Ciência Animal Brasileira
e-ISSN 1809-6891

Ciência Animal Brasileira

DOI: 10.1590/1809-6891v22e-68826

Section: Veterinary Medicine
Research article

Postoperative evaluation of analgesia promoted by the use of dexmedetomidine alone and associated with morphine as an intramuscular pre-anesthetic medication in bitches submitted for ovariohysterectomy

Avaliação pós-operatória da analgesia promovida pelo uso da dexmedetomidina isolada e associada à morfina em cadelas submetidas à ovariohisterectomia

Fernanda Silva Pereira[1], Aline Bossa Perotto[1], Fábio Dumit Pizzinatto[1], Dábila Araújo Sônego[1], Lianna Ghisi Gomes[1*], Alexandre Pinto Ribeiro[1], Luciana Dambrósio Guimarães[1]

[1]Universidade Federal do Mato Grosso (UFMT), Cuiabá, MT, Brazil
*Correspondent: liannaghisi@gmail.com

Received
May 03, 2021.
Accepted
September 24, 2021.
Published
November 12, 2021.

www.revistas.ufg.br/vet
visit the website to get the how to cite in the article page.

Abstract
This study aimed to evaluate the postoperative analgesic efficacy of dexmedetomidine alone and when associated with morphine in patients under general inhalational anesthesia with isoflurane and undergoing elective ovariohysterectomy (OH). Twenty healthy bitches were selected via physical and laboratory examinations. Prior to the study, they underwent a 24-h period of adaptation to the environment and observers. They were then randomly divided into two groups: the dexmedetomidine group receiving a dose of 10 µg/kg, and dexmedetomidine group (10 µg/kg) associated with morphine receiving a dose of 0.3 mg/kg, administered via the intramuscular route. Thereafter, patients were induced with propofol and maintained with isoflurane diluted in 100% oxygen administered through a calibrated vaporizer. To verify postoperative analgesia, pain assessments were performed using the modified Glasgow (EGM) and Melbourne (EM) scales. For sedation assessment, the Dobbins scale was used at different times: before the administration of pre-anesthetic medication (T0) and at another six times in the postoperative period, 1 (T1), 2 (T2), 4 (T3), 8 (T4), 12 (T5), and 24 (T6) h after orotracheal extubation. No statistical differences were observed between groups in the scales according to Dunn's Kruskal-Wallis post hoc test, and between the times a statistical difference was noticed by the Friedman test ($p<0.05$) for the EGM and EM scale scores, but there was no need for analgesic rescue. Therefore, we found that isolated dexmedetomidine and morphine produced adequate analgesic effects in the postoperative period of bitches submitted for OH.
Keywords: dogs; α-2-agonist; opioids; pain.

Resumo
Objetivou-se avaliar a eficácia analgésica pós-operatória da dexmedetomidina isolada e associada à morfina em pacientes submetidas à anestesia geral inalatória com isoflurano e submetidas à ovariohisterectomia eletiva (OH). Vinte cadelas saudáveis foram selecionadas a partir de exames físico e laboratoriais. Previamente ao estudo, foram submetidas a um período de 24 horas de adaptação ao ambiente e aos observadores. Ato contínuo, foram divididas aleatoriamente em dois grupos: grupo dexmedetomidina, na dose de 10 µg/Kg (GD) e grupo dexmedetomidina (10 µg/Kg) associado com morfina, na dose de 0,3 mg/Kg (GDM), administrados pela via intramuscular (IM). Ato contínuo, as pacientes foram induzidas com propofol e mantidas com isoflurano diluído em oxigênio 100% e administrado através de vaporizador calibrado. Para verificação da analgesia pós-operatória foram realizadas avaliações de dor por meio de escalas de Glasgow Modificada (EGM) e de Melbourne (EM). Para avaliação de sedação, por meio da escala de Dobbins (ED), em diferentes tempos: antes da administração da MPA (T0), e em mais 6 tempos no período pós-operatório, uma (T1), duas (T2), quatro (T3), oito (T4), 12 (T5) e 24 (T6) horas após a extubação orotraqueal. Não foram observadas diferenças estatísticas entre os grupos nas escalas de acordo com o teste de Kruskal-Wallis *post-hoc* de Dunn; e entre os tempos notou-se diferença estatística pelo teste de Friedman ($p<0,05$) para EGM e EM, porém não houve necessidade de resgate analgésico. Portanto, conclui-se que a dexmedetomidina isolada e associada a morfina produziu efeito analgésico adequado no período pós-operatório de cadelas submetidas a OH.
Palavras-Chave: cães; α-2-agonista; opioides; dor.

Introduction

Ovariohysterectomy (OH) is one of the most frequently performed surgeries in veterinary medicine, with a mild to moderate degree of pain, requiring the use of analgesics as part of the therapeutic protocol[1,2]. For this, it is interesting to combine different drugs, for example, α-2-agonists and opioids, for a multimodal approach and effective analgesia[3,4].

Dexmedetomidine is an α-2 adrenergic receptor agonist drug that acts on the spinal and supraspinal structures, acting on the brainstem and dorsal horn receptors of the spinal cord[5]. It produces sedation, muscle relaxation, and analgesia; reduces heart rate and cardiac output; increases systemic vascular resistance; and can cause sinus arrhythmias and atrioventricular blocks[6]. Furthermore, compared with the representatives of the same class, it has minor side effects. It is noteworthy that its use in veterinary medicine has been explored exponentially[3,4,7,8,9]. Its association with

opioids is common and helps to reduce the undesirable effects of α-2 adrenergic agents, in addition to enhancing the analgesic and sedative effects[10]. Due to adverse effects related to the cardiovascular system, its use is restricted to healthy patients[5].

In addition to being potent analgesics, opioids have sedative and hypnotic properties. They are used to control acute and chronic pain, either with or without other drugs[6]. Morphine is the reference drug for opioids, produces adequate analgesia due to its high affinity for the μ receptor, reduces the release of excitatory neurotransmitters, and hyperpolarizes the neuronal membrane, resulting in a reduction in pain from the nociceptive stimulus[6,11], in addition to being effective in the treatment of moderate to severe perioperative and postoperative pain in small animals[11,12].

The control and evaluation of postoperative pain are constant concerns. The assessment is subjective and individual and is a challenge for the veterinarian[13,14]. The presence of multiple evaluators and use of different scales are necessary to assess the patient's behavior and physiological parameters to ensure objective and satisfactory results[5,15].

This study aimed to evaluate the analgesic effects of the use of dexmedetomidine alone or associated with morphine administered as a pre-anesthetic medication (MPA) of bitches undergoing elective OH in the postoperative period.

Material and methods

Patients

This study was approved by the Ethics Committee on the Use of Animals of the Universidade Federal do Mato Grosso (UFMT) under protocol number 23108.924849/2018-13 and consent of the tutors through an authorization term.

Twenty adult bitches from the routine of the Veterinary Hospital of UFMT, *Campus* Cuiabá, were selected to undergo elective OH. They were aged between 1 and 6 years, weighing between 5 and 15 kg, and were classified as class I, according to the American Society of Anesthesiology (ASA), after clinical and laboratory evaluation (complete blood count and serum biochemistry).

Experimental Design

Prior to the study, the bitches were submitted to a 24-h period of adaptation to the environment and observers, placed in individual cages, and submitted to solid and water fasting for 12 and 4 h, respectively. They were randomly divided into two groups to receive treatments consisting of 10 μg/kg of dexmedetomidine alone (GD; Dexdomitor®) or associated with 0.3 mg/kg of morphine (GDM; Dimorf®) administered intramuscularly (IM) as MPA.

After 35 min of MPA, trichotomy of the abdominal region and forearm was performed. Afterward, the cephalic vein was catheterized, and fluid therapy was administered with Ringer's lactate solution (10 mL/kg/h) and cephalothin (25 mg/kg; Generic Hipolabor Farmacêutica®), intravenously as antibiotic prophylaxis.

Anesthesia was induced with propofol (Propovan®) until there was no resistance to

orotracheal intubation, which was performed with an appropriate probe for the size of the animal, followed by anesthetic maintenance with isoflurane (1 mL/mL, Isoforine®) administered through a calibrated vaporizer, with a diluting flow of 100% oxygen and an anesthetic system appropriate for the weight of each animal. They were maintained on a surgical anesthetic plan as proposed by Guedel, with no eyelid reflex, rostromedially rotated eyeball, and absent involuntary movements, in addition to cardiovascular parameters within the physiological values for the species.

At the end of the anesthetic procedure, when presenting a swallowing reflex, the bitches were extubated and placed in kennels and kept under observation until complete anesthetic recovery. The surgical procedures lasted 45 min and were always performed by the same surgical team to avoid interference with the study results. None of the patients required analgesic rescue during the surgical procedure; therefore, there was no interference in the postoperative evaluations.

Postoperative Evaluation

The verification of postoperative analgesia was similar to that described in the literature[16]; pain assessments were performed using the modified Glasgow (EGM)[11] and Melbourne (EM) scales, and sedation assessments were performed using the Dobbins (ED) scale[17] with the aim of evaluating the interference of sedation on pain assessment. The evaluations were performed by two evaluators who were blinded to the drugs used in MPA.

The evaluations were carried out at the following times: before the administration of MPA (T0) and six more times in the postoperative period after extubation (1 [T1], 2 [T2], 4 [T3], 8 [T4], 12 [T5], and 24 [T6] h). If any patient received a score equal to or greater than 3.3 on the EGM, they would receive analgesic rescue with morphine at a dose of 0.5 mg/kg, IM, and were excluded from further evaluations. At the end of the evaluations, all bitches received meloxicam (0.2 mg/kg; Maxicam®) subcutaneously.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism software, version 7.04, for Windows (GraphPad Software, Inc., La Jolla, California, USA). Data were tested for normality using the Kolmogorov–Smirnov test. Thereafter, the differences in nonparametric data between times within each group were analyzed using the Friedman test and between groups using the Kruskal–Wallis test, followed by Dunn's test when appropriate. The incidence of treatment failure was analyzed using Fisher's exact test, and differences were considered significant at $p<0.05$.

Results

No patient required analgesic rescue during postoperative evaluation. The EGM, EM, and ED scale sores showed no statistically significant differences between the groups. For the ED, there was no statistically significant difference in terms of time (Figure 1).

There was a statistically significant difference in relation to T0 in the EM scale score in both groups (Figure 2). In T1 ($p<0.001$) and T2 ($p<0.01$), the values were statistically

different in relation to T0 ($p<0.05$). In the GD group, there was a statistically significant difference in T1 ($p<0.001$) compared with T0.

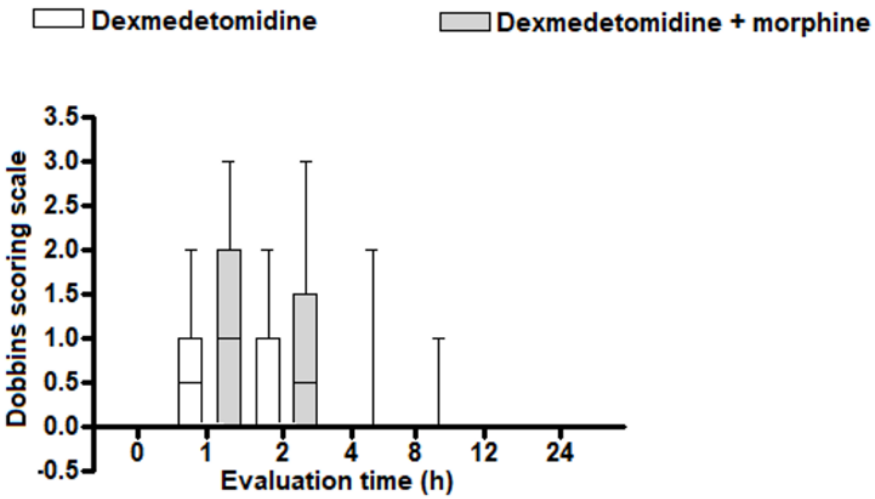

Figure 1. Postoperative evaluation using the Dobbins (ED) scale score of bitches undergoing ovariohysterectomy with dexmedetomidine alone (10 µg/kg, GD) and associated with morphine (0.3 mg/kg, GDM) as a pre-anesthetic medication (MPA), at different times: before the administration of MPA (T0) and 1 (T1), 2 (T2), 4 (T3), 8 (T4), 12 (T5), and 24 (T6) h after orotracheal extubation.

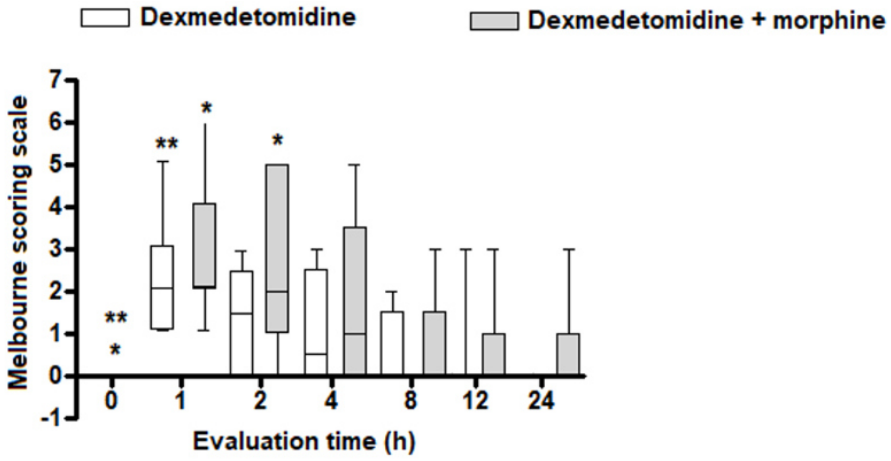

Figure 2. Postoperative evaluation using the Melbourne (EM) scale score of bitches undergoing ovariohysterectomy with dexmedetomidine alone (10 µg/kg, GD) and associated with morphine (0.3 mg/kg, GDM) as a pre-anesthetic medication (MPA), at different times: before the administration of MPA (T0) and 1 (T1), 2 (T2), 4 (T3), 8 (T4), 12 (T5), and 24 (T6) h after orotracheal extubation. *Values that show statistical difference in the GDM group compared with T0. **Values that show statistical difference in the GD group compared with T0 ($p<0.05$).

For the EGM scale scores, the GDM group at T1 ($p<0.01$) and T2 ($p<0.05$) had significantly different values compared with that at T0 ($p<0.05$), and there was no statistical difference in the GD group (Figure 3).

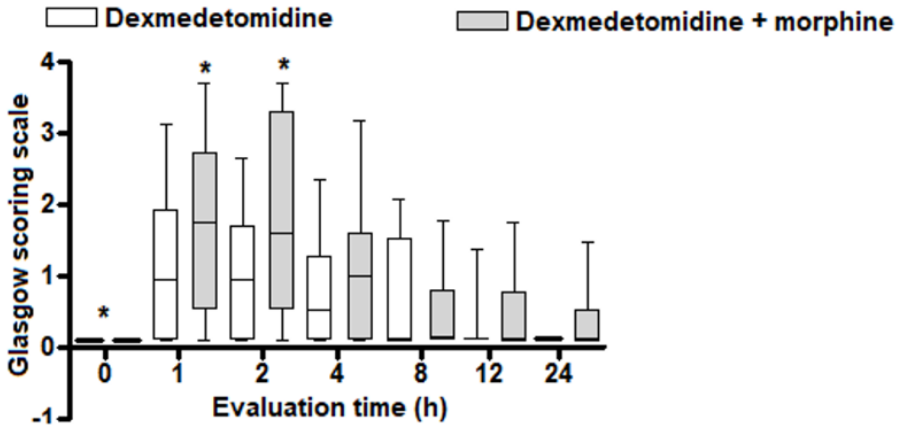

Figure 3. Postoperative evaluation using the modified Glasgow (EGM) scale score of bitches undergoing ovariohysterectomy with dexmedetomidine alone (10 µg/kg, GD) and associated with morphine (0.3 mg/kg, GDM) as a pre-anesthetic medication (MPA), at different times: before the administration of MPA (T0) and 1 (T1), 2 (T2), 4 (T3), 8 (T4), 12 (T5), and 24 (T6) h after orotracheal extubation. *Values that showed statistical difference in the group GDM compared with T0 ($p<0.05$).

Discussion

It is known that the therapeutic dose of morphine varies between 0.1 and 0.5 mg/kg[18], and considering its association with an α-2 adrenergic receptor agonist drug, it was decided to use an intermediate dose of 0.3 mg/kg IM to minimize possible side effects. Dexmedetomidine, when used as MPA in dogs, is administered at doses of 1–10 µg/kg IM. Another form of use is continuous infusion, and doses of 1, 3, and 5 µg/kg/h are known to promote adequate postoperative analgesia[19]. It is noteworthy that dexmedetomidine analgesia and duration are dose-dependent[18], and analgesiometric studies suggest that both the intensity and duration of analgesia of α-2 adrenergic receptor agonists are dose-dependent[4].

In this study, we chose to use 10 µg/kg of dexmedetomidine alone and associated with 0.3 mg/kg of morphine for the implementation of multimodal analgesia. Dexmedetomidine dose was extracted from published studies[10,20,21], which observed moderate sedation and analgesia, corroborating the data found in this study.

Dexmedetomidine has the ability to potentiate the effects of opioids and other sedatives in humans, and this attribute indicates that this drug can be administered at low doses, since the antinociceptive synergism with opioids has already been

recognized[8,21]. However, the results did not show synergism between the drugs used, since there was no statistical difference between the groups. On the contrary, other studies[10,21] showed that the combination of dexmedetomidine with morphine promoted the potentiation of antinociception when compared with the administration of the same alone.

In the present study, it was not necessary to perform analgesic rescue in any of the bitches. This fact may be related to the dose of dexmedetomidine and morphine used, as observed by other authors[10] who used the dose of 10 µg/kg of dexmedetomidine associated with 0.5 mg/kg of morphine, IM, observing a suitable analgesic effect in bitches. It is noteworthy that we used a similar dose of dexmedetomidine, and we chose to reduce the dose of morphine to 0.3 mg/kg, and even with a lower opioid dose, when compared with the dose used in a previous study[10], adequate analgesia was obtained. However, studies that used low doses of isolated dexmedetomidine (5 µg/kg) and associated morphine (0.3 mg/kg) via the IM route in MPA demonstrated the need for analgesic rescue[16], a fact also observed by other authors[19] who found the need for analgesic rescue in 22% of patients who received dexmedetomidine infusion (1 µg/kg/h) after the OH surgical procedure, concluding that dexmedetomidine did not provide satisfactory analgesia in the postoperative period, which differs from the findings of the present study, since the dose of dexmedetomidine used alone and in association was effective for pain control in the postoperative period.

The times used for the assessments through the scales are described in the literature[10,16,22] and were used to measure pain in bitches submitted for OH. Changes in animal behavior in response to pain can be difficult to interpret after surgery; for this reason, more than one evaluator and scoring system were considered for adequate pain assessment, corroborating other authors[19,23]. In this study, no statistical differences were observed between the groups based on the scales used.

The EGM scale is a useful scale for measuring perioperative pain based on the interpretation of behavioral signs for evaluation. In this scale, the subjectivity and variability on the part of the evaluator are limited, increasing the precision of the observed scores. The score ranges from 0 to 24 points, indicating that the higher the score, the greater the occurrence of postoperative pain[11]. Since it allows a detailed observation of the animals' behavior, this scale was used as a reference to verify the need for analgesic rescue in this study. Additionally, there was no statistical difference between the values at different times for the GD group, but for the GDM group at T1 and T2, the values differed statistically in relation to T0, although there was no need to perform analgesic rescue at these times, as the patients did not reach the score indicated for carrying out the same, proving the analgesic effect of drugs during the postoperative period.

Another scale used was the EM scale based on behavioral and physiological responses, considered efficient for the assessment of postoperative pain in bitches undergoing OH[24], but this scale assesses a smaller number of variables for pain behavior when compared with the EGM scale[19]. In the present study, it was found that at T1 and T2, the values were statistically different in relation to T0 for the GDM group; in the GD group, there was a significant difference in T1 compared with T0. Despite this, no patient achieved a score indicating a painful situation and the need for analgesic

support.

The ED scale was used to verify the sedation score, and its assessment is extremely important, since the level of consciousness can inevitably affect pain assessment[19,25,26]. There was no influence of the sedation score on pain assessment between the groups at various times, which can be attributed to a significant time from application in MPA until the first postoperative evaluation.

Conclusion

It was concluded that dexmedetomidine alone and associated with morphine, used as a MPA via the IM route produced an adequate analgesic effect in the postoperative period. However, there was no potentiation of the effects of dexmedetomidine in combination with morphine. Despite this, the use of protocols for postoperative pain control in bitches undergoing elective OH is recommended.

Declaration of interest

The authors declare no conflicts of interest.

References

1. Goethem BV, Schaefers-Okkens A, Kirpensteijn J. Making a rational choice between ovariectomy and ovariohysterectomy in the dog: A discussion of the benefits of either technique. Veterinary Surgery [Internet]. 2006 Feb. [cited 2021 Apr 30];35(2):136-143. Available from: https://doi.org/10.1111/j.1532-950X.2006.00124.x.

2. Mathews K, Kronen PW, Lascelles D, Nolan A, Robertson S, Steagall PVM, Wright B, Yamashita K. Guidelines for recognition, assessment and treatment of pain. Journal of Small Animal Practice [Internet]. 2014 May. [cited 2021 Apr 30];55(6):E10-68. Available from: https://doi.org/10.1111/jsap.12200.

3. Otero ARS, Barbosa VF, Carneiro RL, Martins-Filho EF, Azevedo MC, Santos BCP, Gordilho-Filho AO, Costa-Neto JM. Avaliação da infusão continua de dexmedetomidina ou dexemedetomidina-midazolam sobre variáveis cardiorrespiratórias e qualidade da recuperação anestésica, em cadelas submetidas à ovaiosalpingohisterectomia. [Evaluation of continuous infusion of dexmedetomidine or dexmedetomidine-midazolam on cardiorespiratory variables and quality of anesthetic recovery, in bitches submitted to ovariosalpingohysterectomy]. Revista Brasileira de Medicina Veterinária [Internet] 2016 Abr-Jun. [cited 2021 Apr 29];38(2):168-172. Available from: http://www2.rbmv.org/index.php/BJVM/article/download/209/844. Portuguese.

4. Lemos VCC, Sande JQ, Barbosa VF, Costa-Neto JM, Martins-Filho EF, Iwassa CHD. Avaliação da dexmedetomidina e do tramadol, associados ao midazolam, em gatas anestesiadas com isoflurano e submetidas à ovário-histerectomia. [Evaluation of dexmedetomidine and tramadol, associated with midazolam, in cats anesthetized with isoflurane, undergoing ovariohysterectomy]. Arquivo Brasileiro de Medicina Veterinária e Zootecnia [Internet]. 2017 Nov-Dec. [cited 2021 Apr 29];69(6):1521-1528. Available from: https://doi.org/10.1590/1678-4162-9426. Portuguese.

5. Hunt JR, Grintt NJ, Taylor PM, Murrel JC. Sedative and analgesic effects of buprenorphine, combined with either acepromazine or dexmedetomidine, for premedication prior to elective surgery in cats and dogs. Veterinary Anaesthesia and Analgesia [Internet]. 2013 May. [cited 2021 Apr 30];40(3):297-307. Available from: https://doi.org/10.1111/vaa.12003.

6. Maiante AA, Teixeira-Neto FJ, Beier SL, Corrente JE, Pedroso CEBP. Comparison of the cardio-respiratory effects of methadone and morphine in conscious dogs. Journal of Veterinary Pharmacology and Therapeutics [Internet]. 2008 July. [cited 2021 Apr 28];32:317-328. Available from: https://doi.org/10.1111/j.1365-2885.2008.01042.x.

7. Vilela NR, Nascimento PJ. Uso de dexmedetomidina em anestesia. [Dexmedetomidine in anesthesiology] Revista Brasileira de Anestesiologia [Internet]. 2003 Jan-Fev. [cited 2021 Apr 28];53(1):97-113. Available from: https://bjan-sba.org/article/10.1590/S0034-70942003000100013/pdf/rba-53-1-97.pdf. Portuguese.

8. Afonso J, Reis F. Dexmedetomidina: papel atual em anestesia e cuidados intensivos [Dexmedetomidine: current role in anesthesia and intensive care]. Revista Brasileira de Anestesiologia [Internet]. 2012 Jan-Fev. [cited 2021 Apr 29];62(1):118-133. Available from: https://doi.org/10.1590/S0034-70942012000100015. Portuguese.

9. Poerschke AC, Soares AV, Dorneles FS, Duck MRK. Cloridrato de dexmedetomidina como medicação pré-anestésica ou sedativo em cães – Relato de dois casos. [Dexmedetomidine hydrochloride as premedication or sedative in dogs -report of two cases] Veterinária e Zootecnia [Internet]. 2017 dez [cited 2021 Sep 20]; 24(4):697-702. Available from: https://rvz.emnuvens.com.br/rvz/article/view/235/110. Portuguese.

10. Cardoso CG, Marques DRC, Silva THM, Mattos-Junior E. Cardiorespiratory, sedative and antinociceptive effects of dexmedetomidine alone or in combination with methadone, morphine or tramadol in dogs. Veterinary Anaesthesia and Analgesia [Internet]. 2014 Nov. [cited 2021 Apr 29];41(6):636-643. Available from: https://doi.org/10.1111/vaa.12172.

11. Murrell JC, Psatha EP, Scott EM, Reid J, Hellebrekers LJ. Application of a modified form of the Glasgow pain scale in a veterinary teaching centre in the Netherlands. The Veterinary Records [Internet]. 2008 Mar. [cited 2021 Apr 29];162(13):403-408. Available from: https://doi.org/10.1136/vr.162.13.403.

12. Fantoni D, Garofalo NA. Fármacos analgésicos opioides. In: Tratamento da dor na clínica de pequenos animais. Rio de Janeiro: Elsevier; 2012. p. 538. Portuguese.

13. Luna SPL. Dor, senciência e bem-estar em animais: sensiência e dor. Ciência Veterinária nos Trópicos [Internet]. 2008 Apr. [cited 2021 Apr 30];11(1):17-21. Available from: http://rcvt.org.br/suplemento11/17-21.pdf. Portuguese.

14. Castro DS, Silva MFA, Shih AC, Motta PPA, Pires MVM, Scherer PO. Comparison between the analgesic effects of morphine and tramadol delivered epidurally in cats receiving a standardized noxious stimulation. Journal of Feline Medicine and Surgery [Internet]. 2009 Dec. [cited 2021 Apr 30];11(12)948-953. Available from: https://doi.org/10.1016/j.jfms.2009.04.009.

15. Gaynor JS. Other drugs used to treat pain. In: Gaynor JS, Muir WW (Eds). Handbook of veterinary pain management. 2nd ed. Mosby Elsevier, 2009. p. 260-279. Available from: https://doi.org/10.1016/B978-0-323-04679-4.X0036-6.

16. Costa TAF, Mascarenhas LC, Anunciação-Filho WM, Sônego DA, Campos GMD, Ribeiro AP, Flôres FN, Guimarães LD. Avaliação da analgesia pós-operatória da dexmedetomidina isolada e associada à morfina quando utilizada na medicação pré-anestésica em cadelas submetidas à ovariosalpingohisterectomia eletiva [Evaluation of postoperative analgesia of dexmedetomidine alone or associated to morphine as premedicants in bitches undergoing ovariosalpingohisterectomy]. Acta Scientiae Veterinareae [Internet] 2019 Mar. [cited 2021 Sep 20];2019(47):1646. Available from: https://doi.org/10.22456/1679-9216.90827.

17. Dobbins S, Brown NO, Shofer FS. Comparison of the Effects of Buprenorphine, Oxymorphone Hydrochloride, and Ketoprofen for Postoperative Analgesia After Onychectomy or Onychectomy and Sterilization in Cats. Journal of the American Animal Hospital Association [Internet] 2002 Nov. [cited 2021 Sep 20];38(6):507-514. Available from: https://doi.org/10.5326/0380507.

18. Oostrom HV, Doornenbal A, Schot A, Stiene PJ, Hellebrekers LJ. Neurophysiological assessment of the sedative and analgesic effects of a constant rate infusion of dexmedetomidine in the dog. The Veterinary Journal [Internet]. 2011 Dec. [cited 2021 Apr 30];190(3):338-344. Available from: https://doi.org/10.1016/j.tvjl.2010.11.025.

19. Blanco EG, Mora JMV, Camarillo JAI, Arceo CHS, González MEB, Arcique CMA, Cano GM, Steagall PV. Postoperative analgesic effects of either a constant rate infusion of fentanyl, lidocaine, ketamine, dexmedetomidine, or the combination lidocaine-ketamine-dexmedetomidine after ovariohysterectomy in dogs. Veterinary Anaesthesia and Analgesia [Internet] 2015 May. [cited 2021 Apr 29];42:(3)309-318. Available from: https://doi.org/10.1111/vaa.12215.

20. Canfrán S, Bustamante R, González P, Cediel R, Goméz de Segura IA. Comparison of sedation scores and propofol induction doses in dogs after intramuscular administration of dexmedetomidine alone or in combination with methadone, midazolam or methadone plus midazolam. The Veterinary Journal [Internet]. 2016 Apr. [cited 2021 Apr 30];210:56-60. Available from: https://doi.org/10.1016/j.tvjl.2016.01.015.

21. Karna SR, Chambers P, Singh P, Lopez-Villalobos N, Kongara K. Evaluation of analgesic interaction between morphine, maropitant and dexmedetomidine in dogs undergoing ovariohysterectomy. New Zealand Veterinary Journal [Internet]. 2021 Jun [cited 2021 Sep 20];9:1-12. Available from: https://doi.org/10.1080/00480169.2021.1927231.

22. Almeida MR, Luna SPL, Alves RM, Hashimoto HH, Almeida RM. Sobre a analgesia pós-operatória da morfina, cetamina ou da associação em cadelas submetidas à ovariosalpingohisterectomia eletiva. [About post operatory analgesia of morphine, ketamine or their comnination in bitches undergoing elective ovariohysterectomy]. Ciência Rural [Internet]. 2013 Jul. [cited 2021 Apr 30];43(7):1271-1276. Available from: https://doi.org/10.1590/S0103-84782013000700020. Portuguese.

23. Lemke KA, Creighton CM. Analgesia for anesthetized patients. Topics in Companion Animal Medicine

[Internet]. 2010 May. [cited 2021 Apr 30];25(2):70-82. Available from: https://doi.org/10.1053/j.tcam.2009.12.003.

24. Pohl VH, Carregaro AB, Lopes C, Garlet C, Marques JS. Correlação entre as escalas visual analógica, de Melbourne e filamentos de Von Frey na avaliação da dor pós-operatória em cadelas submetidas à ovariosalpingohisterectomia. [Correlation between visual analog scale, Melbourne pain scale and Von Frey filaments in post-operatory pain evaluation in bitches submitted to ovaryhysterectomy]. Ciência Rural [Internet]. 2011 Jan. [cited 2021 Apr 29];41(1):154-159. Available from: https://doi.org/10.1590/S0103-84782011000100025. Portuguese.

25. Epstein M, Rodan I, Griffenhagen G, Kadrlik J, Petty M, Robertson S, Simpson W. 2015 AAHA/AAFP Pain management guidelines for dogs and cats. Journal of Feline Medicine and Surgery [Internet]. 2015 Feb. [cited 2021 Apr 29];51(2): 67-84. Available from: https://doi.org/10.1177/1098612X15572062.

26. Guillot M, Rialland P, Nadeau MÈ, Castillo JRE, Gauvin D, Troncy E. Pain induced by a minor medical procedure (bone marrow aspiration) in dogs: comparison of pain scales in a pilot study. Journal of Veterinary Internal Medicine [Internet]. 2011 Sep-Oct. [cited 2021 Apr 29];25(5):1050-1056. Available from: https://doi.org/10.1111/j.1939-1676.2011.00786.x