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Pre-emptive methadone or tramadol analgesia for mastectomy and ovariohysterectomy in bitches¤

Analgesia preventiva con tramadol o metadona para mastectomia y ovario histerectomía en perras

Analgesia preventiva com tramadol ou metadona para mastectomia e ováriohisterectomia em cadelas

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Abstract

Background: mastectomy and ovariohysterectomy (OVH) in bitches are critical surgeries and pain control can be challenging. **Objective:** to evaluate the efficacy of pre-emptive analgesia with methadone (MET) or tramadol (TRA) in postoperative pain intensity, cardiorespiratory effects, and anaesthetic/analgesic consumption in female dogs undergoing mastectomy and OVH. **Methods:** a prospective randomized blind clinical trial was used to evaluate 48 bitches of various breeds, aged 10 ± 3.7 years, weighing 16 ± 12 Kg, and with multiple mammary tumours. The animals were distributed in two groups: TRA group received 5 mg/Kg tramadol and MET group 0.5 mg/Kg methadone intramuscularly, 10 min prior to anaesthesia induction with propofol followed by maintenance with isoflurane. Heart (HR) and respiratory (RR) rates, mean arterial pressure (MAP), propofol induction dose (PID), oxyhemoglobin saturation (SpO_2), end-tidal isoflurane concentration (EtISO), and carbon dioxide pressure ($EtCO_2$) were measured during the intra-operative period. Post-operative pain was evaluated for 12 h and rated according to the Melbourne scale. Rescue analgesia (0.5 mg/Kg methadone, 2 mg/Kg lidocaine, or 0.01 mg/Kg/min ketamine IV) was given when necessary and post-operative analgesic consumption recorded. Statistical tests were used to compare treatments. **Results:** rescue analgesia requirements, pain score, PID and analgesic consumption were significantly lower ($p<0.05$) in MET group. The HR was higher in TRA group, while $EtCO_2$ and MAP were higher in MET group ($p<0.05$). **Conclusion:** methadone was more effective than tramadol in pre-emptive analgesia but not completely adequate on controlling pain in bitches subjected to

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unilateral mastectomy and OVH. Methadone led to lower cardiovascular depression and lower propofol dose required for anesthesia induction. However, increased $EtCO_2$ and special care with patient ventilation is advised.

Keywords: *anesthesia, canine, hypercapnia, opioids.*

Resumen

Antecedentes: la mastectomía en perras es un procedimiento severamente álgido y el control del dolor es un desafío. **Objetivo:** evaluar la eficacia del tratamiento analgésico preventivo con metadona (MET) o tramadol (TRA) sobre la intensidad del dolor postoperatorio, parámetros cardiorrespiratorios y consumo de anestésicos/analgésicos en perras sometidas a ovariohisterectomía (OVH) y mastectomía. **Métodos:** ensayo clínico prospectivo aleatorizado ciego en 48 perras de diversas razas, edad 10 ± 3,7, peso corporal 16 ± 12 Kg y con múltiples tumores mamarios. Los animales fueron distribuidos en dos grupos: el grupo TRA recibió 5 mg/Kg de tramadol y el grupo MET 0,5 mg/Kg de metadona por vía intramuscular 10 min antes de inducir anestesia con propofol seguido de mantenimiento con isofluorano. Las variables evaluadas fueron: frecuencia cardíaca (HR), respiratoria (RR), presión arterial media (MAP), dosis de inducción con propofol (PID), saturación de oxihemoglobina (SpO_2), concentración de isofluorano (EtISO) y presión de dióxido de carbono ($EtCO_2$) medidos durante el proceso intra-operativo. El dolor postoperatorio fue evaluado de acuerdo con la escala de Melbourne durante 12 h. Analgesia de rescate (metadona 0.5 mg/Kg, lidocaína 2 mg/Kg, o ketamina 0.01 mg/Kg/min IV) se suministró cuando se consideró necesario, y se registró el consumo de analgésico posterior a la cirugia. Se aplicaron pruebas estadísticas para comparar los tratamientos. **Resultados:** los requerimientos de rescate analgésico, intensidad del dolor, PID y consumo analgésico fueron significativamente menores ($p<0,05$) en el grupo MET. La HR fue mayor en el grupo TRA, mientras que $EtCO_2$ y MAP fueron mayores en el grupo MET ($p<0,05$). **Conclusión:** la administración preventiva de MET es más eficaz que el tramadol, pero no completamente adecuada para el control del dolor posoperatorio en perras sometidas a mastectomia unilateral y OVH. La metadona promueve menor depresión cardiovascular y requerimiento de propofol para inducción anestésica. Sin embargo, incrementa la $EtCO_2$ por lo que se recomienda cuidado especial con la ventilación de estos pacientes.

Palabras clave: *anestesia, canino, hipercapnia, opioide.*

Resumo

Antecedentes: a mastectomia em cadelas é um procedimento severamente álgido e o controle da dor é um desafio. **Objetivo:** avaliar a eficácia da analgesia preventiva com metadona (MET) ou tramadol (TRA)sob intensidade da dor pós-operatória, parâmetros cardiorrespiratórios e consumo anestésico/analgésico em cadelas submetidas à ovariohisterectomia e mastectomia. **Métodos:** ensaio clínico prospectivo cego randomizado em 48 cadelas, de diferentes raças, idade 10 ± 3,7 anos, peso 16 ± 12 Kg com tumores mamários múltiplos. Os animais foram distribuídos em dois grupos: grupo TRA, tramadol 5 mg/Kg e grupo MET, metadona 0,5 mg/Kg por via intramuscular, administrados 10 min antes da indução anestésica com propofol e manutenção com isofluorano. As variáveis mensuradas foram: frequência cardíaca (FC), respiratória (fR), pressão arterial média (PAM), dose de indução propofol (PID), saturação da oxihemoglobina (SpO_2), concentração de isofluorano (EtISO) e pressão de dióxido de carbono ($EtCO_2$) ao final da expiração. A dor pós-operatória foi avaliada durante 12 h com a escala de Melbourne. A necessidade de resgate (metadona 0,5 mg/Kg, lidocaína 2 mg/Kg, ou cetamina 0,01 mg/Kg/min IV) analgésico e o consumo pós-operatório de analgésicos foram registrados. Testes estatísticos foram utilizados para comparar os tratamentos. **Resultados:** a necessidade de resgate analgésico, escore de dor, PID e o consumo de analgésicos foram menores ($p<0,05$) no grupo MET. A FC maior no grupo TRA, enquanto $EtCO_2$ e PAM maiores no grupo MET ($p<0,05$). **Conclusões:** a administração preventiva de metadona foi mais eficaz, mas não totalmente adequada para o controle da dor pós-operatória do que o tramadol, promovendo redução na depressão cardiovascular e o requerimento de propofol para indução da anestesia. No entanto, aumentou a $EtCO_2$, recomendando cuidado especial com a ventilação destes pacientes.

Palavras chave: *anestesia, canino, hipercapnia, opióide.*

Introduction

Post-operative pain hinders recovery, slows wound healing, causes immunosuppression, impairs homeostasis and metabolism, and increases tissues catabolism (Bufalari *et al*., 2007). The increase in circulatory catecholamine is responsible for electrolytic, hemodynamic, and neuroendocrine

changes (Desborough, 2005). Most anaesthetic drugs do not eliminate the neuronal processes involved with pain (Duarte and Saraiva, 2005), thus, opioid pre-emptive analgesia can play an important role in preventing central sensitization (Wordliczek *et al*., 2002) and reduce the magnitude and duration of post-operative pain.

Unilateral mastectomy is the treatment of choice for mammary tumours in bitches (Stratmann *et al*., 2008) and it consists of complete surgical removal of one mammary gland chain, adjacent tissues, and lymph nodes. This technique results in an extremely painful post-operative period (Lana *et al*., 2007). Preemptive analgesic treatment in these patients can be challenging due to surgical manipulation and aggression on different tissues, and the advanced age of bitches usually affected by mammary tumours (Papich, 2000).

Methadone is a mu (μ), delta (δ), and kappa (κ) opioid receptors agonist; N-methyl-D-aspartate (NMDA) antagonist; and 5-hydroxytryptamine (5-HT) and norepinephrine reuptake inhibitor, with similar potency to morphine (1:1). Tramadol is a weak μ receptor agonist and 5-HT and noradrenaline reuptake inhibitor, with ten times lower potency than morphine (1:10). These drugs act on different stages of the nociceptive pathway, with proven efficacy and few side effects in dogs (Pereira *et al*., 2001; Pereira *et al*., 2013).

These analgesics are presented as appropriate therapeutic options in the prevention and control of post-operative pain derived from aggressive surgical procedures in dogs (Mastrocinque and Fantoni, 2003; Pereira *et al*., 2013; Teixeira *et al*., 2013; Cardozo *et al*., 2014). However, due to the importance of NMDA receptors on central sensitization pathophysiology (Sarrau *et al*., 2007), we hypothesize that methadone could provide acceptable analgesia, maintain cardiorespiratory physiology, and lead to less anesthetic consumption than tramadol. Thus, the aim of this study was to compare the efficacy of pre-emptive methadone or tramadol analgesia on post-operative pain control, anaesthetic/analgesic consumption and intra-operative cardiorespiratory effects in bitches subjected to therapeutic ovariohysterectomy and unilateral mastectomy.

Material and Methods

Ethical considerations

This study was approved by the Ethics Committee on the Use of Animals (CEUA) of the UNESP- Univ. Estadual Paulista (protocol no. 9189/2012). Dog owners were required to sign an informed consent agreement and commit to provide the recommended post-operative care. The animals were hospitalized for 2 days, closely monitored, and re-assessed every 5 days until suture removal at 10 days post-surgery. Patients were discharged following complete clinical recovery.

Experimental design

To reach a 75% statistical power (Based on pilot study results and calculated with Minitab 16® software), this study analysed 48 bitches (n = 48) of various breeds that were admitted for unilateral mastectomy as treatment for mammary tumours. The inclusion criteria were: The American Society of Anesthesiologists (ASA) Physical Status ASA I and II; normal values for complete blood count, alanine aminotransferase, blood urea nitrogen, creatinine, and total plasma proteins; absence of hypertension, arrhythmogenic cardiomyopathy, dilated congestive heart failure, history of endocrine disorders, and no analgesic or anti-inflammatory treatment for at least two weeks prior to the surgical procedure. A prospective randomized blinded clinical trial was used. Food and water were removed 12 and 2 hours prior to surgery, respectively.

Prior to initial manipulation and drugs administration (time 0), heart (HR) and respiratory rates (RR) were determined by thoracic auscultation. The right cephalic vein was cannulated with a 20-gauge catheter for saline solution infusion at 10 mL/Kg/h and 30 mg/Kg cephalothin (IV) administration (ABL-Antibióticos do Brasil, Cosmópolis, Brazil)**.** The dogs were randomly (raffle) distributed into two experimental groups (n = 24): the TRA group received 5 mg/Kg tramadol (Cristalia Laboratories, Itapira, Brazil) and the MET group 0.5 mg/Kg methadone (Cristalia Laboratories, Itapira, Brazil) intramuscularly (IM), diluted in saline to a final volume of 0.1 mL/Kg. The anaesthetist was unaware of which premedication had been administered.

Ten min later (Giorgi *et al* 2010; Slingsby *et al*., 2015), anaesthesia was induced by intravenous (IV) administration of 2 mg/Kg propofol boluses (Cristalia Laboratories, Itapira, Brazil), repeated every 60 sec until loss of palpebral reflex. The total propofol induction dose (PID) was recorded. The animals were intubated with an appropriate (in size) orotracheal tube and anaesthesia maintained with isoflurane in oxygen (FiO_2 = 1.0; 100 mL/Kg/min) via a circle breathing circuit with spontaneous ventilation. The anaesthetist adjusted the vaporizer to maintain an adequate surgical anaesthesia plane based on standardized anaesthesia parameters: rostroventral rotation of the eye, absence of palpebral and pupillary reflex, and maintenance of mean arterial pressure (MAP > 60 mmHg). A 22-gauge catheter was inserted in the caudal auricular artery for invasive blood pressure measurement.

After anaesthetic stabilization (time 10 min), the following parameters were evaluated using a multiparametric monitor (DX2023®, Dixtal Biomedical Industry Ltd, São Paulo, Brazil): HR, RR, MAP, oxyhemoglobin saturation (SpO_2), end-tidal isoflurane concentration (EtISO), and carbon dioxide pressure ($EtCO_2$). Subsequently, and at least 20 min after analgesics administration (time 20 min), the OVH procedure was initiated and unilateral mastectomy performed by the same experienced surgical team. The same parameters were then recorded every 10 min (time 20 to 110 min), until the end of the surgical procedure. Electrocardiographic and physical parameters (temperature, capillary refill time, mucous membrane colour) were continuously monitored during anaesthesia and anaesthetic intercurrences recorded and treated accordingly.

Once the surgical procedure was over, isoflurane anaesthesia was discontinued and extubation was made after laryngeal reflex recovery. Animals were placed in individual recovery cages where post-operative pain was rated by a trained evaluator (blinded for analgesic treatment) according to the University of Melbourne Pain Scale (Firth and Haldane, 1999) and recorded for 12 hours: every 30 min during the first 4 hours after extubation and then every hour for the subsequent 8 hours. If the pain score was equal or greater than 12, rescue analgesia with 0.5 mg/Kg methadone IV was given. Pain evaluation continued in all patients (data were not included in pain score after rescue) and if it was subsequently determined that clinical analgesia was needed, 2 mg/Kg lidocaine (Cristalia Laboratories, Itapira, Brazil) IV was administered, followed by continuous infusion of 0.01 mg/Kg/min ketamine for at least one hour (Ceva Animal Health, Paulínia, Brazil). Post-operative analgesics consumption (PAC) was calculated based on the number of applications required by each patient. At the end of the 12-h pain evaluation period, 4 mg/Kg tramadol and 0.2 mg/Kg meloxicam IM (Cristalia Laboratories, Itapira, Brazil) were administered to all animals. Patients were discharged on the next day and recommendations given on the medications to be used.

Statistical analyses

Minitab 16 software (Minitab Inc. State College, USA) was used for statistical analysis. For cardiorespiratory parameters, normality of residuals and homoscedasticity of variances were previously tested (Shapiro test, variance test) and real or transformed data were compared between groups by repeated measures ANOVA and Tukey's hoc-test. Anaesthesia complications between groups were compared by Chi-square test. EtISO, pain score, and analgesic consumption were compared by Friedman test and Dunns hoc-test. Rescue analgesia in time was compared by Kaplan Meier survival test ($p<0.05$).

Results

Age, body weight, and anaesthetic, surgical, and extubation times (Table 1) were similar ($p>0.05$) between groups. Anaesthetic complications that required intervention, such as clinical cardiorespiratory depression and cardiac arrhythmias (sinus bradycardia and atrioventricular block) were observed in 19% (9/48) of the bitches. There was no significant relationship ($p>0.05$) between these complications and the analgesic drugs used (Table 1). Animals that required treatment for these complications were removed from cardiovascular evaluation and all interventions were successful.

Table 1. Mean ± SD of clinical parameters of bitches pre-medicated with methadone (MET) or tramadol (TRA) prior to ovariohysterectomy and unilateral mastectomy.

Clinical parameters	Group	
	MET	TRA
Age (years)	9.8 ± 1.1	9.9 ± 0.9
Body weight (Kg)	18.6 ± 4.1	17.1 ± 3.5
Surgical time (min)	117.7 ± 2.4	117.3 ± 3.4
Anaesthetic time (min)	142.8 ± 9.3	140.3 ± 13.1
Extubation time (min)	7.8 ± 2.1	7.2 ± 2.6
Anaesthetic complications (n°)	5	4

HR remained within reference values throughout the experimental period, with no significant difference between times or treatments ($p>0.05$), except at 10 min of evaluation (HR>120 beats/min), when tachycardia was present in the TRA group ($p = 0.03$; Figure 1a). MAP was significantly higher ($p = 0.02$) in the MET group during min 10, 70, 90, and 100 (Figure 1b).

No significant difference ($p>0.05$) was observed in SpO_2 between groups at any given time. The RR was similar between the groups, although the baseline value (0 min) was significantly greater ($p = 0.04$) than the subsequent times in both groups (Figure 2a). The $EtCO_2$ was significantly higher ($p = 0.04$) in MET than TRA at 20, 40, 50, 60, 70, and 80 min (Figure 2b). PID was signif icantly lower ($p<0.001$) in MET (5.4 ± 1.1 mg/Kg) than in TRA group (6.9 ± 1.2 mg/Kg; Figure 3a); however, no significant difference ($p>0.05$) in EtISO was observed between groups (Figure 3b).

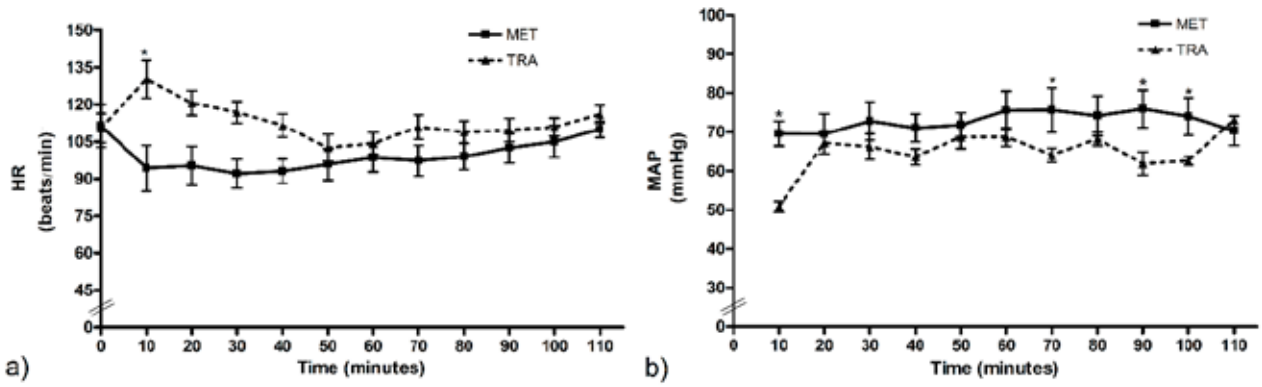

Figure 1. Mean ± SD of (a) heart rate (HR beats/min) and (b) mean arterial pressure (MAP mmHg) of bitches pre-medicated with methadone (MET) or tramadol (TRA) prior to ovariohysterectomy and unilateral mastectomy. *Significant difference between groups ($p<0.05$).

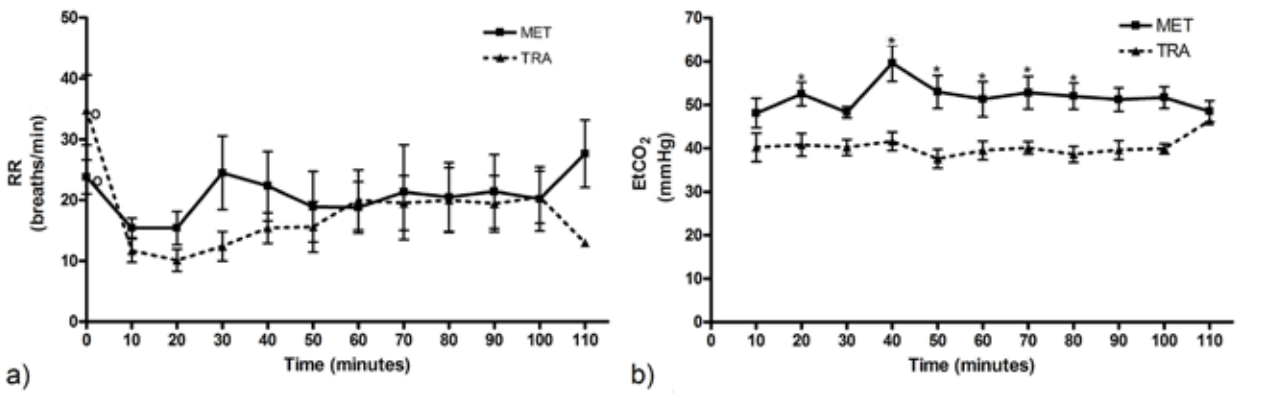

Figure 2. Mean ± SD of (a) respiratory rate (RR breaths/min) and (b) end-tidal carbon dioxide pressure ($EtCO_2$ mmHg) of bitches pre-medicated with methadone (MET) or tramadol (TRA) prior to ovariohysterectomy and unilateral mastectomy. *Significant difference between groups ($p<0.05$).

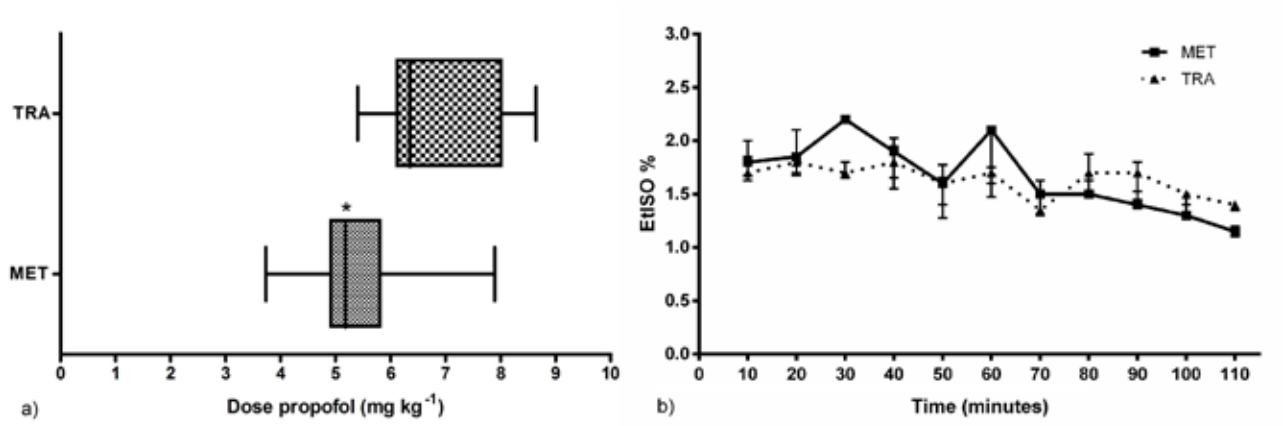

Figure 3. Median ± IQR of (a) propofol induction dose (mg/Kg) and (b) end-tidal isoflurane concentration (EtISO %) of bitches pre-medicated with methadone (MET) or tramadol (TRA) prior to ovariohysterectomy and unilateral mastectomy. *Significant difference between groups ($p<0.05$).

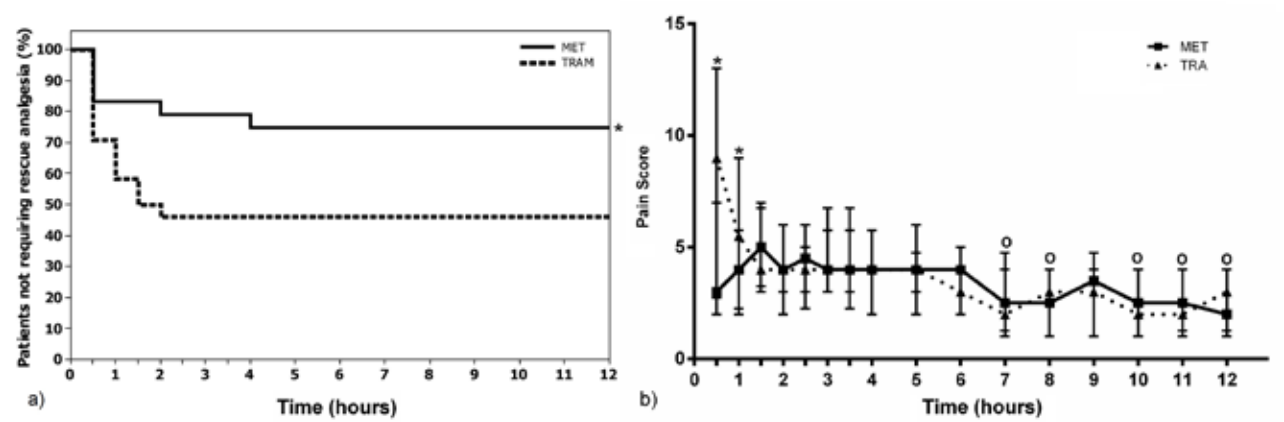

Figure 4. a) Kaplan Meier survival curves for rescue analgesia need and b) median ± IQR of pain score according to the University of Melbourne pain scale within the first 12 hours following ovariohysterectomy and unilateral mastectomy in bitches pre-medicated with methadone (MET) or tramadol (TRA). *Significant difference between groups. °Significant difference from the initial time ($p<0.05$).

Post-operative rescue analgesia requirements were significantly lower ($p = 0.04$) in MET (6/24 animals) than in TRA (13/24 animals) (Figure 4a). Pain intensity was significantly greater ($p = 0.04$) during the first hour in the TRA and decreased significantly ($p<0.01$) in both groups after 7 hours (Figure 4b). PAC was significantly lower ($p<0.01$) in MET (0.4 ± 0.3 applications) than in TRA (1.25 ± 0.7 applications).

Discussion

Pre-emptive methadone administration resulted in superior post-operative pain control than tramadol; however, it was not sufficient as solo analgesia in bitches submitted to OVH and mastectomy. Methadone resulted in fewer rescue analgesia requirements, less post-operatory analgesic consumption, and better post-operative pain scores than pre-emptive tramadol. The findings from this study corroborate the results of Cardozo *et al*. (2014), who compared tramadol to two different doses of methadone (0.5-0.7 mg/Kg) in dogs subjected to orthopaedic surgery. This effect may be attributed to the wide action of methadone on the nociceptive pathway, giving it superior anti-nociceptive potency and duration (Gourlay *et al*. 1982; Sarrau *et al*., 2007), thus leading to a more effective block of central sensitization (Dyson, 2008; Gottschalk *et al*., 2011).

The propofol sparring effect observed in the MET group (20%) has been described for other opioids (Short and Bufalari 1999; Covey-Crump and Murison 2008; Kaur *et al*., 2013) and for the methadone/dexmedetomidine association (Canfrán *et al*., 2016) and can be attributed to the strong sedative effect of methadone on dogs (Monteiro *et al.,* 2009), which was not observed when tramadol was used. However, the sedation in these animals was not evaluated and is a limiting factor in the present study. In contrast, isoflurane requirements were similar in both groups corroborating the results by Leibetseder *et al*. (2006) and Guedes *et al.* (2005) in dogs undergoing surgical procedures.

The two analgesics examined in this study resulted in different cardiovascular effects. The HR was significantly higher and MAP lower in the TRA group compared to the MET group at time 10 (anaesthetic stabilization) and the values were considered outside normal clinical ranges (MAP < 65 mmHg and HR > 120 bpm), concluding that animals experienced clinical hypotension and reflex tachycardia. This could be due to the higher PID used in this group (6.9 ± 1.2 mg/Kg) as propofol causes a dose-dependent hypotensive effect (Branson, 2007) in addition to the hypotensive effect related to the high doses of tramadol (≥ 5 mg/Kg) administered, causing an increased release of nitric oxide in the vascular endothelium (Raimundo *et al*., 2008; Monteiro *et al*., 2009). On the other hand, the MET group exhibited significantly higher MAP at certain times (10, 70, 90, 100 min) and lower HR (non-significant 10 to 50 min) than the TRA group. However, these parameters are considered to be within the expected ranges and are in agreement with Pereira *et al*. (2013) and Cardozo *et al*. (2014). The cardiovascular effects of methadone are attributed to elevated blood arginine-vasopressin levels that increase peripheral vascular resistance and, consequently, MAP elevation and reflexive HR decrease (Hellebrekers *et al.,* 1989; Maiante *et al*., 2008). Nevertheless, the lack of a significant difference in HR between groups after surgical manipulation (20 min) can be explained by the incomplete block of noxious stimuli, which enables the release of catecholamine (Desborough, 2005; Leibetseder *et al*., 2006).

Due to institutional limitations, blood gas analysis was not performed and thus, $EtCO_2$ and SpO_2 measurements were used to estimate ventilation and oxygenation (Grosenbaugh and Muir, 1998). Clinical hypercapnia ($EtCO_2$ > 45 mmHg) was present in the MET group for most of the study period. This alteration reflects respiratory depression, a common dose-dependent side effect of pure agonist opioids that can be exacerbated by anaesthetics (Papich, 2000). Pereira *et al*. (2013) did not observe changes in the respiratory parameters of dogs that received methadone, probably due to the lower dose used (0.3 mg/Kg). Although $EtCO_2$ was significantly higher in MET group, the expected physiological variation in RR was not observed, similarly to the results reported by Leibetseder *et al*. (2006).

The drugs used in this study had no effect on the prevalence of anaesthetic complications. Credie *et al*. (2010) reported bradycardia, sinus arrest, and ventricular escape rhythm when methadone was used, corroborating with cardiac depression and arrhythmias observed in the present study. However, studies using tramadol have reported no clinical complications (Mastrocinque and Fantoni, 2003; Monteiro *et al*., 2009) and the different results observed in this study were probably due to the high intensity of the surgical pain stimuli, which promotes the release of catecholamine (Desborough, 2005).

It can be concluded that methadone was more effective than tramadol in pre-emptive analgesia but not completely adequate on controlling pain in bitches subjected to unilateral mastectomy and OVH. Furthermore, methadone reduces propofol induction dose and analgesic consumption, while maintaining adequate blood pressure. These properties render methadone a good drug for multimodal anaesthesia in this type of procedures; however, it should be associated to others analgesic drugs for better post-operative pain management. Methadone alone can lead to significant clinical hypercapnia, thus special ventilation care is advised.

Conflicts of interest

The authors declare they have no conflicts of interest with regard to the work presented in this report.

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