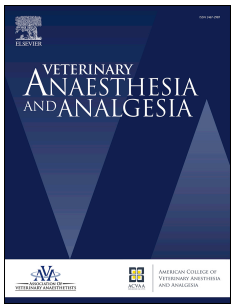

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Sedative effects and changes in cardiac rhythm with intravenous premedication of medetomidine, butorphanol and ketamine in dogs

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Running head:

Four premedication protocols in healthy dogs

Authors' contributions

BS: study design; acquiring patients; collection, analysis and interpretation of data; preparation of manuscript.

CV: study design, data analysis and interpretation, preparation of manuscript.

EES: study design; collection, analysis and interpretation of data; preparation and critical revision of manuscript.

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None

Conflict of interest statement

The authors declare no conflict of interest.

Abstract

Objective

To determine the sedative effects and characteristics of cardiac rhythm with intravenous premedication of medetomidine, butorphanol and ketamine in dogs.

Study design

Prospective, blinded, randomized clinical trial.

Animals

A total of 116 client-owned healthy dogs undergoing elective surgery.

Methods

Dogs were randomized to receive medetomidine 5 μg kg^{-1} (group M), butorphanol 0.2 mg kg^{-1} (group B), a combination of medetomidine 5 μg kg^{-1} and butorphanol 0.2 mg kg^{-1} (group MB) or medetomidine 5 μg kg^{-1}, butorphanol 0.2 mg kg^{-1} and ketamine 1 mg kg^{-1} (group MBK) intravenously (IV). Sedation was assessed using a numerical descriptive scale. Heart rate (HR) and rhythm were monitored; propofol dose (mg kg^{-1} IV) to allow orotracheal intubation was documented. Data were analysed using ANOVA, accounting for multiple testing with the Tukey honest significant difference test.

Results

Sedation scores varied significantly between all groups at all timepoints, except between MB and MBK at the four timepoints. HR decreased in all groups: most in M and MB, least in B. HR in MBK was initially higher compared to M and MB. Arrhythmias occurred in all groups: group B showed 2nd degree atrioventricular blocks

occasionally, all other groups showed additionally ventricular escape complexes and bundle branch blocks.

Dose of propofol required for orotracheal intubation was significantly higher in group B (5.0 ± 2.0 mg kg^{-1}) compared to group M (2.6 ± 0.6 mg kg^{-1}). Although no difference could be demonstrated between groups MB (1.4 ± 0.6 mg kg^{-1}) and MBK (0.9 ± 0.8 mg kg^{-1}), both groups required significantly less propofol than group M.

Conclusion and clinical relevance

Medetomidine-based premedication protocols led to various bradyarrhythmias. Addition of subanaesthetic doses of ketamine to medetomidine-based protocols resulted in higher HRs, fewer bradyarrhythmias and fewer animals that required propofol for intubation without causing side effects in healthy dogs.

Keywords butorphanol, ECG, ketamine, medetomidine, premedication

Introduction

Medetomidine is an α_2-adrenoceptor-agonist commonly used alone or in combination with opioids such as butorphanol to achieve sedation in dogs (Ko et al. 1996; Muir et al. 1999; Yamashita et al. 1999; Ko et al. 2000; Girard et al. 2010; Puighibet et al. 2015). It provides dose-dependent moderate to profound sedation and analgesia (Nilsfors et al. 1989) which is associated with severe bradycardia predominantly caused by vasoconstriction. Vasoconstriction results in increased arterial pressure and vomiting during the onset of sedation (Nilsfors et al. 1989; Hellebrekers et al. 1998; Pypendop & Verstegen 1998; Kuo & Keegan 2004; Gómez-Villamandos et al. 2006). Butorphanol is a synthetic opioid that acts mainly as κ-opioid receptor-agonist and a partial antagonist at the μ-opioid receptor (KuKanich & Papich 2018). The sedative qualities of butorphanol are mild to moderate with little effect on the cardiovascular and respiratory systems (Trim 1983; Tyner et al. 1989). In addition, butorphanol at a dose of 0.4 mg kg^{-1} proved effective in preventing cisplatin-induced vomiting (Moore et al. 1994). Combined with medetomidine, butorphanol enhances the sedative effect of medetomidine (Ko et al. 1996; Girard et al. 2010; Puighibet et al. 2015) while preventing vomiting induced by medetomidine (Yamashita et al. 1999). Ketamine is a phencyclidine derivative that acts as an agonist on the N-methyl-D-aspartate receptor. It is an induction agent that stimulates sympathetic activity resulting in an increase in heart rate (HR) (Kennedy & Smith 2015; White & Yates 2017) and arterial blood pressure (Traber et al. 1970). Synergistic effects of medetomidine, opioids and ketamine in various combinations have been described in several studies and the combination seems to be safe for use in healthy small animals (Tomizawa et al. 1997; Sylvestre et al. 2020; Arenillas et al. 2021).

The objective of this study was to evaluate the overall benefit of adding ketamine to commonly used premedication protocols based on butorphanol and medetomidine. Therefore, the first aim of this study was to compare numerical sedation scores in dogs given medetomidine alone (group M), butorphanol alone (group B), medetomidine and butorphanol combined (group MB) or a combination of medetomidine, butorphanol and ketamine (group MBK) as intravenous premedication. The second aim was to determine the effect of each protocol on HR and the incidence of cardiac arrhythmias. The final aim was to compare the amount of propofol required to allow orotracheal intubation between groups. We hypothesized that the addition of ketamine to medetomidine and butorphanol would have the following effects: a shorter onset and deeper sedation level, less pronounced bradycardia, fewer cardiac arrhythmias and a lower dose of propofol required for orotracheal intubation (Väisänen et al. 2002).

Material and methods

This prospective, blinded, randomized clinical study was conducted in the Clinic of Anaesthesiology and perioperative Intensive Care of the Vetmeduni Vienna, Austria. The protocol was discussed and approved by the Institutional Ethics and Welfare Committee in accordance with good scientific practice guidelines and national legislation (BMWFW-68.205/0221-WF/V/3b/2016). All owners provided informed written consent prior to their dogs´ participation in the study.

Animals

A total of 116 client-owned adult dogs [American Society of Anesthesiologists (ASA) physical status I and II] that were eligible for elective surgery were enrolled in this study (Table 1). In designing this study, a power analysis was performed regarding the

84 expected effects of premedication on the level of sedation. Calculations indicated that a
85 minimum of 25 animals per group would be required. The sample size of 29 dogs per
86 group was selected to allow for possible failures, such as equipment malfunction.
87 Previous studies have used a similar number of animals (Raszplewicz et al. 2013).
88 Individuals were included in the study if they were at least 12 months old and weighed
89 between 8 and 45 kg. Doberman Pinscher, Pinscher and Boxer dogs were excluded from
90 the study.

91 Instrumentation and study design

92 Dogs were presented at the small animal clinic on the day of the procedure and were
93 kept in a quiet room to avoid any interference from a noisy and busy hospital
94 environment. Food but not water was withheld for 8 to 12 hours before general
95 anaesthesia. Each dog was weighed and clinically examined. A 20-gauge, 3.3 cm
96 catheter (Vasofix; B. Braun Melsungen AG, Germany) was inserted either into the
97 cephalic or the saphenous vein.

98 Dogs were randomly allocated to one of four groups by drawing pre-labelled pieces of
99 paper from an envelope: medetomidine 5 µg kg^{-1} (NarcoStart; Le Vet B.V.,
100 Netherlands) (group M), butorphanol 0.2 mg kg^{-1} (Alvegesic; ALVETRA u. WERFFT
101 GmbH, Austria) (group B), medetomidine 5 µg kg^{-1} in combination with butorphanol
102 0.2 mg kg^{-1} (group MB) or medetomidine 5 µg kg^{-1} in combination with butorphanol
103 0.2 mg kg^{-1} and ketamine 1 mg kg^{-1} (Ketamidor; Richter Pharma AG, Austria) (group
104 MBK). Drugs were drawn up in a syringe and diluted to 0.1 mL kg^{-1} with 0.9% saline.
105 The randomization as well as the preparation of drugs was performed in such a fashion
106 that the evaluator of the outcome variables was blinded to the allocated group. A Holter-
107 electrocardiogram (ECG; Televet 100; Engel Engineering Service GmbH
108 Heusenstamm, Germany) was placed on the dog at least 15 minutes before recording 10

minutes of baseline ECG (BL ECG). HR and rhythm were recorded, and animals with consistent pre-existing arrhythmias were excluded from the study. Premedication was administered intravenously over a period of 20 seconds immediately after starting a second ECG recording (treatment ECG) with a minimal recording time of 21 minutes. Adverse events such as signs of nausea, vomiting and apnoea for more than 15 seconds were noted. Sedation scores were evaluated and documented by the main observer before and 5, 10, 15 and 20 minutes after drug administration using a numerical descriptive scale (NDS) modified from Gurney et al. (2009) (Appendix A). Categories included were overall appearance, spontaneous posture, response to noise (handclap), eye position, palpebral reflex, and toe-pinch response, resulting in a possible score between 0 (no sedation) and 16 (maximum sedation). Scores up to 5 were categorized as mild sedation, 5 to 10 as moderate sedation and greater than 10 as profound sedation. Oxygen (FIO_2 = 1.0, 4 L minute^{-1}) was provided with a mask attached via a circle system to an anaesthesia machine (Leon plus; Heinen + Löwenstein GmbH, Austria) as soon as the animal tolerated it without struggling. After recording the ECG for 20 minutes, general anaesthesia was induced with propofol 1% (Propofol "Fresenius" 1%; Fresenius Kabi GmbH, Austria) according to a predetermined scheme. Dogs were given 1 mg kg^{-1} propofol over 20 seconds followed by a pause of 40 seconds after which orotracheal intubation was attempted. If this was unsuccessful owing to a light level of anaesthesia, a further bolus of 1 mg kg^{-1} was administered followed by a 40 second pause. Beginning with the third bolus, the dose of propofol was reduced to 0.5 mg kg^{-1}. This was continued until successful intubation was achieved. Total administered dose of propofol (mg kg^{-1}) was noted. ECG recordings were analysed after completion of the study. Average HR was calculated for the unpremedicated animal using baseline ECG. HR in sedated dogs was calculated for the following periods: 1-6 minutes, 6-11 minutes, 11-16 minutes, and 16-21 minutes after start of the treatment ECG. In case of

equipment failure, lost electrodes or unreadable ECG passages, HR was calculated using at least 1 minute of unaffected recording in the observed period. The quantity and quality of arrhythmias occurring during the observation period were documented for each animal. Recorded data were entered into a Microsoft Excel spreadsheet (Microsoft Corporation, WA, USA).

Statistics

Linear models were used for analysis with the target variables: numerical descriptive score, the difference in the log of HR before and after sedation, and log of propofol administered (mg kg^{-1}). With sedation score and HR as target variables, groups were compared at different time-points (5, 10, 15 and 20 minutes); with propofol as target variable, the total amount was compared among groups. In all cases, Tukey honest significant difference (HSD) tests of pairwise differences were employed to account for multiple testing. With the sedation score and HR as target variables, within each group differences among time-points or time periods were analyzed with a linear model [Analysis of variance (ANOVA)] where time and individual were included as factors. Arrhythmias occurred rarely, but then clustered, such that linear model assumptions would have been violated. Results with this target variable are therefore only presented descriptively. As data on arrhythmias were not normally distributed, the results with this outcome variable are only presented descriptively. Occurrence and type of arrhythmia were counted for each group in the observed time periods (1-6, 6-11, 11-16 and 16-21 minutes). Statistical analyses were performed using the R-programming language (R Core Team 2017). For all statistical analyses, a *p*-value below 5% ($p < 0.05$) was considered statistically significant.

Results

A total of 116 dogs were included in this study, four of which were excluded from further analysis. Reasons for exclusion were multiple premature ventricular extrasystoles (VPCs) in the baseline ECG in one dog in group M, ventricular escape complexes and bundle branch block (BBB) in treatment ECG in one dog in group MB, which was therefore given atipamezole (Narcostop, Le Vet B.V., Netherlands), technical problems in one dog in group MBK and a sudden cancellation of the surgical procedure in one dog in group MB. Another two dogs each presented with two VPCs in the 10-minute baseline ECG but remained in the study. Therefore, a total number of 112 dogs were studied (group B: $n = 29$; group M: $n = 28$; group MB: $n = 27$; group MBK: $n = 28$).

In two dogs from group B, propofol was not administered using the standardized scheme but faster due to signs of excitation. Signs of nausea were observed in one dog (3%) of group B and in 2 dogs (7%) of group M. While eight dogs (29%) in group M vomited. No other adverse effects such as apnoea for more than 15 seconds were observed.

All dogs showed increased sedation compared to baseline values (median 0.0; $p < 0.001$). With the numerical sedation score as target variable, the timepoint (5, 10, 15, 20 minutes) had a significant overall influence ($p < 0.001$) with sedation increasing with time in all dogs. For all timepoints, the influence of group (M, B, MB, and MBK) was significant. At all timepoints, group B had the lowest sedation score (median 1.0-3.0), group M a moderate sedation score (median 6.0-9.0) and groups MB and MBK had high sedation scores (MB: median 12.0-15.0; MBK: median 13.0-15.0) (Fig. 1). For all timepoints, comparisons among groups (adjusted for multiple testing by Tukey's HSD) showed significant differences ($p < 0.0001$) for all pairs except between MB and MBK,

185 which was not significant at any timepoint (Fig. 1). The highest sedation score (16) was
186 observed exclusively in two dogs of the MBK group.

187 An overall decrease in HR compared to baseline ECG was observed in all groups ($p <$
188 0.001). Group B showed overall a mild reduction of HR with some variation: in five
189 dogs, HR even increased more than 20% in at least one of the observed time periods.
190 All protocols that included the use of medetomidine showed a further decrease in HR.
191 Dogs in group B showed consistently higher HR compared to all other groups. Groups
192 M and MB showed the most distinct bradycardia (group M 46-52% and group MB 46-
193 52% from baseline values) (Fig. 2). At all time periods, the influence of group (M, B,
194 MB, and MBK) was significant and groups M and MB had the lowest HR (compared to
195 baseline). However, pairwise comparisons between M and MB groups did not show
196 significant differences in HR at any time period (adjusted for multiple testing by
197 Tukey's HSD). HR in group MBK was higher than in groups M and MB only at time
198 periods 5 and 10 minutes ($p < 0.05$). Differences between MBK and both M and MB
199 groups became smaller and not statistically significant at time periods 15 and 20
200 minutes (Fig 2). In group MBK three dogs showed a higher HR than baseline values: in
201 one dog this increase was observed during the first 5 minutes (118% of BL), in another
202 dog during the first 5 and 10 minutes (140% and 125% of BL, respectively) and in
203 another dog for 15 minutes (128%, 143% and 105% of BL).

204 Arrhythmias were detected in all groups after premedication. Second degree AV blocks
205 were detected in 19 dogs (68%) for group M, three dogs (10%) for group B, 14 dogs
206 (48%) for group MB and 12 dogs (43%) for group MBK. Ventricular escape complexes
207 were detected in three dogs (11%) for group M, zero dogs (0%) for group B, six dogs
208 (21%) in group MB and two dogs (7%) in group MBK. BBBs were detected in two
209 dogs (7%) in group M, zero dogs (0%) for group B, three dogs (10%) in group MB and

one dog (4%) in group MBK. In order to compare the total occurrence of arrhythmias between the groups, all arrhythmic beats were summed per group over the observation period of 20 minutes. The lowest number of arrhythmias was observed in group B, which consisted exclusively of second degree atrioventricular (AV) blocks, $n = 64$). Dogs of group M showed a total of 947 second degree AV blocks ($n = 947$), ventricular escape complexes ($n = 11$) and BBB ($n = 8$). A single dog in group M presented eight ventricular escape complexes, at least one occurring every 5 minutes and six BBB in the first 5 minutes; during baseline ECG two VPCs were observed. A total of 548 second degree AV blocks, 286 ventricular escape complexes and 117 BBB were observed in group MB. Two dogs accounted for the majority of ventricular escape complexes and BBB in group MB. Most arrhythmias occurred in the first 10 minutes after premedication (268 ventricular escape complexes and 114 BBB), in the last 10 minutes 18 ventricular escape complexes and three BBB were observed. Of all the protocols containing medetomidine, group MBK showed the fewest arrhythmias: 173 second degree AV blocks, seven ventricular escape complexes and one BBB (Table 2).

The administered dose of propofol per kg required to allow orotracheal intubation varied significantly ($p = 0.001$) among groups (Fig. 3). Group B required significantly more propofol than all other groups (5.0 ± 2.0 mg kg^{-1}), followed by group M (2.6 ± 0.6 mg kg^{-1}). A single dog in group MB and 10 dogs in group MBK did not require any propofol to allow orotracheal intubation 21 minutes after premedication. The remaining dogs in MB and MBK groups required the smallest amount of propofol (1.4 ± 0.6 mg kg^{-1} and 0.9 ± 0.8 mg kg^{-1}, respectively), but no significant difference was observed between groups.

Discussion

The results of this study indicate that the administration of different premedication protocols produced different levels of sedation; dogs in group B showed mild sedation, dogs in group M moderate sedation, and dogs in groups MB and MBK showed profound sedation. A decrease in HR was observed in all groups. While it was mild in group B, it resulted in severe bradycardia and bradyarrhythmias in all groups that received medetomidine. However, bradyarrhythmias were less frequently observed when ketamine was added (group MBK). It seemed that the required amount of propofol to achieve orotracheal intubation decreased with increasing sedation scores.

The doses of medetomidine (5 µg kg^{-1}) , butorphanol (0.2 mg kg^{-1}) and ketamine (1 mg kg^{-1}) were chosen to provide a measurable level of sedation when used individually while still being within the published dose ranges for use within a combination (Muir et al. 1999; Yamashita et al. 1999; Ko et al. 2013; Kellihan et al. 2015). Premedication with only ketamine (1 mg kg^{-1}) was discarded because of the possible adverse effects. Not all effects occurred as anticipated.

As expected, administration of butorphanol achieved the lowest sedation score in this study, followed by moderate sedation with medetomidine (Girard et al. 2010). The difference in onset and depth of sedation between groups MB and MBK did not reach statistical significance, as onset was similar and dogs in both groups scored mostly in the upper range of the scale and were profoundly sedated. As previously described, the addition of butorphanol to medetomidine prevented signs of nausea and vomiting (Yamashita et al. 1999). Numerical descriptive scores have often been used to evaluate the level of sedation in dogs (Grint et al. 2009; Gurney et al. 2009; Girard et al. 2010; Raszplewicz et al. 2013; Arenillas et al. 2020). These scales allow high consistency and very good reliability when assessing sedation levels, even between multiple raters (Wagner et al. 2017). However, in this study, evaluation was limited due to

instrumentation, for example: part of the original sedation scale includes “resistance against lateral recumbency”, which could not be performed because it would have disturbed the ECG reading. To compensate for this, we decided to add the variable “toe pinch response” and used more detailed criteria for “spontaneous posture”. Both criteria were used in a study published by Girard et al. (2010). The inclusion of further variables in the scoring system , such as “jaw and tongue relaxation” might have revealed finer differences in sedation outcomes between groups MB and MBK.

Changes in HR (Pypendop & Verstegen 1998; Gómez-Villamandos et al. 2006; White & Yates 2017; Kato et al. 2021) and the occurrence of arrhythmias (Kramer et al. 1996) with the studied drugs have been described in previous studies. However, we are unaware of a direct comparison between a single premedication drug *versus* a drug mixture without the addition of other drugs (i.e., parasympatholytic drugs). A decrease in HR was observed in all groups; group B showed overall a mild reduction of HR, although some dogs had even higher HRs than at those BL. Although all precautions were taken to create a quiet and undisturbed study environment, some of these increases in HR may be attributed to environmental disturbances (Trim 1983) for example noise from outside (barking dogs, lawnmowers) and from within the animal hospital (doors slamming, shouting, people accidentally entering the study room). In other dogs, the stress of an unfamiliar environment may have been too great to be eased with butorphanol alone. One of these dogs even started growling and showed excitation during induction. In the first 10 minutes, HRs of dogs in group MBK decreased significantly from BL values compared to groups M and MB ($p < 0.05$). This “stabilization” of HR was described in other studies (Moens & Fargetton 1990; Arenillas et al. 2021) and was probably caused by the indirect sympathomimetic effects of ketamine (Traber et al. 1970; White et al. 1982). Owing to its limited duration of

285 action (Vlerick et al. 2020), these effects subsided over time (White & Yates 2017;
286 Vlerick et al. 2020).

287 As expected, arrhythmias in group B were sporadic and associated with mild
288 bradycardia. All dogs given medetomidine showed more arrhythmias, most of them in
289 group MB. Two dogs with no arrhythmias in their BL ECG were responsible for most
290 of the observed ventricular escape complexes and BBB in group MB, with most
291 arrhythmias occurring in the first 10 minutes (275 ventricular escape complexes + 114
292 BBB). Atipamezole was given to one of these two dogs, at 12 minutes and 50 seconds
293 after premedication due to safety concerns and arrhythmias ceased immediately after
294 that. The second dog's cardiac rhythm spontaneously returned to normal sinus rhythm 9
295 minutes after premedication. Owing to the clustered occurrence of cardiac arrhythmias
296 in the MB group, no statistical analyses could be performed. However, it could be a
297 coincidence that the dogs in group MBK had the lowest number of arrhythmias among
298 the medetomidine-based premedications. More likely this effect may have been caused
299 by an increase in sympathetic tone produced by ketamine (Traber et al. 1972; White et
300 al. 1982), resulting in a higher HR in MBK for the first 10 minutes. This increased
301 sympathetic tone may be a critical advantage during sedation with minimal monitoring,
302 such as radiographs. Even in the clinical setting, the first few minutes after
303 premedication are rarely monitored as well as after induction of general anaesthesia.
304 Furthermore, orotracheal intubation represents a potential vagal stimulus that could
305 affect HR and rhythm.

306 As observed in other studies (Väisänen et al. 2002; Canfrán et al. 2016), the amount of
307 propofol needed to achieve orotracheal intubation was inversely correlated with the
308 level of sedation provided by the four premedication protocols. Dogs of group B with
309 mild sedation needed the largest amount of propofol, moderately sedated dogs of group

M required less propofol and profoundly sedated dogs of group MB and MBK needed the smallest amount of propofol. Although no statistical difference in the requirement of propofol could be demonstrated between groups MB and MBK, it is noteworthy that 10 dogs in group MBK did not require any propofol at all, compared to only one dog in group MB. Using a different induction scheme or a constant rate infusion of propofol may have shown significant differences in propofol dose. An attempt to achieve orotracheal intubation 10 minutes after premedication may have resulted in even fewer dogs in group MBK requiring propofol to allow orotracheal intubation. Due to the limited duration of action of ketamine, the dogs may have redistributed or metabolized most of the ketamine at the time of anaesthetic induction in our study (Schmitz et al. 2010; Vlerick et al. 2020). Other studies have shown reduced requirements of induction agents after the administration of subanaesthetic doses of ketamine (Bustamante et al. 2020) or the use of two induction agents (Kennedy & Smith 2015).

Healthy dogs (ASA I-II), at least 12 months old with a bodyweight between 8 and 45 kg, were selected owing to safety concerns for the dogs - the administration of an α_2-adrenoceptor-agonist - and for practical reasons (permanent ECG monitoring had to be placed on the dog). The maximum weight of 45 kg was chosen to limit the impact of allometry but also to demonstrate the utility of these drugs in clinical practice. Purebred Doberman Pinschers, Pinschers and Boxers were excluded as a precaution, since heart disease is particularly common in these dogs (Wess et al. 2010a). Although all dogs appeared healthy on clinical examination, three dogs in this study had cardiac arrhythmias before premedication administration. A 2-year-old Labrador Retriever did not undergo general anaesthesia owing to frequent VPCs and died 3 weeks later without apparent cause. Therefore, and in accordance with (Wess et al. 2010b) a 5 minute ECG before anaesthetic premedication may be useful to detect potentially undiagnosed arrhythmias, and increase the safety of the procedure.

Conclusion

All premedication protocols evaluated in the present study in healthy dogs resulted in sedation. Sedation levels increased over the study period, giving the drugs time to reach targeted effects. Medetomidine based combinations caused more bradyarrhythmias compared to butorphanol alone. Second degree AV blocks occurred most frequently, but ventricular escape complexes and BBB were also observed in the first 10 minutes after premedication. Hence, dogs premedicated with IV medetomidine should be monitored closely. Adding ketamine to medetomidine premedications increased the HR and reduced the incidence of arrhythmias, and therefore their combination is advisable, especially in clinical situations with limited monitoring.

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Appendix A Numerical descriptive scale for assessing degree of sedation in dogs.

Overall appearance	0 awake and normal
	1 tranquil
	2 stuporous
Spontaneous posture	0 standing no effect
	1 standing but tired
	2 lying but able to rise
	3 sternally recumbent
	4 laterally recumbent
Response to noise (handclap)	0 body movement
	1 head movement
	2 ear twitch
	3 no reaction
Eye position	0 normal
	2 rotated ventrally
Palpebral reflex	0 brisk
	1 slow
	2 absent
Toe-pinch response	0 normal
	1 slight damping
	2 moderate damping
	3 no response

Reproduced and modified from Gurney et al. (2009)

Figure legends

Figure 1 Sedation score of dogs 5 (a), 10 (b), 15 (c) and 20 minutes (d) after premedication with intravenous medetomidine 5 µg kg^{-1} [(M), *n* = 28], butorphanol 0.2 mg kg^{-1} [(B), *n* = 29], medetomidine 5 µg kg^{-1} in combination with butorphanol 0.2 mg kg^{-1} [(MB), *n* = 27] or medetomidine 5 µg kg^{-1} in combination with butorphanol 0.2 mg kg^{-1} and ketamine 1 mg kg^{-1} [(MBK), *n* = 28]. *Significant difference in sedation score between groups ($p < 0.001$). Data are presented as median (horizontal line), interquartile range (box ends), 1.5 times the interquartile range (whiskers), with values exceeding the whiskers plotted as open circles.

Figure 2 Ratio of HR compared to baseline values of dogs in time periods 1-6 (a), 6-11 (b), 11-16 (c) and 16-21 minutes (d) after premedication with intravenous medetomidine 5 µg kg^{-1} [(M), *n* = 28], butorphanol 0.2 mg kg^{-1} [(B), *n* = 29], medetomidine 5 µg kg^{-1} in combination with butorphanol 0.2 mg kg^{-1} [(MB), *n* = 27] or medetomidine 5 µg kg^{-1} in combination with butorphanol 0.2 mg kg^{-1} and ketamine 1 mg kg^{-1} [(MBK), *n* = 28]. *Significant difference in HR ($p < 0.001$). †Significant difference in HR ($p < 0.05$). Data are presented as median (horizontal line), interquartile range (box ends), 1.5 times the interquartile range (whiskers), with values exceeding the whiskers plotted as open circles.

Figure 3 Propofol dose (mg kg^{-1}) required to achieve endotracheal intubation of dogs, approximately 22 minutes after premedication with intravenous medetomidine 5 µg kg^{-1} [(M), *n* = 28], butorphanol 0.2 mg kg^{-1} [(B), *n* = 29], medetomidine 5 µg kg^{-1} in combination with butorphanol 0.2 mg kg^{-1} [(MB), = 27] or medetomidine 5 µg kg^{-1} in combination with butorphanol 0.2 mg kg^{-1} and ketamine 1 mg kg^{-1} [(MBK), *n* = 28]. *Significant difference in

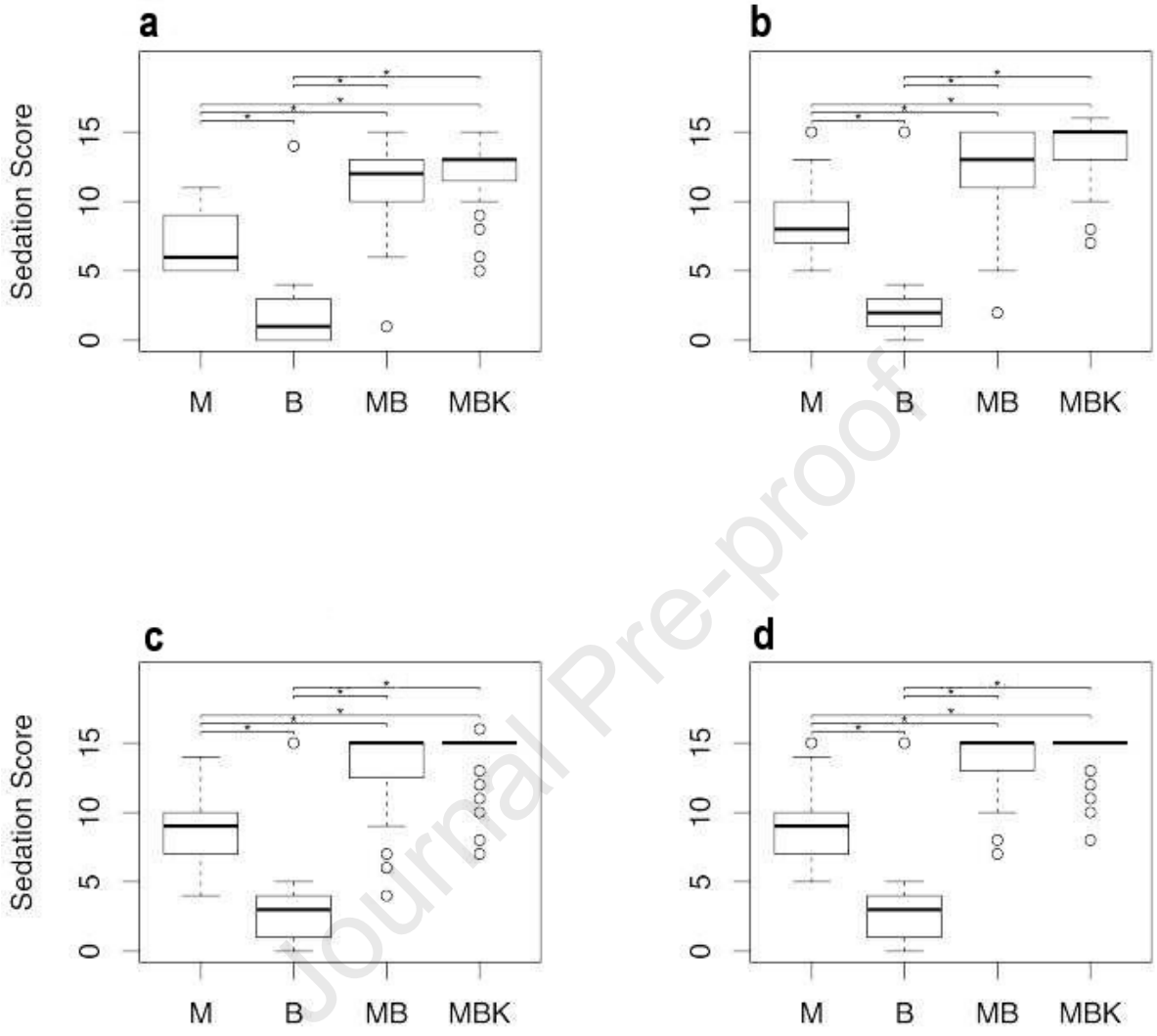
propofol dose ($p < 0.001$). †Significant difference in HR ($p < 0.01$). Data are presented as median (horizontal line), interquartile range (box ends), 1.5 times the interquartile range (whiskers), with values exceeding the whiskers plotted as open circles.

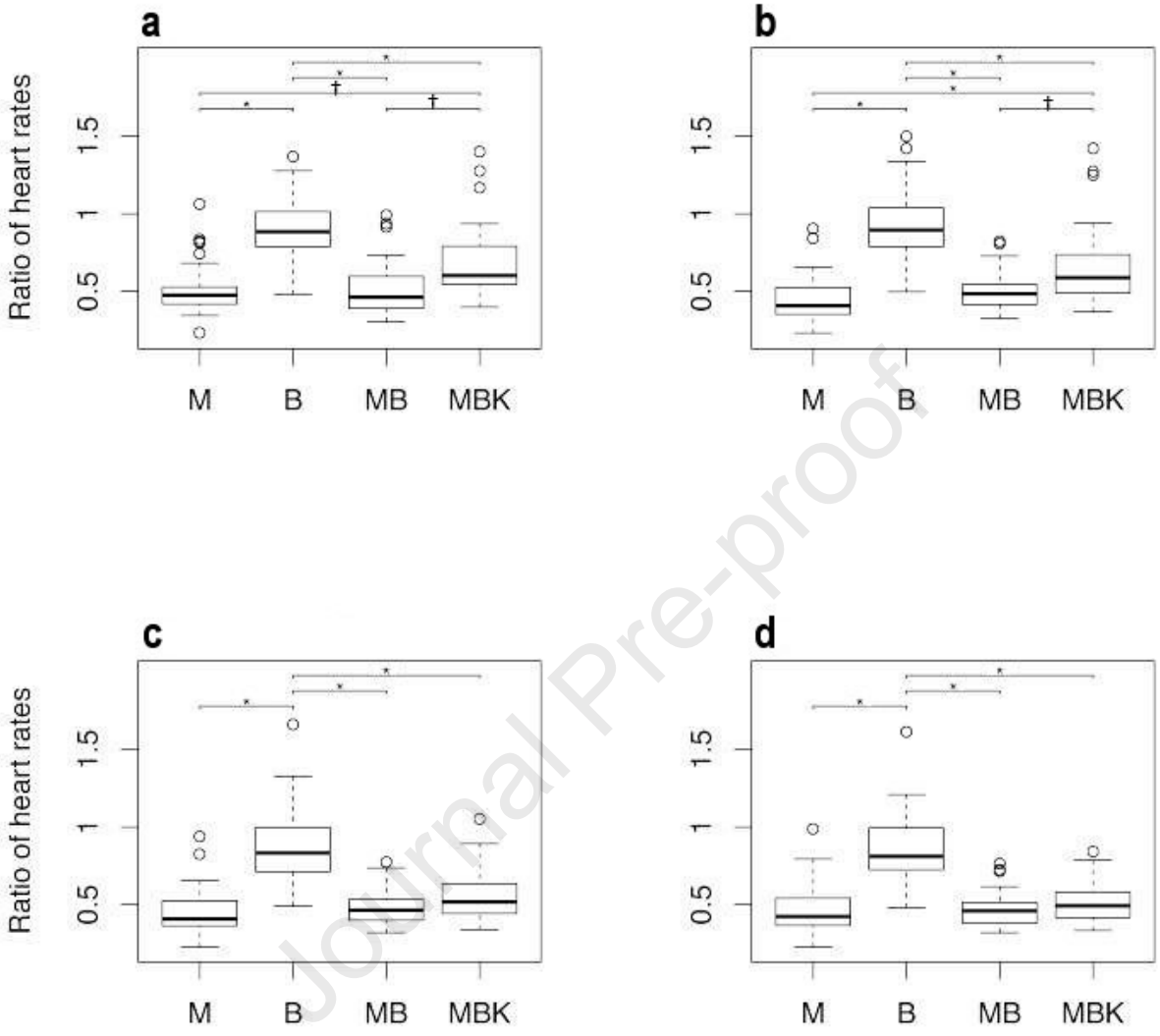
Table 1 Demographic information of the 116 dogs enrolled in the study and the reason for anaesthesia. The dogs were randomly allocated to four study groups medetomidine 5 μg kg^{-1} (M), butorphanol 0.2 mg kg^{-1} (B), medetomidine 5 μg kg^{-1} in combination with butorphanol 0.2 mg kg^{-1} (MB) or medetomidine 5 μg kg^{-1} in combination with butorphanol 0.2 mg kg^{-1} and ketamine 1 mg kg^{-1} (MBK) IV. Age (months) is presented as range from youngest to oldest and mean in brackets. Weight (kg) is presented as range from lightest to heaviest and mean in brackets. Sex is presented in total numbers for male (m), male castrated (mc), female (f) and female spayed (fs) dogs. Type of procedures performed are listed as total numbers for each group and were assigned to five categories (castration, ophthalmologic procedure, dental procedure, biopsy and other).

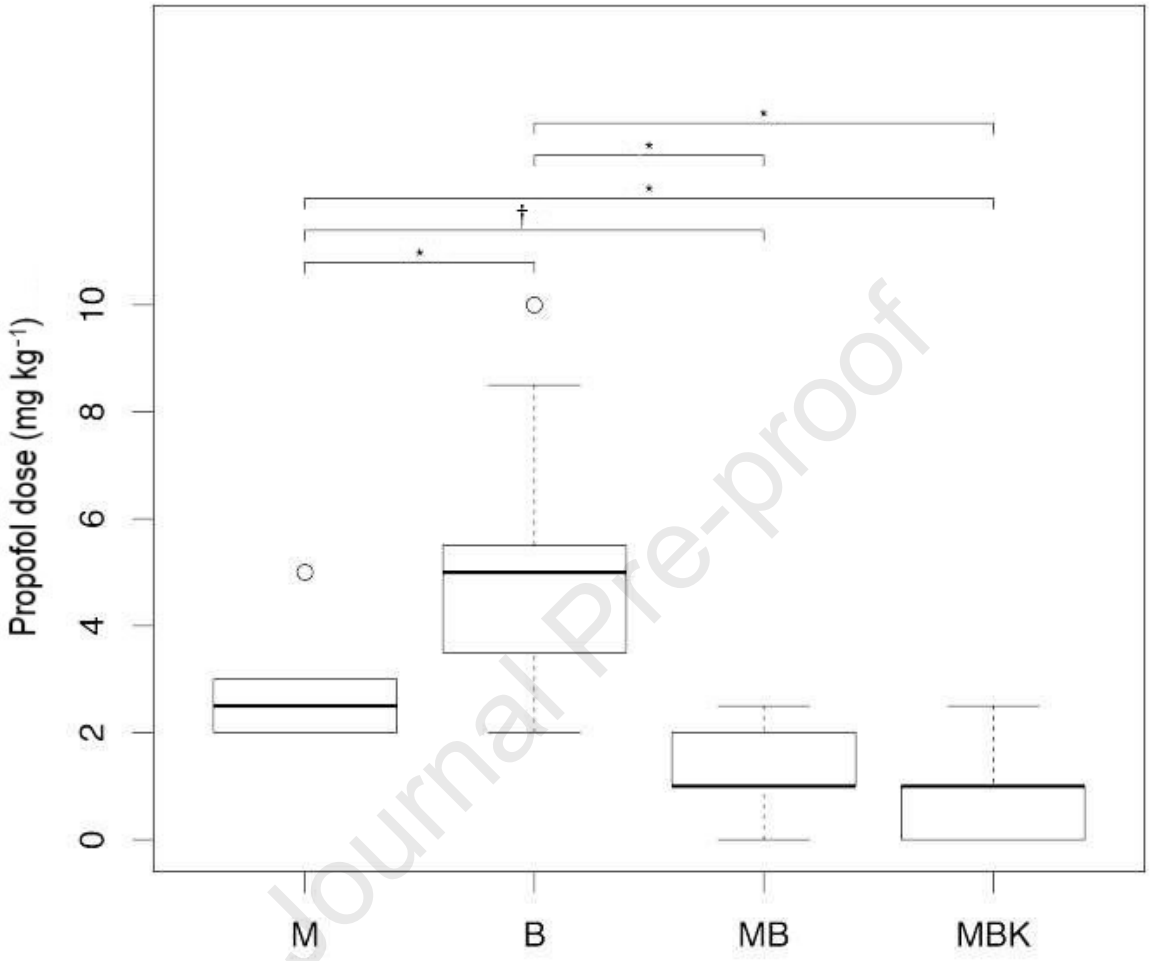
Group	Demographic information			Procedure performed				
	Age (months)	Weight (kg)	Sex (m/mc/ f/fs)	Castration	Ophthalmological procedure	Dental procedure	Biopsy	Other
M	12-116 (58)	8.7-39.0 (22.4)	13 m 2 mc 10 f 4 fs	9	6	6	4	4
B	14-100 (41)	8.2-40.2 (23.4)	10 m 2 mc 11 f 6 fs	13	7	7	1	1
MB	12-132 (49)	9.7-40.3 (24.1)	7 m 4 mc 15 f 3 fs	15	5	6	1	2
MBK	12-88 (29)	9.3-45.0 (26.9)	17 m 1 mc 9 f 2 fs	19	4	6	0	0

Table 2 Type of arrhythmia, time (minutes) after intravenous administration of premedication drug(s) (M medetomidine 5 µg kg^{-1}, B butorphanol 0.2 mg kg^{-1}, MB medetomidine 5 µg kg^{-1} and butorphanol 0.2 mg kg^{-1}, MBK medetomidine 5 µg kg^{-1}, butorphanol 0.2 mg kg^{-1} and ketamine 1.0 mg kg^{-1}) and total occurrence (*n*) of arrhythmias recorded in the 113 dogs, which were randomly allocated to one of the four groups.

Type of arrhythmia	**Time (minutes) after administration of premedication**	**Group M (*n*)**	**Group B (*n*)**	**Group MB (*n*)**	**Group MBK (*n*)**
Second degree atrioventricular block	1-6	238	4	231	36
	6-11	280	7	93	23
	11-16	215	20	125	59
	16-21	214	33	99	55
Ventricular escape complexes	1-6	5	0	133	1
	6-11	2	0	135	6
	11-16	3	0	17	0
	16-21	1	0	1	0
Bundle branch block	1-6	6	0	45	1
	6-11	0	0	69	0
	11-16	2	0	3	0
	16-21	0	0	0	0







Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: