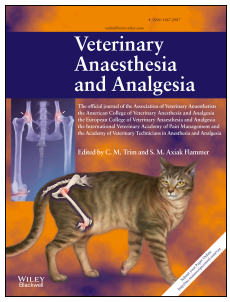
Accepted Manuscript



Clinical comparison of alfaxalone, ketamine and propofol following medetomidine and methadone in dogs

Kate L. White, David Yates

PII: S1467-2987(17)30079-X

DOI: 10.1016/j.vaa.2016.12.057

Reference: VAA 105

To appear in: *Veterinary Anaesthesia and Analgesia*

Received Date: 11 February 2016

Revised Date: 18 November 2016

Accepted Date: 12 December 2016

Please cite this article as: White KL, Yates D, Clinical comparison of alfaxalone, ketamine and propofol following medetomidine and methadone in dogs, *Veterinary Anaesthesia and Analgesia* (2017), doi: 10.1016/j.vaa.2016.12.057.

Running head: Alfaxalone, ketamine and propofol in dogs

RESEARCH PAPER

Clinical comparison of alfaxalone, ketamine and propofol following medetomidine and methadone in dogs

Kate L White[a] & David Yates[b]

[a]School of Veterinary Medicine and Science, University of Nottingham, Sutton Bonington, UK

[b]RSPCA Greater Manchester Animal Hospital, 411 Eccles New Road, Salford, UK

Correspondence: Kate White, School of Veterinary Medicine and Science, University of Nottingham, Sutton Bonington, Loughborough, Leics LE12 5RD, UK.

E-mail: Kate.White@nottingham.ac.uk

Acknowledgements

Jessica Pierce for data collection.

Abstract

Objective To compare the clinical effects of alfaxalone, ketamine and propofol in dogs following premedication with medetomidine and methadone.

Study design Prospective, 'blinded' and randomized clinical study.

Animals Seventy-five male dogs presented for neutering at a charity clinic.

Methods Dogs were allocated to receive alfaxalone, ketamine or propofol following premedication with medetomidine (20 μg kg^{-1}) and methadone (0.2 mg kg^{-1}). Dogs were temperament scored prior to premedication. Quality of sedation, induction of anaesthesia, recovery and recovery environment were scored by simple descriptive scales. Physiological variables during anaesthesia were recorded. Continuous numerical data were analysed using ANOVA with repeated measures as necessary. Non-parametric data were analysed using Kruskal-Wallis tests and multiple comparisons using Dunn's test. Statistical significance was set at $p < 0.05$.

Results The mean (± SD) dose of alfaxalone was 0.6 ± mg kg^{-1}, ketamine 1.5 ± 0.7 mg $kg^{-1}$and 0.8 ± 0.3 mg kg^{-1} for propofol. Alfaxalone inductions were significantly smoother compared to ketamine but not to propofol. Only 1 of 75 of the inductions were deemed poor. There were no differences in cardiopulmonary variables between groups except immediately after induction of anaesthesia. There were no differences in quality of recovery between groups.

Conclusions and clinical relevance All three induction agents provided reliable, predictable anaesthesia conditions that were clinically indistinguishable and ideal for teaching anaesthesia skills. The medetomidine and methadone premedication resulted in profound, heavy sedation and quality of induction of anaesthesia was better with alfaxalone compared to ketamine. No significant difference in induction quality was detected between alfaxalone and proprofol or propofol and ketamine, and these findings are likely to be of limited clinical significance when choosing an induction agent.

Keywords alfaxalone, anaesthesia, dog, ketamine, propofol

Introduction

Alfaxalone, propofol and ketamine are all used as intravenous induction agents in the dog with differing popularity. The true differences between the three induction agents alfaxalone, ketamine and propofol following an alpha 2 agonist/opioid premedication is not known. The effects of these induction drugs may be overstated during anaesthesia teaching, because they are often used concurrently with other agents reducing the potential discriminating properties. There are many factors that can affect the quality of induction and recovery, namely behaviour and/or temperament of the dogs, premedication, anaesthetic protocol, postoperative pain, and ambient environment. The choice of premedication can dramatically affect the anaesthetic induction, maintenance, and recovery. It is uncommon nowadays in clinical studies to use an induction agent without premedication in view of the benefits that preemptive analgesia, anxiolysis and sedation confer on the animal and the handlers. Favourable reports of the sedation afforded by methadone and low dose medetomidine have been reported (Puighibet et al. 2015).

Studies undertaken in children have shown that anxiety and temperament can influence the quality of recovery, with intense preoperative anxiety predisposing to a restless recovery from anaesthesia (Vlajkovic & Sindjelic 2007). One canine study however demonstrated that the behaviour of the dogs did not significantly influence the recovery phase (Jiménez et al. 2012). Dogs judged to be calm and of a happy demeanour scored equally on the simple descriptive scale (SDS) and the visual analogue scale (VAS) compared to nervous dogs during recovery. The kennel environment is also presumed to affect the patients' emergence and comfort in the recovery period. There remains the assumption that a quiet and stress free environment will enhance recovery. No studies have evaluated these factors in detail, but a few reports include the level of noise in the

recovery area (Jiménez et al. 2012; Mathis et al. 2012) and Mathis and co-workers concluded that the noise was probably of limited significance in two populations of cats recovering after alfaxalone or propofol (Mathis et al. 2012).

In practice, the choice of any protocol should be at the discretion of the veterinary surgeon, and this decision should be evidence based rather than opinion based. In an environment where teaching of anaesthesia takes place, there is the need for the instructors to offer an unbiased appraisal of the evidence, ample opportunity for acquisition of practical skills coupled with patient safety. During the final year of training of veterinary students there is a requirement to ensure students become effective, and skills must be actively taught rather than acquired through reading or traditional didactic teaching. One crucial factor in developing expertise is the deliberate practice undertaken (Ericsson 2007) and it is imperative that students have ample opportunities to deliberate practice in a safe supportive environment. In addition to deliberate practice, real-time feedback and time for problem-solving plus opportunities for repeated performance to refine behaviour will ensure the experiential learning is optimized and go some way to ensuring that student becomes a self-regulated learner (Ericsson 2015).

This study had two aims, firstly, the major aim was to evaluate whether the choice of induction agent had an impact on the quality of induction, maintenance, and recovery in healthy dogs undergoing anaesthesia for castration. A secondary aim was to evaluate the suitability of different protocols for the teaching of anaesthesia and surgery to final year veterinary students and consider the experiential learning.

Materials and methods

The study was carried out at RSPCA Greater Manchester Animal Hospital. Ethical approval was granted prior to the study by the University of Nottingham ethics committee (Ref 1424 150325) and informed owner consent was obtained prior to enrolment. A pilot study was undertaken. A sample size calculation indicated that 25 dogs per group would be required to show a statistically significant difference. It was estimated that the size of the sample should be of at least 75 dogs to have an 80% power and 95% confidence level of detecting a 25% difference in induction and recovery scores as assessed by a four point simple descriptive scale (SDS) based on a pilot study, using an ordinal logistic regression model relying on a proportional odds assumption.

Animals

Seventy-five male dogs were enrolled in the study (71 were client owned and 4 RSPCA dogs being neutered prior to rehoming). All owners were participating in a heavily discounted neutering scheme offered by the RSPCA Greater Manchester Animal Hospital. On admission, dogs were examined and assigned American Society of Anesthesiologists (ASA) status, and a temperament score on a four point simple descriptive scale adapted from previous studies with categories of 1) calm; 2) happy; 3) nervous; and 4) aggressive (Jiménez et al. 2012).

Exclusion criteria were ASA status > II, dogs weighing greater than 50kg or less than 2 kg, dogs with abnormal testicular pathology or cryptorchidism.

Sedation protocol

Dogs were fasted overnight and had free access to water up until the time of premedication.

All dogs were weighed and received premedication based on bodyweight of a mixture of 20 μg kg^{-1}medetomidine (Sedator; Dechra, UK) and 0.2 mg kg^{-1} methadone (Comfortan; Dechra) intramuscularly (IM) into the quadriceps muscle. Following premedication all dogs were left undisturbed for 15 minutes and the degree of sedation was scored using a modified numeric rating scale based on previous studies (Gurney et al. 2009; Maddern et al. 2010). Sedation was categorized as: 1) Profound/Heavy, impossible to arouse; 2) Good, heavily sedated but possible to arouse when stimulated; 3) Moderate, moderate sedated and easily aroused with minimal stimulation; 4) Inadequate, no apparent effect of the premedication and no indication of sedation; 5) Excited, more difficult to handle than prior to premedication.

Induction of anaesthesia

Dogs were allocated using a random number generator (www.randomizer.org) to one of the following three groups alfaxalone (Alfaxan; Jurox, UK), ketamine (Anesketin; Dechra) or propofol (PropoFlo Plus; Zoetis, UK) and induction drugs were administered intravenously (IV) over 60 seconds by final year veterinary students. Incremental doses, if required, were only administered after 60 seconds had elapsed. Dogs' tracheas were intubated with an appropriate sized cuffed endotracheal tube. The dose of induction agent and quality of induction and recovery was recorded by a scorer unaware of the induction agent used, using a modified numeric rating scale used in a feline study (Mathis et al. 2012) Induction score were categorized as: 1) Very smooth, with gradual patient relaxation, no movement or vocalization and first intubation attempt successful; 2) Good, some swallowing, coughing, tongue or jaw movement, and a slight degree of physical movement; 3) Poor, swallowing, coughing, some distress or excitement; 4) Very poor, major distress or excitement. Isoflurane (Isoflo; Zoetis) in oxygen was delivered via an appropriately sized breathing system (circle or Ayre's T-piece with

Jackson Rees modification). All animals were allowed to breathe spontaneously. Following orotracheal intubation all dogs received 0.2 mg kg $^{-1}$ meloxicam (Metacam; Boehringer-Ingelheim, UK) subcutaneously and amoxicillin (Betamox; Norbrook, UK) 15 mg kg $^{-1}$ IM. All dogs underwent castration surgery on heated operating tables (Burtons, UK).

Maintenance of anaesthesia

Clinical criteria used to assess depth included respiratory rate [f_R (calculated manually from observing chest excursions)], pulse rate [PR (calculated manually from recording pulse rate over 15 seconds)], eye position, palpebral reflex, jaw tone and spontaneous movement. Other parameters recorded included vaporizer setting and incidence of apnoea (defined as cessation of respiratory movements >60 seconds). All dogs were monitored continuously and parameters recorded at 5-minute intervals. Rectal temperature was recorded prior to recovery.

Recovery

At the end of the surgical procedures the isoflurane was discontinued, dogs were extubated and the quality of recovery assessed by using a simple descriptive scale by a scorer unaware of the induction agent, with categories 1) Very smooth, no excitement, trembling, paddling or vocalization; 2) Smooth, some excitement or paddling or vocalization on recovery; 3) Poor, sustained vocalization, paddling or excitement on recovery; 4) Very poor, extreme excitement, paddling, vocalization with risk of injury, intervention necessary. The noise in the recovery area was also described (Appendix A). Behavioural scores and mentation scores were recorded on discharge.

Student experience

Informal feedback about the surgical and anaesthesia experience was gained from veterinary nurses and students involved in the study.

153

154 Statistical analyses

155 Statistical tests were performed using GraphPad Prism (GraphPad Software, CA, USA)
156 version 6. Continuous numerical data sets were tested for normality using the
157 D'Agostino Pearson test and analyzed using the analysis of variance (ANOVA) and
158 with repeated measures as necessary. Multiple comparisons were performed if the
159 ANOVA showed significance. Normally distributed data are presented as mean ±
160 standard deviation (SD). Non-parametric data were analyzed using Kruskal-Wallis tests
161 and multiple comparisons using Dunn's test. Non-parametric data are presented as
162 median (interquartile range). Categorical (ordinal) data are reported as mean proportions
163 within each category for each induction drug and compared using logistic regression
164 analyses with an ordinal scale. Results were considered significant when $p < 0.05$.

165

166 **Results**

167 Animals

168 A total of 75 dogs weighing 11.2 (2.0 – 46.5) kg were recruited and randomly allocated
169 to receive one of three induction agents. All dogs completed the study. There were no
170 significant differences in weights and temperaments between the three groups. The
171 demographic data from the three groups are presented in Table 1.

172 Sedation

173 Time from premedication to induction of anaesthesia, PR after premedication and
174 sedation scores were not significantly different between groups (Table 2).

175 Induction

176 The subjective quality of induction was significantly different between the groups. Only
177 1 of 75 of the inductions were deemed poor and this was following propofol. Alfaxalone

178 inductions were significantly smoother (p = 0.003) compared to ketamine but not to
179 propofol (Fig. 1). The alfaxalone group had the most scores of 1 (very smooth
180 induction) (Table 2). The dose of alfaxalone for induction was 0.6 ± 0.2 mg kg^{-1}, and
181 for ketamine 1.5 ± 0.7 mg kg^{-1} and for propofol 0.8 ± 0.3 mg kg^{-1}.
182 Pain on injection was noted in 2 of 75 dogs, one whilst receiving alfaxalone and one
183 whilst receiving ketamine.
184 Maintenance of anaesthesia
185 Apnoea lasting longer than 60 seconds was noted on 4 occasions in dogs receiving
186 propofol (n=3) and ketamine (n=1). Vaporizer settings ranged between 0.5−1.5 % for
187 dogs on T piece breathing systems and 1.0−2.0% on circle breathing systems. There was
188 no significant difference between the three groups for vaporizer setting in animals using
189 the same breathing systems. No dogs required additional increments of induction agents
190 during anaesthesia.
191 Pulse rates were significantly different between groups at 5 minutes after induction
192 (Table 2). There was no significant difference in pulse rates between groups before
193 induction (p = 0.916) or at any time points after 5 minutes or over time from induction
194 to 60 minutes (p = 0.511) (Fig. 2).
195 Respiratory rates were not significant different between groups, but were significantly
196 different over time from induction to 60 minutes (p=0.001).
197 Recovery
198 Recovery data were unremarkable between groups with no difference in duration of
199 anaesthesia, surgery, recovery scores or environmental noise in the recovery area. One
200 dog in the propofol group vomited in recovery. All but two dogs (which remained in the
201 hospital as they were to be rehomed) were discharged within several hours of
202 extubation, and the dog's preanaesthetic demeanour compared with its post anaesthetic

demeanour. No reversal of the alpha-2 agonist was performed or considered necessary. Two dogs that were frightened, aggressive and uncooperative on admission were discharged uneventfully and deemed no longer to showing the same behaviours. A small number of dogs from all groups were slightly sedated on discharge. There was no difference in mentation scores at discharge between groups (Table 2).

Temperature was not significantly different between groups at the end of the procedure.

Student experience

All students were able to induce anaesthesia without intervention from the instructor. In cases of perivascular administration of the induction agents, all students were successful with subsequent attempts under close supervision and encouragement. In all cases where tracheal intubation failed, students were able to identify the mistake, rectify the situation and went on to successfully intubate the patient with no untoward effects. Transition to inhalational agent was uneventful in all cases and no patients required incremental doses of induction agent. One student was responsible for the surgery and one for the anaesthesia for each patient under the supervision of the instructor. Informal feedback from students highlighted opportunity to compare and contrast different induction agents, gain confidence with their use, refine and improve practical skills in an unhurried and supportive environment in healthy animals, and was compared by them to their experiential learning in other intra and extra mural studies.

Discussion

Anaesthetic protocols

All three induction agents provided very similar anaesthetic profiles. The profound sedation that was achieved in most dogs in this study will have in part contributed to the relatively small doses of induction agent required for induction of anaesthesia and

endotracheal intubation. Raekallio and co-workers concluded that the hypoxaemia following IV 0.02 mg kg^{-1} medetomidine and 0.1 mg kg^{-1} L-methadone (and fenpipramide) limited the clinical usefulness of the combination at those dosages (Raekallio et al. 2009) however our study used IM administration and this will have altered the peak effect and bioavailability of the drug (Dyck et al. 1993). All but one of the dogs in this study were ASA I, and a possible short lived degree of hypoxaemia would have likely caused minimal clinical signs and adverse effects, however an alpha 2 agonist and opioid combination may cause respiratory depression and hypoxaemia and patients should be regularly assessed and some may benefit from oxygen supplementation (Enouri et al. 2008). Doses of the induction agent were substantially reduced from data sheet dosages and serve to illustrate the magnitude of possible dose sparing that the premedication drugs afford. The ketamine and propofol doses were similar to other studies using medetomidine and hydromorphone premedication (Enouri et al. 2008). The reduction of the data sheet alfaxalone dose from 2 mg kg^{-1} to the dose used in this study 0.6 mg kg^{-1} demonstrates the necessity to titrate the induction drug to effect to avoid overdose.

Adverse events

The number of adverse events in this study was very few (1 incidence of vomiting on extubation in the propofol group, and 1 dog per group exhibiting profound bradycardia, and pain on injection in two dogs receiving ketamine and alfaxalone) in contrast to similar studies. The most likely explanation is the premedication protocol. The incidence of adverse events that occurred during the induction phase was less than other investigations of anaesthetic induction with alfaxalone (Muir et al. 2008) propofol (Sano et al. 2003a; Sano et al. 2003b) and ketamine (White et al. 2001). This may be attributed to the relatively profound sedation thereby limiting the effect the induction

agent contributed. No dogs demonstrated cyanosis or unexpected respiratory depression following premedication.

Student experience

These anaesthesia conditions contributed to a learning environment where students could proceed methodically, cautiously without undue haste and/or pressure. This profound sedation provided excellent conditions for IV administration of agents. The IV administration of induction agent was undertaken by final year veterinary students without complication, demonstrating that venous access was not so compromised 15 minutes after administration of the alpha 2 agent so as to hinder intravenous administration of drugs. Students appreciated the operative conditions, and were able to easily secure IV access, induce a plane of anaesthesia suitable for intubation, intubate carefully and slowly, with multiple attempts where necessary, secure the airway and maintain anaesthesia and recording parameters in a logical, considered manner.

The operative conditions facilitated a calm and low stress teaching environment conducive to affording the students ample time to safely carry out all stages of anaesthesia process, allowing supervised mistakes and feedback to occur whilst still maintaining a high standard of patient care. Training in practical skills such as securing intravenous access and airway management are essential components of any veterinary anaesthesia curriculum and whilst didactic teaching remains important it is no substitute for hands on practice. Nevertheless, it oftentimes difficult to ensure sufficient exposure to healthy normal patients undergoing anaesthesia such that every student can practise these core skills in a controlled supportive environment. The combinations in this study afforded such conditions and exposed students to three different induction agents to compare operative conditions. Usually students are trained using part task trainers for tasks such as intravenous access and intubation and may then use high fidelity

simulators designed to reproduce the task in a veterinary context. Whilst unproven this approach is considered to aid in honing technical, cognitive and decision making skills, but still falls short of training on live patients. It is necessary that those involved in teaching anaesthesia can plan to provide opportunities that meet the student needs rather than teaching whilst providing a service on inappropriate patients. The combinations used in this study afforded an excellent teaching environment, and illustrated that differences between agents were clinically difficult to detect.

Limitations

One of the limitations of this study was the lack of more comprehensive monitoring during anaesthesia, and in view of this it is impossible to comment for example on the effect the drugs on blood pressure; the operative conditions however were simulated to represent typical primary care practice for the students. Areas for future research included the assessment of methods of teaching veterinary anaesthesia to students and veterinary surgeons.

Conclusions

We conclude, all three induction agents provide consistent, reproducible, and clinically similar conditions following medetomidine and methadone premedication highly suitable for teaching and assessing anaesthesia procedural skills.

296 **References**

297

298 Dyck JB, Maze M, Haack C et al. (1993) The pharmacokinetics and hemodynamic
299 effects of intravenous and intramuscular dexmedetomidine hydrochloride in
300 adult human volunteers. Anesthesiology 78**,** 813-820.
301 Enouri SS, Kerr CL, Mcdonell WN et al. (2008) Cardiopulmonary effects of anesthetic
302 induction with thiopental, propofol, or a combination of ketamine hydrochloride
303 and diazepam in dogs sedated with a combination of medetomidine and
304 hydromorphone. American Journal Of Veterinary Research 69**,** 586-596.
305 Ericsson KA (2007) An expert-performance perspective of research on medical
306 expertise: the study of clinical performance. Medical education 41**,** 1124-1130.
307 Ericsson KA (2015) Acquisition and maintenance of medical expertise: a perspective
308 from the expert-performance approach with deliberate practice. Academic
309 medicine : journal of the Association of American Medical Colleges 90**,** 1471-
310 1486.
311 Gurney M, Cripps P, Mosing M (2009) Subcutaneous pre-anaesthetic medication with
312 acepromazine–buprenorphine is effective as and less painful than the
313 intramuscular route. Journal of Small Animal Practice 50**,** 474-477.
314 Jiménez CP, Mathis A, Mora SS et al. (2012) Evaluation of the quality of the recovery
315 after administration of propofol or alfaxalone for induction of anaesthesia in
316 dogs anaesthetized for magnetic resonance imaging. Vet Anaesth Analg 39**,** 151-
317 159.
318 Maddern K, Adams VJ, Hill NAT et al. (2010) Alfaxalone induction dose following
319 administration of medetomidine and butorphanol in the dog. Vet Anaesth Analg
320 37**,** 7-13.

321 Mathis A, Pinelas R, Brodbelt DC et al. (2012) Comparison of quality of recovery from
322 anaesthesia in cats induced with propofol or alfaxalone. Veterinary anaesthesia
323 and analgesia 39**,** 282-290.
324 Muir W, Lerche P, Wiese A et al. (2008) Cardiorespiratory and anesthetic effects of
325 clinical and supraclinical doses of alfaxalone in dogs. Vet Anaesth Analg 35**,**
326 451-462.
327 Puighibet Z, Costa-Farre C, Santos L et al. (2015) The sedative effects of intramuscular
328 low-dose medetomidine in combination with butorphanol or methadone in dogs.
329 Vet Anaesth Analg 42**,** 590-596.
330 Raekallio MR, Räihä MP, Alanen MH et al. (2009) Effects of medetomidine, l-
331 methadone, and their combination on arterial blood gases in dogs. Vet Anaesth
332 Analg 36**,** 158-161.
333 Sano T, Nishimura R, Mochizuki M et al. (2003a) Clinical usefulness of propofol as an
334 anesthetic induction agent in dogs and cats. J Vet Med Sci 65**,** 641-643.
335 Sano T, Nishimura R, Mochizuki M et al. (2003b) Effects of midazolam-butorphanol,
336 acepromazine-butorphanol and medetomidine on an induction dose of propofol
337 and their compatibility in dogs. J Vet Med Sci 65**,** 1141-1143.
338 Vlajkovic GP, Sindjelic RP (2007) Emergence delirium in children: Many questions,
339 few answers. Anesthesia and Analgesia 104**,** 84-91.
340 White KL, Shelton K, Taylor PM (2001) Comparison of diazepam–ketamine and
341 thiopentone for induction of anaesthesia in healthy dogs. Vet Anaesth Analg 28**,**
342 42-48.
343

Figure legends

Figure 1 Induction of anaesthesia scores for dogs that had received alfaxalone (*n*=25), ketamine (*n*=25) or propofol (*n*=25). Induction of anaesthesia was significantly smoother following alfaxalone (p = 0.003).

Figure 2 Pulse rates [median (range)] in dogs following induction of anaesthesia with alfaxalone, ketamine or propofol (*n* = 25 in each group). For drug doses see Table 2.

Table 1 Clinical details of 75 dogs undergoing anaesthesia for castration randomly allocated to receive alfaxalone, ketamine or propofol as induction agents. Data are presented as median (interquartile range) or number of dogs.

	Group		
	Alfaxalone	Ketamine	Propofol
ASA status (I:II)	25:0	24:1	25:0
Body mass (kg)	13 (7–27)	10 (6–22)	11 (6–18)
Age (months)	50 (10–84)	31 (10–44)	28 (8–48)
Temperament Score	1 (1–2)	1 (1–2)	2 (1–3)
Breed			
American Bulldog	0	0	1
Bichon Frise	2	1	0
Border Terrier	1	0	0
Basset hound	0	2	0
Beagle	0	0	1
Border Collie	1	0	0
Boxer	0	1	0
Cocker Spaniel	4	1	0
Cairn Terrier	0	1	0
Chinese Crested	0	1	0
Chihuahua	2	1	0
Cavalier King Charles	0	1	0

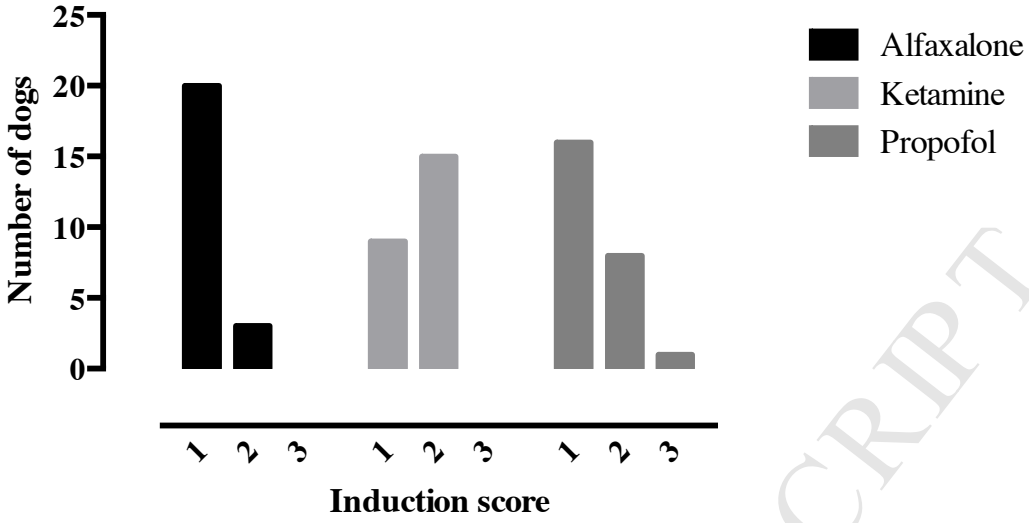
Spaniel			
Dalmatian	0	0	1
French Bulldog	0	0	1
German Shepherd Dog	2	2	0
Jack Russell Terrier	0	1	1
Labrador	0	1	0
Lhasa Apso	1	0	0
Pug	1	0	0
Rottweiler	1	0	1
Staffordshire Bull	3	3	4
Terrier			
Shi Tzu	0	4	1
Tibetan Terrier	0	0	1
Cross bred	5	4	10
Yorkshire Terrier	2	3	1

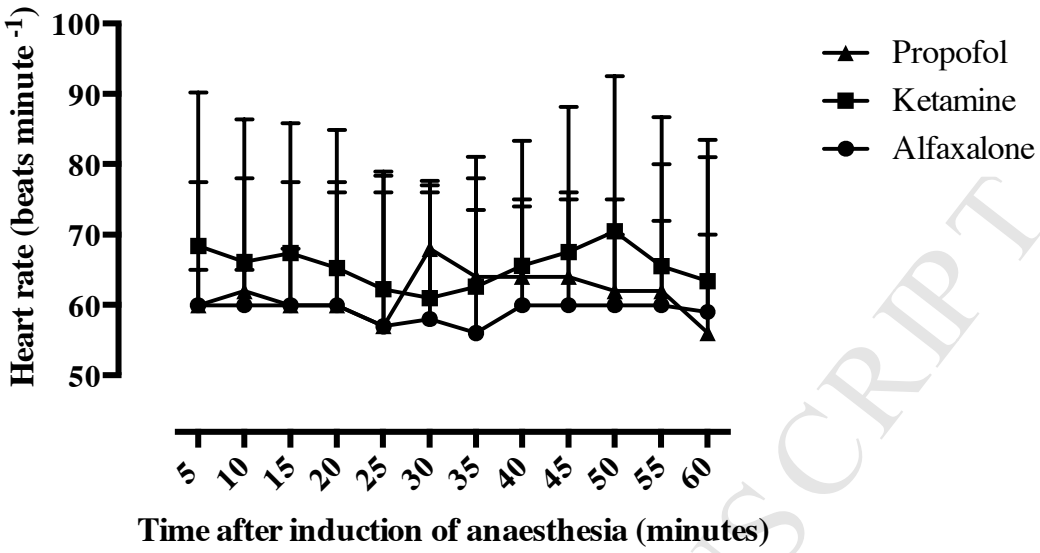
ASA, American Society of Anesthesiologists

Table 2 Sedation, induction and recovery scores, pre and post induction pulse rate, duration of surgery and anaesthesia, rectal temperature, expressed as median (interquartile range) in 75 dogs premedicated with medetomidine and methadone and induced with either alfaxalone, ketamine or propofol for castration. The dose of induction agent is expressed as mean ± standard deviation.

	Alfaxalone	Ketamine	Propofol	*p* value
Sedation Score	1 (1–2)	1 (1)	1 (1–2)	0.118
Pre-induction pulse rate (beats minute^{-1})	56 (45–62)	54 (41–65)	56 (46–60)	0.994
Post-induction pulse rate beats minute^{-1})	55 (50–62)	65 (61–80)	57 (44–64)	0.003
Time from premedication to induction (minutes)	24 (21–31)	22 (192–9)	20 (15–29)	0.367
Induction Score	1 (1–1)	2 (1–2)	1 (1–1)	0.003
Dose of induction agent (mg kg $^{-1}$)	0.6 ± 0.2	1.5 ± 0.7	0.8 ± 0.3	N/A
Recovery score	2 (1–2)	2 (1–2)	2 (1–2)	0.892

Temperature on recovery (° Celsius)	37.2 (36.7-37.4)	37.5 (37.1-38.1)	37.1 (36.4-37.7)	0.066
Duration of surgery (minutes)	54 (47-67)	48 (39-70)	56 (49-72)	0.338
Duration of anaesthesia (minutes)	72 (66-85)	69 (57-83)	84 (67-96)	0.158
Recovery environment noise score	3 (3-4)	3 (3-4)	3 (3-4)	0.793





Appendix A Description of the noise in the recovery environment

Categories	Description
1 No noise	
2 Small amount of noise	Personnel entering and leaving the ward but no conversation or other significant noise
3 Moderate amount	Personnel entering and leaving the ward, some conversation
4 Very noisy	Loud conversation, constant noise, dogs barking/whining, radio playing loudly