

# Analgesia of Epidural Tramadol in Dogs Submitted to Orchiectomy

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## ABSTRACT

Epidural tramadol in veterinary medicine has been studied in only a few instances. In this case, 36 dogs submitted to orchiectomy received 6.0 mg/kg of lidocaine combined with 1.0 mg/kg of tramadol, 0.1 mg/kg of morphine or 0.01 ml/kg of 0.9% NaCl by epidural route. Analgesia was assessed at 4, 8, 12, 18 and 24 hours after surgery. There were no differences between morphine and tramadol over the time of evaluation within these groups, and no complementary analgesia was necessary. In the NaCl group, analgesia was needed at 4, 8 and 12 hours. Epidural tramadol provides an analgesic effect comparable to that of morphine during the first 12 hours post-surgery.

## INTRODUCTION

Postoperative analgesia is of the utmost importance because pain causes various deleterious effects that hinder the recovery of the patient<sup>1</sup>. Among these harmful effects are negative protein balance, decreased food intake, release of stress hormones, self-mutilation, weight loss, delayed healing of

surgical wound, immunosuppression and increase in arterial pressure<sup>2,3</sup>.

The parenteral use of opioids for management of pain is well established in anesthesiology. However, these substances have relatively short half-lives and there is often need for reapplication, which increases the incidence of collateral effects. When utilized through the epidural route, they bind to specific receptors in the spinal cord. There, the start of their action and duration of their effects are dependent on liposolubility<sup>4</sup>. Morphine is considered the prototype of agonist opioids and its main pharmacologic effect is analgesia, induced by an increase in serotonin synthesis<sup>5</sup>. Therefore, therapy with epidural morphine is advantageous because its water solubility allows drug concentration to remain elevated in cerebrospinal fluid for prolonged periods<sup>4</sup>, resulting in alleviation of pain for up to 24 h<sup>6,7</sup>. Popilskis et al.<sup>8</sup> demonstrated that in dogs submitted to thoracotomy, morphine administered epidurally was more effective in the treatment of postoperative pain than morphine injected by the intravenous route. Tramadol is a relatively unstudied synthetic

opioid when administered via the epidural route in veterinary medicine<sup>9-12</sup>. Two complementary models define its mechanism of action. The first results from the binding of its (+) enantiomer to mu-opioid receptors, whose affinity is about 6000 times less than that of morphine<sup>13,14</sup>. However, its main active metabolite, O-desmethyltramadol, is 6 times more potent than tramadol and possesses a 200-fold greater affinity for mu-opioid receptors<sup>15</sup>. The second mechanism

involves the inhibition of noradrenaline reuptake by the (-) enantiomer through the increased release of serotonin and inhibition of its reuptake by the (+) enantiomer<sup>16</sup>. Various studies suggest that tramadol produces a local and spinal anesthetic effect while also increasing the postoperative analgesic period and reducing the consumption of analgesics<sup>14,17,18</sup>. Mastroncinque & Fantoni<sup>19</sup> reported no difference in the effectiveness of postoperative analgesia

**Table 1** – Scoring system used to evaluate post-operative analgesia of epidural administration of tramadol (1.0 mg/kg), morphine (0.1 mg/kg) or 0.9% NaCl (0.01 ml/kg) in dogs submitted to orchietomy.

CATEGORY	DESCRIPTOR	SCORE
Physiological Data		0
A)	Physiologic data within reference range Percentage increase in HR relative to pre-procedural rate	1
B)	>20%	2
	>50%	3
	>100%	1
	Percentage increase in f relative to pre-procedural rate	23
C)	>20%	1
	>50%	2
	>100%	2
D)	Rectal temperature exceeds reference range	0
E)	Salivation	2
F)	Dilated Pupils	3
Response Palpitation A) (choose only one)	No change from pre-procedural behavior	0
	Guards/reacts when touched	0
	Guards/reacts before touched	1
B)	Eating	0
C)	Restless (pacing continuously, getting up and down)	2
D)	Rolling, Thrashing	3
Mental Status (choose one)	Submissive	0
	Over Friendly	1
	Wary	2
	Agressive	3
Posture A)	Guarding or protecting affected area	2
B)	Lateral Recumbency	0
	Sternal Recumbency	1
	Sitting or standing, head up	1
	Standing, head hanging down	2
	Moving	1
	Abnormal Posture(prayer position, hunched back)	2
Vocalization (Choose one)	Not vocalizing	0
	Vocalizing when touched	2
	Intermittent vocalization	2
	Continuous vocalization	3

between morphine and tramadol given by the intravenous route in female dogs submitted to ovariectomy, but morphine induced greater respiratory depression. The use of tramadol adjuvant to local anesthesia in humans prolonged the active period of the block without causing side effects<sup>18</sup>. In addition, epidural tramadol produced adequate analgesia for a 4-hour period in dogs submitted to knee surgery<sup>12</sup>. When a comparison between postoperative analgesia with xylazine alone, versus a combination of xylazine and epidural tramadol was made in dogs, a longer period of antinociception was observed with the combination, demonstrating that the two drugs have synergistic effect<sup>9</sup>.

Therefore, the aim of this study was to determine if the addition of tramadol to an epidural injection of lidocaine would provide adequate postoperative analgesia in dogs submitted to elective orchiectomy, utilizing epidural morphine for comparison.

## **MATERIALS AND METHODS**

### **Animals**

The Ethics Committee of the Upis Veterinary Teaching Hospital (protocol number 003-07) approved the experimental design. Thirty-six mongrel dogs aged 2- to 7-years-old were utilized; they weighed 6.6 to 21.2 kg and were considered healthy after clinical and laboratory tests. The dogs fasted for 12 h and water was withheld for 2 hours prior to surgery. They were then divided randomly into 3 groups of equal number. All surgical procedures (elective orchiectomies) were performed by the same surgeon (SM) and did not take longer than 20 minutes.

### **Anesthetic procedure**

The dogs were pre-medicated with 0.5 mg/kg of xylazine (Rompum 2% - Bayer S.A. - Animal Healthy - São Paulo, SP, Brazil) given intramuscularly. The cephalic vein was cannulated for the administration of 10 ml/kg/h Ringer's lactate solution throughout the surgical procedure. After five minutes of pre-medication, anesthetic induction was carried out with 12.5 mg/kg of thiopental

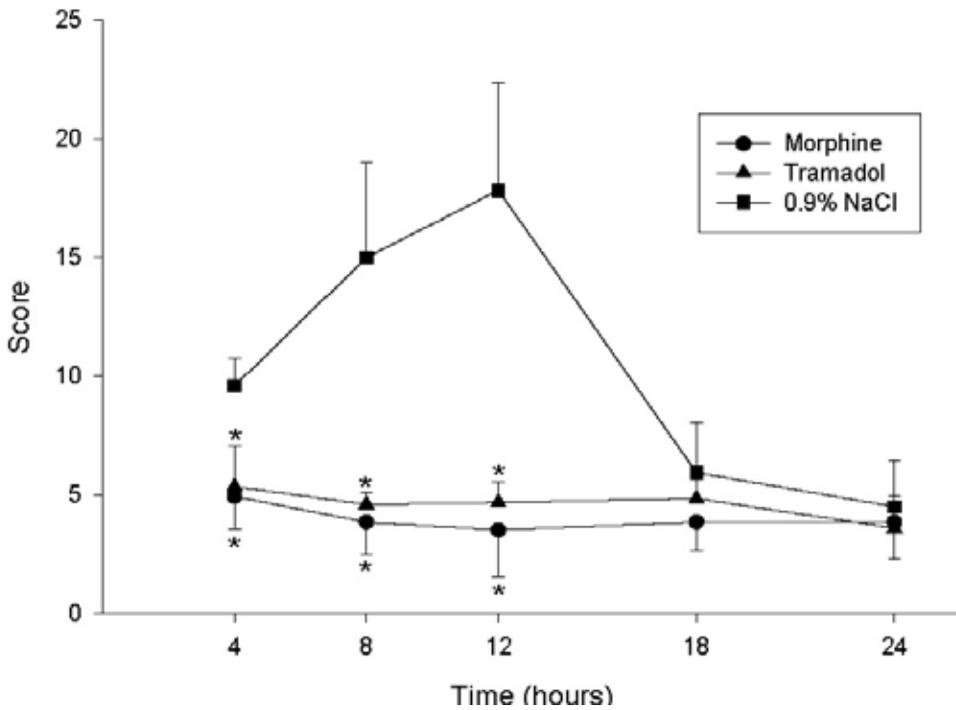
(Thiopental 1g - Cristalia Chemical and Pharmaceutical Products, Itapira, SP, Brazil) given intravenously for execution of the epidural procedure. The epidural injection was performed in the lumbosacral space using the technique described by Jones<sup>6</sup>.

The epidural protocol consisted of 6.0 mg/kg of lidocaine without vasoconstrictor (Xylestesin 2% - Cristalia Chemical and Pharmaceutical Products, Itapira, SP, Brazil) combined with 1.0 mg/kg of tramadol in group T (Tramal 100 mg/ml - Carlo Erba S.A. - Duque de Caxias, RJ, Brazil), 0.1 mg/kg of morphine in group M (Dimorf 10 mg/ml - Cristalia Chemical and Pharmaceutical Products, Itapira, SP, Brazil), or 0.01 ml/kg of 0.9% NaCl solution in group C. Drugs were administered in the same syringe by the same person (AE). Following the epidural injection, the animals were maintained in a ventral recumbency position for 20 minutes to allow uniform distribution of the drugs in the epidural space, and due to the latency period of lidocaine. After this period, the animals were positioned in the dorsal recumbency on a surgical bed for execution of the orchiectomy.

Propofol (Prove 1% - Claris Pharmaceutical Products Ltda. - São Paulo, SP, Brazil) was reserved for intraoperative administration (1.5 mg/kg, IV) if there was a need for complementary chemical restraint. Fentanyl (Fentanest - Cristalia Chemical and Pharmaceutical Products, Itapira, SP, Brazil) was reserved to improve analgesia (3.0 µg/kg, IV) during the surgery if necessary. The criteria for fentanyl administration was based on an increase in heart rate or arterial pressure, a respiratory rate greater than 15% from the values before the start of surgery, and/or sudden voluntary gross movements of the animals. If the animals demonstrated movements in the forelimbs and head without the alterations in the physiologic variables cited above, the propofol was administered. Anesthetic monitoring was conducted throughout the surgical procedures with a multiparameter monitor (Life window 6000, Digicare Biomedical Technology, USA),

**Figure 1** Variation of evaluationscores (mean  $\pm$  SD) of dogs treated with tramadol (n=12), morphine (n=12) or 0.9% NaCl (n=12) after orchiectomy.

\*significant differences in relation to NaCl treatment ( $p < 0.05$ )



used for non-invasive determination of pulse oximetry, heart rate, cardiac rhythm, and arterial pressure in addition to observation of respiratory movements and voluntary movements of the animals. After surgery, the dogs were taken to a hospitalization ward with individual stalls for total anesthetic recovery and postoperative analysis of the treatments described.

### Postoperative evaluation

Evaluation of post-surgical analgesia was conducted using a scale composed of physiologic and behavioral parameters<sup>20</sup> (Table 1). Analysis was conducted at 4, 8, 12, 18 and 24 hours (T4, T8, T12, T18, T24) after the end of the local anesthetic effect and always by the same researcher (RMA) who had no knowledge of the drugs administered by the epidural route. The end of the local anesthetic effect of lidocaine was considered the moment that the animals regained movement and sensation in their hind limbs. Rescue analgesia during the postoperative

period was offered to the animal by intramuscular administration of morphine (0.2 mg/kg) in cases where the evaluation score exceeded ten.

### Statistical analysis

The software Sigma Stat for Windows version 2.0 (Jandel Corporation, San Rafael, CA, USA) was utilized for statistical analysis. The scores obtained by the analgesic evaluation scale were tabulated and submitted to the Mann-Whitney test to determine differences between the groups over time, and to the Wilcoxon test to determine differences among the times in the same group. The level of significance for the statistical tests was set at  $p \leq 0.05$ .

### RESULTS

During the whole surgical procedure, the animals remained awake and calm and the variables heart rate, pulse oximetry, arterial pressure and respiratory rate were normal,

indicating adequate anesthesia and analgesia. Intraoperative administration of complementary analgesic was not required based on the chosen criteria. Additional chemical restraint was needed in one dog that did not cooperate with the dorsal recumbency position in the surgical bed, and that animal received a single injection of propofol.

After surgical intervention, all the dogs regained motor activity and sensation in the lower limbs without major problems. The mean times for each group were  $119 \pm 2$  min (group M),  $119 \pm 3$  min (group T) and  $118 \pm 3$  min (group C) from the start of epidural anesthesia. In the postoperative period, the only collateral effect observed was constipation in one dog from group M and one dog from group T.

There were no significant differences between the morphine and tramadol treatments during the evaluation of these same groups (Figure 1). Based on a pain assessment scale with a maximum score of 27, the highest values obtained from groups T and M were 8 and 9 at T4. Thus, there was no need for rescue analgesia during the first 24 h after surgical intervention in these 2 groups. However, the score exceeded 10 in 10 dogs of group C at 4, 8, and 12 hours of pain evaluation. In these animals, the intramuscular rescue analgesia with morphine decreased the pain scores.

## DISCUSSION

In the present study, surgeries were performed on 12 animals without the combination of analgesics with lidocaine (group C), but for humanitarian reasons, an analgesic was administered during the postoperative period if the pain score exceeded 10. In other studies, surgical stimulus was carried out without the inclusion of such a control group. However, the absence of a control group made it impossible to conclude if treatments provided an adequate analgesia for this type of surgical procedure<sup>19,21,22</sup>. As observed in our study, the animals of group C demonstrated higher pain scores during the evaluation period, as compared to treated groups. Because the objective of this study

was to determine if tramadol was capable of producing postoperative analgesia, the control group was necessary to demonstrate that the absence of epidural analgesic would result in elevated scores. Without a control group, results would be inconclusive for this type of surgery if both groups had demonstrated low scores.

In animal research, it can be difficult to estimate pain due to limited communication between subject and researcher. In addition, it has been demonstrated that techniques for measuring pain normally utilized in humans are not accurate in animals<sup>23</sup>. Therefore, the model for pain evaluation used in this study was the University of Melbourne scale<sup>20</sup>, which includes a combination of 6 categories (physiologic and behavioral) for the determination of pain. This method differentiates between physiologic and behavioral responses to pain, and between individuals clinically normal or in a state of hyperalgesia. It also supplies consistent results when performed by different observers<sup>20</sup>.

Epidural anesthesia with lidocaine is indicated in small-sized animals for perianal and peri-vulvar surgeries, orchietomy, cesarean delivery, and orthopedic surgery procedures of the hind limbs, with a mean anesthetic working time of 2 hours<sup>6,24</sup>. As observed in our study, the inclusion of lidocaine in the epidural protocol conferred anesthesia for a similar period to that described. This permitted the performance of orchietomies without major problems, or the need for supplemental anesthetic or analgesic.

The combination of local anesthesia technique with opioids has advantages because the main site of nociceptive modulation by opioids is the dorsal horn of spinal cord, and the administration of small doses results in good analgesia with few systemic effects<sup>25</sup>. Morphine was chosen as the standard analgesic for comparison since various studies have shown that it has a potent analgesic effect when administered by the epidural route<sup>6-8,26,27</sup>. Some studies support the use of epidural tramadol because

its analgesic effect has been equated to that of morphine<sup>28,29</sup>. The results of this study are in agreement with the previous research. The pain scale values obtained demonstrate that both tramadol and morphine were able to provide adequate analgesia, reducing pain sensitivity during experimental observation. However, the intensity of the stimulus utilized (orchietomy) may or may not have been sufficient for assessment during such a prolonged period. The groups observed did not demonstrate statistical differences among their pain scores at the final times evaluation (T18 and T24). Previous studies that evaluated epidural tramadol utilized observation periods of 4 hours (orthopedic surgery in dogs and horses) and 6 hours (ovariohysterectomy in dogs), which are both much shorter than that recommended by our surgery team<sup>10-12,19</sup>.

Side effects caused by the administration of opioids via epidural route are normally reported after the use of high doses, administration for prolonged periods, or after an increase in dose<sup>30,31</sup>. Epidural morphine can cause various collateral effects not seen in this study, such as pruritus, urinary retention, hypoventilation and hypotension<sup>6,25,32</sup>. These adverse reactions were also evidenced when morphine was given by the intramuscular or intravenous routes<sup>7</sup>. Kona-Boun et al.<sup>31</sup> reported a case of myoclonus followed by urinary retention in a dog after intrathecal injection of morphine. Urinary retention can occur due to the relaxing effect of morphine on the detrusor muscle of the bladder<sup>33</sup>. In this study, tramadol, however, did not lead to collateral effects of concern after epidural administration in dogs or horses<sup>9-12</sup>. The constipation that occurred in two dogs during the post-surgical period can be explained by the action of opioids in reducing intestinal motility<sup>27</sup>, which does not make their use contraindicated in the management of postoperative pain.

## CONCLUSIONS

This study showed that epidural tramadol provides an analgesic effect comparable to that of morphine during the first 12 hours

post-surgery, without substantial side effects. Consequently, tramadol may be an optional postoperative analgesic in dogs submitted to orchietomy. Further studies with other surgical stimuli are needed to confirm our results.

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