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Analgesic effect of epidural maropitant and the combination of maropitant and lidocaine in cats subjected to ovariohysterectomy

Efeito analgésico do maropitant e da combinação de maropitant e lidocaína por via epidural em gatas submetidas à ovariohisterectomia

Efecto analgésico del maropitant epidural y la combinación de maropitant y lidocaína en gatas sometidas a ovariohisterectomía

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Abstract
The present study aimed to evaluate the efficacy of epidural maropitant administered with or without lidocaine for post-operative analgesia in cats. Forty cats submitted to epidural administration of treatments followed by ovariohysterectomy were assessed in this study. The cats were randomly distributed into experimental groups: epidural control group (ECG), which received saline; epidural lidocaine group (ELG), which received 3 mg/kg of 2% lidocaine without vasoconstrictor; epidural maropitant group (EMG), which received 1 mg/kg of maropitant; and epidural lidocaine and maropitant group (ELMG), which received 3 mg/kg of 2% lidocaine without vasoconstrictor and 1 mg/kg of maropitant. In all groups, sacrococcygeal epidural administration was performed. Physiological variables were measured during the surgical procedure. Post-operative pain was assessed over six hours by using a visual analogue scale and a multidimensional scale for assessment of post-operative pain in cats. During the surgical procedure, the heart rate in the ELMG was lower than that in the EMG. The ECG required a higher quantity of rescue analgesia in the post-operative period. The EMG and ELMG showed lower pain scores than the ECG. Epidural administration of lidocaine and maropitant, alone or in combination, provided similar analgesic effects in the post-operative period. Although the results indicate analgesic effects of lidocaine and maropitant used alone for two hours and the combination for three hours, the clinical use is limited because the duration of analgesia is too short for postoperative analgesia.
Keywords: Antagonist neurokinin-1 receptor; Health teaching; Nociception; Pain.

Resumo

O presente estudo teve como objetivo avaliar a eficácia do maropitant epidural administrado com ou sem lidocaína para analgesia pós-operatória em gatos. Quarenta gatas submetidas à tratamento com epidural seguida de ovariohisterectomia foram avaliadas neste estudo. As gatas foram distribuídos aleatoriamente em grupos experimentais: grupo controle epidural (GCE) recebeu solução salina; grupo lidocaína epidural (GLE) recebeu 3 mg/kg de lidocaína a 2% sem vasoconstritor; grupo maropitant epidural (GME) recebeu 1 mg/kg de maropitant; e grupo lidocaína epidural e maropitant (GLEM) recebeu 3 mg/kg de lidocaína a 2% sem vasoconstritor e 1 mg/kg de maropitant. Em todos os grupos foi realizada administração epidural sacrococcígea. As variáveis fisiológicas foram mensuradas durante o procedimento cirúrgico. A dor pós-operatória foi avaliada ao longo de seis horas usando uma escala visual analógica e uma escala multidimensional para avaliação da dor pós-operatória em gatos. Durante o procedimento cirúrgico, a frequência cardíaca no GLEM foi menor do que no GME. O GCE exigiu maior quantidade de analgesia de resgate no pós-operatório. O GME e GLEM apresentaram escores de dor mais baixos do que o GCE. A administração epidural de lidocaína e maropitant, isoladamente ou em combinação, proporcionou efeitos analgésicos semelhantes no pós-operatório. Embora os resultados indiquem efeitos analgésicos da lidocaína e do maropitant usados isoladamente por duas horas e da combinação por três horas, o uso clínico é limitado porque a duração do tempo de analgesia é muito curta para analgesia pós-operatória.

Palavras-chave: Antagonista de receptor neurocinina 1; Ensino em saúde; Nocicepção; Dor.

Resumen

El presente estudio tuvo como objetivo evaluar la eficacia del maropitant epidural administrado con o sin lidocaína para la analgesia postoperatoria en gatos. En este estudio se evaluaron cuarenta gatos sometidos a tratamiento epidural seguido de ovariohisterectomía. Los gatos fueron asignados aleatoriamente a grupos experimentales: el grupo de control epidural (GCE) recibió solución salina; el grupo de lidocaína epidural (GLE) recibió 3 mg/kg de lidocaína al 2% sin vasoconstrictor; el grupo de maropitant epidural (GME) recibió 1 mg/kg de maropitant; y el grupo de lidocaína epidural y maropitant (GLEM) recibió 3 mg/kg de lidocaína al 2% sin vasoconstrictor y 1 mg/kg de maropitant. En todos los grupos se realizó administración epidural sacrococcígea. Las variables fisiológicas se midieron durante el procedimiento quirúrgico. El dolor posoperatorio se evaluó durante seis horas utilizando una escala analógica visual y una escala multidimensional para evaluar el dolor posoperatorio en gatos. Durante el procedimiento quirúrgico, la frecuencia cardíaca en el GLEM fue menor que en el GME. El GCE requirió mayor cantidad de analgesia de rescate postoperatoria. El GME y el GLEM tuvieron puntuaciones de dolor más bajas que el GCE. La administración epidural de lidocaína y maropitant, solos o en combinación, proporcionó efectos analgésicos posoperatorios similares. Aunque los resultados indican efectos analgésicos de la lidocaína y el maropitant usados solos durante dos horas y en combinación durante tres horas, el uso clínico es limitado porque la duración de la analgesia es demasiado breve para la analgesia posoperatoria.

Palabras clave: Antagonista del receptor de neuroquinina-1; Enseñanza en la salud; Nocicepción; Dolor.

1. Introduction

Although opioids are the most frequently used analgesics, they can cause adverse effects such as cardiorespiratory depression (Mathews et al., 2014). Therefore, studies have attempted to identify other drugs that may be used for the treatment of pain, such as tricyclic antidepressants, anticonvulsants, serotonin and noradrenaline reuptake inhibitors, and antiemetics (Mathews et al., 2014; Cashmore et al., 2009; Epstein et al., 2015; Adrian et al., 2017; Steagall and Monteiro, 2018). Maropitant, which is an antiemetic used clinically in cats and dogs (Hickman et al., 2008; Kraus, 2013), is one such drug. It is a selective antagonist of neurokinin-1 receptor (NK1) in the central and peripheral nervous systems (De La Puente-Redondo et al., 2007). The NK1 receptor and substance P are involved in pain modulation and the inflammatory process; therefore, blockade of this receptor can generate an antinociceptive effect (Quartara & Maggi, 1998; Patacchini et al., 2004; Garcia-Recio & Gascón, 2015; Xiao et al., 2016).

Administration of maropitant as an intravenous bolus, with or without continuous infusion, has been shown to reduce the minimum alveolar concentration (MAC) of isoflurane and sevoflurane in cats and dogs (Avillar et al., 2012; Niyom et al., 2013; Okano et al., 2015; Fukui et al., 2015). Furthermore, a recent study demonstrated a significant reduction in post-operative rescue analgesia in cats subjected to ovariohysterectomy when receiving continuous infusion of maropitant during the trans-anesthetic period (Correa et al., 2019).

The use of epidural analgesics is advantageous because of long duration of action and the low required doses (Castro et al., 2009). In cats and dogs, both anesthesia and analgesia through the epidural space can be used for both elective and emergency surgical procedures (Robertson & Taylor, 2004; Valverde, 2008; DeRossi et al., 2016; Fernandez-Parra et al., 2017; Steagall et al., 2017). Although some drugs such as α_2-adrenergic agonists and ketamine are used for the purpose of analgesia, opioids are used more frequently (Valverde, 2008; Steagall et al., 2017). In cats with urethral obstruction, administration of sacrococcygeal epidural lidocaine has demonstrated excellent patient comfort without the risk of spinal cord perforation or subarachnoid application (O'hearn & Wright, 2011).

The objective of the present study was to determine whether sacrococcygeal epidural administration of maropitant or a combination of maropitant and lidocaine promotes post-operative analgesia in cats subjected to ovariohysterectomy. Studies on the administration of epidural maropitant are scarce, the hypothesis was that its epidural use have an post-operative analgesic effect in cats subjected to elective ovariohysterectomy due to the presence of NK1 receptors in the spinal cord.

2. Methodology

The randomized clinical trial was conducted after obtaining approval by the Ethical Commission in the Use of Animals (CEUA) of the State University of Santa Cruz - UESC (protocol 08/18), and in accordance with the guidelines on care and use of laboratory animals issued by the National Council for Animal Experimentation Control (Brazil).

Animals and groups

A total of forty cats aged 3.7 ± 2.6 years (6 months to 8 years) and weighing 2.8 ± 0.36 kg (2.4 to 3.7 kg), were admitted for elective ovariohysterectomy at the Veterinary Hospital of the State University of Santa Cruz (UESC). The owners were briefed, and they signed written informed consent agreeing to participate in the study. For inclusion in the study, the cats had to weigh above 2 kg and be co-operative temperament. Pregnant cats were not accepted. The animals had no contraindications to epidural punctures, such as pelvic fracture, dermatitis, or obesity. A hemogram analysis and biochemical assessments were performed before beginning the experiment, and only animals without clinical and/or laboratorial abnormalities were included in the study.

The animals were hospitalized for 24 h prior to the surgical procedure for adaptation to the environment and the assessor. The animals were fasted for 8 h and did not consume water for 2 h. The anesthesiologist was responsible for inhalation anesthesia and another anesthesiologist for sacrococcygeal epidural procedures, and the same surgeon was responsible for all surgical procedures.

Study design

Cats were randomly divided into four treatment groups (10 each group), all cats had an equal chance of being assigned to any group. In all groups, the epidural dose was calculated in mg/kg, and the final volume was adjusted with 0.9% saline to 0.25 ml / kg (Hermeto et al., 2015). In all groups, administration was performed through the sacrococcygeal epidural route.

- Epidural control group (ECG): received only saline solution (sodium chloride 0.9%; Fresenius Kabi Brazil Ltd., Brazil);
- Epidural lidocaine group (ELG): received 3 mg/kg of lidocaine without vasoconstrictor (lidocaine hydrochloride 2%, Hipolabor Farmacêutica, Brazil);
- Epidural maropitant group (EMG): received 1 mg/kg of maropitant (Cerenia®, Zoetis, Brazil);

- Epidural lidocaine and maropitant group (ELMG): received 3 mg/kg of lidocaine without vasoconstrictor and 1 mg/kg of maropitant.

Procedures

After clinical assessment, the cats were pre-medicated with acepromazine (0.05 mg/kg) (Acepromazine 2%, Syntec, Brazil) and morphine (0.3 mg/kg) (Morphine sulfate 10 mg/mL; Hipolabor Sanval, Brazil), both injected into the semitendinosus muscle. Fifteen minutes after pre-anesthetic medication was administered, hair removal was performed from the surgical site and the sacrococcygeal region was performed. An intravenous 24 G catheter (Safelet radio-opaque catheter; Nipro Medical Corporation Produtos Médicos Ltd., Brazil) was inserted into the cephalic vein using an aseptic technique for administration of fluid treatment (Ringer lactate, 5 mL/kg/h; Fresenius Kabi Brazil Ltd) and propofol. Anesthetic induction was carried out with propofol (5 mg/kg) (Propotil; BioChimico Indústria Farmacêutica Ltd., Brazil) and lidocaine used topically on the larynx. After induction, the trachea of the animals was intubated (endotracheal tube number 3.0 mm or 3.5 mm) and the supply of oxygen (300 mL/kg/min) and isoflurane (1.5 Vol.%) (Isoforine, Cristália Prod. Químicos Farmacêutica Ltda, Brazil) was initiated in a non-rebreathing system (Mapleson breathing systems, Jackson Rees) for maintenance anesthesia. Cephalothin (30 mg/kg intravenous) (Ceflen; Agila, Brazil) was used for prophylactic antibiotic therapy before beginning the induction and surgery.

The animals were positioned in sternal recumbency and the sacrococcygeal space was identified, antisepsis of the region was performed, and the region was subsequently covered with a sterile surgical drape. A 26 G needle (Technical needle for Tuohy epidural puncture) was inserted into the space between the sacral vertebra and the first coccygeal vertebra identified by palpation (O'hearn & Wright, 2011) for administration of the agents corresponding to the group. To verify the correct position of the needle, suction of the needle drip, lack of resistance during application, and anal sphincter relaxation after application were observed, the last of which was observed only in animals from the ELG and ELMG due to the presence of lidocaine.

Ovariohysterectomy was performed via midline incision caudal to the umbilicus by an experienced surgeon in all animals. During the surgical procedure, the following vital signs were evaluated with the assistance of a multi-parameter monitor (LifeWindow™ LW9xVet): heart rate (HR), respiratory rate (RR), esophageal temperature (T), end tidal carbon dioxide partial pressure ($ETCO_2$), concentration of isoflurane at the end of expiration (Etiso) and oxygen saturation (SpO_2). Systolic arterial pressure (SAP) was measured with a vascular doppler (Portable Vascular Doppler Medmega DV 610) using a rotator cuff measuring 30%-40% of the circumference of the radio-ulnar region of the animal. The physiological parameters were evaluated at different times, these being: M1 – before beginning the surgical procedure (base values); M2 – after incision of the abdominal musculature; M3 – after clamping of the right ovarian pedicle; M4 – after clamping of the left ovarian pedicle; M5 – after ligature of the body of the uterus; M6 – suture of abdominal musculature; and M7– end of the surgical procedure. The concentration of isoflurane was increased when an increase in heart rate, respiratory rate and blood pressure was observed in comparison with normal values for the species under general anesthesia.

There were two anesthesiologists, one of whom performed the epidural administration of the drugs and knew the groups, and the other anesthesiologist who performed inhalation anesthesia and monitoring and postoperative pain assessment and did not know the assignment to the groups (blinded).

Pain assessment

Pain assessment in the post-operative period started an hour after extubation and continued every hour for 6 h. Two scales were used for pain assessment: the visual analogue scale (VAS) (0 = no pain and 100 mm = worst pain possible) and the

Multidimensional Scale of UNESP-Botucatu for assessment of post-operative pain in cats. After pain assessment, the animals were stimulated to move around the assessment room and were observed for two minutes to verify motor function, which was categorized as follows by Hermeto et al., 2015: 0 – normal motor function. 1 – slight motor incoordination; the cat has difficulty maintaining a standing position; 2 - moderate motor block; the cat is reclining, with movement of the rear limbs; 3 - complete motor block; the cat is in sternal decubitus, without movement of the rear limbs.

Rescue analgesia with morphine (0.2 mg/kg/IM) was performed when the VAS value was ≥ 40 mm (Slingsby and Waterman-Pearson, 1998) and/or when the score on the Multidimensional Scale of UNESP-Botucatu for Assessment of Post-operative Pain was ≥10. A score ≥10 was considered for analgesic rescue because it corresponds to 33.3% of the scale value and is a point at wich pain relief is strongly recommended (Brondani et al., 2013). At the end of the assessment (6 h after extubation), 0.2 mg/kg IM of meloxicam (Maxicam 0.2%; Ourofino, Brazil) was administered to all the cats. After six hours of pain assessment, the cats returned to the home with their owners.

Statistical analyses

All the collected data were analyzed using Prism 5 for Windows (GraphPad Software. La Jolla CA, USA). The sample size was based on a previous pilot experiment, considering the sample calculation the standard deviation, the difference between the mean to be obtained in the sample and the true mean, and the critical values of the Student t distribution. The data were tested for normal distribution using the Kolmogorov-Smirnov test. All the data followed a normal distribution (FC, PAS, *RR*, SpO_2, Etiso, T, body weight, duration of anesthesia, duration of surgery and extubation time) and were subjected to analysis of variance (two-way ANOVA), with the means being compared using the Bonferroni post-hoc tests. The non-parametric data (scales of pain assessment) were subjected to the Kruskall-Wallis test and Mann Whitney test, when these groups were compared with the control group, and the Fisher exact test was used to compare the number of analgesic rescues. For all tests, the significance level was 95% ($P < 0.05$).

3. Results

Body weight (ECG 3.0 ± 0.4 kg; ELG 2.8 ± 0.2 kg; EMG 2.9 ± 0.3 kg; ELMG 2.9 ± 0.2 kg; P = 0,58), duration of anesthesia (ECG 39.5 ± 5 min; EMG 41 ± 6 min; ELG 41.3 ± 6 min; ELMG 45 ± 4 min; P = 0,17), duration of surgery (ECG 22 ± 2 min; EMG 24 ± 2 min; ELG 24 ± 4 min; ELMG 26 ± 2 min; P > 0,05), and extubation time (ECG 4 ± 2 min; EMG 5 ± 2 min; ELG 4 ± 2 min; ELMG 6 ± 2 min; P = 0,33) showed no significant difference among the groups studied. In the post-operative period, no animal showed complete motor function in the hindlimbs. None of the cats exhibited salivation or vomiting during the experimental period in any of the treatment groups.

During the surgical procedure, the HR in the ELMG was lower than that in the EMG ($P = 0.03$) in M1, M2, M4, and M5; there were no significant differences among the other groups. Etiso was higher in the ECG at some moments in comparison to the EMG (M4), ELG (M4 and M5), and ELGM (M4, M5, M6 and M7) ($P < 0.05$). The RR, SAP, T, $ETCO_2$, and SpO_2 parameters did not show statistically significant differences among the groups (Table 1), being maintained in the normal range for the species (O'hearn & Wright, 2011).

Table 1: Variables (mean ± standard deviation) of the physiological parameters observed during the surgical procedure.

Variables	Groups	Times						
		M1	M2	M3	M4	M5	M6	M7
HR (bpm)	ECG	156.6±27.7	145.8±24.2	187.3±23.3	187.1±26.2	178.8±19.1	172.7±20.3	174.7±17.3
	ELG	161.0±31.6	155.2±31.6	161.1±31.8	179.7±19.2	167.3±17.8	161±15.5	161.7±22.6
	EMG	166.1±23.0*	162.7±24.9*	178.6±22.5	180.1±25.0*	176.2±15.0*	173.7±25.5	168.1±23.2
	ELMG	132.7±15.7*	130.9±35.8*	168.5±39.0	159.5±29.5*	154.3±27.5*	148.3±18.4	146.9±29.1
SAP (mmHg)	ECG	75.2±14.6	83.9±8.8	116.5±34.5	117.6±30.7	103.8±21.3	98.3±13.5	104.0±11.6
	ELG	77.7±16.6	74.1±8.4	97.7±17.5	101.9±17.3	93.2±15.6	94.9±20.1	112.2±30.9
	EMG	83.1±19.1	72.5±14.3	96.0±21.5	107.1±21.5	103.5±31.6	94.2±16.9	95.7±11.3
	ELMG	86.6±19.3	82.5±7.6	98.1±26.3	103.6±29.5	89.0±23.3	89.7±19.6	91.0±13.3
***RR* (mpm)**	ECG	30.3±11.1	28.6±11.4	29.8±11.5	27.5±12.1	29.4±12.6	24.0±10.5	25.6±9.8
	ELG	32.0±9.2	24.8±3.8	29.1±5.1	27.1±7.8	25.7±9.3	20.7±7.6	23.7±8.1
	EMG	30.3±6.3	26.7±7.4	28.3±7.9	25.5±6.2	23.7±7.6	22.3±6.2	21.2±6.3
	ELMG	28.4±11.3	24.6±9.5	26.0±9.5	27.2±8.6	24.1±8.9	20.8±7.6	22.4±8.4
$ETCO_2$	ECG	40.1±4.7	41.3±6.2	40.9±5.6	39.0±4.3	40.8±6.6	40.4±5.8	39.9±5.7
	ELG	31.8±8.0	33.4±9.5	33.8±8.5	34.2±8.6	34.5±8.3	33.9±9.5	33.2±8.1
	EMG	33.7±6.0	35.6±6.3	35.5±5.0	35.7±5.7	34.4±4.5	35.4±4.7	36.2±4.5
	ELMG	34.4±5.5	36.3±7.4	36.1±6.9	35.4±7.0	36.6±7.1	37.6±5.8	35.7±4.4
SpO_2 (%)	ECG	97.8±1.9	98.9±1.4	98.7±0.9	99.0±1.1	98.8±1.0	99.2±0.9	99.2±0.7
	ELG	98.4±1.4	98.6±1.6	99.3±0.5	98.9±0.6	98.8±1.0	99.1±0.7	98.4±1.3
	EMG	98.5±1.3	97.1±2.7	98.4±2.0	99.1±1.1	98.8±1.4	99.4±0.7	99.0±1.7
	ELMG	98.3±1.5	99.1±1.2	99.3±1.1	99.4±0.9	98.7±1.1	99.2±0.9	99.3±1.0
Etiso (V%)	ECG	1.2±0.2	1.3±0.3	1.5±0.2	1.6±0.2*	1.6±0.3*	1.3±0.2*	1.2±0.1*
	ELG	1.3±1.2	1.2±1.1	1.1±0.1	1.1±0.2*	1.0±0.1*	1.0±1.1*	0.9±0.1*
	EMG	0.9±0.14	1.2±0.09	1.1±0.1	1.2±0.2*	1.2±0.2	1.1±0.1	0.9±0.1
	ELMG	1.1±0.2	1.1±0.1	1.2±0.2	1.1±0.1*	1.1±0.2*	0.9±0.2*	0.8±0.1*
T (°C)	ECG	37.7±0.5	37.4±0.5	37.2±0.6	37.0±0.6	37.0±0.7	37.0±0.7	37.0±0.7
	ELG	37.0±0.7	36.8±0.8	36.6±0.7	36.3±0.7	36.1±0.8	35.8±0.9	35.5±0.9
	EMG	37.1±0.9	37.1±0.8	36.9±0.9	36.8±1.0	36.6±0.9	36.5±1.0	36.7±1.0
	ELMG	37.2±0.7	37.0±0.8	36.6±1.0	36.5±1.0	36.2±1.1	36.1±1.2	36.0±1.3

* significant difference between groups (P <0.05). ECG = epidural control group, ELG = epidural lidocaine group, EMG = epidural maropitant group, ELMG = epidural lidocaine and maropitant group. HR: heart rate; bmp: beats per minute; SBP: systolic blood pressure; mmHg: millimeters of mercury; RR: respiratory rate; mpm: movement per minute; $ETCO_2$: partial pressure of carbon dioxide at the end of expiration; SpO_2: oxygen saturation; Etiso: expired isoflurane concentration; V%: volume percent; T: body temperature; ° C: degree Celsius. M1 – before beginning the surgical procedure (base values); M2 – after incision of the abdominal musculature; M3 – after clamping of the right ovarian pedicle; M4 – after clamping of the left ovarian pedicle; M5 – after ligature of the body of the uterus; M6 – suture of abdominal musculature; and M7– end of the surgical procedure. Source: Prepared by the authors.

One hour after extubation, the animals did not present sedation. There was a significant difference ($P < 0.05$) in the number of cases requiring rescue analgesia when comparing the ECG (20 total rescues), with the ELG (10 total rescues), EMG (11 rescues), and ELGM (10 total rescues). The control group (2 cats) received analgesic rescue from the first hour. The group that received only lidocaine (3 cats) or only maropitant (1 cat) received rescue after the second hour and the group that received the combination of lidocaine and maropitant (1 cat) received rescue after the third hour (Table 2).

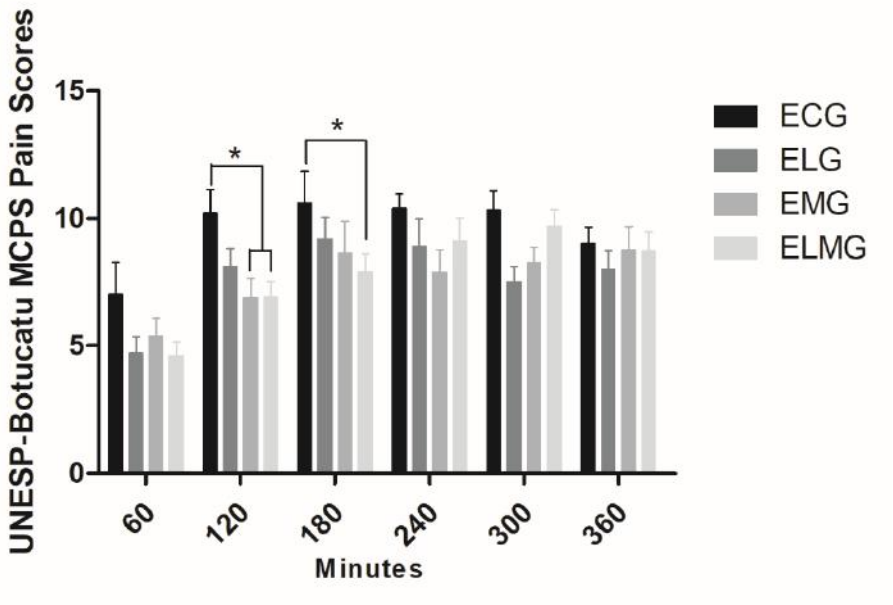
Table 2: Number of cats that received analgesic rescue using the UNESP-Botucatu multidimensional scale and Visual Analogue Scale.

Groups	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours	Total
ECG	2	3	1	3	1	0	10 (100%)
ELG	0	3	1	3	0	0	7(70%)
EMG	0	1	3	2	0	1	7 (70%)
ELMG	0	0	1	3	1	1	6 (60%)

The table includes the first administration of analgesic rescue. ECG = epidural control group, ELG = epidural lidocaine group, EMG = epidural maropitant group, ELMG = epidural lidocaine and maropitant group. Source: Prepared by the authors.

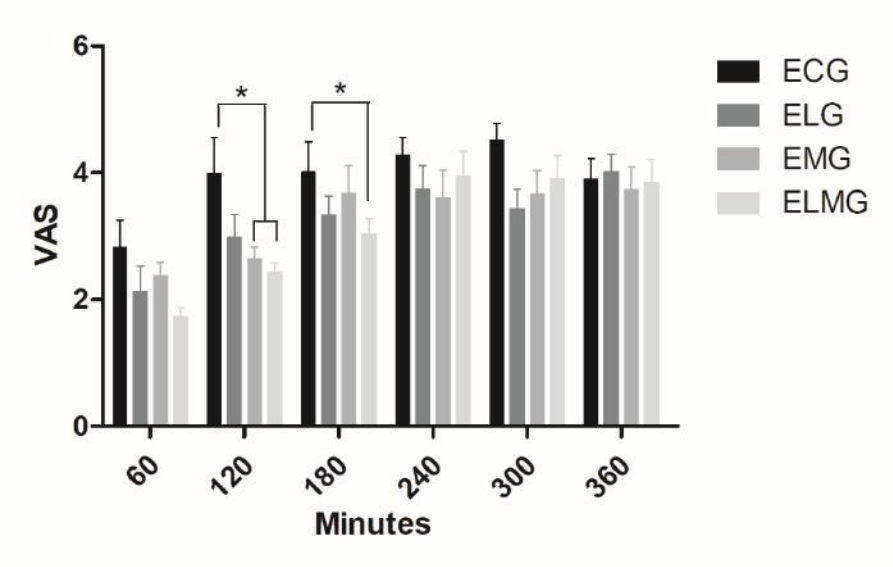
Pain scores on both assessments were lower in the EMG than in the ECG ($P < 0.05$) at the second evaluation time (Figures 1 and 2). The ELMG showed lower pain scores in relation to the ECG ($P < 0.05$) at the second and third evaluation times on VAS and the Multidimensional Scale of UNESP-Botucatu for assessment of post-operative pain in cats (Figures 1 and 2).

Figure 1. Scores on the multidimensional scale of UNESP-Botucatu for assessment of pain in cats after ovariohysterectomy.



Result expressed by the mean ± standard error of the mean. *P < 0,05. ECG = epidural control group, ELG = epidural lidocaine group, EMG = epidural maropitant group, ELMG = epidural lidocaine and maropitant group. 1: one hour; 2: two hours; 3: three hours; 4: four hours; 5: five hours, and 6: six hours after extubation. Source: Prepared by the authors.

Figure 2: Scores on the visual analogue scale for pain in cats after ovariohysterectomy.



Result expressed by the mean ± standard error of the mean. *P<0,05. ECG = epidural control group, ELG = epidural lidocaine group, EMG = epidural maropitant group, ELMG = epidural lidocaine and maropitant group. 1: one hour; 2: two hours; 3: three hours; 4: four hours; 5: five hours, and 6: six hours after extubation. Source: Prepared by the authors.

4. Discussion

To our knowledge, this is the first study to evaluate post-operative pain in cats treated with maropitant via sacrococcygeal epidural administration after ovariohysterectomy. The results suggest that the use of maropitant in isolation or in combination with lidocaine has an antinociceptive effect through this route in comparison with administration of saline solution. In the present study, the combination of lidocaine and maropitant or the use of these medications in isolation showed similar effects in reducing the requirement of rescue analgesia in the post-operative period.

Lidocaine is frequently used as a local anesthetic in cats and dogs for various surgical procedures, and it shows fast onset of a block (5 minutes), albeit with a short duration (60 minutes) (Robertson and Taylor, 2004; O'hearn and Wright, 2011). The groups that received only lidocaine (ELG) and only maropitant (EMG) required rescue analgesia two hours into the post-operative period, while the group that received both maropitant and lidocaine (ELMG) required rescue analgesia three hours after the operation. While evaluating the use of lidocaine through epidural administration, previous studies (DeRossi et al., 2016) also observed that the animals that received only lidocaine required rescue analgesia after two hours in the post-operative period. These results are similar in female dogs subjected to ovariohysterectomy that received only lumbosacral epidural lidocaine (Hermeto et al., 2017).

The lidocaine dose was chosen in accordance to a previous study (Hermeto et al., 2015), in which epidural administration of 3 mg/kg lidocaine was performed in cats for analgesia evaluation. The dose of 1 mg/kg of maropitant was chosen based on an experimental study carried out to evaluate the MAC of sevoflurane with tail-clamp technique after epidural administration of maropitant in dogs (Avillar et al., 2012).

In the present study, no significant differences were observed between the ECG and EMG findings for HR, SAP, and T, in agreement with the findings reported by another studies dogs (Avillar et al., 2012) after epidural administration of maropitant in dogs. Sacrococcygeal epidural administration of lidocaine did not alter the studied physiological parameters, corroborating the results obtained by other studies after the use of epidural lidocaine in cats (Fernandez-Parra et al., 2017; Hermeto et al., 2015; Lawal & Adentunji, 2009). After epidural administration of 4 mg/kg (0.25 ml/kg) of lidocaine in the lumbosacral region in cats, observed a reduction in HR, RR, T, and SAP, although these variables remained within clinically

acceptable values for the species (DeRossi et al., 2016). The difference between the results obtained in the present study in relation to those observed by another studies (DeRossi et al., 2016) is probably due to the administration site of the lidocaine and the dose used.

The administration of lidocaine alone and its combination with maropitant reduced the quantity of isoflurane required for anesthesia. The reduction in Etiso in the treatment groups reflects the isoflurane sparing effect of the utilized medications (Boscan et al., 2011).

The duration of anesthesia provided by epidural lidocaine without vasoconstrictor is around 37 to 53 minutes, possibly lasting up to 90 minutes with vasoconstrictor (Hermeto et al., 2015; Lawal & Adentunji, 2009; Adentunji et al., 2002). The use of lidocaine in isolation does not provide adequate analgesia for the post-operative period, necessitating the addition or use of other medications (DeRossi et al., 2016; Hermeto et al., 2015). The significantly lower values observed in the ELMG on pain assessment scales (Figures 1 and 2) at two and three hours post-operatively further confirm the necessity of administering another drug with lidocaine, since lidocaine in isolation (ELG) was not capable of causing such a decrease.

Lidocaine blocks sensory and motor fibers non-specifically (Babos et al., 2013; Estebe, 2017), while maropitant blocks NK1 receptors for substance P. NK1 receptors are present in the dorsal horn of the spinal cord, modulating the transmission of the noxious stimulant and also in peripheral sensory fibers involved in the transmission of impulses caused by a noxious stimulation (Garcia-Recio & Gascón, 2015; Boscan et al., 2011). The antinociceptive action of maropitant is probably related to the blockade of NK1 receptors in the spinal cord. Since the clinical effect of maropitant is comparable to that of lidocaine, the advantage of using maropitant would be its selectivity to the NK1 receptor. As the administration of both lidocaine and maropitant alone promoted a short analgesic effect (2 hours) in the postoperative period, based on these results, these drugs should not be used to obtain analgesia in the postoperative period in cats after ovariohysterectomy.

Despite the similar effects indicated by statistical analysis, the ELMG received the first rescue analgesia at three hours post-operatively; thus, the necessity of analgesic requirement was possibly prolonged in this group by at least 1 hour. This could have been caused by a potentiation effect between lidocaine and maropitant, since the groups with isolated drugs (ELG and EMG) required the first rescue within 2 hours of evaluation.

Another study (Avillar et al., 2012) administered 1 mg/kg of epidural maropitant to dogs to evaluate the MAC of sevoflurane, but no alteration was observed. Maropitant administered through other pathways produced a reduction in the MAC of inhalation anesthetics in cats and dogs, suggesting an antinociceptive effect (Niyom et al., 2013; Boscan et al., 2011; Marquez et al., 2015; Swallow et al., 2017). Administration by bolus and continuous infusion reduced the use of analgesics in the post-operative period in cats subjected to ovariohysterectomy (Correa et al., 2019). The antinociceptive effect of maropitant in cats subjected to ovariohysterectomy found in the post-operative period in the present study is probably due to the ample expression of substance P and its NK1 receptor in the spinal cord, which are involved in the processing of pain (Garcia-Recio and Gascón, 2015).

Blockade of NK1 receptors reduces the central sensitization that occurs after surgical procedures. Some studies have demonstrated that human patients that received NK1 antagonists required lower doses of analgesics (Kakuta et al., 2011), pain relief and allodynia (Garcia-Recio & Gascón, 2015; Dulin et al., 2017). Furthermore, studies on rats demonstrated decreased tolerance to opioids and increased antinociceptive activity with the use of fosaprepitant (Prasoon et al., 2016). Therefore, although the treatments are similar, in a clinical evaluation, the use of maropitant seems to be more advantageous, as it selectively blocks the NK1 receptor and has an antinociceptive effect similar to lidocaine.

5. Conclusion

Sacrococcygeal epidural administration of lidocaine and maropitant in isolation provided similar analgesic effects in the post-operative period. Although the results indicate analgesic effects of lidocaine and maropitant used alone for two hours and the combination for three hours, the clinical use is limited because the analgesia time is too short for postoperative analgesia.

As this is the first study of the administration of maropitant via the sacrococcygeal epidural route in cats, further studies using other doses are needed in this species.

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