RESEARCH ARTICLE

IJVAR *International Journal of Veterinary and Animal Research*
E-ISSN: 2651-3609 4(2): 44-48, 2021

The Comparison of The Effects of Medetomidine and Alfaxalone on Sedation in Cats

Mert Soykan Besler[1a], Zeynep Pekcan[1b*]

[1] Kırıkkale University, Faculty of Veterinary Medicine, Veterinary Surgery, Kırıkkale Turkey

[a]ORCID: 0000-0002-4790-8329; [b]ORCID: 0000-0003-1047-5280

*Corresponding Author
E-mail: vetzeynep@yahoo.com

Received: June 11, 2021
Accepted: July 04, 2021

Abstract

This study was conducted to compare the sedative and cardiovascular effects of alfaxalone and medetomidine in cats. In the study, 18 owned cats brought for X-ray, ultrasound, dental examination, ear diseases examination, and bandage change were used. The cats were randomly divided into two groups; 4 mg/kg alfaxalone was intravenously administered to one group and 0.08 mg/kg medetomidine to the other group. After the application, movement changes and sedation conditions were recorded. Sedation score, analgesia score, heart rate, respiratory rate, and side effects were also recorded. The sedation score was higher and the duration of sedation was longer in the medetomidine group, and the differences were statistically significant. As a result, it was concluded that alfaxalone and medetomidine have clinically similar sedative and analgesic efficacy, medetomidine should be preferred in applications requiring prolonged sedation in cats, and alfaxalone is more reliable in animals with cardiovascular problems.

Keywords: Alfaxalone, anesthesia, cat, medetomidine, sedation.

INTRODUCTION

Alfaxalon is an injectable neurosteroid anesthetic used for sedation, induction of anesthesia, and/or total intravenous anesthesia in cats and dogs. After the administration, muscle relaxation, loss of consciousness, and/or general anesthesia have been observed. The recommended application dose for induction of anesthesia is 4-5 mg/kg intravenously in cats (Ferre et al., 2006; Muir et al., 2008; Warne et al., 2014).

Alfaxalone causes minimal changes in cardiac output and blood pressure (Muir et al., 2008; Muir et al., 2009). It has few effects on respiration. It is short-acting and has no cumulative effect (Ferre et al., 2006; Whittem et al., 2008). These properties have recently given popularity to alfaxalone for short-term sedation and/or anesthesia induction in cats.

Medetomidine is an α2-adrenoceptor agonist drug, frequently used for premedication in veterinary anesthesia. It provides sedation, analgesia and muscle relaxation in pets when used at recommended doses (Pypendop et al., 1999 Nilsfors et al., 1989; Okumuş, 2003). It can cause first and second-degree heart blocks in dogs. The most prominent side effects of α2-adrenoreceptor agonists are bradycardia on the cardiovascular system. The duration and severity of bradycardia depend on the dose of the drug administered. Low doses cause a short-term reduction in pulse rate and shorter-term bradycardia (Sinclair, 2003; Lemke, 2004).

This study aims to investigate and compare the sedative and analgesic efficacy of alfaxalone and medetomidine in cats.

MATERIALS AND METHODS

The animal material of this study consisted of owned cats, brought to Kırıkkale University Research and Animal Hospital and Vet World Veterinary Clinic, which do not allow X-ray and ultrasound examination, for caring dental diseases, ear diseases, removal of sutures, abscess drainage, bandage changes, etc. After physical examination and blood results, ASA 'class I' cats were included in the study. Before the study, animal owners were informed, and "consent forms" were obtained.

Food and water restrictions were not applied to the animals used in the study until 2 hours before anesthesia. The study was carried out on 18 cats regardless of breed, weight, sex, and age, and the cats were randomly divided into 2 groups. 4 mg/kg alfaxalone (Alfaxalone 10 ml, Jurox) was administered to the alfaxalone group for pre-anesthesia, and 0.08 mg/kg medetomidine (Domitor 10 ml, Vetoquinol) was intravenously administered to the medetomidine group.

After the application, the cats were observed at 15-minute intervals for the first hour, and then at 30-minute intervals, their movements, sedation status, pulse, and respiratory rates were recorded by the same person for 90 minutes period. Side effects (vomiting, salivation, excitation, tremor, foot movements, agitation, etc.) were also recorded.

The heart rate was determined by placing the hand on the thorax to the heart region or listening to the sounds with a stethoscope. Thoracic movements were monitored for respiratory rate. The animals were kept at room temperature for 2 hours, and no additional heating was applied. Animals were not given any fluid supplementation during observation. After an entirely awakening, it was handed over to its owners.

In the evaluation of sedation score, Bhalla et al. (2018)'s sedation scoring system was used. In this scoring, the changes that occurred in the animal at certain intervals were evaluated before and after the sedative drug

administration. Accordingly, “0” indicates that the animal is awake, while “10” indicates that it is in deep sedation. These categories and their scores are given in the table below

Apart from these, palpebral reflex, jaw tone, tongue retraction and salivation status, location of bulbus oculi, palpebra tertia protrusion, vomiting, muscle tremors, and opisthotonus-like posture, GAG reflex, and deep pain sensation were investigated during the sedation.

Table 1: Scale used to score sedation in cats after intravenous administration of alfaxalone or medetomidine (Bhalla et al., 2018).

CRITERIA	SCORE	DEFINATION
Posture	0	Standing position, walking
	1	In sternal or lateral position but stands when stimulated
	2	Remains in sternal recumbency and resists lateral recumbency
	3	Remains in lateral recumbency but might lift head
	4	Remains in lateral recumbency even when stimulated, flat out
Response the clipper sounds	0	Reacts strongly when clippers turned on
	1	Reacts mildly when clippers turned on
	2	No reaction to clippers being turned on
Response to clipping	0	Reacts strongly when hair is clipped
	1	Reacts mildly when hair is clipped
	2	No response to hair being clipped
Response to restraint	0	Alert, readily resists restraint (looks, lifts head)
	1	Alert but minimally responds to restraint (appears sedated)
	2	No reaction to restraint

In addition to these parameters the first sleep minute, the first head lifting minute, the first sternal position minute, first standing minute, first licking minute, first stretching minute and first tremor minute was recorded to evaluate the duration of action of both drugs.

All the data obtained at the end of the study were statistically evaluated in the SPSS program. Normality control of the data was done with the Shapiro-Wilk test. Those that did not come from the normal distribution were presented as median and Interquartile range. The Wilcoxon signed-ranks non-parametric test was used for the analysis of time-dependent changes within the group. The difference between the groups at the same time was evaluated by using the Mann-Whitney-U test. The value of $P < 0.05$ was considered statistically significant.

RESULTS

During the sedation period, no negative behavior and temperament of the animals included in the study were observed.

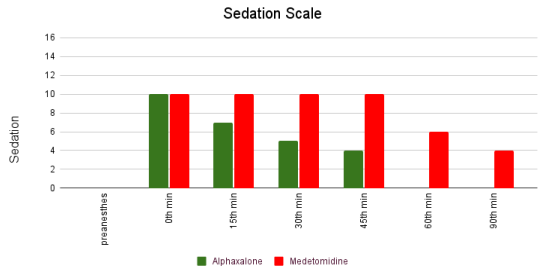

Figure 1. Time-dependent change of sedation score in cats treated with alfaxalone and medetomidine

The changes in sedation at certain time intervals after the animals were given 4 mg/kg alfaxalone and 0.08 mg/kg medetomidine intravenously for pre-anesthesia were given in Fig. 1. It was recorded that sedation occurred in a short period of time after the sedative drug was administered to the animals, and the differences over time were statistically significant in both groups ($P<0.000$). While the sedation scores were the same in both groups at the 0th minute, it was shorther (beginner to wake up) in the alfaxalone group than the medetomidine group. The difference in sedation score was statistically significant in the 15th, 30th, 45th, 60th, and 90th minutes when both groups were compared ($P<0.000$). Sedation scores remained high in the medetomidine group until the end of the study ($P<0.014$), they started to decrease after the 15th minute in the alfaxalone group, and after the 60th minute, the effectiveness of alfaxalone was disappeared (Figure 1).

7 out of 9 animals in both groups moved to the lateral position (within 0 min) immediately after the administration and remained lateral even when stimulated (shaving machine sound, grip, and physical stimulation). The remaining 2 animals in both groups moved to the lateral position, but they could only raise the head when stimulated.

The longest time between the first minute of sleep and the first minute of the head lift in alfaxalone-administered animals was 20 minutes. A complete sedation was not recorded in one animal, it was only remained in the lateral position. This time was limited to 3 minutes in one animal. In the medetomidine group, the difference between the first minute of sleep and the time to head lift ranged from 48 to 64 minutes. In other words, the duration of sedation was recorded to be longer in the medetomidine group than in the alfaxalone group. In the medetomidine group, the difference between the time after the first head lift and the time to the first sternal position was determined to be short.

The tremor was severe in 8 out of 9 animals in the alfaxalone group. The onset of the first tremor was 2-14 minutes after administration. The tremor started as severe from the first moment it was observed and continued at a mild level as time passed and was observed until the first sternal position. The sedation times of the animals in the alfaxalone group varied between 17-56 minutes. The tremor was not observed in any animals in the medetomidine group.

The palpebral reflex was not lost in all animals in either group. It was observed that the jaw tone loosened with the sedation of the animal in both groups and started to return to normal with the decrease of the effect of the drug. It was observed that the tongue retraction

disappeared according to the depth of anesthesia and the reflex returned to normal as the depth of anesthesia decreased. Salivation was not observed in any animal. It was observed that the bulbus oculi kept their position in the center, and the pupils were mydriatic.

There was no vomiting, and no opisthotonus-like posture was observed in either group. While palpebra tertia protrusion was observed within the first 15 minutes in 5 of 9 animals in the alfaxalone group, no palpebra tertia protrusion was observed in any animal in the medetomidine group. The gag reflex was not lost in any animal. Deep pain sensation was recorded at all times in all animals.

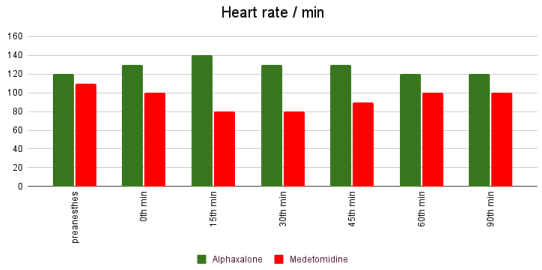

Figure 2. Time-dependent variation of heart rate in cats treated with alfaxalone and medetomidine

Figure 2 shows the changes in heart rate at specific time intervals after 4 mg/kg alfaxalone and 0.08 mg/kg medetomidine were given intravenously to animals for pre-anesthesia. Accordingly, while the heart rate remained within the reference ranges at all time intervals in cats, it was noted that the changes in the medetomidine group over time were statistically significant (P<0.02), while the changes in the alfaxalone group were not statistically significant (P<0.122). Significant changes in heart rate were observed at the 15th, 30th, and 45th minutes after medetomidine administration. When the comparison was made between the groups, there was no statistical difference in pre-anesthesia. However, it was determined that the heart rate decreased in the medetomidine group after drug administration and remained low until the end of the study, and the difference was found to be statistically significant at all times (P<0.024) (Figure 2).

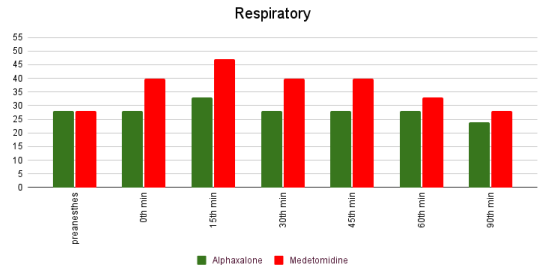

Figure 3. Time-dependent variation of respiratory rate in cats treated with alfaxalone and medetomidine.

Figure 3 shows the changes in respiratory rates at certain time intervals after administration of 4 mg/kg alfaxalone and 0.08 mg/kg medetomidine intravenously. Accordingly, while respiratory rates of cats remained within the reference ranges at all time intervals, it was noted that the changes in the medetomidine group were statistically significant (P<0.012), while the changes in the alfaxalone group were not significant (P<0.43). It was observed that respiratory rates increased over time in the medetomidine group. The increase in respiratory rate was statistically significant at the 0th, 15th, 30th, 45th, and 60th minutes. When the comparison was made between the groups simultaneously, there was no statistical difference in pre-anesthesia. However, it was determined that respiratory rates increased in the medetomidine group after drug administration and remained high within 45 minutes, and the difference was statistically significant at 0, 15, 30, and 45 minutes (P). <0.006) (Fig. 3). Apnea did not occur in any of the cats.

DISCUSSION AND CONCLUSION

This study aimed to observe the preanesthetic and sedative effects of alfaxalone and medetomidine (patients which do not allow clinical and radiological examinations and small surgical interventions) in cats. In order to observe the clinical effects of the drugs, antagonists were not used. No undesirable side effects (respiratory arrest, cardiac arrest, death, etc.) were recorded in any animal.

In some studies, it has been stated that the effect of alfaxalone begins rapidly, provides sufficient muscle relaxation, and any accumulation is reported after repeated use. It has been recorded that recovery from anesthesia is rapid and causes minimal respiratory depression (Ferre et al., 2006; Muir et al., 2008). The reported results from this study was similar with other researchers. It has been noted that animals move into a lateral position within seconds of alfaxalone injection and stand up in a short amount of time. When the duration of the recovery was compared, it was determined that the duration of action of alfaxalone was significantly shorter than medetomidine. In other words, if the procedure requiring sedation expected to take a short time, it would be more appropriate to prefer alfaxalone.

Studies conducted have shown that alfaxalone has no analgesic properties (Warne et al., 2014). In our study, deep pain sensation never disappeared in the alfaxalone group. This situation brings the necessity of adding another analgesic drug to the anesthesia protocol, especially in painful situations.

Alfaxalone can be administered intravenously (IV), intramuscularly (IM), intraperitoneally (IP), or by immersion. In the United States, the Food and Drug Administration (FDA) approved method of administration for both dogs and cats is IV. The dose of alfaxalone to be administered without premedication is 4-5 mg/kg IV or 10 mg/kg IM (Ferre et al., 2006; Muir et al., 2008; Warne et al., 2014). In this study, alfaxalone was administered as 4 mg/kg IV. In practice, it was observed that 7 out of 9 animals came to the lateral position immediately after the alfaxalone administration. It has been observed that some of the cats come to the lateral position immediately even before the finishing of intravenous injection. Because 7 animals sedated in such a short time, it led to the contradiction whether there was a problem in the way of administration in animals which the sedation begin later. Vascular access was opened before the administration of drugs to animals, but perhaps the movement of the cats during the fixation of the intravenous line led to the thought that the applied catheter might have come out of the vein and the application could be subcutaneous or intramuscular.

Alfaxalone is frequently compared to propofol, which is commonly used for IV anesthesia induction. Unlike propofol, alfaxalone has not been associated with injection site pain in dogs or humans. In addition, local irritation and inflammation have not been widely recorded after administration (Ferre et al. 2006; Muir et al. 2008;

Buisman et al., 2015; Tamura et al. 2015). There was no observation of local irritation in any animal during the administration of medetomidine and alfaxalone following the administrations.

It has been recorded that alfaxalone has few adverse effects on the cardiovascular system in cats, maintains heart rate even at increasing doses, and reduces systemic vascular resistance at a minimal level (Whittem et al., 2008; Muir et al., 2009). In this study, the decrease in the animals' heart rate was minimal, supporting the studies.

A study comparing three anesthesia induction protocols (alfaxalone, midazolam, and ketamine, propofol) used to evaluate laryngeal function in cats found that alfaxalone was the only protocol to maintain arytenoid cartilage movement in all cats (Nelissen et al., 2012). For this reason, it has been recorded that cats anesthetized with alfaxalone do not have an appropriate depth of anesthesia for intubation (Herbert and Murison, 2013). Considering the previous studies and the results obtained from this study, it was concluded that the gag reflex continued after alfaxalone administration. If the animals were to be intubated, another pre-anesthetic substance should be added to the anesthesia protocol.

After alfaxalone administration, it has been recorded that the eye remains in the center. In a study comparing propofol anesthesia, it was recorded that the eye remained more on center (Warne et al., 2014). These results demonstrate that eye position is not reliable in assessing depth of anesthesia during induction in cats anesthetized with alfaxalone; consequently, other variables such as muscle tone, relaxation of the jaw, absence of reflexes (pedal pulling, palpebral, cornea, swallowing, and coughing), response to noxious stimuli should be considered more in the evaluation of the depth of anesthesia.

Medetomidine is an α2-adrenoceptor agonist drug that has been widely used in small animal medicine. It has recorded that medetomidine produces sedation and analgesia when applied at the recommended dose in dogs and cats (Pypendop et al., 1999). Alpha-2 agonists are potent antinociceptives; Although their analgesic effects are sufficient for minor surgical procedures, on the other hand, it is insufficient for significant interventions. McSweeney (2012) recorded that the duration of clinical analgesia was limited to 2-4 hours and recorded that the analgesic effect could be antagonized with atipamezole injection (Murrell, 2005; McSweeney et al., 2012; Tayari et al., 2015). Compared to alfaxalone, it is considered that medetomidine should be preferred, especially when analgesia is required. However, in our study, it was noted that medetomidine did not provide adequate analgesia, so both drugs were weak in cases requiring analgesia.

The dose of medetomidine was denoted 0.08 mg/kg (IV), and the procedure was carried out by taking this dose into account during the applications. Medetomidine can be given IM, IV, or SC; subcutaneous administration is not recommended. While IV alone administered medetomidine takes effect in 2 minutes, analgesia lasts for 45 minutes, and sedation takes 60-90 minutes (Sinclair, 2003). In this study, sedation duration was longer than 60 minutes in all animals except 3 out of 9 animals. This situation makes it preferable to administer the antagonist in sedation with medetomidine when the procedure is over. However, in cases where atipamezole is not available, or the side effects of medetomidine are not desired, it is concluded that there is no harm in preferring alfaxalone because of its typical side effects on the cardiovascular system and its shorter duration of action than medetomidine.

Alternatives were sought since the cardiovascular changes caused by α2-adrenoreceptor agonist applications in veterinary medicine. Studies have recorded that medetomidine adinistrations cause a decrease in heart rhythm and cardiovascular depression (Granholm et al., 2006; Santos et al., 2010; McSweeney et al., 2012;). In this study, statistically significant decreases in heart rate were recorded from the 0th minute and continued until the end of 90 minutes in the medetomidine group. Blood pressure values were not recorded in our study, but when the literature is examined, it is understood that hypertension begins right after the administration of medetomidine and that there may be long-term hypotension following it. In this study, however, it was observed that medetomidine did not cause any clinically significant side effect in the circulation. The heart rate remained in between the clinical reference ranges, and the effect on blood pressure was considered clinically insignificant since the animals recovered without any problems. The decrease in heart rhythm was thought to be due to the parasympathetic effect of sedation. It was concluded that when administered at these doses, medetomidine can cause a decrease in heart rate for a certain period, and it can be used in animals without heart disease. We can say that, as literature recommendations advise, it would be more appropriate to prefer alfaxalone, especially for patients have heart disease and circulatory disorders.

The effects of α-2 adrenoreceptor agonists on the respiratory system in pets show diversity with the drug, the dose administered, the route of administration, and the animal species. Occasionally, minor respiratory depression may observe. Doses that cause deep sedation in dogs, cats, and horses can reduce respiratory rate (Okumuş, 2003; Lemke, 2004). The dose of medetomidine administered in this study is the recommended dose for cats. It could not be mentioned whether there was any respiratory depression since the blood gases of the animals were not measured; yet, it was observed that respiratory rates increased in most of the animals compared to the pre-anesthetic value. It was thought that it would not be accurate to comment on respiration without knowing the tidal volume. However, since there is no apnea or cyanosis in any animal, it has been concluded that it can be used in healthy animals without apparent respiratory distress, but care should be taken because it can change the respiratory rate.

Salivation recorded after α-2 adrenergic agonist administration to animals is due to nausea (Tayari et al., 2015), followed by vomiting in many patients. Vomiting not only cause animals under stress but also increases the risk of aspiration pneumonia. Vomiting rates vary in studies, and the difference in the incidence of vomiting has not been fully explained. It has been recorded that the rate of vomiting after administration of medetomidine varies between 3-50% (Granholm et al., 2006; McSweeney et al., 2012). While some researchers state that vomiting may be related to the fasting time of the animal (Tayari et al., 2015), others argue that the administered dose may make a difference (McSweeney et al., 2012). Considering other studies with a lower rate of vomiting, it is seen that animals are premedicated after 12 hours of fasting (Zeiler et al., 2014). There is no record of salivation and/or vomiting by any animal in this study. The absence of vomiting and salivation was related to the fact that the number of animals used in this study was low.

As a result, it was founded that 4 mg/kg alfaxalone and 0.08 mg/kg medetomidine can be used in cases where sedation is required in cats. Furthermore, it was founded that medetomidine should be preferred in cases where more prolonged sedation is required, and both drugs are clinically safe, but alfaxalone is more reliable in animals with cardiovascular problems.

Acknowledgements
This study is produced from M.S. Besler's master thesis, a student at the Institute of Health Sciences in Kirikkale University.

Financial support
This research received no grant from any funding agency/sector.

Conflict of Interest
The authors declared that there is no conflict of interest.

REFERENCES

Bhalla RJ, Trimble TA, Leece EA, Vettorato E. 2018. Comparison of intramuscular butorphanol and buprenorphine combined with dexmedetomidine for sedation in cats. J Feline Med Surg 20(4):325-331

Buisman M, Wagner MC, Hasiuk MMM, et al. 2015. Effects of ketamine and alfaxalone on application of a pain assesment scale. J Feline Med Surg 18(8):643-651.

Ferra PJ, Pasloske K, Whittem T, et al. 2006. Plasma pharmacokinetics of alfaxalone in dogs after an intravenous bolus of alfaxan-CD RTU. Vet Anaesth Analg 33:229-236.

Granhom M, Mckusick B, Westerholm FC, Aspergen JC. 2006. Evaluation of the clinical efficacy and safety of dexmedetomidine or medetomidine in cats and their reversal with atipamezole. Veterinary Anaesthesia and Analgesia, 33(4), 214-223.

Herbert GL, Murison PJ. 2013. Eye position of cats anaesthetised with alfaxalone or propofol. Veterinary Record 172, 365.

Lemke KA. 2004. Perioperative Use Of Selective Alpha-2 Agonists And Antagonists İn Small Animals. The Canadian Veterinary Journal, 45:475-480.

Mcsweneey PM, Martin DD, Ramsey DS, Mckusick B. 2012. Clinical efficacy and safety of dexmedetomidine used as a preanesthetic prior to general anesthesia in cats. Journal of the American Veterinary Medical Association, 240(4), 404-412.

Muir W, Lerche P, Wies A, et al. 2008. Cardiorespiratory and anesthetic effects of supraclinical doses of alfaxalone in dogs. Vet Anaesth Analg 35:451-462.

Muir WW, Lerche P, Wiese A, et al. 2009. The cardiorespiratory and anesthetic effects of clinical and supraclinical doses of alfaxalone in cats. Vet Anaesth Analg, 36:42-54.

Murrell CJ, Hellebrekers LJ. 2005. Medetomidine and dexmedetomidine: A review of cardiovascular effects and antinociceptive properties in thedog. Vet Anaest. Analg., 32, 117-127.

Nelissen P, Corletto F, Aprea F, White RAS. 2012. Effect of three anesthetic induction protocols on laryngeal motion during laryngoscopy in normal cats. Veterinary Surgery 41, 876–883.

Nilsfors L, Garmer L, Adolfsson A. 1989. Sedative and analgesic effects of medetomidine in dogs an open clinical study. Acta Veterinaria Scandinavica Supplementum, 85: 155–159.

Okumuş Z. 2003. Köpeklerde α2 Adrenoseptör agonistleri ve antagonistlerinin etkileri. Veteriner Cerrahi Dergisi, 9 (1–2):68–73.

Pypendop B, Verstegen J. 1999. Cardio-respiratory effects of a combination of medetomidine, midazolam and butarphanol in dogs. Am J Vet Res, 60: 1148-1154.

Santos LCP, Ludders JW, Erb HN, Basher KL, Kirch P, Gleed RD. 2010. Sedative and cardiorespiratory effects of dexmedetomidine and buprenorphine administered to cats via oral transmucosal or intramuscular routes. Veterinary Anaesthesia and Analgesia, 37(5), 417-424.

Sinclair DM. 2003. A review of the physiological effect of α2- agonists related to the clinical use of medetomidine in small animal practice. Canadian Veterinary Journal, 44.

Tamura J, Tomohito I, SHO F, et al. 2015. The pharmacological effects of the anesthetic alfaxalone after intramuscular administration in dogs. J Vet Med Sci 77(3):289-296.

Tayari H, Vannozzi I, Brigantia A. 2015. Methadone and dexmedetomidine combination as premedicant agents for ovariectomy in cats. American Journal of Animal and Veterinary Sciences, 10(2), 101.

Warne LN, Beths T, Fogal S, Bauquier SH. 2014. The use of alfaxalone and remifentanil total intravenous anesthesia in a dog undergoing a craniectomy for tumour resection. Canadian Veterinary Journal 55, 1083-1088.

Whittem T, Pasloske KS, Heit MC, et al. 2008. The pharmacokinetics and pharmacodynamics of alfaxalone in cats after single and multiple intravenous administration of Alfaxan at clinical and supraclinical doses. J Vet Pharmacol Ther 31:571-579.

Zeiler GE, Dzikiti BT, Fosgate GT, Stegmann FG, Venter, FJ, Rioja E. 2014. Anaesthetic, analgesic and cardiorespiratory effects of intramuscular medetomidine-ketamine combination alone or with morphine or tramadol for orchiectomy in cats. Veterinary Anaesthesia and Analgesia, 41(4), 411-420.