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Preoperative epidural administration of lidocaine-methadone or lidocaine-fentanyl in female dogs undergoing elective ovariohysterectomy[1]

Administração epidural pré-operatória de lidocaína-metadona ou lidocaína-fentanil em cadelas submetidas à ovário-histerectomia eletiva

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Abstract

We compared the analgesia and cardiopulmonary changes induced by epidural methadone or fentanyl in combination with lidocaine in female dogs undergoing elective ovariohysterectomy and anesthetized with propofol. Eighteen female dogs were randomly assigned to two groups and given either methadone (0.3 mg kg^{-1}) + 2% lidocaine without vasoconstrictor (LM) or fentanyl (5 µg kg^{-1}) + 2% lidocaine without vasoconstrictor (LF). The drugs were administered epidurally in a volume of 0.25 ml kg^{-1}. Heart rate (HR), respiratory rate (RR), rectal temperature (RT), systolic blood pressure (SBP), and blood glucose levels were recorded before and 15 minutes after premedication (T0 and T1); 15 minutes after epidural administration (T2); five minutes after dermotomy (T3); five minutes after clamping of the ovarian pedicle (T4); five minutes and 1, 3, 6, 12, 18, and 24 hours (T5, T6, T7, T8, T9, T10, and T11, respectively) after surgery. The number of additional propofol injections and total propofol dose (mg kg^{-1}) were recorded. Analgesia was assessed using a numerical descriptive scale. SBP and HR were similar in both groups, but hypotension was detected in animals from both groups at different times. Respiratory rate decreased significantly at T6 in the LF group and was lower than in the LM group. Hypothermia was observed in animals from both groups, but RT was significantly lower than baseline values only at T4 in the LM group. Blood glucose levels increased significantly only in the LF group at T4, T7, and T8. All animals in the LF group and eight animals in the LM group required additional propofol injections at T4, but no significant differences were detected in the number of propofol injections and total propofol dose between the LF (3 ± 1 injections, 7.5 ± 4.5 mg kg^{-1}) and LM (2 ± 2 injections, 4.5 ± 3.4 mg kg^{-1}) groups. The latency period, anesthetic period, and the duration of surgery were similar in both groups. No animals required rescue analgesia. The lidocaine-methadone and lidocaine-fentanyl combinations caused minimal cardiorespiratory changes, but did not abolish pain at the time of handling of the ovarian pedicle.

Key words: Anesthesia. Analgesia. Opioid. Epidural.

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Resumo

Comparou-se a analgesia e alterações cardiopulmonares promovidas pela metadona ou fentanil, associados à lidocaína, por via epidural, em cadelas submetidas à ovário-histerectomia eletiva e mantidas anestesiadas pelo propofol. Foram utilizadas 18 cadelas, distribuídas em dois grupos: LM – metadona (0,3 mg kg^{-1}) + lidocaína 2% sem vasoconstrictor; e LF – fentanil 5 μg kg^{-1} + lidocaína 2% sem vasoconstrictor. Os fármacos foram administrados por via epidural, num volume de 0,25 mL kg^{-1}. Registraram-se: frequências cardíaca (FC) e respiratória (*f*), temperatura retal (TR), pressão arterial sistólica (PAS) e glicemia, antes e 15 minutos após a medicação pré-anestésica (T0 e T1); 15 minutos após a epidural (T2); cinco minutos após a dermotomia (T3); cinco minutos após o pinçamento dos pedículos ovarianos (T4); cinco minutos, uma, 3, 6, 12, 18 e 24 horas (T5, T6, T7, T8, T9, T10 e T11, respectivamente) após o término da cirurgia. Mensuraram-se ainda o número de repiques de propofol e o consumo total, em mg kg^{-1}. Avaliou-se a analgesia através de escala descritiva numérica. Não houve diferença significativa na PAS e na FC entre os grupos, porém ocorreu hipotensão em alguns momentos em ambos os grupos. Ocorreu redução significativa na frequência respiratória no momento T6 no grupo LF, sendo esta menor que no grupo LM. Ocorreu hipotermia em ambos os grupos, porém houve diferença estatística, em relação ao valor basal, apenas no momento T4 no grupo LF. A glicemia aumentou significativamente apenas no grupo LF, nos momentos T4, T7 e T8. Todos os animais do grupo LF e oito animais do grupo LM necessitaram de repique de propofol no T4, porém não houve diferença significativa quanto ao número de repiques e ao consumo total de propofol entre os grupos LF (3 ± 1 repiques; 7,5 ± 4,5 mg kg^{-1}) e LM (2 ± 2 repiques; 4,5 ± 3,4 mg kg^{-1}). Os períodos de latência e hábil anestésico e de duração do procedimento cirúrgico foram semelhantes em ambos os grupos. Nenhum animal necessitou de analgesia de resgate. As associações lidocaína-metadona ou lidocaína-fentanil promovem mínimas alterações cardiorrespiratórias, porém não são suficientes para abolir a dor no momento da manipulação do pedículo ovariano.

Palavras-chave: Anestesia. Analgesia. Opioide. Peridural.

Introduction

The epidural administration of drugs has been regarded in recent years as one of the best techniques for promoting analgesia and local anesthesia. According to Valadão et al. (2002), the use of epidural opioids has reduced the occurrence of adverse effects caused by these types of drugs because they are administered in smaller doses (FREITAS et al., 2008). The onset of the analgesic effect of epidural drugs varies between opioids and is dependent on the time at which they cross the meninges to reach the cerebrospinal fluid and the spinal cord (MCMURPHY, 1993).

Methadone is an opioid agonist that acts on μ receptors and has affinity for N-methyl-D-aspartate (NMDA) receptors. The drug has high fat solubility, which favors rapid epidural absorption (CAMPAGNOL et al., 2012); its latency is 10 minutes and the duration of analgesia in dogs is six hours when the drug is administered epidurally at a dose of 0.3 mg kg^{-1} (LEIBETSEDER et al., 2006).

Fentanyl is a synthetic morphine-derived opioid estimated to have approximately 100 times the potency of morphine (FREITAS et al., 2008). There is considerable debate as to the role of epidurally administered fentanyl because its low cerebrospinal fluid potency and high lipid solubility reduces its meningeal permeability (JONES, 2001). Fentanyl reaches peak effect between three and five minutes, its plasma half-life is approximately 45 minutes, and its elimination half-life is three to 12 hours. The epidural fentanyl doses associated with adverse cardiorespiratory effects such as cardiovascular and respiratory depression and analgesic effects remain unclear and may range from one to 20 μg kg^{-1} (NAGANOBU et al., 2004).

Ovariohysterectomy is one of the most common elective surgical procedures in veterinary surgery. The most painful stimuli during this procedure are believed to occur in the dermotomy and ligation of the ovarian pedicle. According to Ishiy et al. (2002), epidural administration of 5 mg kg^{-1} lidocaine alone is not sufficient to produce anesthesia for ovariohysterectomy in dogs because it only blocks up to the fourth or fifth lumbar vertebra, whereas the ovaries are innervated by the third and fourth lumbar nerves (DINIZ et al., 2013).Thus, further research on the associations of analgesic drugs with lidocaine and their pharmacokinetics and adverse effects when administered epidurally is needed to obtain more effective anesthesia with minimal side effects.

This study compared the perioperative and postoperative effects induced by methadone and fentanyl associated with lidocaine on anesthesia, analgesia, and cardiopulmonary function in female dogs anesthetized with propofol and undergoing elective ovariohysterectomy.

Materials and Methods

Eighteen clinically normal client-owned mongrel female dogs aged 3 ± 1 years old (mean ± SD), weighing 16.65 ± 4.2 kg and treated at the Veterinary Hospital of the Federal University of Campina Grande (HV/UFCG), Patos, state of Paraíba, Brazil were included in the study. The dogs were previously considered healthy on the basis of a preoperative physical examination and blood and biochemical analyses (urea, creatinine, alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase [ALP]. The study protocol was approved by the Research Ethics Committee at CSTR/UFCG (protocol 93-2013) and owners provided written consent to enroll their animals in the study.

Dogs were housed in individual cages for seven days for adaptation and given commercial dog food and water *ad libitum*. On the day before surgery, hair in the ventral abdominal region, dorsal lumbosacral region, and right radial region was clipped, and food and water were withheld for 12 h and 4 h, respectively.

The premedication consisted of intramuscular (IM) administration of acepromazine (0.1 mg kg^{-1}) (Acepran 1%, Vetnil, Louveira, SP, Brazil) and midazolam (0.3 mg kg^{-1}) (0.5% midazolam hydrochloride; Roche, São Paulo, SP, Brazil). Ten minutes before induction of anesthesia, a 22-gauge catheter was inserted into the right cephalic vein for administration of propofol (Propovan 1%, Cristália Pharmaceutical Chemicals Ltd., Itapira, SP, Brazil). Lactated Ringer's solution (Equiplex Pharmaceutical Industry, Aparecida de Goiânia, GO, Brazil) was given during surgery at a rate of 10 ml kg^{-1} $hour^{-1}$.

Propofol was administered intravenously (IV) in a dose-response manner. A lack of response to needle insertion for epidural puncture was used as the endpoint for complete anesthesia. Posterior epidural anesthesia was achieved after skin asepsis in the lumbosacral region with 0.5% chlorhexidine solution (Riohex 0.5%, Rioquímica, São José do Rio Preto, Brazil). The needle (BD™ Tuohy Epidural Needle, Becton Dickinson, São Paulo, SP, Brazil) was introduced into the epidural space and needle position was confirmed by the 'hanging drop' technique using a drop of saline (0.9% NaCl) solution (Cristália Pharmaceutical Chemicals Ltd.) placed in the needle hub. Epidural anesthesia was performed in up to one minute by an experienced anesthesiologist who was unaware of the study protocol.

Dogs were assigned at random to the methadone or fentanyl groups; LM group: methadone (0.3 mg kg^{-1}) (Metadon 1%, Cristália Pharmaceutical Chemicals Ltd.) + lidocaine (Xylestesin 2%, Cristália Pharmaceutical Chemicals Ltd.) without vasoconstrictor to achieve a dose of 0.25 ml kg^{-11}.

LF group: fentanyl (5 µg kg^{-1}) (Fentanest 0.005%, Cristália Pharmaceutical Chemicals Ltd.) + lidocaine without a vasoconstrictor to achieve a dose of 0.25 mL kg^{-1}.

After the epidural administration of the drugs, dogs were placed in sternal recumbency for 15 min for drug diffusion and immobilized in the supine position on a surgical trough lined with a thermal electric mattress (Brasmed, Paulínia, SP, Brazil). Following asepsis of the operative field, ovariohysterectomy was performed according to the technique proposed by MacPhail (2013). All surgeries were performed by the same surgical team following the same technique. Dogs were transferred back to their cages after they had completely recovered from general anesthesia.

The following experimental times were considered: immediately before and 15 min after premedication (T0 and T1); 15 min after epidural puncture (T2); five min after dermotomy (T3); five min after clamping of the ovarian pedicle (T4); five min and one, three, six, 12, 18, and 24 h (T5, T6, T7, T8, T9, T10, and T11, respectively) after the surgical procedure.

Heart rate (HR, bpm), respiratory rate (RR, f), rectal temperature (RT, °C), and systolic blood pressure (SBP, mmHg) were recorded at T0–T11. HR was measured using a stethoscope (Becton Dickinson). RR was measured by counting the number of breaths for one minute (breaths/min) and RT was measured with a TH186 digital clinical thermometer (G-Tech, Duque de Caxias, RJ, Brazil). Systolic blood pressure was measured noninvasively using an ultrasonic Doppler (DV610 portable vascular doppler; Medmega Electronic Products Ltd., Franca, SP, Brazil). A pneumatic cuff with a width 40% of the circumference of the limb was placed around the middle of the left radius. Blood pressure was averaged from three readings at each experimental time. Blood glucose (mg dL^{-1}) was measured from one drop of capillary blood taken from the ear using a portable glucometer (Accu-Chek® Performa, Roche) at T0, T3, T4, T7, T8, T9, and T11, before physiological testing.

The propofol dose in mg kg^{-1} used to achieve sedation for the epidural puncture was also recorded. In addition, during surgery, dogs were given half the total propofol dose used for epidural anesthesia when HR and SBP increased more than 10% over baseline values. The number of spikes and total dose given in mg kg^{-1} were also recorded.

The degree of muscle relaxation during ligation of pedicles and uterine stump was recorded by the surgeon using a table of scores adapted from Albuquerque et al. (2013), as follows: 0 (poor): no muscle relaxation/difficulty to pull the pedicle; 1 (regular): little muscle relaxation/less resistance to pull the pedicle; 2 (good): good muscle relaxation/no difficulty to pull the pedicle, but not totally relaxed; and 3 (great): excellent muscle relaxation/pedicle totally relaxed.

The time elapsed between the termination of epidural administration and the loss of the anal reflex, defined as the lack of response to stimulation of the anal sphincter with a hypodermic needle; the latency period, defined as the time from loss of superficial pain to interdigital pinching in both hind limbs with a 16-cm Crile hemostatic forceps locked in the first ratchet tooth; and the anesthetic period, defined as the time from loss of superficial pain (negative response to interdigital pinching) to recovery of pain sensibility (drawing of the pinched limb) were recorded. The time in minutes from termination of epidural drug administration to onset of sternal recumbency (sternal recovery) and standing position (full recovery) was also recorded.

Analgesia was evaluated in the postoperative period by a single trained observer who was unaware of the study protocol using a numerical descriptive scale (PIBAROT et al., 1997) (Table 1) with scores ranging from 0 to 25. Analgesia was classified as severe (scores 0–8), moderate (9–16), or poor (> 16). Morphine (0.5 mg kg^{-1}, IM) was given when scores were > 16. Behavioral and physical changes such as drooling, vomiting, mydriasis, hyperthermia, and euphoria were recorded during the anesthetic recovery period.

After the last experimental period, dogs were given meloxicam (0.2 mg kg^{-1}, IM) (Maxicam 2%, Ourofino, Cravinhos, SP, Brazil), returned to their owners, and given the same drug every 24 h for three days.

Two-way analysis of variance (ANOVA) with multiple comparisons followed by the Tukey's test for normally distributed data or the Friedman test for non-normally distributed data was used to compare differences between groups over time. Analgesia and muscle relaxation scores were analyzed using the Mann-Whitney U test. Anesthetic recovery between groups at each experimental time was compared using the Student's t test or the Mann-Whitney U test. Normally and non-normally distributed data are reported as mean ± standard deviation and median ± interquartile range, respectively. All analyses were performed using BioEstat software version 5.0 (Instituto Mamirauá, Tefé, AM, Brazil). Data were considered significant at $p < 0.05$.

Table 1. Criteria for assessing the level of analgesia.

Interactive behavior	Alert and responds to human voice and touch	0
	Responds timidly	1
	Does not respond immediately	2
	Does not respond or responds aggressively	3
HR, *f*, BP	≤ 10% higher than the preoperative value	0
	11–30% higher than the preoperative value	1
	31–50% higher than the preoperative value	2
	50% higher than the preoperative value	3
Salivation	Normal	0
	Above normal	1
Vocalization	Without vocalization	0
	Vocalization present and controlled without medication	1
	Vocalization present and uncontrolled	2
Agitation	Asleep or calm	0
	Light agitation	1
	Moderate agitation	2
	Severe agitation	3
Posture	Sternal recumbency or moving calmly	0
	Defending and protecting the affected area, including fetal position, or lateral recumbency	1
Reaction to manipulation of surgical area	Without audible or visible reaction after four manipulations	0
	Audible or visible reaction after the 4th manipulation	1
	Audible or visible reaction between the 2nd and 3rd manipulation	2
	Audible or visible reaction in the 1st manipulation	3
Response to manipulation	Without response	0
	Minimum response, tries to avoid it	1
	Turns head in the direction of surgical area, slight vocalization	2
	Turns head with the intention of biting, severe vocalization	3

Source: adapted from Pibarot et al. (1997).

Results and Discussion

All surgeries were performed using a single recommended surgical procedure and there were no complications. No significant difference in duration of surgery was observed between the two groups (Table 2).

Table 2. Mean values for time to loss of anal reflex (in minutes), latency period, duration of anesthesia, duration of surgery, and time to sternal recovery and full recovery in female dogs undergoing elective ovariohysterectomy. Dogs were given epidural methadone (0.3 mg kg^{-1}) with lidocaine (LM group) or epidural fentanyl (5 µg kg^{-1}) with lidocaine (LF group).

Parameter	Group	
	LM	LF
Loss of anal reflex	1±0	1±0
Latency period	2±0.75	1±0.75
Duration of anesthesia	200±60	150±34
Duration of surgery	59±4	52±7
Sternal recovery	135±25	125±20
Full recovery	194±52	147±19

Data are reported as mean ± standard deviation. Second student t test at the 5% level of significance.

There were no significant differences in the latency period and time to loss of anal reflex between the groups (Table 2), indicating that these parameters, which are associated with the use of lidocaine, were not affected by the administration of opioids. The latency period for the LF group in this study was similar to that reported by Cassu et al. (2010) in a study that also investigated the effect of lidocaine associated with epidural fentanyl, whereas the latency period for the LM group was shorter than that reported by Monteiro et al. (2008) using the same protocol in dogs. The anesthetic period and the sternal and full recovery times were similar between groups (Table 2), indicating that the anesthetic effect of lidocaine was similarly affected by both methadone and fentanyl.

No significant changes in SBP over time compared with baseline values were detected for both groups (Table 3). Hypotension (SBP < 90 mmHg) has been previously reported (MONTEIRO et al., 2008) and is likely caused by the central depressant effects of opioids, even when they are administered epidurally (FREITAS et al., 2008). Nevertheless, in the current study no animal showed clinical signs of reduced tissue perfusion and hypotension, weak pulse, pale mucous membranes, or cold extremities, supporting the notion that a slight decrease in cardiovascular parameters is well tolerated by healthy anesthetized animals (TAMANHO et al., 2010).

No significant changes in heart rate over time were detected between or within groups (Table 3) and values were within the physiological range for dogs. The epidural administration of opioids may have contributed to the lack of autonomic response, i.e., the analgesia provided by the opioids administered may have prevented any increases in heart rate (CARREGARO et al., 2014).

Respiratory rate decreased significantly from baseline to T6 in the LF group, but this reduction was clinically irrelevant because RR was initially high, possibly due to stress associated with handling during measurement of baseline parameters. In addition, respiratory rate was significantly lower in the LF than in the LM group at T6 (Table 3), consistent with the findings of Leibetseder et al. (2006), who reported no respiratory depression in dogs administered epidural methadone, and Freitas et al. (2008), who observed a reduction in respiratory rate of dogs given 4 µg kg^{-1} of epidural fentanyl associated with lidocaine. The significant difference between groups observed at T6 has no clinical relevance because methadone and fentanyl are pure *mu* opioid agonists with high lipid solubility that have similar effects on respiratory depression (VALADÃO et al., 2002). In addition, the analgesia provided by methadone and fentanyl may have contributed to minimize stress in the perioperative period, improving patient comfort and reducing respiratory rate in both groups.

Hypothermia was observed in both groups following epidural opioid administration despite the use of a thermal mattress to maintain body temperature. Rectal temperature remained below the physiological norm for dogs up to three hours after surgery (T7) in both groups, but it was significantly lower than baseline values at T4 in the LM group. The reduction in body temperature may have been caused by the action of acepromazine, which causes reduction of the body temperature by depressing the hypothalamic thermoregulatory system and peripheral vasodilation (ARENA et al., 2009). This change can also be attributed to the thermolytic action of opioids (FREITAS et al., 2008) and the heat loss caused by laparotomy and the immobility induced by general-epidural anesthesia (CASSU et al., 2008). In addition, the decrease in basal metabolic rate associated with arterial and venous vasodilation caused by propofol administration may have contributed to the reduction in this physiologic variable (FANTONI, 2014).

Even though hyperglycemia is considered a metabolic response to surgical stress (LAMONT et al., 2000), serum glucose levels remained within the physiological range for dogs during surgery (SERÔDIO et al., 2008). Some animals experienced hypoglycemia at baseline probably due to fasting. No significant differences in serum glucose concentrations were detected between the groups, but glucose levels increased significantly at T4, T7, and T8 compared to baseline values in the LF group. The perception of nociceptive stimuli generated during clamping of the ovarian pedicle was likely responsible for the elevation of blood glucose levels observed at T4, which increases serum cortisol levels, hepatic gluconeogenesis, and blood glucose levels (ROMERO; BUTLER, 2007). A high glucose level in the postoperative period (T7 and T8) might be attributed to a persistent nociceptive effect after removal of the painful stimulus (FOX et al., 1998). The lack of variation in glucose levels in the LM group suggests that the methadone + lidocaine combination was more effective in suppressing the response to nociception, despite the lack of difference in glucose levels between the two groups (Table 3).

No significant differences in propofol dose for sedation, total propofol dose, and number of additional propofol injections were detected between the groups (Table 4). All animals in the LF group and eight dogs in the LM group required additional propofol at the time of ovarian pedicle clamping. This result suggests that the cranial epidural spread of methadone and fentanyl was insufficient to achieve the innervation of the ovarian pedicle, which is located on the third and fourth afferent lumbar nerves (DINIZ et al., 2013), preventing the blockade of nociceptive stimuli from handling of ovarian pedicles.

No significant changes in muscle relaxation scores were detected between the groups: 67% of animals in the LM group scored as excellent and 33% scored as good, whereas 40% of dogs scored as excellent, 26.7% scored as good, and 33.3% scored as regular in the LF group. This result indicates that the two protocols were similarly effective in the relaxation of ovarian pedicles during surgery.

The pain scale used in this study has been described for quantifying pain in dogs (PIBAROT et al., 1997; NEVES et al., 2012). No significant difference in analgesia scores was observed between the groups (Table 3) and no animals required rescue analgesia, indicating that the combination of lidocaine with fentanyl or methadone have similar postoperative analgesic efficacy in female dogs undergoing ovariohysterectomy. Conversely, Freitas et al. (2008) reported that some dogs given epidural fentanyl (4 μg kg^{-1}) associated with lidocaine required rescue analgesia. Similarly, another study that evaluated the analgesic effects of epidural methadone (0.3 mg kg^{-1}) and fentanyl (5 μg kg^{-1}) reported that approximately 50% of dogs in both groups required rescue analgesia (DINIZ et al., 2013).

The behavioral and physical changes observed in dogs in the LM group included intense vocalization in one animal one hour after surgery, apathy in one animal, and hypersalivation and euphoria from the end of surgery (T5) to six hours after surgery (T8) in one animal. Excessive salivation can be attributed to the parasympathomimetic action of opioids (MAIANTE et al., 2008); vocalization and euphoria have been reported as possible effects induced by methadone (STEAGALL et al., 2006) and may also be due to the intrinsic temperament of the animal in the presence of pain. No adverse effects were detected in the LF group, probably due to the low dose of fentanyl administered.

Table 3. Systolic blood pressure (SBP), pain scores, heart rate (HR), respiratory rate (RR), rectal temperature (RT) and serum glucose levels in female dogs undergoing elective ovariohysterectomy. Dogs were given epidural methadone (0.3 mg kg^{-1}) with lidocaine (LM group) or epidural fentanyl (5 µg kg^{-1}) with lidocaine (LF group).

Time	SBP (mmHg)		Pain scores		HR (bpm)		RR (breaths/ min)		RT (°C)		Glucose (mg/dL)	
	LM	LF	LM	LF	LM	LF	LM	LF	LM	LF	LM	LF
T0	111±19	108±18	–	–	121±41	107±20	31±9	39±16	38.4±0.3	38.3±0.2	72.5±6.2	76±4.7
T1	95±16	101±13	–	–	103±20	122±41	34±7	28±6	38.5±0.7	38.5±0.6	–	–
T2	95±15	84±8	–	–	98±15	89±13	15±6	15±3	37.1±0.4	37.4±0.3	–	–
T3	93±9	90±19	–	–	80±32	103±31	15±6	20±8	36.6±0.6	37.1±1.0	86.5±5.2	87.5±10.7
T4	112±25	110±16	–	–	110±51	110±16	15±6	18±5	36.4±0.7*	37.1±1.0	92.0±20	96.5±12.7*
T5	84±20	83±17	–	–	123±67	120±26	19±11	17±5	36.9±0.8	37.3±0.5	–	–
T6	88±17	100±11	4.0±3.4	3.0±2.5	116±50	119±15	20±0[a]	14±3*[b]	36.8±1.2	36.9±0.8	–	–
T7	95±8	99±12	3.8±4.2	3.5±2.6	99±28	116±25	20±6	22±7	37.8±0.5	38.0±0.5	88.5±13.2	96.0±18.5*
T8	106±23	109±21	5.2±3.6	3.5±3.2	113±31	131±43	20±12	26±10	38.4±0.7	38.7±0.5	84.5±7.7	95.5±7.7*
T9	109±20	125±12	4.5±2.7	4.2±2.9	114±24	108±36	21±5	23±5	38.2±0.7	38.6±0.5	88.0±13.2	87.5±19.5
T10	122±26	130±28	6.0±3.0	6.5±3.0	113±29	118±30	27±6	35±16	38.7±0.4	38.3±0.4	–	–
T11	132±17	127±13	8.3±3.6	6.8±2.5*	106±25	121±29	28±12	24±6	38.6±0.4	38.5±0.3	92.0±12.7	89.0±5.7

Data are reported as mean ± standard deviation or median ± interquartile deviation.*Significantlydifferent from T0 ($p<0.05$); [#]significantly different from LM ($p<0.05$).

Table 4. Mean values (± standard deviation) for propofol dose for sedation, total propofol dose, and number of additional propofol injections in female dogs undergoing elective ovariohysterectomy. Dogs were given epidural methadone (0.3 mg kg^{-1}) with lidocaine (LM group) or epidural fentanyl (5 µg kg^{-1}) with lidocaine (LF group).

Propofol	Group	
	LM	LF
Sedation (mg kg^{-1})	4.3±2.5	3±0.8
Total dose (mg kg^{-1})	4.5±3.4	7.5±4.5
N. of injections	2±2	3±1

Conclusions

The combination of epidural lidocaine-methadone or lidocaine-fentanyl caused minimal cardiorespiratory changes in the doses given, but was not able to alleviate pain at the time of ovarian manipulation in female dogs undergoing ovariohysterectomy. The absence of changes in blood glucose levels in the LM group suggests that methadone provides greater perioperative analgesia than fentanyl.

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