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# Comparison of fentanil or remifentanil prolonged continuous infusion in dogs undergoing elective ovariohysterectomy

**Gabriela Borges Conterno[1*] Samuel Jorge Ronchi[1] Felipe Comassetto[1] Luara da Rosa[1] Mariana Baron[1] Karoline Simião Sabino[1] Nilson Oleskovicz[1]**

[1]Universidade do Estado de Santa Catarina (UDESC), 88503-140, Lages, SC, Brasil. E-mail: gabrielaconterno@hotmail.com. *Corresponding author.

**ABSTRACT**: It aimed to compare the trans anesthetic clinical and perioperative analgesic effects by prolonged continuous infusion of fentanyl (GF, bolus of 5 µg/kg and continuous infusion (CI) of 15 µg/kg/h) or remifentanil (GR, CI of 18 µg/kg/h) in dogs undergoing to elective ovariohysterectomy. Twenty female healthy dogs were premedicated with acepromazine, inducted to unconsciousness with propofol and kept under anesthesia with isoflurane. The M0 (baseline) was recorded and animals were randomly allocated in GF (n = 10) or GR (n = 10), recording clinical and blood gas parameters every 15 minutes (M15…M120) for two hours and, after, during surgery, adjusting the opioid rate according to surgical requirement. The isoflurane vaporization reduced by up to 47% and 42% in GF and GR, respectively, when compared to M0. During the first two hours of CI, six animals of each group required atropine intervention and three animals of GF required ephedrine. The number of rate adjustments during intraoperative was significant higher in GR when compared to GF (P = 0.0248). By the Log-rank test, there was a higher possibility of not receiving analgesic rescue in the first 30 minutes of postoperative in GF when compared to GR (P < 0.0001) and all animals required analgesic rescue during the firsts 3 and 6 hours in GR and GF, respectively. It is concluded that, when the proposal continuous infusions were compared, fentanyl required fewer analgesic rescues during perioperative, nonetheless, it is recommended rate adjustment during intraoperative and additional analgesia for postoperative for both treatments.
**Key words**: dogs, nociception, ovariohysterectomy, opioid, perioperative.

## Comparação entre a infusão contínua prolongada de fentanil ou remifentanil em cadelas submetidas a ovariohisterectomia eletiva

**RESUMO**: Objetivou-se comparar os efeitos clínicos intraoperatórios e analgésico perioperatório ofertados pela infusão contínua prolongada de fentanil (GF, *bolus* de 5 µg/kg e infusão contínua (IC) de 15 µg/kg/h) ou remifentanil (GR, IC de 18 µg/kg/h) em cadelas submetidas a ovariohisterectomia eletiva. Vinte cadelas hígidas foram pré-medicadas com acepromazina e induzidas com propofol e mantidas sob anestesia com isoflurano. Registrado M0 (basal) os animais foram alocados aleatoriamente em GF (n = 10) ou GR (n = 10), registrando parâmetros clínicos e hemogasométricos a cada 15 minutos (M15...M120), totalizando 02h e, posteriormente, durante o procedimento cirúrgico, sendo a taxa do opioide alterada conforme o requerimento cirúrgico.A vaporização de isoflurano reduziu em até 47% e 42% no GF e GR, respectivamente, em relação ao M0. Durante as primeiras duas horas de IC, seis animais de cada grupo necessitaram de intervenção com atropina e três animais do GF de efedrina. O número de ajustes de taxas no intraoperatório foi significativamente maior no GR comparado ao GF (P = 0,0248). Pelo teste de Log-rank, houve maior probabilidade de não receber resgate analgésico nos primeiros 30 minutos de pós-operatório no GF comparado ao GR (P < 0,0001) e todos os animais necessitaram de resgate analgésico dentro das primeiras três e seis horas no GR e GF, respectivamente. Conclui-se que, nas taxas propostas, a utilização de fentanil necessitou de menos resgates analgésicos no intra e pós-operatório, no entanto, recomenda-se ajuste de taxa intraoperatória e analgesia suplementar pós-operatória em ambos os tratamentos.
**Palavras-chave**: cães, nocicepção, ovariohisterectomia, opioide, perioperatório.

## INTRODUCTION

Surgical procedures typically elicit nociceptive stimuli that trigger autonomic nervous system responses during general anesthesia. Therefore, the use of drugs to inhibit such stimuli plays a major role in anesthesia protocols (PASCOE, 2000). Among these drugs, opioids are widely employed to ensure adequate analgesia during surgical interventions (MWANGI et al., 2018).

Fentanyl is a fast-acting opioid that exhibits a high affinity towards µ-opioid receptors (PASCOE, 2000). In humans, it has been observed that fentanyl can exhibit a residual effect when administered through prolonged continuous infusion (CI) protocols lasting over two hours (HUGHES et al., 1992). A previous study in dogs demonstrated that the total clearance of fentanyl (10 µg/kg/h) decreased as the duration of infusion increased, underscoring its cumulative effect in this species (SANO et al., 2006).

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On the other hand, remifentanil, another μ-opioid receptor full agonist, possesses a pharmacokinetic profile characterized by a notably shorter elimination half-time compared to fentanil (5.59 vs. 182.1 minutes), making it an ideal choice for extended CI (HOKE et al., 1997; SANO et al., 2006), since remifentanil does not lead to cumulative effects.

Comparison studies between these two opioids have indicated that postoperative analgesia achieved with fentanyl surpasses remifentanil's in various species, primarily due to the lower cumulative effect associated with remifentanil (SIMONI et al., 2008; SAURI-ARCEO et al., 2014). Furthermore, this unique characteristic results in shorter postoperative recovery times (KURUM et al., 2012).

This study aimed to evaluate the clinical and analgesic effects of prolonged CI of fentanyl or remifentanil and compare their residual analgesic effects by determining the time to first postoperative rescue analgesia in female dogs undergoing elective ovariohysterectomy.

## MATERIALS AND METHODS

Twenty female dogs, carefully selected based on their clinical history, physical examination, and hematological and biochemical parameters (alanine aminotransferase, albumin, urea, creatinine, and total plasma protein levels), were enrolled for elective ovariohysterectomy. Exclusion criteria included deviations in the aforementioned parameters, unruly behavior, or any history indicative of systemic disease. The animals were acclimatized for 24-hours in an isolated area within the hospital's facilities and subjected to 12-hour fasting for food and 6-hour fasting for water.

On the study day, the dogs were premedicated with 0.05 mg/kg acepromazine (Acepran 0.2%, Vetnil Indústria e Comércio de Produtos Ltda., Louveira, SP, Brazil) administered intramuscularly (IM). Venous access through the cephalic vein was established 20 minutes after tranquilization. The dogs were induced into unconsciousness for endotracheal intubation with 1 mg/kg propofol (PROpovan, Cristália, São Paulo, SP, Brazil) administered intravenously (IV) in 4 mg/kg total concentration. Endotracheal intubation was followed by connection to a circular valve system with partial gas reinhalation (DatexOhmeda 9100c, GE Healthcare, Barueri, SP, Brazil) at a diluted oxygen flow rate of 50 ml/kg/min for inhalation anesthesia with isoflurane (Isoflorine, Cristália, São Paulo, SP, Brazil) at a concentration at the end of expiration (EtISO) of 1.4 V%. Arterial access was then achieved via the dorsal foot artery, and M0 was recorded 10 min later (baseline moment without surgical stimulation).

The animals were randomly assigned to two groups: Group Remifentanil (GR) (n = 10) received saline bolus followed by CI of remifentanil (18 μg/kg/h; REMIfas, Cristália, São Paulo, SP, Brazil); Group Fentanyl (GF) (n = 10) received bolus (5 μg/kg) followed by CI of fentanyl (15 μg/kg/h). The administration volumes and rates for both groups were identical to maintain blinding of the treatments using a universal syringe volumetric infusion pump (ST 670, Samtronic, São Paulo, SP, Brazil).

The animals remained unstimulated under a fixed-rate CI regimen for 2 h and the EtISO was adjusted to ensure that the animals were maintained in plane 2 of Stage III, according to Guedel's classification. The assessments began 15 min after the start of CI and lasted for 2 h (M15, M30, M60,... M120). After the total time elapsed, the surgical procedure of elective ovariohysterectomy was initiated, and the following moments were recorded: M1, immediately after celiotomy; M2, after clamping the right ovarian pedicle; M3, after clamping the left ovarian pedicle; M4, after clamping the cervix; M5, after myorrhaphy; M6, after dermorrhaphy.

The following parameters were assessed using a multiparameter monitor (Carescape Monitor B650; GE Healthcare, São Paulo, SP, Brazil): heart rate (HR) measured using electrocardiography in lead II; respiratory rate (*f*) measured using capnography; peripheral oxygen saturation ($SpO_2$) level measured using pulse oximetry, with a sensor attached to the tongue; mean arterial pressure (MAP) measured using an invasive method; body temperature (Tc) through a transesophageal sensor; end-tidal carbon dioxide concentration ($EtCO_2$) measured using capnometry, with a side-streamsensor attached to the tracheal tube outlet (the sensor was automatically calibrated for each animal); expired fraction of isoflurane (EtISO) measured using a gas analyzer, with a sensor attached to the tracheal tube outlet (the sensor was calibrated and checked for the warranty period). The vaporizer and gas analyzer of the multiparameter monitor were calibrated using the DH-004 (FI-21 Riken Keiki ®) and DH-025 (Standard Gas Mixture, White Martins ®) equipment. In addition, to assess the MAP, the arterial access was connected to a tube filled with heparinized solution as well as to a pressure transducer, which was leveled at the height of the cartilage of the manubrium (right atrium), to ensure that it was reset, with the local atmospheric pressure used as a reference.

Furthermore, during M0, M15, M45, M75, and M120, the arterial blood was collected for

blood gas analysis (Cobas b 121; Roche Diagnóstica Brasil Ltda, São Paulo, SP, Brazil) and the following parameters were determined: hydrogen potential (pH), partial pressure of oxygen ($PaO_2$), partial pressure of carbon dioxide ($PaCO_2$), arterial oxygen saturation ($SaO_2$), bicarbonate concentration ($HCO_3$), and base deficit or base excess (BD or EB, respectively).

Atropine (0.044 mg/kg, IV) was administered under anesthesia if the animals had HR of < 50 bpm and/or when the decrease in HR was accompanied with a decrease in the MAP of < 60 mmHg. If only MAP decreased, ephedrine was administered (0.1 mg/kg, IV). If $EtCO_2$ values were > 50 mmHg, volume-cycled mechanical ventilation was initiated with the aim of maintaining normocapnia ($EtCO_2$ between 35 and 45 mmHg): initial tidal volume (Vc) of 10 ml/kg; *f* of 10 mpm; inspiration:expiration ratio of 1:2 (adjusted as necessary, limiting Vc to 20 ml/kg and *f* to 20 mpm). Regard to intraoperative rescue analgesia, if at least two of the three variables (HR, MAP, and/or *f*) increased by 20% relative to M120 (of baseline surgical moment), the intraoperative rate of fentanyl/remifentanil increased by 20%, following the criteria proposed by KURUM et al. (2012).

The infusion was discontinued immediately at the end of the surgical procedure, and the extubation time was recorded. Postoperative pain was assessed 30 min after extubation and then every hour after extubation for a total of 6 h. The animals were evaluated using the visual analog scale and short form of the Glasgow Composite Pain Scale (GCS), and rescue analgesia was required when GCS scores were ≥ 6. The evaluation lasted for 6 hours postoperatively, even if the animal had scored for rescue analgesia at certain previous point. Rescue analgesia consisted of 0.2 mg/kg meloxicam (Maxicam 0.2%, Ourofino Saúde Animal, Vinhedo, SP, Brazil) and 25 mg/kg dipyrone (Dipyrone 50%, Ibasa, Porto Alegre, RS, Brazil), both IV.

Regarding statistical analysis, the Shapiro–Wilk normality test was performed, and data with a normal distribution were subjected to two-way analysis of variance followed by Dunnett's test to determine differences relative to the baseline. Further, they were subjected to an unpaired t-test to detect differences between the groups. The study was divided into preoperative assessment, which covered the period from M0 to M120, considering M0 as the baseline, and intraoperative assessment, which covered the surgery period, considering M120 as the baseline. Regarding both intra- and postoperative rescue analgesia, survival curves were analyzed using the Mantel–Cox test to detect differences in its occurrence. Finally, Fisher's exact test was used to compare the groups regarding the number of animals rescued during the 30-min postoperative assessment. Results were presented as mean ± standard deviation and the significance was set at 95% ($P \leq 0.05$).

## RESULTS

All animals initially enrolled in this study were included without any exclusions. The animals were of mixed breeds and had a mean age of 16.2 ± 6.3 months in GF and 16.4 ± 6.91 months in GR (P = 0.9472). However, a notable difference was observed in the animal's weight (P = 0.032), with a mean weight of 15.26 ± 4.04 kg in GF and 11.29 ± 3.57 in GR. Surgical duration was similar, 58 ± 4 and 57 ± 3 minutes for GF and GR, respectively (P = 0.7934). The total infusion time, including the first 2 hours and the duration of the surgical procedure, amounted to 191 ± 3 minutes in GF and 188 ± 3 minutes in GR (P = 0.5209).

In the initial 2 hours of continuous infusion (CI), six animals in each group required atropine, with an additional need for ephedrine in three animals from GF, resulting in two administrations per animal. During this period, HR exhibited a 33% decreased in GF at M120 when compared to M0 and a 30% decrease in GR at M15 compared to M0 (Table 1). Notably, MAP demonstrated a 24% increase at M60 compared to M0 in GF and a 21 increase at M105 compared to M0 in GR (Table 1).

In terms of respiratory dynamics, both groups exhibited a reduction in *f*, 29% and 33% decrease in GF and GR, respectively, at M15 compared to M0 (Table 1). Furthermore, there was a notable elevation in $EtCO_2$, with a 25% increase in GF and a 23% increase in GR at M15 when compared to M0 (Table 1). Mechanical ventilation was initiated for all animals during the first 2 hours of CI. Additionally, $PaCO_2$ was 13% higher in GR than in GF at M15 (Table 2). Additionally, the GR exhibited a decrease in pH at M15 and M45 in comparison to M0 (P = 0.001 and P = 0.0025, respectively). On the other hand, bicarbonate ($HCO_3$) levels were higher at M15 relative to M0 in both GF and GR (P = 0.0412 and P = 0.0028, respectively) (Table 2). Moreover, oxygen saturation ($SpO_2$) displayed a significant increase from M60 to M120 in comparison to M0 within GF (P < 0.05) (Table 1).

Thought the study, EtISO exhibited a steady linear decrease, with statistically lower values from M30 to M120 in GF and from M15 to M120 in GR, both compared to M0. This reduction in

Table 1 - Mean values and standard deviation of heart rate (HR), respiratory rate *(f)*, mean arterial pressure (MAP), expired fraction of carbon dioxide ($EtCO_2$), peripheral oxygen saturation ($SpO_2$), expired fraction of isoflurane (EtISO), and body temperature ($T_c$) of female dogs initially premedicated with acepromazine (0.05 mg/kg), induced with propofol (4 mg/kg), and maintained under inhalation anesthesia with isoflurane (1.4 V%) (M0). After administering fentanyl (2.5 µg/kg bolus followed by 15 µg/kg/h continuous infusion [CI]) (GF, n = 10) or remifentanil (bolus of 0.9% saline solution followed by 18 µg/kg/h CI) (GR, n = 10), all parameters were recorded at M15, M30, M45, M60, M75, M90, M105, and M120, i.e., every 15 min. During these moments, the animals remained unstimulated, and isoflurane was adjusted to maintain the animals in the plane 2 of Stage III, according to Guedel's classification.

| | | M0 | M15 | M30 | M45 | M60 | M75 | M90 | M105 | M120 |
|---|---|---|---|---|---|---|---|---|---|---|
| FC (bpm) | GF | 115 ± 21 | 83 ± 34 | 96 ± 51 | 93 ± 40 | 93 ± 35 | 86 ± 25 | 93 ± 30 | 83 ± 20 | 77 ± 16 A |
| | GR | 111 ± 17 | 73 ± 17 A | 85 ± 38 | 90 ± 33 | 97 ± 30 | 96 ± 26 | 87 ± 30 | 83 ± 28 | 77 ± 23 |
| *f* (mpm) | GF | 14 ± 6 | 10 ± 4 A | 15 ± 3 | 17 ± 3 | 17 ± 3 | 16 ± 3 | 16 ± 3 | 16 ± 4 | 16 ± 4 |
| | GR | 15 ± 5 | 10 ± 4 A | 16 ± 4 | 17 ± 2 | 17 ± 2 | 17 ± 2 | 16 ± 3 | 16 ± 3 | 16 ± 3 |
| PAM (mmHg) | GF | 62 ± 10 | 58 ± 8 | 62 ± 9 | 70 ± 12 | 77 ± 16 A | 69 ± 7 | 69 ± 9 | 66 ± 5 | 65 ± 5 |
| | GR | 65 ± 6 | 60 ± 12 | 67 ± 15 | 76 ± 12 | 79 ± 10 | 74 ± 10 | 77 ± 13 | 79 ± 14 A | 76 ± 7 |
| $EtCO_2$ (mmHg) | GF | 40 ± 5 | 50 ± 6 A | 46 ± 8 | 43 ± 3 | 42 ± 4 | 41 ± 4 | 41 ± 5 | 40 ± 5 | 41 ± 5 |
| | GR | 43 ± 6 | 53 ± 9 A | 45 ± 7 | 44 ± 6 | 42 ± 4 | 40 ± 3 | 41 ± 2 | 40 ± 1 | 39 ± 3 |
| $SpO_2$ (%) | GF | 96 ± 2 | 97 ± 2 | 97 ± 2 | 97 ± 2 | 98 ± 1 A | 97 ± 1 A | 98 ± 1 A | 98 ± 1 A | 98 ± 1 A |
| | GR | 96 ± 3 | 98 ± 2 | 98 ± 2 | 97 ± 2 | 97 ± 2 | 97 ± 2 | 98 ± 2 | 98 ± 2 | 98 ± 2 |
| EtISO (V%) | GF | 0.98 ± 0.20 | 0.76 ± 0.26 | 0.7 ± 0.26 A | 0.66 ± 0.24 A | 0.6 ± 0.18 A | 0.62 ± 0.18 A | 0.62 ± 0.20 A | 0.56 ± 0.17 A | 0.52 ± 0.15 A |
| | GR | 1.0 ± 0.26 | 0.71 ± 0.16 A | 0.58 ± 0.21 A | 0.61 ± 0.26 A | 0.66 ± 0.30 A | 0.62 ± 0.24 A | 0.64 ± 0.30 A | 0.61 ± 0.28 A | 0.65 ± 0.33 A |
| Tc (ºC) | GF | 37.2 ± 0.6 | 36.7 ± 0.8 | 36.3 ± 0.8 | 36.2 ± 0.8 | 36.2 ± 0.9 | 36.3 ± 0.9 | 36.2 ± 0.9 | 36 ± 0.9 | 35.8 ± 1 |
| | GR | 37.2 ± 0.6 | 36.7 ± 0.9 | 36.3 ± 0.9 | 36 ± 0.9 | 36.2 ± 1.1 | 36 ± 1.3 | 36.4 ± 1.4 | 36.4 ± 1.7 | 36.3 ± 1.8 |

Uppercase letters (A): Difference in all values with respect to M0 determined using two-way ANOVA followed by Dunnett's test ($P \leq 0.05$).

isoflurane vaporization reached up to 47% in GF and 42% in GR relative to M0 (Table 1). Furthermore, body temperature (Tc) displayed a consistent decrease at all time points relative to M0 in both groups (Table 1).

During surgery, the MAP significantly increased by 43%, 50%, and 30% at M2, M3 and M4 compared to M120, respectively, in GF, and by 28% at M2 and M3 relative to M120 in GR (Table 3). The EtISO was notably higher at M1 and M2 in GF, as well as at M1, M2, and M3 in GR, relative to their respective M120 (Table 3). In terms of intraoperative analgesic adjustments, GF exhibited a higher likelihood of not requiring rescue analgesia compared to GR ($P = 0.0438$). Additionally, GF required a lower number of rescue analgesia interventions per animal in comparison to GR: 0.5 ± 0.22 and 1.5 ± 0.34 rescues, respectively. Following the adjustments of intraoperative rates in both groups, the final mean rate was 17 ± 4.9 in GF and 22.2 ± 4.8 µg/kg/h in GR.

Notably, the extubation time was significantly shorter in GR than in GF (5 ± 1 vs. 9 ± 1 min; $P = 0.0139$). In the postoperative period, 70% of GR animals required rescue analgesia within the first 30 minutes after extubation, in contrast to 40% of GF animals ($P < 0.0001$) (Table 4). The estimated time to the first analgesic rescue was 144 ± 41 min in GF and 81 ± 29 min in GR. All animals reached the rescue score at one of the evaluation moments and were rescued only once within the 6-hour evaluation period, with no significant difference between the groups at each evaluation moment (Table 5).

## DISCUSSION

Opioids typically induce bradycardia by affecting vagal nuclei (REITAN et al., 1978). This bradycardic response can be mitigated by the administration of anticholinergics, with act on M2 muscarinic receptors found in the sinoatrial and atrioventricular nodes (ILKIW et al., 1994; SIMÕES et al., 2016). A canine study evaluating CI of fentanyl at bolus dose of 5 µg/kg and CI of 9 µg/kg/h, either with or without concurrent atropine CI, yielded results akin to those reported in the presented study, resulting in HR reduction of 35% and 43% at 120 and 300 minutes in the fentanyl group, as compared to the group administered both fentanyl and atropine (SIMÕES et al., 2016). Comparable findings were reported in a study assessing the hemodynamic profile of remifentanil in dogs at infusion rates of 9 and 54 µg/kg/h, which led to a decrease in HR of up to 32 bpm (MONTEIRO et al., 2010b).

Inhaled agents are recognized for their dose-dependent impact on reducing MAP

Table 2 - Mean values and standard deviation of hydrogen potential (pH), arterial partial pressure of oxygen ($PaO_2$), arterial partial pressure of carbon dioxide ($PaCO_2$), arterial oxygen saturation ($SaO_2$), serum bicarbonate concentration ($HCO_3$), and base deficit (BD) of female dogs initially premedicated with acepromazine (0.05 mg/kg), induced with propofol (4 mg/kg), and maintained under inhalation anesthesia with isoflurane (1.4 V%) (M0). After the administration of fentanyl (2.5 µg/kg bolus followed by 15 µg/kg/h continuous infusion [CI]) (GF, n = 10) or remifentanil (a bolus of 0.9% saline solution followed by 18 µg/kg/h CI) (GR, n = 10), all parameters were recorded at M15, M45, M75, and M120 at 15, 45, 75, and 120 min after baseline (M0), respectively. During these moments, the animals remained unstimulated, and isoflurane was adjusted to maintain the animals in plane 2 of Stage III, according to Guedel's classification.

| | | M0 | M15 | M45 | M75 | M120 |
|---|---|---|---|---|---|---|
| pH | GF | 7.37 ± 0.02 | 7.29 ± 0.02 | 7.32 ± 0.04 | 7.34 ± 0.03 | 7.33 ± 0.03 |
| | GR | 7.46 ± 0.3 | 7.24 ± 0.05 A | 7.28 ± 0.09 A | 7.34 ± 0.04 | 7.35 ± 0.04 |
| $PaO_2$ (mmHg) | GF | 480 ± 35 | 483 ± 56 | 500 ± 52 | 487 ± 48 | 496 ± 60 |
| | GR | 500 ± 51 | 486 ± 37 | 516 ± 32 | 496 ± 67 | 509 ± 46 |
| $PaCO_2$ (mmHg) | GF | 35 ± 5 | 46 ± 4 Aa | 41 ± 6 A | 39 ± 5 | 41 ± 6 |
| | GR | 39 ± 4 | 53 ± 9 Ab | 43 ± 7 | 39 ± 5 | 38 ± 4 |
| $SaO_2$ (%) | GF | 100 ± 0.2 | 100 ± 0.1 | 100 ± 0.2 | 100 ± 0.2 | 100 ± 0.2 |
| | GR | 99 ± 0.4 | 99 ± 0.4 | 99 ± 0.4 | 100 ± 0.2 A | 100 ± 0.4 A |
| $HCO_3$ (mmol/L) | GF | 20.1 ± 2.1 | 21.4 ± 1.7 | 20.6 ± 1.8 | 20.7 ± 1.2 | 20.7 ± 2 |
| | GR | 20.8 ± 0.9 | 22.4 ± 1.4 | 21.0 ± 1.6 | 20.8 ± 1.4 | 20.3 ± 1.1 |
| DB (mmol/L) | GF | -5.0 ± 1.8 | -5.1 ± 1.8 | -5.4 ± 1.8 | -5.1 ± 1.1 | -5.3 ± 1.9 |
| | GR | -2.5 ± 4.3 | -3.0 ± 4.6 | -3.5 ± 5.0 | -3.1 ± 4.1 | -3.5 ± 4.3 |

Uppercase letters (A): Difference in all values with respect to M0 after two-way ANOVA followed by Dunnett's test ($P \leq 0.05$).
Lowercase letters (a, b): Difference in all values between the two groups via the t-test ($P \leq 0.05$).

(SCHEEREN et al., 1999). In the current study, despite no notable disparity in MAP between the two groups, it is noteworthy that only the GF required ephedrine administration. This observation might be attributed to the potential release of vasopressin associated with remifentanil infusion, which could serve to mitigate its blood pressure depressant effects (MONTEIRO et al., 2010b).

Moreover, opioids have been shown to reduce the vaporization of inhalation agents (MONTEIRO et al., 2010a; SIMÕES et al., 2016), thereby reducing their harmful effects. The administration of fentanyl at rates of 9 and 12 µg/kg/h resulted in an EtISO of 0.69 V% and 0.3 V%, respectively (SIMÕES et al., 2016); WILLIAMSON et al., 2017). Similarly, when remifentanil (18 µg/kg/h) was administered in female dogs undergoing mastectomy, it was observed 47% of reduction in EtISO (BEIER et al., 2015), consistent with the present study, in which a maximum reduction in isoflurane vaporization of up to 47% and 42% relative to M0 was observed in GF and GR, respectively. Although there was a significant reduction in EtISO relative to M0 at M15 in GR and at M30 in GF, both drugs appear to cause a similar dose-dependent reduction at the minimum alveolar concentration of isoflurane (CRIADO et al., 2003; GLASS et al., 1999). In addition, the respiratory depression caused by opioids leads to a reduction in f, consequently resulting in $CO_2$ accumulation and pH changes, with compensatory $HCO_3$ responses, which is a result of opioids centrally-mediated interaction with µ receptors (DAHAN et al., 2001; PRKIC et al., 2012). In another study in which transdiaphragmatic pressure was evaluated in dogs, the combination of isoflurane and CI of fentanyl at a rate of 12 µg/kg/h caused a significant depression in diaphragmatic contractility (PAVLIDOU et al., 2013).

High $PaCO_2$ values of approximately 65 mmHg have been reported in dogs when administering fentanyl at doses three times lower than those used in the present study (KEATING et al., 2013). Similarly, the administration of remifentanil even at clinical doses (6–60 µg/kg/h) caused significant respiratory depression in dogs (PRKIC et al., 2012). In these situations, the use of mechanical ventilation in protocols with remifentanil is associated with $EtCO_2$ values within the normal range (ALLWEILER et al., 2007; MONTEIRO et al., 2010a), as observed in the present study, in which all animalsexceeded the upper threshold (> 45 mmHg) and thus required mechanical ventilation. This may have contributed to higher values of both peripheral and arterial oxygen saturation (FANTONI et al., 2016).

Table 3 - Mean values and standard deviation of heart rate (HR), respiratory rate *(f)*, mean arterial pressure (MAP), expired fraction of carbon dioxide ($EtCO_2$), peripheral oxygen saturation ($SpO_2$), expired fraction of isoflurane (EtISO), body temperature ($T_c$), and flow rate of fentanyl or remifentanil (µg/kg/h) (CI rate) in female dogs initially premedicated with acepromazine (0.05 mg/kg), induced with propofol (4 mg/kg), and maintained under inhalation anesthesia with isoflurane, which was adjusted to maintain the animals in plane 2 of Stage III, according to Guedel's classification. Then, fentanyl (2,5 µg/kg bolus followed by 15 µg/kg/h continuous infusion [CI]) (GF, n = 10) or remifentanil (a bolus of 0.9% saline solution followed by 18 µg/kg/hCI) (GR, n = 10) (M120) was administered. Subsequently, the surgical procedure was performed: celiotomy (M1), followed by clamping of the right ovarian pedicle (M2), clamping of the left ovarian pedicle (M3), clamping of the cervix (M4), myorrhaphy (M5), and dermorrhaphy (M6).

| | | M120 | M1 | M2 | M3 | M4 | M5 | M6 |
|---|---|---|---|---|---|---|---|---|
| HR (bpm) | GF | 77 ± 16 | 75 ± 15 | 91 ± 25 | 76 ± 15 | 74 ± 11 | 75 ± 21 | 77 ± 14 |
| | GR | 77 ± 23 | 71 ± 24 | 93 ± 24 | 87 ± 27 | 73 ± 22 | 79 ± 18 | 86 ± 24 |
| *f* (mpm) | GF | 16 ± 4 | 15 ± 5 | 15 ± 4 | 15 ± 4 | 15 ± 4 | 15 ± 4 | 15 ± 4 |
| | GR | 16 ± 3 | 16 ± 2 | 15 ± 2 | 15 ± 2 | 15 ± 2 | 15 ± 2 | 15 ± 2 |
| MAP (mm Hg) | GF | 65 ± 5 | 64 ± 9 | 93 ± 19 A | 98 ± 18 A | 85 ± 20 A | 71 ± 12 | 71 ± 11 |
| | GR | 76 ± 7 | 70 ± 10 | 98 ± 11 A | 98 ± 10 A | 87 ± 15 | 76 ± 15 | 72 ± 14 |
| $EtCO_2$ (mm Hg) | GF | 41 ± 5 | 41 ± 6 | 39 ± 5 | 39 ± 5 | 41 ± 5 | 42 ± 6 | 43 ± 6 |
| | GR | 39 ± 3 | 39 ± 2 | 39 ± 4 | 40 ± 4 | 39 ± 2 | 40 ± 3 | 42 ± 2 |
| $SpO_2$ (%) | GF | 98 ± 1 | 98 ± 2 | 98 ± 2 | 97 ± 3 | 98 ± 2 | 98 ± 1 | 98 ± 2 |
| | GR | 98 ± 2 | 98 ± 2 | 98 ± 2 | 98 ± 2 | 98 ± 2 | 99 ± 2 | 99 ± 2 |
| EtISO (V %) | GF | 0.52 ± 0.15 | 0.75 ± 0.23 | 0.72 ± 0.13 | 0.72 ± 0.11 | 0.71 ± 0.15 | 0.70 ± 0.22 | 0.66 ± 0.15 |
| | GR | 0.65 ± 0.33 | 0.91 ± 0.18 | 0.91 ± 0.19 | 0.87 ± 0.25 | 0.80 ± 0.28 | 0.72 ± 0.25 | 0.77 ± 0.211 |
| Tc (° C) | GF | 35.8 ± 1 | 35.8 ± 1 | 35.8 ± 1 | 36 ± 1 | 36 ± 1 | 36 ± 1.1 | 36 ± 1.3 |
| | GR | 36.3 ± 1.8 | 36.1 ± 2 | 36.1 ± 2 | 36.1 ± 2 | 36.1 ± 2 | 36.4 ± 2 | 37 ± 2 |
| IC rate | GF | 15 ± 0 | 15 ± 0 | 17 ± 4 | 18 ± 6 | 18 ± 6 | 18 ± 6 | 18 ± 6 |
| | GR | 18 ± 0 | 18 ± 0 | 24 ± 0 | 24 ± 6 | 24 ± 6 | 24 ± 6 | 24 ± 6 |

Uppercase letters (A): Difference in values with respect to M0 determined using two-way ANOVA followed by Dunnett's test ($P \leq 0.05$).

The analgesic efficacy of drugs can be assessed based on changes in physiological parameters such as MAP, EtISO, and serum cortisol (OLIVA et al., 2019). Several researchers have reported an increase in cortisol levels during ovariohysterectomies, especially during clamping of the ovarian pedicles (ALBUQUERQUE et al., 2015; PAOLOZZI et al., 2011), during which an increase in MAP was observed in the present study relative to M120. It can therefore be deduced that CI of fentanyl or remifentanil at the initially proposed rates proved ineffective in adequately inhibiting the nociceptive response during ovarian clamping. This inadequacy is evidenced by the necessity to increase the infusion rates. After the adjustments, the MAP remained stable in both groups, and the final mean rates (± standard deviation) were 17 ± 4.9 and 22.2 ± 4.8 µg/kg/h in GF and GR, respectively. Moreover, the comparison of the intraoperative antinociceptive effects showed a greater probability of not receiving rescue analgesia in GF based on the log-rank test ($P = 0.0438$). In another study comparing the administration of both drugs under anesthesia with intravenous propofol (0.5 mg/kg/min) in female dogs undergoing the same procedure

Table 4 - Number of animals female dogs undergoing elective ovariohysterectomythat received rescue analgesics at 30, 60, 120, 180, 240, 300, and 360 min after extubation. Then, fentanyl (2.5 µg/kg bolus followed by 15 µg/kg/h continuous infusion [CI]) (GF, n = 10) or remifentanil (a bolus of 0.9% saline solution followed by 18 µg/kg/h CI) (GR, n = 10) was administered. Opioid infusion was administered for 120 min before surgery without any stimulus as well as during the surgical procedure. The animals were administered with rescue analgesics when they scored ≥6 points on the short form of the Glasgow Composite Pain Scale (GCS).

| ----------Postoperative assessment moments (in minutes) after extubation---------- | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 30 | 60 | 120 | 180 | 240 | 300 | 360 |
| GF | 4/10 | 1/10 | 1/10 | 1/10 | 0/10 | 2/10 | 1/10 |
| GR | 7/10 | 0/10 | 1/10 | 1/10 | 0/10 | 1/10 | 0/10 |

Table 5 - Mean values and standard deviation of GCS scores at 30, 60, 120, 180, 240, 300, and 360 min after extubation of animals undergoing elective ovariohysterectomy with administration of fentanyl (2.5 µg/kg bolusfollowed by 15 µg/kg/h continuous infusion [CI]) (GF, n = 10) or remifentanil (a bolus of 0.9% saline solution followed by 18 µg/kg/h CI) (GR, n = 10). Opioid infusion was administered for 120 min before surgery without any stimulus as well as during the surgical procedure. The animals received postoperative rescue analgesics when they scored ≥ 6 points on the GCS.

| | ----------Postoperative assessment moments (in minutes) after extubation---------- | | | | | | |
|---|---|---|---|---|---|---|---|
| | 30 | 60 | 120 | 180 | 240 | 300 | 360 |
| GF | 6.1 ± 3.8 | 2.1 ± 2.8 | 1.8 ± 2.7 | 1.6 ± 2.5 | 1.4 ± 2.2 | 1.7 ± 2.7 | 0.6 ± 1.8 |
| GR | 6.2 ± 3.2 | 1.1 ± 1.8 | 1.0 ± 1.6 | 1.3 ± 2.3 | 1.2 ± 2.5 | 0.5 ± 1.5 | 0.0 ± 0.0 |

using the same flow rate of fentanyl as that used in the present study and 36 µg/kg/h of remifentanil, no rate adjustment or additional postoperative analgesia was required (KURUM et al., 2012).

The extubation time was shorter in GR than in GF (5 ± 1 vs. 9 ± 1 min), which can be explained by the pharmacokinetics of the opioids. Remifentanil is metabolized by plasma esterases and is thus eliminated considerably faster than fentanyl, which depends exclusively on hepatic metabolization. In addition, prolonged infusions can lead to saturation of the metabolization sites and decreased elimination rate (HOKE et al., 1997; SANO et al., 2006).

In the first 30 min after extubation, compared with GR animals, only some GF animals required rescue analgesia (Table 4), however, all animals in the study required analgesic intervention during the 6 h of postoperative evaluation. This can be explained by the pharmacokinetics of the agents used. In dogs, fentanyl in prolonged CI (3 h and 4 h) was shown to have a prolonged elimination half-life (182.1 ± 68 vs. 157.1 ± 87.5 min) (SANO et al., 2006). In contrast, in a pharmacokinetic study in dogs, remifentanil was shown to have a short elimination half-life of only 5.59 ± 0.62 min (HOKE et al., 1997).

This study is subject to certain limitations. The administration of atropine and ephedrine to the study animals may have influenced the recorded heart rate and blood pressure values, respectively. Moreover, the continued assessment of animals until 6 hours postoperatively, even if they had already reached the rescue analgesic score, could potentially affect the pain scores, resulting in artificially lower scores.

## CONCLUSION

Both drugs exhibited significant respiratory depressant effects at the administered doses, emphasizing the importance of vigilant respiratory monitoring and assistance when using these agents. While the administration of fentanyl at the specified infusion rate demonstrated less intraoperative rescue analgesics, we recommend careful rate adjustments for both treatments. In comparison to remifentanil, the use of fentanyl led to a delayed demand for postoperative analgesia, but it's noteworthy that all animals in both groups eventually required rescue analgesia. Therefore, the provision of supplementary analgesia in the postoperative period remains crucial for both protocols.

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## AUTHORS' CONTRIBUTIONS

All authors contributed equally to the creation of the manuscript.

## BIOETHICS AND BIOSECURITY COMMITTEE APPROVAL

CEUA, Universidade do Estado de Santa Catarina (UDESC), 8763090418.

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