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Effect of doxepin on quality of life in Labradors with laryngeal paralysis: A double-blinded, randomized, placebo-controlled trial

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Abstract

Background: Laryngeal paralysis commonly affects older Labrador retrievers. Currently, dogs with severe disease require surgical intervention, most commonly arytenoid lateralization. Anecdotally, doxepin has been proposed to help dogs with laryngeal paralysis.

Hypothesis: Doxepin will improve quality of life measures assessed by owners of Labrador retrievers with laryngeal paralysis not requiring emergency surgery.

Animals: Twenty-two Labrador retrievers with laryngeal paralysis.

Methods: Dogs were randomized to receive doxepin (3-5 mg/kg q12h PO) or placebo for 28 days. Owners completed quality-of-life assessments before and after completing the study. Data were compared between groups using Rank-Sum tests or Fisher's exact tests.

Results: The 2 groups of dogs did not differ at baseline except for owner-perceived degree of ataxia (owners of dogs receiving doxepin considered them more ataxic than owners of dogs receiving placebo). After 28 days, owner-assessed quality of life measures did not differ between dogs receiving doxepin or placebo (dogs worsening: doxepin = 2, placebo = 1; dogs unchanged: doxepin = 6, placebo = 7; dogs improved: doxepin = 4, placebo = 2; $P = .84$). Dogs receiving placebo had a greater improvement in client-assessed overall health than dogs receiving doxepin (mean ranks: doxepin = 4.36, placebo = 6.64; $P = .04$). The study was terminated at this interim analysis.

Conclusions and Clinical Importance: Doxepin did not appear to improve any measures of owner-assessed quality of life in Labrador retrievers with laryngeal paralysis.

KEYWORDS
arytenoid intervention, dogs

1 | INTRODUCTION

Laryngeal paralysis is the predominant observed abnormality of an idiopathic degenerative polyneuropathy of geriatric dogs (termed Geriatric Onset Laryngeal Paralysis and Polyneuropathy), most often affecting Labrador retrievers.[1–8] Laryngeal paralysis results in both an inability to abduct the arytenoids during inspiration and a failure to adduct the arytenoids during swallowing, preventing normal closure of the larynx as food passes into the esophagus. Clinical consequences include changes in bark tone, exercise intolerance, coughing,

respiratory distress, hyperthermia, aspiration pneumonia, and death.[6,8] Many dogs with severe clinical signs require surgery, the most common procedure being unilateral arytenoid lateralization.[1,2,9–11]

Although unilateral arytenoid lateralization alleviates the obstructive component of the disease and improves the quality of life for many dogs, surgery is expensive and can result in short- and long-term postoperative complications.[1,2,4] Complications include immediate postoperative respiratory distress (short-term) and failure to resolve clinical signs (long-term).[1,12] Between 8% and 21% of dogs develop aspiration pneumonia after surgery.[4,9,12–14] An alternative medical treatment that ameliorates clinical signs or delays the need for surgery in dogs with laryngeal paralysis is highly desirable.

Doxepin, a tricyclic antidepressant that primarily inhibits reuptake of serotonin and norepinephrine, is used mostly to treat depression, migraines, and insomnia in humans.[15] It antagonizes multiple serotonin, muscarinic, histamine, and dopaminergic receptors, and its mechanism of action is complex and poorly understood. Anecdotal evidence in veterinary medicine suggests that doxepin improves clinical signs in dogs with laryngeal paralysis. In an unpublished survey of veterinarians who have used doxepin to treat laryngeal paralysis in dogs, 83% of 147 respondents reported observing an improvement in clinical signs as reported by the owners. Of these, 98% reported that the improvement was detectable within 3 weeks. Duration of response ranged from 1 month to >1 year. Adverse events were reported by 32 respondents (22%), consisting of lethargy or hyperexcitability in 26 of these cases. Thus, despite the lack of any critical studies examining the efficacy of doxepin in managing laryngeal paralysis in dogs, some clinicians prescribe doxepin for this disease.

Therefore, using a prospective randomized, placebo-controlled double-blinded study, we examined whether or not doxepin confers a clinical benefit to Labrador retrievers with laryngeal paralysis. We hypothesized that clients would assign higher quality-of-life scores to doxepin-treated dogs than placebo-treated dogs.

2 | MATERIALS AND METHODS

2.1 | Study design

We conducted this randomized, double-blinded, placebo-controlled clinical trial at 2 centers. The study protocol was approved by the Cornell University College of Veterinary Medicine Institutional Animal Care and Use Committee (Protocol #Protocol 2014-0107, granted 11/20/2014). The study was funded by a grant from the ACVIM Foundation (Zoetis SAIM Respiratory Grant, #15-11 ZOETIS). All clients completed an informed consent form.

2.2 | Animals

Client-owned Labrador retrievers with suspected laryngeal paralysis were recruited by 2 of the investigators (J. Sammarco, B. Cerroni) at their referral centers.

2.3 | Inclusion and exclusion criteria

We considered dogs eligible if they were Labrador retrievers with laryngoscopic evidence of laryngeal paresis or paralysis with or without apparent peripheral neuropathy for which no apparent cause could be identified. Dogs with evidence of hypothyroidism or receiving thyroid supplementation were excluded from the study. Dogs with any comorbidities likely to affect their ability to complete the study were excluded. Dogs with a history of conditions with contraindications to doxepin treatment (based on data from humans: urine retention, glaucoma, severe cardiac disease) were excluded. Dogs receiving drugs known to increase doxepin concentrations in humans or known to potentiate serotonin syndrome were excluded. Dogs with laryngeal paralysis likely to require surgical intervention either at presentation or during the study were excluded—this was determined subjectively by the examining investigator and based on the severity of clinical signs described by the owner or at presentation.

2.4 | Randomization and allocation concealment

One investigator (M. Rishniw) randomized dogs to receive either doxepin or a similar capsule of psyllium husk in a randomized block design, with blocks of 4 dogs. We did this to ensure reasonably equal groups at the interim analysis. Randomization was not stratified on any criteria. The randomization sequence was generated using a digital coin-toss (https://www.random.org/coins/?num=4&cur=60-usd.0025c-ct). The investigator then assigned a code to dogs allocated to receive doxepin (A) or placebo (B)—the investigators involved in examining and managing the cases could only identify the treatments by these letters and did not know which letter referred to doxepin and which referred to placebo. The investigator performing the randomization kept the list concealed from all other investigators or clients.

2.5 | Blinding

Only the lead investigator (M. Rishniw) knew the randomization sequence and allocation codes. At the conclusion of the study for each dog, the investigators managing the case (J. Sammarco or B. Cerroni) could open an envelope to reveal the allocation for that dog. This was done because dogs being administered placebo were offered a 1-month course of doxepin as an open-label trial.

2.6 | Study treatments

Doxepin 100 mg capsules (Mylan Pharmaceuticals Inc, Canonsburg, Pennsylvania) were administered PO at a dose of 3 to 5 mg/kg q12h. For all dogs, this equated to 1 capsule q12h. The placebo capsules were administered under the assumption that they contained 100 mg doxepin. Doxepin was used off-label in this study—the drug is not licensed for use in dogs.

2.7 | Concomitant treatments

Routine ecto- and endo-parasite treatment was permitted. Dogs receiving nonsteroidal anti-inflammatory drugs for osteoarthritis could continue to receive these treatments.

Any dog experiencing a respiratory crisis during the study requiring emergency arytenoid lateralization was permitted to undergo that procedure and was eliminated from the study.

2.8 | Schedule of events

Every potentially eligible dog underwent an initial complete physical and neurological evaluation. Dogs considered presumptively eligible had a CBC, routine biochemistry panel, and thyroid panel performed. A week later, all dogs still eligible based on bloodwork results underwent a laryngoscopic examination with light propofol anesthesia to confirm the laryngeal dysfunction and its severity. At this time, the client completed the baseline questionnaire, as did the examining clinicians. We had originally proposed an ultrasonographic evaluation of the vocal chords at this visit.[16] However, the radiologist was unable to obtain satisfactory images in the first 3 dogs examined, and this procedure was eliminated from the protocol. A final recheck examination was performed on or as close to day 28 as possible (on the day of the last doxepin dose). At this examination, the client completed a recheck questionnaire before the examination, and the clinician completed a physical and neurological examination. Once completed, the allocation was revealed to the client and clinician and the client was offered the choice of a 1-month open label trial of doxepin (if originally prescribed placebo) or offered the choice of continuing with doxepin (at their own cost, if originally prescribed doxepin).

2.9 | Baseline laryngoscopic examination

All dogs underwent a laryngoscopic examination by 1 of 2 investigators (J. Sammarco or B. Cerroni). Each dog was positioned in sternal recumbency and anesthetized with propofol (10 mg/mL) at up to 5 mg/kg administered slowly, IV, over 1 to 2 minutes until the mouth could be opened without obvious stress. Dogs were not intubated and a laryngoscope was used to perform laryngeal examination. The investigators assessed laryngeal motion during respiratory excursions, with an assistant verbally identifying the start of each inspiration to aid accurate identification of any paradoxical movement.

2.10 | End points

The primary outcome measure was "clinical improvement" as determined by the client. This was assessed by a series of questionnaires, administered to the client before examination. Briefly, the client was asked to choose whether they believed the dog's signs had improved, remained unchanged, or had deteriorated. Additionally, clients answered questions about the nature of the disease at baseline and at the 28-day re-evaluation, and also used a visual analog scale to quantify the perceived degree of dysfunction in each category. Full questionnaires are included as appendices.

The secondary outcome was the clinician's assessment of the condition based on physical examination findings at baseline and at the 28-day re-evaluation.

Patients entering the open-label phase of the study were contacted after a month via email or telephone interviews to estimate the perceived effect of doxepin.

2.11 | Statistical analyses

2.11.1 | Power analysis

An a priori power analysis was performed to determine the sample population required for the study using a dedicated sample size platform.[17] The primary outcome was the proportion of dogs in each group that were improved at the study completion. Improvement would be assessed by a simple question: "Do you think your pet's quality of life is worse, better, or unchanged since beginning the medication?" The proportion of responses of "better" vs "unchanged or worse" and the proportion of responses of "better or unchanged" vs "worse" between the 2 groups would be compared. Sample size calculations were as follows:

$$\alpha = .045, \beta = .2$$

$$\text{Proportion responding in placebo (control) group} = 0.25$$

$$\text{Proportion responding in doxepin group} = 0.8$$

We determined the study would require 18 patients per group. To allow for losses during the study, 20 patients per group (40 dogs total) were to be recruited. We based our proportions on the results of the unpublished survey that we had conducted before designing the study. In that survey, 83% of respondents claimed that dogs experienced a benefit after being administered doxepin; however, 30% of these respondents claimed that this effect was observed only by the clients. We estimated that a placebo effect would occur in 25% of dogs administered placebo.

2.11.2 | Interim analysis

With the possibility that the drug would have a more noticeable effect (90% of doxepin group appear to be responding, based on evaluation of the primary end point), an interim analysis of the primary endpoint was performed after enrolling 20 dogs (10 dogs per group). We evaluated the primary end point of improvement as assessed by quality of life questionnaires (proportion improved in each group) by a Fisher's exact test for the comparison of 2 independent proportions.[18] For this analysis, α was set at .005 and β was set at .2. If this analysis detected

a difference in responses of 65% or greater, the study would be terminated early. If the *P* value was >.5 at this analysis, the study also would be terminated early, under the assumption that recruitment of additional dogs into the study would be unlikely to alter the probability of finding a statistically significant difference between the groups.

2.11.3 | Final analysis

We evaluated the primary end point of improvement as assessed by quality of life questionnaires (proportion improved in each group) by a Fisher's exact test for the comparison of 2 independent proportions. We further compared the baseline visual analog scale quality of life scores between groups by Rank-Sum tests.[18] We then calculated the change in visual analog scale scores for each dog (baseline minus recheck score) and compared these changes in scores between the 2 groups using Rank-Sum tests. Because of the relatively small sample size, we did not adjust the nominal *P* value for any of these secondary comparisons, using the approach that a positive finding, might warrant further evaluation to confirm the observation, and accepting that this positive finding could be a false positive result.

Finally, we followed the CONSORT guidelines when preparing the manuscript to optimize clarity of reporting our findings.

3 | RESULTS

We enrolled 25 dogs between February 2016 and March 2020; 22 dogs completed the study (Figure 1). Three dogs were excluded from analysis: 2 failed to complete the recheck evaluations, and 1 suffered an acute crisis and was withdrawn from the study to undergo an emergency arytenoid lateralization. All dogs ultimately included in the study had unremarkable bloodwork and normal thyroxine concentrations.

Twelve dogs were randomized to receive doxepin and 10 dogs received placebo. Of the 2 dogs failing to return for recheck evaluation, 1 had been assigned to the doxepin group and the other had been assigned to the placebo group. The dog requiring an emergency arytenoid lateralization had been assigned to the placebo group.

The median dose of doxepin administered to the 12 dogs in the doxepin group was 3.2 mg/kg q12h (range, 2.9-4.0 mg/kg). Dogs received medications for a median of 28 days (range, 27-35 days). Three dogs had pill counts at recheck evaluation that exceeded the estimated residual pills by 1 pill, indicating that these dogs missed 1 of their doses during the 28-day period.

We could detect no differences at baseline between groups except for "owner-perceived ataxia" (Table 1). All dogs in which respiratory noise was evaluated by an investigator (19/22) exhibited stridor either at rest or when panting during the physical examination. All dogs except 1 exhibited absent arytenoid abduction on inspiration bilaterally. The remaining dog (assigned to placebo group) exhibited minimal arytenoid abduction on inspiration bilaterally. Eight of 11 dogs in the doxepin group and 9/10 dogs in the placebo group, in which the clinician attempted to elicit a gag reflex, showed a poor or absent gag reflex. Five Labrador retrievers assigned to receive doxepin and 2 Labrador retrievers assigned to receive placebo had concurrent decreased hindlimb reflexes. These neurologic deficits failed to improve in any of the dogs.

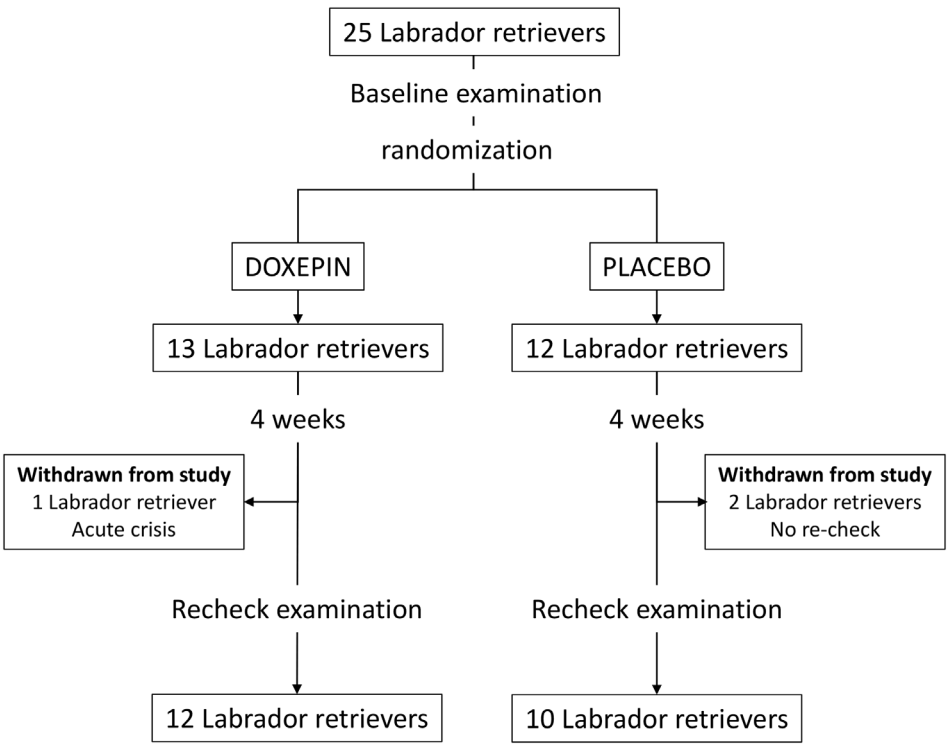

FIGURE 1 Study flowchart

TABLE 1 Baseline characteristics (median, range) of Labrador retrievers with laryngeal paralysis receiving either doxepin or placebo

Variable	Doxepin n = 12	Placebo n = 10	*P* value
Age (y)	11.9 (7.6, 13.1)	11.8 (8.1, 12.9)	
Weight (kg)	32.9 (25.0, 38.9)	31.8 (27.5, 55.3)	
Sex (F/M)	8/4	4/6	
Veterinary overall assessment (mm)[a]	103 (78-117)	109 (94-121)	.24
Client overall assessment (mm)[a]	114 (73-123)	103 (58-120)	.42
Client quality of life assessment (mm)[a]	98 (42-117)	106 (69-123)	.2
Stridor (mm)[a]	44 (15-96)	41 (33-67)	.42
Breathing difficulty (mm)[a]	72 (39-123)	88 (29-107)	.72
Coughing (mm)[b]	80 (52-112)	93 (37-138)	.8
Exercise (mm)[a]	73 (18-121)	71 (24-120)	.9
Activity (mm)[a]	61 (22-110)	69 (26-108)	.36
Mobility (mm)[b]	77 (53-144)	75 (44-136)	1.0
Ataxia (mm)[b]	90 (54-129)	121 (74-137)	**.02**

[a]All scores are reported as marked lengths on a visual analog scale. The higher the score, the better the assessed variable.
[b]All scores except coughing, mobility and ataxia had a maximum possible score of 123; coughing, mobility, and ataxia had a maximum possible score of 144.
Note: P values in bold are <0.05.

TABLE 2 Client-perceived changes in overall quality of life in Labrador retrievers with laryngeal paralysis receiving doxepin or placebo

	Client-perceived change in quality of life Number (%) of dogs responding		
	Worse	No change	Better
Doxepin (n = 12)	2 (17)	6 (50)	4 (33)
Placebo (n = 10)	1 (8)	7 (58)	2 (17)

We could detect no differences in client-perceived improvement in the doxepin group at the interim analysis ($P = .84$; Table 2). Therefore, based on the predetermined criteria, we terminated the study at this point.

When we compared changes in client-perceived characteristics, we could detect no benefit of doxepin for any characteristic (Table 3). Clients of dogs assigned to receive placebo gave their dogs a greater improvement in "overall health assessment" at the recheck visit than clients of dogs assigned to receive doxepin.

3.1 | Open-label study

Of the 12 dogs originally assigned to receive doxepin, 4 clients elected to continue doxepin treatment indefinitely. Of these, 3 felt that the drug helped although follow-up with these dogs was for only 1 month.

Of the 10 dogs originally assigned to receive placebo, 9 clients elected to receive complimentary doxepin for 1 month. Of these, 4 clients felt that the drug did not help, while 5 felt that it helped at a 1- to 2-month follow-up.

4 | DISCUSSION

Our double-blinded, randomized, placebo-controlled study failed to identify a benefit of administering doxepin to Labrador retrievers with laryngeal paralysis at the interim analysis, warranting early termination of the study. Assessment of all the available measured variables failed to demonstrate any benefit in any subanalyses. Based on these results, we cannot recommend the routine administration of doxepin to Labrador retrievers for the treatment of laryngeal paralysis.

We conducted the study without any knowledge, preconception, or consideration of a putative mechanism by which doxepin would improve laryngeal function or clinical signs associated with laryngeal paralysis. Instead, we tested the anecdotal evidence in a more rigorous manner—had we detected an effect, further studies would be warranted to examine mechanisms by which doxepin might exert a benefit.

Our study stresses the need for randomized, controlled, and blinded clinical trials when assessing subjective responses to medical interventions. Two clients in the placebo arm reported improvement in their dogs. Similarly, several clients in the open-label component of the study thought their dogs improved after receiving doxepin. This underscores the high probability of a caregiver placebo effect and optimism bias in interventional studies, as other investigators have reported.[19]

All dogs in our study were lightly anesthetized with propofol to evaluate laryngeal function. Studies have shown varied and

TABLE 3 Changes in client-assessed characteristics (median, range) in Labrador retrievers with laryngeal paralysis receiving doxepin or placebo

Variable[a]	Doxepin n = 12	Placebo n = 10	*P* value
Client overall assessment	−14 (−76 to 8)	0 (−20 to 35)	**.04**
Client quality of life assessment	−2 (−31 to 5)	−9 (−24 to 12)	.75
Stridor	20 (−33 to 48)	16 (−29 to 95)	.71
Breathing difficulty	8 (−69 to 43)	0 (−29 to 38)	.84
Coughing[b]	17 (−69 to 85)	2 (−25 to 72)	.73
Exercise	−4 (−19 to 27)	−1 (−25 to 73)	.64
Activity	−1 (−20 to 27)	−4 (−29 to 10)	.57
Mobility[b]	−6 (−41 to 33)	25 (−9 to 69)	.06
Ataxia[b]	0 (−51 to 37)	4 (−16 to 66)	.54

[a]All scores are reported as differences in mm between baseline values and post-treatment values in marked lengths on a visual analog scale. Positive scores reflect improvement, negative scores reflect worsening. Differences between groups were compared with Rank-Sum tests.
[b]All scores except coughing, mobility and ataxia had a minimum/maximum possible score of ±123; coughing, mobility, and ataxia had a minimum/maximum possible score of ±144.

inconsistent results of propofol anesthesia on laryngeal function in dogs.[20–22] All the dogs in our study received <5 mg/kg propofol (often <3 mg/kg), which might not suppress arytenoid movement as much as higher doses. All dogs had adequate laryngeal exposure and respiratory excursions during laryngeal examination. Therefore, we were confident of the diagnosis of laryngeal paralysis in all cases, based on the laryngeal evaluation.

Our study was not designed to assess safety or harm. We observed no dramatic, catastrophic adverse events in any of the dogs receiving doxepin, but cannot make any claim about the safety of administering doxepin to dogs. Our unpublished anecdotal data (a survey of veterinarians) suggest that adverse events are uncommon and consist mostly of either sedation or excitement.

We used an unvalidated quality of life questionnaire for this study. Therefore, whether we would be able to accurately identify small differences between groups remains unknown. Furthermore, our study examined client perceptions of quality of life and improvement in clinical signs over only a 1-month period of doxepin administration. We based this on anecdotal evidence from clients and veterinarians who suggested that doxepin improved breathing in Labrador retrievers (and other breeds) with laryngeal paralysis within this same time frame. Furthermore, because clients are unlikely to agree to repeat laryngoscopic evaluations and because we considered that client satisfaction with the outcome matters more than any objective measure of improved function, we used a questionnaire to determine whether doxepin exerted any clinically meaningful benefits. Therefore, we did not have the opportunity to determine whether arytenoid abduction changed after doxepin administration.

Our study only examined a small number of Labrador retrievers with laryngeal paralysis. However, based on the sample size calculations, we should have been able to detect a difference in proportions of dogs responding of 0.55, so, assuming 2 dogs receiving placebo showed improvement, we would require 8 dogs receiving doxepin to also demonstrate improvement. However, we performed the interim analysis mostly to determine if continuing the study would be futile. We would only have required 5 dogs receiving doxepin to show improvement to continue the study to conclusion. Our results at the interim analysis suggested that recruiting additional dogs would be unlikely to change our outcome, so we terminated the study.

5 | CONCLUSIONS

Our small prospective randomized, placebo-controlled clinical trial failed to identify any consistent effect of doxepin in client-perceived improvement in quality of life of Labrador retrievers with laryngeal paralysis.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by Cornell University College of Veterinary Medicine IACUC, protocol number 2014-0107, granted November 20, 2014.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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REFERENCES

1. Snelling SR, Edwards GA. A retrospective study of unilateral arytenoid lateralisation in the treatment of laryngeal paralysis in 100 dogs (1992–2000). *Australian Veterinary Journal*. 2003;81(8):464-468. https://doi.org/10.1111/j.1751-0813.2003.tb13361.x.
2. Hammel SP, Hottinger HA, Novo RE. Postoperative results of unilateral arytenoid lateralization for treatment of idiopathic laryngeal paralysis in dogs: 39 cases (1996-2002). *J Am Vet Med Assoc*. 2006;228:1215-1220.
3. Schofield DM, Norris J, Sadanaga KK. Bilateral thyroarytenoid cartilage lateralization and vocal fold excision with mucosoplasty for treatment of idiopathic laryngeal paralysis: 67 dogs (1998-2005). *Vet Surg*. 2007;36:519-525.
4. MacPhail CM, Monnet E. Outcome of and postoperative complications in dogs undergoing surgical treatment of laryngeal paralysis: 140 cases (1985-1998). *J Am Vet Med Assoc*. 2001;218(12):1949-1956.
5. Gaber CE, Amis TC, LeCouteur RA. Laryngeal paralysis in dogs: a review of 23 cases. *J Am Vet Med Assoc*. 1985;186:377-380.
6. Kitshoff AM, Van Goethem B, Stegen L, Vandekerckhov P, De Rooster H. Laryngeal paralysis in dogs: An update on recent knowledge. *Journal of the South African Veterinary Association*. 2013;84(1): https://doi.org/10.4102/jsava.v84i1.909.
7. Thieman KM, Krahwinkel DJ, Sims MH, Shelton GD. Histopathological Confirmation of Polyneuropathy in 11 Dogs With Laryngeal Paralysis. *Journal of the American Animal Hospital Association*. 2010;46(3): 161-167. https://doi.org/10.5326/0460161.
8. Sample SJ, Stilin A, Binversie EE, Baker LA, Hardie RJ. Late-onset laryngeal paralysis: owner perception of quality of life and cause of death. *Vet Med Sci*. 2020;6:306-313.
9. Perez Lopez P, Barnes DC, Nelissen P, Demetriou J. Outcome of two variations of a surgical technique performed for canine unilateral arytenoid lateralisation. *Vet Rec*. 2019;185:1-8.
10. Sample SJ, Hardie RJ, Stein J, Webb J. Evaluation of Translaryngeal Percutaneous Arytenoid Lateralization (TPAL) in dogs with experimentally created laryngeal paralysis. *Res Vet Sci*. 2018;117:239-245.
11. Monnet E. Surgical Treatment of Laryngeal Paralysis. *Veterinary Clinics of North America: Small Animal Practice*. 2016;46(4):709-717. http://dx.doi.org/10.1016/j.cvsm.2016.02.003.
12. Wilson D, Monnet E. Risk factors for the development of aspiration pneumonia after unilateral arytenoid lateralization in dogs with laryngeal paralysis: 232 cases (1987–2012). *J Am Vet Med Assoc*. 2016; 248:188-194.
13. Weinstein J, Weisman D. Intraoperative evaluation of the larynx following unilateral arytenoid lateralization for acquired idiopathic laryngeal paralysis in dogs. *J Am Anim Hosp Assoc*. 2010;46:241-248.
14. Millard RP, Tobias KM. Laryngeal paralysis in dogs. *Compend Contin Educ Vet*. 2009;31:212-219.
15. Almasi A, Meza CE. Doxepin [Internet]. Stat Pearls. 2020. https://www.ncbi.nlm.nih.gov/books/NBK542306/. [Accessed October 6, 2020].
16. Rudorf H, Barr FJ, Lane JG. The role of ultrasound in the assessment of laryngeal paralysis in the dog. *Vet Radiol Ultrasound*. 2001;42: 338-343.
17. Dupont WD, Plummer WD. Power and sample size calculations. A review and computer program. *Control Clin Trials*. 1990;11:116-128.
18. Hammer O, Harper DAT, Ryan PD. PAST: paleontological statistics software package for education and data analysis. *Paleontol Electron*. 2001;4:1-9.
19. Conzemius MG, Evans RB. Caregiver placebo effect for dogs with lameness from osteoarthritis. *J Am Vet Med Assoc*. 2012;241:1314-1319.
20. Brown MB, Dugat DR, Lyon SD, et al. Comparison of methohexital and propofol as induction agents for evaluation of laryngeal function in healthy dogs. *Vet Surg*. 2019;48:70-78.
21. McKeirnan KL, Gross ME, Rochat M, Payton M. Comparison of propofol and propofol/ketamine anesthesia for evaluation of laryngeal function in healthy dogs. *J Am Anim Hosp Assoc*. 2014;50:19-26.
22. Ambros B, Gaunt MC, Duke-Novakovski T, Taylor SM. Effects of alfaxalone, thiopental, or propofol and diazepam on laryngeal motion in healthy dogs. *Can Vet J*. 2018;59:791-795.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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