

## A comparison of extradural tramadol and extradural morphine for postoperative analgesia in female dogs undergoing ovariohysterectomy<sup>1</sup>

Tramadol peridural comparativamente à morfina para analgesia pós-operatória em cadelas submetidas à ovariosalpingohisterectomia

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### ABSTRACT

**PURPOSE:** To compare the postoperative analgesic effects of the extradural tramadol or morphine in female dogs undergoing ovariohysterectomy.

**METHODS:** Sixteen female dogs were randomly assigned to two groups of eight animals each and received morphine (0.1mg kg<sup>-1</sup> M group) or tramadol (2mg kg<sup>-1</sup> T group). The pre-anesthetic medication was intravenously (iv) acepromazine (0.05mg kg<sup>-1</sup>). Anesthesia was induced with propofol (4mg kg<sup>-1</sup>iv) and maintained with isoflurane. The degree of analgesia was evaluated using a numerical rating scale that included physiologic and behavior variables. Dogs were scored at one, three, six and 12 hours after surgery by one blinded observer. Dogs were treated with morphine (0.5mg kg<sup>-1</sup>) if their scores were >6. Serum cortisol was measured before the pre-anesthetic medication was administered (basal), at the time of the ovarian pedicle clamping (T0), and at 1 (T1), 6 (T6) and 12 (T12) hours postoperative.

**RESULTS:** The pain score did not differ between morphine and tramadol treatments. Rescue analgesia was administered to one dog in the T treatment group. Serum cortisol did not differ between treatments.

**CONCLUSION:** The extradural administration of morphine or tramadol is a safe and effective method of inducing analgesia in female dogs undergoing ovariohyterectomy.

**Key words:** Analgesics, Opioid. Tramadol. Morphine. Analgesia. Ovary. Hysterectomy. Dogs.

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### RESUMO

**OBJETIVO:** Comparar o efeito analgésico pós-operatório do tramadol em relação à morfina quando utilizados por via peridural em cadelas submetidas à ovariosalpingohisterectomia (OSH).

**MÉTODOS:** Dezesesseis cadelas foram aleatoriamente distribuídas em dois tratamentos, com oito animais em cada, tratadas com morfina (0,1mg kg<sup>-1</sup>, M) e tramadol (2mg kg<sup>-1</sup>, T). A medicação pré-anestésica foi feita por via intravenosa (iv) com acepromazina (0,05mg kg<sup>-1</sup>), seguindo-se indução e manutenção anestésicas com propofol (4mg kg<sup>-1</sup> iv) e isofluorano, respectivamente. O grau de analgesia foi avaliado uma, três, seis e 12 horas após o término da cirurgia, com escala descritiva numérica, que incluiu a observação de alterações fisiológicas e comportamentais. Animais com escore > 06 foram tratados com morfina (0,5mg kg<sup>-1</sup>). A concentração sérica de cortisol foi mensurada antes da sedação (basal), ao término da cirurgia (T0), 1 (T1), 6 (T6) e 12 (T12) horas após a cirurgia.

**RESULTADOS:** Os escores de dor e a concentração sérica de cortisol não diferiram entre os tratamentos. Analgesia de resgate foi necessária em um cão do tratamento T.

**CONCLUSÃO:** A administração peridural de morfina e de tramadol resulta em analgesia adequada e de longa duração em cadelas submetidas à ovariosalpingohisterectomia.

**Descritores:** Analgésicos Opióides. Tramadol. Morfina. Analgesia. Ovário. Histerectomia. Cães.

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## **Introduction**

Several studies have shown satisfactory results following extradural (ED) opioid administration for postoperative pain relief<sup>1-3</sup>.

The analgesia associated with ED administration of opioids is reportedly of longer duration and higher potency when compared with systemic administration of the same drugs<sup>2,4</sup>. Additionally, the incidence of adverse effects, such as respiratory depression, bradycardia, vomiting, and urinary retention, is lower after ED administration when compared with parenteral administration<sup>5,6</sup>. Thus, many opioid drugs have been investigated for ED administration both in humans<sup>7-9</sup> and dogs<sup>1-3,10</sup>.

Tramadol is a synthetic codeine analog which is a weak  $\mu$ -receptor agonist<sup>11</sup>. It also inhibits neuronal reuptake of norepinephrine and 5-hydroxytryptamine<sup>12</sup>. The analgesic effects of ED tramadol have been evaluated in human studies<sup>7,13-16</sup>, which have suggested that it is as effective as morphine for moderate pain management.

Although the use of tramadol has become increasingly popular for postoperative pain control in companion animals, only a few studies have evaluated its effects by extradural route in dogs<sup>10,17</sup>.

The purpose of this study was to compare postoperative analgesia of tramadol and morphine following extradural administration for ovariohysterectomy in dogs.

## **Methods**

This study was approved by the Institutional Animal Research Ethical Committee (protocol number 107/06), and permission for the participation of each dog was obtained from the owner. Sixteen healthy adult, crossbreed, female dogs, which weighed 4.5 to 26kg (11 $\pm$ 12kg) were evaluated. Animals undergoing elective ovariohysterectomy were selected for this study using a physical examination and laboratory tests (complete blood cell count, urea, creatinine, alanine aminotransferase and aspartate aminotransferase).

After withdrawal of food and water for 12 and 3 hours, respectively, the animals underwent the same anesthesia protocol. All dogs were sedated with 0.05mg kg<sup>-1</sup> of acepromazine maleate (Acepran 0.2%, Univet, Sao Paulo, Brazil) administered intravenously (IV). Fifteen minutes after sedation, anesthesia was induced with 4 to 5mg kg<sup>-1</sup> (IV) of propofol (Propovan, Cristalia, Itapira, Brazil). The trachea was intubated, and anesthesia was maintained with isoflurane under spontaneous ventilation using

a partial rebreathing system (Samurai III, Takaoka, Sao Paulo, Brazil) with an oxygen flow of 1L<sup>-1</sup>min<sup>-1</sup>. Ringer's solution (10mL kg<sup>-1</sup> h<sup>-1</sup>) was infused IV using a peristaltic infusion pump (LifeMed, Fars 600, Sao Paulo, Brazil) throughout the surgical procedure.

All dogs were prepared for ED analgesia: hair in the lumbosacral area was clipped, and the dogs were placed in sternal recumbency. Each was randomly assigned to receive 2mg kg<sup>-1</sup> of tramadol (Tramadon, Cristalia, Itapira, Brazil) (T, n=8) and 0.1mg kg<sup>-1</sup> of morphine (Tramadon, Cristalia, Itapira, Brazil) (M, n=8) by the extradural route. In both treatments, the drugs were diluted with a saline solution to produce a total volume of 0.25mL kg<sup>-1</sup>. Extradural injection was performed at the lumbosacral (L7-S1) space. Correct spinal needle placement was confirmed by a lack of resistance to injection<sup>3</sup>. The opioids were injected over a 2 minutes period. All animals underwent routine ovariohysterectomy through a 2- to 3- cm midline incision by the same experienced surgeon.

During the anesthetic procedure, end tidal carbon dioxide (PEtCO<sub>2</sub>), inspired carbon dioxide, expired and inspired isoflurane concentration (%), arterial oxygen saturation of hemoglobin (SpO<sub>2</sub>%) and heart rate (HH) were measured with a capnograph, pulse oximeter and gas analyzer continuously (VAMOS plus, Dräger, SP, Brazil.). The end-tidal concentration of isoflurane was adjusted on the basis of arterial pressure and heart rate changes as well as using the conventional signs of anesthesia. Systolic arterial blood pressure (SABP) was measured by noninvasive method using a Doppler ultrasonic (Doppler 841-A, Parks Medical Electronics, Las Vegas, EUA).

During the first 12 hours postoperative, the animals underwent a blind evaluation of the analgesia degree using a numerical pain scale<sup>18</sup>, with postoperative measurements at 1, 3, 6 and 12 hours. Pain scores were assigned, and the maximum possible scores obtained was 20 (Table 1).

**TABLE 1** - Criteria used for scoring postoperative pain in dogs.

Observation	Criteria	Score
Heart rate	<= 10% above preoperative value	0
	11% - 30% above preoperative value	1
	31% - 50% above preoperative value	2
	> 50% above preoperative value	3
Respiratory rate	<= 10% above preoperative value	0
	11% - 30% above preoperative value	1
	31% - 50% above preoperative value	2
	> 50% above preoperative value	3
Arterial blood pressure	<= 10% above preoperative value	0
	11% - 30% above preoperative value	1
	31% - 50% above preoperative value	2
	> 50% above preoperative value	3
Salivation	Normal	0
	Above normal	1
Mydriasis	No	0
	Yes	1
Vocalization	Quiet	0
	Crying, responds to calming attempts	1
	Crying no response	2
Agitation	Asleep or calm	0
	Mild agitation	1
	Moderate agitation	2
Body position	Severe agitation	0
	Sternal and relaxed	1
	Protecting the incision site, including lateral and fetal position	2
Response to palpation of the incision site	No response	0
	Mild response, looks at incision site	1
	Turns head for the incision site, mild vocalization	2
	Turns head with intention to bite, severe vocalization	3

Scores of 0 to 5 indicated mild pain, scores of 6 to 9 indicated moderate pain, and scores of more than 10 indicated severe pain. Additional analgesia was given (intramuscular morphine at 0.5 mg kg<sup>-1</sup>) to dogs that scored 6 or more.

Venous blood samples were collected from the jugular vein to measure of cortisol before the pre-anesthetic medication was administered (basal), at the time of the ovarian pedicle clamping (T0), and at 1 (T1), 6 (T6) and 12 (T12) hours post-ovariohysterectomy. Serum samples were stored at -70C and analyzed within 12 months after collection. Cortisol levels were quantified using a solid-phase radioimmunoassay (Coat-A-Count Cortisol - DPC, California, USA).

Duration of surgery and time to endotracheal extubation were recorded as well as the occurrence of adverse effects such as nausea, vomiting, tremors, excitement and drooling.

Data were recorded as mean±SD. The data analyzed using an analysis of variance with the F test followed by Tukey's test using Graphpad software. Differences between treatments at each time point, differences in time for each treatment, and the interaction between treatment and time were investigated. A P-value less than 0.05 was considered significant.

## Results

There were no differences (P>0.05) between the groups in terms of mean age (24 and 20 months for the T and M groups, respectively), body weight (16±8 and 15.6±7 kg for the T and M groups, respectively), surgical time (40±3 and 39±2 minutes for the T and M groups, respectively) and extubation time (5±3, 4.5±2 minutes for the T and M groups, respectively).

The median pain score did not significantly differ between the tramadol and morphine treatments at any time point (Figure 1).

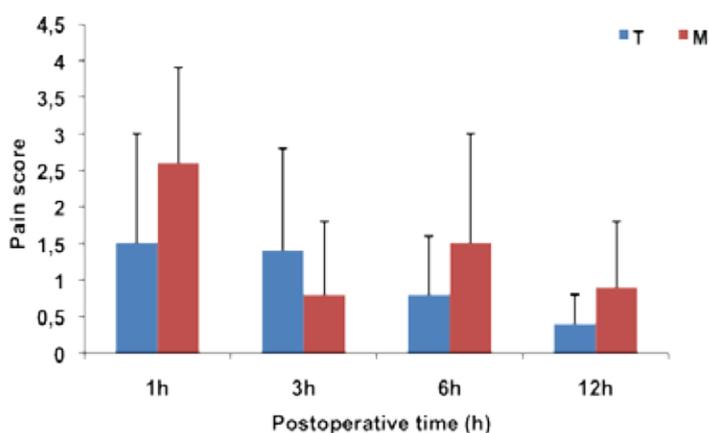


FIGURE 1 - Mean±SD pain scores in dogs treated with tramadol (T) and morphine (M) at each time postoperative period.

One dog in the T group required additional analgesia within 6 hours postoperative. Rescue analgesia was not required by any of the dogs who received morphine.

Serum cortisol concentrations did not significantly differ between treatment groups or times (Figure 2).

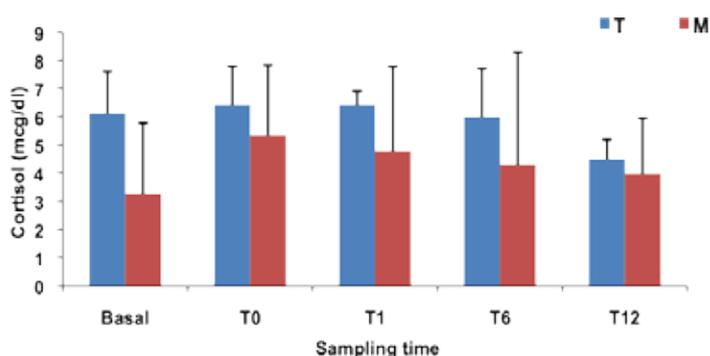


FIGURE 2 - Mean±SD serum cortisol concentration in dogs treated with tramadol (T) and morphine (M) at each time postoperative period. T0, at the time of the ovarian pedicle clamping; T1, 1 hour; T6, 6 hours; T12, 12 hours after tracheal extubation.

Undesirable side effects were not observed in any of the dogs.

## Discussion

The current study confirms previous reports in humans<sup>7,16</sup> and dogs, which have shown similar postoperative analgesia profiles following extradural administration of tramadol or morphine. In both groups, the postoperative pain score was low, and the median values were less than six at 12 hours postoperative, which implies that both regimens provide adequate analgesia for dogs undergoing ovariohysterectomy.

The effects of ED morphine have been well documented

in dogs. Several studies have reported the high analgesic efficacy and long duration of action of ED morphine<sup>2,5,19,20</sup>. Nevertheless, a few published studies have described the analgesic properties and the efficacy of extradural tramadol in dogs<sup>10,17</sup>.

Pharmacokinetic and pharmacodynamic studies in humans have demonstrated that the analgesic effects of tramadol result mainly from the actions of the (+) M1 enantiomer<sup>21,22</sup>. According to Vettorato *et al.*<sup>10</sup>, the pharmacokinetic parameters of intravenous tramadol are equivalent to those produced by extradural tramadol. The rapid and effective production of M1 was observed after both routes of administration. Immediately after tramadol injection, M1 attained concentrations >10ng/mL for a period of eight hours. In humans, this value is considered the lowest concentration associated with therapeutic efficacy<sup>20</sup>. Although this concentration has not been evaluated in dogs, the results of this study and those previously reported<sup>10,17</sup> demonstrate that tramadol provides satisfactory analgesia during the early postoperative period. In the present study, rescue analgesia was not required for any dogs given ED morphine; this was likely because of the long duration of drug action. The duration of action of extradural morphine in dogs undergoing ovariohysterectomy is at least 16 hours<sup>2</sup>. Regarding tramadol treatment, one dog received additional analgesia at six hours postoperative, while the other dogs in this group did not require rescue analgesia, which is in agreement with other studies<sup>10,17</sup>. Vettorato *et al.*<sup>10</sup> have demonstrated that dogs undergoing surgical repair of ruptured cranial cruciate ligaments and treated with ED tramadol do not require rescue analgesia within the first 8 hours of extubation. Almeida *et al.*<sup>17</sup> have reported long-lasting postoperative analgesia in dogs undergoing orchiectomy. The authors observed similar analgesic effects with ED tramadol/lidocaine and morphine/lidocaine and no dog required rescue analgesia during the first 24 hours postoperative.

Pain recognition and assessment in animals is challenging because of their inability to communicate, the complexity of pain perception and variation in behavioral responses. Different pain scoring systems have been developed to assess the efficacy of analgesic techniques. Several investigators have reported the use of a variety of scales (visual analog, numerical rating, simple descriptive and composite) developed and correlated specifically for dog<sup>1,23,24</sup>. The pain scoring system employed in the current study has been previously described for pain quantification in dogs<sup>17,18,23</sup>. In addition, only one observer scored all dogs to avoid interobserver variability in the subjective evaluation.

Other attempts to gather objective data regarding pain and analgesics have included the evaluation of stress-related hormones and metabolites. Previous studies have shown satisfactory

agreement between pain score and plasma catecholamine and serum cortisol levels<sup>25-27</sup>. In the current study, both tramadol and morphine were effective at preventing the postoperative stress response, using serum cortisol as a guideline. In both treatments groups, serum cortisol did not exceed the reference range (0.96 to 6.81 mg/dl) at any evaluated time point. In humans, extradural administration of opioids has been shown to have favorable effects on metabolites and hormonal variables in the immediate postoperative period<sup>28</sup>. Previous studies have reported that dogs receiving ED morphine<sup>29</sup> or ED methadone<sup>3</sup> have lower postoperative serum cortisol levels than those receiving the same analgesic by IV administration.

In addition to their analgesic effects, both treatments provided satisfactory post-anesthetic recovery. No adverse effects were observed in the current study, which is in agreement with previous results reported in dogs<sup>2,10,17</sup>.

### Conclusions

The extradural tramadol provides an analgesic effect similar to extradural morphine in dogs undergoing ovariohysterectomy. Additionally, both treatments inhibit the stress response and do not induce adverse effects, resulting in a safe option for analgesia in female dogs.

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