Evaluation of tramadol, an "atypical" opioid analgesic in the control of immediate postoperative pain in dogs submitted to orthopedic surgical procedures

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Abstract

The degree of analgesia after the preemptive administration of tramadol or flunixin meglumine was evaluated in thirty dogs submitted to orthopedic surgical procedures. Dogs received tramadol (2mg/kg) or flunixin meglumine (1.1mg/kg). Cardiovascular and respiratory depression were not observed during anesthesia. Animals treated with tramadol showed a higher score of analgesia. The quality of recovery of animals treated with tramadol was much better as it was free from excitation and discomfort, and presented a higher degree of sedation. We could conclude that tramadol can be applied successfully in preemptive analgesia, since recovery from anesthesia is accompanied by adequate analgesia and is free from excitation and discomfort.

Key-words:
Analgesia (Veterinary).
Analgesics, opioid (Administration and dosage).
Dogs.
Pain, Postoperative (medicament).
Orthopedics (Veterinary).
Tramadol.
Flunixin Meglumine.

Introduction

According to the classification of pain as proposed by Ready[1], pain occuring in the postoperative period is classified as acute, and is characterized by disagreeable emotional and sensory experiences arising from tissue lesions. There are those who still think that pain does not represent any great harm to animals. However, relief from this suffering is of humanitarian concern and biological interest. False concepts such as fear of camouflaging manifestation of surgical complications, inducement of respiratory depression or the idea that animals do not feel pain, place restrictions on analgesic therapy to this day. Nevertheless, different approaches have been evaluated with the purpose of attaining the best result to alleviate postoperative distress. Analgesics are administered either during the operation (mainly to reduce the concentration of anesthetics), in the postoperative period, or before the surgical insult, which is known as pre-emptive therapy[2,3,4]. Various agents can be used for this purpose, including the centrally acting analgesics and non-steroidal anti-inflammatory (NSAIAs) agents. Welsh, Nolan and Reid[4] and Lascelles, Butterwor and Waterman[2] obtained low scores of pain in dogs receiving carprofen pre-operatively while Brodbelt, Taylor and Stanway[5] obtained the same results with morphine and buprenorphine.

Tramadol is a potent centrally acting analgesic indicated for controlling moderate to severe pain in man and laboratory animals[6,7,8]. Although its mechanism of action is not entirely understood, data suggest that tramadol produces antinociception via an opioid (predominantly μ) mechanism and also via a separate non-opioid mechanism (probably related to its ability to inhibit neuronal uptake of norepinephrine or serotonin). These two mechanisms contribute to tramadol's analgesic profile[6,7,8]. Studies carried out in man indicate that tramadol, as opposed to morphine, causes less respiratory depression, does not release histamine and when administered in therapeutic dosages does not have any effect on heart rate, ventricular function and blood pressure,

thereby causing less side effects than morphine[6,9]. It also does not cause the adverse effects associated with the decrease in prostacycline and prostaglandins synthesis which can occur when using non-steroidal anti-inflammatory products[8].

The purpose of this study was to evaluate the use of tramadol in preemptive analgesia in dogs, and compare it with flunixin meglumine.

Materials and Methods

Thirty dogs of various breeds, male and female, ASA II (risk category according to the American Society of Anesthesiologists), with ages ranging from eight to 120 months and weighing from 3.5 to 40 kg, were submitted to orthopedic surgical procedures (femur fracture repair, cefalectomy, artroplasty) with a maximum duration of two hours. The dogs were distributed at random into two groups of fifteen dogs each. Dogs in group one received acepromazine as the pre-anesthetic medication (0.1 mg/kg) mixed with tramadol (2.0 mg/kg) in the same syringe and administered intramuscularly, and dogs in group two received flunixin meglumine (1.1 mg/kg) instead of tramadol. Fifteen minutes later, anesthesia was induced using thiopentone to effect (mean 9.0 mg/kg). After oral endotracheal intubation, utilizing a rebreathing circuit or for animals weighing below 10kg, a non-rebreathing circuit, anesthesia was maintained with halothane in 100% oxygen. Halothane was used at the required concentration to maintain the animal on a surgical plane of anaesthesia (initially around 1.3 MAC). No intra-operative analgesics were administered. Throughout the whole procedure, animals received lactated Ringer's solution at 5 to 10 ml/kg/hour. Cardiovascular parameters consisting of cardiac rate (HR) and rhythm as well as non-invasive arterial pressure were continuously monitored during anesthesia by means of a standard EKG monitor and by an oscillometric system (Criticare, USA). Peripheral oxyhemoglobin saturation through pulse oximetry, respiratory rate (RR), inspired and end tidal halothane concentration, end tidal carbon dioxide concentration as well as inspired oxygen concentration were all analyzed by means of a multianalyzer monitor constituted of an pulse oximetry,

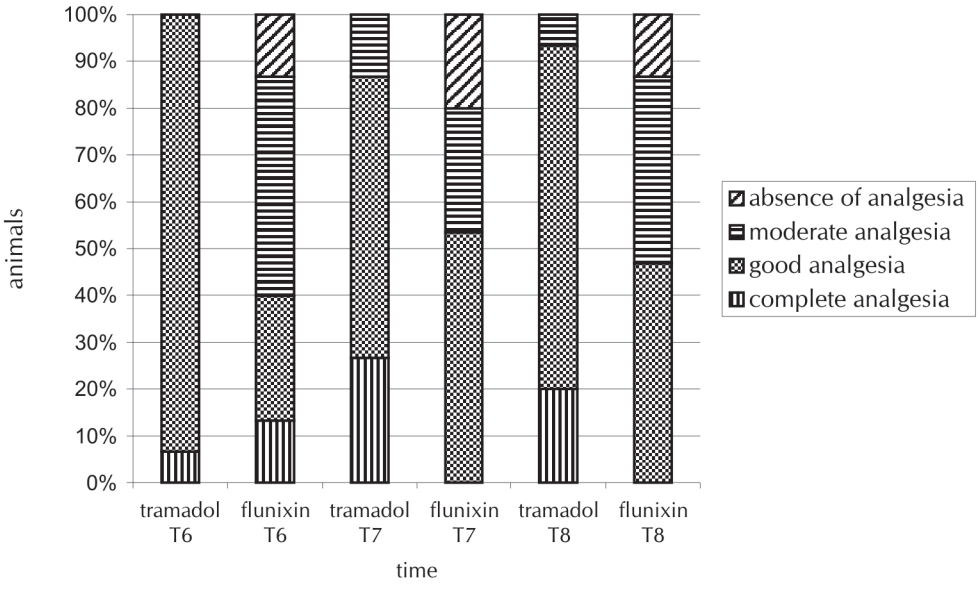

Figure 1 - Degree of analgesia in animals treated with tramadol and flunixin meglumine submitted to orthopedic surgeries (T6: after extubation, conscious, $p < 0,05$; T7: 30 minutes after T6, $p < 0,05$; T8: 60 minutes after T6, $p < 0,05$)

Table 1 - Details of the dogs included in the study

	Group 1 (n = 15) tramadol	Group 2 (n = 15) flunixin meglumine
Males/females	9/6	8/7
Age (mean)	1y 8m ± 19,5	1y 9m ± 30,5
btw (mean)	14,15 kg ± 9,16	9,9 kg ± 6,6
Surgery time (mean)	90,3 min ± 26,6	87,0 min ± 34,4
Extubation time (mean)	7,9 min ± 11,1	6,0 min ± 4,9

capnograph and gas analyzer (Criticare Poet, USA). The following time points were considered for statistical analysis purposes: T0: before pre-anesthetic medication (PAM); T1: 15 minutes after PAM; T2 5 minutes after induction; T3: 15 minutes after induction; T4: 30 minutes after induction; T5: 60 minutes after induction.

The quality of the animal's postoperative recovery was assessed using two different evaluation methods, based on the level of discomfort/pain presented by the subject. The first method used a measurement of the level of discomfort/pain and was based on observation of signs such as crying, whimpering, restlessness and general discomfort. It was also based on the animal's reaction to stimuli (pressure) applied to the area of the lesion, either directly or through bandages, or through handling of the areas adjacent to the injured area in accordance to the scaling method proposed by Lascelles and Waterman[10]. The scale consisted of: 0. Complete analgesia, without evident signs of discomfort or reaction to pressure applied to the area of the lesion; 1. Good analgesia, without evident signs of discomfort, but reaction to pressure applied to the area of the lesion; 2. Moderate analgesia, with some evidence of discomfort, being accentuated when pressure is applied to the area of the lesion; 3. Absence of analgesia, with evident signs of persistent discomfort, made worse by pressure applied to the area of the lesion.

The second method used in the postoperative evaluation was the VAS or

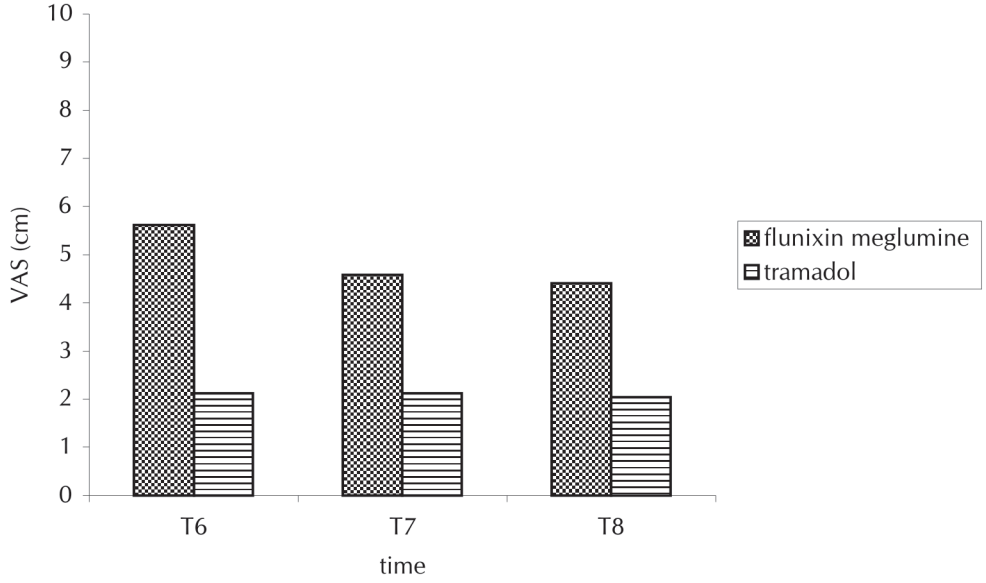

Figure 2 - Degree of analgesia in dogs treated with tramadol and flunixin meglumine obtained with a subjective pain scale (VAS) after the orthopedic surgery (T6: after extubation, conscious, $p < 0,05$; T7: 30 minutes after T6; T8: 60 minutes after T6, $p < 0,05$)

Table 2 - Number of dogs undergoing each surgical procedure

Surgical procedure	Group 1 tramadol	Group 2 flunixin meglumine
Fracture femur repair	10	8
Cefalectomy	2	3
Artroplasty	3	4

Table 3 - Breed distribution for the tramadol (T) and flunixin meglumine (F) groups (number per groups)

Miniature Pinscher	0T	1F
Mongrel	7T	7F
Rottweiler	1T	0F
Fila Brasileiro	1T	0F
Siberian Husky	1T	1F
Cocker Spaniel	1T	2F
Poodle	3T	4F
Fox Paulistinha	1T	0F

Visual Analogue Scale, where zero represents the absence of pain and 10 (cm), the worst pain imaginable. The animal is evaluated and a mark is given[11,12,13]. In order to assess the degree of sedation in the postoperative phase, the VAS was used on a scale from zero to 100 (mm), where zero represents an alert animal and 100 (mm), an animal under maximum sedation[11]. The postoperative evaluation of pain using the scoring systems mentioned above, was carried out at the following times: T6: after extubation with the animal responding to a verbal command; T7: 30 minutes from T6; T8: 60 minutes from T6. In order to maintain a similarity in the evaluation of the degree of analgesia and sedation between the two groups, the first evaluation time was considered when the animals were conscious, responding to verbal commands. Heart and respiratory rate were also assessed at these time points. All animals were evaluated by the same person who was blinded to the experimental protocol. Statistical comparison of parametric data (cardiovascular and respiratory parameters) was performed by use of an analyses of variance (ANOVA) being those differences between values within a group, submitted to the analysis of variance followed by the Tukey test. To compare differences between groups, a Student *t* test was used. Non-parametric data (sedation and pain) were analyzed using the Mann-Whitney test for unpaired data. All tests were performed utilizing a computer program (Instat-2 – Graphpad). Significance was established at $P < 0,05$.

Results and Discussion

Comparing the two groups, no significant differences in relation to body weight, breed, age and sex distribution as well as the parameters obtained during anesthesia were observed (Table 1, 3 and 4). The surgical procedures are listed on table 2.

The average surgery time for group 1 was 90.3 ±26.6 min. and for group 2, 87.0 ±34.4 min. The first postoperative evaluation was carried out after 32.6 ±18.8 minutes for group 1 and 29.6 15.2 minutes for group II from the end of the surgical procedure. The average extubation time in group 1 was 7.9 ±11.1 minutes and in group 2, 6 ±4.9 minutes. There were no significant differences between the two groups with regard to the parameters mentioned above (Table 1). In relation to the scale proposed by Lascelles and Watterman[10] for evaluation of postoperative analgesia, the animals treated with tramadol obtained a higher degree of analgesia with the difference between the two groups being statistically significant (Figure 1). In relation to the VAS score, the animals treated with tramadol also showed less pain compared to the group treated with flunixin meglumine (Figure 2). With regard to the degree of sedation, the animals treated with tramadol

Table 4 - Cardiovascular, respiratory and anesthetic parameters measured in animals treated with tramadol and flunixin meglumine preemptively

		Time					
Parameter	Group	T0	T1	T2	T3	T4	T5
HR	tramadol	116.8±28.0	112.6±18.5	138.3±28.1*	118.7±22.6	108.5±15.1	102.4±13.3
beat/min	flunixin	118.7±20.7	112.7±21.9	138.9±26.3*	124 ± 20.2	116.1±22.1	111.4±30.1
SAP	tramadol	119.9±22.6	113.0±15.6	124.8±14.0	114.4±16.6	110.9±14.2	111.6±15.3
mm/Hg	flunixin	143.9±39.0	122.7±25.9	118.5±16.4	112.2±23.7	115 ±21.7	116.4±16.8
MAP	tramadol	-	-	95.0 ±11.0	86.8 ±15.8	84.4 ±18.6	83.2 ±17.7
Mm/Hg	flunixin	-	-	88.4 ±17.8	80.3 ±20.8	80.4 ±20.1	84.4 ±14.1
DAP	tramadol	-	-	74.6 ±14.5	66.4 ±12.8	63.2 ±15.9	62.8 ±18.2
Mm/Hg	flunixin	-	-	64.6 ±19.5	58.8 ±17.4	59.8 ±15.5	64.0 ±19.2
SpO2	tramadol	-	-	96.8 ±1.4	97.6 ±1.0	96.8 ±1.4	97.0 ±1.1
%	flunixin	-	-	96.5 ±2.1	96.9 ±0.9	96.4 ±1.6	97.0 ±1.3
RR	tramadol	42.7 ±17.7	33.4 ± 19.5	16.6 ±4.7*	16.3 ±6.7*	21.0 ±7.9*	22.5 ±10.0
mov/min	flunixin	59.5 ±17.0	54.7 ± 23.5	22.6 ±12.5*	22.2 ±8.5*	26.6 ±13.2*	32.4 ±17.1*
ETCO2	tramadol	-	-	37.6 ±4.6	36.4 ±4.3	33.5 ±7.3	36.6 ±6.5
%	flunixin	-	-	38.3 ±9.0	37.7 ± 8.0	33.4 ±7.8	34.5 ±7.0
% INS	tramadol	-	-	1.14 ±0.58	1.24 ±0.54	1.32 ±0.72	1.07 ±0.50
Halothane	flunixin	-	-	1.44 ±0.87	1.24 ±0.66	1.04 ± 0.66	1.04 ±0.59
% EX	tramadol	-	-	0.92 ±0.39	1.06 ±0.35	1.24 ± 0.55	1.06 ±0.62
Halothane	flunixin	-	-	1.15 ±0.69	1.04 ±0.55	1.0 ±0.52	0.78 ±0.56

HR – Heart rate; SAP – systolic arterial pressure ; MAP – Mean arterial pressure ; DAP – diastolic arterial pressure ; SpO2 – oxyhemoglobin saturation ; RR – respiratory rate ; ETCO2 – endtidal carbon dioxide concentration; %INS – concentration of halothane in the inhaled air; %EX – concentration of halothane in the exhaled air; * Differs statistically from T1 ($p < 0,05$). All values are mean + SD.

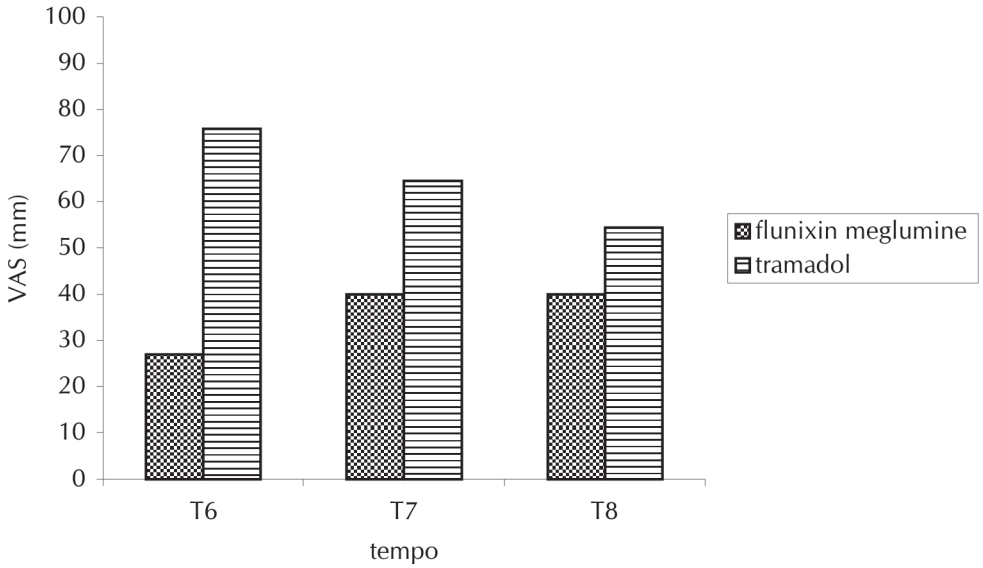

Figure 3 - Degree of sedation in dogs treated with tramadol and flunixin meglumine obtained with a subjective sedation scale (VAS) after orthopedic surgeries (T6: after extubation, conscious, $p < 0,05$; T7: 30 minutes after T6, $p < 0,05$; T8: 60 minutes after T6)

were more sedated soon after coming out of anesthesia and 30 minutes after the operation (Figure 3). Heart rate in the postoperative period did not show any significant difference from the values obtained before pre-medication. The lowest value obtained for respiratory rate in the postoperative period was 14 m.p.m. in a dog of group 1. Respiratory rate varied from a minimum value of 14 to a maximum of 25 m.p.m. in dogs of both groups.

In the present study we evaluated the effects of tramadol, an opioid analgesic that is currently used in man, but, to our knowledge, not presently used in veterinary medicine. Postoperative pain is associated with various undesirable effects such as: self mutilation, suffering, decreased food intake, reluctance to walk, loss of muscular mass, prostration, ventilation disturbances (hypoxia, hypercapnia and acidosis) due to recumbence and an overall delay in recovering normal function. For this reason, much attention has been focused on different approaches to treat pain. Opioid analgesics as well as NSAIDs can be used to control postoperative pain when administered either before the beginning of surgery or after it. Favorable results are appearing regarding the administration of analgesics prior to surgery in man as well in dogs[4,5,14,15,16].

Tramadol is an opioid analgesic agent that produce in man, when administered in equipotents doses, a degree of analgesia that is similar to that one produced by morphine, without the respiratory depression usually pronounced with the μ opioids agonists[7,16]. In the present study we aimed to compare the actions of tramadol with flunixin meglumine, an NSAIDs in the immediate postoperative period as preemptive analgesic in dogs submitted to orthopedic surgeries. Instead of utilizing a placebo, we chose a NSAIDs that for postoperative pain due to an orthopedic procedure would be quite reasonable[17]. Besides that, many studies have been conducted to compare the actions of opioids and NSAIDs. Reid and Nolan[18] compared papaveratum and flunixin in dogs, Fonda[19] compared flunixin with pethidine in cats, Slingsby and Waterman-Pearson[20] pethidine, buprenorphine and ketoprofen in cats and Putland and McCluskey[21] in man compared tramadol with ketorolac, among others. Another reason for debate in the present study could be the administration of flunixin before surgery as some authors could argue that it can cause renal failure due to its action on cyclooxygenase-1. But it is also well know that there is no risk of renal failure in patients treated with NSAIDs if they have normal renal function and also if normovolemia and systemic arterial pressure are maintained during surgery. All animals in the present study had their blood pressure monitored and received fluids during the entire procedure. Another fact that could be in favor of our protocol, is the fact that the argumentation that provides the background to forbid the administration of flunixin meglumine to any animal (in good conditions or not), is based on two reports, where renal failure developed after a single dose of flunixin administered preoperatively in major surgeries, during which the animals did not have their blood pressure monitored, anesthesia was prolonged and they did have little support in the way of fluid therapy[22,23].

The administration of tramadol before surgery was associated with good scores of pain and sedation in the postoperative period which was also verified in man[16]. Some studies reported that some NSAIDs (ketoprofen and carprofen) can be more potent than opioids like butorphanol, oxymorphone and pethidine[2,24,25]. In the present study the use of tramadol, was more effective in treating pain than the use of flunixin, the NSAID chosen for the study. Tramadol in man has the same analgesic effects of morphine[6] and has markedly less clinically significant respiratory depressive effects than morphine[6,11]. In accordance with these authors, this fact could be explained because the analgesic effects of tramadol are mediated by non-opioid receptor mechanisms of action. Indeed, it is a weak m opioid agonist. Many authors comment that the lack of

respiratory and cardiovascular depression observed after the administration of tramadol could be the greatest advantage of its use[6,7,8]. In a study conducted on 150 women submitted to gynecological surgery, it was found that although the analgesic power of tramadol and morphine are similar, tramadol causes less respiratory depression than morphine[6].

In man, studies report that the degree of sedation is enhanced in patients treated with tramadol[8]. In this study, we observed greater sedation in the animals that received tramadol compared to those treated with flunixin, allowing for a smoother anesthetic induction when compared to the animals of the other group.

The most commonly used rating scales for evaluating pain in animals are based on studies of alterations in normal behavior and alterations of the physiological parameters. According to a study conducted by Firth and Haldane[13], the animal's behavior and measuring of physiological parameters, may be used with effectiveness for evaluation and control of postoperative pain in dogs. The subjective ratings for evaluation of pain and sedation such as the VAS, have been applied successfully in human infants[26] and in cats and dogs[4,10,11]. In the present study both methods employed to evaluate postoperative pain were effective since similar results were verified with the two scales.

To avoid that the differences of anesthetic protocols or inhalation anesthetic concentrations could interfere with the scoring of pain in the postoperative period we also measured the inspired and end tidal concentration of halothane during the entire protocol. By doing this we also evaluated if the administration of the two analgesics could have a sparing effect on the MAC of halothane which was not observed as the lower expired value of halothane was 1.07%.

The side effects frequently caused by tramadol are nausea and vomiting, which can be prevented by administering metoclopramine[7]. In this study, none of the fifteen (15) animals treated with tramadol manifested emesis during the postoperative evaluation. In the group treated with flunixin meglumine, one animal presented retching. Cats and dogs are more susceptible than humans to the adverse effects of NSAIAs. Veterinarians therefore must be familiar with NSAIAs and the potencial each has for unwanted side effects. Some of these drugs carry a high risk for gastric ulceration and nephrotoxicity, so the contraindications and benefits versus risks should be considered. We could not notice any adverse effect after the administration of flunixin, but we have to bear in mind that it was applied only once.

Our results indicate that tramadol can be successfully used for postoperative pain control in dogs. Nonetheless, the duration of its action must be determined by further studies.

Avaliação da eficácia do tramadol, um analgésico opióide atípico, no controle da dor pós-operatória em cães submetidos a procedimentos cirúrgicos ortopédicos

Resumo

Comparou-se a qualidade da analgesia pós-operatória após administração preemptiva de tramadol (2 mg/kg/grupo 1) e flunixin meglumine (1,1 mg/kg/grupo 2) em 30 cães submetidos a procedimentos cirúrgicos ortopédicos. Os animais tratados com tramadol apresentaram maior grau de analgesia comparado ao grupo do flunixim meglumine. A qualidade do retorno anestésico dos animais tratados com tramadol foi superior, livre de excitação e desconforto e com grau de sedação superior ao grupo do flunixin meglumine. Não foram observadas alterações cardiovasculares e respiratórias durante a anestesia. Podemos concluir que o tramadol

Palavras-chave:
Analgesia (Veterinária).
Analgésicos opióides (Administração e dosagem).
Cães.
Dor pós-operatória (medicamentos).
Cirurgia ortopédica (Veterinária).
Tramadol.
Flunixin Meglumine.

pode ser utilizado como analgésico preemptivo em cães submetidos a procedimentos cirúrgicos ortopédicos, já que o retorno anestésico apresentou adequada analgesia, livre de desconforto e excitação.

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