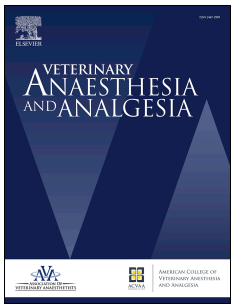

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RESEARCH PAPER

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Running head (short title)

Evaluation of analgesic, sympathetic and motor effects of 1% and 2% lidocaine administered epidurally in dogs undergoing ovariohysterectomy

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Abstract

Objective To compare, *versus* a control, the sensory, sympathetic and motor blockade of lidocaine 1% and 2% administered epidurally in bitches undergoing ovariohysterectomy.

Study design Randomized, blinded, controlled clinical trial.

Animals A total of 24 mixed-breed intact female dogs.

Methods All dogs were administered dexmedetomidine, tramadol and meloxicam prior to general anesthesia with midazolam–propofol and isoflurane. Animals were randomly assigned for an epidural injection of lidocaine 1% (0.4 mL kg^{-1}; group L1); 2% (0.4 mL kg^{-1}; group L2) or no injection (group CONTROL). Heart rate (HR), respiratory rate (f_R), end-tidal partial pressure of carbon dioxide ($P_E'CO_2$), and invasive systolic (SAP), mean (MAP) and diastolic (DAP) arterial pressures were recorded every 5 minutes. Increases in physiological variables were treated with fentanyl (3 µg kg^{-1}) intravenously (IV). Phenylephrine (1 µg kg^{-1}) was administered IV when MAP was < 60 mmHg. Postoperative pain [Glasgow Composite Pain Score–Short Form (GCPS–SF)] and return of normal ambulation were recorded at 1, 2, 3, 4 and 6 hours after extubation.

Results There were no differences over time or among groups for HR, f_R, $P_E'CO_2$ and SAP. MAP and DAP were lower in epidural groups than in CONTROL (p = 0.0146 and 0.0047, respectively). There was no difference in the use of phenylephrine boluses. More fentanyl was administered in CONTROL than in L1 and L2 (p = 0.011). GCPS–SF was lower for L2 than for CONTROL, and lower in L1 than in both other groups (p = 0.001). Time to ambulation was 2 (1–2) hours in L1 and 3 (2–4) hours in L2 (p = 0.004).

Conclusion and clinical relevance Epidural administration of lidocaine (0.4 mL kg^{-1}) reduced fentanyl requirements and lowered MAP and DAP. Time to ambulation decreased and postoperative pain scores were improved by use of 1% lidocaine compared with 2% lidocaine.

Keywords analgesia, dog, epidural, lidocaine, ovariohysterectomy.

Introduction

Epidural administration of local anesthetics is a widely used technique in veterinary medicine for several surgical procedures, including ovariohysterectomy (Jones 2001; Almeida et al. 2007; Natalini et al. 2010; Diniz et al. 2013; Ismail et al. 2016; Hermeto et al. 2017). However, conduction block of sympathetic and motor nerves from epidurally administered local anesthetics may limit the use of this technique because the vasodilatory effects of general anesthetics may be augmented or delay to ambulation may extend time to discharge (Torske & Dyson 2000; Brown 2005). When the volume of the epidural solution remains the same, the duration and magnitude of conduction block is associated with the dose of the local anesthetic (Gomez de Segura et al. 2009). Solutions containing low concentration of bupivacaine and ropivacaine have been successfully used to provide effective epidural analgesia while minimizing the magnitude and duration of motor blockade (Lacassie et al. 2007; Veering et al. 2003; Gomez de Segura et al. 2009; Abelson et al. 2011).

Lidocaine is the most widely used local anesthetic in veterinary practice (Vickroy 2018). When injected epidurally in dogs at a concentration of 2% and a volume of 0.3 mL kg^{-1}, lidocaine results in effective analgesia and motor block lasting approximately 120 minutes (Almeida et al. 2010). Data on the effects of 1% lidocaine administered epidurally in dogs is scarce. Therefore, we compared the sensory, sympathetic and motor blockade of lidocaine 1% and 2% administered epidurally in bitches undergoing ovariohysterectomy, and compared them with a control group without epidural anesthesia. We hypothesized that 1% lidocaine epidurally would result in 1) superior postoperative analgesia than a control group without an epidural; 2) fewer animals with intraoperative arterial hypotension; and 3) a shorter duration of motor block than dogs administered 2% lidocaine epidurally.

Materials and methods

Animals

The Animal Care and Use Committee of the Faculty of Veterinary Sciences, UNCPBA, Argentina approved the protocol (no. 087/04). A group of 24 mixed-breed intact female dogs from a local rescue shelter [mean ± standard deviation (SD)] aged 2.4 ± 1.4 years and weighing 20.0 ± 5.4 kg admitted for ovariohysterectomy were enrolled in a randomized, blinded, controlled study. Dogs were classified as American Society of Anesthesiologists physical status 1 based on physical examination, complete blood count and serum biochemical analyses. Dogs were excluded if their physical status was > 1, if they were pregnant or if they had received any medication within 30 days prior to surgery.

Anesthetic management

Food but not water was withheld for 12 hours before anesthesia. All dogs were administered dexmedetomidine (5 µg kg^{-1}; Dexdomitor, 0.5 mg mL^{-1}; Zoetis, BA, Argentina), tramadol (2 mg kg^{-1}; Tramadol; John Martin SRL, BA, Argentina) and meloxicam (0.2 mg kg^{-1}; Meloxivet, 5 mg mL^{-1}; John Martin SRL) intramuscularly (IM). After 15 minutes, a catheter was placed in a cephalic vein and oxygen was supplemented *via* facemask for 5 minutes. General anesthesia was induced with midazolam (0.2 mg kg^{-1}; Midazolam, 5 mg mL^{-1}; Richmond Vet Pharma, BA, Argentina) and propofol (Propovet, 10 mg mL^{-1}; Richmond Vet Pharma) administered intravenously (IV) until loss of the palpebral and swallowing reflexes. The trachea was intubated with a cuffed tube, and anesthesia was maintained with isoflurane in oxygen using a rebreathing circle circuit while dogs breathed spontaneously. A 22 gauge indwelling catheter was placed in the right or left dorsal pedal artery and the pressure waveform was transduced through a heparinized saline-filled (2 IU mL^{-1}, Riveparin; Rivero Laboratorio, BA, Argentina) noncompliant tubing to a transducer (Truwave Disposable Pressure Transducer set; Edwards Lifesciences LLC, CA, US) positioned at the point of the

shoulder. The transducer was previously calibrated using a mercury manometer over the range 0–200 mmHg. Saline (Solución NaCl 0.9%; Tecsolpar Laboratorios, BA, Argentina) was infused at 5 mL kg^{-1} $hour^{-1}$. Heart rate (HR) measured by electrocardiography, respiratory rate (f_R) and end-tidal carbon dioxide ($P_E'CO_2$) measured by the capnograph, esophageal temperature, invasive systolic, mean and diastolic arterial pressures (SAP, MAP and DAP, respectively) were recorded every 5 minutes using a multiparameter monitor (Goldway UTF4000; Goldway US Inc., NY, USA). Ovariohysterectomies were performed by the same experienced veterinarian. A median laparotomy was performed in all dogs approximately 30 minutes after induction of anesthesia.

Study protocol

Animals were randomly allocated into 3 groups of eight dogs each. Randomization was performed by removing labels from an opaque envelope and conducted in 4 blocks; each envelope contained 6 labels, 2 for each group. Group L2 was assigned an epidural with 2% lidocaine (0.4 mL kg^{-1}; Lidocaina, 20 mg mL^{-1}; Laboratorio Over SRL, SF, Argentina); group L1 was assigned an epidural with 1% lidocaine (0.4 mL kg^{-1}; 2% lidocaine diluted 1:1 with 0.9% saline); group CONTROL was assigned no epidural injection. The area over the lumbosacral space was clipped and cleansed with chlorhexidine in all dogs, regardless of group allocation. Approximately 20 minutes after induction of anesthesia in L1 and L2, with the dog in sternal recumbency, an 18 gauge, 80 mm Tuohy needle (Perican; B Braun Melsungen AG, Germany) was inserted into the epidural space at the lumbosacral junction using the loss-of-resistance technique with 1 mL of air (Perifix LOR; B Braun Melsungen AG) to identify correct placement. The anesthetic solution was injected manually over 1 minute and after 5 minutes the dog was positioned in dorsal recumbency. All epidural

injections were performed by the same investigator (PN). An investigator unaware of treatment allocation became the anesthesia provider thereafter (FL).

The isoflurane vaporizer was set at 1.5% with an oxygen flow of 1 L minute^{-1} and remained unchanged throughout the duration of anesthesia. Baseline values for HR, arterial blood pressure or f_R were established immediately before surgical incision. Increases in those physiological variables were treated with IV fentanyl (3 µg kg^{-1}; Nafluvent, 0.05 mg mL^{-1}; Fada Pharma SA, BA, Argentina) at the discretion of the attending anesthetist. Phenylephrine (1 µg kg^{-1}; Fadalefrina, 10 mg mL^{-1}; Fada Pharma SA) was administered IV when MAP was < 60 mmHg. Upon completion of surgery, isoflurane was discontinued and the dogs were allowed to recover from anesthesia; no other medication was administered. Dogs remained under the care of the attending anesthetist for the next 6 hours. A Glasgow composite pain scale – short form (GCPS–SF) was recorded at 1, 2, 3, 4 and 6 hours after extubation. Rescue analgesia with morphine (0.5 mg kg^{-1}; Morfina, 10 mg mL^{-1}; Fada Pharma SA) IM was administered if the score was > 6/24, or > 5/20 when motor blockade was still present (Reid et al. 2007). At the same time points, dogs were encouraged to walk with a leash. The ability to ambulate was assessed as a binary outcome, defined as walk with noticeable ataxia (lack of coordination) or not. Time to first return of ambulation without ataxia was recorded.

Statistical analysis

Normality of data was evaluated with a Q-Q plot, histograms and with a Shapiro–Wilk test of the residuals. Age, body weight, dose of propofol, duration of surgery (from skin incision to closure), duration of anesthesia (from induction to extubation) and time from epidural injection to end of surgery, were compared among groups with a Kruskal Wallis test. Total intraoperative doses of fentanyl, phenylephrine and the postoperative GCPS–SF scores were compared among groups with generalized linear mixed models, with a Poisson distribution

and a log link function. Patient identification (ID) was included as a random effect and group as fixed effect with an LSD Fisher's *post hoc* test. Differences in HR, f_R, $P_{E'}CO_2$, SAP, MAP, DAP among groups, were assessed with linear mixed-effect models with a LSD Fisher's *post hoc* test. Treatment, time and their interaction were considered as fixed effects, and animal ID was included as a random effect. For time to ambulation, groups were compared using a survival graph; differences were analyzed with a log-rank test. Significance was set at $p < 0.05$. Results are summarized as mean ± SD for parametric data and median (range) for nonparametric data.

Results

All dogs completed the procedures without intraoperative and postoperative complications. There were no differences among groups for age, body weight, dose of propofol, duration of anesthesia or duration of surgery (Table 1).

There were no differences over time or among groups for HR, f_R, $P_{E'}CO_2$ and SAP ($p = 0.08$, 0.09, 0.14, 0.56, respectively). However, MAP and DAP were lower in groups L1 and L2 than in group CONTROL ($p = 0.0146$ and 0.0047, respectively) (Fig. 1).

There was no difference in the number of intraoperative phenylephrine boluses among groups ($p > 0.999$). Dogs in group CONTROL were administered significantly more boluses of fentanyl than those in groups L1 and L2 (without differences between the epidural groups; $p = 0.011$; Table 1).

Significant effects of time, treatment and their interaction on GCPS–SF were found (all $p < 0.001$; Fig. 2). Among groups, GCPS-SF scores were lower in group L2 than in CONTROL, and lower in L1 than in both other groups (all $p = 0.001$). Time to ambulation occurred 2 (1–2) hours after extubation in dogs in group L1, and at 3 (2–4) hours in group L2 ($p = 0.004$; Fig. 3).

Discussion

Sensory nerve fibers from the dorsal root ganglia of the caudal thoracic (T10) to the cranial lumbar (L4) segments innervate the ovaries in dogs (Chien et al. 1991). Similar spinal segments (T9 to L3) supply the abdominal muscles, subcutaneous tissue, abdominal skin and the underlying parietal peritoneum (Evans & de Lahunta 2013). In the current study, a lidocaine volume of 0.4 mL kg^{-1} for epidural injection was based on a study that demonstrated that a total volume of 0.4 mL kg^{-1} of bupivacaine 0.25% solution injected epidurally desensitized spinal nerves up to T7 (Freire et al. 2010). In the present study, inclusion of epidural injections of 1% or 2% lidocaine was associated with fewer fentanyl boluses being administered during surgery than in the control group. Similarly, previous studies have demonstrated the analgesic efficacy of epidural anesthesia for ovariohysterectomy (Almeida et al. 2007; Diniz et al. 2013; Hermeto et al. 2017); however we have found no communication reporting the use of lidocaine 1%.

Undesirable effects have been reported with the use of epidural administration of local anesthetics. Sympathetic fiber block has been proposed as the most frequent adverse effect associated with epidural administration of local anesthetics, leading to vasodilation with or without hypotension (Reynolds 1987; Brown 2005). In the present study, MAP was significantly lower in dogs in groups L1 and L2 compared with the control group, possibly as a result of a mild regional vasodilatory effect of epidural nerve block (Reynolds 1987; Sakonju et al. 2011). However, blood pressure group mean values remained within normal values reported for dogs (SAP 115 mmHg, MAP 80 mmHg and DAP 70 mmHg) (Ruffato et al. 2015) in all groups; therefore, administration of phenylephrine was not different among groups.

During the first 6 hours of anesthesia recovery, pain scores did not exceed the study limit and no animal in any group was administered rescue analgesia. Within these limits, the assigned GCPS–SF scores were significantly lower in the groups including epidural nerve blocks than in the control group, and values in dogs administered 1% lidocaine were significantly lower than those in dogs administered 2% lidocaine. It is possible that the longer duration of absent motor and sensory functions in dogs in group L2 contributed to increased anxiety in those animals, which may in turn result in higher GCPS–SF scores. In humans, long-lasting insensitivity in an extremity is associated with discomfort and lower patient satisfaction (Droog et al. 2019).

Limitations of the present study should be noted. The end-tidal alveolar concentration of isoflurane was not measured, which would have confirmed a constant anesthetic administration, and the uptake of isoflurane may have been affected by other factors, such as alveolar ventilation and cardiac output which were not measured. To minimize this variation, the fresh gas flow, vaporizer setting, and breathing circuit were standardized. A standardized protocol to guide the administration of fentanyl in case of nociceptive response would have provided greater control of anesthetic management, even though the anesthetist was the same for all animals and was unaware of group allocation.

Conclusion

Lumbosacral epidural administration of 1% or 2% lidocaine at a volume of 0.4 mL kg^{-1} resulted in a reduction of intraoperative fentanyl administration without significant intraoperative cardiovascular and respiratory rate alterations compared with no epidural treatment in bitches undergoing ovariohysterectomy. Compared with 2% lidocaine, epidural lidocaine 1% resulted in lower postoperative pain scores and a shorter time to return to ambulation.

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Authors' contributions

PN: obtained funding, study design, data interpretation, writing the manuscript. FL: anesthetic management, data collection. MC, VC and VG: animal preparation, surgical procedure, editing the manuscript. ML, PV, MDS and MMF: study design, data interpretation, statistical analysis, manuscript revision. All authors read and approved the final version of the manuscript.

Conflict of interest statement

The authors declare no conflict of interest.

References

Abelson AL, Armitage-Chan E, Lindsey JC, Wetmore LA (2011) A comparison of epidural morphine with low dose bupivacaine versus epidural morphine alone on motor and respiratory function in dogs following splenectomy. Vet Anaesth Analg 38, 213–223.

Almeida RM, Escobar A, Maguilnik S (2010) Comparison of analgesia provided by lidocaine, lidocaine-morphine or lidocaine-tramadol delivered epidurally in dogs following orchiectomy. Vet Anaesth Analg 37, 542–549.

Almeida TF, Fantoni DT, Mastrocinque S et al. (2007) Epidural anesthesia with bupivacaine, bupivacaine and fentanyl, or bupivacaine and sufentanil during intravenous administration of propofol for ovariohysterectomy in dogs. J Am Vet Med Assoc 230, 45–51.

Brown DL (2005) Spinal, epidural and caudal anesthesia. In: Miller's Anesthesia (6th edn). Miller RD (ed). Elsevier Churchill Livingston, USA. pp. 1653–1683.

Chien CH, Li SH, Shen CL (1991) The ovarian innervation in the dog: a preliminary study for the base for electro-acupuncture. J Auton Nerv Syst 35, 185–192.

Diniz MS, Kanashiro GP, Bernardi CA et al. (2013) Extradural anesthesia with lidocaine combined with fentanyl or methadone to ovariohysterectomy in dogs. Acta Cir Bras 28, 531–536.

Droog W, Hoeks SE, Van Aggelen GP et al. (2019) Regional anaesthesia is associated with less patient satisfaction compared to general anaesthesia following distal upper extremity surgery: a prospective double centred observational study. BMC Anesthesiol 19, 115.

Evans HE, de Lahunta, A (2013) Spinal nerves. In: Miller's Anatomy of the Dog (4th edn). Evans H, de Lahunta A (eds). Saunders Elsevier, USA. pp. 611–657.

Freire CD, Torres ML, Fantoni DT et al. (2010) Bupivacaine 0.25% and methylene blue spread with epidural anesthesia in dog. Vet Anaesth Analg 37, 63–69.

Gomez de Segura IA, Menafro A, García-Fernández P et al. (2009) Analgesic and motor-blocking action of epidurally administered levobupivacaine or bupivacaine in the conscious dog. Vet Anaesth Analg 36, 485–494.

Hermeto LC, Rossi RD, Bicudo ND et al. (2017) The effect of epidurally administered dexamethasone with lignocaine for post-operative analgesia in dogs undergoing ovariohysterectomy. A dose-response study. Acta Cir Bras 32, 307–318.

Ismail ZB (2016) Epidural analgesia in cattle, buffalo, and camels. Vet World 9, 1450–1455.

Jones RS (2001) Epidural analgesia in the dog and cat. Vet J 161, 123–131.

Lacassie HJ, Habib AS, Lacassie HP, Columb MO (2007) Motor blocking minimum local anesthetic concentrations of bupivacaine, levobupivacaine, and ropivacaine in labor. Reg Anesth Pain Med 32, 323–329.

Natalini CC (2010) Spinal anesthetics and analgesics in the horse. Vet Clin North Am Equine Pract 26, 551–564.

Reid J, Nolan AM, Hughes JM et al. (2007) Development of the short-form Glasgow Composite Measure Pain Scale (CMPS-SF) and derivation of an analgesic intervention score. Anim Welfare 16, 97–104.

Reynolds F (1987) Adverse effects of local anaesthetics. Br J Anaesth 59, 78–95.

Ruffato M, Novello L, Clark L (2015) What is the definition of intraoperative hypotension in dogs? Results from a survey of diplomates of the ACVAA and ECVAA. Vet Anaesth Analg 42, 55–64.

Sakonju I, Maeda K, Karasawa K et al. (2011) Plasma concentration and cardiovascular effects of lidocaine during continuous epidural administration in dogs anesthetized with isoflurane. J Vet Med Sci 73, 393–398.

Torske KE, Dyson DH (2000) Epidural analgesia and anesthesia. Vet Clin North Am Small Anim Pract 30, 859–874.

Veering BT (2003) Cardiovascular and pulmonary effects of epidural anaesthesia. Minerva Anestesiol 69, 433–437.

Vickroy TW (2018) Local anesthetics. In: Veterinary Pharmacology and Therapeutics (10th edn). Riviere JE, Papich MG (eds). John Wiley & Sons, USA. pp. 369–386.

Figure 1 Mean ± standard deviation of (a) heart rate, (b) respiratory rate (f_R), (c) end-tidal partial pressure of carbon dioxide ($P_E'CO_2$) and (d-f) systolic (SAP), mean (MAP) and diastolic (DAP) invasive arterial pressures from 24 female dogs that underwent ovariohysterectomy and were randomly assigned to one of three groups: CONTROL (no epidural), L1 and L2 (0.4 mL kg^{-1} epidural administration of 1% or 2% lidocaine, respectively). Overall MAP and DAP were lower for both epidural groups than for the CONTROL group (p = 0.0146 and 0.0047, respectively).

* Significantly different from CONTROL ($p < 0.05$).

Figure 2 Median (range) Glasgow composite pain scale - short form (GCPS-SF) from 24 female dogs that underwent ovariohysterectomy and were randomly assigned to one of three groups: CONTROL (no epidural), L1 and L2 (0.4 mL kg^{-1} epidural administration of lidocaine 1 % and 2 %, respectively). * Significantly different from CONTROL at all time points ($p < 0.05$). † Significantly different from group L2 at times 2–6 hours ($p < 0.05$).

Figure 3 Percentage of female dogs that recovered normal ambulation after ovariohysterectomy and epidural administration of 1% or 2% lidocaine (groups L1 and L2, respectively).

* Significantly different from group L2 ($p < 0.05$).

Table 1 Age, weight, propofol dose, duration of anesthesia, duration of surgery, number of phenylephrine (1 µg kg^{-1}) boluses, number of fentanyl (3 µg kg^{-1}) boluses for 24 female dogs that underwent ovariohysterectomy and were randomly assigned to one of three groups: CONTROL (no epidural), L1 and L2 (0.4 mL kg^{-1} epidural administration of 1% or 2% lidocaine, respectively). Data are presented as median (range). The reported *p* value characterizes the comparison among groups ($p < 0.05$).

Variable	**Group**			***p***
	CONTROL	L1	L2	
Age (years)	2.0 (1.0–3.0)	2.0 (1.0–5.0)	1.5 (0.5–5.0)	0.29
Body weight (kg)	23 (15–33)	20 (12–24)	17 (14–26)	0.17
Propofol dose (mg kg^{-1})	2.2 (1.0–3.2)	2.7 (1.5–5.0)	3.2 (1.9–4.8)	0.17
Duration of anesthesia (minutes)	99 (94–138)	99 (75–104)	91 (80–103)	0.099
Duration of surgery (minutes)	54 (49–93)	53 (32–63)	46 (40–57)	0.15
Boluses of phenylephrine (1 µg kg^{-1} per bolus)	0 (0–2)	0 (0–0)	0 (0–1)	0.3
Boluses of fentanyl (3 µg kg^{-1} per bolus)	2 (1–4)	1 (0–2)*	0 (0–1)*	0.0008

* Significantly different from group CONTROL ($p < 0.05$).