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Magnesium sulfate and ketamine as analgesic and anesthetic adjuvants in total intravenous anesthesia in cats

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ABSTRACT: This study assessed the efficacy of magnesium sulfate and ketamine hydrochloride in reducing the demand for propofol, remifentanil, and postoperative rescue analgesia in cats undergoing elective ovariohysterectomy. Thirty cats were premedicated with acepromazine (0.05 mg/kg) and morphine (0.3 mg/kg) intramuscularly and induced to unconsciousness with propofol for orotracheal intubation. The continuous infusion (CI) of propofol and remifentanil were started and animals and were randomly allocated into three groups: the magnesium sulfate group (MG) received one bolus (50 mg/kg) and CI (80 mg/kg/h) of magnesium sulfate; the ketamine group (KG) received bolus (0.5 mg/kg) and CI (1.8 mg/kg/h) of ketamine hydrochloride; the control group (CG) received bolus and CI of 0.9% saline solution. Cardiovascular and respiratory functions, extubation time, and rescue postoperative scores were assessed and data were described with a significance level of 95% ($P < 0.05$). The infusion period of treatments was 21.5 ± 3.4 and 21.0 ± 2.4 minutes in the KG and MG, respectively ($P = 0.194$). The infusion rates of remifentanil ($P = 0.336$) and propofol ($P = 0.716$) were similar between groups. Analysis of the postoperative pain scales revealed no significant intergroup differences in rescue frequency, rescue score, and time to the first rescue analgesia. In conclusion, the proposed protocols were safe and effective, yet it is noteworthy that both magnesium sulfate and ketamine failed to demonstrate significant additional postoperative analgesic or adjuvant anesthetic effects.
Key words: NMDA, ovariohysterectomy, postoperative, propofol, remifentanil.

Sulfato de magnésico e cetamina como adjuvantes analgésicos e anestésicos na anestesia total intravenosa em felinos

RESUMO: Objetivou-se avaliar a eficácia do sulfato de magnésio e cetamina em reduzir o requerimento de propofol, remifentanil e o resgate analgésico pós-operatório de gatas submetidas à ovariohisterectomia eletiva. Trinta gatas foram pré-medicadas com acepromazina (0,05 mg/kg) e morfina (0,3 mg/kg), intramuscular, e induzidas a inconsciência com propofol para intubação orotraqueal. As infusões contínuas (IC) de propofol e remifentanil foram iniciadas e os animais foram aleatoriamente alocados em três grupos: grupo sulfato de magnésio (MG) que recebeu bolus (50 mg/kg) e IC (80 mg/kg) de sulfato de magnésio; grupo cetamina (KG) que recebeu bolus (0,5 mg/kg) e IC (1,8 mg/kg/h) de cetamina; grupo controle (CG) que recebeu bolus e IC de solução salina 0,9%. As funções cardiovasculares e respiratórias, o tempo de extubação e a pontuação de resgate pós-operatório foram registrados e descritos com nível de significância de 95% ($P < 0.05$). O tempo de infusão dos tratamentos foi de 21,5 ± 3,4 e 21,0 ± 2,4 minutos no KG e MG, respectivamente ($P = 0.194$). As taxas de infusões de remifentanil ($P = 0.336$) e propofol ($P = 0.716$) foram similares entre grupos. Na análise de dor pós-operatória as escalas não demonstraram diferenças entre grupos quanto a número de resgates, pontuação de resgate ou tempo para o primeiro resgate. Em conclusão, os protocolos propostos foram seguros e efetivos. Contudo, o sulfato de magnésio e cetamina não demonstraram analgesia pós-operatória adicional ou efeitos adjuvantes anestésicos significativos.
Palavras-chave: NMDA, ovariohisterectomia, pós-operatório, propofol, remifentanil.

INTRODUCTION

Total intravenous anesthesia (TIVA) is a technique that induces hypnosis, muscle relaxion, and analgesia exclusively through intravenous (IV) administration (MCILROY & LESLIE, 2019). The combination of different drugs, known as multimodal anesthesia/analgesia, aims to minimize adverse effects and promote better hemodynamic stability during anesthesia procedure (BROWN et al., 2018). For instance, when propofol and remifentanil are combined, it exhibits a synergic effect, reducing the required dose of propofol by up to 50% in humans (NIMMO et al., 2019). Since propofol exhibits a distinct cumulative effect in cats compared to dogs and humans, resulting in a prolonged residual effect, and remifentanil is rapidly metabolized by non-specific plasma and tissue esterases, the combination of both drugs seems to be

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effective and safe in female cats (CORREA et al., 2007; PADILHA et al., 2011; GEHRCKE et al., 2013; COMASSETTO et al., 2015).

A very popular choice as anesthetic adjuvants are the non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors, such as ketamine and magnesium sulfate that, when administered at sub-anesthetic doses, have been shown to reduce central sensitization (EPSTEIN et al., 2015; SHIN et al., 2020). Ketamine infusion in cats significantly decreases central sensitization and infusion rate of propofol, without cardiovascular changes (ILKIW & PASCOE, 2003; EPSTEIN et al., 2015). Also, in humans, magnesium sulphate leads to a lower requirement for propofol and postoperative analgesics (SHIN et al., 2020; TSAOUSI et al., 2020). However, studies involving magnesium sulphate in dogs undergoing ovariohysterectomy under inhalation anesthesia have yielded conflicting results regarding its effectiveness in controlling antinociception (ANAGNOSTOU et al., 2008; RIOJA et al., 2012).

There is a lack of substantial scientific evidence regarding the use of magnesium sulfate as an anesthetic and analgesic adjuvant in cats. Consequently, the present study assessed the efficacy of the continuous infusion (CI) of magnesium sulfate and ketamine hydrochloride when administered to cats undergoing elective ovariohysterectomy under total intravenous anesthesia with propofol and remifentanil. The study aimed to examine the impact of both drugs on perioperative cardiorespiratory parameters, propofol and remifentanil requirement, and postoperative analgesic efficacy.

The hypothesis was that the CI of magnesium sulfate or ketamine hydrochloride would lead to a reduction in the requirement for remifentanil and propofol, as well as the need for postoperative rescue analgesia, when compared to a control placebo group.

MATERIALS AND METHODS

The study was designed as a randomized controlled clinical trial, and the sample size was determined using data from a prior study (TSAOUSI et al., 2020). Calculations were performed using OpenEpi Epidemiologic Statistic for Public Health, version 3.0, with a power of 0.8 and an alpha of 0.05, which indicated a minimum requirement of six animals per group. In total, thirty young adult domestic female cats (*Felis catus*) of mixed breed and non-neutered, were officially included in the study. The cats owners provided their consent for participation.

The recruited cats underwent thorough an evaluation of the clinical, physical, hematological/biochemical, and behavioral history. The inclusion criteria were the classification as ASA I, according to American Society of Anesthesiologists. Any cats currently undergoing treatment, displaying aggressive behavior during clinical evaluation, being obese (body condition score > 6 on a scale of 1-9), or confirmed as pregnant via abdominal ultrasound on the day of admission were excluded from the study.

Approximately 24 hours prior to the administration of pre-anesthetic medication, the cats were admitted individually to separate rooms. The place was well-lit with both natural and artificial lighting and maintained at room temperature (20 ºC) with air conditioning. Interactive objective for cats were provided, and the animals were free to explore the place under the supervision of the evaluators during the initial 24 hours of the study. This allowed the evaluators to mimic postoperative assessments and become familiar with the specific characteristics of each animal.

The cats were provided wet food and underwent a 6-hour period of fasting before receiving the pre-anesthetic medication, with water *ad libitum*. After fasting, the cats were assessed to establish their baseline scores (scales described below). Subsequently, acepromazine (0.05 mg/kg) and morphine (0.3 mg/kg) were administered via intramuscular injection and, after 30 minutes, the cats were transferred to the operating room.

Peripheral access was established through the cephalic vein, and anesthesia was induced with IV propofol (1 mg/kg) at 30-second intervals until the swallowing reflex, eyeball rotation, and lateral and medial palpebral reflexes were lost. Following this, 0.1 ml of 2% lidocaine was administered periglottically for orotracheal intubation with a murphy tube that was connected to the anesthetic machine (Datex Ohmeda 9100c, GE Healthcare®), through a non-rebreathing anesthetic circuit Mapleson D and 100% oxygen supply (200 ml/kg/min). Subsequently, CI of propofol was started at an initial rate of 0.22 mg/kg/min using a syringe pump (Samtronic® ST 670 syringe pump). This initial rate was adjusted throughout the study by 20% as necessary to maintain the second plane from the third anesthetic stage, which was defined as the absence of the medial palpebral reflex, jaw tone relaxed, and with ventrally rotated eyeballs according to Guedel's Stages of Anesthesia (DOUGLAS, 1958). The same evaluators (FC and LDR) responsible for these adjustments were blind to the treatment groups. The

study adhered to the maintenance guarantee period of the anesthesia system and syringe pumps used.

After intubation, the cats were positioned in dorsal recumbency on a mattress equipped with a WarmAir forced-air heating system (Tradevet®). The cats were prepared for surgery, which involved the following steps: full trichotomy of the ventral abdomen; trichotomy and peripheral accesses in the right and left medial saphenous veins; and trichotomy of the caudal metacarpal region for monitoring systolic blood pressure. The evaluators responsible for postoperative assessment (GBC, TLDS and NO) were blinded to the treatment groups throughout the study.

Following a 10-minute stabilization period to ensure that the anesthetic plane was consistent, moment zero (M0) was recorded, and the cats were randomly allocated into three groups (n = 10 animals each): the magnesium sulfate group (MG), the ketamine group (KG), and the control group (CG). Right after M0 assessment, IV boluses of the treatments were administered over a 15-minute period: 50 mg/kg of magnesium sulfate in MG and an equivalent volume of 0.9% saline solution in KG and CG. Five minutes after the start of the treatment bolus administration, CI of remifentanil (0.2 µg/kg/min) was initiated through another access to maintain the therapeutic window of the drug.

Following the 15-minute bolus infusion, a second bolus was administered, consisting of 0.5 mg/kg of IV ketamine hydrochloride in KG and an equivalent volume of 0.9% saline solution in the MG and CG. At the time of the second bolus administration, the baseline (M1) was recorded, and infusions were initiated in the three groups as follows: CI of magnesium sulfate (80 mg/kg/h) in MG; CI of ketamine hydrochloride (1.8 mg/kg/h) in KG with a final volume equivalent to MG, diluted in 0.9% saline solution; and CI of 0.9% saline solution in CG, using the corresponding volume of MG. The treatment infusions were prepared by the same two operators, the only ones who knew the treatment groups (GSJ and LBG).

The surgical procedure was performed by the same surgeon (VAR) and assistant (TLDS), and the assessment points designed during surgery were: celiotomy (M2); clamping of the right ovarian pedicle (M3); clamping of the left ovarian pedicle (M4); clamping of the cervix (M5); after myorrhaphy (M6); and after dermorrhaphy (M7). At the conclusion of the surgical procedure, all infusions were stopped and the surgical and extubation times were documented in minutes.

All assessment moments (M0 to M7) were monitored using a GE Healthcare® B650 multiparameter monitor (DatexOhmeda). The following parameters recorded were heart rate (HR, in beats per minute, bpm) using electrocardiography, peripheral oxygen saturation (SpO_2, in %) through pulse oximetry, respiratory rate (f, in movements per minute, mpm) and partial pressure of CO_2 at the end of exhalation ($EtCO_2$ in mmHg) using capnography with a side stream sensor, and esophageal temperature (T in ºC) measured using transesophageal thermometer. Additionally, systolic arterial pressure (SAP in mmHg) was determined using a vascular Doppler (Parks Medical®, model 811-B for veterinary use), an aneroid sphygmomanometer and a cuff sized at 40% of the animal's thoracic limb circumference.

If, during M2 to M7, at least two parameters (HR, f and/or SAP) increased at least by 20% compared to the baseline (M1), the remifentanil flow rate was adjusted by 0.05 µg/kg/min, and so on, as required. In case HR dropped below 90 bpm, atropine (0.044 mg/kg, IV) was administered and, similarly, if SAP values fell below 90 mmHg, ephedrine (0.1 mg/kg, IV) was administered. For $EtCO_2$ values above 45 mmHg, assisted ventilation was provided (10 mpm) until the parameter normalized. Likewise, if the animal experienced apnea, assisted ventilation was administered (10 mpm) until spontaneous respiratory movements were observed. Any animals facing additional complications were excluded from the study. At the end of surgery all the infusions were stopped.

After extubation, the cats were returned to the acclimatization room, and the postoperative pain assessment were conducted at the following time points: 1, 2, 4, 6, 8, 12 and 24 hours after extubation. These assessments were carried out using the UNESP-Botucatu Multidimensional Composite Scale for Assessing Postoperative Pain in Cats (EMAD U-B) (BRONDANI et al., 2011), except for the measurement of blood pressure included in the scale. Analgesic rescue was recommended when the pain score reached or exceeded 6 points, as per previous guidelines (BENITO et al., 2016), when blood pressure is not included. Additionally, the cats were evaluated using the Feline Grimace Scale (FGS) (EVANGELISTA et al., 2019) and analgesic rescue was recommended when the FGS score reached or exceeded 4 points. When a rescue score was obtained in at least one of the scales, meloxicam (0.1 mg/kg) was administered subcutaneously (SC), regardless of the score on the other scale. All animals were re-evaluated 15 minutes after the administration and if it

returned to a rescue score, morphine (0.1 mg/kg) was administered SC. All animals were assessed for 24 hours after extubation at the already mentioned time points, even after possible analgesic rescue. Also, the animal was excluded from the study if rescue score was observed again after morphine administration.

The statistical analysis was performed using the GraphPad Prism® statistical software, version 9.3.0. Data are presented as means and standard deviation and all analyses were performed considering a significance level of 95% ($P < 0.05$). Initially, the data were subjected to the Shapiro–Wilk normality test. One-way ANOVA with Tukey's post-hoc test was used to perform concomitant intergroup comparisons. Two-way ANOVA with Bonferroni post-hoc test was used to compare the vital parameters between baseline and the other moments. The chi-square test was used to investigate the occurrence of postoperative rescue. One-way ANOVA with Tukey's post-hoc test was used to determine the intergroup differences in scores. In addition, the log-rank test for the survival curve was used to determine the time to rescue using the pain scales. Finally, the chi-Square test was used to assess inter-scale agreement.

RESULTS AND DISCUSSION

Each group consisted of 10 animals (CG = 10; KG = 10; and MG = 10). There were no significant intergroup differences in terms of age (months) ($P = 0.546$) with values as follows: CG = 12.5 ± 7.2; KG = 14.6 ± 8.2; and MG = 16.1 ± 6.1. Similarly, there were no significant differences in weight (kg) ($P = 0.841$), as follows: CG = 2.8 ± 0.5; KG = 2.9 ± 0.3; MG = 2.8 ± 0.4. Also, there were no significant intergroup differences in terms of the induction dose (mg/kg) of propofol ($P = 0.093$), i.e., CG = 9.7 ± 1.3; KG = 9.4 ± 1.8; and MG = 9.5 ± 1.6. Surgical time (minutes) also did not exhibit significant differences between the groups ($P = 0.194$), i.e., CG = 23.4 ± 3.1; KG = 21.5 ± 3.4; and MG = 21.0 ± 2.4. During the acclimatization period, one animal was excluded from the study and replaced due to difficulties in interacting with the evaluators, displaying aggressive and anxious behavior. Additionally, three animals were excluded from the study and replaced due to methodological failures during surgical and anesthetic preparation.

In this study, the mean remifentanil rates (µg/kg/min) did not exhibit significant differences between the groups ($P = 0.336$), i.e., 0.28 ± 0.05, 0.28 ± 0.03, and 0.26 ± 0.03 in CG, KG, and MG, respectively. During the surgical procedure, the rates ranged from 0.2 to 0.55 µg/kg/min in CG and KG and from 0.2 to 0.45 µg/kg/min in MG (Table 1). The majority of animals (77%) experienced their first analgesic rescue in the left ovarian pedicle (M4), with the exception of two animals in MG and three animals in KG that had their first rescue in the right ovarian pedicle (M3). Additionally, one animal in CG had analgesic rescue only in the cervix (M5), and one animal in MG did not require any change in the rate throughout the procedure. Consequently, a significant difference was observed ($P < 0.05$) between M4 to M7 and M1 (initial rate of 0.2 µg/kg/min) in all groups (Table 1).

Similarly, the mean rates of propofol (mg/kg/min) did not exhibit significant intergroup differences ($P = 0.716$), i.e., 0.24 ± 0.04, 0.23 ± 0.03, and 0.24 ± 0.03 in CG, KG, and MG, respectively. There were no significant differences observed between the moments within each group, and the values remained consistent throughout the procedure (Table 1). However, from the clinical perspective, the mean rates during surgical moments (six moments) tended to be lower in KG (6 of 6) and MG (4 of 6) compared to CG (Table 1). Consequently, the study did not demonstrate statistically significant reduction in the rates of propofol or remifentanil with the use of ketamine or magnesium sulfate.

Ultra-short-action opioids have the potential to reduce the need for propofol during anesthetic maintenance. Remifentanil, when combined with propofol, exhibits a synergistic effect, reducing the propofol requirement by up to 50% in humans (NIMMO et al., 2019). In cats, remifentanil has been shown to promote analgesia and result in a 15-20% reduction in the need for inhaled anesthetics (STEAGALL et al., 2022). In previous studies, the mean remifentanil rate varied between 0.2-0.27 and 0.2-0.28 µg/kg/min in cats anesthetized for ovariohysterectomy, similar to the present study (CORREA et al., 2007; PADILHA et al., 2011). In another study, on cats anesthetized with variable-rate propofol and a fixed rate of remifentanil (0.25 µg/kg/min) reported a 40.9% reduction in the propofol rate (0.13 ± 0.07 with remifentanil and 0.22 ± 0.05 mg/kg/min without remifentanil) (MARKS, 2017). It is worth noting that in this study, the animals remained anesthetized for 150 minutes and were nor subjected to any stimuli, which can contribute to increased rates (CORREA et al., 2007). Additionally, in the study conducted by MARKS (2017), the reduction in the propofol rate began 30 minutes into the infusion, consistent with other authors who recommend gradually reducing the propofol rate over the course of the infusion, typically starting at 30 minutes

Table 1 - Mean values and standard deviation of HR (bpm), StO_2 (%), *f* (mpm), $EtCO_2$ (mmHg), SBP (mmHg), esophageal T (°C) and rates of propofol (mg/kg/min) and remifentanil (µg/kg/min) at each moment (M0 to M7) in CG, GK, and GM. A - Statistically significant difference from baseline (M1) ($P < 0.05$). B - Statistically significant difference from M0 ($P < 0.05$). a or b - Statistically significant difference between groups at the same moment ($P < 0.05$).

	Group	M0	M1	M2	M3	M4	M5	M6	M7
HR (bpm)	GC	130.9 ± 16.95	119.1 ± 14.98	126.7 ± 16.92	162.1 ± 40.17	167.4 ± 42.26	177.7 ± 45.15A	177.1 ± 43.48A	169.1 ± 34.67A
	GK	134 ± 36.42	109.5 ± 33.50B	118.2 ± 39.43	145.6 ± 38.86A	165.3 ± 43.31A	183.6 ± 34.31A	194.7 ± 37.08A	189.5 ± 34.13A
	GM	147.1 ± 16.77	117.0 ± 18.15B	123.8 ± 16.17	148.4 ± 23.14A	164.1 ± 35.36A	176.7 ± 33.94A	171.3 ± 32.50A	158.8 ± 25.45A
StO_2	GC	96.3 ± 3.59	97.3 ± 2.54	96.5 ± 3.10	98.1 ± 2.38	97.7 ± 1.34a	97.9 ± 1.73	98.5 ± 1.58	98.5 ± 1.43
	GK	96.2 ± 3.08	96.5 ± 2.42	96.8 ± 2.15	98.1 ± 1.79	99.2 ± 0.63Aab	98.6 ± 1.26a	98.7 ± 1.16a	98.2 ± 1.75
	GM	98.9 ± 1.73	98.4 ± 1.96	97.1 ± 3.03	96.7 ± 1.70	96.8 ± 1.03b	96.8 ± 1.40a	96.6 ± 1.84a	97.0 ± 1.49
f (mpm)	GC	18.3 ± 4.95	16.1 ± 4.75a	16.9 ± 6.49	16.2 ± 8.09	16.8 ± 7.52	18.5 ± 7.98	16.1 ± 9.64	17.7 ± 5.14
	GK	17.8 ± 5.05	9.8 ± 4.61Ba	11.1 ± 3.18	13.5 ± 4.01	11.3 ± 1.49	13.2 ± 6.99	12.1 ± 6.72	12.4 ± 5.97
	GM	15.8 ± 3.97	13.2 ± 4.59	13.1 ± 3.25	17.4 ± 3.92A	16.4 ± 7.71	17.6 ± 6.74	15.5 ± 5.44	15 ± 5.01
EtCO2 (mmHg)	GC	37.2 ± 7.84	38.4 ± 9.05	37.2 ± 8.74	37.5 ± 10.86	37.1 ± 7.71a	34.1 ± 5.24	36.6 ± 9.37	36.7 ± 8.06a
	GK	37.1 ± 5.49	43.2 ± 5.97B	45.7 ± 6.15	46.0 ± 7.51	46.7 ± 7.51a	43.8 ± 10.89	46.6 ± 9.65	47.2 ± 6.82a
	GM	39.7 ± 6.46	45.0 ± 8.72B	45.3 ± 9.92	42.2 ± 8.44	43.9 ± 9.33	42.6 ± 10.38	44.5 ± 11.92	43.8 ± 11.27
PAS (mmHg)	GC	93.2 ± 27.25	91.3 ± 32.71	100.5 ± 35.73	126.9 ± 46.79	132.8 ± 43.47A	130.3 ± 51.73	115.4 ± 39.78	110.7 ± 32.31
	GK	92.7 ± 20.46	86.2 ± 20.78	93.2 ± 30.50	113.9 ± 40.14	125.6 ± 50.22A	128.6 ± 49.94	121.0 ± 31.03A	110.4 ± 37.83
	GM	99.0 ± 23.54	92.9 ± 23.76	95.0 ± 23.37	125.4 ± 36.29A	133.8 ± 43.68A	140.3 ± 42.24A	127.0 ± 34.86A	117.2 ± 29.74A
T (°C)	GC	37.8 ± 0.50	37.5 ± 0.53B	37.3 ± 0.60	37.3 ± 0.56A	37.1 ± 0.55A	37.1 ± 0.57A	37.1 ± 0.52A	37.1 ± 0.53A
	GK	37.6 ± 0.69	37.5 ± 0.98	37.4 ± 0.94	37.3 ± 0.89A	37.2 ± 0.86A	37.2 ± 0.84A	37.2 ± 0.71	37.3 ± 0.72
	GM	37.6 ± 0.48	37.3 ± 0.51B	37.2 ± 0.51	37.0 ± 0.55A	37.0 ± 0.59A	36.9 ± 0.58A	37.0 ± 0.54A	37.0 ± 0.53A
Propofol rate (mg/kg/min)	GC	0.23 ± 0.04	0.22 ± 0.02	0.24 ± 0.03	0.24 ± 0.03	0.24 ± 0.04	0.25 ± 0.06	0.26 ± 0.05	0.25 ± 0.06
	GK	0.24 ± 0.04	0.24 ± 0.03	0.23 ± 0.03	0.23 ± 0.03	0.23 ± 0.03	0.23 ± 0.04	0.23 ± 0.04	0.23 ± 0.04
	GM	0.23 ± 0.03	0.23 ± 0.04	0.23 ± 0.04	0.24 ± 0.03	0.24 ± 0.03	0.24 ± 0.03	0.24 ± 0.03	0.24 ± 0.03
Remifentanil rate (µg/kg/min)	GC	-	0.20 ± 0.00	0.20 ± 0.00	0.22 ± 0.02	0.28 ± 0.07A	0.32 ± 0.09A	0.36 ± 0.10A	0.38 ± 0.10A
	GK	-	0.20 ± 0.00	0.20 ± 0.00	0.20 ± 0.00	0.27 ± 0.03A	0.33 ± 0.04A	0.38 ± 0.06A	0.40 ± 0.07A
	GM	-	0.20 ± 0.00	0.20 ± 0.00	0.22 ± 0.03	0.26 ± 0.03A	0.29 ± 0.05A	0.31 ± 0.06A	0.34 ± 0.07A

(PASCOE et al., 2006; GEHRCKE et al., 2013; COMASSETTO et al., 2015). In the present study, the short surgical time may have limited the ability to investigate rate reduction over time.

Furthermore, the infusion of ketamine also demonstrated to reduce the minimum infusion rate of propofol and resulted in lower postoperative pain scores in cats (ILKIW & PASCOE, 2003; CORRÊA

et al., 2021). Despite that, when remifentanil (0.33 µg/kg/min) was combined with ketamine (1.8 mg/kg/h), no statistical differences (P = 0.078) were observed in the isoflurane requirement compared to remifentanil alone in cats undergoing to ovariohysterectomy (STEAGALL et al., 2015). The ketamine infusion rate chosen in the present study was based on the previous study conducted by STEAGALL et al. (2015), since both studies also used remifentanil. Despite being considered a moderately high rate (1.8 mg/kg/h), dissociative effects possibly caused by the drug were not reported by STEAGALL et al. (2015) and in the present study, in which normally in the first post operative hour the animals were active and willing to interact with the evaluators and in the assessment room.

Although, the magnesium sulfate is considered a non-competitive antagonist of NMDA receptors such as ketamine, the presence of the magnesium ion in the NMDA channel has no direct antinociceptive effects. It is the ability of magnesium to block the entrance of calcium ions into the cell that prevents central sensitization (SHIN et al., 2020). Theoretically, magnesium sulfate acts on several mechanisms that influence anesthesia, including NMDA receptors, catecholamine release, and reduction of peripheral nociceptive sensitization and stress to surgical stimuli (SHIN et al., 2020; TSAOUSI et al., 2020). These effects may be considered suitable explanations for the actions of the drug as an anesthetic/analgesic adjuvant, which reduces the requirement for propofol and remifentanil in humans (TELCI et al., 2002; TSAOUSI et al., 2020), and some points can be considered in the present study: the rates chosen in human studies are usually used in animal studies (ANAGNOSTOU et al., 2008; RIOJA et al., 2012) and additional studies are needed to implement adjustments. This information is in line with the possibility of exploring different surgical modalities, which has usually been studied with larger samples in humans and can contribute to a more specific use of magnesium sulfate (TELCI et al., 2002; SHIN et al., 2020; TSAOUSI et al., 2020). Finally, although, the administration of magnesium sulfate has yielded conflicting results in different species, the combination of the drug with ketamine seems to produce a synergistic effect on the acute nociceptive control in rats (SAVIC VUJOVIC et al., 2015) and, therefore, the combination can be explored in different species.

Although, the final mean $EtCO_2$ for each group remained under or close to the upper limit stipulated in the study, the use of mechanical ventilation to manage hypercapnia is useful (DONALDSON & BARFIELD, 2020). The final mean $EtCO_2$ was 36.8 ± 1.33, 45.6 ± 1.52, and 43.9 ± 1.16 mmHg in the CG, KG, and MG, respectively, with statistical difference between groups ($P < 0.0001$ between CG and KG or MG and $P < 0.0230$ between KG and MG). The $EtCO_2$ values were significantly lower in the CG than in the KG at M4 and M7 (P = 0.340 and P = 0.203, respectively) (Table 1). Moreover, respiratory rate decreased clinically after induction of anesthesia and continued to decrease after 15 minutes between M0 and M1 (period of treatment boluses and start of remifentanil infusion); it had a significant reduction only in KG ($P < 0.0001$), which was associated with a significant increase in $EtCO_2$ in KG P = 0.0052) and MG (P = 0.0104).

In the present study, HR and SAP had stable final means and showed no significant intergroup differences, i.e., HR (P = 0.846) of 157.0 ± 24.04, 158.1 ± 34.49, and 151.4 ± 23.12 bpm and SAP (P = 0.612) of 115.4 ± 15.72, 111.3 ± 16.14, and 118.8 ± 18.43 mmHg in the CG, KG, and MG, respectively. When HR and SAP were compared between M1 and the other moments, a significant difference was observed at all time points ($P < 0.05$) (Table 1). One animal in KG had hypotension (62 mmHg) during M1 and ephedrine (0.1 mg/kg, IV) was administered, with a satisfactory result (SAP > 90 mmHg). In another study, cats anesthetized with propofol and remifentanil in ovariohysterectomy exhibited bradycardia (lowest value: 68 bpm) and hypotension (lowest medium arterial pressure of 49 mmHg) (CORREA et al., 2007). However, the opposite seemed to occur when high doses of µ-agonist opioids were administered to cats, with excitation and sympathetic stimulation (FERREIRA et al., 2009). The CI of remifentanil or ketamine were reported to induce sympathetic stimulation in cats, resulting in increased HR and SAP (PASCOE et al., 2007). Moreover, magnesium prevents the release of catecholamines in the adrenal medulla and adrenergic terminals, leading to coronary vasodilation and a reduction in HR (MISGANAW et al., 2021). Despite the differences in the effects between the two molecules, no intergroup difference was observed in terms of HR and SAP; however, both parameters significantly increased at certain surgical moments (Table 1), which may be related to the surgical stimulus (CORREA et al., 2007; PADILHA et al., 2011).

Regarding extubation time, there was no significant difference between the groups (P = 0.192), i.e., 3.1 ± 2.5, 5.1 ± 3.2, and 3.5 ± 1.6 min in CG, KG, and MG, respectively. Although the recovery time after propofol CI was longer in cats than in other

species (GEHRCKE et al., 2013; COMASSETTO et al., 2015), the association with remifentanil reduces this period (PASCOE et al., 2006; CORREA et al., 2007; MARKS, 2017; MATA et al., 2010).

Regarding the postoperative analgesic rescue, no intergroup difference was observed in both scales, i.e., three animals from CG, three animals from MG, and four animals from KG obtained rescue scores by the EMAD U-B. Only one animal from MG obtained a rescue score by the FGS and EMAD U-B. The chi-square test showed no significant differences between groups for the EMAD U-B (P = 0.861) and FGS (P = 0.355). All animals had only one rescue (with meloxicam), with no additional interventions (which would have consisted in the administration of morphine), meaning that all the animals that need rescue analgesia reached the required score after the first intervention. Furthermore, the comparison of the highest EMAD U-B score between the animals of all groups (12, 9, and 12 points in CG, KG, and MG, respectively) showed no significant differences between the groups (P = 0.986). Similarly, the log-rank test for the survival curve was used to assess whether the time taken to rescue was different between the groups and there were no significant differences neither in the EMAD U-B (P = 0.863) nor the FGS (P = 0.367). The mean time to first analgesic rescue was 3.3 ± 1.15, 3.0 ± 1.15, and 2.67 ± 1.15 hours in the CG, KG, and MG, respectively.

Although, magnesium sulfate has not shown positive results in analgesic control in dogs (RIOJA et al., 2012) and considering that there is a lack of studies with cats, randomized studies with humans, using different methods, suggest that the use of magnesium sulfate significantly reduces the intensity of postoperative pain, thereby reducing the use of analgesics in urogenital, orthopedic, and cardiovascular surgery (SHIN et al., 2020). The use of magnesium sulfate has been shown to promote analgesia and reduce morphine requirement in humans undergoing hysterectomy (JARAHZADEH et al., 2016). Similarly, ketamine CI has positive effects on postoperative pain control in cats undergoing elective ovariohysterectomy (CORRÊA et al., 2021).

In the present study, the chi-square test was used to assess the agreement between the results of the two scales and the scales did not show associated results (P = 0.150), in which 30% of the animals (9 of 30) did not obtain the same result of rescue or not with the two scales. Of the animals that need rescue analgesia in the study (10 of 30), only one animal (in MG) had a rescue score on both scales, with 4 points in the FGS. Among the animals with a rescue score obtained in the EMAD U-B, four had a score of 0, three had a score of 3, and two had a score of 2 in the FGS at the time of rescue.

In cats, behavioral changes due to pain can be shown in a very subtle way depending on their personality and previous reaction to pain (BRONDANI et al., 2011). A series of behavioral features can suggest pain in cats, including altered posture, protection or excessive licking of the painful area, and changes in facial expression, especially squinting (BRONDANI et al., 2009; BRONDANI et al., 2011). In a study conducted by WATANABE et al. (2022), cats previously sedated with dexmedetomidine and butorphanol obtained high FGS scores 30 minutes after the end of inhalation anesthesia, even without previous painful stimulation. In addition, although, the presence of the evaluator during the postoperative recordings was not significant, it led to a 51.7% reduction in FGS scores in cats undergoing dental procedures (WATANABE et al., 2020). There is still no information on whether prolonged acclimatization periods or the presence of evaluators alter FGS scores (WATANABE et al., 2020). One of the explanations for the low facial scores obtained in the present study is the acclimatization period since the animals may have made a positive association between the presence of the evaluators and receiving food and social interaction. The association of changes in facial expression with other behavioral characteristics analyzed by multidimensional scales helps to refine the assessment, using parameters with a high reliability index such as posture, activity, and reactions to palpation of the surgical wound (BRONDANI et al., 2011).

The study had some limitations: the time the animals remained anesthetized during the study (preparation + bolus + surgical procedure) may not have been sufficient to determine the reduction in propofol rates, as described in the literature. The total mean time of the procedure was 50 minutes, with the last 20 minutes (on average) consisting of the surgical procedure. While during the preparation period the animals were highly stimulated, the following bolus period had no stimulation, at which point the attempts to reduce the rates were unsuccessful, possibly due to the short infusion time. Moreover, the use of morphine as pre-anesthetic medication associated with remifentanil infusion for a procedure with moderate pain potential such as ovariohysterectomy may have offset the activities of ketamine and magnesium sulphate infusions. However, based on the level of experience of the surgeons, it was decided not to have a fourth group without remifentanil infusion.

To date, there are no studies on the use of magnesium sulfate in cats for analgesia/anesthesia, so the choice of bolus dose and CI was based on pilot studies and not literature based, since the rates used in the present study were higher than those reported in dogs. Pilot studies have confirmed the safety of such rates. Finally, the lack of correlation of postoperative analgesic rescue between the EMAD U-B for acute pain in cats and the FGS may be linked to the lack of familiarity of the evaluators with the FGS, and further studies correlating the two scales are required.

CONCLUSION

The total intravenous anesthesia protocol with propofol and remifentanil associated with magnesium sulfate or ketamine hydrochloride was shown to be safe for elective ovariohysterectomy in cats. However, the addition of magnesium sulfate or ketamine hydrochloride failed to reduce the rates of propofol and remifentanil infusion and did not lead to any differences in postoperative analgesia. Further studies are recommended to assess different rates of magnesium sulfate, as well as its ability to act as an anesthetic adjuvant for other surgical modalities and species.

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DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest. The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

AUTHORS' CONTRIBUTIONS

All authors contributed equally for the conception and writing of the manuscript. All authors critically revised the manuscript and approved of the final version.

BIOETHICS AND BIOSECURITY COMMITTEE APPROVAL

The study was conducted with the approval of the Ethics and Animal Welfare Committee of the University under protocol number 9191210721. It took place within the premises of the University's Veterinary Hospital, separated from the hospital's regular activities.

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