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Evaluation of Ketamine in Premedication on Postoperative Rescue Analgesia Requirement in Cats Undergoing Ovariohysterectomy

Avaliação da Cetamina na Pré-Medicação Sobre a Necessidade de Analgesia de Resgate Pós-Operatória em Gatas Submetidas à Ovariohisterectomia

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Abstract

Feline ovariohysterectomy is a routine surgery that may cause neglected pain. This work evaluated, in a prospective, comparative, randomized and blind study, the ketamine in comparison to morphine in preanesthetic medication on postoperative analgesia requirement in cats undergoing ovariohysterectomy. Thirty healthy female cats were divided into morphine group (MG, n = 15) and ketamine group (KG, n = 15). Cats received intramuscular dexmedetomidine (10 µg/kg), and either ketamine (5 mg/kg) or morphine (0.3 mg/kg) as premedication. The anesthesia was induced with propofol and maintained with isoflurane in oxygen. Sedation and analgesia were evaluated using the GRINT, and UNESP-Botucatu scales, respectively, immediately after extubation, and hourly for 6 hours following the ovariohysterectomy. Rescue analgesia was performed with morphine (0.1 mg/kg) when pain scores were ≥ 8 on the UNESP-Botucatu scale. The side effects were observed after surgery, including mydriasis in all animals from both groups, dysphoria in 80% of the KG group and in 20% of the MG, sedation in fourteen (93.33%) animals of the MG group, but not in the KG group (p <0.001). In the KG group, 13 animals required only one rescue analgesia (86.66%), while 11 animals in the MG group (73.33%) required multiple and consecutive rescue analgesia. The need for rescue analgesia in the MG group was 5.34 times higher than in the KG group (p <0.05). This study suggests a reduced need for analgesic opioids in the treatment of postoperative pain.

Keywords: Analgesia. Feline. Opioid. Pain. Sedation.

Resumo

A ovariohisterectomia felina é uma cirurgia de rotina que pode causar dor negligenciada. Este trabalho avaliou, em um estudo prospectivo, comparativo, aleatório e cego, a cetamina em comparação com a morfina na medicação pré-anestésica sobre necessidade de analgesia pós-operatória em gatas submetidas à ovariohisterectomia. Trinta gatas saudáveis foram divididas em grupo morfina (MG, n = 15) e grupo cetamina (KG, n = 15). Os gatos receberam dexmedetomidina intramuscular (10 µg/kg) e cetamina (5 mg/kg) ou morfina (0,3 mg/kg) como pré-medicação. A anestesia foi induzida com propofol e mantida com isoflurano em oxigênio. A sedação e a analgesia foram avaliadas pelas escalas GRINT e UNESP-Botucatu, respectivamente, imediatamente após a extubação e a cada 6 horas após a ovariohisterectomia. A analgesia de resgate foi realizada com morfina (0,1 mg/kg) quando os escores de dor foram ≥ 8 na escala UNESP-Botucatu. Os efeitos colaterais foram observados após a cirurgia, incluindo midríase em todos os animais de ambos os grupos, disforia em 80% do grupo KG e em 20% do MG, sedação em quatorze (93,33%) animais do grupo MG, mas não no grupo KG. Grupo KG (p <0,001). No grupo KG, 13 animais necessitaram de apenas uma analgesia de resgate (86,66%), enquanto 11 animais do grupo MG (73,33%) necessitaram de analgesia de resgate múltipla e consecutiva. A necessidade de analgesia de resgate no grupo MG foi 5,34 vezes maior do que no grupo KG (p < 0,05). Este estudo sugere uma menor necessidade de opióides analgésicos no tratamento da dor pós-operatória.

Palavras-chave: *Analgesia. Felino. Opióide. Dor. Sedação.*

1 Introduction

Feline ovariohysterectomy is a routine surgical procedure that may frequently cause a significant degree of intra and postoperative pain without appropriate management (Wagner *et al.,* 2008), and the requisition of research is outlined to improve the level of animal's care for analgesia (Gates *et al.,* 2020). Pain treatment is a veterinarian's ethical duty, given the many negative consequences of untreated pain through the reduction of animals' welfare, however, accurate recognition and treatment of pain in felines remains an obstacle (Robertson, 2008; Epstein *et al.,* 2015; Tomsič *et al.,* 2021), as felines pain symptoms may be lost even by diligent observers (Lamont, 2002; Epstein *et al.,* 2015; Buisman *et al.,* 2017).

There is renewed interest in the use of the ketamine as an analgesic (Ruel; Steagall, 2019), even though the effective clinical usage remains limited due to the absence of a standard dose, as well as non-consensus on administration, effect duration, and potency of ketamine in felines (Steagall, 2020). In humans, ketamine affects opioid receptors, acting on alpha, beta, and catecholamine receptors, increasing morphine's analgesic effect, reducing both the pain and adverse effects of morphine, whether administered simultaneously or not, providing a morphine-sparing effect (Weinbroum, 2003; Galinski *et al.,* 2007; Ahern *et al.,* 2013; Beaudoin *et al*.,

2014; Best *et al.,* 2014).

Opioids are already known as efficacious against animals' perioperative pain, on the other hand, even though morphine used alone is effective in a clinical setting, it may cause excitement and dysphoria, especially in cats with painless symptoms (Epstein *et al.,* 2015). Clinical trials prospects that low opioid doses associated with other drugs would effectively control feline pain without undesirable effects (Steagall, 2020), and more recently it has been suggested that ketamine analgesic properties can occur mainly due to non-competitive and nonspecific antagonism of the N-methyl D-aspartate receptors (Ruel; Steagall, 2019; Steagall, 2020), and also several other signaling systems such as cholinergic, serotoninergic and adrenergic (Petrocchi *et al.,* 2019).

The effects of ketamine in the pain treatment of cats are still lacking. The hypothesis of this study is that ketamine in premedication would provide a morphine-sparing effect on analgesic rescue, controlling the postoperative pain and reducing the opioids requirement. This study aimed to evaluate the effects of ketamine and morphine in the premedication controlling the postoperative pain in cats that underwent elective ovariohysterectomy.

2 Material and Methods

This work was approved by the Ethics Committee for the Use of Animals of Universidade UNOPAR (number 0035/18) and internationally recognized high standards ('best practice') of veterinary clinical care for the individual patient were followed. This work involved the use of owner client's animals. A written or verbal informed consent was obtained from the legal custodian of all animals described in this work for the procedures undertaken.

Thirty healthy short-haired female cats, 15 to 24 months, with an average of 2.42 ± 0.23 kg bodyweight (range 2.1 to 2.6 kg), were randomly and blindly assigned to either the ketamine or morphine groups using the Research Randomizer program (www.randomizer.org). All the cats underwent 12 hours of food and water fasting. The study included only healthy animals based on physical exam, complete blood count, and biochemistry profile, in accordance with the requirements of the American Society of Anesthesiology (ASA) of health classification.

Only docile animals were admitted to the study, those who accepted body manipulation and abdominal palpation, as well as kept good posture, temperament and comfort when kept in cages. Appetite was evaluated offering wet cat food, although the animals were not allowed to eat due to the previous fasting. All the experiment procedures were performed by only one surgeon, one anesthesiologist, and one experienced evaluator, and they were all blind to the treatments, since all the drugs used were handed to the evaluators by the pharmacist of the veterinary hospital.

The ketamine group (KG; n = 15) received 5 mg/kg of ketamine, while the morphine group (MG; n = 15) received 0.3 mg/kg of morphine as a pre-anesthetic agent, equally intramuscular (IM) in the quadriceps. At the same time of the morphine or ketamine administrations, both groups also received, dexmedetomidine 10 µg/kg, IM in the contralateral quadriceps. After 15 minutes of the pre-anesthetic administration, sedation levels were assessed using the GRINT scale (0 to 21) (Grint *et al.,* 2009). The anesthesia was induced with propofol until reaching the second plane of the third anesthetic stage and maintained with isoflurane in oxygen (Samurai KTK, Takaoka) in the minimum alveolar concentration (MAC) systemically adjusted in 2.0 %. Heart rate, electrocardiogram, temperature, and peripheral hemoglobin oxygen saturation were monitored with a multiparametric monitor (Dixtal DX 2023; Dixtal Biomédica Ind., Brazil), blood pressure was monitored with vascular Doppler (DV 610V; Medmega Ind., Brazil), and spontaneous ventilation was applied to all the animals. Five minutes after the beginning of surgery, Cefazolin (30 mg/kg; IM) was administered as a prophylactic antibiotic. At the end of the surgery, the isoflurane was turned off and atipamezole was injected (10 µg/kg) in the lumbodorsal muscle, since it is an α2-antagonist that competitively inhibits α2-adrenergic receptors. It safely and reliably reverses the effects of dexmedetomidine. Duration of the surgery and extubation time were recorded. The animals were kept in the left lateral recumbency and extubation was performed at the swallowing reflex return.

The postoperative evaluations comprehended the analgesia assessment by Universidade Estadual de São Paulo - Botucatu Scale (UNESP-Botucatu) (0 to 30) (Brondani *et al.,* 2012), and GRINT scale (0 to 21) (Grint *et al.,* 2009) for sedation assessment, all applied systematically and simultaneously immediately after extubation 0 hour (T0h), and 1 hour (T1h), 2 hours (T2h), 3 hours (T3h), 4 hours (T4h), 5 hours (T5h), and 6 hours (T6h) after extubation. When the score was ≥ than 8 in the UNESP-Botucatu scale, morphine rescue (0.1 mg/kg, IM) was administered in the epaxial muscle. The side effects of mydriasis, excitation, dysphoria and sedation after analgesic rescue were evaluated.

The administration of rescue analgesia in the KG provided the opportunity to evaluate if ketamine in premedication would reduce the postoperative rescue analgesia requirement in cats undergoing ovariohysterectomy.

The animals were observed during all pre and postoperative evaluations and videos were produced for documentation purposes. After one hour of the sixth evaluation, regardless of the group and the last required rescue, IM dexamethasone (0.2 mg/kg) and tramadol (2 mg/kg) were administered for the cats' medical release.

Statistical analyses were performed using GraphPad Prism. The Mann-Whitney test was used for analysis between the groups, and the Friedman test was used between times

with the Dunn's post-test. The rescue analgesia variable was analyzed considering the binomial distribution, and the odds ratio test was used to compare the differences between the groups. A *p* value of <0.05 was considered statistically significant.

3 Results and Discussion

To the best of our knowledge, this is the first study about ketamine providing a morphine-sparing effect in cats. Ketamine in premedication has not provided satisfactory analgesia in the cats' ovariohysterectomy postoperative period, as indicated by the rescue analgesia required soon after one hour of extubation, whereas morphine group required rescue analgesia for multiple and consecutive times only after three hours of extubation. In view of this, ketamine may have acted additionally to the low morphine analgesic rescue dose (0.1 mg/kg), showing a morphine-sparing effect promoting satisfactory analgesia in 100% of the animals that required rescue analgesia only once without adverse effects.

Our results highlighted a better analgesic effect by ketamine's action on the opioid receptors, insomuch as MG animals received full mu-opioid rescues multiple times that were not as effective as ketamine's additional effects on opioid receptors observed in the single rescue performed on KG. After all, the ketamine mechanism of action is not only the antagonism of the NMDA receptor but also several other signaling systems such as cholinergic, serotoninergic, and adrenergic (Petrocchi *et al.,* 2019), ketamine whether administered simultaneously or not to morphine, providing a morphine-sparing effect in humans (Ahern *et al.,* 2013; Beaudoin *et al*., 2014; Best *et al.,* 2014; Galinski *et al.,* 2007; Weinbroum, 2003).

The individual average amount of propofol for anesthesia induction was 4.81 mg/kg for the KG and 4.77 mg/kg for the MG ($p > 0.05$). The average duration of the surgeries was 13.5 ± 0.7 minutes for the KG and 14.1 ± 0.6 minutes for de MG, without statistical difference ($p > 0.05$). The body temperature (between 37.8 °C and 38.1 °C), peripheral hemoglobin oxygen saturation (> 98%), and blood pressure (> 100 mmHg) kept normal in both groups during all the surgical procedure, as also there were no intercurrences or need for extra drug administration.

Average extubation time, in minutes, was higher in the MG group (12.31 ± 1.07) than in the KG group (7.12 ± 0.97), with statistical difference (*p* value < 0.05). No animal in either group experienced pain immediately after extubation (T0h), and sedation was present only in MG (Table 1).

Table 1 - Median (minimum-maximum) of pain and sedation scores on the UNESP and GRINT scales in the morphine and ketamine groups in each evaluation time

Scales	Group	T0h	T1h	T2h	T3h	T4h	T5h	T6h	p value
UNESP (0 to 30)	KG	0	6.5(3-16)	6(1-16)	5(0-15)	4(1-7)	4.5(2-9)	4.5(2-7)	p <0.005
MG	0	5.5(1-10)	5.5(-10)	6(1-9)	5.5(3-10)	5.5(1-8)	2.5(1-5)		
GRINT (0 to 21)	KG	1 (0-1)	5(2-14)	4.5(0-8)	3.5(0-6)	2.5(1-6)	3(0-6)	3(0-8)	p <0.001
MG	5 (4-7)	3(2-7)	2.5(2-7)	2(1-7)	2(1-4)	2(1-4)	2(1-6)		

KG = Ketamine Group; MG = Morphine Group; T0h = Extubation time; T1h = 1 hour, T2h = 2 hours, T3h = 3 hours, T4h = 4 hours, T5h = 5 hours, and T6h = 6 hours after extubation.
Source: research data.

The smallest requirement of analgesic rescue in the KG may be also explained because ketamine is well-known as N-methyl-D-aspartate receptors antagonist, that can regulate the opioid receptors and sodium channels functions and increases signaling through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, and these myriads of molecular and cellular mechanisms are responsible for a various pharmacological functions including pain relief (Doan; Wang, 2018).

According to Padilha *et al.* (2015), a ketamine dose of 0.5 mg/kg has not produced satisfactory analgesia in postoperative period of ovariohisterectomized cats, but sufficient analgesia was reached when the same ketamine dose was associated with a low methadone dose (0.3 mg/kg), although caused excitement. Another study reported a ketamine dose of 2.5 mg/kg associated with a high morphine dose (0.5 mg/kg) promoted a better analgesic effect when compared to morphine alone in female dogs following OH (Almeida *et al.,* 2013). Comparably, the ketamine pre-anesthetic dose of the present study, 5 mg/kg, was higher than the doses employed by Padilha *et al.,* (2015) and Almeida *et al.,* (2013), but unlike these studies about the synergistic effect of ketamine and morphine, this study evaluated the possibility of reduction in the analgesic rescue requirement of morphine with ketamine in the pre-anesthetic medication through the possible morphine-sparing effect, and not synergism.

The findings of the present study suggest an adjunct effect of ketamine with an opioid, moreover, enlighten the analgesic effect of ketamine without the undesirable opioids adverse effects in cats. Although ketamine herein was encompassed

the pre-anesthetic protocol and the analgesic rescue was performed between one or two hours after extubation, studies show that ketamine whether administered simultaneously or not provide a morphine-sparing effect in humans (Ahern *et al.,* 2013; Beaudoin *et al*., 2014; Best *et al.,* 2014; Galinski *et al.,* 2007; Weinbroum, 2003).

Rescue analgesia started three hours after extubation in the MG, in agreement with the morphine plasma half-life of 94 minutes, and the rescue interval of four to six hours (Taylor *et al.,* 2001). Thus, all analgesic rescues were performed in the MG in the appropriate intervals, but a single dose of rescue analgesia was not enough for controlling pain, in addition to causing excitement and dysphoria. Cats produce low quantities of morphine-3-glucuronide and do not produce morphine-6-glucuronide, the active metabolites responsible for analgesia (Ruel; Steagall, 2019; Steagall, 2020; Taylor *et al.,* 2001), which may explain the multiple rescues required in the MG, as those animals received only morphine as analgesic, without the ketamine morphine-sparing effect observed in the KG.

A statistical difference was seen between groups for analgesic rescue requirements (p value < 0.005). The KG required analgesic rescue only once per animal, in 13 animals (86.66%), as 10 animals received analgesic rescue only in the T1h, and another three animals only in the T2h, elucidating that only one analgesic rescue was enough for the animal's analgesia care in the KG. On the other hand, in the MG group, only one (6.66%) animal reached sufficient analgesia with a single rescue in the T5h, and other 11 animals (73.33%) required analgesic rescues more than once, as six animals received analgesic rescues in the T3h and T4h, another two animals in the T4h and T5h, and some animals required analgesic rescues three times, as three animals required in the T3h, T5h, and T6h, so a total of 26 doses of rescue analgesia were administered in the MG. Comparing the two groups, the need for rescue analgesia in the MG were 5.34 times as high as that of in the KG.

Similarto the results presented here, ketamine reduced additional doses of opioids when used as an adjunct for opioids in human acute pain treatment (BOWERS *et al.,* 2017). This can be explained by the additional effects of ketamine on opioid receptors, which spreads its analgesic effects on alpha, beta, and catecholamine receptors, improving the analgesia and reducing adverse effects (Ahern *et al.,* 2013; Beaudoin *et al*., 2014; Best *et al.,* 2014; Galinski *et al.,* 2007; Weinbroum, 2003), as demonstrated that ketamine reduced postoperative opioid requirement in rats (Campos *et al.,* 2006).

After the extubation (T0h), mydriasis was observed in all the animals from both groups, whereas dysphoria was more frequent in the KG (12/15, 80%) than in the MG (3/15, 20%). Sedation was not observed in the KG but was present in 14 animals (93.33%) from the MG (p value <0.001). Morphine administration frequently causes accentuate sedation in cats (Steagall, 2020), and occurred in 93.33% of the MG, whereas there was no occurrence of sedation in the KG. This may be evident by the lower average extubation time observed in the KG, as the cats had earlier swallowing reflex return, already reported by studies with ketamine (Slingsby; Waterman-Pearson, 2000).

Side effects were seen in all the animals following administration of rescue analgesia. It is important to emphasize that only mydriasis was observed in all those 13 animals that received analgesic rescue in the KG, but more severe side effects were experienced by the eleven animals of the MG, since the second dose of rescue analgesia resulted in sedation and mydriases in 100% (13/13) and dysphoria in 92.33% (12/13) of the cats.

This study used a validated scale to assess pain in cats. Surprisingly, there are a few studies that assess the systemic morphine effects in cats following OH using a scale validated for the species, and even though there are studies that confirmed the limited analgesic effect of morphine in cats that have undergone OH (Almeida *et al.,* 2013; Kongara *et al.,* 2021), Stanway *et al.* (2002) demonstrated that buprenorphine seemed to provide better postoperative analgesia than morphine.

Even if the half-life of ketamine has been reported to be around 80 minutes (Hanna *et al.,* 1988), a hypothesis to justify the better ketamine premedication performance for the postoperative pain control is that it may have occurred mainly due to ketamine adjunct effect of improving the analgesia and reducing adverse effects by its action on opioid receptors, acting to spread its analgesic effect (Best *et al.,* 2014), as ketamine may produce antinociception through central desensitization or via antagonization of NMDA activity (Pekoe; Smith, 1982), supporting the hypothesis of this work. Large-scale studies are still warranted to confirm these promising results.

The present study limitations comprise the lack of a group to assess the synergistic effect of ketamine and morphine when administered together as it would also have been interesting to have a morphine and ketamine group (MKG) to compare to the separate drug protocols. The slightly low sample size and the variable absorption of IM injection in the analgesic rescue also limited our study. In addition, the ketamine mechanism that provided a morphine-sparing effect in cats should be elucidated.

4 Conclusion

Ketamine was found to be more effective as a pre-anesthetic medication, since it has reduced analgesics requirements and adverse effects commonly observed in cats that receive opioids. This study suggests a reduced need for analgesic opioids in the treatment of postoperative pain of cats undergoing ovariohysterectomy when premedicated with ketamine.

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References

AHERN, T.L. *et al*. Effective analgesia with low-dose ketamine and reduced dose hydromorphone in ED patients with severe pain. *Am. J. Emerg. Med*., v.31, n.5, p.847-851, 2013. doi: 10.1016/j.ajem.2013.02.008

ALMEIDA, M.R. *et al*. About post operatory analgesia of morphine, ketamine or their combination in bitches undergoing elective ovariohysterectomy. *Cien Rural*., v.43, n.7, p.1271-1276, 2013. doi: 10.1590/S0103-84782013000700020

BEAUDOIN, F.L. *et al*. Low-dose ketamine improves pain relief in patients receiving intravenous opioids for acute pain in the ED: results of a randomized, double-blind, clinical trial. *Acad. Emerg. Med*., v.21, n.11, p.1193-1202, 2014. doi: 10.1111/acem.13172

BEST, W.; BODENSCHATZ, C.; BERAN, D. World Health Organisation Critical Review of Ketamine. 36th WHO Expert Committee on Drug Dependence report, 6.2. Geneva: World Health Organisation, 2014.

BOWERS, K.J.; *et al*. Ketamine as an adjunct to opioids for acute pain in the emergency department: a randomized controlled trial. *Acad. Emerg. Med***.**, v.24, n.6, p.676–685, 2017. doi: 10.1111/acem.13172

BRONDANI, J.T. *et al*. Validity and responsiveness of a multidimensional composite scale to assess postoperative pain in cats. *Arq. Bras. Med. Vet. Zootec.*, v.64, n.6, p.1529-1538, 2012. doi:10.1590/S0102-09352012000600019

BUISMAN, M. *et al*. The influence of demeanor on scores from two validated feline pain assessment scales during the perioperative period. *Vet. Anaesth. Analg*., v.44, n.3, p.646-655, 2017. doi: 10.1016/j.vaa.2016.09.001

CAMPOS, A.R. *et al*. Ketamine-induced potentiation of morphine analgesia in rat tail-flick test: role of opioid-, alpha2-adrenoceptors and ATP-sensitive potassium channels. *Biol. Pharm. Bull.*, v.29, n.1, p.86-89, 2006. doi: 10.1248/bpb.29.86

DOAN, L.V.; WANG, J. An update on the basic and clinical science of ketamine analgesia. *Clin. J. Pain*., v.34, n.11, p.1077-1088, 2018. doi: 10.1097/AJP.0000000000000635

EPSTEIN, M.E. *et al*. AAHA/AAFP pain management guidelines for dogs and cats. *J. Feline Med. Surg*., v.17, n.3, p.251–272, 2015. doi: 10.1177/1098612X15572062

GALINSKI, M. *et al*. Management of severe acute pain in emergency settings: ketamine reduces morphine consumption. Management of severe acute pain in emergency settings: ketamine reduces morphine consumption. *Am. J. Emerg. Med*., v. 25, n.4, p.385-390, 2007. doi: 10.1016/j.ajem.2006.11.016

GATES, M.C. *et al*. Cross-sectional survey of anaesthesia and analgesia protocols used to perform routine canine and feline ovariohysterectomies. *Vet. Anaesth. Analg*., v.47, n.1, p.38-46, 2020. doi: 10.1016/j.vaa.2019.06.008

GRINT, N.J. *et al*. Does pethidine affect the cardiovascular and sedative effects of dexmedetomidine in dogs? *J. Small. Anim. Pract.*, v.50, n.2, p.62-66, 2009. doi: 10.1111/j.1748-5827.2008.00670.x

HANNA, R.M. *et al.* Pharmacokinetics of ketamine HCl and metabolite I in the cat: a comparison of i.v., i.m., and rectal administration. *J. Vet. Pharmacol. Ther*., v.11, n.1, p.84-93, 1988. doi: 10.1111/j.1365-2885.1988.tb00125.x

KONGARA, K. *et al*., Effects of tramadol, morphine or their combination in dogs undergoing ovariohysterectomy on peri-operative electroencephalographic responses and post-operative pain. *N. Z. Vet. J.*, v.60, n.2, p.129-135, 2012. doi: 10.1080/00480169.2011.641156

LAMONT, L.A. Feline perioperative pain management. *Vet. Clin. North Am. Small Anim*., v. 32, n.4, p.747, 2002. doi: 10.1016/s0195-5616(02)00028-1

PADILHA, V.S. *et al*. Avaliação da analgesia pós-operatória da metadona, da cetamina ou da sua associação em gatas submetidas a ovariossalpingo-histerectomia. *Arq. Bras. Med. Vet. Zootec.*, v.67, n.2, p.372-380, 2015. doi: 10.1590/1678-6930

PEKOE, G.M.; SMITH, D.J. The involvement of opiate and monoaminergic neuronal systems in the analgesic effects of ketamine. *Pain*, v.12, n.1, p.57-73, 1982. doi: 10.1016/0304-3959(82)90170-1

PETROCCHI, J.A. *et al*. Peripheral antinociception induced by ketamine is mediated by the endogenous opioid system. *Eur. J. Pharmacol.*, v.865, p.172808. doi: 10.1016/j.ejphar.2019.172808

Robertson, A.S. Managing pain in feline patients. *Vet. Clin. North Am. Small Anim*. *Pract*., v, 38, p.1267-1290, 2008. doi: 10.1016/j.cvsm.2008.06.008

RUEL, H.L.M. et al. Adjuvant analgesics in acute pain management. *Vet. Clin. North Am. Small Anim*. *Pract.*, v.49, n.6, p.1127-1141, 2019. doi: 10.1016/j.cvsm.2019.07.005

SLINGSBY, L.S.; WATERMAN-PEARSON, A.E. The post-operative analgesic effects of ketamine after canine ovariohysterectomy: a comparison between pre-or post-operative administration. *Res. Vet. Sci*., v.69, n.2, p.147-152, 2000. doi: 10.1053/rvsc.2000.0406

STANWAY, G.W. A preliminary investigation comparing pre-operative morphine and buprenorphine for postoperative analgesia and sedation in cats. *Vet. Anaesth. Analg*., v. 29, n.1, p. 29-35, 2002. doi: 10.1046/j.1467-2987.2001.00062.x

STEAGALL, P.V. Analgesia: What Makes Cats Different/ Challenging and What Is Critical for Cats? *Vet. Clin. North Am. Small Anim*. *Pract*., v.50, n.4, p.749–767, 2020. doi: 10.1016/j.cvsm.2020.02.002

STEAGALL, P.V. *et al*. Effects of subcutaneous methadone, morphine, buprenorphine or saline on thermal and pressure thresholds in cats. *J. Vet. Pharmacol. Ther*., v.29, p.531-537, 2006. doi: 10.1111/j.1365-2885.2006.00800.x

TAYLOR, P. M. *et al*. Morphine, pethidine and buprenorphine disposition in the cat. *J. Vet. Pharmacol. Ther.*, v.24, n.6, p.391–398, 2001. doi: 10.1046/j.1365-2885.2001.368goblin.x

TOMSIČ, K. *et al*. A survey study on the recognition and treatment of pain in dogs and cats by Slovenian veterinarians. *Vet. Anaesth. Analg*., v.4, n.3, p.334-343, 2021. doi: 10.1016/j.vaa.2020.11.007

WAGNER, A.E. Multicenter, randomized controlled trial of pain-related behaviors following routine neutering in dogs. *J. Am. Vet. Med. Assoc*., v.233, n.1, p.109-115, 2008. doi: 10.2460/javma.233.1.109

WEINBROUM, A.A. A single small dose of postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine-resistant pain. *Anesth. Analg*., v.96, n.3, p.789-795, 2003. doi: 10.1213/01.ANE.0000048088.17761.B4