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Evaluation of the isoflurane-sparing effects of a constant rate infusion of remifentanil undergoing mastectomy in dogs

Avaliação da concentração expirada de isoflurano em infusão continua de remifentanil em cadelas submetidas a mastectomia

Suzane Lilian Beier[1*]; Ademir Cassiano da Rosa[2];
Cláudio Roberto Scabelo Mattoso[3]; Aury Nunes de Moraes[2];
Nilson Oleskovicz[2]; Adriana Vieira Klein[4]; Ademar Luiz Dallabrida[2]

Abstract

The aims of this study were to evaluate the effects of two constant rate infusions of remifentanil on end tidal isoflurane (ETiso) in dogs undergoing mastectomy surgery. Eighteen bitches, 12±2 years of age, weighing 15±5 Kg were randomized into 3 groups (n=6/group) and underwent unilateral mastectomy due to mammary neoplasia. All animals received the premedications of morphine (0.5 mg Kg^{-1}) and acepromazine (0.03 mg Kg^{-1}) by intramuscular route (IM). Propofol dose-effect was used for induction of anesthesia. The animals were intubated and connected to a circle breathing system, and IPPV (intermittent positive pressure ventilation) was used to maintain normocapnia with an oxygen flow rate of 2 L/min and FiO_2 100%. Anesthesia was maintained with isoflurane and saline solution (control group [GCON], n=6) or intravenous infusion of remifentanil at a rate of 0.15 µg $Kg^{-1}min^{-1}$ (REMI 0.15 n=6) or 0.3 µg $Kg^{-1}min^{-1}$ (REMI 0.3 n=6). Cardiopulmonary variables and ETiso were monitored before and every 15 minutes after the start of surgery. The data were analyzed by ANOVA with multiple repetitions between moments and ANOVA followed by the Student Newman Keuls test (≤0.05) for comparisons between groups. Heart rate was lower at all moments in the REMI 0.15 and REMI 0.3 groups than in the GCON, and heart rate was not significantly different between the two remifentanil infusion groups. Additionally, the arterial blood pressure values (SAP, MAP and DAP) were not different between all groups. Baseline values (before surgery) of ETiso were not different between the 3 groups. After the start of surgery, ETiso ranged from 1.37±0.3 to 1.05±0.19 in the control group; in the REMI 0.15 and REMI 0.3 groups, ETiso was 36.5% and 65.7% lower than in the control group (M15). Remifentanil infusion reduced ETiso in a dose-dependent manner in animals undergoing radical mastectomy without causing significant cardiopulmonary alterations.

Key words: Dogs, mastectomy, remifentanil, isoflurane

Resumo

Os objetivos deste estudo são a avaliação dos efeitos de duas taxas fixas de infusão continua de remifentanil na concentração expirada de isoflurano (ETiso) em cadelas submetidas à mastectomia. Foram utilizadas 18 cadelas, 12±2 anos de idade e pesando 15±5 Kg. Os animais foram distribuídos

[1] Profª Drª, Deptº de Clínica e Cirurgia Veterinárias, Escola de Veterinária, Universidade Federal de Minas Gerais, UFMG, Belo Horizonte, MG, Brasil. E-mail: suzanelb@yahoo.com.br

[2] Profs. Drs. e Profs. Mestres, Deptº de Medicina Veterinária, Centro de Ciências Agroveterinárias, Universidade do Estado de Santa Catarina, UDESC, Lages, SC, Brasil. E-mail: cassivetr@hotmail.com; a2anm@cav.udesc.br; a2no@cav.udesc.br; a2ald@cav.udesc.br

[3] Discente de Pós-Doutorado, Dr., M.e, Médico Veterinário, Deptº de Clínica e Cirurgia Veterinárias, Escola de Veterinária, UFMG, Belo Horizonte, MG, Brasil. E-mail: crsmattoso@yahoo.com

[4] M.e, Médica Veterinária, Faculdade de Medicina, Universidade Estadual Paulista, UNESP, Botucatu, SP, Brasil. E-mail: adriklein@gmail.com

[*] Author for correspondence

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aleatoriamente em 3 grupos (n=6/grupo) e submetidos à mastectomia unilateral devido a neoplasia mamária. Todos os animais foram pré-medicados com morfina (0,5 mg Kg^{-1}) e acepromazina (0,03 mg Kg^{-1}), ambas por via intramuscular (IM). A indução da anestesia foi realizada com propofol (dose-efeito). Os animais foram intubados e conectados a um sistema circular com reinalação de gases. Foi utilizada ventilação com pressão positiva intermitente para manutenção de normocapnia com fluxo de oxigênio de 2 L/min e FiO_2 de 100%. A anestesia foi mantida com isoflurano e solução salina (grupo controle [GCON], n=6) ou infusão intravenosa de remifentanil na taxa de 0,15 μg $Kg^{-1}min^{-1}$ (REMI 0,15 n=6) ou 0,3 μg $Kg^{-1}min^{-1}$ (REMI 0,3 n=6). As variáveis cardiovasculares e a ETiso foram monitoradas antes e a cada 15 minutos após o início da cirurgia. Os dados foram analisados por ANOVA com repetições múltiplas para comparações entre momentos e ANOVA seguida de teste Student Newman Keuls (≤0.05) para comparações entre grupos. A frequência cardíaca foi menor em todos os momentos nos grupos REMI 0,15 e REMI 0,3 em comparação com GCON, sendo que não foram encontradas diferenças estatísticas para essa variável entre os dois grupos com infusão de remifentanil. Adicionalmente, os valores de pressão arterial (PAS, PAM e PAD) não apresentaram diferenças entre grupos. Os valores basais (antes da cirurgia) de ETiso não apresentaram diferenças entre os 3 grupos. Após o início da cirurgia, a ETiso variou entre 1,37±0,3 e 1,05±0,19 no grupo controle; nos grupos REMI 0,15 e REMI 0,3 a ETiso foi 36,5% e 65,7% menor que no grupo controle (M15). A infusão de remifentanil reduz a ETiso de forma dose dependente em animais submetidos a mastectomia radical sem causar alterações cardiopulmonares significativas.
Palavras-chave: Cães, mastectomia, remifentanil, isoflurano

Introduction

Intra-operative opioid infusions have been widely used as part of balanced anesthetic techniques in humans and animals (MICHELSEN; HUG, 1996; ILKIW et al., 1994; TONNER, 2005). This method of opioid administration can reduce the amount of other anesthetic agents used (HALL et al., 1987; HELLYER et al., 2001), reduce postoperative pain by providing preemptive analgesia (TAYLOR; BRENNAN, 2000) and reduce the overall stress response to surgery (LASCELLES, 2000).

Opioid analgesics are commonly used for this purpose in humans, as there is evidence that preoperative use of these agents can prevent central nervous system hypersensitization, reduce postoperative analgesia requirements and improve overall recovery from surgical procedures (WOOLF; CHONG, 1993).

Remifentanil is an ultra-short-acting agent with a context-sensitive half-time of approximately 3 minutes (FELDMAN et al., 1991; WESTMORELAND et al., 1993). Remifentanil differs from other opioid drugs in that it possesses an ester linkage that allows it to be broken down by plasma cholinesterases, resulting in reasonably predictable pharmacokinetics. After intravenous administration of remifentanil, the peak effect is achieved rapidly, and rapid elimination of remifentanil results in complete recovery from its systemic effects within 5-10 minutes (HOKE et al., 1997). Elimination of remifentanil does not depend on hepatic or renal function. These properties make remifentanil an ideal drug for constant and variable rate infusions (EGAN, 2000). Remifentanil has the dose-dependent anesthetic sparing effect that is characteristic of volatile anesthetics but also exhibits a ceiling effect that is characteristic of other opioid drugs. For opioids with a ceiling effect, increasing doses beyond a certain level does not further reduce the minimum alveolar concentration of volatile anesthetics (MICHELSEN et al., 1996). However, remifentanil is a potent respiratory depressant that causes decreases in respiration rate and tidal volume (EGAN et al., 1993).

Material and Methods

This study was approved by the Institutional Animal Care Committee (CETEA – CAV UDESC) under protocol number 1.09.09. Eighteen client-owned female dogs were admitted for unilateral mastectomy due to mammary neoplasia. Preoperative screening included thoracic radiography, CBC

(complete blood cell count), serum biochemical analyses and electrocardiography. Dogs with abnormal laboratory data, clinical signs of systemic disease or evidence of lung metastasis were not included in the study. Dogs were randomly and equally assigned to 3 groups (control, remifentanil low dose and remifentanil high dose).

Dogs were fasted overnight and deprived of water in the morning of the surgery. All dogs were premedicated with 0.03 mg kg^{-1} acepromazine maleate (Acepran 1% – Lab. Univet S.A. Indústria Veterinária – São Paulo, Brazil) and 0.5 mg kg^{-1} morphine sulfate (Dimorf 10 mg/ml – Cristália – Itapira/SP, Brazil) administered intramuscularly (IM). After 30 minutes, both cephalic veins were aseptically catheterized with a 20-gauge catheter (Angiocath- BD- Juiz de Fora/MG, Brazil). Anesthesia induction was performed with propofol (Diprivan- Zeneca, Cotia, Brazil) dose effect. After endotracheal intubation, the dogs were connected to a circle breathing system, and anesthesia was maintained with isoflurane (Isoforine – Lab. Cristália Produtos Químicos e Farmacêuticos Ltda. – Itapira, Brazil) in oxygen, (flow rate of 100 ml kg^{-1} min^{-1}) and intermittent positive pressure ventilation (IPPV) was used to maintain normocapnia between 35 and 45 mmHg. Dogs were positioned in dorsal recumbency with a warm blanket (Brasmed Veterinária – Paulínia/SP, Brazil) throughout anesthesia, and body temperature was monitored using an esophageal temperature probe. Throughout anesthesia, a balanced electrolyte solution (lactated Ringer's solution – Lab. Sanobiol Ltda – São Paulo, Brazil.) was administered intravenously (IV) at a rate of 10 mL $kg^{-1}min^{-1}$ using a peristaltic infusion pump.

The dorsal pedal artery was aseptically catheterized with a 22-gauge catheter (Angiocath – BD – Juiz de Fora/MG, Brazil) connected to a blood pressure transducer system to measure SAP (systolic arterial pressure), DAP (diastolic arterial pressure), and MAP (mean arterial pressure). The zero reference point of the pressure transducer was set at the level of the heart.

The HR (heart rate) and rhythm were obtained from ECG tracings. Adhesive electrodes were placed to obtain a continuous lead II ECG (Dixtal DX 2010, Philips Healthcare, Barueri/SP, Brazil).

After induction of anesthesia, a CRI (constant rate infusion) of either saline 0.9% NaCl solution (control group – GCON), 0.15 μg $kg^{-1}min^{-1}$ remifentanil (Ultiva- Lab. GlaxoWellcome – Rio de Janeiro/RJ, Brazil) (low dose group) or 0.30 μg $kg^{-1}min^{-1}$ remifentanil (high dose group) was initiated.

An experienced anesthetist adjusted the vaporizer (Isoflurane vaporizer – Fortec Keighley Yorkshire/England) settings to maintain a surgical depth of anesthesia. Determination of surgical depth of anesthesia was based on clinical signs, including the absence of palpebral reflexes, absence of jaw tonus, and MAP from 60 to 90 mmHg.

Hypotension was defined as SAP <90 mmHg or MAP <60 mmHg and was managed by decreasing the isoflurane concentration and using rapid IV fluid infusions (20 mL kg^{-1}) for 15 minutes. Bradycardia (HR <60 beats minute) lasting >5 minutes was treated with atropine (Atropina – Hypofarma – Ribeirão das Neves/MG, Brazil) (0.04 mg kg^{-1} IV).

At the end of surgery, the infusion of remifentanil was stopped, and IPPV was discontinued. Ventilation was supported manually until spontaneous ventilation resumed. At the moment that spontaneous breathing resumed, the endotracheal tube was disconnected from the circle breathing system and the dog was positioned in lateral recumbency. Additional postoperative analgesia was administered at the end of surgery and included morphine (0.5 mg kg^{-1}) IM, and meloxicam (Maxicam 0.2% – Lab. Ouro Fino – Cravinhos/SP, Brazil) (0.2 mg kg^{-1}) IV.

Baseline data were collected 30 minutes after the initiation of the infusions, and surgery commenced immediately after the collection of baseline data. Arterial blood gas samples, cardiovascular variables (HR, SAP, DAP, and MAP), ETiso (end tidal expired isoflurane), $ETCO_2$ (end tidal expired CO_2), and esophageal temperature values were obtained at

baseline and at 15-minute intervals for 60 minutes after the initiation of surgery.

All statistical analyses were carried out using computer statistical software (SigmaStat, Brazil). Data are presented as means ± SD. The data were submitted ANOVA with repeated measures between moments and were compared between groups using the Student Newman Keuls test. Differences were considered significant at $p < 0.05$.

Results

Cardiopulmonary data were tabulated (Table 1). Except at baseline, HR values were significantly lower in the remifentanil group than in the control group. There were no differences between the REMI 0.15 and REMI 0.3 groups. In the REMI 0.3 group, one dog received atropine (0.02 mg kg^{-1} IV) because of bradycardia (HR< 60 beats min^{-1}) associated with SAP< 90 mmHg. Systolic, median and diastolic pressures did not differ between the 3 groups, and despite the reduction in HR, blood pressure was normal, with SAP above 90 mmHg. However, for most time points, blood pressure was transiently higher in the control group than in the REMI 0.15 and REMI 0.3 groups.

End-tidal isoflurane concentrations were determined (Figure 1). Prior to initiation of surgery (baseline), there were no significant differences in ETiso concentration between the 3 groups. The dogs in the GCON, REMI 0.15 and REMI 0.3 groups required ETiso concentrations of 0.92±0.29%, 0.65±0.36% and 0.58±0.23%, respectively. After the surgery was started, there were remifentanil dose-dependent reductions in ETiso concentration of 36.5% and 65.7% in the REMI 0.15 and REMI 0.3 groups, respectively.

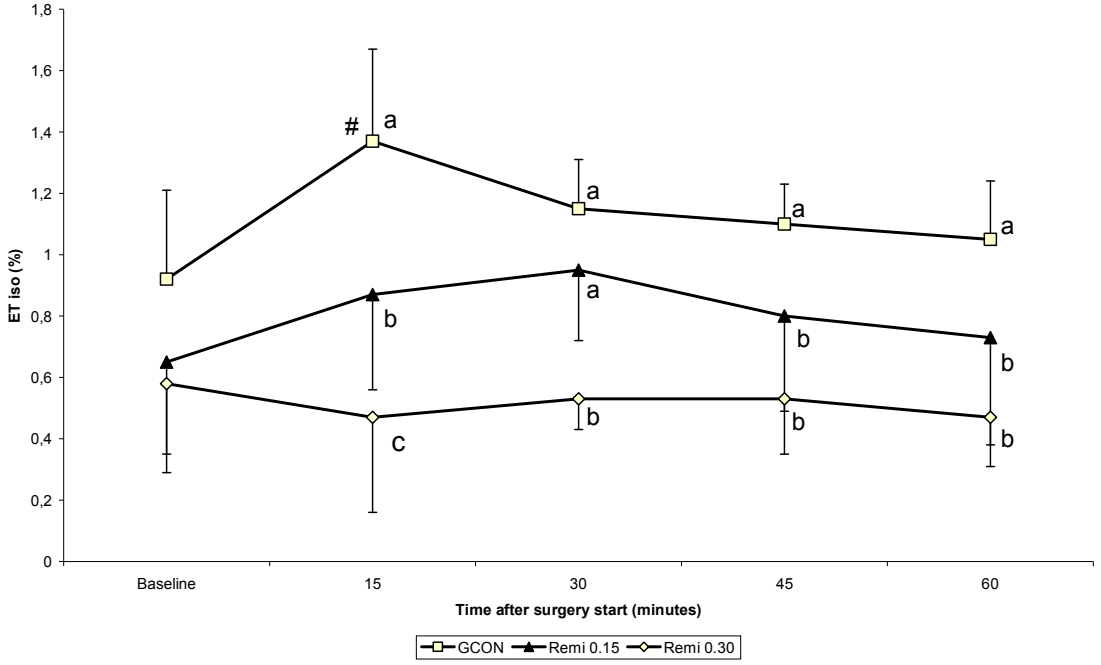
In the REMI 0.3 group, a reduction in PaO_2 (partial pressure of oxygen in arterial blood) was observed at the termination of anesthesia (moment M60) compared to baseline. No significant differences between the 3 groups were found for the values of pH (hydrogen ionic potential), $PaCO_2$ (partial pressure of CO_2 in arterial blood) or HCO^-_3 (bicarbonate). The pH values in the REMI 0.15 and REMI 0.3 groups were lower than those of the control group at moments M30 and M60. Additionally, in the REMI 0.15 and REMI 0.3 groups, the $PaCO_2$ values were increased at moments M30 and M60 compared to baseline. At baseline, BT was lower in the REMI 0.3 group than in the other groups. For all dogs, recovery from anesthesia was smooth and quiet without vocalization.

Table 1. Mean and standard-deviation (mean±SD) of heart rate (HR), respiratory rate (f_R), end-tidal expired isoflurane (ETiso), end-tidal expired CO_2 ($EtCO_2$), systolic arterial blood pressure (SAP), mean arterial blood pressure (MAP), diastolic arterial blood pressure (DAP), hydrogen ionic potential (pH), partial pressure of CO_2 in arterial blood ($PaCO_2$), partial pressure of oxygen in arterial blood (PaO_2), level of bicarbonate (HCO^-_3), and body temperature (TºC) in dogs undergoing unilateral mastectomy, before surgery (BL) and at 15, 30, 45 and 60 minutes after initiation of the administration of physiologic saline (GCON), 0.15 $\mu g\,kg^{-1}\,min^{-1}$ remifentanil (REMI 0.15) or 0.3 $\mu g\,kg^{-1}min^{-1}$ remifentanil (REMI 0.30).

Variables	Group	Moments				
		Baseline	M15	M30	M45	M60
HR	GCON	79±20	85±26	99±22[a]	106±17Aa	107±20Aa
	G 0.15	70±3	69±26	77±27	70±13b	81±20
	G 0.3	51±7	64±17	71±29	73±25b	72±24b
f_R	GCON	10±2	9±3	12±3	13±5	14±5[a]
	G 0.15	8±17	9±3	10±4	9±2	10±1
	G 0.3	8±2	7±2	7±2	10±3	9±3b
ETiso	GCON	0,92±0,29	1,37±0,3Aa	1,15±0,16a	1,1±0,13a	1,05±0,19a
	G 0.15	0,65±0,36	0,87±0,31b	0,95±0,23a	0,8±0,31b	0,73±0,35b
	G 0.3	0,58±0,23	0,47±0,31c	0,53±0,1b	0,53±0,18b	0,47±0,16b
$ETCO_2$	GCON	31±5	32±7	32±5	33±5	32±4a
	G 0.15	35±6	37±2	38±5	38±5	37±4b
	G 0.3	34±4	36±6	38±5	40±5	40±5b
PAS	GCON	106±8	97±10	110±15	103±17	108±19
	G 0.15	94±16	89±14	93±14	90±16	96±13
	G 0.3	85±15	100±21	100±21	91±12	91±14
PAM	GCON	70±11	72±10	81±14	75±14	80±16
	G 0.15	64±6	64±5	66±7	61±9	68±14
	G 0.3	60±9	72±20	72±8	64±9	65±11
PAD	GCON	55±12	61±7	68±14	64±10	66±17
	G 0.15	49±7	51±4	53±7	47±9b	54±13
	G 0.3	47±7	61±19	61±7	52±7	54±12
pH	GCON	7,35±0,08	-	7,27±0,07b	-	7,32±0,04a
	G 0.15	7,35±0,08	-	7,28±0,07b	-	7,28±0,05b
	G 0.3	7,36±0,04	-	7,31±0,03a	-	7,29±0,03b
$PaCO_2$	GCON	34±8	-	43±8a	-	38±8b
	G 0.15	36±10	-	43±9a	-	44±6a
	G 0.3	34±4	-	40±3b	-	44±7a
PaO_2	GCON	238,5±58,6b	-	246,7±86,2b	-	300,9±33,4
	G 0.15	336,7±103b	-	321,7±52,6b	-	273,7±88,2
	G 0.3	412,8±46,2a	-	393,9±81,4a	-	339,5±39,2a
HCO^-_3	GCON	18,6±2,2	-	19,3±2,5	-	19,4±2
	G 0.15	19±2,4	-	19,7±2,1	-	20,5±1,7
	G 0.3	19,1±1,5	-	20,3±1,1	-	19,4±2,3
TºC	GCON	37,7±0,7a	-	37,0±0,5a	-	36,7±0,3
	G 0.15	37,0±1,2a	-	36,7±0,9b	-	36,5±0,7
	G 0.3	36,3±0,4b	-	36,0±1,0b	-	36,2±1,1

Differents subscripts a and b indicate significant differences between groups by ANOVA test ($p \leq 0.05$); uppercase A in the line indicates a significant difference from baseline in the same group by ANOVA one way test, followed by Student Newman Keuls test ($p \leq 0.05$).

Figure 1. End-tidal isoflurane in REMI 0.15, REMI 0.3 and GCON. # indicates a significant difference from baseline in the same group; differents subscripts a and b indicate significant differences between groups.



Discussion

For protocols of balanced anesthesia, opioid analgesic infusions are commonly used in combination with inhalation anesthetics, as opioid analgesic infusions reduce the MAC of inhalation anesthetics (STEAGALL et al., 2006; MONTEIRO et al., 2010) and reduce the rate of infusion of intravenous anesthetics (CARARETO et al., 2004). Remifentanil has a pharmacokinetic profile that is ideal for continuous infusion with rapid onset of action and elimination, and its elimination is independent of hepatic and renal function (HOKE et al., 1997; EGAN, 2000).

Premedication with acepromazine and morphine influences the ETiso requirement, and this was observed in the GCON, as ETiso remained near 1 MAC during surgery in that group. Although isoflurane concentrations are influenced by these drugs, the premedication and induction anesthetics used were the same for the control and experimental groups and, therefore, did not influence the comparison between the experimental (remifentanil) and control groups. The evaluation of baseline values after 30 minutes of remifentanil initiation confirmed 100% equilibrium in remifentanil concentration in the plasma across the blood-brain barrier due to the pharmacokinetic properties of remifentanil (half-life alpha occurs at 5.3 minutes) (HOKE et al., 1997).

The MAC is the end-tidal concentration of a volatile anesthetic that prevents gross purposeful movement to a supramaximal noxious stimulus in 50% of the population (EGER et al., 1965). In dogs, mean isoflurane MAC values have been reported to range from 1.2% to 1.8% (STEFFEY; HOWLAND JÚNIOR, 1977). The reduction in ETiso by remifentanil observed in this study occurred in a dose-dependent manner, with the REMI 0.15 and REMI 0.3 groups having lower values than the GCON.

End-tidal isoflurane concentrations were determined (Figure 1). Prior to initiation of surgery (baseline), there were no significant differences in ETiso concentration between the 3 groups. The dogs

in the GCON, REMI 0.15 and REMI 0.3 groups required ETiso concentrations of 0.92 ± 0.29%, 0.65 ± 0.36% and 0.58 ± 0.23%, respectively. For this clinical study, standard nociceptive stimuli (unilateral mastectomy) were used, and all surgeries were performed by the same surgeon with depth of anesthesia controlled by the same anesthetist; this procedure reduced variability, especially in regards to intraoperative isoflurane requirements.

In the present study, 15 minutes of surgery (M15) was the moment of greatest nociceptive stimuli, as indicated by the largest reduction in isoflurane requirement at that moment compared to the GCON, 65.7% and 36.5% in the REMI 0.3 and REMI 0.15 groups, respectively. The findings of this study are consistent with those of Monteiro et al. (2010), who obtained reductions of isoflurane requirement of 59% and 43% with the same doses of remifentanil as those used in this study (0.3 and 0.15 μg $kg^{-1}min^{-1,}$ respectively). However, Monteiro´s study used electrical stimulus. Ferreira et al. (2009) did not observe a significant difference in MAC in cats at remifentanil rates of 0.25, 0.5 and 1.0 μg $kg^{-1}min^{-1}$, with reductions of 23.4, 29.8 and 26%, respectively. Because atropine may alter inhalant uptake into the lungs due to changes in cardiac output, the dog that received atropine (n=1) in the REMI 0.3 group was removed from the statistical analysis of ETiso concentration.

Allweiler et al. (2007) performed a study of orthopedic surgeries in dogs with meperidine (2 mg kg^{-1}) as the only pre-anesthetic medication and observed ETiso values between 0.78 and 0.65 V% with remifentanil infusion rates of 0.1 and 0.25 μg kg^{-1} min^{-1}, respectively, and this difference was not statistically significant. The use of opioids as pre-anesthetic medications potentiated the effects of remifentanil infusion at both rates tested (0.15 and 0.3 μg kg^{-1} min^{-1}), making it possible to perform the surgery; furthermore, even with the lower rate of remifentanil infusion, the requirement of isoflurane was reduced.

In this study, the REMI 0.15 and REMI 0.3 groups had lower heart rates than the control group at all moments. In the GCON, heart rate was higher during the 60 minutes of the surgery than at baseline. This elevation in heart rate during the surgical procedure in the GCON was due to sympathetic stimulation, which can occur due to insufficient analgesia prior to surgical stimuli. In the remifentanil infusion groups, the heart rates were lower at baseline (measured at 30 minutes after infusion initiation without surgical stimuli) than in the GCON, which was due to vagal stimulation by this opioid via binding to μ-opioid receptors (ALLWEILER et al., 2007). The dose and speed of administration of remifentanil can directly influence negative chronotropism (JAMES et al., 1992). Similarly, a dose-dependent reduction in heart rate was observed in rats (MICHELSEN et al., 1996), dogs (MURRELL et al., 2005; ALLWEILER et al., 2007; MONTEIRO et al., 2011; GIMENEZ et al., 2011) and humans (GLASS, 1995).

The arterial pressure values SAP, MAP and DAP remained stable and indicated normotension throughout surgery in all 3 groups; therefore, the remifentanil infusion rates used in this study preserved the integrity of baroreflex activity, and these findings were similar to those of Howie et al. (2001). Despite the decreased heart rate in the remifentanil groups, which can decrease cardiac output, the arterial pressure values were stable, probably due to an increase in systemic vascular resistance (ILKIW et al., 1994).

Because atropine may be a confounding factor when interpreting cardio-vascular data (HR, SAP, DAP, and MAP), the dog that received atropine (one dog in the REMI 0.3 group) was removed from the statistical analysis of these variables.

Monteiro et al. (2011) used a different constant rate of remifentanil infusion and obtained similar results to those of this study, including decreased heart rate and cardiac index and stable arterial pressure (although a significant increase in arterial blood pressure was observed with the higher infusion

rate of remifentanil (0.9 μg kg^{-1} min^{-1})), which can be explained by an increase in the systemic vascular resistance index, which is correlated with an increase in vasopressin level.

Francis et al. (2008) also found that remifentanil in combination with inhalation anesthetics can cause bradycardia and decrease cardiac output, but it can also increase systemic vascular resistance up to 120% through stimulation of vasopressors, such as angiotensin II and vasopressin, to maintain arterial blood pressure at normal values in dogs. Allweiler et al. (2007) observed higher values of arterial blood pressure in animals treated with remifentanil than in the control group. μ-agonist opioids can release vasopressin into the circulation, but the mechanism of this effect it not yet clear (HELLEBREKERS et al., 1989). Vasopressin acts on V1 receptors located in the smooth muscle cells of blood vessels to induce vasoconstriction, which increases systemic vascular resistance (LEHTINEN et al., 1984).

IPPV was used to maintain $ETCO_2$ values at eucapnia and to maintain a stable respiratory standard and respiratory rate, as respiratory depression is a common adverse effect of pure μ-agonist opioids (AMIN et al., 1995). In all groups in this study, $ETCO_2$ values were maintained within acceptable limits. When using remifentanil, the cardiopulmonary system must always be monitored and respiratory support must always be used, because remifentanil causes pronounced respiratory depression (ALLWEILER et al., 2007).

In the REMI 0.15 and REMI 0.3 groups, pH decreased and $PaCO_2$ increased during surgery compared to the baseline values, and this indicates that IPPV was not effective in some animals. The PaO_2 values were also lower than expected for animals breathing 100% oxygen ($FiO_2 = 1$), as was the case for all 3 groups in this study. The PaO_2 values were 3 to 5 times the fraction of inspired oxygen, which led to an imbalance in ventilation perfusion in all groups. Oxygenation and alveolar gas exchange were not efficiently performed, even with ventilation maneuvers, due to the more advanced age of some animals (the majority of animals were geriatric). Many of the geriatric animals may have had pulmonary injuries related to age, such as alveoli fibrosis, collapse of the alveoli septa, vascular fibrosis, decrease in pulmonary elasticity, and decrease in ventilator activity (WAHBA, 1983). These alterations could decrease the functional alveolar surface area, which may impair the ventilation/oxygenation and consequently result in higher $PaCO_2$ values, lower PaO_2 values and lower pH, which was observed in all 3 groups of this study, even with the use of IPPV. The HCO_3^- values remained within the acceptable range for canines in all groups, none of which showed any disturbances of an acid-base nature.

The transition period between the end of remifentanil infusion and recovery deserved special attention due to the context of analgesia in this study. After the end of the surgical procedure (60 min.), the animals received morphine at a dose of 0.5 mg kg^{-1} IM. The remifentanil infusion was maintained for 30 minutes based on the onset time of morphine to avoid insufficient analgesia, because after ending remifentanil infusion, the systemic effects of remifentanil are lost within 5 to 10 minutes (HOKE et al., 1997). In the REMI 0.15 and REMI 0.3 groups, all animals resumed spontaneous ventilation within the first 10 minutes after the end of infusion, and the recovery period was considered smooth, with no animal showing signs of pain or excitation, which indicated the efficiency of the analgesic protocol with intraoperative remifentanil.

Even with the use of a thermal mattress to avoid a decrease in temperature in the animals, a decrease in temperature was observed in all groups during the surgical procedure. This decrease in body temperature can be attributed to a decrease in metabolic activity and depression of the thermoregulatory system due to the use of central nervous system depressor drugs. Hypothermia can result in slower enzymatic elimination of remifentanil, extending the effects of this drug even after the end of infusion (RUSSELL et al., 1997).

In summary, intravenous remifentanil had great efficiency as part of a balanced anesthesia protocol through the reduction of the requirement of isoflurane in dogs undergoing mastectomy surgery. During remifentanil administration, close monitoring of HR and mean arterial blood pressure is mandatory and IPPV must be available.

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