Comparison of the effects of buprenorphine and methadone in combination with medetomidine followed by intramuscular alfaxalone for anaesthesia of cats undergoing ovariohysterectomy.

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Abstract

Objectives: The aim of this study was to compare quality of anaesthesia and analgesia between methadone and buprenorphine in combination with medetomidine after induction with intra-muscular (IM) alfaxalone in cats undergoing ovariohysterectomy.

Methods: Fifty-one female cats (ASA I - II), median age 12 months (range 2 – 60), weighing 2.5 ± 0.5 kg were recruited to the study. Cats were randomly allocated to receive medetomidine (600 µg/m^2) and buprenorphine (180 µg/m^2) (group MB) or medetomidine (500 µg/m^2) and methadone (5 mg/m^2) (group MM) IM. Anaesthesia was induced 15 minutes later using alfaxalone (3 mg/kg) IM. Anaesthesia was maintained with isoflurane in oxygen. All cats received meloxicam pre-operatively. Quality of premedication and induction and intraoperative physiological parameters were recorded. Atipamazole (50% of medetomidine dose) was administered at the end of surgery. Cats were assessed

post operatively by the same blinded observer using SDS, NRS, DIVAS and UNESP Botucatu multidimensional composite pain scales, at 10, 20 and 30 minutes post extubation. Parametric and non-parametric data were compared using Student's t-test or Mann-Whitney U tests, respectively.

Results: Forty-one cats completed the study. No significant differences were detected between groups before or during anaesthesia. No cats required rescue analgesia. DIVAS scores at 10 minutes were significantly less in MM group compared to MB. No differences between groups at any other time points were detected using the four metrology instruments.

Conclusions and relevance: Both protocols provided good anaesthesia conditions for ovariohysterectomy in the cat.

Introduction

Ovariohysterectomy (OVH) in cats is a routine surgical procedure carried out in private veterinary practices and animal shelters in the UK.[1,2] In a shelter environment especially, cats of an array of ages (including young kittens) and temperaments (including feral animals) are commonly admitted, many with little

56 or no prior clinical history.[1] Physical restraint and intra-venous (IV) access may be
57 limited, making intra-muscular (IM) administration of anaesthetic drugs
58 preferable.
59
60 *Sedation and Analgesia*
61 There are several existing drug combinations commonly used for IM feline
62 anaesthesia. In the case of feral and shelter animals, there is a need for a profound
63 level of sedation, in order to allow a thorough examination prior to neutering.
64 Medetomidine is reported to have a sparing effect on dosage of induction agents
65 and was the drug of choice in this study.[3] Addition of an opioid to the
66 combination can further reduce induction agent dosage while providing
67 profound and long lasting peri-operative analgesia.[4–8] Peri-operative analgesia is
68 especially important given OVH has been described by Mathews et al. as causing
69 moderate pain to the patient dependent on the degree of surgical trauma[9,10]. In
70 this study, the sedative and analgesic effects of buprenorphine and methadone
71 were investigated.
72

Anaesthesia

Alfaxalone is a synthetic neuroactive steroid, with market authorisation in the UK for IV but not IM administration. The preparation is licensed for the IM route in Australia, New Zealand and South Africa.[11] Following IV administration, a number of studies have found minimal impact on the cardiorespiratory system and provision of smooth inductions and fast recoveries.[12–16] However, Mathis et al. observed a greater frequency of paddling and trembling during the recovery period following alfaxalone induction; than with propofol induction. Few studies have investigated alfaxalone as an IM induction agent in cats.[17–19] Only one of these was for use for an invasive procedure (castration),[17] while another included minor procedures only.[18]

The aims of this study were to compare the quality of anaesthesia and analgesia between methadone and buprenorphine in combination with medetomidine prior to induction of anaesthesia with IM alfaxalone.

Materials and Methods

This study took place at the RSPCA XXX. Ethical approval was granted from the Ethical Committee at the University of XXX (ATCS number 1559). A power calculation demonstrated that 50 animals were required (25 per group) for a 90% likelihood of showing a 10mm increase in DIVAS scale. The study was a prospective, randomized, blinded clinical trial.

Animals

Fifty-one entire female cats were recruited from the RSPCA XXX Animal Hospital. Of these, 33 were owned and 18 were un-owned shelter animals undergoing assessment and preparation for rehoming. All owners provided informed consent for the cat to be included in the study. Cats were starved for 12 hours prior to admission. Following admission, cats received a physical and behavioural assessment; and were then left undisturbed in a heated kennel for 10 minutes. A temperament score was given (0=quiet, 1=anxious, 2=nervous, 3=aggressive). Inclusion criteria were healthy female cats (ASA I or II) with a body condition score

106 less than 6/9. Systemically unwell cats, were excluded, as were cats receiving
107 analgesic drugs.
108
109 *Premedication*
110 Animals were randomly assigned to group MB (medetomidine and
111 buprenorphine) or MM (medetomidine and methadone) (www.randomizer.org).
112 Group MB received 600 μ g/m^2 medetomidine and 180 μ g/m^2 buprenorphine
113 and group MM received 500 μ g/m^2 medetomidine and 5mg/m^2 methadone via
114 deep IM injection into the quadriceps muscle. Heart rate (HR) respiratory rate
115 (RR), mucous membrane colour, capillary refill time (CRT), aural temperature and
116 subjective strength of peripheral pulses were monitored prior to premedication
117 and at 5-minute intervals thereafter. Subcutaneous meloxicam was administered
118 at 3mg/m^2 in group MB and 2.5mg/m^2 in group MM. A single blinded observer
119 subjectively assessed sedation quality by assessing demeanour, muscle
120 relaxation, palpebral response, responses to clapping, ocular lubricant application
121 and sub-cutaneous meloxicam administration.
122

Anaesthesia

Fifteen minutes after the premedication anaesthesia was induced by IM administration of 3mg/kg alfaxalone (Alfaxan, Jurox) into the quadriceps muscle and any responses were recorded. In a shelter environment, IV access is rarely prioritised for routine procedures in healthy animals, given time pressures and the relative low risk for the patient. Therefore, IV catheterisation was only carried out in pregnant and ASA category II animals. Five minutes later, the induction quality was assessed by subjective parameters, including palpebral response, level of jaw tone and response to prophylactic IM amoxicillin administration (administered into the quadriceps muscle in the opposite leg to the alfaxalone). The response to laryngeal application of lidocaine (Intubeaze, Dechra) and endotracheal intubation were recorded. Anaesthesia was maintained with isoflurane (Isoflo, Zoetis) in 100% oxygen delivered via an Ayre's T piece (with Jackson-Rees Modification, closed tail bag and paediatric APL) and adjusted as necessary during surgery. All cats were placed in dorsal recumbency on a heated table. Intra-operative monitoring included HR, RR, mucous membrane colour, SPO2% lingual probe (model VE-H100B, Eden Instruments Inc.), indirect

measurement of systolic (SAP), mean (MAP) and diastolic arterial blood pressures (DAP) (MDPRO Cat and Dog Blood Pressure Monitor, MemoDiagnostic) and aural temperature (VT-150 Instant Animal Ear Thermometer, Vet-Temp). Observations were undertaken by an individual unaware of the treatment group.

Surgery

All cats underwent midline ovariohysterectomy by a single surgeon.

Recovery

Upon completion of surgery, isoflurane was discontinued and oxygen was supplied for 5 minutes before extubation. Immediately after extubation, atipamezole was administered IM into the quadriceps muscle at 50% of the original volume of medetomidine. The animal was subsequently placed into a heated kennel.

Assessment of Pain

Pain assessments by a blinded observer were carried out at 10 minutes, 20 minutes and 30 minutes after extubation. Four metrology scales were utilised at each of these time points. These included Simple Descriptive Scale (SDS), Numerical Scale (NS), Dynamic Interactive Visual Analogue Scale (DIVAS) and the UNESP Botucatu multidimensional scale.

Statistical Analysis

Statistical analysis was carried out using GraphPad Prism 7 (GraphPad software, CA, USA). Continuous data was assessed for normality using the D'Agostino & Pearson test. Parametric and non-parametric data were analysed using the student t-test and Mann-Whitney U test/ two-sample Wilcoxon test, respectively. Normally distributed data are presented as mean ± standard deviation (SD) and non-parametric data are presented as median and range. Statistical significance was set at $p < 0.05$.

Results

Animals

Fifty-one female cats were recruited to this study over an eight month period. All animals were ASA category I except for one cat with a grade II systolic heart murmur but otherwise healthy and asymptomatic, classed as ASA category II. There were no significant differences in weights, ages or temperaments of cats between groups (Table 1).

Ten animals were withdrawn at various points of the study in view of their unsuitability for re-homing and euthanised (MB = 4, MM = 5), or a failed administration of atipamezole (MM = 1). Forty-one (MB = 21 MM = 20) underwent OVH and subsequent pain scoring assessments.

Premedication

There was a mild decrease in body temperature, HR, and RR post-sedation, but these remained within normal limits. There were no significant differences in these parameters or the quality of sedation between groups after premedication (Table 2).

Induction

There were no significant differences between the quality of induction after alfaxalone administration. There were no significant differences in MBP, SBP, DBP, HR or RR between the groups after induction (Table 2). There were no significant differences in response to laryngeal spray between groups MB and MM. Intubation scores were variable (Table 2) but were not found to be significantly different between the two groups.

Maintenance of Anaesthesia and Surgery

There were no obvious incidences of PIA (Post Induction Apnoea) measured by assessing respiratory rate; although general assessment of cardiopulmonary function was limited in this setting and for this population of healthy cats. Isoflurane vaporizer settings ranged between 0.5 and 1.5% and no significant difference was found between vaporizer settings or surgery time between groups MB and MM. During surgery, there were no significant differences in mucous membrane colour, moisture or CRT, SBP, MBP, DBP, temperature, HR or RR between the two groups.

Recovery and Pain Assessment

Temperature, HR and RR were reduced from the first initial reading to the readings during recovery but were not found to be different between the two groups (Table 3).

Of the four metrology scales utilised in this study at three time points, none indicated necessary administration of rescue analgesia (Table 4). At 10 minutes the DIVAS pain score was significantly higher in the MB group compared to the MM group ($p = 0.0272$) (Figure 1).

Discussion

Intramuscular combinations for feline anaesthesia are useful in both private practice, as well as high throughput shelters focusing on population control. Drug combinations often include α -2-adrenoreceptor agonists, opioids and ketamine,.[20–22] However, alternatives for ketamine may be desirable given a) the uncertainty of its future availability and b) the increase in myocardial oxygen

223 demand, leading to a higher risk in fractious/feral cats where examination may be
224 unfeasible, particularly if there is underlying cardiac disease.[22,23]
225
226 This study investigated IM protocols in cats undergoing OVH. Anaesthetic and
227 analgesic qualities were compared between methadone and
228 buprenorphine combined with medetomidine following induction of anaesthesia
229 with IM alfaxalone.
230
231 In both groups MB and MM, sedation was profound enough to fully examine cats
232 and induce anaesthesia smoothly. Post-sedation, HR, RR and temperature
233 decreased slightly but remained within normal limits. Other subjective parameters
234 such as palpebral response, and responses to ocular lubricant and sub-cutaneous
235 meloxicam injection also indicated a deep level of sedation in both groups.
236 Slingsby et. al. and Grint et al. also found superior sedation quality when
237 combining opioids with medetomidine.[6,7] These results are expected given that
238 opioids and alpha-2-adrenergic agonists work synergistically due to sharing post-
239 receptor mechanisms of action.[24] A slightly lower dose of medetomidine and

meloxicam were administered in group MM, as methadone is a full μ-agonist and its sedative and analgesic effects were expected to be more profound than buprenorphine. This was based on extensive experience with the 'Kitten Quad' protocol, featuring the same doses of methadone, buprenorphine and medetomidine as this study.[1] The body surface area (BSA) of dosing and the simplicity of using equal volumes of the alpha-2 agonists and opioid drugs were chosen for the 'Kitten Quad' to improve potential uptake of the regime in clinical practice. The BSA dosing improves reliability in smaller patients and improves affordability in larger patients when compared to standard linear dosing.

Induction of anaesthesia with 3mg/kg IM alfaxalone was well tolerated and allowed smooth intubation on the first attempt in the majority of patients, with a minority requiring a 45-60 second delay and one subsequent attempt. All cats could be intubated. Grubb et al. described discomfort and severe reactions following 5mg/kg alfaxalone IM, likely caused by volume, as IM administration of alfaxalone itself does not cause tissue irritation (technical notes, Jurox).[25] In the current study, 70% of animals exhibited no reaction, with the remainder a small leg twitch. One limitation of the IM route is that it cannot be given "to effect",

meaning that some animals may receive more drug than necessary. Post-induction, there were no incidences of PIA and minimal signs of cardiorespiratory depression. Other studies have also observed minimal depressive cardiorespiratory effects, with mixed reports regarding prevalence of PIA (IV route only).[13,14,16,22,25–27] To the knowledge of the authors, PIA has not been reported with IM administration, possibly because this allows a more gradual delivery of the drug to the bloodstream.

As a common procedure resulting in moderate pain, OVH was the chosen surgical procedure for the study.[9,10] Intra-operatively, cardiovascular parameters remained stable and fractional inspired isoflurane concentration was lower compared to similar studies.[13,16] Transient, mild-moderate hypotension (MBP <70mmHg) occurred in both groups, similar to findings by Zaki et. al., which may have been caused by the combination of the isoflurane and alfaxalone.[14] However a non-invasive blood pressure monitor was used, making accurate conclusions regarding this observation difficult.

Post-operatively, patients exhibited overall smooth and excitement-free recoveries. This may be due to the synergism between opioids and alpha-2-adrenergic agonists.[28] Assessments showed 75% of cats exhibiting a normal posture and 90% eating within 30 minutes. At 10 minutes post-operatively, DIVAS pain scores were significantly higher in group MB than MM, but not high enough to prompt rescue analgesia administration. This could be due to the full μ-agonist classification of methadone and therefore higher potency in provision of analgesia.[29] There could also be a difference in time of onset of analgesia, which may differ between methadone and buprenorphine.[4] At all other measured time points, there were no significant differences in pain scores or physiological parameters between groups MB and MM.

Multi-modal analgesia was augmented with a SC meloxicam injection 5 minutes after induction. This may have contributed to a lack of rescue analgesia being necessary in the recovery period, and whilst in some studies the NSAID is omitted for comparisons to be made, this study included a pre-operative NSAID to represent the typical clinical scenario and because of the superior analgesia it

offers.[24,30] Although some pre-clinical studies have suggested analgesic properties of alfaxalone, the clinical significance of this is unclear. [31–33]

There were no adverse events in this diverse study population, inclusive of pre-pubertal and pregnant cats. Other studies have found alfaxalone suitable in young cats, although the drug was administered IV.[14,34]

This practice-based study involved a number of limitations. Intravenous catheters were not placed in healthy cats, posing a risk in rare cases of adverse drug reactions and difficult intubations. Each patient's need for IV access should be assessed individually, and emergency equipment readily available. More comprehensive intra-operative monitoring may have provided better understanding of the cardiovascular effects. During recovery, background disruption from the busy hospital and/or nervous/aggressive nature of cats may have affected behavioural interpretations. However, this was also deemed representative of a realistic clinical setting. Further study on the effectiveness of these protocols on truly "feral" cats is recommended, as there were no feral cats

309 in the current study population. The number suggested by the initial power
310 calculation was not reached, due to a number of omissions including staff
311 availability. A larger study population may have indicated significant differences
312 at other time points. If recovery assessments were carried out for longer than 30
313 minutes, further insights may have been gained into the duration of analgesia of
314 each protocol, but may have also shown differences between the scoring tools
315 used. It should be noted that although pain scores were only recorded up to 30
316 minutes post-operatively, animals were continually and closely monitored
317 beyond this time until discharge. One validated scale for acute pain and three
318 unvalidated scales were used in this study as this reflects to some extent some of
319 the scales being used in different practice environments and evaluate differences
320 with one observer.
321
322 Conclusions
323 Methadone and buprenorphine combined with medetomidine at the given doses,
324 provided safe and stable sedation in ASA I cats, and subsequent IM alfaxalone
325 provided a plane of anaesthesia suitable for carrying out invasive surgery

perceived to cause moderate pain. Following this protocol, animals were found to recover smoothly, with no requirements for rescue analgesia. Multimodal analgesia is recommended, and in this study, meloxicam was administered pre-operatively.

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Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

References

1. Joyce A, Yates D. Help stop teenage pregnancy!Early-age neutering in cats. *J Feline Med Surg* 2011; 13: 3–10.
2. The Cat Group. Policy Statement 1: Timing of neutering, http://www.thecatgroup.org.uk (accessed 14 December 2017).
3. Selmi AL, Mendes GM, Lins BT, et al. Comparison of xylazine and medetomidine as premedicants for cats being anaesthetised with propofol-sevoflurane. *Vet Rec* 2005; 157: 139–43.
4. Robertson SA, Taylor PM, Lascelles BDX, et al. Changes in thermal threshold response in eight cats after administration of buprenorphine, butorphanol and morphine. *Vet Rec* 2003; 153: 462–5.
5. Bortolami E, Murrell JC, Slingsby LS. Methadone in combination with acepromazine as premedication prior to neutering in the cat. *Vet Anaesth Analg* 2013; 40: 181–193.
6. Grint NJ, Burford J, Dugdale AHA. Investigating medetomidine-buprenorphine as preanaesthetic medication in cats. *J Small Anim Pract* 2009; 50: 73–81.

7. Slingsby LS, Bortolami E, Murrell JC. Methadone in combination with medetomidine as premedication prior to ovariohysterectomy and castration in the cat. *J Feline Med Surg* 2015; 17: 864–872.
8. Hall TL, Duke T, Townsend HG, et al. The effect of opioid and acepromazine premedication on the anesthetic induction dose of propofol in cats. *Can Vet J = La Rev Vet Can* 1999; 40: 867–70.
9. Mathews K, Kronen P, Lascelles D, et al. Guidelines for Recognition, Assessment and Treatment of Pain. *J Small Anim Pract* 2014; 55: E10–E68.
10. Mathews KA. Pain assessment and general approach to management. *Vet Clin North Am Small Anim Pract* 2000; 30: 729–55.
11. Jurox Alfaxan. 2017; (Package Insert).
12. Warne LN, Beths T, Whittem T, et al. A review of the pharmacology and clinical application of alfaxalone in cats. *Vet J* 2015; 203: 141–148.
13. Taboada FM, Murison PJ. Induction of anaesthesia with alfaxalone or propofol before isoflurane maintenance in cats. *Vet Rec* 2010; 167: 85–9.
14. Zaki S, Ticehurst K, Miyaki Y. Clinical evaluation of Alfaxan-CD® as an intravenous anaesthetic in young cats. *Aust Vet J* 2009; 87: 82–87.

15. Mathis A, Pinelas R, Brodbelt DC, et al. Comparison of quality of recovery from anaesthesia in cats induced with propofol or alfaxalone. *Vet Anaesth Analg* 2012; 39: 282–290.
16. Muir W, Lerche P, Wiese A, et al. The cardiorespiratory and anesthetic effects of clinical and supraclinical doses of alfaxalone in cats. *Vet Anaesth Analg* 2009; 36: 42–54.
17. Khenissi L, Nikolayenkova-Topie O, Broussaud S, et al. Comparison of intramuscular alfaxalone and ketamine combined with dexmedetomidine and butorphanol for castration in cats. *J Feline Med Surg* 2017; 19: 791–797.
18. Adami C, Imboden T, Giovannini AE, et al. Combinations of dexmedetomidine and alfaxalone with butorphanol in cats: application of an innovative stepwise optimisation method to identify optimal clinical doses for intramuscular anaesthesia. *J Feline Med Surg* 2016; 18: 846–853.
19. Rodrigo-Mocholí D, Belda E, Bosmans T, et al. Clinical efficacy and cardiorespiratory effects of intramuscular administration of alfaxalone alone or in combination with dexmedetomidine in cats. *Vet Anaesth Analg*

2016; 43: 291–300.

20. Granholm M, McKusick BC, Westerholm FC, et al. Evaluation of the clinical efficacy and safety of dexmedetomidine or medetomidine in cats and their reversal with atipamezole. *Vet Anaesth Analg* 2006; 33: 214–223.

21. Navarrete R, Domínguez JM, del Mar Granados M, et al. Sedative effects of three doses of romifidine in comparison with medetomidine in cats. *Vet Anaesth Analg* 2011; 38: 178–185.

22. Cremer J, Riccó CH. Cardiovascular, respiratory and sedative effects of intramuscular alfaxalone, butorphanol and dexmedetomidine compared with ketamine, butorphanol and dexmedetomidine in healthy cats. *J Feline Med Surg* 2017; 1098612X1774228.

23. Clutton ER. Cardiovascular Disease. In: Seymour C, Duke-Novakovski T (eds) *BSAVA Manual of Small Animal Anesthesia and Analgesia*. BSAVA, 2007, pp. 200–219.

24. Fernandez-Parra R, Adami C, Dresco T, et al. Dexmedetomidine-methadone-ketamine versus dexmedetomidine-methadone-alfaxalone for cats undergoing ovariectomy. *Vet Anaesth Analg* 2017; 44: 1332–1340.

411 25. Grubb TL, Greene SA, Perez TE. Cardiovascular and respiratory effects, and
412 quality of anesthesia produced by alfaxalone administered intramuscularly
413 to cats sedated with dexmedetomidine and hydromorphone. *J Feline Med*
414 *Surg* 2013; 15: 858–865.
415 26. Beths T, Touzot-Jourde G, Musk G, et al. Clinical evaluation of alfaxalone
416 to induce and maintain anaesthesia in cats undergoing neutering
417 procedures. *J Feline Med Surg* 2014; 16: 609–615.
418 27. Whittem T, Pasloske KS, Heit MC, et al. The pharmacokinetics and
419 pharmacodynamics of alfaxalone in cats after single and multiple
420 intravenous administration of Alfaxan® at clinical and supraclinical doses.
421 *J Vet Pharmacol Ther* 2008; 31: 571–579.
422 28. Ossipov MH, Harris S, Lloyd P, et al. Antinociceptive interaction between
423 opioids and medetomidine: systemic additivity and spinal synergy.
424 *Anesthesiology* 1990; 73: 1227–35.
425 29. Kerr C. Pain management I: systemic analgesics. In: Seymour C, Tanya
426 Duke-Novakovski (eds) *BSAVA Manual of Canine and Feline Anaesthesia*
427 *and Analgesia*. British Small Animal Veterinary Association, 2014, pp. 89–

428 103.
429 30. Benito-de-la-Víbora J, Lascelles BDX, García-Fernández P, et al. Efficacy of
430 tolfenamic acid and meloxicam in the control of postoperative pain
431 following ovariohysterectomy in the cat. *Vet Anaesth Analg* 2008; 35: 501–
432 510.
433 31. Murison PJ, Martinez Taboada F, Taboada FM. Effect of propofol and
434 alfaxalone on pain after ovariohysterectomy in cats. *Vet Rec* 2010; 166:
435 334–5.
436 32. Pathirathna S, Brimelow BC, Jagodic MM, et al. New evidence that both T-
437 type calcium channels and GABAA channels are responsible for the potent
438 peripheral analgesic effects of 5 α -reduced neuroactive steroids. *Pain*
439 2005; 114: 429–443.
440 33. Jevtovic-Todorovic V, Covey DF, Todorovic SM. Are neuroactive steroids
441 promising therapeutic agents in the management of acute and chronic
442 pain? *Psychoneuroendocrinology* 2009; 34 Suppl 1: S178-85.
443 34. O'Hagan B, Pasloske K, McKinnon C, et al. Clinical evaluation of alfaxalone
444 as an anaesthetic induction agent in cats less than 12 weeks of age. *Aust*

445 *Vet J* 2012; 90: 395–401.

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447

Parameter	Group	
	MB (n = 21)	**MM (n=20)**
Age (months)	12 (3 -48)	14 (2 -48)
Weight (Kg)	2.4 ± 0.5	2.3 ± 1.0
Temperament Score (0-3)	1 (1-3)	1.5 (1-3)

Table 1: Demographic data of the 41 female cats that completed the study. 51 cats were recruited to the study, nine cats were unsuitable for rehoming and underwent euthanasia during anaesthesia, and 1 cat did not receive atipamezole at the correct time and was excluded from the study. Data are presented as mean ± standard deviation, or median (range) as appropriate. There were no significant differences between groups.

Parameter		Group MB (n = 21)	Group MM (n = 20)
Baseline (prior to premedication)			
Temperature (° Celsius)		38.5 ± 0.8	38.4 ± 0.7
Heart rate (beats/minute)		166 ± 28	172 ± 24
Respiratory rate (breaths/minute)		54 ± 16	52 ± 15
Post-premedication			
Temperature (° Celsius)		38.0 ± 0.9	38.1 ± 0.8
Heart rate (beats/minute)		105 ± 29	105 ± 32
Respiratory rate (breaths/minute)		40 ± 11	40 ± 12
IM alfaxalone injection response	**Score**		
No physical response	0	14	12
Any physical response including leg twitches or movement	1	5	5
Not recorded		2	3
Post-induction of anaesthesia			
Time from Sedation to Induction (minutes)		15-16	13-15
Temperature (° Celsius)		37.8 ± 0.9	37.8 ± 0.7
Heart rate (beats/minute)		110 ± 28	121 ± 36
Respiratory rate (breaths/minute)		40 ± 9	40 ± 10
SAP (mm Hg)		136 ± 31	139 ± 30
MAP (mm Hg)		101± 21	105 ± 24
DAP (mm Hg)		84 ± 20	85 ± 19
Ease of Intubation	**Score**		
Very Smooth: First attempt successful, no patient response	1	12	14
Smooth: Some movement of jaw or tongue, mild coughing	2	6	3
Poor: Swallowing, coughing and signs of distress	3	2	1
Very Poor: Unsuccessful intubation, signs of severe distress	4	1	0
Not recorded		0	2

Surgery			
Surgery duration (minutes)		24 ± 8	22 ± 8
Extubation			
Temperature at time of extubation (° Celsius)		35.8 ± 1.1	35.6 ± 0.9
Heart rate at time of extubation (beats/minute)		102 (72 - 128)	98 (76 - 186)
Respiratory rate at time of extubation (breaths/minute)		28 (12 - 48)	24 (20 - 64)

Table 2: Changes in physiological parameters, scores for induction and intubation and timing of procedures in 41 cats undergoing ovariohysterectomy. Cats either received medetomidine/buprenorphine (MB, n = 21) or methadone/medetomidine (MM, n = 20) prior to IM induction of anaesthesia with alfaxalone. There were no significant differences between groups.

Parameter	MB (n = 21)			MM (n = 20)		
	10 minutes	**20 minutes**	**30 minutes**	**10 minutes**	**20 minutes**	**30 minutes**
HR (beats/minute)	144 ± 26	153 ± 24	158 ± 34	152 ± 30	156 ± 30	156 ± 33
RR (breaths/minute)	30 ± 7	30 ± 9	30 ± 7	34 ± 7	36 ± 10	35 ± 7
Temperature (° Celsius)	35.5 ± 0.7	35.7 ± 0.6	36.1 ± 0.7	35.3 ± 0.9	35.5 ± 1.1	36.1 ± 1.2

Table 3: Mean (± standard deviation) heart rate, respiratory rate, and aural temperature of 41 cats undergoing ovariohysterectomy during the first 30 minutes of recovery. Cats either received medetomidine/buprenorphine (MB, n = 21) or methadone/medetomidine (MM, n = 20) prior to IM induction of anaesthesia with alfaxalone. There were no significant differences between groups, or within groups at any timepoint.

Pain scoring system	Time (minutes)	medetomidine/buprenorphine (MB) n = 21	medetomidine/methadone (MM) n = 20	*p*
NRS (0-4)				
	10	0-2 (0)	0-2 (0)	0.387
	20	0-4 (0)	0-1 (0)	0.416
	30	0-2 (0)	0-0 (0)	0.107
SDS (0-3)				
	10	1-3 (1)	1-2 (1)	0.395
	20	1-3 (1)	1-2 (1)	0.311
	30	0-2 (1)	0-1 (2)	0.285
DIVAS (0-100mm)				
	10	0-54 (2)	0-21 (1)	0.027*
	20	0-36 (2)	0-7 (2)	0.474
	30	0-20 (2)	1-6 (2)	0.346
UNESP-Botucatu MFPS (0-30)				
	10	0-4 (1)	0-5 (1.5)	0.66
	20	0-5 (0)	0-4 (0.5)	0.818
	30	0-5 (1)	0-3 (0)	0.524

Table 4: Median (range) scores of the three metrology instruments (numeric rating scale (NRS), simple descriptive scale (SDS), dynamic interactive visual analogue scale (DIVAS) and UNESP-Botucatu multidimensional pain scale) in 41 cats undergoing ovariohysterectomy. Cats either received medetomidine/buprenorphine (MB, n = 21) or methadone/medetomidine (MM, n = 20) prior to IM induction of anaesthesia with alfaxalone. * < p 0.05 between the two groups.

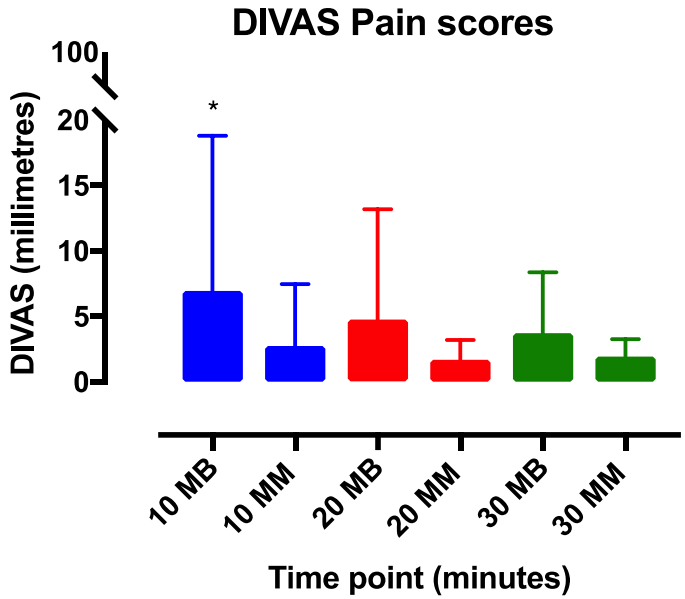

Figure 1 Post operative pain scores evaluated with a dynamic interactive visual analogue scale (DIVAS) at 10, 20 and 30 minutes after extubation in 41 cats undergoing ovariohysterectomy after medetomidine/buprenorphine (MB),(n = 21) or methadone/medetomidine (MM), (n= 20) followed by intramuscular alfaxalone.
* < 0.05 between the two groups (MB, MM).

490