Different rates of tramadol infusion for peri and postoperative analgesia in dogs undergoing orthopedic surgery

[*Comparação de diferentes taxas de infusão de tramadol para analgesia peri e pós-operatória em cães submetidos a procedimentos cirúrgicos ortopédicos sob anestesia geral inalatória*]

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ABSTRACT

The study aimed to determine the continuous rate infusion of tramadol associated with peri- and postoperative analgesia for orthopedic surgeries in dogs, as well as cardiorespiratory and adverse effects. Thirty dogs aged 4.2 ± 1.2 years and weighing 15.1 ± 0.9kg were enrolled in the study, premedicated intramuscularly with acepromazine (0.04mg kg^{-1}) and tramadol (2mg kg^{-1}); anesthesia was induced with propofol and maintained with isoflurane in oxygen. Three infusion rates were compared, comprising three experimental groups: G2: 2.0mg kg^{-1} h^{-1}; G2.5: 2.5mg kg^{-1} h^{-1}; and G3: 3.0mg kg^{-1} h^{-1}. Surgery was initiated 15 minutes following the start of tramadol infusion. During anesthesia, animals were monitored in predefined time points: immediately after tracheal intubation and start of inhalation anesthesia (T0); surgical incision (TSI); final suture (TFS) and end of tramadol infusion (TEI), which was maintained for at least 120 minutes and prolonged according to the duration of surgery. Postoperative analgesia was evaluated through an interval pain scoring scale and the Melbourne pain scale. The mean time of tramadol infusion was greater than 120 minutes in all groups and no differences were found among them (141 ± 27 minutes in G2, 137 ± 27 minutes in G2.5 and 137 ± 30 minutes in G3). Perioperative analgesia was regarded as short and did not correlate with infusion rates. Tramadol infusion provided adequate analgesia with cardiorespiratory stability Analgesia was not dose-dependent, however, and residual postoperative effects were short-lasting, which warrants proper postoperative analgesia following tramadol infusion. Additional studies are required using higher infusion rates and standardized nociceptive stimulation in order to determine how doses influence tramadol analgesia and whe therthereis a limit to its effect in dogs.

Keywords: dogs, orthopedics, analgesia, opioid

RESUMO

Objetivou-se determinar a infusão de taxa contínua de tramadol associada à analgesia peri e pós-operatória para cirurgias ortopédicas em cães, além de efeitos cardiorrespiratórios e adversos. Foram utilizados 30 cães, com idade média de 4,2±1,2 anos e pesos médios de 15,1±0,9kg, pré-medicados por via intramuscular com acepromazina (0,04mg/kg) e tramadol (2mg/kg). A anestesia foi induzida com propofol e mantida com isoflurano em oxigênio. Foram comparadas três taxas de infusão, compreendendo três grupos experimentais: G2: 2,0mg/kg; G2,5: 2,5mg/kg[1]; e G3: 3,0mg/kg. A cirurgia começou 15 minutos após o início da infusão de tramadol. Durante a anestesia, os animais foram monitorados nos seguintes momentos: imediatamente após a intubação traqueal e o início da anestesia inalatória (T0); incisão cirúrgica (TSI); final de sutura (TFS) e final da infusão de tramadol (TEI), que foi mantida por, pelo menos, 120 minutos e prolongada de acordo com a duração da cirurgia. A analgesia pós-operatória foi avaliada por escalas de pontuação de dor, conforme a

escala intervalar de avaliação de dor e a escala de contagem variável de avaliação de dor da Universidade de Melbourne, a cada uma hora. O tempo médio de infusão de tramadol foi maior que 120 minutos em todos os grupos, e não foram encontradas diferenças entre elas (141±27 minutos em G2, 137±27 minutos em G2,5 e 137±30 minutos em G3). A analgesia perioperatória foi adequada na maioria dos indivíduos e a pós-operatória foi considerada curta, não correlacionada àquelas com diferentes taxas de infusão. A infusão de tramadol nas taxas estudadas produziu analgesia adequada com estabilidade cardiorrespiratória. A analgesia não foi dose dependente, no entanto os efeitos residuais pós-operatórios foram considerados curtos, o que determina a necessidade de analgesia adequada após infusão contínua de tramadol. Estudos adicionais que utilizam taxas mais elevadas de infusão de tramadol e estimulação nociceptiva padrão são necessários para determinar em que medida as doses influenciam a analgesia de tramadol e se há um limite nos seus efeitos nos cães.

Palavras-chave: cães, ortopedia, analgesia, opioide

INTRODUCTION

In the last decade, pain management has become a major concern in animal healthcare, especially in small companion animals. Pathophysiological responses are initiated with pain and comprise cardiovascular, metabolic and neuroendocrine events that contribute to slower healing processes and cause behavioral changes (Kissin, 2000; Vadivelu *et al.*, 2014). Proper recognition and treatment of pain is therefore crucial (Karrasch *et al.*, 2015), along with ethical and humane issues regarding pain management in animals. Clinical assessment of pain poses a challenge in animals due to the subjectivity, complexity and multidimensionality of the experience of pain (Paolozzi *et al.*, 2011).

Tramadol is an opioid analgesic of central action (Ide *et al.*, 2006) that has gained attention in veterinary anesthesia and analgesia due to its distinct mechanism of action, associated with less adverse effects compared to other opioids (Mastrocinque and Fantoni, 2003). Tramadol is commercialized as a racemic mixture (1:1) containing two enantiomers. It is metabolized in the liver to M1 (O-desmethyltramadol), which has a 200-time greater affinity for mu receptors compared to the original molecule (Kukanich and Papich, 2004). This metabolite also provides analgesia through inhibition of serotonin and epinephrine reuptake in the spinal cord (Karrasch *et al.*, 2015).

In view of all these mechanisms, tramadol has been indicated for management of moderate to severe pain and has been successfully used for peri- and postoperative analgesia of dogs subjected to orthopedic surgery (Yazbek and Fantoni, 2005; Vettorato *et al.*, 2010). Tramadol also produces significant reduction on minimal alveolar concentration (MAC) of volatile agents in dogs when used through constant rate infusion (CRI) (Seddigh *et al.*, 2009, Mahidol *et al.*, 2015).

This study is justified by the growing importance of pain management in animals and by the safety of tramadol as an effective analgesic with minimal adverse effects in dogs. In addition, studies regarding the use of tramadol by CRI are still scarce and, therefore, the primary objective of this study was to determine the rate of tramadol infusion associated with peri- and postoperative analgesia in dogs subjected to orthopedic surgery. The secondary aim was to determine cardiorespiratory and adverse effects the use of tramadol. Plasma concentrations of cortisol, blood glucose and blood gas variables were also assessed during tramadol infusion. The main hypothesis of the study was that tramadol infusion would suffice to maintain adequate analgesia during orthopedic procedures in dogs.

MATERIALS AND METHODS

The study followed the guidelines of CONCEA (National Council for Animal Experimentation Control), and the experimental procedure was approved by the Institutional Animal Care Committee (protocol no. 00476/2011).

Thirty dogs from the clinical care service of the institution's veterinary hospital were enrolled in the study. Dogs presented various orthopedic conditions, including long bone fractures, cranial cruciate ligament rupture, patellar luxation and hip dislocation.

Criteria for inclusion in the study were normal results on physical examination (heart rate, systolic blood pressure, respiratory rate, mucosal coloration, capillary refill time and rectal temperature), complete blood count, hepatic (alanine transaminase and alkaline phosphatase) and renal function (creatinine and urea nitrogen) and negative Leishmaniasis test (endemic region). Exclusion criteria comprised any changes on clinical tests. Animals that received previous treatment with tramadol were suspended from medications the day before each procedure. Animals were equally distributed among groups in order to achieve homogeneity of different surgeries in each group.

Prior to general anesthesia, animals were fasted for 12 hours and water was withheld for 2 hours. Baseline variables included heart rate (HR, beats minute^{-1}), respiratory rate (F_R, movement's minute^{-1}), systolic arterial blood pressure (SABP, mmHg) and rectal temperature (RT, °C). Premedication was given intramuscularly and comprised acepromazine (Acepran 1%; Acepromazine 1%; Univet, Brazil) at 0.04mg kg^{-1}, in combination with tramadol (Tramadon 50mg mL^{-1}; Tramadol 50mg mL^{-1}; Cristália chemicals and pharmaceuticals Ltda., Brazil) at 2mg kg^{-1}.

Following 20 minutes of premedication, the cephalic vein was aseptically catheterized for fluid administration (Lactated Ringer's Solution; Medical Line, Brazil) at 10mL kg^{-1} h^{-1} and for induction to anesthesia with propofol (Propovan 10mg mL^{-1}; Propofol 10mg mL^{-1};Cristália chemicals and pharmaceuticals Ltda., Brazil) at 3mg kg^{-1} and midazolam (Dormire 5mg mL^{-1}; Midazolam 5mg mL^{-1};Cristália chemicals and pharmaceuticals Ltda., Brazil) at 0.2mg kg^{-1}.

Intubation was carried out immediately after induction and the tracheal tube was coupled to a rebreathing circle system. Anesthesia was maintained with isoflurane (Isoforine; Isoflurane; Cristália chemicals and pharmaceuticals Ltda., Brazil) at variable concentrations depending on individual requirements for surgical anesthesia. End-tidal isoflurane (ET´$_{ISO}$) was monitored throughout the surgery by a gas analyzer calibrated before each procedure using a standard gas sample (Quick CalTM calibration gas; Datex-Engstrom Division Instrumentarium Corp; Finland). Following instrumentation, the

contralateral cephalic vein was catheterized for tramadol infusion, which was started after a 2mg kg^{-1} bolus and comprised different rates, or three groups: (G2) 2mg kg^{-1} h^{-1}; (G2.5) 2.5mg kg^{-1} h^{-1}; and (G3) 3mg kg^{-1} h^{-1}. Surgery was initiated 15 minutes following the start of CRI.

During anesthesia, animals were monitored at predefined time points: immediately after tracheal intubation and start of inhalation anesthesia (T0); surgical incision (TSI); final suture (TFS) and end of tramadol infusion (TEI), which was maintained for at least 120 minutes and prolonged according to the duration of surgery. In addition, other time points were defined as important moments of nociceptive stimulation, such as manipulation of the periosteum or joint (T1) and any other (T2) according to the type of surgery: (1) femur head resections comprised the use of an osteotome to remove the head of the femur and osseous incongruences; (2) osteosyntheses using external fixation or intramedullary pin comprised the use of a gauge or a bone clamp and periosteum perforation with an electric drill; (3) knee surgeries for cranial cruciate ligament rupture comprised trochlear groove deepening and periosteum perforation.

Data collection comprised the following variables: electrocardiography (ECG; Digital Electrocardiograph; TEB; Brazil), HR, F_R, esophageal temperature (ET), non-invasive systolic, mean and diastolic arterial blood pressures (SABP, DABP and MABP, respectively), end-tidal carbon dioxide tension (ET´CO_2), oxyhemoglobin saturation (SpO$_2$) and ET´$_{ISO}$. Venous blood samples were obtained from the jugular vein into lithium heparin syringes for blood lactate measurements using a portable device (Accutrend lactate; Roche Diagnostic Brazil Ltda., Brazil), for tramadol and O-desmethyl tramadol dosing through high performance liquid chromatography (HPLC) and for serum cortisol dosing through chemiluminescence. Blood lactate was measured at baseline and at all time points during general anesthesia, whereas tramadol and M1 were continuously dosed at 30-minute intervals following the end of suture until rescue analgesia was required. Serum cortisol was dosed at all time points and every hour following the end of suture until the administration of rescue analgesia as well.

Blood gas analyses were performed on venous blood samples obtained at TSI, T1, T2, TFS and TEI for assessment of arterial oxygen tension (PaO_2), arterial carbon dioxide tension ($PaCO_2$), base excess (BE), bicarbonate, glucose and electrolytes (Na^+, K^+, iCa^{2+}, and Cl^-). Analyses were performed immediately after blood sampling using a portable analyzer (i-Stat, Abbott, Brazil).

Animals were positioned over electrical pads in order to maintain body temperature above 36.5°C and recumbency was determined by the type of surgery. If signs of nociception were detected throughout the surgery (20% increase in HR, F_R or ABP compared to measurements taken before surgical incision – baseline), fentanyl (Fentanest 0,05mg/mL^{-1}; Fentanyl 0,05mg/mL^{-1}; Cristália chemicals and pharmaceuticals Ltda., Brazil) was given intravenously at 2,5µg kg^{-1} followed by a CRI at 5µg kg^{-1} h^{-1} until the end of surgery.

Postoperative evaluations were only performed on subjects who underwent tramadol CRI without need for fentanyl analgesia. Pain assessment was initiated immediately after subjects regained conscience from anesthesia and every 30 minutes (T30, T60, T90… Tn) until pain scores were reached for rescue analgesia: 3.0 for the Glasgow composite pain scale (Morton *et al.*, 2005) and 8.0 for the Melbourne pain scale (Firth e Haldane, 1999). Rescue analgesia comprised subcutaneous injection of meloxicam (Bioflac 5mg/mL^{-1}; Meloxicam 5mg/mL^{-1}; Cristália chemicals and pharmaceuticals Ltda., Brazil) at 0.2mg kg^{-1} and intravenous morphine (Dimorf 10mg/mL^{-1}; morphine 10mg/mL^{-1}; Cristália chemicals and pharmaceuticals Ltda., Brazil) at 0.1mg kg^{-1}, followed by epidural injection of 0.1mg kg^{-1} morphine in saline solution at 0.3mL kg^{-1}. Effective analgesia was defined as no requirement for additional analgesia.

Data were subjected to analysis of variance for repeated measures and mean comparisons were performed using Tukey's test. The respiratory rate was analyzed using Kruskal-Wallis' test for group comparisons and Friedman's test for time point comparisons, followed by Dunn's post-hoc test.

Variable associations were tested using chi-square test of Fisher's exact test. Time to rescue analgesia and pain scores were analyzed using Kruskal-Wallis' test for group comparisons. Statistical significance was considered when P< 0.05 and analyses were performed by SAS (Statistical Analysis System).

RESULTS

The mean age and body weight of the subjects included in G2, G2.5 and G3 were 5.3±3.6, 4.4±2.9 and 2.9±1.3 years and 14.1±9.6, 15.2±14.1 and 15.9±11.1kg, respectively. The type of surgery and time (morning/afternoon) were homogenously distributed in all groups (P= 1.0000) (Tab. 1). The duration of surgery was slightly shorter in G2.5 (76±26 minutes), although no differences were found among groups (G2: 95±31 minutes and G3: 85±47 minutes).

The total time of infusion prior to the start of surgery, which was determined to be at least 15 minutes, was 40±16, 39±15 and 39±7 minutes in G2, G2.5 and G3, respectively. During this time, patients were correctly positioned and the surgical team prepared for surgery.

The mean time of tramadol infusion was greater than 120 minutes in all groups and no differences were found among them (141±27 minutes in G2, 137±27 minutes in G2.5 and 137±30 minutes in G3).

With regard to perioperative evaluations, HR, F_R, SpO_2, SABP, MABP and DABP did not differ among groups. Electrocardiography showed no relevant changes throughout the study in all groups. Mean RT dropped compared to baseline RT, reaching a minimum mean value of 35.7±0.9°C in G3.

Blood lactate did not differ among groups, although means decreased significantly over time compared to baseline in all three groups, with 1.8±0.8mmol L^{-1} in G2; 1.7±0.7mmol L^{-1} in G2.5 and 1.5±0.5mmol L^{-1} in G3 at TFS. Serum cortisol and blood glucose did not differ among groups and a significant increase was observed over time compared to baseline (Table 2). Tramadol and M1 differed between G2.5 and G3 and peak plasma concentrations were reached at TFS. Both variables increased over time during surgery compared to the initial values at TSI (Table 3).

Table 1. Type of surgery performed in each subject inside each group

Animal	Group	Procedure
Animal 1	G2.5	Femur head resection
Animal 2	G2.0	Intramedullary pin
Animal 3	G3.0	Knee surgery*
Animal 4	G2.5	External fixation
Animal 5	G3.0	Femur head resection
Animal 6	G2.0	Femur head resection
Animal 7	G2.5	Intramedullary pin
Animal 8	G3.0	External fixation
Animal 9	G2.0	Femur head resection
Animal 10	G3.0	External fixation
Animal 11	G2.5	Femur head resection
Animal 12	G2.0	Intramedullary pin
Animal 13	G2.0	External fixation
Animal 14	G3.0	Intramedullary pin
Animal 15	G2.5	Intramedullary pin
Animal 16	G2.0	Knee surgery*
Animal 17	G3.0	Intramedullary pin
Animal 18	G2.5	External fixation
Animal 19	G3.0	Femur head resection
Animal 20	G2.5	External fixation
Animal 21	G2.0	Knee surgery*
Animal 22	G2.0	Knee surgery*
Animal 23	G2.5	Knee surgery*
Animal 24	G3.0	Femur head resection
Animal 25	G3.0	Knee surgery*
Animal 26	G2.0	Femur head resection
Animal 27	G2.5	Knee surgery*
Animal 28	G2.5	Intramedullary pin
Animal 29	G3.0	Knee surgery*
Animal 30	G2.0	External fixation

*Knee surgery: cranial cruciate ligament rupture, which comprised deepening of the trochlear groove and periosteum perforation.

Table 2. Mean (X) ± standard deviation (S) of blood glucose (mg dL^{-1}) and serum cortisol (ng dL^{-1}) of dogs subjected totramadol infusion at 2 (G2), 2.5 (G2.5) or 3 (G3) mg kg^{-1} h^{-1}

Time point	Blood glucose (X ± S)			Serum cortisol (X ± S)		
	G2	G2.5	G3	G2	G2.5	G3
Baseline	96±11	93±10	97±20	3.76±1.67	4.28±3.36	4.08±2.04
TSI	107±17	93±9	99±28	2.58±2.31	2.56±1.19	2.58±2.29
T1	133±26*	116±25*	111±27	6.97±4.10*	5.72±3.31†	6.00±3.02†
T2	133±26*	112±31*	114±30*	8.29±3.55*	7.06±3.66†	6.78±2.84†
TFS	129±28*	112±24*	105±20	6.79±1.91*	8.25±4.77*†	6.18±3.24†
TEI	129±28*	110±24	102±21	6.99±2.30*	8.73±5.45*†	5.34±2.16†

G2=G2.5=G3. *Differs from baseline according to Tukey test (P< 0.05).†Differs from TSI according to Tukey test(P< 0.05). Serum cortisol transformed to log.
TSI - surgical incision, T1 –manipulation of the periosteum or joint, T2 - important times of nociceptive stimulation,TFS - final suture and TEI - end of tramadol infusion.

Table 3. Mean (X) ± standard deviation (S) of plasma tramadol (μg mL^{-1}) and M1 (ng mL^{-1}) of dogs subjected to tramadol infusion at 2 (G2), 2.5 (G2.5) or 3 (G3) mg kg^{-1} h^{-1}

Time point	Plasma tramadol (X ± S)		
	G2	G2.5	G3
TSI	0.99±0.43	1.56±0.84	1.77±0.57[‡]
T1	1.26±0.50	1.61±0.46	2.19±0.47[‡]
T2	1.40±0.59	1.82±0.58	2.22±0.42[‡]
TFS	1.51±0.73[*]	2.00±0.64[*]	2.56±0.69[*‡]
TEI	1.42±0.59	1.95±0.63[*]	2.37±0.58[*‡]
Time point	Plasma M1 (X ± S)		
TSI	0.69±0.23	1.02±0.45[‡]	1.08±0.58[‡]
T1	0.89±0.38[*]	1.14±0.33	1.40±0.38[‡]
T2	0.90±0.44	1.21±0.41	1.43±0.36[‡]
TFS	1.07±0.45[*]	1.39±0.49[*]	1.66±0.55[*‡]
TEI	1.06±0.47[*]	1.36±0.49[*]	1.68±0.38[*‡]

*Differs from baseline according to Tukey test (P< 0.05). ‡Differs from G2 according to Tukey test (P< 0.05). Data transformed to log.
TSI - surgical incision, T1 – manipulation of the periosteum or joint, T2 - important times of nociceptive stimulation, TFS - final suture and TEI - end of tramadol infusion.

The ET´$_{ISO}$, as well as blood gas variables, did not differ among groups or time points. Values ranged from 0.7% (one animal in G2.5) to 1.8% (one animal in G3) at TSI. The need for perioperative fentanyl was not related with group or type of surgery. Most cases where fentanyl was required belonged to G3 (four animals). In addition, tramadol analgesia was more effective in osteosyntheses using external fixation compared to other surgeries. Effective analgesia was defined as no requirement for additional analgesia in 85.7% of the subjects (6/7). On the other hand, osteosyntheses performed with medullary pins showed slightly less efficacy, as tramadol CRI sufficed for 71.4% animals (5/7). During knee joint surgeries and femoral head ostectomies, which involve the periosteum and the joint capsule, tramadol sufficed for 75% (6/8) and 62.5% (5/8) of the procedures, respectively.

Postoperative pain assessment using pain scales did not differ among groups with regard to mean time to rescue analgesia (Table.4). Individually, however, results were different. Six subjects required additional analgesia during the first 30 minutes of recovery from general anesthesia. These animals received rescue analgesia immediately and were excluded from further evaluations. Pain scales (Glasgow composite pain scale and Melbourne pain scale) were used in a total of 14 subjects and no correlation was found between duration of analgesia and score. Data are presented as medians, where G2=30; 62.5=60; and G3=60 minutes. Postoperative analgesia was longer in two subjects, in which rescue analgesia was administered after 150 and 210 minutes (G3 and G2, respectively).

Table 4. Mean (X) ± standard deviation (S) and median (Med) of time to rescue analgesia (minutes) of dogs subjected to tramadol infusion at 2 (G2), 2.5 (G2.5) or 3 (G3) mg kg^{-1} h$^{-1,}$ following general anesthesia with isoflurane

Time to rescue analgesia (minutes)					
G2		G2.5		G3	
(X ± S)	Med	(X ± S)	Med	(X ± S)	Med
55.7±68.0	30	54.0±25.1	60	66.0±49.3	60

G2=G2.5=G3 Kruskal-Wallis test:P = 0.3581.

DISCUSSION

Tramadol analgesia through continuous infusion at different rates was satisfactory in most subjects undergoing different types of orthopedic surgery. However, postoperative residual analgesia was short-lived and greater infusion rates plasma concentrations of tramadol and O-desmethyltramadol were not associated with greater efficacy.

Tramadol given by CRI provided cardiovascular and respiratory stability in healthy dogs. Hypotension and respiratory depression were not observed in any subjects, corroborating other studies regarding the use of this agent by different routes and at different doses (Mastrocinque and Fantoni, 2003; Yazbek and Fantoni, 2005; McMillan *et al.*, 2008; Vettorato *et al.*, 2010). Paolozzi *et al.* (2011) have observed only a few cardiorespiratory changes that were not dose-related when using intravenous tramadol at 1, 2 and 4mg kg^{-1} in bitches undergoing ovariohysterectomy.

Tramadol is reportedly devoid of respiratory depression due to its weak interaction with opioid receptors. In addition, analgesia is potentiated by non-opioid mechanisms, which are not associated with cardiorespiratory changes (Ide *et al.*, 2006) compared to other opiates (Karrasch *et al.*, 2015).

The efficacy of analgesia with a given drug has been demonstrated in previous studies by physiological changes that indicate pain. Serum cortisol dosing was an interesting addition to this assessment in various studies, since this is a hormone that increases its levels during surgery and postoperative pain (Mastrocinque and Fantoni, 2003; Caldeira *et al.*, 2006). Cortisol levels showed an increase over time during the postoperative period, which can be related to clearance of tramadol and onset of postoperative pain.

Albuquerque *et al.* (2015) have reported higher levels of cortisol during ovariohysterectomies at the time of vessel clamping when compared to physiological levels, corroborating another study by Paolozzi *et al.* (2011) and the present study. At T1, serum cortisol increased significantly, suggesting that tramadol, regardless of the rate of infusion, did not inhibit the stress response caused by surgical trauma. However, apart from the sensation of pain, cortisol levels can vary due to other factors, such as fear, anxiety, surgical time and environment (Fox *et al.*, 1994; Vadivelu *et al.*, 2014).

Many studies have shown that tramadol produces effective analgesia through different routes and at various doses in dogs undergoing ovariohysterectomy or orthopedic surgeries (Kukanich and Papich, 2004; Yazbek and Fantoni 2005; Vettorato *et al.*, 2010). In this scenario, Benitez *et al.* (2015) compared the clinical efficacy of orally administered hydrocodone, acetaminophen and tramadol for postoperative pain management following tibial ostectomy in dogs and have not observed any differences among drugs.

In this study, perioperative analgesia provided by tramadol infusion sufficed for most procedures. No correlation was found, however, between the need for additional analgesia and the rate of tramadol infusion. This can be ascribed to the proximity of the rates used in this study (0.5mg kg^{-1} range between groups), which might not evidence differences among groups.

This study investigated plasma concentrations of tramadol at different rates of continuous infusion. Plasma concentrations can vary according to dose, route of administration and species.

Giorgi *et al.* (2010) have reported a 92% bioavailability and 80-125% bioequivalence of tramadol. After intramuscular administration, tramadol reached a peak of 2.52μg mL^{-1} at 0.34 hours. There were no differences between IM and IV administration, and the effective plasma concentration was reached after a few minutes, lasting for 6 to 7 hours in both cases.

McMillan *et al.* (2008) have investigated the pharmacokinetics of IV tramadol and M1 in dogs and have reported short elimination half-life, which corroborates the findings of Kukanich and Papich (2004) of 1.28, 2.04 and 1.36 hours after tramadol administration at 1, 2 and 4mg kg^{-1}, respectively. Those results are similar to the findings of this study, where plasma concentrations of tramadol and M1 were low, indicating rapid elimination.

Longer elimination times were observed by Itami *et al.* (2016) when investigating the pharmacokinetics of intravenous tramadol. Values varied from 953.1±292.4 to 1702.3±439.6mg kg^{-1} in young and middle-aged animals, respectively.

One study regarding the influence of genes on M1 formation has showed that low concentrations of M1 are associated with high levels of M2 and are mediated respectively by CYP2D15 and CYP2B11 / CYP3A12. Furthermore, Giorgi *et al.* (2010) have found low M1 concentrations and similar levels of other metabolites after both IV and IM administration.

Surgical planes of anesthesia are usually at 1.2 to 1.4 times the MAC, which are close to 1.69% of isoflurane in dogs (Figueiró *et al.*, 2016). Vettorato *et al.* (2010) have observed values between 1.3 and 1.4% (approximately 1 MAC) at the start of surgery with tramadol analgesia, corroborating another study reporting lower ET'_{ISO} after tramadol analgesia in dogs (Mastrocinque and Fantoni, 2003). It is worth noting that the type of pain (somatic vs. visceral pain) and surgery were different between these two studies and thus comparisons might not reflect real similarities.

The anesthetic requirement was not correlated with different rates of tramadol infusion in this study. The lowest and highest rates were respectively associated with reductions of 26±8% and 36±12% on the ET'_{ISO}. Although not statistically significant, the highest rate seemingly caused a greater reduction compared to the lowest rate of tramadol infusion.

Seddigh *et al.* (2009) have observed significant reduction on sevoflurane concentrations with CRI of tramadol at two rates: (1) 1.5mg kg^{-1} bolus followed by 1.3mg kg^{-1} h^{-1}; and (2) 3mg kg^{-1} bolus followed by 2.6mg kg^{-1} h^{-1}. Another study comparing a combination of tramadol and morphine to morphine alone has demonstrated a significant decrease in the end-tidal concentration of sevoflurane with the combined opioids (Mahidol *et al.*, 2015).

Recognizing and quantifying pain still poses a challenge for many professionals (Vettorato *et al.*, 2010). The ideal pain scale should be objective, reliable and easy to apply. In this study, two already validated scales were used

and results were useful for pain recognition. Scales were not different in identifying the time to administer rescue analgesia. Six subjects needed additional analgesia shortly after recovery (30 to 60 minutes). This demonstrates the short duration of tramadol residual analgesia and warrants the need for postoperative analgesia following surgery with tramadol infusion.

The short period of residual analgesia can be explained by pharmacokinetic characteristics of tramadol. Studies investigating wider and more diversified populations are warranted in order to determine the true prevalence of M1 and whether tramadol analgesia is dose-dependent. This would then clarify possible metabolic differences that might interfere with the degree of analgesia, as seen in human populations.

In this study, adverse reactions such as excitation or vomiting were not observed even with the highest rate of infusion. Animals in G3 received a total of 10mg kg^{-1} of tramadol, including premedication, bolus and the 2-hour CRI. A few studies report considerable incidence of vomiting even at low doses (Kukanich and Papich, 2004). Paolozzi *et al.* (2011) have observed vomiting in 50% of dogs that received intravenous tramadol at 4mg kg^{-1}, but none at 1 and 2mg kg^{-1}, which suggests that this effect might be related to higher doses. Other studies report low incidence or absence of adverse reactions to tramadol in dogs (Ide *et al.*, 2006; Vettorato *et al.*, 2010).

The findings of this study demonstrate the success of tramadol through continuous rate infusion for orthopedic procedures in dogs. However, due to the small number of subjects and the variability of nociceptive stimuli, additional studies using a higher number of subjects and standardized stimulation are required to effectively demonstrate the effects of tramadol for perioperative analgesia in dogs.

CONCLUSIONS

Constant rate infusion of tramadol at the studied rates produced adequate analgesia associated with cardiorespiratory stability and no adverse effects in most dogs undergoing orthopedic surgery. Analgesia was not dose-dependent, however, and postoperative residual effects were short-lived, which warrants proper postoperative analgesia following tramadol infusion. The lowest infusion rate can therefore be used for

most orthopedic surgeries in dogs. This study is the first regarding continuous infusion of tramadol for perioperative analgesia in the canine species. Additional studies using higher rates of tramadol infusion and standardized nociceptive stimulation are required in order to determine to what degree doses influence tramadol analgesia and whether there is a limit to its effects in dogs.

ACKNOWLEDGEMENTS

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