



Evaluation of tumescent local anesthesia, epidural technique, and dexmedetomidine infusion in bitches undergoing mastectomies: A randomized study of perioperative and postoperative analgesia

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[Avaliação da anestesia local tumescente, técnica epidural e infusão de dexmedetomidina em cadelas submetidas a mastectomias: estudo randomizado avaliação analgésica perioperatória e pós-operatória]

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ABSTRACT

Total unilateral mastectomy is the standard technique for treating mammary tumors in dogs. Combined with multimodal analgesia, different anesthetic techniques improve pain control. This study evaluated the transoperative and postoperative analgesic efficacy of continuous dexmedetomidine infusion (GD), tumescence (GT), and epidural block (GE) using the Short Form of the Glasgow Composite Measure Pain Scale (CMPS-SF) in dogs undergoing mastectomy. Eighteen dogs were randomly assigned to three groups of six animals each. Vital parameters, including heart rate (HR), oxygen saturation (SpO₂), systolic (SBP), diastolic (DAP), and mean arterial pressures (MAP), expired carbon dioxide fraction (FeCO₂), expired isoflurane fraction (FeISO), and body temperature (T°C), were recorded. GD demonstrated a reduction in HR. FeISO requirements decreased by 25.6%, 8.12%, and 7.27% in GD, GT, and GE, respectively. GE required the highest number of intraoperative rescue interventions (10), followed by GD (5) and GT (4). Postoperatively, GD necessitated the most rescue interventions (10), followed by GE (7) and GT (3). GT provided superior postoperative analgesia, lasting up to 8 hours, while the other groups required rescue within the first hour of postoperative assessment. In conclusion, the tumescence technique offered more effective perioperative pain control, with prolonged postoperative analgesia.

Keywords: dexmedetomidine, dogs, Glasgow, mastectomy, tumescence

RESUMO

A mastectomia unilateral total é a técnica padrão para o tratamento de tumores mamários em cães. Quando combinada com analgesia multimodal, diferentes técnicas anestésicas melhoram o controle da dor. Objetivou-se avaliar a eficácia analgésica transoperatória e pós-operatória da infusão contínua de dexmedetomidina (GD), tumescência (GT) e bloqueio epidural (GE), utilizando-se a escala curta de dor de Glasgow (CMPS-SF) em cadelas submetidas à mastectomia. Dezoito cães foram randomicamente divididos em três grupos de seis animais. Foram registrados os parâmetros vitais, incluindo frequência cardíaca (FC), saturação de oxigênio (SpO₂), pressões arteriais sistólica (PAS), diastólica (PAD) e média (PAM), fração expirada de dióxido de carbono (FeCO₂), fração expirada de isoflurano (FeISO) e temperatura corporal (T°C). A GD demonstrou redução na FC. As necessidades de FeISO diminuíram em 25,6%, 8,12% e 7,27% na GD, na GT e no GE, respectivamente. O GE necessitou do maior número de intervenções intraoperatórias de resgate (10), seguido da GD (5) e da GT (4). No pós-operatório, a

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GD necessitou de mais resgates analgésicos (10), seguida do GE (7) e da GT (3). A GT garantiu analgesia superior por até oito horas, enquanto os outros grupos precisaram de resgate na primeira hora. Em conclusão, a técnica de tumescência ofereceu melhor controle perioperatório da dor, com analgesia pós-operatória prolongada.

Palavras-chave: dexmedetomidina, cães, Glasgow, mastectomia, tumescência

INTRODUCTION

Mammary tumors are the most common neoplasms in female dogs and surgical resection is the recommended treatment in these cases. However, this type of intervention promotes extensive tissue dissection, resulting in moderate to severe pain (Fantoni and Garofalo, 2012). The mammary gland, a modified apocrine sweat gland, is the main site of tumor development in intact female dogs (Sleekx et al., 2011). Mastectomy remains the gold standard treatment for most of these tumors, except in cases of inoperable metastatic disease and inflammatory mammary carcinomas (Sleekx et al., 2011). Postoperative pain resulting from surgery may involve inflammatory, neurogenic, and visceral components (Parsa et al., 2009). Preemptive multimodal analgesia, including systemic and local or regional administration of analgesics, is necessary to minimize perioperative discomfort in patients after mastectomy surgery (Grubb and Lobprise 2020; Vullo et al., 2021).

Among the most commonly used options for analgesia in total unilateral mastectomy, we have the tumescent anesthesia technique, which consists of applying a sterile solution associated with a local anesthetic and a vasoconstrictor (Abimussi et al., 2014); the epidural analgesia technique, which involves the administration of a local anesthetic with or without an opioid in the epidural space (between the dura mater and the limits of the spinal canal), providing prolonged analgesia (Mangabeira et al., 2019); and analgesia by continuous infusion of analgesic and sedative drugs, such as dexmedetomidine, a potent α -2 adrenergic capable of occupying pain-modulating receptors and promoting sedation (Sarotti et al., 2019).

Intra- and postoperative pain control is performed through a multimodal approach, which combines the use of drugs with different mechanisms of action and non-pharmacological techniques (Mitch and Hellyer, 2014). Opioids are widely used to control acute pain; however,

human studies have reported that opioids cause negative impacts on the immune system, such as immunosuppression and inhibition of natural killer cell action (Paul et al., 2021), and their use in cancer patients has been questioned. In this context, recent studies have suggested that local anesthetics may enable a significant decrease in the use of opioids and other immunosuppressive drugs, thus contributing to a better prognosis (Sanches et al., 2020). Regional anesthesia techniques are often associated with general anesthesia in dogs to facilitate recumbency and restraint during the surgical procedure. Adding Tumescent local anesthesia (ALT) can significantly reduce the need for inhalation of anesthetic agents, improving recovery by providing prolonged postoperative analgesia (Vullo et al., 2021).

The present study aimed to evaluate cardiovascular stability, perioperative and postoperative analgesic efficiency, and the requirement for intraoperative isoflurane using three different analgesic techniques in female dogs undergoing unilateral total mastectomy: tumescence with ropivacaine, continuous infusion of dexmedetomidine, and epidural anesthesia with ropivacaine associated with morphine. The central hypothesis is that the tumescence technique will promote more effective perioperative pain control, reducing the need for rescue analgesics, reduced requirement for inhaled anesthetics, and lower postoperative pain scores. In addition, the epidural anesthesia technique is expected to be similar to continuous dexmedetomidine infusion in controlling perioperative pain, but with a reduced need for inhaled anesthetics and intraoperative and postoperative analgesic rescues compared to continuous dexmedetomidine infusion.

MATERIAL AND METHODS

This study was approved by the Ethics Committee for the Use of Animals (CEUA/UDESC) under protocol number 2369250920. Eighteen females with no age or

weight restrictions and mammary neoplasms were used. Exclusion criteria included animals with abnormalities in hematological and biochemical tests (alanine aminotransferase, alkaline phosphatase, serum albumin, total serum protein, gamma-glutamyltransferase, urea, and creatinine), as well as cardiovascular alterations detected by electrocardiogram. Animals with lung metastases identified by chest radiography, as well as those with aggressive behavior, which would make postoperative evaluations impossible, were also excluded. The selected animals were admitted in advance (24 hours before the procedure), allowing for precise and correct fasting of 6 and 12 hours for water and food, respectively.

A baseline behavioral assessment was performed during this preoperative hospitalization period, being later compared to the postoperative evaluation using the Glasgow composite measure pain scale-short (CMPS-SF). A total of 18 animals were allocated into three study groups: GD (dexmedetomidine group), GT (tumescence group), and GE (epidural group). The evaluator was different from the operator who performed the blockades.

Pre-anesthetic medication consisting of 0.2% acepromazine maleate (Acepran 0.2%; Vetnil, SP, Brazil) at a dose of 0.02mg/kg, associated with midazolam (Dormire 5mg/mL; Cristália, SP, Brazil) at a dose of 0.5 mg/kg, administered intramuscularly (IM), was administered on the day of the experimental design. For anesthetic induction, propofol (Propovan 1%; Cristália, SP, Brazil) dose/effect was administered intravenously (IV), through a syringe coupled to a syringe pump, respecting the rate of 1mg/kg/min, until the appropriate moment for orotracheal intubation was reached. Then, lidocaine without vasoconstrictor (Xylestesin 10%; Cristália, SP, Brazil) was applied in the periglottic region. Subsequently, intubation was performed using a Murphy-type endotracheal tube of appropriate size for the patient and with a high-volume, low-pressure cuff. Once intubated, the patient was connected to the anesthetic system (Ohmeda, B650 monitor; GE Healthcare, IL, USA) in a closed system with controlled ventilation in the cycled ventilation mode at a tidal volume of 10mL/kg, initial *f* (respiratory rate) of 10mpm (adjusted to the normocapnia EtCO₂ range at 35–45 mm/Hg),

inspiration/expiration ratio of 1:2, fraction of inspired oxygen (FIO₂) of 40%, and 0cm/H₂O of PEEP (positive end-expiration pressure). Then, inhalation anesthesia was started using isoflurane with vaporization adjusted to 1.3V% in a calibrated vaporizer assessed using the E-CAIOVX spirometry sensor coupled to the device (Ohmeda, B650 monitor; GE Healthcare, IL, USA) to maintain the adequate anesthetic plane (rotated eyeball and without medial palpebral reflex) and adjusted as needed.

The dorsal pedal artery was then catheterized, starting with antisepsis of the site using 70% alcohol. Then, 0.5mL of 2% lidocaine without vasoconstrictor (Xylestesin 2%; Cristália, SP, Brazil) was administered in the region close to the artery pulsation using a 1mL syringe and a 13 x 0.33mm needle. After the anesthetic blockade, 5 minutes were waited to ensure its effectiveness. Arterial catheterization was then performed using a 22- or 24-G venous catheter (Safelet-ETFE; Nipro, SP, Brazil), according to the animal size, and attached to a PRN plug (Becton Dickinson, PR, Brazil). The arterial catheter was connected to a pre-calibrated disposable pressure transducer (Utah/ Biotrans) and a monitor (Datex-Ohmeda, B650 monitor; GE Healthcare, IL, USA). Calibration accuracy was assessed using the dynamic response test (square wave test). This system was connected via a low-compliance pressure tube containing heparinized saline from a pressurized bag at 300mmHg. Heparinized saline (10IU/mL) was infused at a rate of 2.5mL/hour throughout the procedure to prevent clot formation. After preparation and dressing, the animals were randomly allocated to the experimental groups and the baseline moment (T0) was measured after 15 minutes.

Each animal was randomly allocated to one of the following groups (n=6): in the dexmedetomidine group (DG), the animals received a bolus of dexmedetomidine (Dexdomitor 0,5mg/mL; Zoetis, SP, Brazil) of 1µg/kg intravenously (IV), followed by continuous infusion (CRI) at a rate of 1µg/kg/h. In the tumescence group (GT), a 0.05% ropivacaine solution was administered, consisting of 233.3mL of refrigerated Ringer's lactate, plus 16.7mL of 0.75% ropivacaine (Ropivacaína 0.75%; Cristália, SP, Brazil) and 0.5mL of adrenaline (Adren 1mg/mL; Hipolabor, MG, Brazil). This solution was applied to the

subcutaneous space of the corresponding mammary chain at a dose of 15mL/kg, using a Klein cannula, coupled to a system consisting of a macrodrip set, a three-way stopcock, and a refrigerated solution. This technique was defined as tumescence. Finally, in the epidural group (GE), the animals were positioned in sternal recumbency, with the pelvic limbs extended cranially. After palpation of the space between the lumbar (L7) and sacral (S1) vertebrae, a Tuohy needle was inserted until it passed the yellow ligament, with confirmation performed by the hanging drop test (Gutierrez test). Then, a glass syringe was attached and the absence of resistance during administration of the solution was verified. Thus, the animals received 2mg/kg of 0.75% ropivacaine associated with 0.1mg/kg of 1% morphine via the epidural route, diluted, when necessary, with sterile intravenous solution (Ringer's lactate) until the volume was completed at 0.3mL/kg to ensure adequate cranial progression of the content.

All dilutions were performed at the beginning of the study. Continuous infusion consisted of diluting dexmedetomidine in a 20mL syringe, and the flow rate was standardized at 10mL/h using a properly calibrated syringe pump (ST670; Samtronic, SP, Brazil). The data from moment T1 were collected 15 minutes after treatment administration. Thus, the animal was released for surgical antisepsis and subsequent total unilateral mastectomy procedure using the technique proposed by Fossum (2014) and with a standardized surgeon for all procedures.

The evaluation moments during the study were: T0, corresponding to the baseline moment 15 minutes after the end of the dressing; T1, corresponding to 15 minutes after the start of treatment administration; T2, evaluated immediately after skin clamping with Backhaus clamps; T3, evaluated immediately after surgical incision; and T4 onwards, corresponding to evaluations performed every 15 minutes until the end of the procedure.

The parameters were assessed using a multiparameter monitor (DatexOhmeda, B650 monitor; GE Healthcare, IL, USA). The following parameters were measured at all moments: heart rate (HR), using electrocardiography; respiratory rate (*f*), using a gas analyzer with a side stream sensor;

peripheral oxygen saturation (SpO₂), using a sensor placed on the patient's tongue; fractional expired carbon dioxide (FeCO₂), measured by capnography using a gas analyzer; fractional expired isoflurane (FeISO), using a gas analyzer; body temperature (T°C), using an esophageal sensor; and systolic blood pressure (SBP), diastolic blood pressure (DAP), and mean arterial pressure (MAP), using the catheterized artery connection to the pressure transducer. In addition, the time in minutes required for surgical removal of the mammary chain (MC) was assessed.

The fentanyl (Fentanest 0.05mg/mL, Cristália, SP, Brazil) consumption required to abolish the sympathetic autonomic response to surgical nociceptive stimulus was assessed during the intraoperative period. Fentanyl was administered in bolus at a dose of 2.5µg/kg whenever at least two of the three parameters (HR, MAP, and *f*) showed a 20% increase relative to the animal baseline value (T0), characterizing the need for analgesic rescue. The total surgical time and extubation time (interval in minutes between the cessation of inhaled anesthetics and the patient's extubation) were recorded at the end of the procedure. In addition, all animals received compressive dressing during the anesthetic recovery period. After extubation, the patients were medicated with dipyrone (25mg/kg) (Analges 500mg/mL; Agener, SP, Brazil) and meloxicam (0.2mg/kg) (Flamavet 0.2%; Agener, SP, Brazil) and then transferred to the postoperative room, where postoperative evaluations began.

The animals were assessed in the postoperative period for analgesia by the Glasgow composite measure pain scale-short (CMPS-SF). Nociception assessments were performed 1, 2, 4, 8, 12, and 24 hours after extubation, with the baseline assessment (T0) corresponding to the preoperative acclimatization period, during which the behavioral patterns of each animal were observed. The assessments were conducted by two evaluators, one experienced and the other inexperienced, both blinded to the protocols administered and the group to which the animals belonged. Animals that presented a score equal to or higher than 6 on the CMPS-SF (scale from 0 to 24) received rescue analgesia with morphine 0.5mg/kg (Dimorf 1%, Cristália, SP, Brazil) intramuscularly (IM). Analgesia was

supplemented with ketamine 1mg/kg (Ketamin 5%, Cristália, SP, Brazil) associated with acepromazine 0.02mg/kg IM after three consecutive rescues with morphine in the same animal, and the animals continued to be included in the postoperative evaluations.

Statistical analysis was performed using GraphPad Prism 7.0 by submitting the variables to the Shapiro-Wilk normality test. The variables that passed the normality test were compared between groups by analysis of variance (ANOVA) followed by Tukey's test and within the same group by ANOVA with multiple repetitions followed by Dunnett's test. The comparison between groups for the data that did not pass the normality test was performed by Wilcoxon's test and within the same group by the Friedman analysis. Survival analysis (Kaplan-Meier analysis) was performed for rescues. Statistical difference was considered when $p \leq 0.05$.

The sample size was determined using statistical calculation software (OpenEpi, version 3.0; OpenEpi, TN, USA), with a 5% significance level (two-tailed), 80% statistical power (beta of 20%), and the assumption that a mean difference of 20% in intraoperative rescues would be clinically significant, assuming a 5% standard deviation (SD). Therefore, a sample size of 18 animals would be necessary to detect this difference, with the animals randomly allocated in a randomized and blinded manner (1-1-1), using the software available at www.randomization.com, into three study groups: GD (dexmedetomidine group), GT (tumescent group), and GE (epidural group). The evaluator was not the same operator who performed the blockades.

RESULTS

All enrolled animals (a total of 18 female dogs) completed the study successfully. The results of hematology and biochemistry testing were within reference limits for all animals. The study population demonstrated homogeneity in terms of age (9.11 ± 2.34 years, $p=0.2049$) and body mass (13.94 ± 7.7 kg, $p=0.0682$) across all groups. In addition, there were no differences between the study groups regarding the time to remove the mammary chain (MC) (10.83 ± 4.756 , $p=0.3603$), surgical time (53.22 ± 15.57

$p=0.0702$), and extubation time (13.33 ± 7.137 , $p=0.0853$).

HR in GD during the intraoperative period (Table 1) was lower at all moments than T0, with a mean reduction in HR of 38.92% ($p=0.0184$). In contrast, this parameter in GE was only lower at moments T4 and T5 than at baseline, with a mean reduction of 12.74% ($p=0.0191$). SpO_2 always remained within the reference limits, with no differences between treatments or groups. $EtCO_2$ was above the normocapnia range in GE at baseline, but its values returned to the normal range shortly after controlled ventilation was instituted.

The isoflurane requirement showed some specific differences in T2 when compared to GT and GD, with a 25.6% reduction ($p=0.0439$). However, no significant difference was observed in the total isoflurane requirement, but GE and GT presented lower requirements, with values of 8.12% ($p=0.0672$) and 7.27% ($p=0.0821$) compared to GD.

No statistical differences were observed between groups for the data collected regarding SBP. However, SBP values always remained higher relative to the other treatments, with a significant increase in T3 compared to T0 in GD ($p=0.0208$). Likewise, MAP presented higher values, and differences were observed for T1 when comparing GD and GE ($p=0.0134$). However, the animals presented no hypotension or hypertension at any time.

The GE required a higher number of intraoperative analgesic rescues (Table 1), totaling 10, 4, and 5, respectively for GE, GT, and GD. However, no statistical differences were observed between groups (Figure 1).

Regarding rescues in the postoperative period, GT presented the lowest number of analgesic interventions, with three rescues performed at hours 8, 12, and 24. GD required a total of 10 rescues, occurring at hours 1, 1, 1, 2, 4, 8, 8, 12, 12, and 24, while GE had seven rescues, distributed at hours 1, 2, 4, 4, 8, 12, and 24. The statistical comparison showed a significant difference between GT and GD ($p=0.04660$), as shown in Figure 2.

DISCUSSION

The results demonstrate that the three protocols used in this study were effective in providing analgesia during the intra- and postoperative periods in mastectomy procedures. The reduction in heart rate (HR) observed in the group treated with dexmedetomidine (GD) can be largely attributed to the pharmacological effect of this drug, which is an alpha-2 agonist. Dexmedetomidine exerts its action by inhibiting the release of norepinephrine at presynaptic α_2 receptors, which decreases sympathetic stimulation. In addition, the drug reduces baroreceptor sensitivity and increases vagal activity, resulting in bradycardia (Afonso & Reis, 2012; Costa et al., 2018; Comassetto et al., 2023). These mechanisms explain the significant reduction in HR, corroborating previous findings in the literature.

Although a reduction in heart rate (HR) was observed in the dexmedetomidine group (GD), a

slight increase in blood pressure, especially diastolic blood pressure (DAP), was observed. This phenomenon can be explained by the pharmacological action of dexmedetomidine on α_2A , α_2B , and α_2C receptors. Prejunctional α_2 receptors, predominantly of the α_2A subtype, are responsible for inhibiting norepinephrine release in sympathetic nerve endings and noradrenergic neurons of the central nervous system (Parra et al., 2021). However, the three α_2 receptor subtypes are also present in vascular smooth muscle, where they induce vasoconstriction, resulting in increased blood pressure (Fayyaz et al., 2009). This effect is particularly evident in the elevation of DAP observed in the group treated with dexmedetomidine, suggesting an increase in peripheral vascular resistance probably due to vasoconstriction mediated by the activation of post-junctional α_2 receptors, which would result in increased afterload, raising DAP (Afonso and Reis, 2012; Parra et al., 2021; Comassetto et al., 2023).

Table 1. Mean Values and Standard Deviations for Heart Rate (HR), Peripheral Oxygen Saturation (SpO₂), End-Tidal Carbon Dioxide (EtCO₂), Systolic, Diastolic, and Mean Arterial Blood Pressure (SBP, DAP, MAP), Body Temperature (T°C), and transoperative analgesic rescue in bitches undergoing mastectomy, allocated into Three Groups: GD (dexmedetomidine group), GT (tumescence group), and GE (epidural group)

	Groups	T0	T1	T2	T3	T4	T5	T6	T7
HR (beats/min)	GD	116±14	74±19 [†]	75±19 [†]	73±18 [†]	69±15 [†]	69±20 [†]	66±21 [†]	70±18 [†]
	GT	92±11	90±15	94±17	98±13	83±16	86±11	75±13	87±14
	GE	102±19	96±20	100±22	101±22	89±20 [†]	89±19 [†]	99±14	97±16
SpO ₂ (%)	GD	97±01	97±01	97±01	97±02	98±01	98±01	98±01	96±04
	GT	96±01	95±02	95±02	94±02	96±02	94±02	95±03	97±01
	GE	98±02	97±02	98±02	97±03	97±02	97±01	97±01	98±01
EtCO ₂ (mmHg)	GD	46±05	49±05	46±07	43±06	40±04	39±03	39±03	43±07
	GT	44±06	41±06	41±06	39±04	40±03	38±04	41±03	47±10
	GE	52±05	48±06	42±05 [†]	39±05 [†]	39±04 [†]	40±03 [†]	39±03 [†]	41±06
FeISO (%)	GD	1.12±0.4	1.24±0.2	1.25±0.2*	1.20±0.2	1.08±0.2	1.00±0.1	0.96±0.1	0.85±0.1
	GT	1.13±0.2	1.00±0.2	0.93±0.1	1.01±0.2	1.01±0.2	1.00±0.1	1.01±0.2	1.13±0.05
	GE	1.04±0.1	1.16±0.1	1.04±0.2	1.09±0.1	1.01±0.1	0.91±0.1 [†]	0.96±0.2	0.89±0.1
SBP (mmHg)	GD	90±20	100±19	102±20	102±22 [†]	101±21	102±16	102±26	99±32
	GT	89±16	93±08	94±10	96±11	98±13	101±23	103±21	120±17
	GE	90±10	91±03	96±07	92±09	90±10	92±08	94±11	91±11
MAP (mmHg)	GD	69±10	77±10•	77±11	80±12	80±14	62±28	81±18	77±28
	GT	62±12	67±04	67±05	68±06	74±12	75±15	72±09	79±05
	GE	63±05	63±03	71±09	67±06	66±04	68±03	71±05	65±01
DAP (mmHg)	GD	59±09	64±10•	64±10	67±10	70±14•	70±14•	71±16	65±27
	GT	51±13	56±05	54±07	56±07	61±11	60±11	57±10	60±06
	GE	50±04	52±05	59±09	54±04	53±03	59±05 [†]	59±03 [†]	53±01
T (°C)	GD	36.8±0.8	36.1±1.0 [†] *	35.9±1.0 [†] *	35.8±0.9 [†] *	35.3±1.1 [†]	35.0±1.1 [†]	34.8±1.1 [†]	35.0±1.1 [†]
	GT	36.0±1.6	33.6±2.1 [†]	33.5±2.1 [†]	33.4±2.1 [†]	33.2±2.1 [†]	33.0±2.0 [†]	33.5±1.3 [†]	34.3±0.5
	GE	36.7±0.5	35.9±0.3 [†] *	35.1±0.7 [†]	34.9±0.8 [†]	34.3±1.1 [†]	34.1±1.2 [†]	34.0±1.1 [†]	34.2±0.8
Transoperative rescues	GD	0	0	0	3	0	0	1	0
	GT	0	0	0	1	1	2	0	0
	GE	0	0	0	2	2	2	2	0

Legend: [†] Statistically differs from T0. * Statistically differs from GT • Statistically differs, ANOVA followed Tukey, p<0.05.

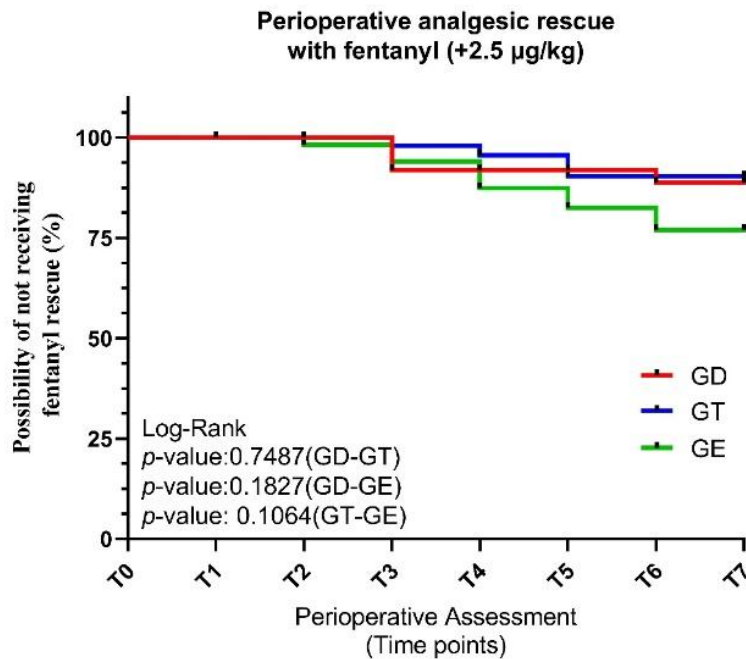


Figure 1. Survival analysis using the Kaplan-Meier method to assess the occurrence of rescue events of perioperative rescue with fentanyl 2.5µg/kg in bitches undergoing mastectomy, allocated into Three Groups: GD (dexmedetomidine group), GT (tumesence group), and GE (epidural group). Data is expressed as numbers of rescues. *Statistically significant differences between groups ($p < 0.05$).

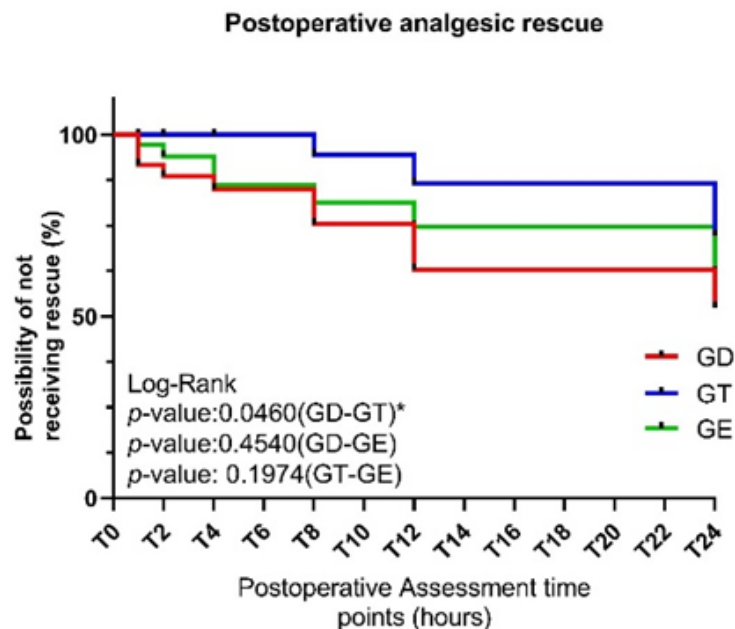


Figure 2. Survival analysis using the Kaplan-Meier method to assess the occurrence of rescue events of postoperative analgesic rescue in bitches undergoing mastectomy, allocated into Three Groups: GD (dexmedetomidine group), GT (tumesence group), and GE (epidural group). Data is expressed as numbers of rescues. *Statistically significant differences between groups ($p < 0.05$).

Regarding isoflurane consumption, studies have demonstrated that the use of balanced anesthesia associated with locoregional blockade significantly reduces inhalational anesthetic consumption (Credie *et al.*, 2013; Rocha *et al.*, 2022). Both the blockade using the tumescence technique (Abimussi *et al.*, 2014) and epidural anesthesia (Tayari *et al.*, 2022) promote this reduction, as they minimize nociceptive stimulus, which results in a lower need for general anesthetic. In addition, continuous dexmedetomidine infusion (Lervik *et al.*, 2012) also reduces inhalational anesthetic consumption, acting mainly centrally. Dexmedetomidine exerts its sedative and anxiolytic effects in the nucleus of the *locus coeruleus*, a region located in the brainstem that contains many α -2 adrenergic receptors and is the main center of noradrenergic innervation in the central nervous system (Elfenbein *et al.*, 2009; Comassetto *et al.*, 2023). Afonso and Reis (2012) observed that dexmedetomidine provided sedation, hypnosis, anxiolysis, amnesia, and analgesia, with the hypnotic effects being dose-dependent and potentiating general anesthetics, reducing the requirement (Afonso and Reis 2012; Comassetto *et al.*, 2023).

The reduction in body temperature in the treatments compared to baseline can be attributed mainly to two important factors: general anesthesia, which reduces metabolism and decreases the response of thermoregulatory centers but was attenuated with the use of a thermal mattress, and the use of a low-temperature tumescent solution in GT (Abimussi *et al.*, 2014). The temperature reduction was observed in all treatments, but it was more pronounced in the group submitted to the tumescence technique. Some authors have suggested that the use of heated solutions can minimize this heat loss. Hunstad and Aitken (2006) recommended the use of solutions of 38–40°C to avoid both heat loss and discomfort during infiltration. However, more recent studies, such as that by Rocha *et al.* (2022), have shown that the use of heated solutions in the tumescence technique does not present significant differences in terms of prevention of hypothermia, with the animals still showing a reduction in body temperature.

The higher need for intraoperative analgesic interventions in the epidural group (GE) may be

associated with the limited extent of the epidural blockade, as the blockade did not reach the most cranial breasts in the volumes used in this study, making complementary analgesia necessary (Tayari *et al.*, 2022). Previous studies using the epidural technique have shown that the distribution of the anesthetic in the epidural space is dependent on the injected volume (Tamanho *et al.*, 2009; Sanches *et al.*, 2020). The administration of larger anesthetic volumes results in a more effective blockade of the cranially located segments. However, this approach can cause motor blockade in cranial nerves and interfere with the function of respiratory muscles, generating significant complications. Despite this, the technique has proven to be effective for mastectomies in female dogs (Tayari *et al.*, 2022). The same authors reported that the impact of epidural injection on the respiratory system can be assessed during surgery, with hypercapnia being an indicator of respiratory depression (Tamanho *et al.*, 2009; Tayari *et al.*, 2022).

The higher sedative efficiency of dexmedetomidine (Zoff and Bradbrook, 2016) in the intraoperative rescues observed in GD and GT may be associated with its central action, as previously discussed, by acting on the *locus coeruleus* promoting sedation, hypnosis, anxiolysis, amnesia, and analgesia (Elfenbein *et al.*, 2009; Comassetto *et al.*, 2023). On the other hand, the tumescence technique promotes analgesia through local anesthetics that delay cell membrane depolarization, reversibly blocking fast voltage-gated sodium channels. This interruption of the action potential along the axon results in an anesthetic effect (Abimussi *et al.*, 2014). The combination with epinephrine, administered into the subcutaneous tissue until it becomes firm and tense (tumescent), facilitates the surgical procedure due to the volume of infiltrated solution, generating hydrodissection (Conroy and O'Rourke, 2013). Blood loss is reduced by the vasoconstriction induced by epinephrine, together with the hydrostatic effect of the large-volume injection, which tamponade the local blood vessels (Conroy and O'Rourke, 2013). In addition, epinephrine significantly prolongs the blockade, providing excellent anesthesia and postoperative analgesia (Abimussi *et al.*, 2014).

Regarding postoperative rescues using the Glasgow composite measure pain scale-short

(CMPS-SF) (Reid *et al.*, 2007), GT showed a lower number of analgesic interventions, a result similar to that found by Abimussi *et al.* (2013) when evaluating the tumescence technique in mastectomies. In the study by Abimussi *et al.* (2013), the first rescue occurred after 7 hours postoperatively, a result comparable to that of the present study, in which the first rescue was necessary only after 8 hours postoperatively. This better pain control in GT can be attributed mainly to the action of ropivacaine, a long-acting local anesthetic that acts on fast voltage-dependent sodium channels, added to the vasoconstrictor effect of epinephrine, which prolongs the remaining analgesia for a longer period (Conroy and O'Rourke, 2013).

In contrast, GD and GE presented rescues in the first hour after surgery, indicating ineffective analgesia. However, GE was more efficient, requiring fewer analgesic interventions compared to GD. This fact can be explained by the epidural blockade and the residual action of morphine, which can provide analgesia lasting up to 18 hours when administered epidurally, especially when associated with ropivacaine. Relatively low morphine doses produce more potent and long-lasting analgesia than when administered parenterally due to its water solubility. The onset of action at a dose of 0.1mg/kg occurs between 20 and 60 minutes, with a duration of 16 to 24 hours (Marucio and Cotes, 2012).

One limitation of this study is the subjective nature of some assessments, such as postoperative analgesia. However, this limitation was offset by the assessment performed by the same blinded evaluators. The use of female dogs that underwent mastectomy also presents a challenge to ensure the homogeneity of the experimental group. Metastases that are not visible on radiographic images may still occur despite the performance of thoracic radiographs.

CONCLUSIONS

In conclusion, the three evaluated techniques proved to be safe for performing mastectomies. However, the tumescence technique proved to be the most efficient in the intraoperative period, in addition to providing analgesia for up to 8 hours postoperatively. The epidural technique, although less effective intraoperatively and requiring more analgesic interventions compared

to the other techniques, provided more satisfactory analgesia in the postoperative period. Furthermore, the tumescence technique presented the highest cardiovascular stability among all the techniques used in the study. In contrast, dexmedetomidine was associated with higher cardiovascular instability.

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