Acta Scientiae Veterinariae, 2022. 50: 1855.

RESEARCH ARTICLE
Pub. 1855

ISSN 1679-9216

Effects of Heated Tumescence Solution in Bitches after Unilateral Mastectomy*

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ABSTRACT

***Background*:** Mammary tumors, for which mastectomy is the main treatment, are the most common neoplasms in bitches. Mastectomy is painful and, in order to reduce the pain stimulus in the transoperative period, tumescent local anesthesia is associated with general inhalation anesthesia. However, despite the numerous benefits of tumescence, intraoperative hypothermia is the most common complication. In Medicine, especially in plastic and dermatological surgery, it is common to use a heated tumescence solution to prevent intraoperative hypothermia; however, in Veterinary medicine, no previous study has examined the advantages and disadvantages of using heated tumescence solution. Thus, this study aimed to investigate the transanesthetic cardiorespiratory effects of heated tumescence solution in bitches submitted to radical unilateral mastectomy.

***Materials, Methods & Results*:** Eight animals were treated with 0.1% lidocaine solution, warmed to 37-42°C, using a Klein's cannula for administration. Chlorpromazine (0.3 mg/kg) and meperidine (3 mg/kg) were used as pre-anesthetic medication intramuscularly, and induction was performed with intravenous propofol and maintenance with isoflurane. The data collection times were as follows: 15 min after starting isoflurane administration (M1), 5 min after tumescence (M2), after beginning of surgical incision (M3), during breast pullout (M4), after clamping of the superficial caudal epigastric vein, and artery (M5), after the beginning of the approximation of the subcutaneous tissue (M6), after the beginning of the intradermal suture (M7), and at the end of the surgical procedure (Mfinal). The heart (HR) and respiratory (*f*) rates, mean arterial pressure (MAP), end-tidal CO_2 concentration ($EtCO_2$), expired isoflurane concentration (EtISO), and rectal temperature (RT) were measured. The HR, *f*, and $EtCO_2$ levels did not differ statistically. The mean EtISO presented in M2 (1.16 ± 0.41) was significantly lower than that in M3 (1.39 ± 0.40) and M4 (1.49 ± 0.49).

***Discussion*:** In the HR analysis, it was found that during all evaluation moments, the means remained within the reference range for the species. Moreover, the values during the breast pullout (M4) did not exceed 20% of those presented minutes before the beginning of the surgery (M2), which was indicative of analgesic rescue, suggesting that the animals did not experience pain. Hypoventilation resulted in an increase in $EtCO_2$ values. Thus, it can be said that in this study, there was no respiratory depression during the transoperative period, as the values of the variables *f* and $EtCO_2$ were within the reference for the species. With regard to the EtISO variable, there was no reduction in the MAC of isoflurane with the use of heated tumescence solution, as reported by some authors (EtISO 0.8%). However, the EtISO values presented here are close to those found in the literature during breast pullout (EtISO between 1.3% and 1.52%), with the use of refrigerated tumescence solution. In addition, the values shown in M4 are within the equivalent of 1 MAC (1.41%) of isoflurane, proving that heated tumescent local anesthesia is a safe technique and an excellent adjunct to inhalation anesthesia, as it provides intraoperative analgesia. Therefore, heated tumescence solution is safe and an excellent adjuvant in general inhalational anesthesia for radical unilateral mastectomy as it did not increase inhaled anesthetic consumption during surgery.

Keywords: tumescent local anesthesia, lidocaine, dogs, inhalation anesthesia, mammary tumors.

DOI: 10.22456/1679-9216.120564

Received: 10 November 2021 Accepted: 15 January 2022 Published: 2 February 2022

*Article based on a Dissertation submitted by the senior author in partial fulfillment of requirements for the Doctor's Degree - Programa de Pós-Graduação em Ciências Veterinárias (PPGCV), Unesp, Jaboticabal.

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INTRODUCTION

Mammary tumors, for which mastectomy is the main treatment, are the most common neoplasms in bitches, affecting approximately 52% of the population over 6 years old [9]. Mastectomy is invasive, bloody, and painful, and to reduce the pain stimulus in the transoperative period, provide postoperative analgesia and rapid recovery of patients, a locoregional anesthesia technique known as tumescence is associated with general inhalation anesthesia [11].

Despite the numerous benefits of tumescent local anesthesia, the most common complication is intraoperative hypothermia, a frequent disorder during the surgical-anesthetic procedure [4]. Intraoperative hypothermia can be even worse in mastectomy surgeries which is associated with tumescent local anesthesia technique since the use of a tumescent solution at 22°C reduces the body temperature by between 0.5°C and 1.0°C compared to the use of a solution heated to 37°C [29].

In Medicine, especially in plastic and dermatological surgery, it is common to use a heated tumescent solution to prevent intraoperative hypothermia [29]. In Veterinary medicine, refrigerated tumescence solution is used between 8 and 12°C [8], but no previous studies have examined the advantages, disadvantages, and possible adverse effects of the use of heated tumescence solution.

Therefore, this study aimed to assess whether a tumescent solution heated to between 37°C and 42°C promotes changes in cardiorespiratory parameters, whether it reduces intraoperative hypothermia, and whether it changes the requirement of inhaled anesthetic in the period of greatest pain.

MATERIALS AND METHODS

Animals

Eight female dogs (*Canis familiaris*) with breast cancer were included, without racial standardization, aged over seven years, weighing between 4 and 20 kg, and classified as ASA I or II according to the criteria established by the American Society of Anesthesiologists.

The patients underwent a basic physical examination, which involved measuring their heart rate (HR) in beats per minute (bpm), their respiratory rate (*f*) in movements per minute (mpm), and their rectal temperature (RT) in degrees Celsius (°C), as well as a qualitative evaluation of the color of the oral mucosa. Laboratory tests of blood count, alanine aminotransferase, serum creatinine, electrocardiogram evaluation, and metastasis research by means of chest radiography in three projections (lateral right, lateral left, and ventro-dorsal) and abdominal ultrasonography were also performed. Only animals without comorbidities, such as lung metastasis or abdominal cavity, advanced cardiomyopathy, and nephropathy, were included in the study.

Preparation of solution

Before infiltration of the tumescence solution, a 250 mL lactated ringer bottle was heated in a microwave for 40 s to reach a temperature between 37 and 42°C. Immediately after that, 12.5 mL of lactated ringer was removed and then added 12.5 mL of 2% lidocaine without vasoconstrictor (Xylestesin®)[1] plus 0.5 mL of adrenaline (Adren®)[2]. At this dilution, the concentration of lidocaine in the tumescent solution was 0.1%.

Experimental design

Before the surgical procedure, patients were subjected to an 8 h fasting without water deprivation [3].

Baseline measurements of HR, *f*, RT and systolic blood pressure (SBP) were recorded before the animals were sedated. Pre-anesthetic medication with meperidine[3] [Pethidine Hydrochloride® - 3 mg/kg, i.m] in association with chlorpromazine[4] [Chlorpromazine Hydrochloride® - 0.3 mg/kg, i.m] was administered intramuscularly.

After 20 min, sedation was established, and a wide trichotomy of the right thoracic limb was performed for venoclysis of the right cephalic vein, of the metatarsal region for catheterization of the dorsal metatarsal artery, as well as of the surgical area.

After cannulating the cephalic vein, anesthesia was induced with propofol (Propovan®)[1] using a sufficient amount to allow orotracheal intubation, which was performed with a Murphy orotracheal tube with a diameter suitable for the size of each patient. The orotracheal tube was connected to an inhalation anesthesia machine (SAT 500)[5], with a valve circuit of adequate volume for the patient's size, for anesthetic maintenance with isoflurane (Isoforine®)[1], using a

calibrated vaporizer (Penlon Pfill - Selectatec Model), under spontaneous ventilation.

To monitor the *f*, end-tidal carbon dioxide tension ($EtCO_2$), and expired fraction of isoflurane (EtISO), the capnograph and gas analyzer sensors were attached to the distal end of the orotracheal tube connected to the anesthetic circuit, and continuous isoflurane administration was started at a concentration sufficient to keep the animal in Plan 2 of the third stage, respecting the concepts described by Massone [18]. A mixture of oxygen and compressed air was used as the diluent to provide the animals with an inspired oxygen fraction (FiO_2) of 0.6.

The bitches were placed in the supine position on an active thermal mattress, where they remained throughout the experimental period. Then, the electrodes of the electrocardiograph and oximeter were placed on the limbs and tongue, and the metatarsal artery was catheterized to measure the mean blood pressure (MBP) with the aid of an aneroid manometer [21].

To infiltrate the solution into the subcutaneous tissue, a small incision was made with a 40 × 12 mm hypodermic needle below the third breast to allow the introduction of the Klein cannula (Klein needle for 20 mL/20 cm syringe)[6], which had a blunt tip. Then, half of the solution was infused toward the cranial breasts through this opening, while the other half was infused toward the caudal breasts.

To avoid contamination, the anesthetic solution intended for tumescence was administered according to the guidelines determined by Lapid [15]. Mastectomy was started 30 min after the administration of the tumescent solution. Before starting the surgical procedure, an antibiotic of the cephalosporin class[7] [Fazolon® - 30 mg/kg, i.v] was administered.

The moments of measurement of parameters were standardized according to the surgical-anesthetic act: 15 min after starting isoflurane administration (M1), 5 min after tumescence (M2), after beginning the surgical incision (M3), during breast pullout (M4), after clamping of the superficial caudal epigastric artery and vein (M5), after the beginning of the subcutaneous tissue approximation (M6), after the start of the intradermal suture (M7), and at the end of the surgical procedure (Mfinal). In these moments, if there was a need for analgesic rescue, it was performed with fentanyl (Fentanest®)[1] in bolus, intravenously, at a dose of 2 µg/kg supplemented with lactated ringer to a volume of 5 mL. Analgesic rescue was considered necessary when one or more cardiorespiratory parameters had a minimum increase of 20% in relation to the values presented in M2.

At the end of the surgery, the administration of inhaled anesthetics was interrupted, and the patients were allowed to be extubated before being sent to the recovery room.

Statistical analysis

Statistical analysis were performed by considering the mean and standard deviation values. Quantitative variables were analyzed using mixed linear models (parametric analysis), and the residuals of the models met the normality assumptions, according to the Cramer-von Mises test at a significance level of 5% ($P \leq 0.05$). All analysis were performed in Software R through the "lme4" package.

RESULTS

The mean age of the subjects was 9.1 ± 1.9 years. The dose of propofol required to allow orotracheal intubation was 3.94 ± 0.63 mg/kg, and the extubation time was 8.12 ± 3.18 min.

The variables HR, *f*, and $EtCO_2$ (Table 1) did not show any statistical differences across moments. The mean of the MBP variable (Table 1) at moment M1 was lower than that at M5, M6, M7, and Mfinal ($P < 0.05$), while those at M2 and M3 were smaller than those at M7 and Mfinal ($P < 0.05$). The mean EtISO (Table 1) presented in M2 was significantly lower than that in M3 and M4 ($P < 0.05$). Regarding the RT (Table 1), M1 had a higher mean than the other moments, and the same condition was observed in the comparison between M2 and the moments following it ($P < 0.05$). Furthermore, in Mfinal RT mean was significantly lower than M3, M4, and M5 ($P < 0.05$).

DISCUSSION

Regarding the methodology, the use of low doses of chlorpromazine and meperidine in pre-anesthetic medication (PAM) is justified by the age of the elderly animals. Geriatric animals have decreased drug clearance, which makes them more susceptible to sedation and analgesia conferred by medications used in the pre-anesthetic protocol [19].

Table 1. Mean values and standard deviation (x ± sd) of the heart rate (HR), mean blood pressure (MBP), respiratory rate (*f*), end-tidal carbon dioxide tension ($EtCO_2$), expired concentration of isoflurane (EtISO), and rectal temperature (RT), in the transoperative period, in bitches under general inhalation anesthesia, in association with a heated tumescence solution of 0.1% lidocaine.

	Variables					
	HR (bpm)	MBP (mmHg)	*f* (mpm)	$EtCO_2$ (mmHg)	EtISO (V%)	RT (°C)
M1	106 ± 18	63 ± 12^{a}	18 ± 13	40 ± 3	1.32 ± 0.40^{ab}	37.3 ± 0.9^{a}
M2	105 ± 25	69 ± 9^{ab}	19 ± 13	35 ± 4	1.16 ± 0.41^{a}	36.2 ± 1.0^{b}
M3	112 ± 25	65 ± 5^{ab}	25 ± 19	35 ± 2	1.39 ± 0.40^{b}	35.5 ± 1.0^{c}
M4	104 ± 9	71 ± 13^{ac}	18 ± 16	37 ± 4	1.49 ± 0.49^{b}	35.4 ± 1.2^{c}
M5	97 ± 13	75 ± 6^{bc}	15 ± 10	38 ± 4	1.35 ± 0.39^{ab}	35.4 ± 1.3^{c}
M6	103 ± 9	77 ± 9^{bc}	15 ± 11	38 ± 4	1.24 ± 0.21^{ab}	35.1 ± 1.1^{cd}
M7	105 ± 11	77 ± 7^{c}	20 ± 13	36 ± 4	1.19 ± 0.20^{ab}	34.8 ± 1.0^{cd}
Mfinal	105 ± 12	76 ± 9^{c}	16 ± 5	36 ± 4	1.25 ± 0.24^{ab}	34.6 ± 0.9^{d}

M1: 15 min after starting isoflurane administration; M2: 5 min after tumescence; M3: after beginning of surgical incision; M4: during breast pullout; M5: after clamping of the superficial caudal epigastric artery and vein; M6: after the beginning of the subcutaneous tissue approximation; M7: after the start of the intradermal suture; Mfinal: at the end of the surgical procedure. Means followed by different lower-case letters indicate significant differences at $P < 0.05$.

As we sought to evaluate the effects of a heated tumescent solution on the consumption of isoflurane, if doses close to the maximum recommended in the PAM were used, it would not be possible to determine whether the change in the amounts consumed was due to tumescent local anesthesia. Indeed, depending on the PAM used, there may be a reduction of up to 30% in the MAC of halogenates [26].

However, despite the use of low doses in PAM, there was no harm to induction, as the mean dose of propofol was between 2 and 5 mg/kg, a value recommended in the literature for premedicated patients [30].

In the HR analysis (Table 1), it was found that during all evaluation moments, the means remained within the reference range for the species [13]. It was also noted that the values during the breast pullout (M4), considered the moment of greatest pain stimulus, did not exceed 20% of the values presented minutes before the beginning of the surgery (M2), which, according to the described methodology is indicative of analgesic rescue. Thus, it can be said that the patients did not experience pain.

Regarding the MBP variable (Table 1), it was observed that the mean values were within the normal range for anesthetized dogs [14].

However, it was observed that the means of M1 were lower, with values very close to 60 mmHg, an acceptable lower limit for MBP without being considered hypotension [12]. This condition may be a consequence of the use of propofol in anesthetic induction since its use is related to decreased peripheral vascular resistance and vasodilation [6,10]. Furthermore, in the consulting literature [6,14], there was a reduction in MBP in the first 20 min after anesthetic induction with propofol, which corroborates the data of the study under discussion in which the MBP values were close to the lower limit 15 min after the start of isoflurane, that is, after induction.

Although the MBP means in M2 were smaller than those in M7 and Mfinal, which was unrelated to the EtISO values (Table 1). It is believed that the means were smaller because of the idle time of anesthesia, that is, the period in which the patients were anesthetized but without the surgical procedure. The M2 data were collected 5 min after the tumescence was performed, which, on average, resulted in 35 min of anesthesia without surgical stimulation, from the beginning of isoflurane administration until M2.

During surgical trauma, even in patients undergoing an adequate anesthetic plane, pro-inflammatory cytokines and hormones, such as catecholamines and cortisol, are released. The sympathetic-adrenal axis helps to maintain blood pressure and blood flow necessary for the normality of the cardiovascular system [20] since catecholamines promote vasoconstriction [27] and cortisol stimulates aldosterone secretion, which increases blood volume [20].

Thus, it can be said that in the time elapsed between the start of isoflurane administration and M2, there is no tissue injury caused by the surgical act, and,

consequently, there is no metabolic response to trauma, as mentioned above. In addition, there is a dose-dependent vasodilator effect of isoflurane [28], which contributes further to the lower MBP values in M2 compared to moments in which there was a stimulus of tissue injury promoted by surgical trauma (M7 and Mfinal).

It is noteworthy that even after the beginning of the surgery (M3) and at the moment of breast pullout (M4), considered the period of greatest pain stimulus in the mastectomy, the MBP values were within the reference range for anesthetized dogs and did not exceed 20% of the values presented in M2. This confirms the efficacy of heated tumescent local anesthesia in controlling intraoperative pain.

Hypoventilation results in increased $EtCO_2$ values [24]. Thus, it can be said that in this study, there was no respiratory depression during the transoperative period, as the values of the variables *f* and $EtCO_2$ (Table 1) were within the reference range for the species at all times during the transoperative period.

Similarly, researchers reported that after low doses of tramadol (2 mg/kg) [5] and methadone (0.3 mg/kg) [23], associated with the concentration of 1.5 MAC of isoflurane, there were no changes in the values of *f* and $EtCO_2$, demonstrating that the synergistic effect of opioids and halogenated agents in reducing respiratory rate is also dose-dependent.

With regard to the EtISO variable (Table 1), there was no reduction in the MAC of isoflurane with the use of heated tumescence solution, contrary to what was founding in the literature, with an EtISO of 0.8% after using a refrigerated tumescence solution [8].

However, the EtISO values presented here are close to those found by other authors who also used refrigerated tumescence solutions, and reported an EtISO between 1.3% and 1.52% at the time of breast pullout [17]. In addition, the values shown in M4 (Table 1) are within the equivalent of 1 MAC (1.41%) of isoflurane [22], proving that heated tumescent local anesthesia is a safe technique and an excellent adjunct to inhalation anesthesia as it provides intraoperative analgesia.

Hypothermia occurred during the transoperative period (Table 1). This situation is common during anesthetic procedures due to the vasodilator effect promoted by the drugs used [10, 28], which contributes to heat exchange. Furthermore, during anesthesia, there is a decrease in metabolism, which reduces heat production [4] and, consequently, predisposes the patient to greater decreases in body temperature.

Unlike what was expected and observed in the consulting literature [25], the use of the heated solution did not prevent the occurrence of intraoperative hypothermia since there was a significant difference between the moments (Table 1). Given this information, 2 hypotheses are proposed. First, the volume of solution infused may have been too small in relation to the animal's body extension to promote heating or avoid cooling.

The second hypothesis, and perhaps the most likely, concerns the possible vasodilation promoted by the heated solution, which would increase the patient's heat exchange with the environment. Beyond that, this heat exchange may have been aggravated during the 30 min that was expected between the end of the infiltration of the solution and the beginning of the surgical incision.

Continuous infusion of lidocaine is known to promote cortical depression, sedation, somnolence [2,7] and increase the anesthetic recovery time of patients anesthetized with propofol or isoflurane [1,16]. Although the study in question did not administer a continuous infusion rate of lidocaine, it was hypothesized that the animals in this study had an extubation time greater than the 6 ± 3 min found in the literature [8] due to a probable greater absorption of lidocaine as a result of local vasodilation promoted by the infiltration of the heated solution.

However, it is not possible to state that there was greater absorption of the local anesthetic because the plasma concentration of lidocaine in the animals was not evaluated, owing to the lack of funding during the execution of the experimental phase.

Other factors can influence extubation time, such as intraoperative hypothermia and volatile anesthetic concentration. However, as the current data are similar to those found in the literature for the aforementioned variables, the possibility that they influenced the extubation time was not considered.

CONCLUSIONS

Based on the results obtained with the methodology used, it can be concluded that the heated tumescence solution is safe, although it does not prevent intraoperative hypothermia. Moreover, it is an excellent adjuvant in general inhalational anesthesia for radical unilateral mastectomy since it did not increase inhaled anesthetic consumption, even at times of greater pain stimulus.

MANUFACTURERS

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***Ethical approval*.** This study was approved by the Ethics Committee on the Use of Animals (CEUA) under protocol No. 004271/18.

***Declaration of interest*.** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of paper.

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