Sedative and Recovery Effects of Intramuscular Alfaxalone-Butorphanol-Midazolam Compared with Medetomidine-Butorphanol-Midazolam in Cats: A Randomized, Blinded Clinical Study

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ABSTRACT

The goals of this study were to evaluate the effectiveness and physiological effects of alfaxalone-butorphanol-midazolam sedation in cats compared with the common sedation protocol used at our institution; medetomidine-butorphanol-midazolam. Thirty-one cats requiring sedation for various procedures were recruited randomly to receive intramuscular butorphanol (0.4 mg/kg) and midazolam (0.3 mg/kg) combined with alfaxalone (2 mg/kg) (ABM; n=16) or medetomidine (0.02 mg/kg) (MBM; n=15). Physiological variables and sedation quality (scale 7-28; 7=awake, 28=deeply sedated) were collected every 10 minutes until recovery. For medetomidine antagonism, the MBM cats received atipamezole intramuscularly. Induction and recovery times were recorded, and recovery quality was scored (1-4 scale: 1=poor, 4=excellent). Evaluations were performed by one blinded observer. Mann-Whitney U test, Fischer's exact and repeated measures mixed-effects were used for analysis, and p<0.05 was set for significance. Six cats (ABM) and three cats (MBM) required an additional dose. At 10-40 minutes sedation scores were significantly better in the MBM (21-24) compared with ABM group (19-20). Significant lower heart rate, higher blood pressure and respiratory frequency were recorded in the MBM group. Time to recovery was significantly faster (9±7 versus 26±21 minutes) and recovery of better quality (4 [1-4] versus 3 [1-4]) in the MBM compared with the ABM group. During recovery, cats in the ABM group showed opisthotonos, twitching, and paddling, which resolved within an hour. In conclusion, at the doses used, ABM was a viable alternative to MBM with less cardiovascular effects, however, sedation plane was inferior and recovery, longer, accompanied by adverse behaviors.

Keywords: Cats; Alfaxalone; Butorphanol; Medetomidine; Midazolam; Sedation.

INTRODUCTION

Cats may require sedation to undergo minor procedures during veterinary visits, especially if they are stressed and resist restraint and handling (1, 2). Medetomidine is a commonly used α2-agonist in cats, which cause significant cardiovascular effects, including initial vasoconstriction, hypertension, reflex bradycardia and reduction in cardiac output (3-5). α2-agonists are often combined with other injectables such as ketamine, opioids and/or benzodiazepines in order to achieve a synergistic effect and thus lower its dose and enhance its sedative effect (6, 7).

Many of the cats submitted for medical treatments in Israel are fractious or difficult to handle without prior deep sedation. A combination of medetomidine-butorphanol-midazolam is commonly used to sedate cats at our Veterinary Teaching Hospital, however, the effects of medetomidine on the cardiovascular system and the resultant decrease in cardiac output may be harmful in geriatric or sick cats (5).

Alfaxalone is a neurosteroid injectable anesthetic, which produces its effects via γ-aminobutyric acid receptor A ($GABA_A$) and can be administered via intravenous or intramuscular (IM) routes (8-10). Alfaxalone has been combined with various sedatives and tranquilizers to produce sedation or anesthesia in cats (11-14). It has also been advocated for use in cats with underlying diseases (15, 16) or in animals with high anesthetic risk (17).

The objectives of this study were to evaluate the sedative and adverse effects of IM alfaxalone-butorphanol-midazolam (ABM) and compare it with medetomidine-butorphanol-midazolam (MBM) protocol in cats. Our hypotheses were that sedation would be similar while cardiovascular effects would be less marked in cats administered ABM compared with MBM, although recovery time of ABM was likely to be longer.

MATERIALS AND METHODS

Animals

The Internal Ethics Review Committee (KSVM-VTH/14_2015) approved this study and a verbal or written informed consent was obtained from the owners or legal guardians. In addition, established internationally recognized high standards ('best practice') of veterinary patient care were followed.

All recruited cats required deep sedation for short (5-30 minutes), minor procedures, such as ultrasound, radiographs, bandage change, blood sampling and physical examination in stray animals prior to neutering, etc. Cats were considered healthy based on physical examination; however, some cats were fractious and required sedation to perform the examination. Inclusion criteria included: age 5-months to 12-years-old with body weight greater than 2 kg and fasting for at least 6 hours. Exclusion criteria were cats requiring general anesthesia following sedation or cats with suspected systemic disease (heart/lung/kidney/liver).

Procedures

Prior to sedation, the cats' temperament was assessed on a 1-4 scale (1=nice, quiet, easy to handle; 2=not nice, but able to handle with restraint; 3=aggressive, struggle, require a lot of restraint or sedation; 4=fractious, cannot be restraint without deep sedation). When it was possible, heart rate (HR) was measured using a stethoscope, respiratory frequency (f_R) by watching chest movements and rectal temperature (RT) with a digital thermometer. All cats were administered 0.4 mg/kg butorphanol (Butomidor; Richter Pharma AG, Wels, Austria; 10 mg/ml) and 0.3 mg/kg midazolam (Midolam; Rafa Laboratories, Jerusalem, Israel; 5 mg/ml). These drugs were combined with alfaxalone (Alfaxan, Jurox, Rutherford NSW, Australia; 10 mg/ml; 2 mg/kg; ABM) or medetomidine (Domitor, Orion Pharma, Espoo, Finland; 1 mg/ml; 0.02 mg/kg; MBM), which were assigned via a random generated list (https://www.random.org/lists/). Drugs were administrated IM in the quadriceps muscles via a squeeze cage using a 21-gauge, 25-mm needle.

Following injection, cats were left in the cage and monitored until becoming laterally recumbent. If lateral recumbency did not occur within 15 minutes or if the cat responded to stimuli during the procedure, an additional dose was administered IM (alfaxalone 1 mg/kg [ABM] or medetomidine 0.01 mg/kg [MBM]).

Sedation quality was scored on a 7-28 scale, including seven parameters, and the total score was summarized (Table 1). Additionally, response to procedure was scored on a 1-4 scale (1=cannot be performed; 2=performed with a lot of restraint; 3=performed with a little restraint; 4=performed without restraint). Vital signs included HR, f_R, RT, indirect measurement of mean arterial blood pressure (MAP) using an oscillometric technique with the cuff (40% circumference) placed above the carpus, and pulse oximetry (SpO_2) with the probe placed on the tongue/ear/paw (Cardell 9402 Vital Signs Monitor, MIDMARK, Tampa, FL, USA). Pain level of the procedures (painful/non-painful) and the noise level at the room (noisy/quiet) were recorded. Data was collected 5 and 10 minutes after injection, and then every 10 minutes until the end of the procedure. Eye drops were instilled for corneal moisture (Hydroxyethylcellulose 0.19% LYTEERS®; Fischer Pharmaceutical, Bnei Brak, Israel).

At the end of each procedure, cats in the MBM group received 0.05 mg/kg atipamezole (Antisedan; Orion Pharma; 5 mg/ml) IM in the epaxial muscles, while cats in the ABM group did not receive any antagonist medication. The assessor was out of the room during antagonist administration (or no administration). Recovery quality was scored on a 1-4 scale (1=poor, severe muscle rigidity, severe twitching/paddling, and severe hypersensitivity to touch/noise/light; 2=fair, moderate muscle rigidity and twitching/paddling,

Table 1. Quality of sedation guidelines (scale 7-28; 7=awake, 28=deeply sedated).

Parameter	Score 1	Score 2	Score 3	Score 4
Body position	Standing or walking	Sternal	Lateral but moving head	Lateral not moving
Pupil Position	Central			Rotated
Response to noise (tested by clapping the hands loudly near the cat's ear and waiting for response)	Jumping	Moving head	Moving ears	Not responding
Palpebral reflex (tested by tapping at the medial canthus and waiting for a blink response)	Spontaneous	Strong	Reduced	Absent
Ear flick reflex (tested by placing the tip of a hemostat gently in the ear and waiting for an auricle flick response)	Spontaneous	Strong	Reduced	Absent
Withdrawal reflex (tested by pinching the middle digit of the hind limb using a hemostat for a few seconds and waiting for a withdrawal response)	Spontaneous	Strong	Reduced	Absent
Jaw tone	Cannot open the jaws	Strong	Reduced	Flaccid

and/or hypersensitivity to touch/noise/light; 3=good, mostly smooth, mild twitching and/or hypersensitivity; 4=excellent, smooth and calm). Time of injection, lateral recumbency, end of procedure, atipamezole injection, sternal recumbency and adverse effects were recorded. All data collection and scorings were performed by one investigator who was unaware of the treatment.

Statistical analysis

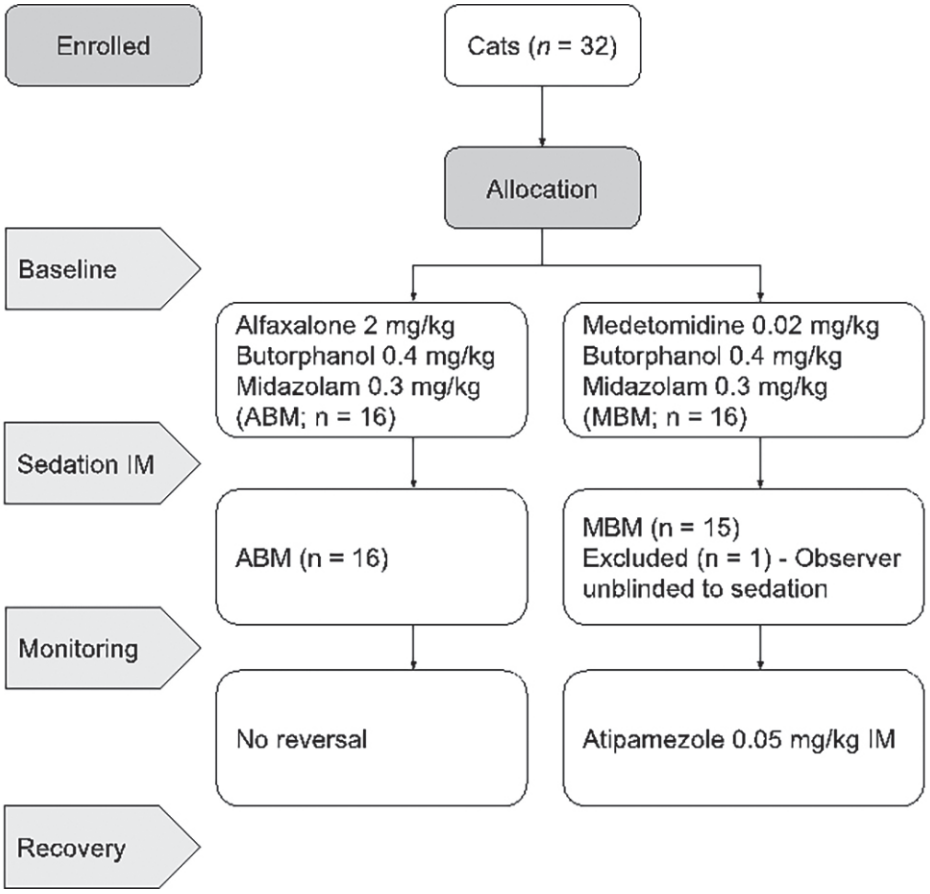
A sample size calculation determined that 12 cats per group would be required to detect a difference of 20±13 beats per minute (bpm) in HR between groups at 30 minutes from injection (yielding a power of 97% with α of 5%) (18). This time point was chosen as the average time between alfaxalone (9) *versus* medetomidine (3) maximum effect on HR (20 *versus* 40 minutes, respectively). Several more cats were recruited to account for differences in procedure length and incomplete data collection.

The Shapiro-Wilk test was used to assess normal distribution of the variables. Quantitative variables were compared by Student's *t*-test for normally distributed variables (presented as mean±standard deviation [SD]). Non-normally distributed variables were analyzed with the Mann-Whitney U-test (presented as median [range; maximum-minimum]), and qualitative variables were compared with Fisher's exact test (median [range]). For testing the relationship between ordinal variables, the Spearman's rank correlation coefficient was used. Wilcoxon signed-rank test was used to compare the HR at different times with baseline in the same group. Due to the small sample size, in both groups a correction for multiple comparison was not done. Repeated measures mixed-effects was used to determine the relationship between independent variables (age, sex, weight, temperament, location and additional drug dose) and sedation quality. Significance was set at p-value<0.05. Analyses were performed with commercial statistical software programs (SPSS Version 22, IBM, New York, NY, USA and STATA Version 14, StataCorp., College Station, TX, USA).

RESULTS

Thirty-two client-owned cats were recruited. The evaluator was accidently exposed to the injection volume of one cat in the MBM group, therefore it was omitted from the study (Figure 1). Data from 31 cats (16 females, 15 males) weighting 4.5±1.7 kg and aged 3.0±3.0 years were analyzed. Except for one Ragdoll cat in the ABM group, all cats were domestic short-haired. There was no difference in sex, temperament, pain/noise or procedure between the groups, however, cats in the ABM group were significantly older (p=0.033) and weighed more (p=0.027) (Table 2). A positive correlation between cats' age and weight (R=0.711) was found. Additionally, in the ABM group a positive correlation

Figure 1. Flow diagram of study design to compare between intramuscular (IM) alfaxalone-butorphanol-midazolam (ABM) *versus* medetomidine-butorphanol-midazolam (MBM) sedation in cats.



was found between cats' age and weight to total sedation time (R=0.737 and R=0.600, respectively). Cats who had a painful procedure were administered non-steroidal anti-inflammatory drugs and when applicable also local anesthesia. There were no differences in induction time (p=0.078), procedure duration (p=1.0) or total sedation time (p=0.131) between groups (Table 2).

Median sedation quality score was significantly higher in the MBM group compared with the ABM group at 5, 10, 20 and 40 minutes (p=0.017, 0.001, p<0.001, p=0.029, respectively; Table 3). Withdrawal reflex was decreased or lost between 5-20 minutes following injection in both groups, and no difference between groups was observed in response to the procedure (Figure 2A). Six cats (38%) in the ABM group and three cats (20%) in the MBM group required an additional dose for performing and completing the procedure (p=0.433). The procedure could not be completed in one cat from each group: ABM- a 5-month-old cat moved at 20 minutes after drugs administration, when handled for blood sampling (non-painful procedure, noisy room), and additional alfaxalone was not sufficient for resedation. MBM- a 2-year-old cat moved at 30 minutes after drugs administration, while placing sutures in a dehiscence incision, although lidocaine infiltration was performed (painful procedure, noisy room), and additional medetomidine was not sufficient for procedure completion.

Mean HR was significantly higher in the ABM group at all time points following injection (Table 4). In the ABM group HR did not change from baseline, while in the MBM group, it decreased significantly at 10-40 minutes following injection. An arrhythmia was heard in two cats in the MBM group (6-months and 1-year old); in one of them atrial premature complexes were suspected. Spontaneous breathing was preserved in all cats throughout sedation. f_R was significantly higher in the MBM group at 5-20 minutes (p=0.016, 0.001, 0.024, respectively; Table 4).

Table 2. Median (range) of demographic data, temperament scores, noise and pain levels, and description of minor procedures performed in cats sedated with an intramuscular combination of alfaxalone-butorphanol-midazolam (ABM; *n*=16) or medetomidine-butorphanol-midazolam (MBM; *n*=15). And mean±standard deviation (SD) induction time (from injection to lateral recumbency), procedure time (from injection to the end of procedure), total sedation time (from injection back to sternal recumbency) and recovery time (from atipamezole administration [MBM] or no antagonist [ABM] to sternal recumbency).

Parameter	ABM	MBM
Female/male	8/8	8/7
Age (years)	4.2 (1-7)*	1 (0.5-1.9)
Weight (kg)	4.5 (3.7-7.1)*	3.5 (3-4.7)
Temperament score	2 (1-4)	2 (1-3)
Noise level	2 (1-2)	2 (1-2)
Pain level	2 (1-2)	2 (1-2)
Procedures`	Blood sampling (5), bandage change (4), oral exam (4), ultrasound & skin biopsy (1), wound debridement (1), haircut (1)	Blood sampling (7), bandage change (4), incision dehiscence suturing (1), castration (1; under local anesthesia), ultrasound (1), radiographs & arthrocentesis (1)
Period (minutes)		
Induction time	10.4±9.1	5.9±2.8
Procedure time	49.6±19.2	49.3±17.7
Total sedation time	75.6±26.6	61.3±24.3
Recovery time	25.9±20.9	12.0±15.6*

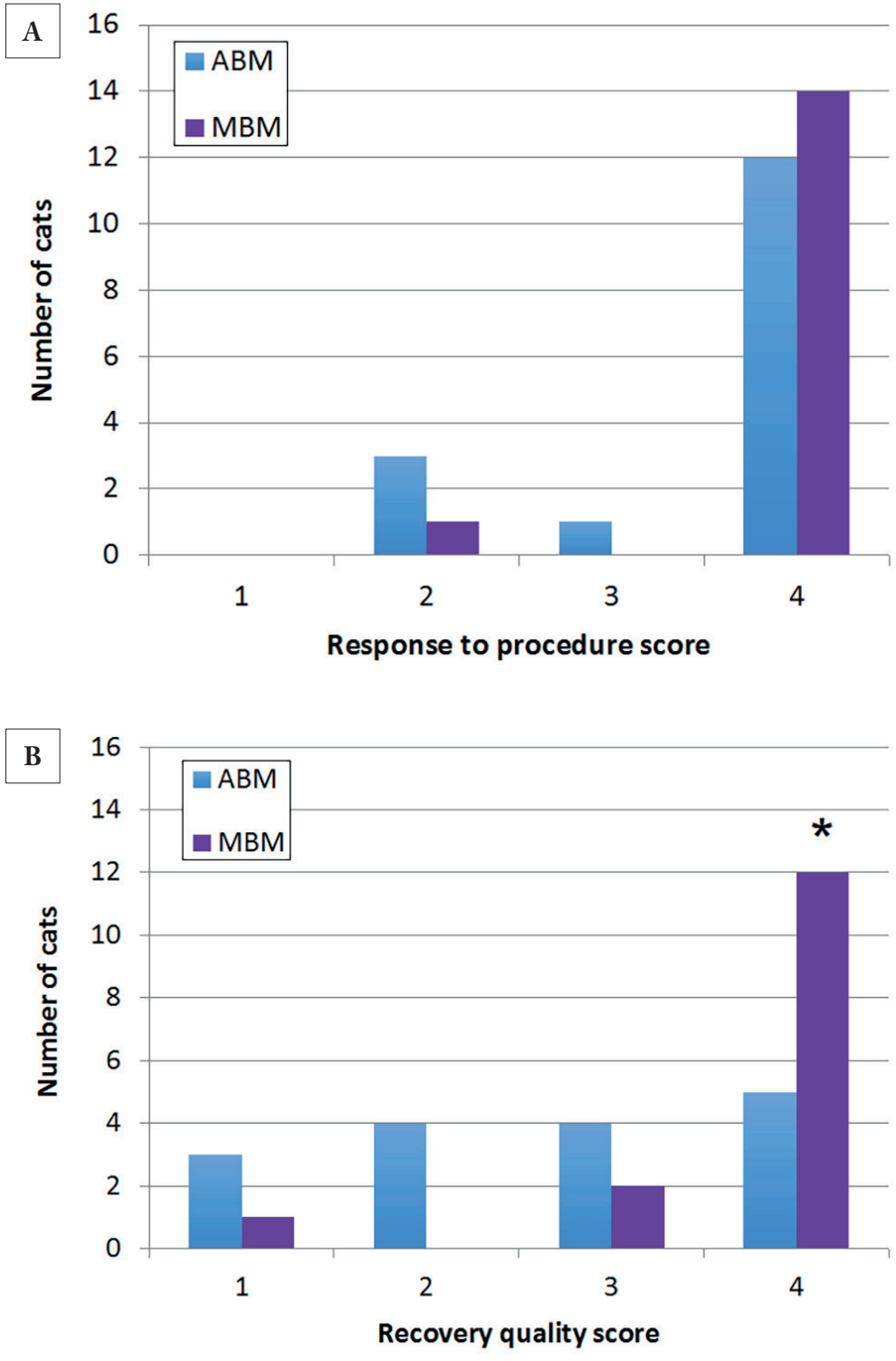
Temperament score used a 1-4 scale (1=easy to handle, 4=cannot be restraint without sedation).
Noise level scoring: 1=noisy, 2=quiet.
Pain level scoring: 1=painful, 2=non-painful.
* Significantly different between groups (p<0.05).

Table 3. Sedation quality scores (scale 7-28; 7=wide awake, 28=deeply sedated; Table 1) in cats at times 5 to 60 minutes following intramuscular administration of alfaxalone-butorphanol-midazolam (ABM; *n*=16) or medetomidine-butorphanol-midazolam (MBM; *n*=15). The number of cats (*n*) is added in parenthesis when not all the cats in the group were assessed at that time point.

Time following injection (minutes)	ABM	MBM
Baseline	7 (7)	7 (7)
5	21 (20-22) (*n*=6)	22.5 (22-23.5) (*n*=8)*
10	20 (18-21.5) (*n*=12)	23 (22-24)*
20	20 (16-21.5)	24 (23-24)*
30	20 (17-21) (*n*=13)	21 (21-24)
40	19 (15-20) (*n*=10)	23 (20-24) (*n*=9)*
50	19 (16.5-19.5) (*n*=7)	21.5 (19-22) (*n*=6)
60	15 (14-23) (*n*=5)	21 (19.5-21.5) (*n*=3)

Data is presented as median (range).
* Significantly different between groups (p<0.05).

Figure 2. Number of cats at each score category of (A) response to procedure (scale 1-4; 1=cannot be performed, 4=performed without restraint) and (B) recovery quality (scale 1-4; 1=poor, 4=excellent) of cats sedated with intramuscular alfaxalone-butorphanol-midazolam (ABM; *n*=16) or medetomidine-butorphanol-midazolam (MBM; *n*=15).



* Significantly different between groups (p<0.05).

Table 4. Physiological parameters collected from baseline to 50 minutes after administration of intramuscular alfaxalone-butorphanol-midazolam (ABM; *n*=16) or medetomidine-butorphanol-midazolam (MBM; *n*=15). The number of cats (*n*) is added in parenthesis when not all the cats in the group were assessed at that time point.

Variable	Group	Time (minutes from injection)						
		Baseline	5	10	20	30	40	50
HR (bpm)	ABM	186±43	182±20*	162±25*	165±20*	157±24*	161±27*	139±34*
		(*n*=9)	(*n*=8)	(*n*=12)			(*n*=10)	(*n*=7)
	MBM	188±22	107±19	100±18	98±17	99±17	101±19	98±2
		(*n*=8)	(*n*=7)				(*n*=10)	(*n*=5)
f_R (rpm)	ABM	53±30	31±9	29±7	31±10	30±7	31±10	32±8
		(*n*=11)	(*n*=6)	(*n*=11)	(*n*=14)	(*n*=11)	(*n*=10)	(*n*=6)
	MBM	49±18	45±12*	46±15*	40±11*	38±15	37±9	35±12
		(*n*=12)	(*n*=8)	(*n*=13)			(*n*=10)	(*n*=5)
RT (°C)	ABM	38.1±0.1	37.9±0.9	37.9±0.9	37.7±0.7	37.3±1.0	37.4±0.9	36.7±0.9
		(*n*=2)	(*n*=5)	(*n*=11)		(*n*=10)	(*n*=8)	(*n*=5)
	MBM	38.6±0.5	38.0±0.6	38.1±0.6	38.1±0.6	37.7±0.5	37.4±0.6	36.9±0.9
		(*n*=2)	(*n*=8)	(*n*=14)	(*n*=14)	(*n*=13)	(*n*=6)	(*n*=5)
MAP (mmHg)	ABM	NR	91±28	98±26	98±24	108±32	117±29	100±32
			(*n*=5)	(*n*=11)	(*n*=15)	(*n*=12)	(*n*=8)	(*n*=6)
	MBM	NR	143±22*	142±20*	125±26*	124±21	114±23	97±17
			(*n*=8)	(*n*=14)	(*n*=14)	(*n*=14)	(*n*=9)	(*n*=5)
MAP (number of cats with values <60 mmHg)	ABM	NR	1	1	0	0	0	1
	MBM	NR	0	0	0	0	0	0
SpO2 (%)	ABM	NR	94±2	94±3	94±3	95±3	95±3	97±2
			(*n*=4)	(*n*=9)	(*n*=13)	(*n*=11)	(*n*=7)	(*n*=5)
	MBM	NR	92±4	94±3	93±4	93±6	95±3	96±2
			(*n*=6)	(*n*=12)			(*n*=8)	(*n*=3)
SpO2 (number of cats with values <90%)	ABM	NR	0	1	1	0	0	0
	MBM	NR	1	1	3	2	0	0

HR, heart rate; bpm, beats per minute; f_R, respiratory frequency; rpm, respirations per minute; RT, rectal temperature; MAP, mean arterial pressure; SpO2, hemoglobin oxygen saturation; NR, not recorded.
Data is presented as mean±standard deviation, unless stated otherwise.
* Significantly greater than the other group (p<0.05).

RT decreased over time in both groups with no difference at any time point. At 50 minutes mean RT was lower than 37.0°C in both groups. Mean MAP was significantly higher in the MBM group at 5-20 minutes (p=0.007, p<0.001, p=0.010, respectively; Table 4). MAP below 60 mmHg was recorded in three different cats from the ABM group, once for each cat, although, these cats were moving during the measurement (paddling and opisthotonos). There was no difference between groups in SpO_2 levels at any time point (Table 4). One cat from the ABM group which experienced SpO_2 lower that 90% also experienced opisthotonos at these time points.

Mean recovery time was more rapid (p=0.046; Table 2), median recovery score better (4 versus 3; p=0.007), and significantly more cats were scored as "excellent" (p=0.017) in the MBM group (Figure 2B). Cats which were administered additional alfaxalone dose (ABM group) had significantly poorer recovery scores (p=0.021). No correlation was found between recovery score and age, weight, or temperament.

Table 5. Adverse effects during recovery in cats following sedation with intramuscular alfaxalone-butorphanol-midazolam (ABM; *n*=16) or medetomidine-butorphanol-midazolam (MBM; *n*=15). Data is presented as the number of cats that showed the adverse effect.

Adverse effect	ABM	MBM
Opisthotonos	10*	0
Twitching	9*	1
Paddling	6*	0
Obsessive licking	3	0

*Significantly different between groups (p<0.05)

Adverse effects were observed mostly in the ABM group during recovery (Table 5). These behaviors ceased without any treatment within an hour following recovery. Correlation was found between opisthotonos and additional alfaxalone dose (p=0.037). Two cats, one from each group, demonstrated aggressive behavior during recovery, both were defined as pleasant before sedation. All cats were discharged home following recovery. Abnormal vocalization was reported for one ABM cat on the day following sedation. That cat was administered a second alfaxalone dose. No other long-term effects were reported.

DISCUSSION

According to the results of the present study, ABM via IM injection route provided sufficient sedation for minor, short, non-painful procedures in most cats. However, sedation quality was better in the MBM group, although no difference was found in the withdrawal reflex or in response to the procedure between groups. One study demonstrated the efficacy of 2.5 mg/kg alfaxalone IM as a sole agent, although, 5-10 mg/kg produced better sedation for longer duration (9). Administration of 2 mg/kg alfaxalone and 0.2 mg/kg butorphanol IM in cats was reported to provide good sedation in one study (16), while in another study sedation was not sufficient and additional alfaxalone dose was required to produce immobility in 11/19 cats (14). Administration of butorphanol (0.2 mg/kg) combined with alfaxalone (2 mg/kg) or dexmedetomidine (0.007 mg/kg) in cats provided sufficient sedation for abdominal ultrasound or CT with no differences in sedation scores between protocols, although these cats were considered nice and habituated to handling (19). In the present study 6/15 cats required an additional alfaxalone dose in order to perform or complete the procedure. It is possible that a dose of 2 mg/kg is too low for young or fractious cats and a higher dose may be necessary (e.g., 2.5-3 mg/kg). In a study comparing butorphanol (0.2 mg/kg) combined with alfaxalone 2 *versus* 5 mg/kg, it was reported that sedation was significantly better for 30 minutes with the higher alfaxalone dose (14). However, it should be taken into account that higher dose will require higher injection volume, which may result in more discomfort compared with a lower volume when administered IM. Additionally, in the present study older cats took longer time to recover, therefore, geriatric cats or cats with comorbidities may require a lower dose than 2 mg/kg.

The median (reference range) for HR in cats was reported to be 190 (128-256) bpm in the hospital setting and 153 (110-250) bpm in the home environment (2). In the ABM group HR values were within the reference range, while in the MBM group they were lower. HR values of the ABM cats are similar to other studies administering up to 5 mg/kg alfaxalone to cats (8, 9, 13, 20, 21). The decrease in HR in the MBM group was anticipated because of medetomidine-induced reflex bradycardia and was reported previously (3-5). Arrhythmias, such as atrioventricular block were reported following medetomidine in cats and dogs (22, 23). Therefore, it is less likely that the arrhythmias heard in the two young cats from the MBM group were present before the sedation but were caused due to medetomidine administration.

All cats in both groups were breathing spontaneously throughout sedation. In the ABM group f_R decreased from baseline values, but remained in the reference range for cats (2). These findings are consistent with studies reporting alfaxalone administration up to 5 mg/kg IM in cats (9, 10). In a study in cats sedated with IM alfaxalone-butorphanol, f_R was also maintained in the reference range (14). In a study investigating target alfaxalone plasma concentrations in cats, only supraclinical plasma concentrations produced hypoventilation ($PaCO_2$>45 mmHg; f_R was not reported) (20). Administration of IM medetomidine (0.05-0.08 mg/kg) (3, 4) or dexmedetomidine (0.01 mg/kg) and butorphanol (0.2 mg/kg) (24) in cats resulted in a significant decreased f_R. At the present study the f_R was higher in the MBM group at the first 20 minutes of sedation. High f_R may be caused by hypoxemia and/or hypercarbia (25). SpO_2 lower than 90% was observed only in 3 cats in the MBM group, however PaO_2 nor $PaCO_2$ were measured. Pulse oximetry have ac-

curacy limitations, such as movement, skin pigmentation, and vasoconstriction (25). The SpO_2 measurements in the MBM group could have been affected by vasoconstriction in the first 20 minutes following drug administration.

In both groups RT decreased over time. Hypothermia following medetomidine was related to muscle relaxation or to α_2-receptors type C2, which are present in the spinal cord and are thought to be involved in thermoregulation (26). In the ABM group the decrease in RT was consistent with other studies in cats sedated with alfaxalone and can be explained by muscle relaxation and vasodilation (9, 13, 21). Therefore, during both sedation protocols it is recommended to monitor RT and provide external heat when needed.

The reference range of MAP in adult awake companion animals is 80-120 mmHg, and under anesthesia MAP should be kept above 60 mmHg (25). However, it was reported in cats that kidney autoregulation is lost below 70 mmHg (27). In the ABM group MAP was generally kept in the acceptable range, except for three readings (three different cats) in which MAP was below 60 mmHg. However, in all three low MAP events the cats were moving during measurement, which may suggest that measurements were less accurate (25). Other studies reporting hypotension in cats following alfaxalone used higher alfaxalone doses (5-15 mg/kg) (9, 10, 21). In a study characterizing hemodynamic effects of subclinical, clinical and supraclinical plasma alfaxalone concentration in cats, MAP decreased with increasing plasma target concentration, although MAP values were higher than 87 mm Hg at all plasma concentrations (20). In the MBM group a biphasic blood pressure pattern was demonstrated, starting with high MAP during the first 20 minutes, followed by a gradual decrease. This biphasic pattern was reported previously (5, 24, 28), and is attributed to the initial peripheral vasoconstriction followed by a secondary central vasodilation (23).

The youngest cat in the ABM group woke up 20 minutes following injection, which could be related to the report that $GABA_A$ receptors subunits β_2 and β_3 have different number and distribution in younger animals, and may have an impact on binding properties of drugs to $GABA_A$ (29, 30). Since alfaxalone functions as a positive modulator of $GABA_A$, an age-related difference may influence alfaxalone affinity to its receptor. Another explanation for the difference could be related to metabolism, which may be quicker in younger animals (31). This can also explain the observation that older cats in the ABM group took longer to recover.

The advantage of adding butorphanol and midazolam to the sedation protocol is their sedative effect and synergism, making the sedation more reliable, while minimally affecting cardiopulmonary function (26, 32, 33). Butorphanol also has analgesic property, which is important when painful procedures are planned (32). Alfaxalone 2.5 mg/kg IM resulted in 60 minutes of anesthesia (from recumbency until the cat was standing), while 5-10 mg/kg provided longer anesthetic duration (9). Combination of 2 mg/kg alfaxalone and 0.2 mg/kg butorphanol IM in cats resulted in 32.1-44.1 minutes sedation until seating/sternal recumbency (14, 16, 34). Sedation duration in the present study was longer probably due to the addition of midazolam.

Recovery time and recovery quality were significantly better in the MBM group, because the ability to antagonize medetomidine, which were expected. Adverse effects observed in the ABM group were reported previously in cats following alfaxalone sedation (9, 14, 15), although a study administering alfaxalone-butorphanol reported smooth recovery (16). A different study, reported poor and prolonged recovery following 5 mg/kg alfaxalone, 0.01 mg/kg dexmedetomidine with/without 0.1 mg/kg hydromorphone, however atipamezole was not administered (12). In the present study an additional alfaxalone dose resulted in decreased recovery score, which was reported previously (35, 36). These findings suggest that lower alfaxalone doses should be used in cats, although it is important to note that the adverse effects were minor and resolved without any treatment within an hour following the procedure.

Limitations to this study include (i) suboptimal comparison between an anesthetic and a sedative drug, which were not administered at equipotent doses, although, to the authors' knowledge such doses were not reported in the literature. (ii) Due to the clinical nature of the study, there was no uniformity as to the procedure, procedure length, pain or noise levels, which could have affected sedation and recovery qualities. (iii) Baseline data was lacking because of the cats' temperament, and because procedural limitations, some data was not collected. (iv) Most cats were young and healthy, and it is unknown whether old and/or sick cats would respond differently to these sedation protocols. Additionally, cats' age and weight were statistically different between groups, which could have potentially affected physiological values and sedation time. (v) Sedation quality scoring was developed by the observer instead of using previously reported scoring

systems. (vi) Direct measurements of MAP and SpO2 are more accurate than indirect techniques, but these could not be established in this clinical study due to the more invasive nature of such techniques.

CONCLUSIONS

ABM administered IM produced short sedation that allowed minor procedures in healthy cats and provided cardiopulmonary stability in comparison to MBM. As a third of the cats required an additional dose, it is suggested that in young/fractious cats a higher alfaxalone dose (2.5-3 mg/kg) may be required. In contrast, our clinical experience suggests that in geriatric/sick cats alfaxalone dose of 1-1.5 mg/kg is sufficient with this combination. During recovery some cats may experience some short-lived opisthotonos and twitching.

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