115 ± 3	115 ± 2
	GFEN	119 ± 5	116 ± 1	116 ± 3	112 ± 6	114 ± 4	113 ± 2
ICa	GDEX	0.8 ± 0.1	0.8 ± 0.2	0.8 ± 0.2	0.9 ± 0.1	1 ± 0.2	0.9 ± 0.1
	GFEN	1.1 ± 0.5	0.7 ± 0.2	0.7 ± 0.1	1 ± 0.2	1 ± 0.2	1 ± 0.1
$cHCO_3$ (mmol/L)	GDEX	18.9 ± 2.3	18 ± 2.5	18.7 ± 2.2	19 ± 0.8	19 ± 2.1	20.2 ± 1.8
	GFEN	19.2 ± 0.8	18.2 ± 1.2	18.2 ± 0.6	19.9 ± 1	19.8 ± 1.6	20.9 ± 1.6
SO_2 (%)	GDEX	99.7 ± 0.2	99.7 ± 0.1	99.7 ± 0.1	99.7 ± 0.1	99.7 ± 0.2	99.7 ± 0.1
	GFEN	99.7 ± 0.2	99.8 ± 0.1	99.8 ± 0.04	99.7 ± 0.1	99.7 ± 0.1	99.4 ± 0.4
BEecf (mmol/L)	GDEX	-5.9 ± 2.1	-7 ± 2	-6.4 ± 0.1	-6.4 ± 0.1	-6.8 ± 2.5	-5.7 ± 1.9
	GFEN	-4.6 ± 0.7	-5.7 ± 1.5	-6.1 ± 0.7	-5.7 ± 0.7	-5.2 ± 1.1	-4.7 ± 1.6
AG (mmol/L)	GDEX	20 ± 2.5	18.7 ± 3.3	19.3 ± 3.4	21 ± 2	20.7 ± 2.5	20 ± 2.9
	GFEN	18.1 ± 2.8	20.5 ± 0.4	20.7 ± 1.1	19.7 ± 1.5	20.4 ± 2.2	19.1 ± 1.6

(a): significant difference ($p < 0.05$) between groups at the same period. Source: Authors.

Lastly, there was no statistical difference in sedation scores between groups 15 minutes after premedication ($p > 0.05$): median degree was 2 [1-3] and 1 [1-2] in GDEX and GFEN, respectively (Table 3) and all dogs were judged to be

adequately sedated. Also, there was no statistical difference in sedation scores between groups during the postoperative ($p > 0.05$).

Table 3 – Scores obtained through an analogue scale for sedation (VAS) 15 min after premedication (M-15) and hourly from the second to the sixth postoperative hour (M0 to M6). Scores obtained through Glasgow composite measure pain scale (GCPS) 24 hours before the study start (M0) and hourly from the second to the sixth postoperative hour (M2, M3, M4, M5 and M6). The analgesic rescue occurred when animals scored 30 (VAS) and/or six (GCPS) points during evaluation.

		Moment						
	Group	**M-15**	**M0**	**M2**	**M3**	**M4**	**M5**	**M6**
Sedation M-15	GDEX	2[1-3]	-	-	-	-	-	-
	GFEN	1[1-2]	-	-	-	-	-	-
Postoperative Sedation	GDEX	-	0[0-0]	0[0-0]	0[0-1]	0[0-0]	0[0-0]	0[0-0]
	GFEN	-	0[0-0]	0.5[0-3]	0[0-3]	0[0-0]	0[0-1]	0[0-0]
VAS	GDEX	-	0[0-0]	0[0-20]	0[0-20]	0[0-25]	0[0-10]	0[0-10]
	GFEN	-	0[0-0]	0[0-40]	0[0-40]	0[0-80]	0[0-70]	0[0-20]
GCPS	GDEX	-	0[0-0]	4[0-8]a	3.5[0-7]a	2[0-8]a	1[0-5]	1[0-5]
	GFEN	-	0[0-0]	3[1-8]a	2[1-10]	1[1-14]	1[0-14]	1.5[0-5]

(a): significant difference ($p < 0.05$) between groups at the same period. Source: Authors.

Compared to baseline (M0), there was statistical difference ($p < 0.05$) in GCPS for both groups in M2 (median degree of 4 [0-8] and 3 [1-8] in GDEX and GFEN, respectively). Furthermore, there was statistical difference in M3 and M4 compared to M0 in GDEX (3.5 [0-7] and 2 [0-8], respectively). Regarding the number of analgesic rescues, by AVA only animals from GFEN achieved analgesic rescue score in M2, M3, M4 and M5 (one animal for each moment). By the GCPS, the analgesic rescue score was achieved in GDEX and GFEN during M2 (2 rescues each group), M3 (2 rescues each group), M4 (1 rescue each group) and M5 (1 rescue in GFEN). There was no statistical difference between groups in the number of analgesic rescues, further the time of occurrence or achieved scores. Recovery was complete after 6 hours and usually smooth in all dogs in the study with no adverse effects.

4. Discussion

In the present study, female dogs under anesthesia for elective ovariohysterectomy with CRI of propofol (0.22 mg/kg/min) in association with CRI of dexmedetomidine (3 µg/kg followed by 1 µg/kg/h) or fentanyl (2.5 µg/kg followed by 10 µg/kg/h) demonstrated similar effects on nociceptive control during intraoperative and, in opposition, different pharmacological effects in the cardiovascular parameters. Furthermore, both protocols demonstrated similar postoperative results for analgesic rescue and sedation scores.

Dexmedetomidine and acepromazine are usually chosen as premedication for the same purpose of sedation, but both drugs are chemically unrelated and capable of producing different undesired effects. Hypotension might occur earlier and last longer when dogs are premedicated with acepromazine compared to dexmedetomidine (Martin-Flores et al., 2019). In addition, propofol dose for induction of anesthesia seems to reduce with acepromazine or dexmedetomidine used as premedication in different species (Dutta et al., 2011; Smith et al., 2017), especially, when combined with opioids, producing more sedation (Canfrán et al., 2016). Comparing both drugs as premedication in dogs, acepromazine (0.05 mg/kg IM) exacerbated hypotension mean while dexmedetomidine (15 µg/kg IM) reduced cardiac output (Grasso et al., 2015). In the present study,

doses for induction of anesthesia were similar (3.38 ± 0.64 mg/kg in GFEN and 3.1 ± 0.64 mg/kg in GDEX) and both demonstrated no sign of excitement or swallowing and good muscular relaxation.

The anesthetic modality known as TIVA is a widely used technique mostly with propofol in association or not with other drugs (Andreoni & Linne Hughes, 2009), besides a better maintenance of arterial blood pressure in dogs (Bustamante et al., 2018). Opioids commonly used in association with propofol include fentanyl, sufentanil or remifentanil and all produce a rapid effect after initial loading dose and maintaining steady-state plasma levels during infusion, associated to its fast biotransformation and elimination (Raffe, 2020). Fentanyl interacts with μ-opioid receptors throughout the central nervous system (CNS), producing sedation and analgesia (Robinson et al., 1999). Studies had found a delay in developing a steady-state plasma concentration of 180 to 240 minutes after CRI administration. In this case, the pharmacokinetic-dynamic (PK-PD) shows that the infusion rate needs to be adjusted to provide patient comfort and physiologic stability (Raffe, 2020). A previous bolus followed by CRI of fentanyl (10 μg/kg and 10 μg/kg/min, respectively) demonstrated a plasma concentration mean of 0.9-1.3 ng/ml in awake dogs (Sano et al., 2006) and an optimal plasma fentanyl concentration for analgesia in humans and dogs was reported to be around 0.9 – 2.0 ng/ml (Varvel et al., 1989; Robinson et al., 1999). The CRI of propofol (0.3 – 0.4 mg/kg/min) and fentanyl (bolus of 2 μg/kg and infusion of 0.5 μg/kg/min) provided stable cardiovascular function and adequate conditions for surgery in dogs (Andreoni & Linne Hughes, 2009). In the present study, the bolus and CRI chosen seems to be adequate for the procedure, which is in line with previous literature (Sano et al., 2006). During surgical moments, the PAS and PAM increased 11.6% (p = 0.2663) and 10.9% (p = 0.427) when compared to baseline (T0), demonstrating a small difference between parameters, which corroborate with the lower HR during surgical moments (10.10% lower, p = 0.1463) compared to previous moments (T0, T1 and T2) and the ventilatory stability.

In a previous study, dexmedetomidine also decreased propofol induction dose and minimum infusion rate preventing movement (bolus of 1 – 2 μg/kg and infusion of 2 μg/kg/h) in dogs (Smith et al., 2017). Dexmedetomidine demonstrates rapid distribution phase with a distribution half-life of 6 minutes and a terminal elimination half-life around 2 hours (Naaz & Ozair, 2014) and it is a high selective α2-receptor agonist acting within the brainstem and in the dorsal horn of the spinal cord, producing sedative and analgesic effects (Murrell & Hellebrekers, 2005). Administration of dexmedetomidine in CRI in dogs had been report, especially for sedation and analgesia (Pascoe et al., 2006; Uilenreef et al., 2008; Van Oostrom et al., 2011; Gutierrez-Blanco et al., 2015; Nagashima et al., 2022). In the present study, the PAS and PAM in GDEX were 6.2% (p = 0.5451) and 9.1% (p = 0.3670) higher during surgical moments when compared to baseline (T0). Also, similarly to GFEN, HR in GDEX reduced by 5.91% during surgical moments when compared to previous moments (T0, T1 and T2), in addition to ventilatory stability. Despite the desirable effects produced by the drug, higher dosages of α2-agonist induce hemodynamic changes, such as increased systemic vascular resistance, inducing to bradycardia, as previous reported in other study (Nagashima et al., 2022). In general, the present study showed blood pressures in GDEX statistically higher than in GFEN, corroborating to previous studies which dexmedetomidine group had an increase in MAP that was not observed in fentanyl group (Nagashima et al., 2022). According to the same study, dogs anesthetized with isoflurane for therapeutic ovariohysterectomy with CRI of dexmedetomidine at 3 μg/kg/h did not impaired peripheral oxygen transport and organ perfusion, then dexmedetomidine seems to not compromise microcirculation, despite its pharmacological effects.

Regarding the physiology variables in the present study, during T4 and T5 the EtCO2 decreased in GFEN compared to baseline, and the reason might be associated with the sympathetic stimulation in these two moments (after clamping the first and second ovarian pedicle, respectively). Elevation of respiratory rate is known as a pain mechanism, which entails possible $EtCO_2$ decrease, due to excessive respiratory movements (Grubb et al., 2020). There were no other physiological indications of pain (HR and blood pressure increase), but this could be an explanation. Hypoventilation can cause hypoxemia and adequate

ventilation is necessary for appropriate oxygen delivery (Grubb et al., 2020). Also, the statistically lower SpO_2 in GDEX compared to GFEN during T1 (94 ± 2 and 97 ± 3, respectively) might not be related to ventilation (Table 1). Dexmedetomidine action on α2 receptor causes peripheral vasoconstriction, showing lower saturation oxygen, as previous demonstrated in intrathecal administration of dexmedetomidine on humans undergoing dynamic hip screw operation (Yazdi et al., 2020). Another point was the failure to readjust the sensor during the recording of each moment of the study, which may have influenced by generating a possible less vascularized region due to the pressure of the equipment under the tongue. Although small breeds, in which such situations can normally occur, were not used in the present study, the association of lack of readjustment with dexmedetomidine could be an explanation.

Moreover, the animals in the present study evidenced mild to moderate hypothermia (according to Oncken et al., 2001 apud Brodeur et al., 2017), registering lower values mostly in GFEN, despite no statistical difference between groups (Table 1). Temperatures lower than 98° F (36.67° C) can result in adverse effects, such as delayed drug metabolism and cardiovascular dysfunction (Grubb et al., 2020). Volatile anesthesia or TIVA seems to have no difference on loss of temperature, commonly observed during anesthesia (Khan et al., 2010). Moreover, propofol and opioids on CRI have a synergism effect promoting vasodilation, mainly caused by propofol, leading to heat redistribution from the center to the surface area (Khan et al., 2010), besides opioids influence the central thermostat, inducing a colder baseline temperature (Clark-Price, 2015).

Another point was the blood gas analyses stability, probably due to the use of young and healthy animals, previously evaluated, in addition to the ventilatory mode, especially for animals treated with fentanyl, that could have promoted a respiratory depression that was prevented for the ventilatory support. This situation was already verified in a previous study in dogs that used ventilatory mode from the presence of apnea after fentanyl application (Moura et al., 2022).

In the present study the pain control during perioperative demonstrated similar results between groups. During the six hours of postoperative evaluation of the total of 8 animals per group, 6 animals in GFEN and 5 animals in GDEX achieved the analgesic rescue score for GCPS, while only 4 animals in GFEN achieved the score for EVA, remembering that animals would have to achieved analgesic rescue score in at least one scale to received morphine. The use of intravenous meloxicam (0,2 mg kg) after the end of surgery could have interfered the real state of pain control of dexmedetomidine and fentanyl, due to meloxicam analgesic mechanism of action (Hernández-Avalos et al., 2020), but despite that, most of the animals in both groups required analgesic rescue, indicating a need for additional postoperative analgesia. In a previous study that evaluated the postoperative analgesic effects of a CRI of fentanyl (2.5 µg/kg/h) or dexmedetomidine (1 µg/kg/h) for 4 hours after elective ovariohysterectomy in dogs, only animals in dexmedetomidine required additional analgesia (25%) (Gutierrez-Blanco et al., 2015), while only one animal (1/16) required postoperative analgesic rescue for therapeutic ovariohysterectomy in dogs when the same drugs were used as CRI during surgery with rate adjustment to increase analgesia (Nagashima et al., 2022). In another study, dogs received bolus followed by CRI of fentanyl during the procedure (5 µg/kg and 5 µg/kg/h, respectively) and CRI of the drug during 8 hours of postoperative (2 µg/kg/h) when submitted to mastectomy and, although the CRI continued after surgery, the plasma fentanyl concentrations decreased below the minimum effective analgesic range for dogs (0.95 – 2.00 ng/ml). Nevertheless, the GCPS did not show sufficient scores for analgesic rescue (Moura et al., 2022). Thus, the doubt as to whether additional analgesia is required, in general, a possible intervention in all the situations will ensure greater comfort for all animals.

5. Conclusion

For dogs submitted to elective ovariohysterectomy the administration of a bolus followed by CRI of dexmedetomidine (5 µg/kg and 1 µg/kg/h, respectively) or fentanyl (2.5 µg/kg and 10 µg/kg/h, respectively) demonstrated to be efficient for nociceptive control during intraoperative. Also, both drugs proved to be safe in maintaining the physiological parameters within the standards for the species. However, both drugs failed to promote efficient postoperative analgesia and it is recommended additional analgesia during this period. The authors recommend future studies for a better understanding of the use of fentanyl and dexmedetomidine in different surgical procedures in dogs.

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