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RESEARCH ARTICLE

Comparative Evaluation of Methadone Administration at Different Periods in Bitches Undergoing Mastectomy

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ABSTRACT

This study aimed to evaluate pain, anesthetic requirements, and cardiorespiratory variables in bitches subjected to mastectomy that received methadone pre, trans, or postoperatively. Thirty-six bitches undergoing unilateral mastectomy were randomly allocated into 3 groups in a prospective blind clinical trial. Preoperative group (PRE) received 0.5 mg/kg methadone IM 20 minutes prior to anesthesia induction and placebo at the trans and postoperative periods, transoperative group (TRA) received 0.5 mg/kg methadone IM 20 minutes after skin incision and placebo at others periods, and the postoperative group (POS) received 0.5 mg/kg methadone IM once surgery was completed and placebo at other periods. Propofol dose was needed for anesthetic induction (PDI). Heart (HR) and respiratory rate (fR), mean arterial pressure (MAP), blood oxygen saturation (SpO_2), end tidal CO_2 pressure ($EtCO_2$), and isoflurane concentration (EtISO) were evaluated every 10 minutes until the end of the surgical procedure. Pain intensity (Melbourne Pain Scale) and rescue analgesia requirements were evaluated for six hours after surgery. Postoperative pain was lower in PRE and TRA (P=0.036); however, no differences (P=0.410) were observed in postoperative rescue analgesia requirements between the groups, even though only 8% of PRE and TRA patients required it against 25% in POS. MAP and $EtCO_2$ were higher (P<0.001) in PRE and TRA, while EtISO was lower (P<0.001). PRE showed lower PDI (P=0.016) and HR (P=0.003). In conclusion, pre and transoperative methadone administration result in preemptive pain relief, reduce anesthetic requirements, and consequently cause less cardiovascular depression in bitches undergoing mastectomy, although it possibly leads to hypoventilation.

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INTRODUCTION

The curative treatment recommended for canine mammary tumors is surgical removal of the mammary glands and lymph nodes (Stratmann *et al*., 2008). This procedure results in an extremely painful postoperative period (Ogilvie and Moore, 2006); which in turn prolongs the recovery time, slows wound healing, and depresses the immune profile, predisposing the animal to clinical complications (Gaynor, 1999). Thus, transoperative analgesia is of paramount importance and has been of great interest in medical research as it has been demonstrated that general anesthesia does not block central or peripheral pain-responsive neuronal processes (Dyson, 2008).

Analgesics applied before (preoperative or preemptive) or during (intraoperative or preventive) surgical stimulation are believed to decrease postoperative pain, hypersensitivity, postoperative analgesic consumption, and induction and maintenance anesthetic requirements; allowing a balanced anesthesia that reduces the cardiorespiratory depression induced by anesthetic drugs (Dyson, 2008). In view of these advantages, experimental studies have shown that pre or intraoperative analgesic protocols were more effective in reducing postoperative pain than post injury administration. However, clinical trials have been contradictory, probably due to the multiple analgesics pathways and varied lasting effects (Møiniche *et al*., 2002).

Methadone is a broad action synthetic opioid, an opioid receptor agonist, NMDA receptor non-competitive antagonist, reuptake inhibitor of norepinephrine, and serotonin and nicotinic receptor blocker. These properties give methadone an outstanding action, as it inhibits central perception of nociception, effectively blocks sensitization, and directly modulates pain conduction pathways (Xiao *et al*., 2001). Furthermore, it has been proven effective as a surgical analgesic in dogs at doses ranging from 0.3 to 0.7 mg/kg given intramuscularly, intravenously, or epidurally; producing lasting analgesic effect (>6h) and causing limited cardiorespiratory alterations (Leibetseder *et al*., 2006; Pereira *et al*., 2013; Cardozo *et al*., 2014; Uscategui *et al*., 2017).

Due to the complex effects of methadone on the nociceptive process and its proven efficacy, potency, and duration as a surgical analgesic; the present study was designed to evaluate whether pre, trans, or postoperative administration of methadone have some impact on pain control, anesthetic requirements, and cardiorespiratory function in bitches undergoing unilateral mastectomy.

MATERIALS AND METHODS

Ethical considerations: The study was approved by the institutional Ethics Committee in the Use of Animals (CEUA 9189/2012). Animal owners were asked to sign an informed consent form and commit to providing the postoperative care recommendations.

Animals: Thirty-six bitches of different weights, ages, and breeds admitted for therapeutic unilateral mastectomy were selected for a prospective placebo controlled randomized blind clinical trial. Dogs were included in the study if they presented ASA physical status I or II; normal complete blood count; and ALT, blood urea nitrogen, and creatinine levels within normal range for the species. Animals were excluded in the presence of hypertension, congestive heart failure, or if they'd received analgesic or anti-inflammatory treatments two weeks prior to admission.

Study design: Dogs undergoing unilateral mastectomy had food and water withheld 8h and 2h prior to surgery, respectively. Body weight (BW), rectal temperature, heart (HR, bpm), and respiratory rate (fR, rpm) were clinically evaluated and recorded before the start of the surgical procedure. The cephalic vein was catheterized, and maintenance fluid therapy (Ringer's lactate 10 mL/kg/h), 0.2 mg/kg meloxicam, and 30 mg/kg cephalothin were administrated intravenously.

The animals were randomly allocated into 3 groups (n=12). Twenty minutes before anesthetic induction, the preoperative group (PRE) received 0.5 mg/kg methadone IM (Mytedom®, Cristália, Brazil) while the transoperative (TRA) and postoperative (POS) groups received 0.05 mL/kg saline (placebo). Neither the anesthetist nor the postoperative evaluator had knowledge of the contents of the injections. After 20 minutes, anesthetic induction was carried out using 1 mg/kg propofol bolus injection IVadministered every 30 seconds until loss of palpebral reflex. The total volume of propofol applied was considered as the propofol dose for intubation (PDI, mg/kg). Animals were intubated with an orotracheal tube attached through a collector tube to a gas analyzer, which was connected to a multiparameter monitor (DX2023®, Dixtal, Brazil) for fR, end tidal carbon dioxide pressure ($EtCO_2$, mmHg), and isoflurane concentration (EtISO%) measurements.

The caudal auricular artery was catheterized and connected to a pressure transducer for mean arterial pressure monitoring (MAP, mmHg). A sensor was positioned on the tongue for HR and peripheral blood oxygen saturation (SpO_2%) measurements. Isoflurane vaporization diluted in oxygen (FiO_2=1.0) through partial rebreathing anesthetic circuit started at the minimum concentration needed to maintain the surgical plane (MAP >60 mmHg, ventral ocular rotation, and lack of protective reflexes and painful motor response). Electrocardiographic tracing and rectal temperature were also continuously monitored.

HR, fR, MAP, Tr, SpO_2, $EtCO_2$, and EtISO were recorded after anesthesia stabilization (0) and every 10 minutes (10 - 100 min) until the end of the anesthetic period. After 10 minutes of evaluation, the unilateral mastectomy procedure was initiated (performed by the same surgical team). Twenty minutes after skin incision, the TRA group received 0.5 mg/kg methadone IM, while the PRE and POS groups received placebo. Once the surgery was completed, the POS group received 0.5 mg/kg methadone IM and the other two groups received placebo. Isoflurane vaporization ceased 20 minutes after and, once swallowing and coughing reflexes were recovered, the endotracheal tube was removed and the time elapsed defined as extubation time.

The animals were immediately transferred to a recovery room, where postoperative pain was evaluated at 30, 60, 90, 120, 150, 180, 210, 240, 300 and 360 minutes and scored according to the Melbourne University Pain Scale (Firth and Haldane, 1999). If the resulting score was ≥12 (Pohl *et al*., 2011), rescue analgesia was provided (0.5 mg/kg methadone, 2 mg/kg lidocaine, 0.01 mg/kg/min ketamine i.v.). Pain evaluation continued in these patients but the data was not included in the study. Once postoperative evaluation ended, the animals received 4 mg/kg tramadol IM and were discharged to an outpatient care, with clinical checkups carried out every five days until complete recovery.

Statistical analysis: Statistical analysis was performed using the R software® (Foundation for Statistical Computing, Austria). Weight, age, PDI, surgical, anesthetic, and extubation times were compared between treatments by one-way ANOVA. HR, fR, MAP, Tr, SpO2, EtCO2, and EtISO were compared between treatments and times by two-way ANOVA and Tukey post-hoc test. Pain scores were compared by Friedman test and Dunn's post-hoc and rescue analgesia requirements by the Kaplan Meier survival analysis. Significance was considered at $P<0.05$ and data are expressed as mean ± standard deviation.

RESULTS

The sample size used allowed a statistical power of approximately 75% for the cardiorespiratory variables and

60% for the pain variables studied. Mixed breed dogs corresponded to 45% of patients; Dachshund, Poodle, and Cocker Spaniels to 42%; and other breeds to 13%. Age (10.0±2.7 years); BW (17.7±12.3 kg); surgical (91.2±13.6 min), anesthetic (129.2±21.1 min), and extubation times (7.6±2.0 min) were not significantly (P>0.05) different between the groups (Table 1).

Some complications were observed during anesthesia. One animal from PRE, two from TRA, and four from POS groups developed hypotension (MAP<60 mmHg); which was successfully controlled by a temporary increase in fluid therapy. Additionally, premature ventricular contractions were detected in a TRA patient, which was not treated, as this arrhythmia was sporadic and did not cause hemodynamic changes. These complications were not significantly related to the groups. Animals that required treatment were removed for cardiovascular evaluation and all interventions were successful.

SPO_2 and fR were similar between groups and times. $EtCO_2$ was higher in PRE and TRA groups, HR was lowest in PRE, and MAP higher in PRE than in TRA group and lowest in POS group (Table 1; Fig. 1).

Anesthetic requirements varied according to the groups, PDI was lower (P=0.016) in PRE (4.3±0 mg/kg) than in TRA (6.2±1.9 mg/kg) and POS (6.5±1.2 mg/kg) groups. In turn, mean EtISO throughout the procedure was higher (P<0.001) in POS (1.84±0.56) than in TRA (1.65±0.37) and PRE (1.62±0.32%) groups and varied with time, being significantly higher (P<0.001) from 30 to 50 minutes after anesthetic induction (Fig. 1) and negatively correlated to MAP (r=-0.217; P<0.001).

Pain score was significantly higher in POS (P=0.036) than PRE and TRA groups from 60-240 minutes of evaluation. Although only 1/12 of patients required rescue analgesia during the first 30 min in PRE and TRA groups, in comparison to 3/12 in the POS group between 30-90 min, these results were not significantly different (P=0.410) (Fig. 2).

DISCUSSION

Pre and transoperative methadone administration showed a preemptive analgesic effect, with postoperative pain scores being lower in these groups and, although not statistically significant, the postoperative group required greater rescue analgesia. Effective postoperative pain management with pre and transoperative therapeutic modalities has been described for some opioids (Richmond *et al*., 1993; Mansfield *et al*., 1996; Griffin *et al*., 1997), tramadol (Wordliczek *et al*., 2002), and NMDA antagonists (Chia *et al*., 1999). This effect is known as preemptive analgesia and has been attributed to methadone for its effective and lasting blocking of nociceptive pathways at different stages of the pain process (Kissin, 2000).

No difference could be observed between PRE and TRA treatments in postoperative pain management. This result is compatible with most clinical trials that tested opioids and NMDA antagonists, as described in Møiniche *et al*. (2002) meta-analysis. Animal clinical trials comparing the effects of application times on postoperative analgesia could not be found; however, rat experimental models have shown that surgical procedures cause two nociceptive stimulation phases, the first as a consequence of tissue damage and the second as a consequence of the inflammatory response to this damage (Brennan et al., 1997). The interaction between these phases is responsible for postoperative hypersensitivity; therefore, to achieve a preventive effect, the analgesic treatment must remain efficient up to the postoperative period. If the first phase can be blocked by the use of intraoperative analgesia, the analgesic effectiveness of these therapeutic modalities can be considered equivalent (Kissin, 2000).

Preoperatory methadone administration reduced the dose of propofol required for induction by approximately 30%, in agreement with the findings by Short and Bufalari (1999) in opioid-premedicated dogs. Propofol-sparing effect has been described for different opioids (Shih *et al*., 2007; Covey-Crump and Murison, 2008; Kaur *et al*., 2013; Uscategui *et al*., 2017) and the methadone/ dexmedetomidine combination (Canfrán *et al*., 2016), probably due to the sedative effect of methadone in dogs (Monteiro *et al*., 2009; Canfrán *et al*., 2016). Furthermore, both pre and transoperative methadone administration reduced isoflurane requirements for surgical anesthetic maintenance. This effect is directly related to μ opioid receptors agonists, which reduce the minimum alveolar concentration (MAC) of volatile anesthetics (Credie *et al*., 2010; Campagnol *et al*., 2012; Uscategui *et al*., 2017).

Bitches that received methadone before or during mastectomy maintained a higher blood pressure than those that received it postoperatively, confirming the cardiovascular effects described for this drug as it elevates arginine-vasopressin plasma levels leading to an increase in peripheral vascular resistance, which causes a reflexive decrease in HR, as seen in the PRE group (Maiante *et al*., 2008). Furthermore, the negative correlation observed between EtISO and MAP may further explain these results due to the isoflurane dose dependent hypotensive effect (Steffey *et al*., 2015), which can be related to the hypotensive complications observed in the POS group. Credie *et al*. (2010) have reported cardiac arrhythmias after methadone administration, which may be linked to the VPCs detected in an animal from the TRA group; however, it could also be an idiosyncratic reaction.

Respiratory depression is a common adverse effect of opioids, it is dose dependent, can be exacerbated by the concomitant use of anesthetics, and is directly linked to μ_2 receptors (Papich, 2000). This was evidenced by $EtCO_2$ increase in PRE and TRA groups, even though significant variations in *f*R or SpO_2 were not observed. Similar results have been described by Leibetseder *et al*. (2006); however, Maiante *et al*. (2008) reported a decrease in partial arterial oxygen pressure without partial carbon dioxide pressure alterations following methadone administration in non-anaesthetized dogs.

This study presents some limitations that should be considered: limited sample size; blood gas analysis was not performed (due to institutional limitations) and ventilation and oxygenation had to be estimated using EtCO2 and SpO2; postoperative pain assessment was performed using a single pain scale and for a limited time. Therefore, further studies with broader and more objective analgesic and cardiorespiratory evaluations are necessary to determine the desired and adverse effects of preemptive methadone administration in dogs subjected to algid surgical procedures.

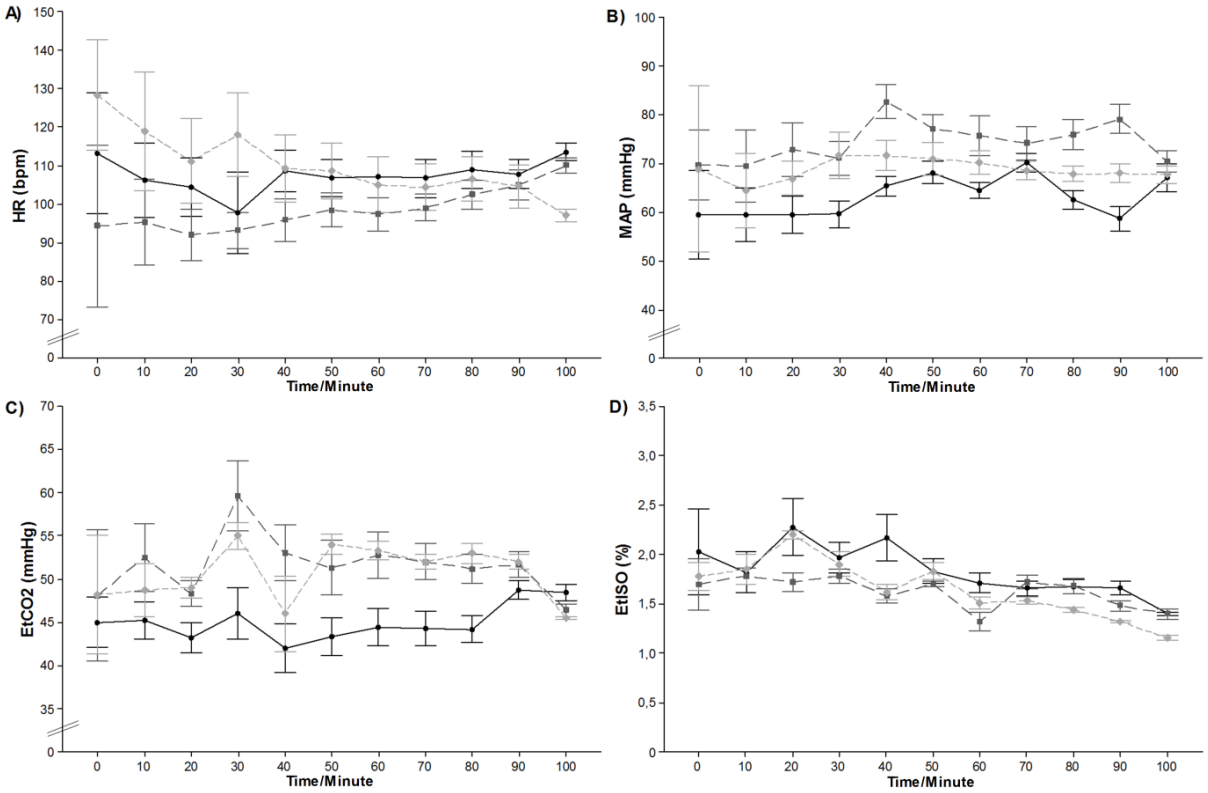

Fig. 1: Mean±SD of: A) Heart rate (HR, bpm), B) Mean arterial pressure (MAP, mmHg), C) End tidal CO_2 pressure ($EtCO_2$, mmHg), and D) End tidal isoflurane concentration (EtISO, %) evaluated after anesthetic induction (0) and every 10 min until the end of anesthesia in 36 bitches subjected to unilateral mastectomy that received 0.5 mg/kg methadone i.m at the pre (PRE, dark grey broken line with ■ mean symbol), trans (TRA, light grey dotted line with ♦ mean symbol), or postoperative periods (POS, black line with ● mean symbol).

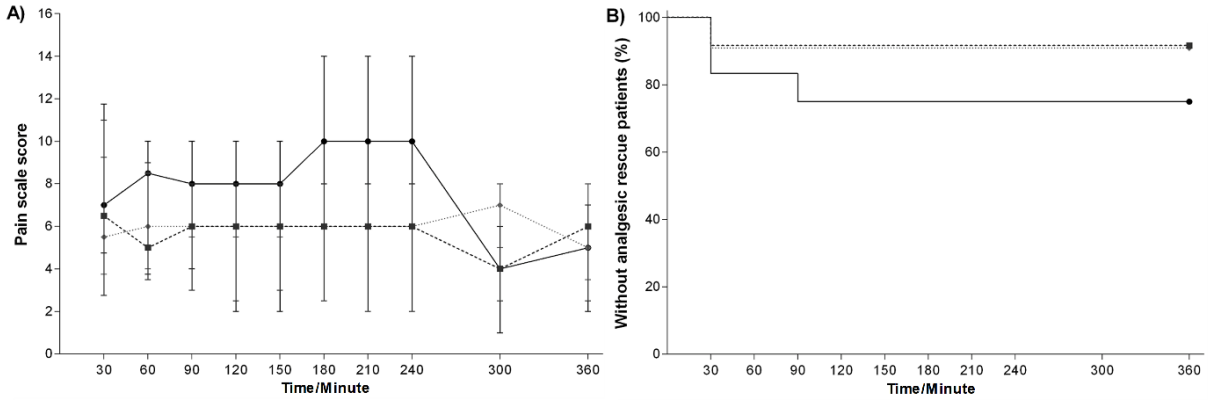

Fig. 2: Median±IQR of: A) Melbourne University Pain Scale Score and B) Kaplan Meier survival curves for rescue analgesia requirements evaluated during the 6 h subsequent to extubation in 36 bitches subjected to unilateral mastectomy that received 0.5 mg/kg methadone i.m at the pre (PRE, dark grey broken line with ■ median symbol), trans (TRA, light grey dotted line with ♦ median symbol), or postoperative periods (POS, black line with ● median symbol); IQR: interquartile range.

Table 1: Mean±SD of clinical parameters of 36 bitches subjected to unilateral mastectomy and received 0.5 mg/kg methadone IM at the pre (PRE), trans (TRA) or postoperative (POS) period.

	PRE	TRA	POS	P value
Age (years)	9.8±3.5	9.9±1.2	10.4±3.2	0.878
Weight (kg)	18.6±12.9	17.4±10.7	17.1±14.3	0.962
Surgical time (min)	89.5±12.7	88.7±11.2	95.5±16.7	0.489
Anesthetic time (min)	130.8±21.5	126.2±15.7	130.5±26.6	0.869
Extubation time (min)	7.8±2.1	7.1±1.7	7.8±2.4	0.688

SD: Standard deviation.

Conclusions: Pre and transoperative methadone administration result in preemptive pain relief, reduce anesthetic requirements, and consequently result in less cardiovascular depression in bitches undergoing mastectomy. However, it possibly leads to hypoventilation and, consequently, special care is recommended when monitoring the ventilation of anaesthetized patients treated with this drug.

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Authors contribution: RARU, MARF and WRRV conceived and designed the study. Uscategui, Tiosso, Moro, Coutinho, and Brito executed the experiment and collected the data. Uscategui, Feliciano, Vicente, Tiosso, and Moro analyzed the data. All authors interpreted this study; critically revised and translated the manuscript; and approved its final version.

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