Laryngeal assessment in dogs: a clinical review

This article reviews the literature describing the anaesthetic and ancillary drugs used during the assessment of laryngeal function in dogs, and summarises the evidence for their use in clinical practice. A review of the literature was conducted using PubMed and Google Scholar, with the search terms 'laryngeal assessment dogs', 'laryngeal collapse', 'laryngeal paralysis', 'premedication laryngeal assessment', 'induction agent laryngeal assessment' and 'dogs'. Further studies and reports were obtained from the reference lists of the retrieved papers. Related anaesthesia textbooks were also reviewed. Drugs used to induce anaesthesia affect laryngeal function by diminishing the laryngeal reflex. Based on the current literature, premedication using acepromazine and an opioid allows for the assessment of laryngeal examination without impairing laryngeal motion. Dexmedetomidine in combination with an opioid may offer an alternative, but there are no studies comparing these sedative drugs directly. Examination times were shorter with propofol compared to alfaxalone, while ketamine was not recommended as an anaesthetic induction agent for this purpose. The use of doxapram hydrochloride may be helpful, particularly when airway assessment remains equivocal. At low doses, doxapram causes minimal increases in arterial blood pressure and heart rate.

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Camilla Ferrero, Anderson Moores Veterinary Specialists, The Granary, Bunstead Barns, Poles Lane, Hursley, Winchester, Hampshire, SO21 2LL; **Karla Borland**, Lumbry Park Veterinary Specialists, Selborne Rd, Alton, GU34 3HL; **Carl Bradbrook**, Anderson Moores Veterinary Specialists, The Granary, Bunstead Barns, Poles Lane, Hursley, Winchester, Hampshire, SO21 2LL **Rachel Bennett**, Department of Equine and Small Animal Medicine, University of Helsinki, Helsinki, Finland.
camilla.ferrero@hotmail.it

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The larynx regulates air flow to the ventilatory tract, protects the lower airway from aspiration during swallowing, and controls phonation. Diseases commonly affecting the larynx include paralysis, collapse, stenosis and neoplasia. Each condition results in an alteration in air flow that can increase the work of breathing. If air flow is completely occluded, collapse may occur. Dogs with conditions affecting the larynx present to their veterinarian with respiratory stridor, a change in phonation, coughing or gagging (Greenfield, 1987; Burbidge, 1995). The presentation and progression of clinical signs can be highly variable. Diagnosis of pathology affecting the larynx is initially based on the animal's clinical history and physical examination. A definitive diagnosis is obtained with a functional and structural laryngeal examination using either sedation or a light plane of general anaesthesia preceding intubation.

Laryngeal assessment can be challenging because the plane of anaesthesia should relax the jaw muscles to allow examination without inhibiting laryngeal reflexes and inspiratory efforts. As the level of anaesthesia increases, breathing may become shallow, or apnoea may occur alongside cessation of active laryngeal movements (Burbidge, 1995). Drugs used to induce anaesthesia reduce laryngeal reflexes (Burbidge, 1995). The effect of different sedative and anaesthetic drug combinations, assessment methods and complementary diagnostic aids for examining the larynx has been investigated.

This review summarises the evidence currently available in the veterinary literature and identifies the most appropriate sedative or anaesthetic drugs for examination of the larynx and its function.

Databases used

PubMed and Google Scholar were used to identify relevant studies for review. The search terms were 'laryngeal assessment dogs, 'laryngeal collapse', 'laryngeal paralysis', 'premedication laryngeal assessment', 'induction agent laryngeal assessment' and 'dogs'. Further studies and reports were obtained from the reference lists of the retrieved papers. In addition, related veterinary anatomy and anaesthesia textbooks up to April 2020 were reviewed. Articles were excluded if they did not provide anaesthetic drug information such as the doses used, the route of administration or their effects on laryngeal function or assessment. Only articles in English or with English translations were selected.

Assessment methods

A definitive diagnosis of laryngeal disease requires laryngeal examination to ascertain if the anatomy and function are abnormal. As previously mentioned, each disease can cause a change in air flow. Premedication and induction agents can further depress the processes of breathing and ventilation, which may lead to apnoea

and hypoxaemia. In clinical practice, examination of the larynx is usually performed before intubation to allow visualisation of the arytenoid movements. The airway is unprotected during examination and in animals already prone to regurgitation, such as brachycephalic breeds, laryngeal dysfunction may further increase the risk of aspiration.

Functional laryngeal examination is required for the diagnosis of laryngeal paralysis and reported examination techniques have focused on this condition specifically. Some pathologies may be identified during laryngeal examination in animals that present with signs of abnormal breathing or ventilation without function assessment (such as neoplasia or arytenoid hyperplasia). Direct visualisation of the larynx with a laryngoscope, oral video-endoscopic laryngoscopy or transnasal laryngoscopy are all techniques used for laryngeal examination. Using video-endoscopic laryngoscopy, the rima glottis surface area can be calculated with the following formula: [(inspiratory measurement – expiratory measurement) / expiratory measurement] x 100. It is an objective measurement generally taken before and after a treatment; an increase in rima glottis surface area is considered indicative of arytenoid motion.

An alternative measurement is the normalised glottal gap area. It is calculated using the formula: (area in pixels height^2) in which the area of each set of three inspiratory and expiratory images is determined from the pixelated image. This value considers any variation in the size of the dog and the distance between the laryngeal ostium and the tip of the endoscope to avoid sources of bias (Omori et al, 1998). An alternative to laryngoscopy via the oral cavity is transnasal laryngoscopy, which has only been used in large breed dogs, because the size of the endoscope limits its use in smaller animals. However, movement of the dog during a light plane of sedation may result in damage to the equipment (Radlinsky et al, 2004).

Diagnosis may be aided by laryngeal ultrasound (echolaryngography) (Rudorf et al, 2001) and computed tomography (CT) (Stadler et al, 2011). When assessing laryngeal function using ultrasound, findings indicative of laryngeal paralysis include asymmetry or absence of motion of the cuneiform processes, abnormal arytenoid movement, paradoxical movement, caudal displacement of the larynx, and laryngeal collapse (Rudorf et al, 2001). With CT imaging, stenosis of the laryngeal inlet, failure to abduct the arytenoid cartilages, collapse of the cartilages into the rima glottis on inspiration and air-filled lateral ventricles are consistent with a diagnosis of laryngeal paralysis (Silverman et al, 1995). Echolaryngography, CT and transnasal laryngoscopy have certain advantages over direct laryngoscopy as they avoid the need for profound sedation or general anaesthesia (Radlinsky et al, 2009; Stadler et al, 2011). However, when compared, direct visualisation during anaesthesia was superior to echolaryngoscopy and equivalent to transnasal laryngoscopy for the evaluation of laryngeal function (Radlinsky et al, 2009).

Table 1. Comparative information of the study design, numbers of dogs enrolled, a priori sample size calculation, laryngeal assessment technique and laryngeal evaluation in the studies reviewed

Reference	Study design	Dogs/cats	A priori power calculation	Laryngeal assessment technique	Laryngeal evaluation
Miller et al (2002)	Prospective	30	No	Videolaryngoscopy	Rima glottis surface area
Gross et al (2002)	Prospective, randomised crossover	8	No	Direct visualisation	Composite scoring system*
Jackson et al (2004)	Prospective, randomised, crossover blinded	6	No	Videolaryngoscopy	Normalised glottis gap area
McKeirnan et al (2014)	Prospective, randomised, blinded	48	No	Direct visualisation	Composite scoring system*
Smalle et al (2017)	Prospective, randomised, crossover blinded	6	No	Direct visualisation	Composite scoring system†
Ambros et al (2018)	Prospective, randomised, crossover blinded	8	Yes	Videolaryngoscopy	Normalised glottis gap area
Norgate et al (2018)	Prospective, randomised blinded	48	No	Direct visualisation	Present/absent
Radkey et al (2018)	Prospective, randomised, controlled crossover	10	Yes	Videolaryngoscopy	Rima glottis surface area
Brown et al (2019)	Experimental study	40	Yes	Videolaryngoscopy and direct visualisation	Rima glottis surface area and composite scoring system*
DeGroot et al (2020)	Prospective, randomised, crossover, blinded	8	No	Videolaryngoscopy	Normalised glottis gap area
Labuscagne et al (2019)	Prospective, randomised, crossover blinded	8	No	Direct visualisation	Composite scoring system†

*Composite scoring system including breathing, swallowing, laryngospasm jaw tone and exposure scores. †Composite scoring system including laryngeal exposure score (breathing, jaw tone, swallowing and laryngospasm score) and laryngeal function score

Effects of sedative and anaesthetic drugs on laryngeal function

The effect of several anaesthetic protocols on arytenoid motion has been reported in dogs (Gross et al, 2002; Jackson et al, 2004; McKeirnan et al, 2014; Smalle et al, 2017; Norgate et al, 2018; Radkey et al, 2018; DeGroot et al, 2020). Study limitations are discussed separately.

In dogs, the use of acepromazine alone, for the evaluation of laryngeal function, has not been investigated. However, acepromazine was evaluated in conjunction with other drugs in two experimental studies that used laryngoscopy as the method of assessment (Jackson et al, 2004; Radkey et al, 2018) (*Table 2*). Jackson et al (2004) used six large breed, clinically normal dogs while Radkey et al (2018) used 10 purpose-bred Beagles as their respective study populations. In the former study, treatments were compared using the normalised glottal gap area, and in the latter the rima glottis surface area was used.

When compared with thiopental alone, acepromazine (0.05 mg/kg) given intramuscularly (IM), followed by propofol or thiopental, reduced arytenoid motion in all dogs (Jackson et al, 2004). However, when acepromazine was combined with oxymorphone (0.05–0.2 mg/kg) IM or at the higher dose of 0.2 mg/kg IM with butorphanol (0.4 mg/kg), no significant difference in arytenoid motion was observed. The authors speculated that the phenothiazine acted synergistically with the intravenous (IV) induction drugs to reduce arytenoid movement since the combination of acepromazine and an opioid did not reduce arytenoid motion.

In the study by Radkey et al (2018), the impact of acepromazine (0.03 mg/kg) and butorphanol (0.2 mg/kg) premedication on arytenoid motion was assessed. Animals were given either the acepromazine-butorphanol combination or an equivalent volume of IV saline followed by the administration of either propofol or alfaxalone. The induction drugs were given IV over 15 seconds. Median increases in rima glottis surface area were greater for combinations using acepromazine and butorphanol than saline and propofol, and significantly greater than those following the use of saline and alfaxalone. The authors identified that a minimal increase of >20% in the rima glottis surface area was needed to detect arytenoid movement with the naked eye. Using this criterion, two of 10 dogs given propofol, zero given alfaxalone, five of 10 given acepromazine-butorphanol and propofol, and five of 10 dogs given acepromazine-butorphanol and alfaxalone had visibly detectable arytenoid motion. The number of coughing, gagging and struggling events was also recorded and translated into an overall quality of assessment score, where one event was considered excellent and six or more was considered poor. Using these criteria, the quality of the examination was improved when using premedication with acepromazine-butorphanol compared to the use of propofol or alfaxalone alone.

While the findings of these two studies differ from one another, this may be because the doses of acepromazine were different, as were the routes of administration. However, both studies suggest that premedication using acepromazine in combination with an opioid can be given to dogs before laryngeal examination.

The use of butorphanol as a sole premedication agent (albeit in combination with glycopyrrolate) was evaluated in two studies (Gross et al, 2002; McKeirnan et al, 2014). Exposure of the larynx was scored as excellent or moderate when butorphanol was given before thiopental or propofol, but significantly reduced following the administration of diazepam and ketamine (Gross et al, 2002), or by propofol alone, or propofol and ketamine (McKiernan et al, 2014). Butorphanol in combination with dexmedetomidine provided an effective sedation protocol for laryngeal assessment (DeGroot et al, 2020). Moreover, when arytenoid motion was assessed immediately before recovery, motion was significantly greater using butorphanol with acepromazine followed by isoflurane mask induction, compared to acepromazine premedication before propofol or thiopental (Jackson et al, 2004).

Norgate et al (2018) evaluated the effect of methadone (0.2 mg/kg IM) combined with acepromazine (0.01 mg/kg IM), followed by either propofol or alfaxalone IV. The study included two groups of dogs, categorised based on whether they were brachycephalic or not (24 dogs in each group). Laryngeal motion was maintained in most dogs (36 out of 48).

Oxymorphone in combination with acepromazine was evaluated by Jackson et al (2004). The authors reported no difference in arytenoid motion when this treatment was compared with thiopental alone. Laryngeal motion following the use of either methadone or oxymorphone as sole premedication agent before the administration of an injectable anaesthetic drug has not been assessed. The combination of hydromorphone and dexmedetomidine is described in the following paragraph (DeGroot et al, 2020).

Dexmedetomidine, the active enantiomer of medetomidine, is a centrally acting α2-adrenoceptor agonist commonly used for sedation and premedication of dogs. Dexmedetomidine does not cause significant ventilatory depression when administered alone in healthy dogs and allows the mouth to be opened and the tongue to be exteriorised (Pettifer and Dyson, 1993). The effect of dexmedetomidine on laryngeal function was evaluated in an experimental study by DeGroot et al (2020). A group of eight healthy hounds (American Society of Anesthesiologists grade I) were sedated with dexmedetomidine (3–15 µg/kg IV) alone, dexmedetomidine combined with butorphanol (0.3 mg/kg IV), or dexmedetomidine combined with hydromorphone (0.1 mg/kg IV). These drug combinations were compared with propofol alone (2–8 mg/kg IV) (*Table 2*). Assessment of laryngeal function used video laryngoscopy and was performed before and after doxapram administration. Digital images were collected to assess normalised glottal gap area. The results were compared between and within treatments, before and after doxapram administration. Laryngeal motion was observed in all dogs given dexmedetomidine with and without opioids, but was absent in two dogs given propofol, which could be indicative of a false positive diagnosis of impaired function. The study concluded that dexmedetomidine (3–15 µg/kg), alone or in combination with an opioid, was an effective sedation protocol, producing sufficient immobilisation to prevent jaw motion without affecting arytenoid abduction (*Table 2*).

Several studies have investigated the use of IV anaesthetic drugs on laryngeal function. Propofol alone was compared with thiopental, alfaxalone and methohexital (Jackson et al, 2004; Smalle et al, 2017; Ambros et al, 2018; Radkey et al, 2018; Brown et al, 2019; Labuscagne et al, 2019). In three studies, no statistically

Table 2. Comparative information describing doses, methods and timing of preanaesthetic medication and induction agents in the studies reviewed

Reference	Preanaesthetic medication	Induction agent(s)	Method of administration	Time from premedication to induction (minutes)
Miller et al (2002)	Butorphanol 0.22 mg/kg IV + acepromazine 0.05 mg/kg SC	Propofol 4 mg/kg IV, then propofol 2 mg/kg IV (following doxapram)	1. Over 30–50 seconds 2. Over 30 seconds	20
Gross et al (2002)	1. Butorphanol 0.5 mg/kg IV + glycopyrrolate 0.01 mg/kg IV 2. Butorphanol 0.5 mg/kg IV + glycopyrrolate 0.01 mg/kg IV 3. Butorphanol 0.5 mg/kg IV + glycopyrrolate 0.01 mg/kg IV	1. Thiopental 20 mg/kg IV 2. Propofol 6 mg/kg IV 3. Diazepam 0.5 mg/kg IV + ketamine 10 mg/kg IV	1. 10 mg/kg as bolus, then to effect 2. Slowly over 1 minute, to effect 3. Slowly over 1 minute, to effect	5
Jackson et al (2004)	1. Acepromazine 0.05 mg/kg IM 2. Acepromazine 0.05 mg/kg IM 3. None 4. Acepromazine 0.05 mg/kg, IM 5. None 6. None 7. Acepromazine 0.2 mg/kg IM and butorphanol 0.4 mg IM	1. Oxymorphone 0.05–0.2 mg/kg IV 2. Thiopental 8–20 mg/kg IV 3. Thiopental 10–20 mg/kg IV 4. Propofol 4–6 mg/kg IV 5. Propofol 6–8 mg/kg IV 6. Ketamine 4–8 mg/kg IV and diazepam 0.2–0.4 mg/kg IV 7. Mask induction with isoflurane (20 minutes later)	Slowly, to effect	20
McKeirnan et al (2014)	1. Butorphanol 0.5 mg/kg IM + glycopyrrolate 0.01 mg/kg IM 2. Butorphanol 0.5 mg/kg IM + glycopyrrolate 0.01 mg/kg IM	1. Propofol 6 mg/kg IV 2. Ketamine 2 mg/kg IV and propofol 2–4 mg/kg IV	Slowly over 1 minute, to effect	20
Smalle et al (2017)	None	1. Thiopental 7.5 mg/kg IV; top-up bolus 1.8 mg/kg 2. Propofol 3 mg/kg IV; top-up bolus 0.75 mg/kg IV 3. Alfaxalone 1.5 mg/kg IV; top-up bolus 0.4 mg/kg IV	Over 1 minute, after 10 seconds a top-up bolus administered over 10 seconds and repeated at 20-second intervals	-
Ambros et al (2018)	None	1. Thiopental 10 mg/kg, top up 2.5 mg/kg 2. Alfaxalone 2 mg/kg, top-up bolus 0.5 mg/kg 3. Propofol 2 mg/kg + diazepam 0.4 mg/kg, top-up bolus 0.5 mg/kg	1. Over 1 minute 2. Over 1 minute 3. Over 1 minute	-
Radkey et al (2018)	1. Saline 2. Acepromazine 0.03 mg/kg IV + butorphanol 0.2 mg/kg IV 3. Saline 4. Acepromazine 0.03 mg/kg IV and butorphanol 0.2 mg/kg IV	1. Alfaxalone 0.5 mg/kg IV 2. Alfaxalone 0.5 mg/kg IV 3. Propofol 0.5 mg/kg IV 4. Propofol 0.5 mg/kg IV	Over 15 seconds, top-up boluses over 15 seconds	5
Norgate et al (2018)	1. Methadone 0.2 mg/kg IM and acepromazine 0.01 mg/kg IM 2. Methadone 0.2 mg/kg IM and acepromazine 0.01 mg/kg IM	1. Propofol 4 mg/kg IV (maximum dose) 2. Alfaxalone 2 mg/kg IV (maximum dose)	Slowly to effect in quarterly increments, each increment administered over 10 seconds with 20-second pause between each bolus	30
Brown et al (2019)	None	1. Propofol 6 mg/kg IV 2. Methohexytal 11 mg/kg	1. Slowly to effect 2. Half as a bolus, then slowly to effect	-
Labuscagne et al (2019)	None	1. Alfaxalone 1.5 mg/kg IV, top-up bolus 0.4 mg/kg IV 2. Thiopental 7 mg/kg IV, top-up bolus 1.8 mg/kg IV 3. Propofol 3 mg/kg IV, top-up bolus 0.75 mg/kg IV	Over 1 minute, 10-second pause, incremental boluses over 10 seconds with a 10-second pause between each bolus	-

Table 2. Comparative information describing doses, methods and timing of preanaesthetic medication and induction agents in the studies reviewed (continued)

Reference	Preanaesthetic medication	Induction agent(s)	Method of administration	Time from premedication to induction (minutes)
DeGroot et al (2020)	1. None 2. Dexmedetomidine 3–15 µg/kg IV 3. Dexmedetomidine 3–15 µg/kg IV and hydromorphone 0.1 mg/kg IV 4. Dexmedetomidine 3–15 µg/kg, IV and butorphanol 0.3 mg/kg IV	1. Propofol 2–8 mg/kg IV 2. None 3. None 4. None	1. Propofol 2 mg/kg IV with incremental doses of 1 mg/kg IV over 1 minute up to 8 mg/kg 2. 3 µg/kg dexmedetomidine ± opioid IV, followed by additional doses of 2 µg/kg IV over 1 minute as required to achieve sedation sufficient for laryngeal examination, up to a maximum total dose of 15 µg/kg IV	-

IM = intramuscular; IV = intravenous; SC = subcutaneous.

significant differences in laryngeal function were observed when propofol was compared to alfaxalone, thiopental or methohexital (Smalle et al, 2017; Ambros et al, 2018; Brown et al, 2019). However, propofol alone did not provide adequate conditions for assessment in two studies (Radkey et al, 2018; Labuscagne et al, 2019). Radkey et al (2018) reported that 80% (8/10) of dogs given propofol (mean dose ± standard deviation: 6.2±2.6 mg/kg) alone did not have arytenoid movement while Labuscagne et al (2019) found paradoxical motion and unilateral paralysis in two dogs with no laryngeal paralysis. In the study by Smalle et al (2017) the median examination times were significantly shorter following propofol injection compared with thiopental and alfaxalone; median (range) 14.1 minutes (8.0–41.8), 5.4 minutes (3.3–14.8) and 8.5 minutes (3.8–31.6) to examination endpoint for thiopental, propofol and alfaxalone respectively.

The effect of alfaxalone on laryngeal function was assessed in two research studies (Smalle et al, 2017; Ambros et al, 2018) and one clinical study (Norgate et al, 2018). Smalle et al (2017) found no significant difference in the total number of arytenoid motions after administration of thiopental, propofol or alfaxalone in six research dogs (*Table 1*). In agreement with this study, Ambros et al (2018) found no difference between thiopental, propofol with diazepam or alfaxalone when they compared the normalised glottal gap area after induction and before recovery. Norgate et al (2018) concluded that there was no significant difference in the laryngeal motion of 48 dogs given either propofol or alfaxalone, when non-brachycephalic and brachycephalic dogs were analysed separately. More than 75% of the 48 dogs maintained laryngeal motion with both induction agents.

Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist commonly used as an anaesthetic induction agent. The effect of ketamine on laryngeal function, in combination with diazepam or propofol, was assessed in three studies (Gross et al, 2002; Jackson et al, 2004; McKeirnan et al, 2014). Gross et al (2002) concluded that visualisation of the larynx in dogs premedicated with butorphanol and glycopyrrolate was more readily accomplished with thiopental (20 mg/kg IV) or propofol (6 mg/kg IV) than with diazepam and ketamine (0.5 mg/kg IV, 10 mg/kg IV). This was because laryngeal exposure was increased by the use of thiopental and propofol (Gross et al, 2002). In this study, a composite scoring system was used to evaluate laryngeal function, including breathing, swallowing, laryngospasm, jaw tone and exposure scores (*Table 1*). Therefore, Gross et al (2002) advised against the use of ketamine for this purpose. Similarly, Jackson et al (2004) advised against the use of ketamine (4–8 mg/kg IV) together with diazepam (0.2–0.4 mg/kg IV) since laryngeal motion was absent in some healthy dogs. Using the same premedication and similar laryngeal assessment criteria as Gross et al (2002), McKeirnan et al (2014) evaluated the quality of laryngeal function assessment using either propofol (6 mg/kg IV) or propofol (2–4 mg/kg IV) preceded by ketamine (2 mg/kg IV). Ketamine failed to have a dose-sparing effect on propofol although, in combination with proprofol, it provided adequate visualisation of the larynx. However, the combination resulted in increased ventilatory depression evidenced by reduced haemoglobin oxygen saturation values. Based on these studies, the use of ketamine alone or in combination with diazepam or propofol is not recommended for laryngeal assessment.

Thiopental has been used as an induction agent to assess laryngeal function in dogs in several studies. These studies have used different methodologies (Gross et al, 2002; Jackson et al, 2004; Smalle et al, 2017; Ambros et al, 2018) and different drug combinations with no premedication (Jackson et al, 2004; Smalle et al, 2017; Ambros et al, 2018) or premedication with butorphanol (0.5 mg/kg IV) and glycopyrrolate (0.01 mg/kg IV), or acepromazine (0.05 mg/kg IM) (Gross et al, 2002; Jackson et al, 2004). The assessments were made via direct visualisation using either a composite scoring system or via video laryngoscopy using the normalised glottal gap area. The doses of thiopental used for laryngeal visualisation were comparable between studies (6.3–14.2 mg/kg mean IV dose). Jackson et al (2004) concluded that thiopental administered alone was the best choice for assessing laryngeal mo-

tion with video laryngoscopy in dogs because arytenoid motion was significantly greater before recovery. Smalle et el (2007) found that thiopental provided better conditions for the detection of arytenoid motion compared to propofol and alfaxalone. However, it caused transient laryngeal lack of motion in all the dogs in the first 2 minutes of an examination. Over time, the total number of arytenoid movements did not differ between groups in this study. Most studies found that thiopental did not differ from propofol or alfaxalone.

Doxapram hydrochloride

Doxapram is a central nervous system (CNS) stimulant. It activates the carotid and aortic chemoreceptors and increases the electrical activity in the inspiratory and expiratory centres of the medulla (Franz, 1985; Arrioja, 2001; Plumb, 2002). The administration of doxapram to healthy, anaesthetised dogs results in increased laryngeal motion (Alsup et al, 1997; Greenfield et al, 1997; Miller et al, 2002). In dogs with experimentally induced laryngeal paralysis, doxapram increased the resistance to airflow and the severity of the obstruction (Greenfield et al, 1997). Doxapram may maximise laryngeal movements and lighten the plane of anaesthesia, thereby allowing a more accurate evaluation of laryngeal function in dogs. The use of doxapram in the assessment of laryngeal paralysis was investigated either as part of the sedation or anaesthetic protocol, or when apnoea occurred (McKeirnan et al, 2014; Radkey et al, 2018; Brown et al, 2019; DeGroot et al, 2020). Although the doses of doxapram ranged from 0.25–2.2 mg/kg IV there was no direct comparison of different doses within a study. In all the studies, doxapram improved respiratory effort and increased the airway size. Although useful in humans, the reported side effects are tachycardia, arrhythmias and CNS excitement (Yost, 2006). In dogs, tachycardia and arrhythmias were not reported in experimental studies (Huffington and Craythorne, 1966; Kim et al, 1971). However, in the studies listed above, the reported side effects were a decreased plane of anaesthesia, increased ventilatory drive, exaggerated laryngeal movements, tachycardia and hypertension (*Table 3*).

Several studies report the benefit of routinely using doxapram during laryngoscopy to increase intrinsic laryngeal motion and to aid the diagnosis of laryngeal dysfunction (*Table 3*). In healthy dogs the effect of doxapram on the area of the rima glottis was assessed by Miller et al (2002). A group of 30 non-brachycephalic dogs were given a combination of acepromazine (0.1 mg/kg), and glycopyrrolate (0.005 mg/kg) subcutaneously, followed by butorphanol (0.22 mg/kg IV) 20 minutes later. Anaesthesia was induced with propofol (4 mg/kg IV) given 5 minutes after the butorphanol. Videolaryngoscopy was used to record laryngeal motion. Doxapram (2.2 mg/kg) was then administered IV and laryngeal motion was recorded. During inspiration at rest, inspiration with doxapram, expiration at rest, and expiration with doxapram, representative breaths for each dog were recorded. The authors found that doxapram administration significantly increased the rima glottis area during both inspiration and expiration and visibly increased ventilatory efforts compared to the resting state.

Tobias et al (2004) investigated the use of doxapram (1.1 mg/kg IV) in dogs with an American Society of Anesthesiologists status score of I and in those with naturally occurring laryngeal paralysis. In healthy dogs premedicated with acepromazine (0.2 mg/kg IM) and butorphanol (0.44 mg/kg IM) and anaesthetised with isoflurane (3–5%) by face mask, doxapram administration resulted in increased breathing efforts with no increase in the normalised glottal gap area. Dogs with suspected laryngeal paralysis were premedicated with acepromazine (0.022 mg/kg IM) and butorphanol (0.44 mg/kg IM). Following doxapram administration, dogs with laryngeal dysfunction showed paradoxical motion of the arytenoids, as evidenced by the decrease in percentage change in normalised glottal gap area. These findings contrast with those reported by Miller et al (2002), which may be explained by different methodologies. Miller et al (2002) examined the dogs in the first 30 seconds after propofol administration using video laryngoscopy. Tobias et al (2004) performed the evaluation in the 15 seconds leading up to recovery, proposing that this allowed better standardisation of the anaesthetic plane.

Labuscagne et al (2019) investigated the effects of pharmaceutical intervention (with doxapram) and mechanical stimulation on laryngeal motion during alfaxalone, propofol or thiopentone anaesthesia in healthy dogs. In this experimental study, the induction end point was defined as the ability to open the jaw without any resistance, with no chewing, swallowing or head movement away from the laryngeal examiner. Absence of a palpebral reflex and regular breathing pattern were also considered part of an adequate plane of anaesthesia. At 2 minutes after the induction end point, doxapram (2.5 mg/kg IV) was administered over 30 seconds. A cotton bud was applied for 5 seconds to the right corniculate process of the arytenoid cartilage at 2, 3 and 5 minutes after the induction end point. Doxapram was superior to mechanical stimulation in stimulating laryngeal motion using thiopental and propofol anaesthesia but less effective when alfaxalone was used as induction agent. The authors did not comment on how they ensured consistent pressure was applied when using the cotton bud, or how this may have affected their results.

Limitations of the studies

The authors describe the results of 11 studies, and several limitations may have influenced their respective outcomes. Only three of these studies provided prospective sample size calculations (Ambros et al, 2018; Radkey et al, 2018; Brown et al, 2019). Two studies included a control group (Radkey et al, 2018; Brown et al, 2019) and in some studies, observers were not blinded to group allocation (Miller et al, 2002; Tobias et al, 2004). The dose and the route of administration of drugs differed between studies, as did the time between premedication and induction of anaesthesia (ranging from 5–45 minutes). The rate of drug administration was also inconsistent. All authors administered drugs to effect, but the time-period for administration was frequently less than 1 minute, potentially shorter than the onset time of the injectable anaesthetic (for example, the onset time of propofol is reported to be up to 2 minutes) (Zoran et al, 1993). In two studies (Jackson et al, 2004; Brown et al, 2019) the time over which the induction agent was administered is not mentioned. In the study by Radkey et al (2018), alfaxalone was administered relatively rapidly (over 15 seconds), which may have led to a greater total dose. Also of importance is the time following induction of anaesthesia, when the laryngeal

Table 3. The effect of the intravenous administration of doxapram hydrochloride to healthy dogs and dogs with laryngeal paralysis

Reference	Ventilatory stimulant	Dose (bolus)/ titration	Health status	Premedication drugs	Drugs used for induction of anaesthesia	Adverse effects	Results	Passive or paradoxical arytenoid motion	Statistical significance
Miller et al (2002)	Doxapram	2.2 mg/kg	ASA 1	Acepromazine/ butorphanol	Propofol	Excitement/ awakening	Doxapram increased laryngeal motion in ASA 1 premedicated dogs	No	Yes
Tobias et al (2004)	Doxapram	1.1 mg/kg	Healthy and with laryngeal paralysis	Acepromazine/ butorphanol	Isoflurane by mask	Intubation was necessary	Healthy dogs differentiated from dogs with laryngeal paralysis with doxapram	Yes, in dogs with laryngeal paralysis	Yes
Jackson et al (2004)	Doxapram	2–5 mg/kg	ASA 1	Acepromazine/ butorphanol	Multiple	N/D	N/D	N/D	NA
McKeirnan et al (2014)	Doxapram	1.1 mg/kg	ASA 1	Butorphanol	Propofol/ ketamine and propofol	None	Doxapram improved respiratory scores and significantly increased the ability to determine normal laryngeal function	No	Yes
Radkey et al (2018)	Doxapram	0.25 mg/kg	ASA 1	Acepromazine + butorphanol/ control group	Alfaxalone/ propofol	Increased respiratory drive	Rima glottidis surface area was significantly less in alfaxalone before doxapram compared with all other treatments and after doxapram, 50% of dogs with alfaxalone had no motion	Yes, in dogs with previously good motion	Yes
Brown et al (2019)	Doxapram vs control	2.2 mg/kg or saline (control)	ASA 1	No	Propofol/ methohexital	Exaggerated laryngeal movements	Doxapram improved breathing scores but not laryngeal function	No	No
DeGroot et al (2020)	Doxapram	1.0 mg/kg	ASA 1	Butorphanol/ dexmedeto-midine/ hydromorphone	Propofol/ dexmedeto-midine	No	Doxapram improved laryngeal function in dogs given dexmedeto-midine. No improvements in the other drug protocols	Yes, before doxapram in propofol group	Yes

Table 3. The effect of the intravenous administration of doxapram hydrochloride to healthy dogs and dogs with laryngeal paralysis (continued)

Reference	Ventilatory stimulant	Dose (bolus)/ titration	Health status	Premedication drugs	Drugs used for induction of anaesthesia	Adverse effects	Results	Passive or paradoxical arytenoid motion	Statistical significance
Labuscagne et al (2019)	Doxapram vs mechanical stimulation	2.5 mg/ kg IV	ASA 1	No	Alfaxalone/ propofol/ thiopental	No	Doxapram more effective in stimulating laryngeal motion. Examination time longest with alfaxalone, despite doxapram	No	Yes

Doxapram was injected intravenously. ASA = American Society of Anesthesiologists; NA = not applicable; N/D = not detected.

KEY POINTS

- Laryngeal examination is required as part of diagnostic investigations in dogs presenting with stridor, change in phonation, coughing and gagging.
- Conditions for laryngeal assessment are a balance between an appropriate plane of anaesthesia allowing muscle relaxation, while minimising depression of laryngeal reflexes.
- Drugs used for premedication and induction of anaesthesia may diminish laryngeal function to differing degrees.
- A variety of anaesthetic drug doses, routes of administration and combinations have been investigated.
- Despite limited evidence, premedication with acepromazine and an opioid before propofol induction may improve the quality of the examination without impairing laryngeal function.

motion was evaluated, as this differed between studies. Arytenoid motion may be absent if the examination is performed too early in the recovery phase, leading to false positive results. Although no assessment technique was superior to another (Radlinsky et al, 2004), the studies used inconsistent methodologies. Subjective and objective assessment methods may have led to variation in the data reported. Even with the calculation of the normalised glottal gap area, variations in the distance between the video scope and the glottal gap area, and assessments by different evaluators, may have generated bias. In general, subjective scoring methods can introduce individual variation when multiple evaluators perform assessments at different time points. Finally, it is important to consider that all studies with one exception (Tobias et al. 2004) assessed the effects of drugs in healthy, American Society of Anesthesiologists I animals and not clinically affected older animals with impaired laryngeal function.

Conclusions

A number of studies have investigated the effects of sedative, opioid and anaesthetic drugs on laryngeal function in dogs. Various drug doses, routes of administration and drug combinations have been investigated using different assessment methods. Although evidence remains limited, data suggest that premedication using acepromazine and an opioid improves the quality of laryngeal examination without impairing laryngeal motion. Dexmedetomidine with an opioid may offer an alternative but there are no studies comparing these sedative drugs explicitly. Examination times are shorter with propofol when compared with alfaxalone, while ketamine is not recommended as an anaesthetic induction agent for this purpose. Doxapram, at a dose of 0.55 mg/kg IV in preference to higher doses, may be sufficient to maximise laryngeal movement, while minimising cardiovascular side effects. However, this study should be repeated in dogs with laryngeal dysfunction to determine whether an assessor can differentiate healthy dogs from those with laryngeal paralysis. CA

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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