

# Epidural Administration of Tramadol as an Analgesic Technique in Dogs Submitted to Stifle Surgery

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## ABSTRACT

Tramadol is a centrally acting analgesic with  $\mu$ -opioid, monoaminergic, and local anesthetic effects. In view of the involvement of the opioid and monoaminergic systems in pain pathways, the study was conducted to evaluate tramadol as an epidural analgesic in dogs. Ten healthy adult dogs (mean  $\pm$  SEM body weight =  $17.3 \pm 3.8$  kg) were premedicated with acepromazine (0.05 mg/kg, IM), induced with thiopental (10 mg/kg, IV), and maintained under anesthesia with halothane in oxygen. Twenty minutes after starting halothane anesthesia, tramadol (1.0 mg/kg in 0.22 mL/kg of sterile water) was administered epidurally at the lumbo-sacral space. Surgery began 15 minutes later. Pulse and

respiratory rates, systolic, mean, and diastolic arterial blood pressure, and pulse oximetry were measured before premedication (baseline), and at fixed intervals after anesthesia induction. Arterial partial pressures of oxygen and carbon dioxide, oxygen-hemoglobin saturation, pH, and plasma bicarbonate concentration were measured at baseline, immediately before the epidural, and at 60, 120, 240, and 360 minutes thereafter. Post-operative analgesia was evaluated for 4 hours using a scoring system. Statistically significant decrease in arterial blood pressure was observed following anesthetic induction, although hypotension was not observed. Partial pressure of carbon dioxide in arterial blood increased significantly from baseline at 60 minutes after epidural tramadol. The remaining variables were not significantly different from baseline values. No variables were significantly

different from values obtained immediately before tramadol administration. Intra-operative antinociception was considered adequate, with satisfactory post-operative analgesia for 4 hours. In conclusion, epidural tramadol seems to produce satisfactory antinociception and analgesia without causing clinically significant hemodynamic and respiratory depression in healthy dogs undergoing stifle surgery.

## INTRODUCTION

Tramadol is a centrally acting analgesic that was introduced in Germany in the late 1970s for use in human medicine, and has been used in the United Kingdom for approximately 8 years.<sup>1,2</sup> In the United States the U.S. Food and Drug Administration approved its oral form for use in humans in 1999.<sup>3</sup> It is a  $\mu$ -opioid receptor agonist with an analgesic potency equal to meperidine and 5- to 10-times less than morphine in humans.<sup>4</sup> Further examinations of the neurochemical profile of tramadol revealed that it inhibits the neuronal uptake of norepinephrine and serotonin.<sup>5-7</sup> More recent studies have shown that tramadol also has local anesthetic action either by producing analgesia after intradermal injection,<sup>8,9</sup> or by reducing pain associated with propofol administration.<sup>10,11</sup>

Tramadol consists of a racemic mixture of 2 enantiomers, (+) tramadol and (-) tramadol.<sup>2</sup> Racemic tramadol inhibits the synaptosomal uptake of norepinephrine and serotonin with about equal potency.<sup>12</sup> The (+) enantiomer is the most potent inhibitor of serotonin uptake, enhances serotonin release and has modest affinity for  $\mu$ -opioid receptors. The (-) enantiomer is the most potent inhibitor of norepinephrine uptake and has the same affinity as the racemate for  $\mu$ -opioid receptors. The monoaminergic effects of the 2 enantiomers are more potent than the opioid action. They also interact in a complementary and synergistic manner to produce antinociception, but do not summate to increase side effects, such as constipation and respiratory depression.<sup>12</sup> The

pharmacological profile of tramadol makes it an attractive drug for epidural administration as an analgesic technique for surgeries in the hind limbs of dogs. Activation of opioid receptors, inhibition of the monoaminergic system, and local anesthetic effects<sup>4,9,12</sup> are likely to decrease transmission and improve modulation of afferent nociceptive signals, resulting in significant analgesia. These possibilities along with a shortage of information on the epidural use of tramadol in the veterinary literature motivated this study. Therefore, the pre-operative epidural administration of tramadol was evaluated as an analgesic technique in dogs submitted to stifle surgery.

## MATERIAL AND METHOD

The study was approved by the Scientific Committee at the Office of Projects of the Rural Sciences Center of the Universidade Federal de Santa Maria, RS, Brazil. Ten adult, clinically healthy, mixed breed dogs, 6 male and 4 female, weighing  $17.3 \pm 3.8$  kg (mean  $\pm$  SEM; range, 12–23 kg) were studied. The dogs were fasted for 12 hours and deprived of water for 2 hours preoperatively. The surgical procedure consisted of experimental excision and replacement of the cranial cruciate ligament in the right limb of each dog.

Acepromazine (Acepran 1%, Andrômaco, São Paulo, SP, Brazil) was given intramuscularly as premedication (0.05 mg/kg), with the induction of anesthesia performed 15 minutes later with thiopental (10 mg/kg; Thionembutal, Abbott, São Paulo, SP, Brazil) given intravenously through a catheter previously placed in the cephalic vein. Following tracheal intubation, halothane (Fluothane, Wellcome-Zeneca, Cotia, SP, Brazil) was delivered in 100% oxygen for anesthetic maintenance, using a semi-closed circle system with a fresh gas flow rate of 30 mL/kg/min. The animals were allowed to breathe spontaneously, and body temperature was maintained in the physiological normal range with the use of an electric warm blanket.

Twenty minutes following anesthetic induction, 1.0 mg/kg of tramadol (Tramal 50, Carlo Erba, Duque de Caxias, RJ, Brazil), diluted in distilled water to a final volume of 0.22 mL/kg, was administered epidurally at the lumbo-sacral space. The dosage rate of tramadol chosen was determined as 1/10 of the systemic dosage used in humans.<sup>5</sup> The technique was performed using a 22-gauge, 3.75-cm spinal needle. Correct placement of the spinal needle in the epidural space was confirmed by the hanging drop technique and by the lack of resistance to administration of 1 mL of air. The dogs remained laterally recumbent with the surgical side down for 10 minutes before being positioned dorsally for surgery. Lactate Ringer's solution was used intra-operatively at a rate of 20 mL/kg/h for the first hour and 10 mL/kg/h thereafter.

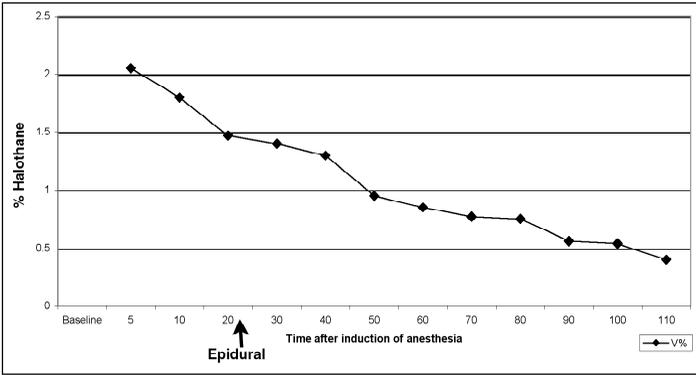
Arterial blood pressure (systolic, mean, and diastolic), pulse rate, respiratory rate, arterial blood oxygen saturation, and arterial blood gases were evaluated. These measurements were taken in the conscious dog before any drug administration (baseline) and after anesthetic induction at 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, and 110 minutes. Arterial blood pressure was measured non-invasively by oscillometry (Dinamap-Critikon, Tampa, FL, USA), with an appropriate cuff (width approximately equal to 40% of the limb circumference) positioned proximally to the carpus. Pulse rate and arterial blood oxygen saturation were obtained with a pulse oximeter (Nellcor N-200, Nellcor Inc., Pleasanton, CA, USA). The oximeter probe was placed on the lip, vulva, or prepuce for the baseline, and on the tongue for intra-operative measurements. Respiratory rate and vaporizer settings (after anesthetic induction) were assessed at these same intervals.

Blood gas analyses were carried out to determine arterial pH, arterial partial pressures of oxygen (PaO<sub>2</sub>) and carbon dioxide (PaCO<sub>2</sub>), oxygen-hemoglobin saturation (SaO<sub>2</sub>), and plasma bicarbonate concentration (HCO<sub>3</sub><sup>-</sup>). These parameters were meas-

ured before premedication (baseline), immediately before the epidural administration of tramadol (before epidural), and then 60, 120, 240, and 360 minutes after the epidural procedure. Blood from the femoral artery was collected anaerobically and immediately stored in ice water, with the evaluation carried out within a period of 1 hour (AVL AG900, Biomedical Instruments, Switzerland).

The vaporizer settings were adjusted to provide an adequate depth of surgical anesthesia. Presence or absence of limb movement, palpebral reflex and any detectable response to surgical stimulation were among the clinical parameters used to assess the depth of anesthesia. Based on this evaluation, dogs were allowed to be as lightly anesthetized as possible during the surgical procedures. Fentanyl (2.5 µg/kg IV) was reserved for intra-operative administration to improve antinociception if necessary. The criteria for administration was based on an increase in pulse rate, mean arterial blood pressure, and/or respiratory rate equal or higher than 15% of the previous value after the start of surgery, in the presence of an adequate depth of anesthesia. At the end of the anesthesia, duration of anesthetic recovery was measured from the time that the vaporizer was turned off to the moment that the dog assumed sternal position.

Post-operative analgesia was evaluated by an investigator (SA) unaware of the drug used epidurally, with the use of a scoring system designed for this study (Appendix A). Baseline assessments for pulse rate, respiratory rate, levels of vocalization, activity, posture, and color of mucous membranes were performed in each dog before the administration of any drug. These assessments were repeated in the post-operative period at 60, 120, and 240 minutes. A 50% increase in pulse or respiratory rate over baseline and/or a total score of subjective assessments  $\geq 3$  points was assumed to be indicative of pain that should be treated with additional analgesics (morphine 0.5 mg/kg IM, repeated after 20 minutes as



**Figure 1.** Intra-operative halothane vaporizer settings in dogs (n = 10) given epidural tramadol (1.0 mg/kg) and submitted to stifle surgery.

## RESULTS

Duration of anesthesia and surgery were  $100.2 \pm 11.2$  and  $77.5 \pm 7.5$  minutes, respectively. Duration of anesthetic recovery was  $81.1 \pm 21.7$  minutes. The surgical conditions were considered very good, with good muscle relaxation, and no excessive bleeding. Intra-operative use of fentanyl was not necessary based on the chosen criteria.

needed). After this 4-hour period, all dogs received 1.0 mg/kg of flunixin meglumine IV, which was continued for 2 additional days, administered subcutaneously every 24 hours.

Statistical analysis was performed using repeated measures analysis of variance to assess changes over time, followed by Bonferroni multiple comparison test when a significant difference was indicated. Differences were considered significant when  $P < 0.05$  and the data are reported as mean  $\pm$  SEM (standard error of the mean). The SEM bars and the indications of statistical significance were omitted from the charts for easier interpretation.

Vaporizer settings were significantly decreased over time (Figure 1). Values for pulse and respiratory rates, systolic, mean, and diastolic arterial blood pressure, and pulse oximetry are shown graphically in Figure 2. Induction of general anesthesia produced a statistically significant decrease in arterial blood pressure although hypotension (mean arterial blood pressure  $<70$  mmHg) was not observed. Values for pH,  $\text{PaO}_2$ ,  $\text{PaCO}_2$ ,  $\text{SaO}_2$ , and  $\text{HCO}_3^-$  are presented graphically in Figure 3. Values for  $\text{PaO}_2$ ,  $\text{PaCO}_2$ , and  $\text{SaO}_2$  increased significantly from baseline during anesthesia, while they were similar to baseline in the post-operative period (120, 240, and 360 minutes after epidural tramadol). None of the cardio-

**Table 1.** Mean  $\pm$  Standard Error of the Mean of Pulse (PR) and Respiratory ( $f$ ) Rates, and Scores Used for Pain Evaluation During 4 Hours of Post-Operative Period in Dogs (n = 10) Submitted to Orthopedic Surgery and Epidural Administration of Tramadol (1.0 mg/kg).

Time	Variables					
	PR (pulses/min)	$f$ (breaths/min)	Vocalization <sup>†</sup>	Activity <sup>†</sup>	Posture <sup>†</sup>	Mucous membrane color <sup>†</sup>
Baseline	94.5 $\pm$ 5.53 <sup>a</sup>	23.4 $\pm$ 4.48 <sup>a</sup>	0 (n=10)	0 (n=10)	0 (n=10)	0 (n=10)
60*	119.2 $\pm$ 9.74 <sup>b</sup>	14.6 $\pm$ 1.41 <sup>b</sup>	0 (n=10)	0 (n=10)	1 (n=1) 2 (n=9)	0 (n=10)
120*	101.2 $\pm$ 7.49 <sup>ab</sup>	15.0 $\pm$ 1.21 <sup>ab</sup>	0 (n=10)	0 (n=10)	1 (n=6) 2 (n=4)	0 (n=10)
240*	113.7 $\pm$ 6.23 <sup>ab</sup>	14.6 $\pm$ 0.83 <sup>b</sup>	0 (n=10)	0 (n=10)	1 (n=9) 2 (n=1)	0 (n=10)

Different letters on the same column indicate statistically significant differences ( $P < 0.05$ ) between times for the respective variable.

\*Time in minutes after end of surgery.

<sup>†</sup>Score (Appendix A) and number of dogs (n).

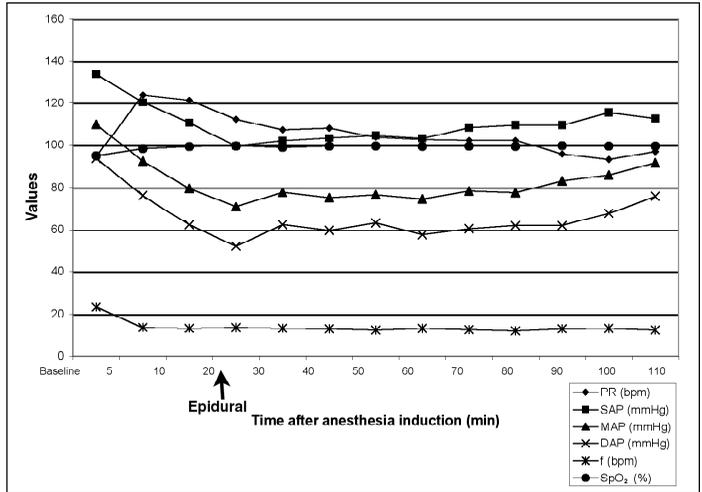
vascular and respiratory variables measured were changed with the epidural administration of tramadol.

The post-operative pain assessment showed that the dogs were apparently comfortable; these data are displayed on Table 1. In the subjective evaluation, all dogs showed no vocalization, were inactive or sleeping, and presented normal mucous membrane coloration throughout 4 hours of evaluation. For posture, most of the dogs were recumbent in the first hour, while in the second and fourth hours most of them were standing spontaneously, although not weight bearing on the operated limb. None of the dogs had a 50% increase in heart or respiratory rate over baseline nor received a total score  $\geq 3$  points, and therefore no additional analgesics were used during the 4 hours of evaluation.

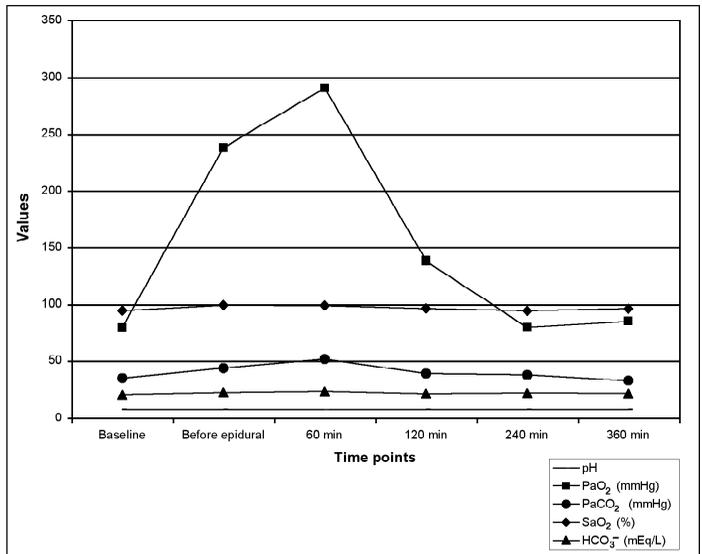
## DISCUSSION

In humans, tramadol has been used epidurally for many years,<sup>13-16</sup> but in veterinary medicine the epidural administration was studied only recently in horses, where tramadol was found to be 10-times less potent than morphine.<sup>17</sup> To date, there are no reports on the epidural administration of tramadol in dogs. Therefore the dose chosen for this study was based on human literature, where tramadol was used epidurally in children at doses of 1.0 to 2.0 mg/kg,<sup>16,18</sup> and from the study done in horses where it was adminis-

tered at a dose of 1.0 mg/kg.<sup>17</sup> Also, as tramadol was 10-times less potent than morphine,<sup>17</sup> the use of 1.0 mg/kg in the present study is likely to be equipotent with the dose of 0.1 mg/kg of morphine commonly used epidurally in dogs.



**Figure 2.** Mean values of pulse rate (PR), systolic arterial blood pressure (SAP), mean arterial blood pressure (MAP), diastolic arterial blood pressure (DAP), pulse oximetry (SpO<sub>2</sub>), and respiratory rate (f) in dogs (n = 10) administered epidural tramadol (1.0 mg/kg) undergoing stifle surgery.



**Figure 3.** Mean values for pH, arterial partial pressures of oxygen (PaO<sub>2</sub>) and carbon dioxide (PaCO<sub>2</sub>), oxygen-hemoglobin saturation (SaO<sub>2</sub>), and plasma bicarbonate concentration (HCO<sub>3</sub><sup>-</sup>) in dogs (n = 10) administered epidural tramadol (1.0 mg/kg) undergoing stifle surgery.

In this study, a decrease in arterial blood pressure, mild hypoventilation, and decrease in respiratory rate were observed with the institution of general anesthesia compared with the baseline values in the conscious animals. This is expected to happen with all the commonly used inhalant anesthetics, as they cause dose-dependent cardiovascular and respiratory depression.<sup>19,20</sup> Tramadol was given epidurally after 20 minutes of general anesthesia, and no changes in arterial blood pressure, pulse and respiratory rates, pulse oximetry, and arterial blood gases were noticed. Similar results have been observed in anesthetized humans<sup>14,15,17,21</sup> and in unanesthetized horses<sup>18</sup> after epidural administration of tramadol. Additionally, intravenous doses up to 2.0 mg/kg in conscious humans, and up to 10 mg/kg in awake or anesthetized dogs had no significant adverse cardiovascular effects.<sup>22,23</sup>

While inhalant anesthetics cause unconsciousness and the patient does not experience pain, even profound planes of anesthesia may not block nociception and many of the autonomic responses related to surgical stimulation.<sup>24</sup> Although clinical evaluation of adequate intra-operative antinociception may be difficult, tachypnea, tachycardia, and hypertension may be observed in anesthetized animals in response to surgical stimulation.<sup>25</sup> Attempts to block these responses by increasing the volatile anesthetic concentration will result in severe respiratory depression.<sup>24</sup> None of these changes were observed in the present study. The anesthetic depth was maintained as light as possible, with most dogs showing palpebral reflexes and some degree of shivering in the second half of the anesthetic procedure, yet surgical conditions were good. Vaporizer settings remained below 1.0% for the surgical period 30 minutes after epidural administration of tramadol to the end of anesthesia, in the present study, with values similar or even lower than the reported minimum alveolar concentration of 0.87% for halothane in dogs.<sup>19</sup>

Noradrenergic descending pathways and the serotonergic system innervate all levels

of the spinal cord, and can modulate afferent pain signals at this level.<sup>26,27</sup> Opioids, noradrenergic, and serotonergic drugs can interact with these systems to produce antinociception,<sup>27</sup> and the use of these drugs in combination significantly improves analgesia.<sup>28-30</sup> This may explain the antinociception obtained with the use of epidural tramadol as its opioid and monoaminergic actions interact at the level of the spinal cord to produce antinociception.<sup>6,12</sup>

The opioid and monoaminergic actions of tramadol are well recognized, and local anesthetic effects also have been demonstrated more recently. The intravenous regional administration of tramadol was shown to reduce the incidence of the painful sensation associated with intravenous administration of propofol in humans.<sup>10,11</sup> Also in humans, intradermal injection of tramadol produced loss of sensation to pin prick, light touch, and cold in one study<sup>8</sup> and surgical analgesia similar to prilocaine in another.<sup>9</sup> Local anesthetic effects, combined with the opioid and monoaminergic actions, support the findings of satisfactory antinociception obtained in the present study.

The use of scores to evaluate the analgesic status of animals may not be accurate in some occasions due to the subjective and complex nature of pain.<sup>31</sup> However, pale mucous membranes due to peripheral vasoconstriction, tachypnea, and tachycardia may occur as a sympathetic response to pain in conscious animals.<sup>25,31</sup> Changes in respiratory rate are good physiologic indicators of pain with a high correlation with subjective methods of evaluation.<sup>31</sup> Furthermore, a patient who is pain free will be calm, quiet, and will often sleep.<sup>31</sup> In the present study, respiratory rate during the post-operative period remained similar or lower than baseline, and the animals were quiet, calm, or asleep, indicating satisfactory post-operative analgesia. Several reports from the human literature have shown effective postoperative analgesia after epidural administration of tramadol.<sup>14,15,18,32,33</sup> In addition, complete analgesia in the perineal and sacral areas for 4 hours has been reported in

horses given tramadol epidurally.<sup>17</sup> Our study suggests that the epidural administration of tramadol may produce at least approximately 5.5 hours of analgesia in dogs.

## CONCLUSION

Epidural tramadol produces satisfactory intra-operative antinociception and post-operative analgesia without causing clinically significant hemodynamic and respiratory depression in healthy dogs undergoing stifle surgery.

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**Appendix A.** Scoring System Used to Subjectively Evaluate Post-Operative Analgesia Through Assessments of Vocalization, Agitation, and Mucous Membrane Coloration of Dogs Submitted to Orthopedic Surgery and Epidural Administration of Tramadol (1.0 mg/kg).

<b>Clinical Sign</b>	<b>Score and Patient Criteria</b>
Vocalization	0 = None 1 = Present, easily controllable by talking to the animal with a calm voice. 2 = Present, controllable with gentle touch and calm voice 3 = Present, not controllable with gentle touch and calm voice
Level of activity	0 = Asleep, inactive, or calm 1 = Uncomfortable, changing position constantly 2 = Agitated, constantly standing up and laying down 3 = Thrashing and destructive behavior
Posture	0 = Standing spontaneously, weight bearing 1 = Standing spontaneously, but non-weight bearing 2 = Recumbent, but able to stand with verbal stimulation, with or without minimal help 3 = Recumbent, refuse to stand with verbal stimulation or minimal help
Mucous membrane coloration	0 = Normal coloration 1 = Pale mucous membrane
<b>Total Score Possible</b>	<b>10 points</b>