Evaluation of Postoperative Analgesic Effect of Systemic Use of Tramadol in Female Dogs that Underwent Ovariohysterectomy

Avaliação do Efeito Analgésico Pós-Operatório do Uso Sistêmico de Tramadol em Cadelas Submetidas à Ovariohisterectomia

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Abstract

Postoperative pain may cause a series of pathophysiological alterations that may be harmful to animals. The study aimed to evaluate the analgesic and sedative effects of morphine versus tramadol in a single intravenous administration in bitches after ovariohysterectomy. Twenty healthy female dogs were divided into groups: MG received 0.5 mg/kg of morphine and TG received 4 mg/kg of tramadol, both administered intravenously at the end of surgery. The analgesia and sedation were evaluated hourly during 6 hours after the procedure, and the following scales were used for the analgesia evaluation: Lascelles, Visual Analogue Scale (VAS), Pain scale from Melbourne, University of Colorado Scale, Glasgow Composite Scale, and University of Guelph Pain Scale. The Grint sedation scale and Valverde sedation scale were used to evaluate sedation. Animals that scored over 5 on the Glasgow Composite Scale and/or greater than 4 on the VAS, received rescue analgesia. Five dogs from the MG and two dogs from the TG required rescue analgesia (p = 0,021). Statistical difference was observed in the VAS (T6h), Glasgow (T4h and T5h), Lascelles (T3h, T4h and T6h), Colorado (T4h and T6h), and Guelph (T3h, T4h, T5h and T6h) scales in the evaluation of analgesia, elucidating that tramadol had lower scores compared with morphine. It was concluded that tramadol promoted satisfactory analgesia in managing postoperative pain and had less severe adverse effects.

Keywords: Analgesia. Acute Pain. Analgesic. Opioids.

Resumo

A dor pós-operatória pode causar uma série de alterações fisiopatológicas que podem ser deletérias para os animais. O estudo teve como objetivo avaliar os efeitos analgésicos e sedativos da morfina versus tramadol em administrações intravenosas únicas no final da cirurgia de cadelas submetidas a ovariohisterectomia. Vinte cadelas hígidas foram divididos em grupos: MG recebeu 0,5 mg/kg de morfina e TG recebeu 4 mg/kg de tramadol, ambos administrados por via intravenosa ao final da cirurgia. A analgesia e a sedação foram avaliadas de hora em hora durante 6 horas após o término da cirurgia. As seguintes escalas foram utilizadas para a avaliação da analgesia: Escala Analógica Visual de Lascelles (EAV), Escala de Dor de Melbourne, Escala da Universidade do Colorado, Escala Composta de Glasgow e Escala de Dor da Universidade de Guelph. Para avaliar a sedação, foram utilizadas a escala de sedação de Grint e a escala de sedação de Valverde. Os animais que atingiram pontos maiores que 5 na Escala Composta de Glasgow e/ou maiores que 4 na EAV, receberam analgesia de resgate. Cinco cães do GM e dois cães do GT necessitaram de analgesia de resgate (p = 0,021). Foi observada diferença estatística nas escalas EVA (T6h), Glasgow (T4h e T5h), Lascelles (T3h, T4h e T6h), Colorado (T4h e T6h) e Guelph (T3h, T4h, T5h e T6h) na avaliação de analgesia, elucidando que o tramadol teve escores menores em comparação com a morfina. Concluiu-se que o tramadol promoveu analgesia satisfatória no manejo da dor pós-operatória e resultou em efeitos adversos menos graves.

***Palavras-chave**: Analgesia. Dor aguda. Analgésico. Opióides.*

1 Introduction

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (RAJA *et al*., 2020). Painful experiences may cause a series of pathophysiological alterations that may be deleterious to the patient, such as immunosuppression, delayed wound healing, acceleration of pathological processes, and others. Therefore, it is a moral and ethical duty to recognize and treat the animals' pain (MWANGI *et al*., 2018). Due to the importance of pain management, especially postoperative pain, drug studies for analgesia in animals are increasing.

Opioids are the oldest and most potent analgesic drugs known, being the main agents used to control postoperative pain in bitches undergoing ovariohysterectomy (MWANGI *et al*. 2018). The effects of opioids are mediated by their connection with specific receptors, present in the central nervous system, inhibiting the transmission *stimuli* to the upper centre, altering nociception and the perception of pain (KLAUMANN *et al*., 2008).

Morphine is considered the standard opioid in Veterinary Medicine, and all the other opioids are compared based on their analgesic potency. In small animals, it is effective in treating moderate to severe perioperative pain (MATHEWS *et al*., 2014). Tramadol is an atypical opioid with a low affinity

for μ receptors, and with monoaminergic action through inhibition of norepinephrine reuptake and serotonin release. When tramadol is metabolized, it produces the metabolite O-desmethyltramadol (M1), resulting from its metabolism by the isoenzymes of the P450 complex in the liver, and this is the main known metabolite that promotes the analgesic effect (GROND; SABLOTZKI, 2004).

Dogs have less concentration of the M1 metabolite than do humans and cats, which led to doubts about its effectiveness in the species. Anyhow, some clinical studies have demonstrated sufficient analgesia for the treatment of moderate pain in dogs when administered intramuscularly (MASTROCINQUE; FANTONI, 2003; CARDOZO *et al*., 2014; KAKA *et al*., 2018), although tramadol may result in an increased requirement for rescue analgesia in the postoperative period (DONATI *et al*., 2021).

Despite the considerable research involving tramadol, its analgesic efficacy in dogs remains controversial. We hypothesized that, unlike the intramuscular route, the administration of tramadol intravenously, could have good analgesic effects in female dogs after ovariohysterectomy. Thus, this study aimed to evaluate the analgesic efficacy of tramadol administered intravenously for the management of postoperative pain in bitches after ovariohysterectomy and the presence of associated adverse events.

2 Material and Methods

This work was approved by the Ethics Committee for the Use of Animals of Universidade Pitágoras Unopar (number 001/18) and internationally recognized high standards ('best practice') of veterinary clinical care for the individual patient were followed. This work involved the use of private owned animals. A written or verbal informed consent was obtained from the legal tutors of all animals described in this work for the procedures undertaken.

Twenty female dogs, aged between 1 to 3 years, weighing 8.6 ± 1.1 kg, participated in this study. The animals were admitted for elective ovariohysterectomy (OH) at the Surgery and Anaesthesiology Department of the University Teaching Hospital. The study included only healthy animals based on physical exam, complete blood count, and biochemistry profile, in accordance with the requirements of the American Society of Anesthesiology (ASA) of health classification.

The dogs underwent pre-anaesthetic evaluation on which the heart rate (HR), respiratory rate (RR), mucosal colour, capillary refill time, degree of hydration, and temperature were evaluated. The female dogs were subjected to an eight-hour food and water fast.

This is a double-blinded study, that was accomplished in a prospective, comparative, and random way. The dogs that were included in the study were randomized by the Research Randomizer program (www.randomizer.org), in two groups: TG (n= 10), which received 4 mg/kg of tramadol, and MG (n

= 10), who received 0.5 mg/kg of morphine, both administered intravenously (IV) at the end of the surgical procedure diluted in NaCl 0.9% solution in a volume of 3 mL infused slowly over 3 minutes.

The dogs received pre-anaesthetic medication comprising acepromazine (0.10 mg/kg), through the intramuscular route (IM). After 15 minutes, cefazolin (30 mg/kg, IV) was performed as antibiotic prophylaxis. Throughout the procedure, lactated Ringer's solution (5 mL/kg/hour) was infused to maintain venous access and hydration.

The female dogs were induced to general anaesthesia by slow intravenous administration of propofol (3-8 mg/kg), until the loss of the laryngotracheal reflex. Then, the bitches were intubated with an appropriately sized orotracheal tube and connected to an anaesthetic circuit. Subsequently, isoflurane in 100% oxygen was administered through a rebreathing circuit and animals were kept in spontaneous ventilation. The patient was placed in the supine position, and the OH surgical procedure started when achieving 2nd plane of the 3rd stage of Guedel's plans. The dogs were monitored using a multiparametric monitor (heart rate, ECG, and oximetry), and indirect blood pressure was assessed by Doppler technique. All procedures were performed by the same surgical team. At the time of the incision, a *bolus* of fentanyl (5 µg/kg, IV), pre-diluted in a saline solution, was slowly administered in all dogs. It was repeated in case of an increase above 15% of the heart rate baseline, to avoid sympathetic activation and maintain analgesia. At the end of the surgery, the study drugs were diluted in 5 mL saline solution (morphine or tramadol), and administered intravenously over 3 minutes. As soon as the animals had a laryngotracheal reflex, they were extubated and sent to the kennel, equipped with appropriate cages, and then anaesthetic recovery and analgesia evaluation were performed.

Pain evaluation was accomplished using the descriptive analysis scale proposed by Lascelles (0 - 3) (LASCELLES *et al*., 1994), the Visual Analogue Scale(VAS) (0 - 10) (LLOYD-THOMAS, 1990), the University of Melbourne Pain Scale (0 - 27) (FIRTH; HALDANE, 1999), the University of Colorado Scale for acute pain evaluation in dogs (0 - 4) (HELLYER *et al*., 2007), the Glasgow Composite Measure Pain Scale (CMPS) (0 - 20) (REID *et al*., 2007), and the Visual Numerical Pain Assessment Scale at the University of Guelph (0 - 10) (MATHEWS, 2000). The dogs were filmed during all analgesia assessments for documentation purpose.

The assessment of sedation was performed using the sedation scale by Grint *et al*. (2009) and Valverde sedation scale (0 - 3) (VALVERDE *et al*., 2004). Dogs that sum up over 5 points on the Glasgow Composite Scale (CMPS) and/or greater than 4 on the VAS, received analgesic rescue according to the group treatment (TG = 2 mg/kg of tramadol or MG = 0.25 mg/kg of morphine, IM).

The evaluations were performed systematically 1 (T1), 2 (T2), 3 (T3), 4 (T4), 5 (T5), and 6 (T6) hours after the end

of the patient's surgery. Only one evaluator accomplished all the evaluations. After six hours of evaluation, subcutaneous application of meloxicam (0.1 mg/kg), tramadol (2 mg/kg), and dipyrone (25 mg/kg) were performed. At all times, the occurrence of adverse effects such as mydriasis, salivation, emesis, agitation, drowsiness, or breathing difficulties were evaluated.

Statistical analyses were performed using Graph Pad Prism 7 Demo. The assumptions of normality and homogeneity of variance were tested with the Shapiro-Wilk test. Pain and sedation scores were compared between different moments in the same group by the nonparametric Friedmann test, while the groups at the same time were compared using the nonparametric Kruskal Wallis test, followed by Dunn's post-test of multiple comparisons when significant. The comparison between groups was performed using the Mann-Whitney test. Parametric data were compared between groups using a non-paired t-test, and the comparison between different moments in a group through a one-way analysis of variance, followed by the Tukey post-test of multiple comparisons. The rescue analgesia variable was analyzed considering the binomial distribution, and the odds ratio test was used to compare the differences between the groups. The level of significance considered was $p < 0.05$ for the tests performed.

3 Results and Discussion

The age of the dogs ranged from 1 to 3 years, with an average weight of 8.6 ($\pm$ 1.1) kg. There was no statistical difference on baseline parameters (HR, RR and temperature) ($p = 0.05$), time of surgery ($p = 0.05$) and anaesthesia ($p = 0.05$) between groups. In the tramadol group, the mean duration of the surgery was 15.9 ($\pm$ 8.3) minutes and in the morphine group, the mean duration of the surgery was 17,6 ($\pm$ 8.3) minutes. There was a statistical difference regarding extubation time ($p = 0.04$), in which the tramadol group showed a greater difference in extubation time (11.7 $\pm$ 2.9 min) compared to the morphine group (8.4 $\pm$ 3.8), so, TG had higher extubation time.

Regarding sedation scales, there was a statistical difference between the groups using the Valverde scale, at T3h, and by the Grint scale, at T4h and T5h time points. In both, morphine had a higher sedation score compared with tramadol. Regarding the times, in all sedation scales and in both groups, a lower degree of sedation was observed at moments T4h, T5h, and T6h when compared T1h. The sedative effect of tramadol was observed in fewer dogs compared to morphine, and this is probably due to its low affinity to the µ receptor, corroborating a previous study that reported slight sedation of tramadol in dogs (PAOLOZZI et al., 2011). In contrast, the morphine group experienced intense sedation in most dogs and for a longer time, a fact that can be explained by the fact that morphine is a pure µ agonist, with greater affinity for this receptor promoting a greater degree of sedation (GOMES et al., 2011).

The present study evaluated the analgesic efficacy of the drug tramadol in the postoperative period of ovariohysterectomy in female dogs. There were 20 dogs in the study, from those, 7 needed to receive analgesic rescue, 5 from the morphine group and 2 from the tramadol group, with statistical difference ($p = 0.021$). In the MG, one dog received analgesic rescue in T2, one in T3, two in T5, and one in T3 and T4. In the TG, one animal was rescued at T1, and another at T1 and T2. Comparing the two groups, the need for rescue analgesia in the MG were 2.15 times higher than in the TG. Tramadol showed satisfactory analgesic efficacy, demonstrated by the lower number of dogs rescued and lower scores on the analgesic scales used, when compared to morphine ($p = 0.021$).

The animals from the morphine group started analgesic rescue approximately three to six hours after their administration, coincides with their short duration when administered systematically (KUKANICH et al., 2005). Although the morphine group has shown a greater number of rescue analgesic medication when compared to the tramadol group, we must consider the half-life of the drugs in question. As the morphine half-life is shorter than tramadol, possibly the animals from the morphine group that needed rescue after 3-4 hours of the medication, probably had low plasma drug levels, which may have interfered with the results of the evaluations final moments. However, despite the limitations, in this study, it was possible to verify the tramadol analgesic effect in the postoperative period of female dogs after OH. Morphine was used as a positive control group because it is considered the standard opioid in veterinary medicine, with which all other opioids are compared in relation to their analgesic potency, and it is considered effective in the treatment of moderate to severe perioperative pain in small animals (MASTROCINQUE; FANTONI, 2003).

Regarding the adverse effects observed in the study, in the TG group, six dogs presented sedation, salivation and drowsiness from the injection until time T2, whereas only one presented mydriasis, as the other dogs had no side effects after the administration of intravenous tramadol. In the morphine group, salivation and sedation was present in all dogs at time T1 and remained in seven dogs simultaneously to persistent sedation until the time T4. Moreover, drowsiness was observed in those seven dogs after de sedation recovery, but mydriasis was not observed. So, more severe adverse effects were observed in the MG.

Regarding analgesia assessments, the tramadol group had significantly lower pain scores than the morphine group, based on the EAV scales (T6h $p = 0.034$), Glasgow (Figure 1) (T4h, $p = 0.003$; T5h, $p = 0.011$), Lascelles (T3h, $p = 0.032$; T4h, $p = 0.032$; T6h, $p = 0.010$), Colorado (T4h, $p = 0.032$; T6h, $p = 0.019$), and Guelph (T3h, $p = 0.037$; T4h, $p = 0.046$; T5h, $p = 0.013$; T6h, $p = 0.015$). On the Melbourne scale, there was no statistical difference between the groups ($p = 0.05$). Table 1 shows the median values (minimum-maximum) of pain scores obtained on analgesia scales.

Figure 1 - A: Pain score obtained by the Glasgow short form composite scale; B: pain score obtained by the Colorado scale; C: sedation score obtained by the Valverde scale; D: sedation score obtained by the Grint scale during the postoperative period of dogs treated with tramadol and morphine
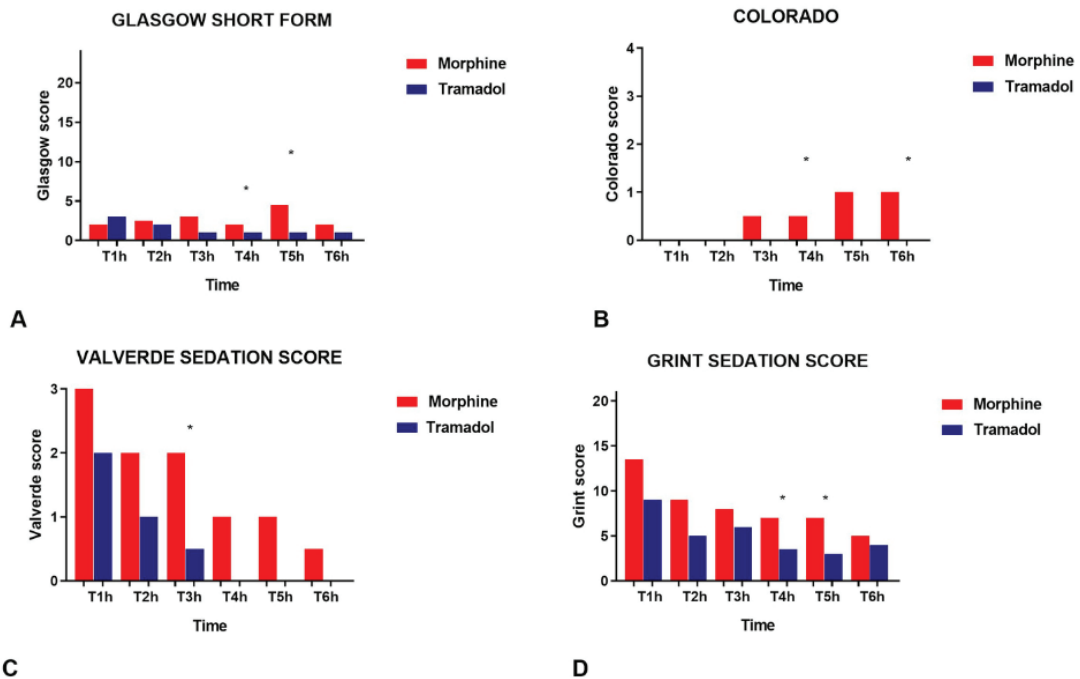
* = p <0.05 between groups.
Source: resource data.

Table 1 - Median (minimum-maximum) values of the pain scores heard on the analgesia scales

Scales	Group	T1h	T2h	T3h	T4h	T5h	T6h
Glasgow	TG	3(1-14)	2(1-12)	1(0-4)	1(0-3)*†	1(0-3)*†	1(0-3)†
	MG	2(1-5)	2.5(1-9)	3(1-8)	2(1-9)	4,5(0-9)	2(0-5)
Vas	TG	0,5(0-5)	0(0-4)	0(0-1)	0(0-1)	0(0-2)	0(0-1)*
	MG	0(0-2)	1(0-3)	1(0-3)	0,5(0-2)	1,5(0-3)	1(0-2)
Melbourne	TG	2,5(0-12)	2(0-9)	2,5(1-5)	2(1-4)	2(1-5)	2(1-8)
	MG	2(0-6)	2,5(0-6)	3(1-6)	2,5(1-5)	2,5(1-6)	4(1-7)
Colorado	TG	0(0-2)	0(0-2)	0(0-1)	0(0-0)*	0(0-1)	0(0-1)*
	MG	0(0-1)	0(0-2)	0,5(0-2)	0,5(0-2)	1(0-1)	1(0-1)
Guelph	TG	1(0-5)	0(0-4)	0(0-2)*	0(0-1)*	0(0-2)*	0(0-2)*
	MG	1(0-3)	1(0-3)	1,5(0-4)	1(0-3)	1,5(0-3)	1(0-3)
Lascelles	TG	0(0-3)	0(0-2)	0(0-0)*	0(0-0)*	0(0-1)	0(0-0)*
	MG	0(0-2)	0(0-2)	0,5(0-2)	0,5(0-2)	1(0-2)	1(0-2)

TG= tramadol group; MG= morphine group; * = different from MG (p<0.05); † = different from T1h (p<0.05)
Source: resource data.

Tramadol main metabolite, the active metabolite O-desmethyltramadol (M1), results from its metabolism by the enzymes of the P450 complex in the liver, is found in less concentration in dogs when compared to cats and humans, which led to doubt of its effectiveness in dogs (GIORGI *et al.*, 2010, KUKANICH; PAPICH, 2011; BENITEZ *et al.*, 2015). However, we may assume that the analgesic effect observed in the present study, might be due to the dose used, which is higher than in most studies; the non-opioid mechanism of action of tramadol; and the higher concentration of the metabolite N, O-desmethyltramadol (DDM) in the canine species, which can promote secondary analgesic effect (GIORGI *et al.*, 2009). In addition, the antinociceptive action of tramadol in dogs is not fully understood and may

involve effects on α2 adrenoceptors, as well as inhibition of norepinephrine reuptake, in addition to the μ receptor agonist action. Despite the low plasma concentrations of tramadol and its active metabolite, analgesic efficacy has already been reported experimentally and clinically (CARDOZO *et al.*, 2014; KAKA *et al.*, 2018; KUKANICH; PAPICH, 2011; MALEK *et al.*, 2012; MASTROCINQUE; FANTONI, 2003).

In the present study, tramadol was effective in controlling postoperative pain in female dogs undergoing ovariohysterectomy. In humans, the analgesic effect of tramadol is comparable to that of morphine (HADI *et al.*, 2006; SILVASTI *et* al., 2000). This fact emphasizes the importance of other mechanisms of action of tramadol, which are not linked to its effect on the μ receptor since the affinity of

the M1 metabolite represents only 10% of the analgesic action promoted by morphine (GROND; SABLOTZKI, 2004).

In a study by Kaka *et al.* (2018), when female dogs received tramadol, at a dose of 4 mg/kg (IV), as pre-anesthetic medication in ovariohysterectomy there was no need for analgesic rescue in any of the 12 dogs involved in the study, demonstrating the analgesic efficacy of the drug in ovariohysterectomy in female dogs. According to Cardozo *et al.* (2014), in a study where the postoperative pain assessment of orthopedic surgeries was performed, it was observed that tramadol at a dose of 4 mg/kg administered in pre anesthetic medication, had less analgesic effect compared to methadone. However, when the dogs were rescued with an increase in the 1 mg/kg dose of tramadol, there was satisfactory analgesia. Therefore, according to the results of Cardozo *et al.* (2014), we can suggest that individual dosage adjustments may be necessary to promote adequate analgesia and considering the type of painful stimulus.

In contrast, another study that compared tramadol to firocoxib in the postoperative period of orthopedic surgery, tramadol did not provide satisfactory analgesic efficacy and was inferior to firocoxib, however, we must consider that the route of administration was oral (4 to 5 mg/kg) and the drugs were administered preemptively (DAVILA *et al.,* 2013). Likewise, in enucleation surgery in dogs, carprofen provided superior analgesia to tramadol and both were also administered orally, but the opioid was administered as pre-anesthetic medication in both groups what certainly interfered with the evaluation (DELGADO *et al.,* 2014). Moreover, it is important to emphasize that the present study offered a new insight on this subject, since the administration of the tramadol was performed at the end of surgery and by the IV route, what is not commonly performed.

According to Kukanich and Papich (2004), studying only six dogs, the tramadol M1 metabolite has an elimination half-life of 1.69 ± 0.45 and 2.18 ± 0.55h following intravenous and oral administration, respectively. In addition, the maximum plasma concentrations of M1 after intravenous and oral administration were 373.91 ± 103.12 ng/mL and 449.13 ± 210.10 ng/mL, respectively. However, the tramadol metabolism in dogs is uncertain and a larger dogs population need to be evaluated to assess the pharmacokinetics routes of this drug (MCMILLAN *et al.*, 2008).

In addition, pharmacogenetics studies is an expanding field, and a few CYP metabolic enzyme pathways have been shown to be polymorphic in dogs, as there are studies that indicate high variability in the response between dogs that may be due to the variable metabolism of tramadol by cytochrome P450 enzymes, due to genetic differences, drug interactions and other extrinsic influences (MARTINEZ *et al.*, 2019).

However, according to Teixeira *et al.* (2013) in a study comparing the association of tramadol with meloxicam, tramadol with dipyrone, and tramadol alone, in which the objective was to show which drug group would be most effective in postoperative pain of unilateral mastectomy with or without ovariohysterectomy in female dogs, observed tramadol with meloxicam was found to have a lower pain score than tramadol itself, or tramadol with dipyrone, suggesting that tramadol combined with a non-steroidal anti-inflammatory result in better postoperative analgesia.

Tramadol has a great advantage over other opioids, it does not clinically alter hemodynamic and respiratory functions, and produces adequate intraoperative and postoperative analgesia. According to Paolozzi *et al.* (2011), tramadol in dogs at doses of 1, 2, and 4 mg/kg IV promoted minimal cardiorespiratory changes. Although there are reports where the use of tramadol when administered at a dose of 4 mg/kg promoted vomiting (Paolozzi *et al.*, 2011), this adverse effect did not occur in the present study.

Painful experiences can lead to a series of potentially deleterious physiological changes, such as immunosuppression, delayed wound healing, and acceleration of pathological processes; therefore, it is a moral and ethical duty to recognize and treat dogs' pain. Hence, a placebo group was not included in this study, because in addition to the aforementioned deleterious effects, it is now recognized that high postoperative pain scores are associated with a higher incidence of postoperative chronic pain (CORRELL, 2017). Thus, the authors are aware that the absence of the placebo group decreases the reliability of the results, but they are convinced that, for ethical reasons, the placebo group would not benefit the dogs involved in the study.

This study had some limitations, such as the low number of dogs, and the absence of objective measures in the assessment of patients' analgesia. However, despite the limitations, the result was consistent since all analgesia scales, except for Melbourne, presented similar results and the analgesic effect of tramadol was evident. Therefore, this work indicates the need for further studies in the field of pharmacology to assess the main mechanism of action responsible for the analgesia conferred by tramadol in dogs, so that we can use this drug more efficiently in multimodal analgesia protocols.

4 Conclusion

It was concluded that tramadol administered at a dose of 4 mg/kg intravenously, in the immediate postoperative period of female dogs that underwent ovariohysterectomy had a satisfactory analgesic effect and had less severe adverse effects.

Acknowledgments

References

BENITEZ, M.E. *et al*. Pharmacokinetics of hydrocodone and tramadol administered for control of postoperative pain in dogs following tibial plateau leveling osteotomy. *Am. J. Vet. Res*., v.76, n.9, p.763-770, 2015. doi: 10.2460/ajvr.76.9.763

CARDOZO, L.B. *et al*. Evaluation of the effects of methadone and tramadol on postoperative analgesia and serum interleukin-6 in dogs undergoing orthopedic surgery. *BMC Vet. Res*., v.6, n.10, p.194, 2014. doi:10.1186/s12917-014-0194-7

CORRELL, D. Chronic postoperative pain: recent findings in understanding and management. *F1000Res*. v.6, p.1-11, 2017. doi:10.12688/f1000research.11101.1.

DAVILA, D. *et al*. Comparison of the analgesic efficacy of perioperative firocoxib and tramadol administration in dogs undergoing tibial plateau leveling osteotomy. *J. Am. Vet. Med. Assoc*., v.243, n.2, p.225-231, 2013. doi: 10.2460/javma.243.2.225

DELGADO, C, *et al*. Carprofen provides better post-operative analgesia than tramadol in dogs after enucleation: A randomized, masked clinical trial. *J. Am. Vet. Med. Assoc*., v.245, p.1375–1381, 2014. doi: 10.2460/javma.245.12.1375

DONATI, P.A. *et* al. Efficacy of tramadol for postoperative pain management in dogs: systematic review and meta-analysis. *Vet. Anaesth. Analg*., v.48, n.3, p.283-296, 2021. doi: 10.1016/j.vaa.2021.01.003

FIRTH, A.M.; HALDANE, S.L. Development of a scale to evaluate postoperative pain in dogs. *J. Am. Vet. Med. Assoc*., v. 214, n.5, p.651-659, 1999.

GIORGI, M, *et al*. Pharmacokinetics of tramadol and metabolites after injective administrations in dogs. *Pol. J. Vet. Sci*., v.13, n.4, p.639-644, 2010. doi: 10.2478/v10181-010-0027-y

GIORGI, M. *et al*., Pharmacokinetics of tramadol and its major metabolites following rectal and intravenous administration in dogs. *N. Z. Vet. J*., v.57, n.3, p.146-52, 2009. doi: 10.1080/00480169.2009.36894

GOMES, V.H. *et al*. Comparison of the sedative effects of morphine, meperidine or fentanyl, in combination with acepromazine, in dogs. *Cienc. Rural*., v.41, p.1411-1416, 2011. doi:10.1590/S0103-84782011005000102

GRINT, N.J.; BURFORD, J.; DUGDALE, A.H. Does pethidine affect the cardiovascular and sedative effects of dexmedetomidine in dogs? *J. Small Anim. Pract*., v.50, n.2, p. 62-66, 2009. doi:10.1111/j.1748-5827.2008.00670.x.

GROND, S.; SABLOTZKI, A. Clinical pharmacology of tramadol. *Clin. Pharmacokinet*, v.43, n.13, p. 879-923, 2004. doi: 10.2165/00003088-200443130-00004

HADI, M.A. *et al*. A comparative study of intravenous patient-controlled analgesia morphine and tramadol in patients undergoing major operation. *Med. J. Malaysia*, v.61, n.5, p.570-576, 2006.

HELLYER, P.W.; ROBERTSON, S.A.; FAILS, A.D. Pain and its management. In: TRANQUILLI, W.J.; THURMON, J.C.; GRIMM, K.A. *Veterinary anesthesia and analgesia.* Blackwell Publishing: Lowa, 2007.

KAKA, U. *et al*. Pre-emptive multimodal analgesia with tramadol and ketamine-lidocaine infusion for suppression of central sensitization in a dog model of ovariohysterectomy. *J. Pain Res*., v.11, n.11, p.743-752, 2018. doi: 10.2147/JPR.S152475

KLAUMANN, P.R *et* al. Patofisiologia da dor. (Pains pathophysiology) (Portuguese) *Arch. Vet. Sci.*, v.13, p.1-12, 2008. doi.org/10.5380/avs.v13i1.11532

KUKANICH B.; PAPICH M.G. Pharmacokinetics and antinociceptive effects of oral tramadol hydrochloride administration in Greyhounds. *Am. J. Vet. Res*., v.72, n.2, p.256-262, 2011. doi: 10.2460/ajvr.72.2.256

KUKANICH, B.; LASCELLES, B.D.; PAPICH, M.G. Pharmacokinetics of morphine and plasma concentrations of morphine-6-glucuronide following morphine administration to dogs. *J. Vet. Pharmacol. Ther*., v.28, n.4, p371-376, 2005. doi: 10.1111/j.1365-2885.2005.00661.x

KUKANICH, B.; PAPICH, M.G. Pharmacokinetics of tramadol and the metabolite O-desmethyltramadol in dogs. *J. Vet. Pharmacol. Ther*., v.27, n.4, p.239-246, 2004. doi: 10.1111/j.1365-2885.2004.00578.x

LASCELLES, B.D.; BUTTERWORTH, S.J.; WATERMAN, A.E. Postoperative analgesic and sedative effects of carprofen and pethidine in dogs. *Vet. Rec*., v.134, n.8, p.187-191, 1994. doi: 10.1136/vr.134.8.187

LLOYD-THOMAS, A.R. Pain management in paediatric patients. *Br. J. Anaesth*., v.64, n.1, p.85-104, 1990. doi: 10.1093/bja/64.1.85

MALEK, S. *et al*. Effect of analgesic therapy on clinical outcome measures in a randomized controlled trial using client-owned dogs with hip osteoarthritis. *BMC Vet. Res*., v.8, n.185, 2012. doi: 10.1186/1746-6148-8-185

MARTINEZ, S.E. *et al*. Absolute Quantitation of Drug-Metabolizing Cytochrome P450 Enzymes and Accessory Proteins in Dog Liver Microsomes Using Label-Free Standard-Free Analysis Reveals Interbreed Variability. *Drug. Metab. Dispos*. v.47, n.11, p.1314-1324, 2019. doi: 10.1124/dmd.119.088070

MASTROCINQUE, S.; FANTONI, D.T. A comparison of preoperative tramadol and morphine for the control of early postoperative pain in canine ovariohysterectomy. *Vet. Anaesth. Analg*., v.30, n.4, p.220-228, 2003. doi: 10.1046/j.1467-2995.2003.00090.x.

MATHEWS, K. *et al*. Guidelines for recognition, assessment and treatment of pain: WSAVA Global Pain Council members and co-authors of this document. *J. Small Anim. Pract*., v. 55, n.6, p.10-68, 2014. doi:10.1111/jsap.12200

MATHEWS, K.A. Management of pain. *Vet. Clin. North. Am. Small Anim. Pract*., v.30, p.729-55, 2000. doi:10.1016/j.cvsm.2008.09.003

MCMILLAN, C.J. *et al*. Pharmacokinetics of intravenous tramadol in dogs. *Can, J, Vet, Res*., v.72, n.4, p.325-331, 2008.

MWANGI, W.E. *et al*. A systematic review of analgesia practices in dogs undergoing ovariohysterectomy. *Vet. World*, v.11, n.12, p.1725-1735, 2018. doi: 10.14202/vetworld.2018.1725-1735

PAOLOZZI, R.J, *et al*. Different doses of tramadol in dogs: analgesic, sedative and cardiorespiratory system actions. *Cienc. Rural*., v.41, n.8, p.1417-1423, 2011.

RAJA, S.N. *et al*. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain*., v.161, n.9, p.1976-1982, 2020. doi: 10.1097/j.pain.0000000000001939

REID, J. *et al*., Development of the short-form Glasgow Composite Measure Pain Scale (CMPS-SF) and derivation of an analgesic intervention score. *Anim. Welfare*., v.16, p.97-104, 2007.

SILVASTI, M. *et al*. Comparison of intravenous patient-controlled analgesia with tramadol versus morphine after microvascular breast reconstruction. *Eur. J. Anaesthesiol*, v.17. n.7, p.448-455, 2000. doi: 10.1046/j.1365-2346.2000.00710.x

TEIXEIRA, R.C. *et al*. Effects of tramadol alone, in combination with meloxicam or dipyrone, on postoperative pain and the analgesic requirement in dogs undergoing unilateral mastectomy with or without ovariohysterectomy. *Vet. Anaesth. Analg*., v.40, n.6, p.641-649, 2013. doi: 10.1111/vaa.12080

VALVERDE, A. *et al*. Effects of acepromazine on the incidence of vomiting associated with opioid administration in dogs. *Vet. Anaesth. Analg*., v.31, n.1, p.40-45, 2004. doi: 10.1111/j.1467-2995.2004.00128.