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Title page

‘A comparison of the effect of propofol and alfaxalone on laryngeal motion in non-brachycephalic and brachycephalic dogs’

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A comparison of the effect of propofol and alfaxalone on laryngeal motion in non-brachycephalic and brachycephalic dogs

Abstract

Objective To compare the effect of propofol and alfaxalone on laryngeal motion under a light plane of anaesthesia in non-brachycephalic and brachycephalic dogs anaesthetized for non-emergency procedures.

Study design Prospective, randomized clinical trial.

Animals A total of 48 client-owned dogs (24 non-brachycephalic and 24 brachycephalic).

Methods A standardized premedication of methadone (0.2 mg kg^{-1}) and acepromazine (0.01 mg kg^{-1}) was administered intramuscularly. Dogs were randomly assigned to be induced with increments of propofol (1 – 4 mg kg^{-1}) or alfaxalone (0.5 – 2 mg kg^{-1}). Laryngeal assessment was performed under a light plane of anaesthesia by a surgeon (GTH) who was unaware of the induction protocol. Laryngeal movement was assessed as either being present when abduction of the laryngeal cartilages upon inspiration was identified or absent when abduction was not recognized. Simultaneously, a 60-second video was recorded. The same surgeon (GTH) and an additional surgeon (NK) re-evaluated the videos one month later. Categorical comparisons were studied using Chi squared and Fisher's Exact tests where appropriate. Pair-wise evaluation of agreement between scorers was undertaken with the kappa statistic (κ).

Results There were no significant differences ($p > 0.05$) identified between the presence or absence of laryngeal motion between dogs administered propofol or alfaxalone, as well as when analysing non-brachycephalic and brachycephalic dogs separately. The majority of dogs (>75%) maintained some degree of laryngeal motion with both protocols. Agreement between assessors was excellent ($\kappa = 0.822$).

Conclusions Alfaxalone maintained laryngeal motion similarly to propofol in non-brachycephalic and brachycephalic dogs.

Clinical relevance Both agents would appear appropriate for allowing assessment of laryngeal motion in non-brachycephalic and brachycephalic dogs. The assessment technique of subjective evaluation of laryngeal motion via per oral laryngoscopy under a light plane of anaesthesia produced consistent results amongst assessors, regardless of the induction agent used.

Keywords alfaxalone, dog, propofol, laryngeal paralysis, larynogoscopy

Introduction

Normal laryngeal motion, which is used as an indicator for laryngeal function, is demonstrated by the abduction of the arytenoid cartilages during inhalation and passive relaxation during exhalation (Gross et al. 2002). Peroral laryngoscopy under a light plane of anaesthesia is the most widely used clinical method for interpretation of laryngeal motion in dogs with 95% interobserver agreement (Broome et al. 2000; Radlinsky et al. 2009; Smith 2000). The ideal anaesthetic protocol should provide relaxation of the jaw muscles, maintenance of laryngeal reflexes and minimal respiratory depression (McKeirnan et al. 2014).

A previous study by Jackson et al. (2004) concluded that intravenous thiopental given to effect was the best choice for assessing laryngeal motion in dogs. Significantly greater arytenoid motion was demonstrated after thiopental administration when compared with other anaesthetic protocols (propofol, ketamine, diazepam and acepromazine). Although thiopental remains a useful agent in veterinary anaesthesia, it is no longer licensed in veterinary species and has therefore been largely replaced by propofol (Clarke et al. 2014).

Alfaxalone is a synthetic neurosteroid that at high concentrations acts as a direct agonist of the $GABA_A$ receptor (Berry 2015). It is used in veterinary practice as an induction agent for anaesthesia. Minimal studies regarding this drug's effect on laryngeal motion and function have been published up until now, especially in a clinical setting. A paper by Smalle et al. (2017) concluded that there was no significant difference in the total number of arytenoid motions after administration of thiopental, propofol or alfaxalone in six research dogs. Nelissen et al. (2012a) also identified no significant difference in arytenoid cartilage motion evaluating healthy cats using video laryngoscopy after administration of alfaxalone, propofol or midazolam/ketamine. On the other hand, a paper looking at the efficacy and safety of alfaxalone in humans (Monagle et al. 2015) identified significantly less airway obstruction and therefore better airway patency after alfaxalone administration compared to propofol.

Laryngeal paralysis is a common airway disorder in large breed dogs (Holt & Brockman 1994; Burbridge 1994) that is diagnosed via subjective airway assessment. It is vital to use an induction agent that maintains laryngeal motion in suspect cases to increase objectivity and accuracy of the assessment method. Moreover, an anaesthetic agent that

maintains laryngeal motion will provide a patent rima glottidis during induction allowing persistent oxygen flow. This may prove safer, especially in breeds where difficult intubation is more likely to occur. Brachycephalic breeds often have congenital defects such as narrowed nares, an overlong soft palate, tracheal hypoplasia and excessive laryngeal tissue (De Lorenzi et al. 2009)]. These defects impose a much higher risk of airway occlusion and secondary hypoxia especially during induction of anaesthesia, before successful intubation has occurred.

The main aim of this study was to assess whether laryngeal motion was present or absent under a light plane of anaesthesia after injecting either alfaxalone or propofol. This was evaluated in a cohort of non-brachycephalic and brachycephalic dogs, prior to routine surgical procedures performed in a university referral hospital. The second aim of this study was to evaluate the degree of inter-observer variability when using peroral laryngoscopy for assessment of laryngeal motion.

Methods and Materials

Animals

The study was approved by the Ethics and Welfare Committee of the Royal Veterinary College (URN 2016 1603) and informed owner consent was obtained. A total of 48 client-owned dogs were included (24 non-brachycephalic and 24 brachycephalic dogs) all of which were admitted to the Queen Mother Hospital requiring general anaesthesia for non-emergency procedures. This sample size was chosen as it was deemed an achievable number of dogs to enrol onto the study within the time frame that it could be performed. The time frame was pre-determined by the ethical committee and surgeon availability. On the basis of a full physical examination and the medical history, all non-

brachycephalic dogs were considered to be American Society of Anaesthesiologists (ASA) grade I – II and all the brachycephalic dogs were considered to be ASA grade ≤ III (Tranquilli and Grimm 2015). Dogs were excluded from the study if they were classified as ASA grade ≥ III (non-brachycephalic) or ≥ IV (brachycephalic), or if they presented with a problem that may impact the nerves relating to the function of the larynx, such as laryngeal paralysis. The dogs were randomly allocated to one of two groups by blindly drawing a number out of an envelope. Anaesthesia was induced with propofol in group P *(n = 24: 12 non-brachycephalic, 12 brachycephalic)* and with alfaxalone in group A *(n = 24: 12 non-brachycephalic, 12 brachycephalic).*

Protocol

Premedication consisted of acepromazine (ACP injection; Novartis, UK) 0.01 mg kg^{-1} and methadone (Comfortan; Dechra, UK) 0.2 mg kg^{-1} injected intramuscularly (IM) into the cervical epaxial musculature 30 minutes prior to induction. The premedication was administered in a quiet preparation room. Immediately prior to induction, an intravenous (IV) catheter was placed in a peripheral vein and a sedation score using a simple descriptive scale ranging from 0 (no change from pre-sedation behaviour) to 3 (very heavily sedated, unable to walk) (Table 1) was assigned.

The maximum dose of each induction agent (propofol 4 mg kg^{-1} or alfaxalone 2 mg kg^{-1}) were calculated for each animal, drawn up and kept hidden. Each drug's dose was chosen following the data sheets' recommendation in premedicated dogs. Estimated lean body weight was used in severely overweight dogs. Prior to the arrival of the assessor, a drape was placed over the IV catheter site to allow the induction agent to be concealed from everyone in the room apart from the injector.

Propofol (Propoflo; Abbott Animal Health, UK) or alfaxalone (Alfaxan; Jurox, Australia) were administered in quarterly increments IV until a light plane of

anaesthesia was achieved; characterized by easy visual access to the larynx, persistence of breathing and the maintenance of a gag reflex. Each increment was administered by hand over 10 seconds with a 20-second pause before the next increment was injected. An experienced board certified small animal specialist surgeon (GTH) was present at each induction and assessed the airway using peroral laryngoscopy. The laryngeal exam was performed by placing the dog in sternal recumbency, holding open the upper jaw to expose the oral cavity, pulling the tongue forward and depressing the base of the tongue just below the epiglottis (epiglottic vallecular) using a laryngoscope. If the plane of anaesthesia was deemed too deep by the surgeon (GTH) for immediate laryngeal assessment, the dog's oral cavity was closed and flow by oxygen was provided whilst being under constant observation from the anaesthetist and surgeon. As soon as the respiration rate increased, the surgeon (GTH) would attempt another laryngeal exam ensuring the return of the gag reflex before beginning the assessment. In each dog laryngeal motion was simply assessed as being either present or absent. This was determined by the degree of arytenoid abduction during inspiration and the amount of rima glottidis observed (Table 2).

During the assessment, a short (30 – 60 second) video was also made of the larynx using an iPhone 6s over at least 4 respiratory cycles, which was to be used later for re-evaluation of laryngeal motion. Following this, the dog was given more induction agent to allow intubation and was no longer followed for the purposes of the study. The dosages of induction agent administered to allow laryngeal assessment and intubation were recorded as well as any complication that occurred.

One month after the last assessment, all the videos were reassessed for the presence or absence of laryngeal motion by the same surgeon (GTH) as well as another board

certified small animal surgery specialist (NK). During reassessment of the videos, a third intermediate answer category (presence of minimal laryngeal motion) (Table 2) was added. This third category was added to refine the grading system and potentially detect more subtle differences between induction agents as during the data collection process varying degrees of laryngeal movement were detected. The videos were evaluated separately by each surgeon. A random number shown at the beginning of each video was used to identify each dog. Following this, a final collaborative assessment was made between the two surgeons who agreed on one assessment category for each dog.

Statistical analysis

Data were analysed using commercial software (SPSS for Mac 2015 version 23; IBM, United States). Normality of the interval variables (weight, age, dose of induction agent required for laryngeal assessment and dose of induction agent required for intubation) was assessed graphically and by using the Shapiro-Wilk test. None of the data were normally distributed and therefore results were reported as median (range). Categorical comparisons (presence or absence of laryngeal motion) were studied using Chi square and Fishers Exact tests as appropriate. Pair-wise evaluation of agreement between scorers in the evaluation of laryngeal motion using the scale with categories was undertaken with the kappa statistic. Results were considered significant when $p \leq 0.05$.

Results

A total of 48 dogs (24 non-brachycephalic; 24 brachycephalic) were recruited for this project. All animals completed the study (Fig. 1). The demographic data of the animals did not differ significantly between the two groups (Table 3). The dose of injectable

anaesthetic that allowed laryngeal assessment in all dogs was 1.9 (0.9 – 5.1) mg kg^{-1} for group P and 0.5 (0.2 – 1.9) mg kg^{-1} for group A. The dose of injectable anaesthetic agent to allow intubation in all dogs was 3.0 (1.1 – 6.9) mg kg^{-1} for group P and 2.0 (0.5 – 3.0) mg kg^{-1} for group A.

Overall the maintenance of some degree of laryngeal motion was identified in a large majority of cases regardless of the induction agent used or whether the dog was non-brachycephalic or brachycephalic. During the initial assessment (Fig. 2), 75% of dogs were evaluated as having laryngeal motion present. During the collaborative assessment (Fig. 3) after the addition of the third scoring category, 87.5% of dogs were assessed as having some degree of laryngeal motion.

There were no significant differences identified between the presence or absence of laryngeal motion in all dogs collectively after either propofol or alfaxalone was administered, as well as when analysing non-brachycephalic and brachycephalic dogs separately, in any of the assessments carried out. *P values* calculated for the initial assessment made by the first surgeon (GTH) - *All dogs: p = 0.63, non-brachycephalic: p = 0.5, brachycephalic: p = 0.653. P values* calculated for the reassessment made by the first surgeon (GTH) – *All dogs: p = 0.571, non-brachycephalicl: p = 0.879, brachycephalic: p = 0.325. P values* calculated for the reassessment made by the second surgeon (NK) - *All dogs: p = 0.607, non-brachycephalic: p = 0.717, brachycephalic: p = 0.154.* There were no statistical differences found between group P and group A in respect to the presence or absence of laryngeal motion in the final collaborative assessment made between the two surgeons (GTH, NK) (*All dogs: p = 0.371, non-brachycephalic: p = 0.879, brachycephalic: p = 0.593).*

Agreement between the surgeons for assessment of laryngeal motion using the scale with three categories was rated as excellent [kappa statistic (κ) = 0.822] displaying very good inter-rater reliability for the assessment method.

In total, three complications were noted during the study. One occurred in group P which involved pain on injection of the induction agent. Two occurred in group A in which excitation was experienced during injection of the induction agent in both dogs. These complications were considered mild and the experiment was continued in all of these dogs without any intervention implemented.

Discussion

There was no significant difference found between the use of either propofol or alfaxalone on the maintenance of laryngeal motion in any of the assessments carried out. This result is consistent with the results of Smalle et al. (2017). On the contrary, Monagle et al. (2015) found that airway patency was maintained better with alfaxalone compared to propofol in humans. The explanation given for the difference in airway patency is attributed to the distribution of $GABA_A$ subunits, targeted by alfaxalone and propofol. Previous work has shown that there is a relative lack of GABA subunits targeted by neurosteroids in the human brainstem compared with the cerebral cortex (Persohn et al. 1992; Wegner et al. 2007) and therefore alfaxalone has little activity in the brainstem (Thornton et al. 1986). The vagus nerve originates from the brainstem and is ultimately responsible for the control of the intrinsic muscles of the larynx via the recurrent and caudal laryngeal nerve (Hermanson & Evans 1993). However, information regarding the distribution of specific GABA subunits in other species

223 including dogs is limited and therefore explaining the difference in the results between
224 the two studies can only be done by speculation.
225
226 Other factors that may have affected laryngeal motion in this study include the
227 premedication given and the speed of administration of the injectable anaesthetic agent.
228 The use of acepromazine as part of the anaesthetic protocol when assessing laryngeal
229 motion has both been advocated and advised against. Jackson et al. (2004) identified
230 that arytenoid motion was significantly less with thiopental and acepromazine than with
231 thiopental alone, suggesting that ACP depresses arytenoid motion. However, the doses
232 used (0.05 mg kg^{-1}) were five times higher than those used in the current study.
233 Moreover, numerous sources actually suggest the inclusion of low dose ACP in the
234 premedication before laryngeal assessment because of its anxiolytic effect (Dugdale
235 2010; Murrell 2016); which decreases stress and therefore the risk of airway occlusion.
236 This was deemed particularly important for the brachycephalic cohort in this study.
237
238 Achieving the optimum level of anaesthesia for laryngeal assessment can be difficult,
239 with the speed of administration of the injectable anaesthetic agent contributing heavily
240 to this. The preservation of the respiratory cycle is necessary to determine accurate
241 arytenoid motion. Rapid IV injection (less than 5 seconds) of propofol and alfaxalone
242 commonly resulted in post-induction apnoea (Amengual et al. 2013). In this study, the
243 anaesthetic agent was given slowly to effect in incremental doses. Another possible
244 method of administration would have been via a constant rate infusion using a syringe
245 driver. This method, in theory, should titrate the injectable anaesthetic agent more
246 precisely allowing the desired level of anaesthesia for laryngeal assessment to be
247 captured instantly. However, when this method was used in cats receiving different

anaesthetic agents for assessing laryngeal motion (Nelissen et al. 2012a), assessment and intubation doses in all the cats were the same suggesting that the appropriate point at which to assess had already been surpassed. From a practical point of view, the method of administration performed in this study required less equipment and is more reflective of common clinical practice.

Both the use of ACP as part of the premedication and the incremental injection of the chosen anaesthetic agent in this study, are factors that in theory would reduce laryngeal motion. Therefore, it would be expected to identify more dogs with the absence of laryngeal motion than truly present. However, despite these factors the majority of dogs (>75%) maintained some degree of laryngeal motion in both the propofol and alfaxalone group, suggesting that they had minimal impact. Moreover, this result supports the use of either injectable anaesthetic agent for laryngeal assessment.

A potential limitation in this study was the use of a scoring system with minimal categories. Smalle et al. (2017) used a much more extensive scoring system comprising of four categories each with two subcategories. Although not validated, the scoring system utilized in this study was adopted from previous studies and adjusted using the grading system for laryngeal function in non-sedated horses (Gross et al. 2002; Robinson 2004; McKeirnan et al. 2014). While no significant difference was found in that study between thiopentone, propofol and alfaxalone, with the much larger subject numbers used in the current study, a potential difference between anaesthetic agents and laryngeal motion may have been detected.

The third intermediate category (minimal laryngeal movement) for the reassessment of the airways was not part of the original study protocol. However, after the initial data collection it was apparent that some dogs had very obvious laryngeal motion and some had minimal. The justification to implement this additional category was to potentially identify a significant difference between obvious and subtle laryngeal motion and whether this could be attributed to either anaesthetic agent, possibly providing some clinical benefit. Due to this alteration, intra-observer variability could not be determined.

Another limitation of the study was that thiopental was not used as a comparative induction agent. Thiopental has historically been considered the best choice for the assessment of laryngeal motion (Jackson et al. 2004) and therefore novel induction agents should be compared to it. However, no licenced thiopental product is available for veterinary patients in the EU or UK, therefore its use could not be justified in clinical patients. Moreover, the fact that thiopental is no longer available gives more reason to find a comparable, accessible alternative for laryngeal assessment.

To the knowledge of the authors, this is the first study to assess the effect of different anaesthetic agents on laryngeal motion in brachycephalic as well as non-brachycephalic dogs. Therefore, an appropriate assessment technique for evaluating laryngeal motion in a cohort of dogs with such a grossly altered respiratory anatomy has not been described before and there may be other factors that should be taken into account when trying to make an accurate assessment. For example, we know that a majority of brachycephalic dogs present with some degree of laryngeal collapse (Monet and Tobias 2012). The effect of laryngeal collapse on laryngeal motion has not been reported although the

incident of both pathologies co-occurring has been described (Nelissen and White 2012b). The degree of laryngeal collapse was not recorded in this study; therefore, it is difficult to determine whether this variable had any impact on the results obtained. Future studies could focus on specific laryngeal assessment in the brachycephalic population, the impact of laryngeal collapse on laryngeal motion and if our current assessment measures for laryngeal motion are even applicable to brachycephalic dogs as they have so many airway malformations.

Conclusion Alfaxalone maintains laryngeal motion similarly when compared to propofol in non-brachycephalic and brachycephalic dogs. Agreement between assessors was excellent.

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Table and figure legends:

Table 1 Description of scoring categories used to assess degree of sedation after premedication with acepromazine 0.01 mg kg^{-1} and methadone 0.2 mg kg^{-1} intramuscularly in 48 dogs.

Table 2 Descriptors used for assessing laryngeal motion.

Table 3 Demographic and other data of all dogs included in this study. Anaesthesia was induced with either propofol (0.9 – 6.9 mg kg^{-1}) (group P all dogs, *n* = 24; group P non-brachycephalic dogs, *n* = 12; group P brachycephalic dogs, *n* = 12) or alfaxalone (0.2 – 3.0 mg kg^{-1}) (group A all dogs, *n* = 24; group A non-brachycephalic dogs, *n* = 12; group A brachycephalic dogs, *n* = 12).

Figure 1 CONSORT flow diagram for this study. Dogs were randomly divided into two groups: group P, in which laryngeal motion was evaluated after the administration of propofol; and group A, in which laryngeal motion was evaluated after the administration of alfaxalone.

Figure 2 Number of dogs in each scoring category (*x* axis) during the initial assessment of laryngeal motion after receiving either propofol or alfaxalone (*y* axis). A 'Present' assessment equates to the maintenance of laryngeal motion and an 'absent' assessment equates to the absence of laryngeal motion.

Figure 3 Number of dogs in each scoring category (*x* axis) during the collaborative re-assessment of laryngeal motion after receiving either propofol or alfaxalone (*y* axis). A

419 ‘present’ assessment equates to the obvious maintenance of laryngeal motion, a
420 ‘Minimal’ assessment equates to marginal laryngeal motion and an ‘absent’ assessment
421 equates to the absence of laryngeal motion.
422
423

Tables

Table 1 Description of scoring categories for degree of sedation after premedication with acepromazine 0.01 mg kg^{-1} and methadone 0.2 mg kg^{-1} intramuscularly in 48 dogs.

Category	Description
0	No change from pre-sedation behaviour
1	Mild sedation (with head slightly lowered)
2	Moderate sedation (with head lowered and ataxia)
3	Very heavily sedated, unable to walk

Table 2 Descriptors used for assessing laryngeal motion.

Assessment answer	**Description**
Obvious laryngeal motion present	Clear abduction of the arytenoid cartilages during inspiration. Maximal rima glottidis observed. Maintenance of laryngeal motion.
Absence of laryngeal motion	No obvious arytenoid abduction during inspiration. Minimal rima glottidis observed. Laryngeal motion not maintained.
Minimal laryngeal motion present	Mild to moderate degree of abduction of the arytenoid cartilages during

	inspiration. Moderate rima glottidis observed. Maintenance of laryngeal motion.

Table 3 Demographic and other data of all the dogs in this study. Anaesthesia was induced with either propofol (0.9 – 6.9 mg kg $^{-1}$) (group P all dogs, *n* = 24; group P non-brachycephalic dogs, *n* = 12; group P brachycephalic dogs, *n* = 12) or alfaxalone (0.2 – 3.0 mg kg $^{-1}$) (group A all dogs, *n* = 24; group A non-brachycephalic dogs, *n* = 12; group A brachycephalic dogs, *n* = 12).

	Dogs	**Group P**	**Group A**
Sex	*Female*	10	8
	Male	14	16
Age (months)	*All*	52.5 (11 – 167)	51.5 (7 – 165)
	Non-brachycephalic	69.5 (11 – 167)	51.5 (7 – 104)
	Brachycephalic	38.5 (12 – 119)	46 (11 – 165)
Weight (kg)	*All*	11.1 (5.8 – 34.7)	11.4 (2.2 – 46.0)
	Non-brachycephalic	16.5 (5.8 – 34.7)	26.8 (5.0 – 46.0)
	Brachycephalic	9.0 (6.2 – 18.8)	10.2 (2.2 – 22.0)
Sedation score	*All*	1 (0 – 3)	2 (0 – 3)
	Non-brachycephalic	1 (0 – 3)	2 (1 – 3)

	Brachycephalic	1(0 – 3)	2 (1 – 3)
Dose of drug to allow laryngeal assessment (mg kg $^{-1}$)	*All*	1.9 (0.9 – 5.1)	0.5 (0.2 – 1.9)
	Non-brachycephalic	1.9 (0.9 – 5.0)	0.5 (0.4 – 1.0)
	Brachycephalic	1.9(0.9 – 5.1)	0.5 (0.2 – 1.9)
Dose of drug to allow intubation (mg kg $^{-1}$)	*All*	3.0 (1.1 – 6.9)	2.0 (0.5 – 3.0)
	Non-brachycephalic	3.0(1.1 – 6.9)	1.0 (0.7 – 3.0)
	Brachycephalic	3.0 (1.1 – 5.1)	1.0 (0.5 – 1.9)
Number of complications	*All*	1	2
	Non-brachycephalic	1	1
	Brachycephalic	0	1