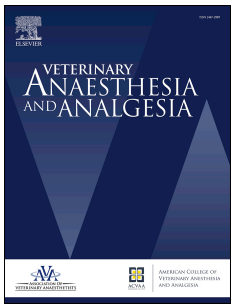
Accepted Manuscript



Dexmedetomidine-methadone-ketamine versus dexmedetomidine-methadone-alfaxalone for cats undergoing ovariectomy

Rocio Fernandez-Parra, Chiara Adami, Thomas Dresco, Thomas M. Donnelly, Luca Zilberstein

PII: S1467-2987(17)30199-X

DOI: 10.1016/j.vaa.2017.03.010

Reference: VAA 163

To appear in: *Veterinary Anaesthesia and Analgesia*

Received Date: 25 March 2016

Revised Date: 13 February 2017

Accepted Date: 14 March 2017

Please cite this article as: Fernandez-Parra R, Adami C, Dresco T, Donnelly TM, Zilberstein L, Dexmedetomidine-methadone-ketamine versus dexmedetomidine-methadone-alfaxalone for cats undergoing ovariectomy, *Veterinary Anaesthesia and Analgesia* (2017), doi: 10.1016/j.vaa.2017.03.010.

Running Head: Ketamine or alfaxalone for cat ovariectomy

RESEARCH PAPER

Dexmedetomidine-methadone-ketamine versus dexmedetomidine-methadone-alfaxalone for cats undergoing ovariectomy.

Rocio Fernandez-Parra*, Chiara Adami §, Thomas Dresco* Thomas M Donnelly* & Luca Zilberstein*

*Department of Veterinary Anesthesiology and Critical Care, Ecole Nationale Vétérinaire d'Alfort, Paris, France.

§Department of Clinical Sciences and Services, Royal Veterinary College, Hatfield, UK.

Correspondence: Rocio Fernandez-Parra, Department of Veterinary Anesthesiology and Critical Care, Ecole Nationale Vétérinaire d'Alfort, Paris, France. 7 Avenue du General de Gaulle, 94704 Maisons-Alfort, France. E-mail: rocio.fernandez@vet-alfort.fr

Acknowledgements

The authors gratefully acknowledge Barbara Steblaj for her help during the preparation of this manuscript.

Authors' contributions

Abstract

Objective To compare the duration, quality of anaesthesia and analgesia and quality of recovery of dexmedetomidine and methadone combined with either ketamine or alfaxalone.

Study design Randomized prospective clinical trial.

Animals Forty-four healthy client-owned cats presenting for ovariectomy.

Methods Cats were randomly assigned to one of two treatment groups: DAM (n=22), which were administered intramuscular (IM) dexmedetomidine (15 μg kg^{-1}), methadone (0.3 mg kg^{-1}) and alfaxalone (3 mg kg^{-1}), and DKM (n=22), which were administered IM dexmedetomidine (15 μg kg^{-1}), methadone (0.3 mg kg^{-1}) and ketamine (3 mg kg^{-1}). During anaesthesia, heart rate, respiratory rate and systolic arterial pressure were measured every 5 minutes. Cats that moved or had poor muscle relaxation were administered an additional 1 mg kg^{-1} intravenously (IV) of either alfaxalone (DAM) or ketamine (DKM). In cases of increased autonomic responses to surgical stimulation, fentanyl (2 μg kg-^{1}) was administered IV. At the end of the surgery, atipamezole (75 μg kg^{-1}) was administered intramuscularly and the times to both sternal recumbency and active interaction were recorded. Quality of recovery was evaluated with a Simple Descriptive Scale. The UNESP-Botucatu multidimensional composite pain scale and a Visual Analogue Scale (VAS) were used to evaluate post-operative analgesia at the return of active interaction and 1, 2 and 3 hours later.

Results The additional anaesthesia and rescue fentanyl requirements were similar between groups. The quality of recovery was better in the DAM group than the DKM group (SDS scores: 0[0-1] and 1[0-3], respectively; $p = 0.002$). Postoperative pain scores decreased progressively over time in both groups with no significant differences

(p = 0.08) between them.

Conclusions and clinical relevance Both protocols provided comparable quality of anaesthesia and analgesia that were suitable for cats undergoing ovariectomy. In combination with methadone and dexmedetomidine, alfaxalone and ketamine showed comfortable and reliable recoveries.

Introduction

Ovariectomy is one of the most common reasons for anaesthesia in young female cats in Europe. Due to the fractious nature of some cats and the limited anaesthesia equipment availability of many small veterinary clinics, an intramuscular (IM) anaesthetic protocol offers distinct advantages. However, the anaesthetic drugs should be safe, well-absorbed by IM route and provide reliable unconsciousness, muscle relaxation and analgesia.

In cats, alpha-2 agonists are commonly used anaesthetic agents because they provide reliable sedation and short-term analgesia (Cullen et al. 1996; Murrell et al. 2005; Nagore et al. 2013). Furthermore, opioid and alpha-2 agonist combinations have a synergistic analgesic effect (Meert et al. 1994; Slingsby et al. 2014) and provide deeper sedation compared with the effect of either agent alone (Girard et al. 2010).

Ketamine is often used in combination with opioids and alpha-2 agonists because it is inexpensive and offers the advantage of producing predictable dissociative and analgesic effects (Ko et al. 2011; Harrison et al. 2011; Carbone 2012). However, repeated dosing of ketamine during anaesthesia has been associated with drug accumulation and delayed recovery in cats (Baggot et al. 1976; Liu et al. 2006). Furthermore, ketamine stimulates the cardiovascular system (increase heart rate (HR), blood pressure and cardiac output) because of central stimulation of the sympathetic

system. This leads to an increase in myocardial work that increases the myocardial oxygen demand leading to impaired cardiovascular function in cats with underlying cardiac disease (Clutton 2007). This effect potentially endangers fractious cats in which preanaesthetic examination is not feasible.

Alfaxalone is a neurosteroid anaesthetic available in Europe in a cyclodextrin based formulation (Alfaxan, Jurox, Australia). It has excellent cardiovascular stability (Muir et al. 2009) and fast clearance from the body, making it suitable for repeated dosing during anaesthesia (Whittem et al. 2008). Consequently, alfaxalone offers some advantages over ketamine when it is used as part of a balanced anaesthetic protocol. Alfaxalone has been used at different dosages to induce anaesthesia intravenously (IV) (Pinelas et al. 2014) and IM (Grubb et al. 2013). Alfaxalone may have analgesic properties, resulting from its blockade of T-type $Ca2^{+}$ channels and potentiation of $GABA_A$ ligand-gated channels (Pathirathna et al. 2005). However, a beneficial analgesic benefit has not been observed clinically (Winter et al. 2003; Murison & Martinez Taboada 2010).

The aim of this study was to compare the anaesthetic, cardiorespiratory, analgesic and recovery quality effects of ketamine or alfaxalone in combination with an alpha-2 agonist (dexmedetomidine) and an opioid (methadone), in cats undergoing ovariectomy.

Materials and methods

The study was approved according to Directive 2010/63/EU by the Chair of the Veterinary University Hospital Ethics Approval Board and informed consent was obtained from all owners.

Animals

The sample size was calculated using a commercial software program (SigmStat and SigmaPlot 12) to detect a Visual Analogue Scale (VAS) difference between groups of 10 mm with a standard deviation of xx using a T-test with 80% power and 5% significance.

Forty-nine clients owned female cats undergoing elective ovariectomy were included in the study (Fig. 1). Cats underwent routine preanaesthetic physical examination in order to assess their health status according to the American Society of Anesthesiologists (ASA) classification. Exclusion criteria were ASA ≥ II, fractious personality and age greater than eight years.

Anaesthesia and surgery

The cats were fasted by the owners for 12 hours before being admitted to the university hospital of Veterinary Medicine of Alfort, France, on the scheduled surgery day. On arrival, a preanaesthetic physical examination was performed. Study-eligible cats were then individually housed in single cages in a dedicated cat room and were randomly assigned, based on drawing numbered pieces of paper from an envelope, to one of two treatment groups. Group DAM (n=22) were administered IM dexmedetomidine (15 µg kg^{-1}; Dexdomitor; Orion Pharma, Finland), methadone (0.3 mg kg^{-1}; Comfortan; Eurovet, Belgium) and alfaxalone (3 mg kg^{-1}; Alfaxan;, Jurox, Australia) and Group DKM (n=22) were administered IM dexmedetomidine (15 µg kg^{-1}), methadone, (0.3 mg kg^{-1}) and ketamine (3 mg kg^{-1} Imalgene 1000; Mérial, France).

All cats were injected IM with one of the two anaesthetic combinations prepared by a veterinarian not directly involved in the study. This individual also equalized the

volume of the DKM solution to that of the DAM solution using sterile saline so the anaesthetist could not discern which treatment combination was being administered. When the injection volume exceeded 1 mL, the anaesthetic combination was administered into two injection sites (right and left lumbar muscles). Times to sternal and lateral recumbency, quality of induction and adverse effects such as vomiting, hypersalivation, distress, tremors, myoclonus and increased muscle tone were recorded. Sternal recumbency was defined as a position in which the legs were tucked under the body and the cat has a decreased responsiveness to its surroundings. Lateral recumbency was defined as a position in which the cat lay on its side and was unresponsive to its surroundings. General anaesthesia was considered induced when the cats were shifted from lateral to dorsal recumbency, and did not attempt to reposition themselves. If general anaesthesia was not induced within 30 minutes after the injection, the cats were reinjected IM with half of the initial doses of both dexmedetomidine and alfaxalone for the DAM group, or dexmedetomidine and ketamine for the DKM group, without methadone and were excluded from the study. Once anaesthesia was induced, a 22-gauge catheter (Delta Med, Italy) was placed in the cephalic vein. All cats were then administered 7 mL kg^{-1} $hour^{-1}$ of sterile saline (NaCl 0.9%, B. Braun, Germany) IV during the procedure.

An IV injection of 20 mg kg^{-1} of amoxicillin (Clamoxyl, GlaxoSmithKline, UK) was administered as soon as the catheter was placed, and then repeated at the end of the surgery. Eye lubricant (Ocrygel; TVM, France) was applied at the beginning of anaesthesia and then every 45 minutes until recovery. For the surgery, cats were positioned in dorsal recumbency. Time from the beginning (first incision of the abdominal wall, coeliotomy) to the end of surgery (last suture knot) was recorded.

Surgeries were performed by final year veterinary students under the direct supervision of in-house surgeons. A multiparametric monitor (Cardiocap II, Datex, IL, USA) was used during anaesthesia. Heart rate and rhythm were monitored by electrocardiography, respiratory rate (f_R) was assessed by visual observation of chest movements, pulse rate and arterial oxygen saturation (SpO_2) were detected by pulse oximetry, and systolic arterial pressure (SAP) was intermittently measured using a Doppler (Doppler Vet BP; Sonomed, Poland) placed over the ulnar artery. The animals were allowed to breathe room air. Cats showing signs of hypoventilation (f_R < 6 breaths minute^{-1}) or severe hypoxemia (SpO_2 < 90%) were intubated, manually ventilated and excluded from the study. Animals with arterial saturation values less than 94% SpO_2, were supplemented with oxygen (FIO_2 100%) at a rate of 2 L minute^{-1} via a mask. In the event that oxygen supplementation did not result in normalization of SpO_2, the cats were intubated to permit manually assisted ventilation with 100% oxygen and excluded from the study. Animals were maintained at a body temperature above 36.5° C by a forced air warmer (Warm Touch; Mallinckrodt Medical, Ireland).

During surgery the depth of anaesthesia was evaluated every 5 minutes, based on the following descriptors: occurrence of spontaneous blinking (yes/no), occurrence of movements during surgical stimulation (yes/no), and inadequate muscle relaxation (yes/no). If two of the above parameters were observed (i.e. yes) then the patient received either alfaxalone 1 mg kg^{-1} IV (DAM) or ketamine 1 mg kg^{-1} IV (DKM).

Intraoperative nociceptive evaluation

For each cat, baseline values for HR, f_R and SAP were determined prior to surgical stimulation. When two of these three parameters increased by 30% above the baseline, 2 µg kg^{-1} fentanyl (Fentanyl; Mylan, France 50 µg ml^{-1}) was administered IV.

Postoperative pain assessment and quality of recovery assessment

At the end of the surgery (defined as time of tying last suture knot), but not earlier than 30 minutes after the last anaesthetic (ketamine or alfaxalone) supplemental dose, all animals received atipamezole 75 µg kg^{-1} IM (Alzane, Zoetis, NJ, USA). Time to sternal recumbency and active interaction (defined as responsiveness to voices, alertness and interest in the surroundings) were recorded. Quality of recovery was evaluated after atipamezole injection until the cat regained sternal recumbency. A simple descriptive scale (SDS) indicated by (0) very smooth recovery, (1) smooth recovery, (2) poor recovery and (3) very poor recovery requiring rescue sedation (dexmedetomidine, 2 µg kg^{-1} IV), was used.

Postoperative pain was evaluated, at the same time points, using two different scoring systems. Firstly, a modified version of the UNESP-Botucatu multidimensional composite pain scale (MCPS) (Brondani et al. 2013), where the maximum total score was 24 instead of 30, because of the exclusion of the subscale "physiological change", which was incompatible with the drug used in our study. Secondly, a Visual Analogue Scale (VAS) was used where 0 mm was labelled as "no pain" and 100 mm as "worst possible pain" (Jensen et al. 2003). The same anaesthetist performed the pain assessments starting at the first spontaneous cat interaction (T0), and then at 1 (T1), 2 (T2) and 3 (T3) hours later. Buprenorphine (Vetergesic; Sogeval, France) 20 µg kg^{-1} IV was administered as postoperative rescue analgesia when a score greater than "two" for the subscale "expression of pain", or a score greater than "three" for the subscale

"psychomotor changes" was recorded on the UNESP-Botucatu MCPS, and/or when the VAS score exceeded 40 mm of the maximum value of 100 mm. At the end of the pain assessment, all cats were administered 0.2 mg kg^{-1} meloxicam (Metacam; Boehringer-Ingelheim, Germany) subcutaneous (SC) and 20 µg kg^{-1} buprenorphine SC, unless buprenorphine had been administered earlier as postoperative rescue analgesia. The same anaesthetist evaluated intraoperative nociception, all assessments of postoperative pain and quality of recovery.

Statistical analysis

Descriptive statistics were performed to assess the normal distribution of data. To compare the intraoperative physiological variables (HR, f_R and SAP) between the two treatment groups, a repeated measures ANOVA (A) followed by a Bonferroni multiple comparison test were used. The time for the first supplemental bolus and the duration of surgery followed a normal distribution. For this reason, a t-test (T) was used. To compare the total dose of intraoperative rescue fentanyl, postoperative rescue buprenorphine and rescue sedation by each group, a Fisher's test (F) was used. Total dose of alfaxalone or ketamine administered to each group, time to active interaction and SDS scores for assessment of recovery quality were analysed with non-parametric tests. For this reason, a Mann-Whitney test was used (MW). The composite pain, UNESP-Botucatu MCPS and VAS scores achieved by each group over time were analysed by repeated measures ANOVA followed by a Bonferroni multiple comparison test.

Statistical analysis was performed using commercially available software (NCSS, 2007; SigmaPlot 12). Values of $p < 0.05$ were considered significant. Data are reported as mean ± standard deviation or median (range).

Results

Animals

Data were normally distributed only for the duration of anaesthesia and the time to anaesthetic induction. Five cats were excluded because of their fractious nature (Fig. 1). The remaining 44 animals were classified as ASA I, and none were rejected after preanaesthetic physical examination. These 44 cats were randomly allocated to the two anaesthetic combination groups. The treatment groups did not differ statistically with respect to age [7 (6-74) months] and body weight [2.8 (1.8-4.1) kg]. Anaesthetic induction was smooth in all animals, additional doses were not required to achieve a surgical plane of anaesthesia, and apnoea, vomiting or emergence reactions were not observedn. The average time from IM injection to sternal recumbency and the time to sternal and lateral recumbency are summarized in Table 1.

Anaesthesia and intraoperative nociceptive evaluation

The duration of surgery was 75 ± 16 minutes for DAM and 69 ± 15 minutes for DKM ($p = 0.22^{T}$). Time to the first supplemental dose after the initial IM injection was different between groups ($p = 0.046^{T}$) (Table 1). There was no difference ($p = 0.44^{MW}$) between groups in the number of alfaxalone doses administered during surgery (Table 1).

There was no difference in HR ($p = 0.23^{A}$) and SpO_2 ($p = 0.26^{A}$) between groups (Table 1). None of the animals required endotracheal intubation, but 18 cats, nine from each group, were administered 100% oxygen supplementation by mask. In these animals, SpO_2 increased to values higher than 94% after a few minutes, at which point the oxygen was disconnected and additional oxygen supplementation was not required again during the study.

The f_R was higher in DAM compared with DKM ($p = 0.013^{A}$) (Table 1). However, the mean SAP was higher in DKM compared to DAM ($p = 0.025^{A}$) (Table 1). Although rescue analgesia with fentanyl was necessary for three cats (14%) in DKM and none in DAM, these proportions were not significant between groups ($p = 0.20^{F}$).

Postoperative pain assessment and quality of recovery assessment

Rescue analgesia with buprenorphine was administered to 9 cats in group DAM and to 8 cats in group DKM ($p = 0.76^{F}$) (Table 2). There was no difference between groups in postoperative pain UNESP-Botucatu MCPS ($p = 0.20$) or VAS scores ($p = 0.63$) at T0, T1, T2 and T3. Repeated measures ANOVA showed an increase pain score from active interaction to 1 hour, after which all pain scores decreased over time in both groups (UNESP-Botucatu MCPS ($p = 0.078$) and VAS ($p = 0.07$), see Table 2).

Rescue sedation was administered to four cats in DKM and no cats in DAM ($p = 0.107^{F}$). Time from IM atipamezole injection to active interaction was 4 (0-28) minutes for DAM and 6 (0-50) minutes for DKM ($p = 0.22^{MW}$). For recovery, SDS scores were better in the DAM group ($p = 0.002^{MW}$), see Table 2.

Discussion

In the present study, both IM protocols showed comfortable and reliable recoveries for ovariectomies. The duration of these teaching-surgeries (72 ± 15 minutes) required multiple supplemental doses that are unlikely to be necessary in a shorter general practice ovariohysterectomy (21 ± 7 minutes, Case et al. 2015).

In our study, both groups were administered a drug mixture containing dexemedetomidine and methadone. After IM injection, no adverse effects such as excitement-dissociation or vomiting were observed. Alpha-2 and μ receptors are found in similar anatomical regions (i.e. in the brain and spinal cord) and they have common signal transduction pathways (G proteins) and mechanisms of action, such as activation of potassium channels in the postsynaptic neuron, making the cell insensitive to excitatory input (Sinclair 2003). This association can provoke synergistic effects if used simultaneously (Ossipov et al. 1990) and could be at the origin of the excitement-free recoveries.

Contrarily to some publications where dexmedetomidine administered alone provoked some emesis (McSweeney et al. 2012; Nagore et al. 2013), no animal presented with these symptoms in this study. It is possible that combination with methadone, which has antiemetic effects (Robertson & Taylor 2004) at sedating doses, blocked the emetic action of dexmedetomidine (Blancquaert et al. 1986). Also, the recent study of Papastefanou et al. (2015) demonstrated that administration of dexmedetomidine and butorphanol together prevented emesis and reduced the incidence and severity of nausea compared with dexmedetomidine alone.

The time to the first supplemental dose was shorter in the DKM group compared to the DAM group. This observation is in contrast to the pharmacokinetics of ketamine and alfaxalone, where the former has a longer half-life compared to the latter in cats

(Whittem et al. 2008). The dilution of ketamine, performed to adjust the DKM solution to an equal injectable volume as the DAM solution, could have affected the redistribution kinetics of ketamine and subsequently the need for an earlier supplemental dose. In addition, palpebral reflex was maintained constantly in the DKM group, unlike the DAM group and could have affected the anaesthetist's perception of the deep plane of anaesthesia, making them more prone to administer a supplemental dose of ketamine.

To maintain a plane of anaesthesia suitable for ovariectomy, it was necessary to reinject alfaxalone every 8-10 minutes following the first IV supplemental dose of 1.0 mg kg^{-1}. These results are in accordance with the Food and Drug Administration's recommendations for alfaxalone (1.1 to 1.3 mg kg^{-1} every 7-8 minutes, NADA, 2012). In our study, the total alfaxalone dose used for the maintenance of anaesthesia was 0.23 (0.10-0.35) mg kg^{-1} $minute^{-1}$. In the study of Schwarz et al. (2014), total intravenous anaesthesia (TIVA) with alfaxalone after premedication with medetomidine and butorphanol was 0.17 ± 0.02 mg kg^{-1} $minute^{-1}$ IV. This difference in effective alfaxalone dose might be because of the different routes of administration (intermittent doses *versus* TIVA) rather than an over-estimation of the anaesthesia requirements in our study. Supplemental doses may require a larger total dose of drug compared with TIVA to maintain a similar plane of anaesthesia. In addition, the extended duration of our teaching-ovariectomies could have influenced the anaesthetic requirements.

Intraoperative rescue analgesia was indirectly used to estimate the absence or presence of nociception. Both combination groups were equivalent for intraoperative analgesia requirements. As ketamine has analgesic effects, in contrast to the questionable clinical analgesic effects of alfaxalone, we were expecting an analgesic

superiority in the DKM group. We believe the analgesic equivalence of both groups is likely the result of the addition of methadone and dexmedetomidine to both protocols. Their strong analgesic properties could have masked differences between the DKM and DAM groups. Moreover, the doses of dexmedetomidine and methadone used produce bradycardia that could have masked tachycardia resulting from pain, and produced profound sedation that could have masked blinking and movement resulting from pain. In order to minimize this possible confounding factor, our physiological baseline values (HR, $_{fR}$ and SAP), were determined after the dexmedetomidine and methadone administration at the moment of induction and before any surgical stimulation.

Overall intraoperative respiratory rate was significantly lower in DKM compared with DAM, but no difference was seen in arterial oxygen saturation (SpO_2). Even though DKM showed a lower respiratory rate, it did not cause respiratory depression. Respiratory depression has been reported with the use of ketamine alone or in combination with an alpha-2 agonist (e.g. medetomidine; Harrison et al. 2011). Likewise, alfaxalone has been also associated, during intravenous induction, with a dose-dependent decrease in respiratory rate and minute volume (Whittem et al. 2008; Beths et al. 2014). However, Grubb et al. (2013) showed no respiratory decrease when alfaxalone was administered intramuscularly to cats, which is in accordance with the results of our study. It is our opinion that the decreased respiratory rate might result from the 1 mg kg^{-1} dose of IV alfaxalone administered during anaesthesia. This dose is close to alfaxalone's inducation dose. This remains to be investigated.

The DKM group had higher systolic blood pressure compared with the DAM group, but there were no differences in HR between the two groups. The similar heart rates in both groups likely results from the bradycardic effect of dexmedetomidine plus

methadone. The higher SAP in the DKM group is expected because of the greater cardiac sympathetic action of ketamine (Peck et al. 2008). Unfortunately, the scientific literature is incomplete concerning the sympathetic effects of alfaxalone and therefore we cannot compare the mechanism on systolic blood pressure.

To evaluate postoperative pain, we used a VAS because it has been widely employed in veterinary research for its ease, rapidity reliability and general assessment of trends (Mich & Hellyer 2009). Nonetheless, VAS can be subjective and moderately imprecise (Mich & Hellyer 2009). As we used a dissociative drug (ketamine), the ideal cut-off point was modified, because of the residual dissociation interference to 40 mm. Moreover, the VAS is not a very precise way to define an "ideal" pain score. To overcome these limitations, we opted for the parallel use of a multidimensional composite UNESP-Botucatu MCPS validated for the cat. This combination of two pain scales offered the best compromise of ease, speed, reliability and objectivity. We did not see any significant difference between groups for postoperative pain assessments. Recently, in a similar study comparing post ovariectomy pain in cats after alfaxalone-alone or ketamine-medetomidine anaesthesia, Kalchofner-Guerrero et al. (2014) reported that anaesthesia with ketamine-medetomidine provided better post-surgical analgesia than alfaxalone alone, but in this study opioids where not used during the surgical procedure. Probably, our pain scales were not sensitive enough to detect slight differences in analgesia between the two groups because the combination of dexmedetomidine plus methadone was efficacious enough to prevent any analgesic difference, if any, being revealed between ketamine and alfaxalone.

Ketamine has also been associated with a confounding effect on the psychomotor subscale of the UNESP-Botucatu MCPS (Buisman et al. 2015). In our

attempt to reduce this interference, we assessed pain after an active interaction with each animal, while in the study of Buisman et al. (2015) pain scale evaluations were performed hourly post-extubation. Similar postoperative pain studies in cats after ovariectomy have included meloxicam administration before (Benito-de-la-Víbora et al. 2008) or at completion of surgery to assure postoperative analgesia. To avoid interference with the pain score assessments we administered meloxicam, only at the end of the study.

We did not observe any statistical difference between groups in recovery values, which were overall of good quality. Dysphoric recoveries are well documented with ketamine (Baggot 1976) but have also been reported after administration of alfaxalone (Zaki et al. 2009; Grubb et al. 2013; Rodrigo-Mocholi D et al. 2015). In the DAM group none of the cats required rescue sedation compared to four animals in the DKM group. This is probably because of the faster pharmacokinetics of alfaxalone (Whittem et al. 2008), and the use of atipamezol to reverse the sedative effects produced by dexmedetomidine. Further investigation is necessary to understand the mechanism of alfaxalone emergence reactions.

Additionally, there were others limitations to this study. First, the large volume of the anaesthetic agents required for IM injection (after equivalency between groups) necessitated administering the drugs into two injections. These lumbar IM injections increased the level of pain and stress. Second, we have included all animals that were administered rescue analgesia and sedation in the final statistics study. This could have lead to bias in the results. Third, learning students performed the ovariectomies, so time of surgery was prolonged. Consequently, multiple additional doses were required. If the

study were transposed to clinical practice supplemental doses would unlikely be necessary, making it a simple protocol.

Conclusion and clinical relevance

In this randomized prospective clinical trial, both anaesthesia protocols were suitable for cats undergoing ovariectomy and were comparable in quality of anaesthesia and analgesia. When combined with methadone and dexmedetomidine, alfaxalone and ketamine showed comfortable and reliable recoveries.

References

Baggot JD, Blake JW. (1976) Disposition kinetics of ketamine in the domestic cat. Arch Int Pharmacodyn Ther 220, 115-124.

Benito-de-la-Víbora J, Lascelles BD, García-Fernández P et al. (2008) Efficacy of tolfenamic acid and meloxicam in the control of postoperative pain following ovariohysterectomy in the cat. Vet Anaesth Analg 35:501-510.

Blancquaert JP, Lefebvre RA, Willems JL. (1986) Emetic and antiemetic effects of opioids in the dog. Eur J Pharmacol 128, 143-150.

Brondani JT, Mama KR, Luna SP et al. (2013) Validation of the English version of the UNESP-Botucatu multidimensional composite pain scale for assessing postoperative pain in cats. BMC Vet Res 9, 143-6148-9-143.

Buisman M, Wagner MC, Hasiuk MM et al. (2015) Effects of ketamine and alfaxalone on application of a feline pain assessment scale. J Feline Med Surg doi:10.1177/1098612X15591590 [Epub ahead of print].

Carbone MG. (2012) Use of dexmedetomidine and ketamine in combination with opioids. J Am Vet Med Assoc 240, 263.

Case JB, Boscan PL, Monnet EL et al. (2015) Comparison of surgical variables and pain in cats undergoing ovariohysterectomy, laparoscopic-assisted ovariohysterectomy, and laparoscopic ovariectomy. J Am Anim Hosp Assoc 51, 1-7.

Caulkett NA, Cantwell SL, Houston DM. (1998) A comparison of indirect blood pressure monitoring techniques in the anesthetized cat. Vet Surg 27, 370-377.

Costello DJ, Borison HL. (1977) Naloxone antagonizes narcotic self-blockade of emesis in the cat. J Pharmacol Exp Ther 203, 222-230.

Cullen LK. (1996) Medetomidine sedation in dogs and cats: a review of its pharmacology, antagonism and dose. Br Vet J 152, 519-535.

Clutton ER. (2007) Cardiovascular disease. In: Manual of small Animal Anesthesia and Analgesia (2nd ed). Seymour C, Duke-Novakovski T (eds). BSAVA, Cheltenham, UK, pp 200-219.

Girard NM, Leece EA, Cardwell J et al. (2010) The sedative effects of low-dose medetomidine and butorphanol alone and in combination intravenously in dogs. Vet Anaesth Analg 37, 1-6.

Pinelas R, Alibhai HI, Mathis A et al. (2014) Effects of different doses of dexmedetomidine on anesthetic induction with alfaxalone--a clinical trial. Vet Anaesth Analg 41, 378-385.

Harrison KA, Robertson SA, Levy JK et al. (2011) Evaluation of medetomidine, ketamine and buprenorphine for neutering feral cats. J Feline Med Surg 13, 896-902.

Jensen MP, Chen C, Brugger AM. (2003) Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. J Pain 4, 407-414.

Kalchofner Guerrero KS, Reichler IM, Schwarz A et al. (2014) Alfaxalone or ketamine-medetomidine in cats undergoing ovariohysterectomy: a comparison of intra-operative parameters and post-operative pain. Vet Anaesth Analg 41, 644-653.

Ko JC, Austin BR, Barletta M et al. (2011) Evaluation of dexmedetomidine and ketamine in combination with various opioids as injectable anesthetic combinations for castration in cats. J Am Vet Med Assoc 239, 1453-1462.

Liu J, Ji XQ, Zhu XZ. (2006) Comparison of psychic emergence reactions after (+/-)-ketamine and (+)-ketamine in mice. Life Sci 78, 1839-1844.

McSweeney PM, Martin DD, Ramsey DS et al. (2012) Clinical efficacy and safety of dexmedetomidine used as a preanesthetic prior to general anesthesia in cats. J Am Vet Med Assoc 240, 404-412.

Meert TF, De Kock M. (1994) Potentiation of the analgesic properties of fentanyl-like opioids with alpha 2-adrenoceptor agonists in rats. Anesthesiology 81, 677-688.

Mich PM, Hellyer PW (2009) Objective, categoric methods for assessing pain and analgesia. In: Handbook of veterinary pain management (2nd ed). Gaynor JS, Muir WW (eds). Mosby Elsevier, Missouri, USA pp. 78-109.

Muir W, 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.

Murison PJ, Martinez Taboada F. (2010) Effect of propofol and alfaxalone on pain after ovariohysterectomy in cats. Vet Rec 166, 334-335.

426 Murrell JC, Hellebrekers LJ. (2005) Medetomidine and dexmedetomidine: a review of
427 cardiovascular effects and antinociceptive properties in the dog. Vet Anaesth
428 Analg 32, 117-127.
429 NADA (New animal drug application) (2012). Freedom of Information Summary.
430 NADA 141-342. Alfaxalone 10 mg/mL Intravenous injectable anesthetic. Cats
431 and Dogs. Available at:
432 http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDr
433 ugProducts/FOIADrugSummaries/UCM326904.pdf. Accessed Feb 29, 2016.
434 Nagore L, Soler C, Gil L et al. (2013) Sedative effects of dexmedetomidine,
435 dexmedetomidine-pethidine and dexmedetomidine-butorphanol in cats. J Vet
436 Pharmacol Ther 36, 222-228.
437 Ossipov MH, Harris S, Lloyd P et al. (1990) Antinociceptive interaction between
438 opioids and medetomidine: systemic additivity and spinal synergy.
439 Anesthesiology 73, 1227-35.
440 Papastefanou AK, Galatos AD, Pappa E et al. (2015) The effect of butorphanol on the
441 incidence of dexmedetomidine-induced emesis in cats. Vet Anaesth Analg 42,
442 608-613.
443 Pathirathna S, Brimelow BC, Jagodic MM et al. (2005) New evidence that both T-type
444 calcium channels and $GABA_A$ channels are responsible for the potent peripheral
445 analgesic effects of 5-alpha-reduced neuroactive steroids. Pain 114, 429-443.
446 Peck TE, Hill SA and Williams M (2008) Pharmacology for Anesthesia and Intensive
447 Care. (3rd ed), Cambridge, UK. pp. 99–134.

448 Pinelas R, Alibhai HI, Mathis A et al. (2014) Effects of different doses of
449 dexmedetomidine on anesthetic induction with alfaxalone--a clinical trial. Vet
450 Anaesth Analg 41, 378-385.
451 Robertson SA, Taylor PM (2004). Pain management in cats--past, present and future.
452 Part 2. Treatment of pain--clinical pharmacology. J Feline Med Surg. 6, 321-33.
453 Rodrigo-Mocholí D, Belda E, Bosmans T et al. (2015) Clinical efficacy and
454 cardiorespiratory effects of intramuscular administration of alfaxalone alone or
455 in combination with dexmedetomidine in cats. Vet Anaesth Analg. doi:
456 10.1111/vaa.12304. [Epub ahead of print].
457 Sinclair MD. (2003) A review of the physiological effects of alpha-2 agonists related to
458 the clinical use of medetomidine in small animal practice. Can Vet J 44, 885-
459 897.
460 Schwarz A, Kalchofner K, Palm J et al. (2014) Minimum infusion rate of alfaxalone for
461 total intravenous anesthesia after sedation with acepromazine or medetomidine
462 in cats undergoing ovariohysterectomy. Vet Anaesth Analg. 41, 480-90.
463 Slingsby LS, Bortolami E, Murrell JC. (2014) Methadone in combination with
464 medetomidine as premedication prior to ovariohysterectomy and castration in
465 the cat. J Feline Med Surg.
466 Tamura J, Ishizuka T, Fukui S et al. (2015) Sedative effects of intramuscular alfaxalone
467 administered to cats. J Vet Med Sci 77, 897-904.
468 Whittem T, Pasloske KS, Heit MC et al. (2008) The pharmacokinetics and
469 pharmacodynamics of alfaxalone in cats after single and multiple intravenous
470 administration of Alfaxan at clinical and supraclinical doses. J Vet Pharmacol
471 Ther 31, 571-579.

472 Winter L, Nadeson R, Tucker AP et al. (2003) Antinociceptive properties of
473 neurosteroids: a comparison of alphadolone and alphaxalone in potentiation of
474 opioid antinociception. Anesth Analg 97, 798-805.
475 Zaki S, Ticehurst K, Miyaki Y. (2009) Clinical evaluation of Alfaxan-CD(R) as an
476 intravenous anesthetic in young cats. Aust Vet J 87, 82-87.
477

Tables

Table 1 Data after injection of intramuscular (IM) dexmedetomidine (15 μg kg^{-1}), methadone (0.3 mg kg^{-1}) and alfaxalone (3 mg kg^{-1})(DAM, n=22) or dexmedetomidine (15 μg kg^{-1}), methadone (0.3 mg kg^{-1}) and ketamine (3 mg kg^{-1}) (DKM, n=22) to cats undergoing ovarioectomy. Cardiorespiratory measurements were taken every 5 minutes during surgery. The number of supplemental doses were the number administered after the first supplemental dose (1 mg kg^{-1} of either alfaxalone or ketamine).

	Group		
Parameter	DAM	DKM	*p*-value
Time to sternal recumbency (minutes)	1 ± 1	2 ± 1	N/A
Time to lateral recumbency (minutes)	2 ± 1	4 ± 2	N/A
Time to first supplemental dose (minutes)	58 ± 18	47 ± 16	0.046*
Number of supplemental doses (n°)	4 (1-6)	3 (1-7)	0.44
HR (beats $minute^{-1}$)	128 ± 29	138 ± 21	0.23
SpO_2 (%)	94 ± 3	94 ± 1	0.26
f_R (breaths $minute^{-1}$)	30 ± 7	25 ± 6	0.013*
SAP (mmHg)	125 ± 16	141 ± 27	0.025*

*Statistically significant between groups. Data are reported as mean ± standard deviation or median (range).

N/A, non-applicable; HR, heart rate; SpO_2, haemoglobin oxygen saturation; f_R, respiratory rate; SAP, systolic arterial pressure

Table 2 Medians and percentiles [10^{th} – 90^{th}] of recovery quality, assessed with a simple descriptive scale (SDS) and postoperative pain assessed with a Visual Analogue Scale (VAS) and the UNESP-Botucatu multidimensional composite pain scale (MCPS) and recorded from 43 cats undergoing elective ovariectomy. Pain assessments were carried out at various time points: as soon as the cats were observed to interact actively with the investigator (T0), and then 1 (T1), 2 (T2) and 3 (T3) hours after that.

	Group	
Parameter	DAM (n=21)	DKM (n=22)
Recovery score	0 (0-1)	1(0-3)
VAS T0	40 (0-60)	20 (0-58)
VAS T1	20 (0-60)	40 (0-78)
VAS T2	20 (0-60)	20 (0-58)
VAS T3	0 (0-40)	20 (0-40)
MCPS T0	2 (0-5)	1 (1-6)
MCPS T1	1 (0-13)	2 (0-10)
MCPS T2	1 (0-5)	1(0-8)
MCPS T3	0 (0-4)	1 (0-7)

The SDS ranged from 0) very smooth recovery to 3) very poor recovery; the VAS ranged from 0) no pain to 100) worst possible pain and the MCPS ranged from 0) no pain to 24) worst possible pain.

DAM, dexemedetomidine, methadone and alfaxalone; DKM (dexemedetomidine, methadone and ketamine.

503 **Figure 1** Consort Flow Diagram

504