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Postoperative Analgesic Effects of Epidural Administration of Methadone, Tramadol, or Nalbuphine in Ovariohysterectomized Dogs

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ABSTRACT

The objective of this study was to evaluate the effectiveness of epidural methadone, tramadol or nalbuphine for postoperative analgesia in dogs. Thirty two healthy female dogs (ASA grade 1) undergoing ovariohysterectomy were randomly allocated into 4 treatments of 8 each: treatment 1 (control group) received 2% lidocaine (LD; 4 mg kg^{-1}), treatment 2 lidocaine and methadone (LDMT; 4 and 0.3 mg kg^{-1}, respectively), treatment 3 lidocaine and tramadol (LDTR; 4 and 2 mg kg^{-1}, respectively) and treatment 4 lidocaine and nalbuphine (LDNB; 4 and 0.3 mg kg^{-1}, respectively). The drugs were administered into the lumbosacral space, diluted in saline solution to a total volume of 0.36 mL kg^{-1}. Heart and respiratory rates, arterial pressures and peripheral SpO_2 were evaluated during the peri-operative period until 240 min. Postoperative pain and sedation were measured after extubation until the first rescue analgesic and thereafter regularly for 18 h. The time to first rescue analgesia was significantly ($p<0.05$) prolonged in dogs in the LDMT group as compared to the control and LDTR or LDNB groups. Although all 3 drug combinations administered epidurally in dogs allowed ovariohysterectomy to be performed with sufficient analgesia, the analgesia was maintained longer with the combination of lidocaine and methadone.

Key words: Analgesic opioids, lidocaine, epidural, postoperative pain, analgesia, dogs

INTRODUCTION

There is currently a major concern among veterinary anesthesiologists about relieving pain in the postoperative period. Commonly this pain relief is achieved by parenteral administration of opioids; however, this route of administration may cause undesirable side effects such as sedation, bradycardia, vomiting, defecation, urinary retention and respiratory depression (Pascoe, 2000). The incidence of these side effects is less evident when drugs are administered by the epidural route. Moreover, epidural administration of opioids produces more profound and prolonged analgesia

compared with that provided by parenteral opioids (Skarda and Tranquilli, 2007). Another benefit of epidural administration of opioids is the lower dose required when compared to IM or IV routes. This likely occurs because drugs are administered in proximity to the receptors that modulate the pain pathway in the spinal cord (Bernards, 2004).

The opiate receptor subtypes (μ, κ and σ) and the advent of drugs with receptor-specific agonist and antagonist properties have further expanded the role of epidural opioids for the intra-operative and postoperative periods (Camann *et al*., 1991). Many of these drugs, such as methadone, tramadol and nalbuphine are used epidurally alone or in combination with local anesthetics in dogs for obtaining prolonged analgesia postoperatively (Vettorato *et al*., 2010; Bosmans *et al*., 2012; Campagnol *et al*., 2012; Frazilio *et al*., 2014).

Methadone, a synthetic μ-opioid is equipotent to morphine and exerts adrenergic agonist and N-methyl-D-aspartate receptor antagonist actions (Matsui and Williams, 2010). Epidural methadone in combination with local anesthetic bupivacaine has been studied in sheep to assess if it induces prolonged analgesia (DeRossi *et al*., 2015). Studies epidural methadone use in dogs has been performed to observe the postoperative analgesic effects (Leibetseder *et al*., 2006; Bosmans *et al*., 2012; Campagnol *et al*., 2012; Diniz *et al*., 2013).

The efficacy of tramadol, a synthetic racemic mixture of the 4-phenyl-piperidine analogue of codeine is attributed to a dual mechanism of action, namely, the interaction with opioid μ receptors and the monoaminergic effect on spinal pain modulation through inhibition of the re-uptake of norepinephrine and serotonin (Raffa *et al*., 1992). The *O*-desmethyltramadol (M1) is the main active product of the hepatic metabolism of tramadol and it has 200-300 times the affinity for μ receptors than tramadol itself, although this affinity is lower than that of morphine (Gillen *et al*., 2000). For these reasons, several studies have suggested that tramadol produces spinal analgesic effects in dogs (Vettorato *et al*., 2010; Almeida *et al*., 2010; Mastrocinque *et al*., 2012).

Nalbuphine is a semisynthetic drug related to both naloxone and oxymorphone. It has a combination of opioid agonist and antagonist effects, namely, it has relatively potent κ-agonist and μ-antagonist activity. The respiratory depression induced by opioids is primarily mediated by the μ-receptor agonist activity (Etches *et al*., 1991). Thus, the μ-antagonist properties of nalbuphine should produce fewer μ-mediated side effects such as respiratory depression, pruritus, nausea and vomiting.

The postoperative analgesic efficacy and the occurrence of the adverse effects of epidural methadone, tramadol, or nalbuphine are limited when used in combination with local anesthetics injected into the epidural space. The aim of this study was to compare cardiovascular and systemic effects and postoperative analgesic duration of epidural methadone, tramadol, or nalbuphine combined with lidocaine in isoflurane-anesthetized dogs undergoing ovariohysterectomy.

MATERIALS AND METHODS

Animals: This study was performed with permission of the ethics committee of the Federal University of Mato Grosso do Sul and owner's consent was obtained. Thirty two female dogs (ASA status 1) were brought to the Veterinary Hospital of the UFMS by their owners to be spayed. A variety of breeds were represented with mixed-breed dogs being predominant. Inclusion criteria were a body weight >10 kg or <20 kg, normal arterial pressure (oscillometric method). Contraindications to epidural administration were previous pelvic fractures, obesity, dermatitis at needle insertion site, coagulopathies and absence of known systemic diseases. All dogs were fasted overnight (12 h) but had free access to water. All anesthetic procedures and epidural injections

were performed by the same anesthetist. All surgeries were performed by the same surgeon in the conventional manner (3-hemostats technique), starting 15 min after epidural injection.

Procedures: All dogs first received pre-anesthesia with 0.05 mg kg^{-1} acepromazine (Acepran 0.2%; Univet SA, SP, Brazil) administered via an over the needle catheter (BD Insyte, Becton Dickinson, Cirúrgicas Ltda, Brazil) inserted into the cephalic vein. Anesthesia was induced with 4-6 mg kg^{-1} propofol (Diprivan 1%; Astra Zeneca do Brasil Ltda, Cotia, Brazil) IV and the trachea was intubated. The dogs were placed in dorsal recumbency and connected to a semi-closed circle system with a precision vaporizer outside the circle. Anesthesia was maintained with isoflurane (Isoforine; Cristália Chemical and Pharmacological Products, Itapira, Brazil) delivered in 100% oxygen and the vaporizer set at 1-2%. All dogs received an infusion of 10 mL kg h^{-1} lactated Ringer's solution during the surgical procedure. Mechanical ventilation was volume-controlled with a tidal volume of 8 mL kg^{-1} and a respiratory rate set to maintain end-tidal CO_2 ($EtCO_2$) between 35 and 45 mm Hg.

Epidural procedures: Each animal was assigned randomly to 1 of 4 pain-management treatments. Treatment 1 was the control, in which dogs received an epidural injection of 2% lidocaine without epinephrine (LD; 4 mg kg^{-1}). In treatment 2, dogs were administered a combination of lidocaine and methadone chlorhydrate (Mytedom, Cristália Chemical and Pharmacological Products, Itapira, Brazil) (LDMT; 4 mg kg^{-1} and 0.3 mg kg^{-1}, respectively). In treatment 3, dogs received a combination of lidocaine and tramadol chlorhydrate (Tramadon, Cristália Chemical and Pharmacological Products, Itapira, Brazil) (LDTR; 4 and 2 mg kg^{-1}, respectively). In treatment 4, they were administered a combination of lidocaine and nalbuphine chlorhydrate (Nubain; Cristália Chemical and Pharmacological Products, Itapira, Brazil) (LDNB; 4 and 0.3 mg kg^{-1}, respectively). In all treatments, a total volume of 0.36 mL kg^{-1} was administered into the epidural space, which was achieved by the addition of saline solution.

After being anesthetized, all drugs were injected epidurally into the lumbosacral space through a 19 SWG Tuohy needle (Becton, Dickinson, São Paulo, Brazil). The correct positioning of the needle was confirmed by the hanging-drop technique and the ease of introduction of a 19 SWG epidural catheter (Portex epidural catheter, Smiths Medical ASD, Inc., Keene, NH, USA) at approximately L_4-L_5 (midlumbar level). All drugs were administered over 1 min and dogs were maintained in sternal recumbency for 15 min to facilitate the uniform spread of the drugs. During the surgical period the end-tidal isoflurane was adjusted as necessary to maintain a stable plane of anesthesia. The HR, arterial pressure (systolic, SAP; diastolic, DAP; mean, MAP), Respiratory Rate (RR) and peripheral SpO_2 were evaluated by means of a multivariable analyzer (Dixtal; DX 2021, Dixtal Biomédica Ind e Com, Ltda, Manaus, Brazil) at baseline (time 0), after induction of anesthesia and before epidural administration of drugs; 15 min after epidural injection and initiation of the surgical procedures; and 30, 45, 60, 90, 120, 180 and 240 min after epidural injection.

Analgesia assessment: After surgery, inhalant anesthetic was discontinued and tracheal extubation was done when animals no longer tolerated the tracheal tube. Analgesia and sedation were measured at 90 min and 2, 4, 6, 8, 10 and 12 h after the epidural injections and every 6 h thereafter until the first rescue analgesic. Evaluations of analgesia and sedation were made according to 2 scales: a Visual Analog Scale (VAS) on which 0 represents no pain or no sedation and 10 represents dogs with the worst pain possible and the scale proposed by the Colorado State

University Veterinary Teaching Hospital (Hellyer and Gaynor, 1998), on which 0 represents no pain and 25 the worst pain possible. In all cases, the additional need for analgesic therapy in the postoperative period was determined by pain scores of 4 or higher for VAS or 10 or higher for the Colorado scale. In this case, first rescue analgesia was administered with morphine (0.5 mg kg^{-1} IM) by a blinded observer. In order to ensure objectivity using these two methods, which can be considered subjective, these assessments were always performed by two trained observers. After extubation, dogs were evaluated for motor function by walking them out of the laboratory room. If dogs were unable to walk when stimulated, they were helped by an observer for a short period of time (15 min). If after this period the animals were unable to stand or walk, motor function was assessed every 15 min until the motor function returned to normal.

Statistical analysis: The quantitative variables were analyzed within and among groups by using analysis of variance (ANOVA) for repeated measures and the post hoc Tukey method was applied. VAS- and Colorado-score-dependent variables were analyzed by Kruskal-Wallis test (Sigma Stat II, Systat Software Inc., San Jose, CA, USA). For all measurements, mean ± standard deviation values or median±confidence interval were determined. For all comparisons, $p<0.05$ was considered statistically significant.

RESULTS

The 4 treatment groups had similar distributions of age, body weight, surgical duration and time of extubation. Demographic data and variables with mean±standard deviation values were during anesthesia and recovery from anesthesia in dogs premedicated with acepromazine induced with propofol and anesthestized with isoflurane that underwent ovariohysterecony after epidural administration of 1 of 4 drug treatments (Table 1). All surgical procedures were able to be performed as preoperatively planned without complications and caused no anesthesiological or surgical abnormalities. All animals in the 4 treatment groups showed good or excellent muscle relaxation of the abdominal wall as reported by the surgeon. Postoperatively, after extubation 4 animals in the LDTR treatment and 2 in the LDNB treatment showed sialorrhea, but did not vomit.

At 90 min after epidural administration of lidocaine (control treatment) the first rescue analgesic was administered because of a VAS score ≥ 4 or Colorado score ≥ 10. Compared with values for the control treatment, the VAS score were significantly lower ($p<0.05$) for dogs receiving LDMT treatment (from 14-16 h), LDTR treatment (from 8-12 h), or LDNB treatment (from 5-8 h). The VAS

Table 1: Mean±standard deviation values for demographic data and variables recorded during anesthesia and recovery from anesthesia in 32 dogs

Variables	LD (n = 8)	LDMT (n = 8)	LDTR (n = 8)	LDNB (n = 8)
Body weight (kg)	15.00±4.3	13.5±2.7	15.70±3.2	12.8±2.2
Age (years)	4.10±1.2	3.3±1.6	3.20±1.4	3.8±1.8
Duration of surgery (min)	43.00±15	40.0±13	38.00±19	45.0±12
EtISO (%)	1.44±0.07	1.2±0.04	1.38±0.05	1.3±0.1
$EtCO_2$ (mmHg)	38.00±2	41.0±1	42.00±2	39.0±1
SpO_2	98.00±1.3	96.0±2.8	95.00±3.3	97.0±1.8
Rectal temperature (°C)	36.90±0.1	37.2±0.2	37.10±0.1	37.4±0.1
Extubation time (min)	6.20±3	7.2±4.6	7.80±4	6.4±8
Interval until standing (min)*	45.00±15	75.0±20	67.00±15	55.0±18

LD: Epidural lidocaine (4 mg kg^{-1}), LDMT: Epidural lidocaine+methadone (4 and 0.3 mg kg^{-1}, respectively), LDTR: Epidural lidocaine+tramadol (4 and 2 mg kg^{-1}, respectively), LDNB: Lidocaine+nalbuphine (4 and 0.3 mg kg^{-1}, respectively), EtISO: End-tidal isoflurane, $EtCO_2$: End-tidal CO_2, SpO_2: Arterial oxygen saturation, *Represents interval from extubation until event

Table 2: Median scores of pain assessment for the VAS and Colorado scores recorded during the postoperative period in 32 dogs

		Time after epidural injections (h)								
Variable	Treatments	1.5	2	4	6	8	10	12	16	18
VAS	LD	2.3±2*	2±0.5	2±1	2±1	3±0	3±1	2±0.5	2±1	2±1
	LDMT	0.0±0	0±0	0±1	0±1	1±1	2±2	2±2	3±1‡	1±1
	LDTR	0.0±0	0±0	0±1	2±2	3±2†	3±1	3±1	1±1	1±0
	LDNB	0.0±1	0±1	2±2	3±1§	2±1	4±0	4±1	1±0	1±0
Colorado	LD	6.0±3*	4±3	3±1	3±2	2±1	2±2	5±2	4±4	3±4
	LDMT	4.0±2	4±2	3±1	2±1	2±2	3±4	5±4	8±3‡	3±2
	LDTR	4.0±2	3±1	3±2	5±3	6±4†	5±5	7±5	4±1	2±1
	LDNB	3.0±1	3±2	4±2	8±4§	7±3	2±2	2±1	2±2	2±1

LD: Epidural lidocaine (4 mg kg^{-1}), LDMT: Epidural lidocaine+methadone (4 and 0.3 mg kg^{-1}, respectively), LDTR: Epidural lidocaine+tramadol (4 and 2 mg kg^{-1}, respectively), LDNB: Lidocaine+nalbuphine (4 and 0.3 mg kg^{-1}, respectively), Time of the first analgesic rescue in the *LD, (‡) LDMT, (†) LDTR and (§) LDNB treatments

scores were significantly lower in the LDMT treatment as compared with values for the LDTR or LDNB treatments at 2, 4 and 12 h. For analgesia values, according to the Colorado score, a decrease in all treatments was observed during the postoperative period when compared with the control treatment. Compared to values for the control treatment, the Colorado score was significantly lower in the LDMT (16 h), LDTR (8 h), or LDNB treatment (6 h) after the epidural injections. The VAS and Colorado scores were significantly lower in the LDMT treatment until 16 h. On average, at 60 min (45-90 min) after extubation no dog showed either marked motor weakness or paralysis and all dogs remained able to walk. Median scores of pain assesment for the VAS and colorado scores were recorded during the postoperative period in 32 dogs premedicated with acepromazine, induced with propofol and anesthtized with isoflurane that underwent ovariohysterectony after epidural administration of 1 of 4 drug treatment (n = 8 in treatmetn) (Table 2).

Dogs in all treatments had changes in HR, RR and arterial pressures as shown in the Table 3. Return to appetite was similar in all treatments and in all dogs (mean±standard deviation, 5.6±3.2 h).

DISCUSSION

In this study, epidural administration of methadone, tramadol, or nalbuphine combined with lidocaine was shown to provide rapid onset of analgesia within 90 min postextubation as pain scores were significantly lower during this time interval compared to the lidocaine treatment. The shorter onset of epidural methadone, which is likely about 20 min, reflects its higher lipid solubility (Cousins and Mather, 1984). Previous studies showed a slow onset of action of epidural tramadol because of extensive systemic absorption after epidural administration (Murthy *et al*., 2000). We maintained an average end-tidal isoflurane (EtISO) of 1.3% in all treatments to maintain stable anesthesia and observed a significant decrease in HR in lidocaine, lidocaine/methadone, or lidocaine/nalbuphine and no change or decrease in mean MAP after 15 min of lidocaine/methadone, lidocaine/tramadol, or lidocaine/nalbuphine injections and the start of skin incision. Although it is not possible to identify the precise time of analgesia onset with our data, it appeared that the analgesic effects of the four treatments were comparable at 15 min after injection.

The use of opioid epidural analgesics enhanced the analgesia obtained through administration of lidocaine. Use of lidocaine alone in doses recommended appeared to be adequate for the anesthetic procedure; however, it did not induce an efficient and prolonged analgesia postoperatively. The three different opioids used in this study (methadone, tramadol and nalbuphine) in combination with epidural lidocaine achieved effective pain relief; however,

Table 3: Mean±standard deviation heart rate (HR; beats/min), respiratory rate (RR; breaths/min), and arterial pressures (SAP, systolic, DAP, diastolic and MAP, mean [mm Hg]) in dogs

	Time (min)								
Treatments	0	15	30	45	60	90	120	180	240
HR									
LD	114.0±14	109.0±19	97.0±16*	96.0±14*	103.0±11	103.0±6	109.0±7	108.0±6	109.0±5
LDMT	113.0±9	101.0±18	92.0±12*	92.0±10*	99.0±15	100.0±13	99.0±14	96.0±11	101.0±12
LDTR	108.0±17	103.0±12	95.0±10	95.0±11	100.0±17	105.0±18	107.0±17	106.0±14	104.0±15
LDNB	103.0±18	112.0±12	106.0±16	105.0±15*	112.0±13*	119.0±21*	116.0±24*	126.0±35‡	117.0±39
RR									
LD	29.0±4	16.0±6*	16.0±6*	15.0±6*	16.0±5*	16.0±3*	17.0±2*	19.0±3*	21.0±1*
LDMT	29.0±6	18.0±6*	16.0±5*	16.0±5*	18.0±5*	21.0±5	20.0±3	21.0±6	22.0±4
LDTR	28.0±4	15.0±2*	15.0±6*	15.0±5*	20.0±8*	20.0±7*	21.0±7	22.0±6	22.0±4‡
LDNB	33.0±11	18.0±8*	14.0±5*	17.0±7*	17.0±3*	21.0±4*	21.0±4*	19.0±6*	18.0±3*‡
SAP									
LD	116.0±12	84.0±9*	92.0±20*	89.0±23*	93.0±17*	102.0±12	109.0±11	115.0±6	113.0±5
LDMT	115.0±16	91.0±13*	89.0±11*	84.0±11*	95.0±11*	106.0±12	108.0±8	109.0±8	108.0±8
LDTR	122.0±8	101.0±19	102.0±19	104.0±18	112.0±18	117.0±16‡	127.0±7‡	125.0±7	119.0±4
LDNB	116.0±17	105.0±13‡	100.0±21	99.0±11	108.0±15	116.0±18	124.0±2‡	117.0±15‡	116.0±13
DAP									
LD	71.0±10	44.0±11*	40.0±12*	42.0±16*	50.0±14*	61.0±9	71.0±7	75.0±6	73.0±8
LDMT	76.0±17	51.0±13*	46.0±12*	45.0±13*	54.0±17*	67.0±20	71.0±11	73.0±9	73.0±12
LDTR	76.0±18	64.0±20	58.0±19	53.0±16	74.0±23	86.0±17‡	89.0±11‡	87.0±16	89.0±7‡
LDNB	68.0±8	53.0±13	58.0±18	54.0±11	71.0±25	78.0±10	89.0±11	82.0±7	80.0±7
MAP									
LD	84.0±15	62.0±7*	62.0±18*	61.0±19*	68.0±16*	78.0±12	84.0±9	90.0±7	90.0±7
LDMT	91.0±15	67.0±15	62.0±12	60.0±12	68.0±12	86.0±13	86.0±11	87.0±7	86.0±9
LDTR	92.0±18	73.0±17‡	77.0±19	77.0±22	88.0±24	94.0±17	103.0±12‡	101.0±14‡	100.0±5
LDNB	79.0±11	73.0±3	75.0±19	73.0±11	82.0±23	93.0±14	104.0±7‡	95.0±11	97.0±10

LD: Epidural lidocaine (4 mg kg^{-1}), LDMT: Epidural lidocaine+methadone (4 and 0.3 mg kg^{-1}, respectively), LDTR: Epidural lidocaine+tramadol (4 and 2 mg kg^{-1}, respectively), LDNB: Lidocaine+nalbuphine (4 and 0.3 mg kg^{-1}, respectively), *Significantly ($p<0.05$) different from value at time point 0, ‡Significantly ($p<0.05$)

significant differences were observed with respect to duration of analgesia between the three treatments. This can be attributed to differences in physicochemical, pharmacokinetic and pharmacodynamic characteristics of the three drugs (Raffa *et al*., 1992; Bosmans *et al*., 2012; Campagnol *et al*., 2012).

Methadone is a synthetic opioid analgesic with pharmacological effects similar to those of morphine; it has a greater long-term effect, but a less sedative effect. When methadone is administered by epidural injection in dogs, it leads to a significant prolongation of postoperative analgesia (Leibetseder *et al*., 2006; Skarda and Tranquilli, 2007; Diniz *et al*., 2013). In this study, we didn't treat dogs with methadone alone epidurally, but when combining methadone (0.3 mg kg^{-1}) with lidocaine we achieved a significant prolongation of postoperative analgesia (840-960 min) after ovariohysterectomy. Our results are similar to those reported by Skarda and Tranquilli (2007), regarding the duration of analgesia (300-900 min). In another study, epidural methadone alone used at the same dose as used in our experiment (0.3 mg kg^{-1}) resulted in postoperative analgesia of half the duration (459 min) (Leibetseder *et al*., 2006). The lidocaine/methadone combination significantly prolonged the duration of analgesia compared to the lidocaine treatment, suggesting that there was an additive or synergistic effect between the two drugs.

After epidural administration in dogs (2 mg kg^{-1}), tramadol produced intra- and postoperative analgesia without significant side effects (Vettorato *et al*., 2010). However, the analgesia produced was not superior to that obtained after IV administration (8 h). On the other hand, epidural

lidocaine/tramadol provided an analgesic effect 12 h after orchiectomy in dogs without side effects (Almeida *et al*., 2010). Similar results were obtained in our experiment (8-12 h) after ovariohysterectomy in dogs.

Nalbuphine is a low lipophilic semisynthetic opioid related to both oxymorphone and naloxone; it has relatively potent μ-antagonist and κ-agonist activity. Nalbuphine administered epidurally reduces the intraoperative isoflurane requirement and provides prolonged postoperative analgesia after ovariohysterectomy in dogs (Frazilio *et al*., 2014). Our study showed a superior analgesic effect of epidural lidocaine/nalbuphine (5-8 h) compared with lidocaine alone (90 min) in dogs undergoing ovariohysterectomy. However, a human study suggested that epidural nalbuphine provided only 2-4 h of effective analgesia following cesarean delivery (Camann *et al*., 1991).

Although the epidural administration of opioids at recommended doses is not responsible for important changes in cardiovascular parameters (Chaney, 1995) the use of high doses of local anesthetics can cause hypotension. Epidural methadone alone did not induce hypotension in isoflurane-anesthetized dogs; however, when combined with ropivacaine hypotension did occur (Bosmans *et al*., 2011). In another study, after epidural methadone (0.3 mg kg^{-1}) was administered in combination with isoflurane (1%) dogs were hypotensive during the first 20 min of surgery, but MAP increased after noxious stimulation to values within the normal range (Leibetseder *et al*., 2006). In our study, methadone combined with lidocaine induced a significant decrease in SAP and DAP, but it does not alter the MAP during the intra-operative period.

The HR, RR and blood pressure were maintained within the reference ranges after epidural injections of lidocaine combined with tramadol in dogs following orchiectomy (Gillen *et al*., 2000; Almeida *et al*., 2010). Similar results were obtained in our study with the lidocaine/tramadol combination. All treatments induced a significant decrease in RR. These changes were likely due to two factors. First, these effects are caused by rostral spread of the drugs with subsequent sympathetic blockade. The high sympathetic blockade can cause hypotension or intercostal muscle weakness by extension of the thoracic vertebrae. Second, the dogs in this study were maintained at an average EtISO of 1.3%, which likely contributed to decrease the arterial pressure.

Nausea and vomiting are common side effects that may be seen following epidural tramadol administration in children (Murthy *et al*., 2000). In the current study, nausea was observed in both the tramadol and nalbuphine treatments after extubation. Return of appetite occurred in all treatments after the dogs received morphine as the first rescue analgesic, so this symptom could be associated with pain.

This study has certain limitations. It is difficult to recognize and measure pain in animals, as well as the different forms of reaction to painful stimuli (experimental or surgical), because of their inability to communicate. We also lacked knowledge of the normal behavioral responses of each individual, which are determined mainly by how the animal is treated by the owners. For example, the type and amount of food provided (homemade food or feed), genetic breed predisposition and whether living with children or other dogs are some factors that may affect the behavior of the animal. There will always be discrepancies in the assessment of pain when a subjective scoring system is used. The VAS and Colorado scale have been used with success in dogs (Hellyer and Gaynor, 1998) and both systems were able to detect possible differences between treatments. These scores were always performed by 2 trained observers, who analyzed the behavior and interaction of the animals when they were encouraged to move and the surgical wound was palpated. These evaluations were always carried out without the presence of the pet owner. Until the first rescue analgesic, the VAS and Colorado scores remained significantly lower in the LDMT, LDTR and

LDNB treatments as compared to LD treatment in the postoperative period. Both scales were sensitive and reliable with both showing nearly simultaneous increases in scores in the presence of pain. The VAS scores have been reported to be more reliable than the categorical approach used by multifactorial pain scoring systems. Other factors, such as mydriasis, salivation, HR and RR may have been affected by the opioids (methadone, tramadol, or nalbuphine) used in this experiment, making the Colorado score less precise. Thus, the administration of morphine IM as postoperative rescue analgesic in this study could have influenced subsequent Colorado scores. Finally, it would have been better to compare treatments with the epidural opioids alone, rather than in combination with lidocaine.

CONCLUSION

The results of this study suggest that the use of epidural lidocaine combined with methadone provides a longer duration of postoperative analgesia as compared to tramadol combined with lidocaine or nalbuphine combined with lidocaine in female dogs undergoing ovariohysterectomy. Methadone, tramadol and nalbuphine did not differ with regard to adverse effects. For these reasons, this combination should be considered an alternative analgesic for the relief of postoperative pain in this type of surgery.

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