Preemptive effect of amantadine as adjuvant in postoperative analgesia of ovaryhisterectomy in dogs

Efeito preemptivo da amantadina como adjuvante na analgesia pós-operatória de ovariohisterectomia em cães

Efecto preventivo de la amantadina como complemento de la analgesia postoperatoria para la ovariohisterectomía en perros

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Abstract

This study aimed to evaluate the preemptive analgesic effect of amantadine on postoperative pain control in female dogs that underwent ovariohysterectomy. Twenty female dog were randomly assigned to two groups of ten. The control group (CONTROL) received oral placebo capsules, while the amantadine (AMANT) group received 5 mg/kg of oral amantadine one hour before sedation. All the animals were premedicated with 3 mg/kg (IM) meperidine, induced with propofol and maintained with isofluorane. The transanesthetic physiological parameters were recorded, and postoperative pain was evaluated every hour after extubation for six hours with the Dynamic Interactive Visual Analog Scale (DIVAS) and mechanical nociceptive threshold (MNT) and when the necessary analgesic rescue was administered (morphine, 0.2 mg/kg (IM)). During the surgical procedure, there was no significant difference in the variables measured between the two groups. Regarding postoperative pain assessment, there was a significant difference in the DIVAS score (p = 0.004) between the groups, in which AMANT required fewer rescues than did CONTROL (p = 0.03). The MNT was significantly higher in AMANT than in CONTROL (p = 0.03). The results suggested that the preoperative administration of amantadine decreased analgesic requirement in female dogs that underwent elective ovariohysterectomy.

Resumo

Este estudo objetivou avaliar o efeito preemptivo da amantadina no controle da dor pós-operatória em cadelas submetidas a ovariohisterectomia. Vinte cadelas foram distribuídas aleatoriamente em dois grupos de dez animais. O grupo controle (CONTROLE) recebeu cápsulas de placebo via oral e o grupo amantadina (AMANTADINA) recebeu 5 mg/kg de amantadina via oral, uma hora antes da medicação pré-anestésica. Todos os animais foram pré-medicados com meperidina 3 mg/kg/IM, indução com propofol e manutenção com isofluorano. Registraram-se os parâmetros fisiológicos trans-anestésicos e a dor pós-operatória foi avaliada a cada hora durante seis horas após a extubação com a escala analógica visual interativa e dinâmica (EAVID), limiar nociceptivo mecânico (LNM) e quando necessário administrou-se resgate analgésico (morfina 0,2 mg/kg (IM)). Durante o procedimento cirúrgico não houve diferença significativa nas variáveis mensuradas entre os dois grupos. Com relação à avaliação de dor no pós-operatório, houve diferença significativa na EAVID (p = 0,004) entre os grupos, em que AMANTADINA necessitou de menos resgates quando comparado ao CONTROLE. E o LNM apresentou valores mais elevados no AMANTADINA com uma diferença significativa (p = 0,03) comparada ao CONTROLE. Os resultados sugeriram que a administração da amantadina no pré-operatório diminuiu requerimento analgésico em cadelas submetidas a ovariohisterectomia eletiva.

Palavras-chave: Amantadina; Analgesia visceral; Nocicepção; Receptor NMDA.

Resumen

Este estudio tuvo como objetivo evaluar el efecto preventivo de la amantadina en el control del dolor postoperatorio en perras sometidas a ovariohisterectomía. Se asignaron al azar veinte perras a dos grupos de diez animales. El grupo de control (CONTROL) recibió cápsulas de placebo por vía oral y el grupo de amantadina (AMANTADINA) recibió 5 mg / kg de amantadina por vía oral, una hora antes de la medicación preanestésica. Todos los animales fueron premedicados con meperidina 3 mg / kg / IM, inducción con propofol y mantenimiento con isofluorano. Se registraron los parámetros fisiológicos trans-anestésicos y se evaluó el dolor postoperatorio cada hora durante seis horas después de la extubación con la escala analógica visual interactiva y dinámica (EAVID), el umbral nociceptivo mecánico (UNM) y, cuando fue necesario, se administró. rescate analgésico (morfina 0,2 mg / kg (IM)). Durante el procedimiento quirúrgico, no hubo diferencia significativa en las variables

medidas entre los dos grupos. Con respecto a la evaluación del dolor postoperatorio, hubo una diferencia significativa en EAVID (p = 0,004) entre los grupos, en los que AMANTADINA requirió menos rescates en comparación con CONTROL. Y el UNM mostró valores más altos en AMANTADINA con una diferencia significativa (p = 0.03) en comparación con CONTROL. Los resultados sugirieron que la administración de amantadina en el período preoperatorio disminuyó la necesidad de analgésicos en las perras sometidas a ovariohisterectomía electiva.

Palabras clave: Amantadina; Analgesia visceral; Nocicepción; Receptor NMDA.

1. Introduction

Acute pain is the result of traumatic, surgical, and infectious events. It begins abruptly, and its duration is predictable and correlated with the severity of the injury (Moran and Hofmeister, 2013). Providing adequate analgesia for every patient who undergoes a surgical procedure is essential so that in addition to promoting their general well-being, they also achieve a better postoperative recovery (Cunha et al., 2004).

Intense and prolonged painful stimuli induce a cascade of events that activate the N-methyl-D-aspartate (NMDA) receptor. This activation is associated with abnormalities in the sensory nervous system (peripheral and central sensitization), resulting in neuronal excitation and abnormal painful stimuli (e.g., spontaneous pain, allodynia, and hyperalgesia) (Collins et al., 2010).

Central sensitization mainly occurs through the activation of NMDA receptors, which can contribute to acute postoperative pain becoming chronic (Gottschalk et al., 2001). Glutamate, an excitatory neurotransmitter, binds to the NMDA-type receptor located in the dorsal horn of the spinal cord. Antagonism of the NMDA receptor contributes to reducing the pain due to the surgical procedure (Galvan et al., 2006).

Amantadine was initially used as an antiviral agent in treating influenza A virus infections. It was also used to treat Parkinson's disease (Aiyer et al., 2017). Amantadine promotes a non-competitive antagonism of NMDA-type glutamatergic receptors and can be useful in decreasing not just the pain, but also the use of analgesics in the post-surgical period (Blanpied et al., 2005). It has inhibitory properties in the modulation of somatic and visceral nociceptive stimuli and is believed to be a safe and effective alternative for the management of postoperative pain (Rashwan and Abdelmawgound, 2013).

One of the measures used to reduce postoperative pain is preemptive analgesia, in which treatment prior to the injury prevents the CNS sensitization (Lascelles et al., 2008; Bufalari et al., 2012) and neuronal reflex hyperexcitability that occurs in the spinal cord in response to stimuli from peripheral nociceptors (Kalchofner Guerrero et al., 2016).

This strategy is used to minimize postoperative pain, thereby shortening the patient's recovery period. However, it does not eliminate the need for other analgesic drugs in the postoperative period (Luna, 2006).

Studies have proven that the use of amantadine can be beneficial in multimodal analgesia in dogs, as it was used as adjuvant analgesia in dogs with osteoarthritis, and also in preemptive analgesia in surgical interventions of patients with osteosarcoma (Fan, 2014). Given these properties, it is believed that amantadine can provide relief during the postoperative period in female dogs undergoing ovariohysterectomy when administered as a part of preemptive analgesia protocols.

Thus, the objective of the study was to evaluate the preemptive effects of amantadine, when administered in the preoperative period for ovariohysterectomy in female dogs, and its influence on cardiovascular parameters during surgery.
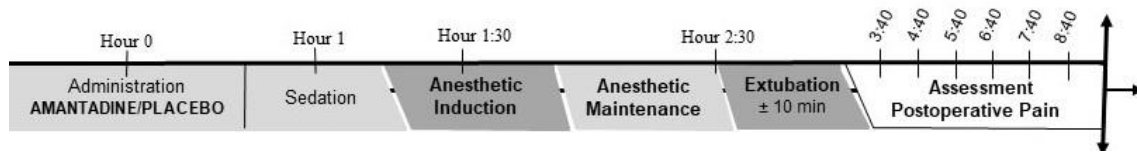
2. Methods

This study was approved by the Animal Use Ethics Committee of Universidade Estadual de Santa Cruz (Ilhéus, Bahia, Brazil; Protocol 024/2016).

Action research study with twenty mixed-breed female dogs (aged 2-8 years), considered healthy based on anamnesis and clinical/laboratory examination, were included in the study carried out at the Veterinary Hospital of Universidade Estadual de Santa Cruz. Clinically ill, pregnant, lactating, and aggressive animals were excluded from the study. The owners received explanations about the experimental design, after which they authorized the inclusion of their animals in the study by signing the informed consent form. Food but not water was withheld for 10 hours before anesthesia.

The initial qualitative assessment was performed 90 minutes before surgery, using a multiparametric monitor (Wato EX-65, Mindray) with the following parameters: heart rate (HR), respiratory rate (f), oxyhemoglobin saturation (SpO2), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and mean arterial pressure (MAP) using the oscillometric method, and body temperature using a rectal thermometer. Then, the animals received either a placebo or amantadine capsules (5 mg/kg) orally (Figure 1).

Figure 1. Schematic representation of timeline for the experiment.

Source: Authors.

The distribution of the animals into groups was done by the method of randomization in blocks, whereby they were randomly assigned to the groups. Thus, the animals were divided into two groups, the CONTROL and AMANT groups, each comprising 10 animals.

All animals received 3 mg/kg of meperidine (Petidina, 50 mg / mL, União Chemical Laboratory) intramuscularly (IM), as pre-anesthetic medication. Then, the animals were monitored to determine the degree of sedation, using the simple descriptive score (Table 1).

Table 1. The Simple Descriptive Sedation Score.

Escore	Criteria
0	Awake patient
1	Mild sedation, less alert but still active (responds to verbal commands)
2	Moderate sedation, drowsy, recumbent but can walk (responds to tactile stimuli)
3	Intense sedation, very drowsy, unable to walk (only responding to painful stimuli)

Source: Modified from Monteiro et al., 2014.

That is, after the application of pre-anesthetic medication, the animals were classified according to the scale mentioned and their behaviors, in sedation score.

A catheter was inserted aseptically into the cephalic vein, and the animals received Ringer's Lactate solution (Lactate Ringer's solution, 500 mL, Fresenius Kabi Brasil Ltda) at the rate of 10 ml/kg/h until the end of the surgical procedure.

Anesthetic induction was performed with propofol (Propotil® 1%, Bio Chimico®) at a dose of 5 mg/kg, intravenously (IV), and after endotracheal intubation, the anesthesia was maintained with isofluorane (Isofluorane®, Cristália) with a closed circuit, 100% oxygen (50

ml /kg/min), through mechanical ventilation, with tidal volume 10 ml / kg, respiratory rate (f) 10 bpm, I:E ratio (1:3), and a peak inspiratory pressure (PIP) of 10 cmH$_2$0. Soon after induction, all animals received cephalothin sodium (Ceflen®, Agila Especialidades Farmacêuticas Ltda, Brazil) at a dose of 30 mg/kg / IV as prophylactic antibiotic therapy.

During the surgical procedure, when there was a 20% increase in the baseline values (after induction) of HR and / or SAP in response to the surgical stimulation, fentanyl was administered (Cloridrato de Fentanil, 50 µg / ml, Hipolabor Laboratório) at a dose of 3 µg/kg/IV. As fentanyl has a rapid onset of action and acts only for about 20 minutes (SANO et al., 2006), the animals that received it still underwent the postoperative pain assessment performed in the study.

The following parameters were monitored using a multiparametric monitor (Wato EX-65, Mindray): esophageal temperature (T); heart rate (HR), respiratory frequency (*f*), oxygen saturation level (SatO2), Etiso, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and media arterial pressure (MAP) by the oscillometric method, with the cuff placed over the median artery at the height of the middle third of the radial ulnar.

Such parameters were evaluated by an anesthesiologist, who was blinded to the study design at the following times: M0: before amantadine administration; M1: before the start of the surgical procedure; M2: after incision of the linea alba; M3: after clamping of the right pedicle; M4: after clamping of the left pedicle; M5: after ligation of the body of the uterus; M6: after suturing of the linea alba; and M7: at the end of the surgery. The surgical procedure was performed by the same surgeon using the incision from the caudal midline to the umbilical scar in all animals.

The quantitative assessment of postoperative pain was performed one, two, three, four, five, and six hours after extubation. Through the Dynamic Interactive Visual Analog Scale (DIVAS), where pain intensity was scored on a 100 mm scale, in which 0 mm (zero) corresponded to the absence of pain and 100 mm corresponded to the worst possible pain. With values equal to or greater than 40 mm, the animals received analgesic rescue.

To determine the mechanical nociceptive threshold (MNT), a digital analgesimeter (EFF-301, Insight Equipment) was used. This device has a pressure transducer connected to a digital force counter expressed in kilograms/force (kgf). The contact of the pressure transducer with the area of the surgical wound was made through an adapted polypropylene tip. In each animal, pressure was applied three centimeters (cm) from the surgical wound, at three points, with three repetitions at each point. Positive responses were considered to be any physical alteration of the animals in relation to the pressure made with the device, such as

restlessness and discomfort. The force value in grams was recorded and considered as a threshold for mechanical sensitivity. Mechanical nociceptive threshold assessments were performed during the six hours of pain assessment after extubation.

In the post-surgical period, morphine (0.2 mg/kg / IM) was used for analgesic rescue, when there was a result ≥ 40 mm from the DIVAS. At the end of the sixth-hour assessment, patients were medicated IM with 0.2 mg/kg of meloxicam (Maxicam 2% injectable 50 ml, Ourofino Saúde Animal Ltda, Brazil), 5 mg/kg of tramadol hydrochloride (Hydrochloride tramadol 100 mg / 2 mL, União Química Farmacêutica Nacional S / A, Brazil) and 25 mg/kg of dipyrone (Santidor 1 g / 2 mL, Santista Laboratório Farmacêutica SA, Brazil). The animals, 10 days after the surgical procedure, returned to the veterinary hospital to remove the skin stitches.

Statistical analyses

A completely randomized design was used. All data collected were analyzed using Prism for Windows (GraphPad Software. La Jolla CA, USA). The data were tested for normal distribution using the Shapiro-Wilk test. The parametric variables (physiological parameters) and the mechanical nociceptive threshold were subjected to two-way analysis of variance (ANOVA), followed by the Bonferroni test. For variables that were not normally distributed, the Mann-Whitney's non-parametric test and Fisher's exact test were used. For all tests, the level of significance was 5%.

3. Results

After the administration of pre-anesthetic medication, none of the animals showed adverse effects such as salivation or vomiting. Table 2 shows the age, body weight, sedation score, propofol dose, duration of anesthesia and surgery, and the time until extubation.

Table 2. Age, body weight, propofol dose, anesthetic time, surgery time, extubation time and sedation score in female dogs undergoing ovariohysterectomy before sedation.

Variables	CONTROL	AMANT
Age (years)	4.1 ± 2.6	5.5 ± 2.6
Body weight (kg)	9.3 ± 4.4	13.8 ± 8.8
Sedation score	1 (1-2)*	1 (1-2)*
Propofol dose (mg/Kg)	6.6 ± 1.9	5.1 ± 0.9
Anesthetic time (minutes)	54.5 ± 10.4	55 ± 10.8
Surgery time (minutes)	34.7 ± 8.8	38.2 ± 8.9
Extubation time (minutes)	7.9 ± 5.1	9.5 ± 4.5

Result expressed by the mean ± standard deviation; * median, range. CONTROL: receiving placebo; AMANT: amantadine 5 mg/kg. Source: Authors.

There was no statistically significant difference in the measured physiological variables (HR, SAP, DAP, MAP, f, EtCO2, SpO2, Etiso, and T) between the CONTROL and AMANT groups (Table 3). ETCO2 values were maintained in the acceptable range (35 - 45 mmHg) for the species.

Table 3. Physiological variables of female dogs undergoing ovariohysterectomy, treated with placebo (CONTROL), or amantadine (AMANT) during general inhalation anesthesia.

		Moments							
Variable	**Groups**	**M0**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**
HR (bpm)	CONTROL	124.5 ± 26.4	124.9 ± 26.7	128.1 ± 16.3	115.7 ± 12.8	107.8 ± 16.0	96.9 ± 22.1	109 ± 17.4	112.1 ± 23.7
	AMANT	122 ± 16,2	124.3 ± 25.1	120 ± 22,4	129.2 ± 27.3	109.4 ± 19.8	103 ± 20.5	103.8 ± 20.2	113.7 ± 13.6
SAP (mmHg)	CONTROL	92.8 ± 24.5	91.3 ± 33.1	106.6 ± 30.2	142.8 ± 33.7	136.5 ± 33.2	128.6 ± 19.7	125.1 ± 35. 8	152,5 ± 44.1
	AMANT	112.9 ± 22.3	106.9 ± 33.6	129.4 ± 35.9	153.6 ± 37.4	134.4 ± 25.6	123.5 ± 26.4	104.5 ± 18.8	121.2 ± 22.4
MAP (mmHg)	CONTROL	74.1 ± 21.6	67.4 ± 40.2	68.1 ± 24.4	110.8 ± 33.1	111.7 ± 22.3	99.4 ± 11.0	92.1 ± 19.6	114.1 ± 27.4
	AMANT	85.7 ± 18.9	76.0 ± 34.2	88.7 ± 23.9	108.8 ± 25.5	100.7 ± 19.1	90.1 ± 21.4	70.9 ± 18.9	88.8 ± 18.7
PAD (mmHg)	CONTROL	66.1 ± 23.0	43.1 ± 13.2	62.3 ± 20.8	92.6 ± 20.4	89.4 ± 13.7	81.7 ± 15.5	72.2 ± 13.8	98.1 ± 25.6
	AMANT	79.5 ± 16.1	58.2 ± 31.7	70.5 ± 18.2	93.6 ± 24.8	81.7 ± 12.6	76.8 ± 21.0	61.4 ± 13.1	74.7 ± 17.3
***f* (bpm)**	CONTROL	87.2 ± 49.5	10.2 ± 1.1	9.8 ± 1.1	9.8 ± 1.1	9.6 ± 1.3	9.8 ± 1.1	9.8 ± 1.5	10.6 ± 4.2
	AMANT	102.8 ± 63.9	12.4 ± 5.6	10.6 ± 0.9	10.4 ± 0.8	10.4 ± 0.8	10.4 ± 0.8	10.7 ± 1.9	13.1 ± 8.5
SpO$_2$ (%)	CONTROL	92.4 ± 4.0	98.9 ± 1.0	98.9 ± 1.4	98.9 ± 0.7	98.2 ± 1.5	97.7 ± 2.6	98 ± 1.9	98.5 ± 1.1
	AMANT	92.5 ± 4.3	98.7 ± 1.2	98.1 ± 1.1	98 ± 2	98.4 ± 1.5	98.7 ± 1.3	98.8 ± 1	98.9 ± 0.7
Etiso (V%)	CONTROL	-	1. 30 ± 0.5	1.41 ± 0.1	1.44 ± 0.2	1.44 ± 0.3	1.31 ± 0.1	1.30 ± 0.2	1,27 ± 0.2
	AMANT	-	1.15 ± 0.3	1.48 ± 0.1	1.37 ± 0.1	1.4 ± 0.1	1.35 ± 0.1	1.26 ± 0.1	1.25 ± 0.1
T (°C)	CONTROL	38.9 ± 0.5	36.9 ± 0.6	36.4 ± 0.6	36.3 ± 0.6	36.1 ± 0.5	36.0 ± 0.5	35.7 ± 0.6	35.4 ± 0.4
	AMANT	39.0 ± 0.9	37.0 ± 0.5	36.6 ± 0.6	36.5 ± 0.5	36.4 ± 0.6	36.3 ± 0.6	35.9 ± 0.4	35.6 ± 0.4

Result expressed by the mean ± standard deviation. M0: before amantadine administration; M1: before the start of the surgical procedure; M2: after incision of the linea alba; M3: after clamping of the right pedicle; M4: after clamping of the left pedicle; M5: after ligation of the body of the uterus; M6: after suturing of the linea alba; and M7: at the end of the surgery. Source: Authors.

In the evaluation of trans-anesthetic analgesic rescues, there was no significant difference between groups (p> 0.05)

Pain assessment was done using the Dynamic Interactive Visual Analog Scale. Significantly higher pain scores were observed in the CONTROL than in the AMANT group (p = 0.004) (Fig. 2).

Figure 2. Dynamic Interactive Visual Analog Scale (DIVAS) scores in female dogs after ovariohysterectomy.
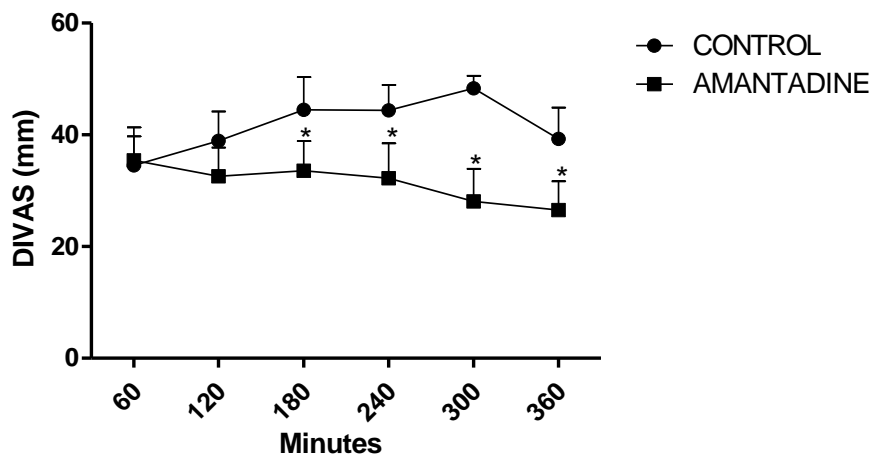
Result expressed by the mean ± SEM. Source: Authors.

In the CONTROL group, all animals needed analgesic rescue over the 6 hours of evaluation, while 50% of animals treated with amantadine needed this support (p = 0.03) (Fig. 3).

Figure 3. Number of animals that received analgesic rescues based on the Dynamic Interactive Visual Analog Scale (DIVAS) to evaluate postoperative pain after ovariohysterectomy.
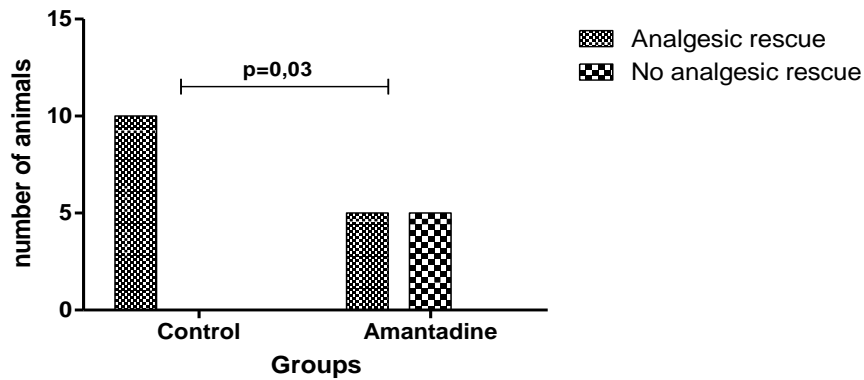
Source: Authors.

The mechanical nociceptive threshold showed a significant difference between treatments (p = 0.03) with higher mechanical threshold values in AMANT, thus showing greater sensitivity in animals in the CONTROL (Fig. 4). The animals did not show salivation or vomiting during the six hours of evaluation in the postoperative period.

Figure 4. Mechanical nociceptive threshold for evaluating postoperative analgesia in female dogs undergoing ovariohysterectomy.
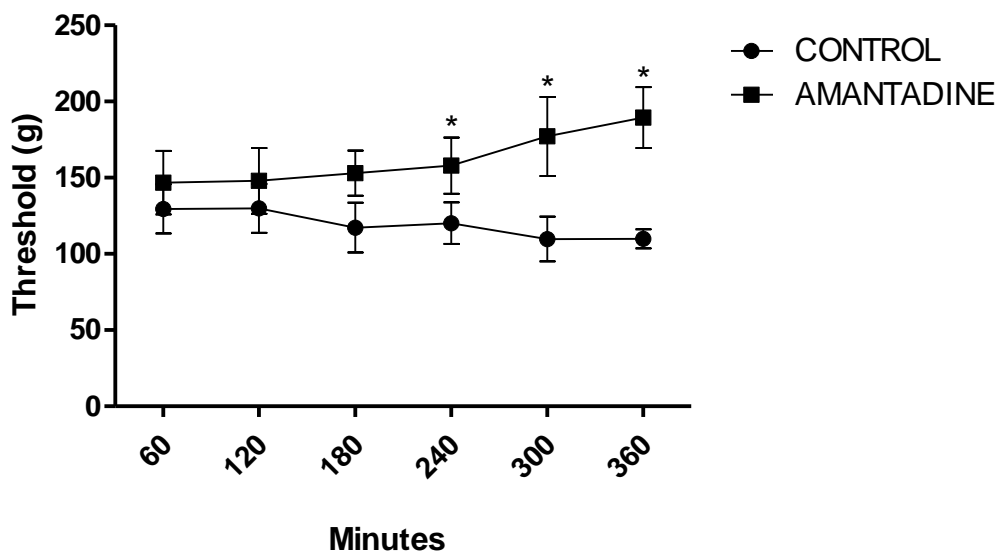
Result expressed by the mean ± SEM. Source: Authors.

4. Discussion

This study evaluated the preemptive treatment with orally-administered amantadine in dogs undergoing ovariohysterectomy by comparing one group treated with placebo and the other with amantadine (5 mg/kg). There were no significant differences between the physiological parameters evaluated during the trans-anesthetic period. A significant difference was found between the groups in terms of postoperative pain assessments, showing a greater MNT in animals in the AMANT.

In human medicine, the effect of amantadine on acute pain has been researched, with investigation of its mechanism of action and its effectiveness in protocols of multimodal analgesia in abdominoplasty and prostate surgeries (Rashwan and Abdelmawgound, 2013; Elmawgood et al., 2015). However, in veterinary medicine, its use is reported in patients with chronic pain (Lascelles et al., 2008). Our study was the first to assess the preemptive effect of amantadine as an adjunct to postoperative analgesia in female dogs undergoing ovariohysterectomy. The results of this study suggest that amantadine administered orally promoted antinociceptive action in female dogs.

Amantadine was administered orally, one hour before sedation, and about 3 hours and 30 minutes before the first evaluation, respecting its pharmacokinetics as described in dogs, in which the time to reach C_{MAX} is 2.6 hours (Norkus et al., 2015; Papich, 2016). In addition, it has a plasma half-life between 11 and 15 hours (Goodman & Gilman, 2012), so, during the pain-assessment period of this study, 6 hours in the post-surgical period, the female dogs were under the pharmacological effects of amantadine (Snijdelaar et. al., 2004).

During the surgical procedure, amantadine had not yet attained its maximum effect, and further studies are needed to assess its effects in the surgical procedure to determine its possible analgesia. In this study, no significant differences were found between the measured physiological variables, indicating cardiovascular stability with the protocol used. No studies with use in the preoperative period were found in the researched literature.

In a study by Abdelmawgoud and Rashwan (2013) in human patients undergoing abdominoplasty, there was no significant difference in the heart rate and MAP between the groups during the surgical procedure, with the use of oral amantadine in the preoperative period.

The greater need for trans-anesthetic analgesic rescue at the moment of incision of the linea alba and clamping of the left pedicle is related to the lack of action of amantadine at the

time of surgery and to nociceptive stimuli resulting from ovarian pedicle traction and ligation (Quessada et al., 2009).

To manage the pain that occurs at certain points during the surgery, short-acting opioids, such as fentanyl, have been used to provide transoperative analgesia, as they have a short and fast analgesic effect of about 20 minutes, when an IV bolus is administered (Steagall et al., 2006). In addition to providing good hemodynamic stability, this drug is administered if needed during surgery to avoid suffering in studies that test drugs with possible analgesic activity, without skewing post-surgical pain assessments (Kukanich and Wiese, 2015).

The Dynamic Interactive Visual Analog Scale (DIVAS) is a semi-objective classification system used to quantify the intensity of the pain (Rialland et al., 2011). It has been considered the gold standard pain assessment tool in humans and widely used in the evaluation of pain by veterinarians (Moran & Hofmeister, 2013). A study demonstrated that DIVAS is a more sensitive scale than the analgesimeter in the evaluation of postoperative pain in that underwent ovariohysterectomy (Pohl et al., 2011). This scale was used as an additional measure of the need for rescue since more than one assessment tool is commonly used to measure postoperative pain (Slingsby et al., 2015, Bortolami et al. 2013).

In this study, the DIVAS scores in the group treated with amantadine were significantly lower than those in the control group. This result is consistent with those of previous studies in which other NMDA receptor antagonists reduced postoperative pain from thoracotomy in humans (Moyse et al., 2017) and demonstrated antinociceptive effect in rats (Wolinska et al., 2017; Doncheva et al., 2019) and in dogs undergoing ovariohysterectomy (Slingsby and Waterman-Pearson, 2010; Almeida et al., 2013; Shah et al., 2018).

Studies assessing postoperative pain in dogs undergoing ovariohysterectomy reported the ineffectiveness of ketamine (Gutierrez-Blanco et al., 2015). However, amantadine may be a more effective treatment alternative since a significantly lower number of analgesic rescues and significantly less painful stimulation in the treated animals were found in the present study. In addition, the results are similar to those observed in a study that also used the DIVAS to assess postoperative pain in dogs, in which there was a significant difference between the group treated with methadone and the one treated with buprenorphine (Shah et al., 2018).

The greatest need for analgesic rescue was evidenced in the third and sixth-hour evaluations, with significantly higher values in CONTROL than in AMANT. This result is in agreement with the reports by Snijdelaar et al. (2004) and Bujak-Giżycka et al. (2012) on

human patients, who reported a reduction in the consumption of morphine in the postoperative period with the use of amantadine.

The method used to evaluate the MNT was based on the paucity of studies with mechanical models to assess the effects of amantadine in dogs. Despite not having been studied in dogs, this method has been used to determine the sensitivity with relative safety and reproducibility in horses (Rédua et al. 2002; Oleoskovicz et al., 2006; Guirro et al., 2009) and in rats (Moura et al. 2015; Cunha et al. 2004).

In CONTROL, the effects of the surgical procedure on pain intensity were clear, with values reported in the first hour of evaluation being significantly higher than those in AMANT. Therefore, the model provided adequate identification of hyperalgesia in dogs, just like the reports by Franco (2011) in horses and Cunha et al. (2004) in mice, showing a significant difference in the applied force between the groups.

5. Conclusion

The use of amantadine as orally-administered preemptive analgesia at a dose of 5 mg/kg was effective in reducing postoperative pain, improving patient comfort, and decreasing the requirement for analgesic rescues. Thus, since this is the first study using amantine for analgesic purposes, further studies in the area and in other species are needed to prove this new therapeutic approach to medication.

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