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Effects of ketamine, midazolam and methadone, combined with local anesthesia, in cats undergoing orchiectomy

Efeitos da cetamina, midazolam e metadona, associados à anestesia local, em gatos submetidos à orquiectomia

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ABSTRACT: Different anesthetic combinations are used for orchiectomy in cats. This study aimed to evaluate the anesthetic and cardiopulmonary effects on the physiological variables of ketamine (10 mg/kg), midazolam (0.2 mg/kg) and methadone (0.3 mg/kg), combined with local anesthesia, in cats undergoing orchiectomy (n = 19 cats). The time for lateral recumbency, degree of sedation, muscle relaxation and nociception were recorded preoperatively. The propofol rescue dose was recorded. The time to head up and quality of recovery were evaluated postoperatively. The time for lateral recumbency was 5 ± 2 minutes. Fifteen minutes after the administration of the ketamine-midazolam-methadone combination, a greater sedative effect, muscle relaxation and less response to noxious stimulation were observed. Propofol was administered to twelve cats under local anesthesia, at a total dose of 1.5 ± 0.8 mg/kg. Surgery was started 28 ± 5 minutes after the administration of ketamine--midazolam-methadone combination. There were no differences in the physiological variables evaluated over the other evaluation times ($p > 0.05$). The recovery quality scores were adequate, and the time to head up was 51 ± 10 minutes. Under the conditions of this study, the ketamine-midazolam-methadone combination did not allow local anesthesia for orchiectomy. Many cats required propofol rescue prior to surgery. This combination promoted minimal changes in physiological variables and prolonged anesthetic recovery.

KEYWORDS: Anesthetic recovery; benzodiazepines; dissociative anesthesia; feline; opioids.

RESUMO: Diferentes combinações anestésicas são usadas para orquiectomia em gatos. O objetivo deste estudo foi avaliar o efeito anestésico e as alterações promovidas nas variáveis fisiológicas pela cetamina (10 mg/kg), midazolam (0.2 mg/kg) e metadona (0.3 mg/kg), combinados com anestesia local, em gatos submetidos à orquiectomia (n = 19 gatos). O tempo para adoção do decúbito lateral, grau de sedação, relaxamento muscular e nocicepção foram registrados no pré-operatório. A dose de resgate de propofol foi registrada. O tempo para o gato erguer a cabeça e a qualidade da recuperação foram avaliados no pós-operatório. O tempo para adoção do decúbito lateral foi de 5 ± 2 minutos. Quinze minutos após a administração da associação cetamina-midazolam-metadona, observou-se maior efeito sedativo e relaxamento muscular, e menor resposta à estimulação nociva. O propofol foi administrado em doze gatos para realização de anestesia local, utilizando a dose total de 1.5 ± 0.8 mg/kg. A cirurgia foi iniciada 28 ± 5 minutos após a administração de cetamina-midazolam-metadona. Não houve diferença nas variáveis fisiológicas avaliadas em relação aos demais tempos de avaliação ($p > 0.05$). Os escores de qualidade de recuperação foram adequados e o tempo para o gato erguer a cabeça foi de 51 ± 10 minutos. Nas condições deste estudo, cetamina-midazolam-metadona não permitiu a realização da anestesia local para orquiectomia. Muitos gatos precisaram de resgate com propofol antes de iniciar a cirurgia. Essa associação promoveu alterações mínimas nas variáveis fisiológicas e longa recuperação anestésica.

PALAVRAS-CHAVE: Recuperação anestésica; benzodiazepínicos; anestesia dissociativa; felino; opióides;.

INTRODUCTION

Ketamine is a dissociative anesthetic used to promote from sedation to anesthesia depending on the dose administered, associations with other drugs and the clinical status of the animal (BERRY, 2015). This drug has analgesic properties, induces dose-dependent cardiovascular stimulation and does not result in significant respiratory depression (ROBERTSON; LASCELLES; TAYLOR, 2003; FERNANDEZ-PARRA et al., 2017).

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Midazolam is a benzodiazepine commonly combined with ketamine, attenuating the occurrence of hypertonia and salivation promoted by this dissociative anesthetic (ILKIW et al., 1996). In cats, the ketamine-midazolam combination induces sedation (ILKIW et al., 1998) and minimal cardiovascular depression (AKKERDAAS et al., 2001).

Methadone is a μ-opioid receptor agonist used to control perioperative pain in cats (FERREIRA et al., 2011), and results in minimal hemodynamic effects (BLEY et al., 2004). Nociceptive responses to orchiectomy may be diminished with prior intratesticular and subcutaneous infiltration of lidocaine (MOLDAL et al., 2013).

The combinations of ketamine with benzodiazepines, alpha$_2$-adrenergic agonist, opioids and phenothiazines are commonly used for short-term anesthesia in cats (BIERMANN et al., 2012; ZEILER et al., 2014; KHENISSI et al., 2017; GOMES et al., 2021; GOMES et al., 2022). To date, no clinical studies using the ketamine–midazolam–methadone combination in cats have been conducted. This study aimed to evaluate the anesthetic and some cardiopulmonary effects of ketamine, midazolam and methadone, combined with local anesthesia, in cats undergoing orchiectomy. We hypothesized that ketamine-midazolam-methadone combined with local anesthesia would result in an adequate anesthetic depth for orchiectomy in cats, with minimal cardiopulmonary effects.

MATERIAL AND METHODS

The study protocol was approved by the Animal Care and Ethics Committee of the Instituto de Veterinária of Universidade Federal Rural do Rio de Janeiro (UFRRJ), Brazil (no. 8471210815). All owners provided written informed consent. Aggressive and obese cats were excluded from the study.

The cats were admitted to the veterinary hospital on the morning of the surgery, fasted for 4 hours with water and 12 hours with food. Each cat was acclimatized inside a metal cage in a small quiet room for at least 20 minutes before anesthesia was induced. The animals were weighed, and the baseline (BL) values of heart rate (HR) (by auscultation), systolic arterial pressure (SAP) (by Doppler ultrasonic), respiratory rate (RR) (by observation of thoracic expansion) and rectal temperature (RT) (using a digital thermometer) were measured. Subsequently, the cat received ketamine (10 mg/kg), midazolam (0.2 mg/kg) and methadone (0.3 mg/kg) mixed in the same syringe, intramuscularly (IM) (semimembranosus muscle) (T0). After the administration, the cat was returned to its metal cage.

The degree of sedation, muscle relaxation and nociception were recorded in that order using the criteria described in Table 1, at 5 (T5), 10 (T10) and 15 (T15) minutes after T0.

The time for lateral recumbency (between T0 and adoption of the lateral recumbency) was recorded. At T15, the animal was removed from the metal cage and the HR, SAP, RR and RT were recorded. After T15 evaluations, a 22 gauge catheter was aseptically placed in the cephalic vein, and fluid therapy with ringer lactate was started (3 mL/kg/hour). Subsequently, the cat was placed in the dorsal recumbency. If the animal did not remain immobile during recumbency, 1 mg/kg of propofol was administered intravenously (IV). The animal was reassessed 1 minute after administration, and if it was not immobilized, another dose of propofol was administered. As soon as the animal showed immobility in dorsal recumbency, trichotomy was performed, the cat was transported to the operating room and antisepsis was performed at the surgical site.

The local anesthetic technique was performed by a surgeon, with one-third of the total volume of lidocaine 2%

Table 1. Sedation, muscle tone and voluntary movement in response to tightness of the interdigital membrane scores.

Sedation	0	No sedation
	1	Sleepy but standing
	2	Lying down, but able to stay in sternal recumbency
	3	Lying down, standing up with difficulty
	4	Lying down, unable to get up
Muscle tone	0	Normal
	1	Slightly weak, tongue cannot be pulled out of the mouth or is withdrawn with difficulty
	2	Weak, tongue can be pulled out of mouth, but the animal is able to put the tongue back into the mouth
	3	Very weak, the tongue can be pulled out of mouth and the animal is unable to put the tongue back into the mouth
Voluntary movement in response to tightness of the interdigital membrane	0	Hypersensitive or normal
	1	Slightly reduced
	2	Moderately reduced
	3	Absent

(4 mg/kg) administered at the right testicle, left testicle and surgical incision line (on the median raphe). If the animal showed voluntary movement in response to local anesthesia, the local anesthetic technique was discontinued. An bolus of propofol (1 mg/kg IV) was administered, and local anesthesia was continued after 1 minute. Orchiectomy was started 10 minutes after local anesthesia. The total rescue dose of propofol administered before the start of the surgery was recorded.

All orchiectomies were performed using a standard technique (OLIVEIRA et al., 2010). During surgery, if the SAP or HR increased by 20% or some voluntary movement was observed, surgery was stopped for 1 minute, and propofol (1 mg/kg) was administered IV. The number of rescue doses of propofol administered during surgery was recorded. The HR, SAP, RR, arterial oxygen saturation (SpO_2) and RT were recorded at T30 and 45 (T45) minutes after T0. The surgical time (between the surgical incision and end of surgery) was recorded. The cat received meloxicam (0.2 mg/kg) IV at the end of surgery.

The time to head up was assessed. The quality of recovery was assessed using a numerical rating scale (1–4): 1, intense excitement, pedaling, vocalization, tremors or vomiting; 2, moderate excitement, pedaling, vocalization, tremors or vomiting; 3, minimal excitement, pedaling, vocalization, tremors or vomiting; and 4, absence of excitement, pedaling, vocalization, tremors and vomiting. The animals were evaluated for 120 minutes starting from T0. All evaluations were performed by a single observer.

The Shapiro–Wilk test was used to assess the normal distribution of the variables. One-way repeated-measures ANOVA, followed by Dunnett's test, was used to detect differences in the HR, SAP, RR and RT between the BL and T15, T30 and T45 values. Variables that were not normally distributed (sedation, muscle relaxation and nociception) were analyzed using the Friedman test, followed by Dunn's multiple comparison test to assess all differences over time. For all analyses, values of $p < 0.05$ were considered significant.

RESULTS

A total of 19 healthy (American Society of Anesthesiologists class I) male mixed-breed cats scheduled for elective orchiectomy, aged 1–4 years and weighing 4.1 ± 1.0 kg [mean ± standard deviation (SD)] were included in the study.

Higher sedation and nociception scores were observed at T15 than at T5 ($p = 0.031$ and $p = 0.017$, respectively; Table 2). Muscle relaxation was greater at T10 and T15 than at T5 ($p < 0.001$, Table 2).

The time for lateral recumbency was 5 ± 2 minutes [mean ± standard deviation (SD)]. Propofol rescue dose was required in two cats for containment in dorsal recumbency. Ten cats required propofol rescue for local anesthesia. The total rescue dose of propofol administered before the start of the surgery was 1.5 ± 0.8 mg/kg.

The surgery was started 28 ± 5 minutes [mean ± standard deviation (SD)] after T0, and lasted 3 ± 1 minutes [mean ± standard deviation (SD)]. The HR, SAP, RR, SpO_2 and RT were not significantly different between the evaluation times ($p > 0.05$, Table 3). No cat required a bolus of propofol during surgery. In the postoperative period, the recovery quality score was 3 (1–4) [median (min–max)] and the time to head up was 51 ± 10 minutes [mean ± standard deviation (SD)].

DISCUSSION

Our first hypothesis was not confirmed; ketamine-midazolam-methadone combined with local anesthesia did not result in adequate anesthetic depth for male cat castration, as it was not possible to perform local anesthesia in most of the cats in this study. At these doses, ketamine-midazolam-methadone had minimal effects on the HR, SAP, RR, SpO_2 and RT.

Table 2. Sedation, muscle relaxation and nociception scores recorded in nineteen cats at 5 (T5), 10 (T10) and 15 (T15) minutes after intramuscular administration of ketamine (10 mg/kg), midazolam (0.2 mg/kg) and methadone (0.3 mg/kg).

Variable	Time (minutes)		
	T5	T10	T15
Sedation (0–4)	4 (2–4)	4 (2–4)	4 (3–4)*
Muscle relaxation (0–3)	1 (0–3)	2(0–3)*	2(1–3)*
Nociception (0–3)	1 (0–3)	2 (0–3)	3 (1–3)*

Table 3. Heart rate (HR), systolic arterial pressure (SAP), respiratory rate (RR), arterial oxygen saturation (SpO_2) and rectal temperature (RT) recorded in cats (n = 19) at baseline (BL) and at 15 (T15), 30 (T30) and 45 (T45) minutes after intramuscular administration of ketamine (10 mg/kg), midazolam (0.2 mg/kg) and methadone (0.3 mg/kg).

Variable	Time (minutes)			
	BL	T15	T30	T45
HR (beats per minute)	180 ± 22	179 ± 31	176 ± 31	185 ± 30
SAP (mmHg)	140 ± 18	136 ± 17	138 ± 19	143 ± 19
RR (breaths per minute)	32 ± 7	25 ± 7	31 ± 9	36 ± 9
SpO_2 (%)	-	-	96 ± 2	95 ± 2
RT (ºC)	38.5 ± 0.5	38.6 ± 0.5	38.5 ± 0.6	38.0 ± 0.5

In the present study, ketamine-midazolam-methadone resulted in lateral recumbency after 5 minutes, longer than that observed with the combination of ketamine (14 mg/kg) and midazolam (0.5 mg/kg) (MARJANI; AKBARINEJAD; BAGHERI, 2015). The use of higher doses in the previous study was likely responsible for the shorter time required to adopt the lateral position. In this study, it is likely that the reduction in muscle tone 10 minutes after the administration of the anesthetic combination was promoted by midazolam (ILKIW et al., 1998); however, the design of the present study did not allow us to make this statement.

In this study, ketamine-midazolam-methadone resulted in a reduction, and even absence of, the response to tightness of the interdigital membrane. This result is likely related to the antinociceptive effects of ketamine and methadone (ROBERTSON; LASCELLES; TAYLOR, 2003; FERREIRA et al., 2011), as midazolam does not affect the nociceptive threshold in cats (ILKIW et al., 1996).

In the present study, we observed a high number of animals that required rescue with propofol, both for positioning in dorsal recumbency and for performing local anesthesia. As the duration of action of ketamine is not long (BERRY, 2015), it is likely that the results of this study were influenced by the long period between the administration of anesthesia and start of the surgery.

The maintenance of the intraoperative HR and SAP values and absence of voluntary movement in response to surgical manipulation may indicate the effectiveness of the anesthetic block in feline orchiectomy, as described in previous studies (ARMSTRONG et al., 2018; MOSER et al., 2020; GOMES et al., 2021; GOMES et al., 2022); however, the action of propofol cannot be disregarded, especially in relation to the maintenance of immobility during surgery.

The HR, SAP, RR and RT did not differ from the BL values and remained within the physiological values for the species (ROBERTSON et al., 2018). Throughout the study, no severe hypoxemia (SpO_2 < 90%) was observed, which is an advantage over protocols that use $alpha_2$-adrenergic agonist in cats (CISTOLA et al., 2004; HARRISON et al., 2011). The largest advantage of the protocol used in this study was the stability of the physiological variables evaluated, which may qualify it as a useful alternative for unstable cats from cardiovascular, respiratory and thermal points of view.

Anesthetic recovery was prolonged in the present study. Cats took 51 minutes to head up, which is almost double the time observed in cats anesthetized with ketamine (14 mg/kg) and midazolam (0.5 mg/kg) (MARJANI; AKBARINEJAD; BAGHERI, 2015). The combination of ketamine-midazolam-methadone and propofol rescues are likely responsible for the longer recovery time in cats. The recovery quality of the cats in the present study was considered adequate because the animals had some head movement, minimal excitement, and few muscle tremors, in addition to the absence of pedaling or vocalization.

The limitations of this study are the long interval between the administration of the anesthetic combination and start of the surgery and the failure to perform the statistical methods of the sample size or power calculation. The non-measurement of postoperative RT during the postoperative period can also be considered a limitation, as hypothermia can influence the anesthetic recovery time.

CONCLUSION

Ketamine (10 mg/kg), midazolam (0.2 mg/kg) and methadone (0.3 mg/kg) did not allow local anesthesia for orchiectomy. Additional doses of propofol were required for dorsal recumbent positioning and performing local anesthesia. At these doses, ketamine-midazolam-methadone had minimal effects on the HR, SAP, RR, SpO_2 and RT, and prolonged anesthetic recovery.

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