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Prospective evaluation of the efficacy of inhaled steroids administered via the AeroDawg spacing chamber in management of dogs with chronic cough

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Abstract

Background: Glucocorticoids are frequently required for management of cough because of inflammatory airway disease (IAD) and airway collapse (AWC).

Objectives/Hypothesis: To determine the efficacy and feasibility of inhaled administration of corticosteroids in controlling cough in dogs with noninfectious airway disease.

Animals: Thirty-six client-owned dogs.

Methods: Dogs were prospectively recruited for this placebo-controlled cross-over study. Inflammatory airway disease was diagnosed through bronchoalveolar lavage cytology. Airway collapse was diagnosed through bronchoscopy, or if dogs were unsuitable anesthetic candidates, by crackles on auscultation, radiographic changes in airway diameter, or fluoroscopy. Dogs were randomly assigned to receive placebo or fluticasone propionate for the first 2 weeks of the trial then crossed over to fluticasone. A quality of life (QOL) survey (best score 0, worst score 85) was completed at 0 and 6 weeks. A visual-analog cough survey was submitted at 0, 2, 4, and 6 weeks to assess cough, feasibility, and adverse effects of treatment.

Results: For 32 dogs, QOL score at study end (**mean 11.3 ± 9.7**) was significantly lower ($P < .0001$) compared to entry (**mean 28.1 ± 14.1**), with a median change of 69% in QOL score, indicating improved quality of life. Cough frequency, duration, and severity were significantly ($P < .0001$) decreased at study end. Feasibility of aerosolized delivery improved with continued use ($P = .05$) with only 1 dog unable to accept inhaled medication.

Conclusion and Clinical Importance: This study supports the utility of fluticasone propionate by inhalation in management of cough in dogs with IAD and AWC.

KEYWORDS
bronchitis, bronchomalacia, fluticasone, metered-dose inhaler

Abbreviations: AWC, airway collapse; BAL, bronchoalveolar lavage; BCS, body condition score; BOAS, brachycephalic obstructive airway syndrome; CB, chronic bronchitis; ELD, eosinophilic lung disease; ER, extended-release; FETCH, functional evaluation of cardiac health questionnaire; HPAA, hypothalamic pituitary adrenal axis; IAD, inflammatory airway disease; MMVD, myxomatous mitral valve disease; SDVAS, visual analog scale; VMTH, veterinary medical teaching hospital.

1 | INTRODUCTION

Common causes of cough in the dog include chronic bronchitis (CB), airway collapse (AWC), and eosinophilic lung disease (ELD). Although distinct diseases, combinations of these disorders also occur, and progressive inflammatory and mechanical insults to the lower airways perpetuate the cough cycle. Airway collapse can sometimes be visualized on plain radiography but fluoroscopy and bronchoscopy increase sensitivity and specificity.[1-3] Computed tomography can also be used to document AWC but general anesthesia is required to obtain inspiratory and expiratory scans.[4] Bronchoscopy and bronchoalveolar lavage (BAL) cytology and culture are required for diagnosis of inflammatory airway diseases (IAD), such as CB and ELD.[1,5] Despite a plethora of treatments, steroids are considered the mainstay.[6,7] While management strategies are not curative, the goal of medical therapy is to minimize the severity of cough, thus improving the quality of life (QOL) for owners and dogs and limiting the progression of airway injury.

In humans and cats with airway disease, inhaled administration of corticosteroids is proven efficacious in controlling cough and is considered standard of care in place of oral administration of corticosteroids.[8-12] Treatment for cough is often multifactorial, and corticosteroids are usually just 1 part of treatment, with use of extended-release (ER) theophylline, weight loss, environmental control, and cough suppressants often employed depending on the clinical situation. While oral administration of corticosteroids is rapidly effective in dogs, discontinuation often results in recrudescence of clinical signs, and long-term oral administration of corticosteroid therapy is typically required.[6] Furthermore, oral administration of corticosteroid therapy can result in systemic adverse effects including polyphagia, weight gain, polydipsia and polyuria, muscle atrophy, and lethargy, which can complicate other facets of medical management for chronic cough.[13] Oral administration of corticosteroids is contraindicated in dogs with diabetes mellitus, renal disease, or significant cardiac disease.[14] In contrast to oral administration of corticosteroids, inhaled administration allows for direct delivery of drug to the airways, resulting in fewer systemic adverse effects and minimal suppression of the hypothalamic pituitary adrenal axis (HPAA).[15,16] Given concerns regarding routine use of oral administration of corticosteroids, inhalation could be a viable alternative for use in the dog. Inhalation of corticosteroids requires use of a metered-dose inhaler, spacer, and facemask. While inhaled administration does require a period of acclimation for the dog, metered-dose inhalers have proven a reliable means of delivering fluticasone to the lower airways.[17]

To date, no prospective study has investigated the efficacy of inhaled corticosteroids in dogs with IAD and AWC but inhaled corticosteroids are anecdotally recommended for management. Smaller retrospective studies have provided preliminary evidence that inhaled corticosteroids are efficacious at controlling cough in CB and in some dogs with ELD.[18,19] The goal of this study was to evaluate the efficacy of inhaled corticosteroids in controlling chronic cough in dogs and to assess the feasibility of inhaled medication administration over a 6-week period. We predicted that the corticosteroid fluticasone propionate by inhalation would reduce cough severity and frequency by at least 50% in dogs with IAD and AWC and would be feasible to administer.

2 | MATERIALS AND METHODS

Client-owned dogs presented to the University of California, Davis Veterinary Medical Teaching Hospital (VMTH) between November of 2020 to May of 2022 for evaluation of chronic cough of at least 2 months duration were screened for inclusion in this prospective, placebo-controlled study. Owners provided informed consent, and the Institutional Animal Care and Use Committee at the University of California, Davis approved all procedures. Enrolled dogs had a physical examination, CBC, serum biochemistry profile, and 3-view thoracic radiographs performed at a minimum. Some dogs had fluoroscopy performed, and all dogs underwent bronchoscopy unless a concurrent medical condition, such as ACVIM myxomatous mitral valve disease (MMVD) stage B2/C[20] or International Renal Interest Society stage III-IV chronic kidney disease,[21] precluded anesthesia. In the latter situation, a diagnosis of AWC was made based on criteria described below. Signalment, weight, body condition score (BCS), duration of cough, co-morbidities, and current and prior therapies were recorded for each dog. The proportion of affected dog breeds in the study cohort was compared to the proportion of breeds of all dogs presented to the teaching hospital from November of 2020 to May 2022 to identify over-represented breeds.

Diagnosis of AWC was made based on documentation of luminal changes in tracheal or bronchial diameter on radiographs or fluoroscopy, or identification of tracheal or bronchial collapse during bronchoscopy.[1,2] When bronchoscopy could not be performed, diagnosis was based on a combination of the following criteria: presence of inspiratory or expiratory crackles or expiratory effort on physical examination, lack of clinical or radiographic evidence of aspiration-related, foreign body, or neoplastic disease, and observation of luminal changes in airway diameter on radiographs or fluoroscopy. Inflammatory airway disease was diagnosed based on documentation of increased cell counts and percentages in BAL fluid. Diagnoses of CB and ELD were made based on documentation of neutrophilic or eosinophilic airway inflammation (respectively) in BAL or tracheal wash fluid, in the absence of bacterial infection.[5,22] Specifically, dogs with CB had greater than 12% neutrophils based on a BAL differential cytology count and dogs with ELD had >14% eosinophils.[23,24] Dogs with BAL lymphocytosis (>20% lymphocytes) were also identified and assigned a diagnosis of IAD.[25] Dogs were excluded if corticosteroids or antibiotics had been administered within 14 days of enrollment. Dogs on cough suppressants for more than 1 month before enrollment were allowed to continue on cough suppressants as long as no contraindications (ie, bronchiectasis) were identified during the workup. Previously prescribed cardiac medications, such as furosemide and pimobendan, were permitted if dogs had been on these drugs for at least 1 month before enrollment. Enrolled dogs were not allowed to receive a new cough suppressant or anti-emetic during the

6-week study period. At the time of enrollment, additional therapeutics, such as weight loss, nebulization, and environmental change were instituted at the discretion of the clinician. Use of additional medications such as ER theophylline was discouraged but was allowed when the primary clinician felt it appropriate for the animal's well-being, which was typically based on the severity of cough ascribed to diagnosed or suspected bronchomalacia. No changes in diet were permitted with the exception of a prescription weight loss diet when deemed necessary.

A random number generator (Random.org, Randomness and Integrity Services Ltd., Dublin, Ireland) was used to determine whether an enrolled dog received a placebo metered-dose inhaler (Emergency Medical Products, Dublin, Ohio, USA) or fluticasone propionate (Flovent, 110 mcg/puff, GlaxoSmithKline, Brentford, Middlesex, UK) at the start of the study. The 2 metal cannisters were similar in appearance and were placed in the plastic dispensing unit made for Flovent with any labels covered with tape. The concentration of fluticasone (110 mcg/puff) used in this study is the mid-range concentration available, and was chosen here based on its use in in a separate study.[18] All dogs were prescribed inhalation of 1 puff of inhaled treatment twice daily for 6-8 breaths through a large or small AeroDawg spacing chamber (Trudell Medical International, London, ON, Canada) depending on dog size. An in-person training session between the owner and clinical team was performed at the beginning of the study to demonstrate appropriate use of aerosolized medications. The owners were instructed to acclimate the dog to the facemask over 2-3 days before activating the metered dose inhaler.

At the time of enrollment and at 6 weeks, owners completed a previously validated QOL survey (functional evaluation of cardiac health [FETCH] questionnaire). The FETCH questionnaire consists of 18 questions for a total of 85 points, with higher scores representing worse QOL. It was designed to assess QOL in dogs with congestive heart failure and correlates with disease severity.[26] This survey was successfully applied to dogs with respiratory disease in a study of pulmonary hypertension.[27] The FETCH survey provides assessment of QOL with significant overlap in clinical signs observed in both cardiac and respiratory disease but does not evaluate cough in depth. Therefore, at the time of enrollment, 2, 4, and 6 weeks, owners also completed a cough survey, which assessed cough characteristics (frequency, duration, severity), ease of administration of inhaled medications, and corticosteroid-related adverse effects using a visual analog scale (VAS; Figures S1 and S2). To assess survey characteristics, 10 dog-owning clients of the VMTH were asked to complete the survey and provide feedback on the ease with which it could be completed and to identify any ambiguities in questions. The survey was then modified into its current state based on this feedback, and free text boxes were included for comments. The questionnaire was designed with both qualitative questions and 100-point VAS. Objective data were obtained from the VAS scale as the distance recorded by owners for each question. A higher score on the 100-point scale corresponded to a more pronounced cough.

To date, no study has used this novel survey to evaluate a cohort of dogs with cough. Therefore, an adequate response to therapy was defined as a reduction in owner-perceived clinical signs by 50% on the 100-point cough survey scale. A power calculation was performed before enrollment. A conservative assumption determined that a standard deviation (SD) of 20 should capture most changes on this scale because the assessment included 100 points. The null hypothesis was defined as no change in the 100-point scale for cough frequency, duration, or severity with an alternative hypothesis that there would be 50% reduction along the 100-point scale for those measures. By performing a 1-arm 2-sided *t* test using a power calculator (Cancer Research and Biostatistics, Seattle, Washington, USA), a sample size of 9 dogs afforded a power of 0.8 with a probability of Type I error of 0.05 and alternative mean of 1.9. Data were stratified among 4 different groups—dogs with IAD, AWC, ELD, and multiple disease processes; therefore, the target population included 36 dogs.

Interim analysis of the placebo arm of the trial was planned after recruitment of ~½ of the dogs in this study (n = 18) to include approximately equal numbers of placebo control and treated dogs. Statistical evaluation was planned to evaluate for differences in FETCH and cough scores.

All surveys were distributed via an online platform (REDCap, Vanderbilt University, Nashville, Tennessee, USA). After completing the survey at the 2-week time point, clients were unmasked to therapy. Dogs receiving placebo were moved to the fluticasone propionate treatment arm, and owners completed cough surveys at 2 and 4 weeks of fluticasone therapy for comparison with other dogs in the study at those same time points. A placebo was used to assess the effects of fluticasone on cough and QOL. Dogs initially receiving placebo were switched to fluticasone because of ethical concerns of withholding treatment longer than 2 weeks. Dogs that did not improve or those cases where owner or dog compliance precluded treatment were transitioned to alternate therapy.

2.1 | Statistical analysis

Dogs were grouped in categories of IAD (CB, ELD, lymphocytic inflammation) with or without AWC and AWC alone. Responses to each VAS measurement and the sum of FETCH scores were assessed for normality using the D'Agostino & Pearson Omnibus method. Normally distributed data are presented as mean ± SD and nonparametric data as median with range.

Summed FETCH survey scores from study entrance were compared to those calculated at completion of the treatment period using a paired *t* test. Results for each question on the VAS and summed responses at day 0, week 2, week 4, and week 6 were assessed using a repeated measures Friedman test followed by Dunn's multiple comparison tests. Data from dogs with a presumptive diagnosis of AWC were compared to that of dogs that had undergone complete diagnostic testing to assess for differences. After completion of the placebo portion of the trial, data were collated for comparison of treatment with fluticasone only, resulting in comparisons of day 0 to day 14 and day 30 of fluticasone treatment. Statistical analyses were performed using a commercially available statistical software package (GraphPad

Prism v 9.4.0, San Diego, California, USA) and significance was set at $P < .05$.

Statistical analysis was performed with all dogs and again separately, without dogs that were prescribed ER theophylline.

3 | RESULTS

A total of 36 dogs were enrolled in the study, however, 4 dogs were dropped from the study because of sudden death (n = 1), euthanasia because of atrial fibrillation (n = 1), poor dog compliance (n = 1), and lack of owner compliance (n = 1). Median age in 32 dogs was 11.3 years (range 4-16 years). Seventeen dogs were castrated males, 2 intact males, and 13 spayed females. Represented breeds included mixed breed dogs (n = 11), Chihuahua (6), Cavalier King Charles spaniel (4), Pomeranian (3), Yorkshire terrier (2), Shih Tzu (2), Australian shepherd (1), Maltese (1), Brussels Griffon (1), and miniature dachshund (1). The Chihuahua and Cavalier King Charles Spaniel were over-represented compared to the general cohort presenting to the University of California, Davis VMTH during this same time frame. Three of the Cavalier King Charles Spaniels had a presumptive diagnosis of AWC and 1 underwent bronchoscopy. Equal numbers of Chihuahuas underwent bronchoscopy as compared to those that did not. Weight for all dogs ranged between 1.6 and 11.3 kg (median, 5.9 kg), and BCS ranged between 4 and 8 (median, 6). Three of the 32 dogs (9%) were prescribed ER-theophylline, however no additional medications were started in the remaining 29 dogs. Of the dogs who were prescribed ER theophylline, 1 was prescribed placebo initially.

Seventeen dogs underwent general anesthesia for bronchoscopy and BAL. Fifteen had a diagnosis of IAD with AWC, 1 had AWC alone, and 1 had IAD alone. For IAD, there was neutrophilic (4), neutrophilic and eosinophilic (3), histiocytic (3), lymphocytic (2), eosinophilic (1), lymphocytic and eosinophilic (2), and neutrophilic, eosinophilic, and histiocytic (1) inflammation. Because of low numbers of dogs within specific categories of inflammation, all dogs were considered together under the umbrella of IAD. Eight of the dogs undergoing bronchoscopy had bronchiectasis of varying degrees. Fifteen dogs had comorbidities that precluded general anesthesia including MMVD Stage B2 (n = 10) and MMVD stage C (n = 5). All dogs in the latter category were assigned a diagnosis of AWC.

During the placebo phase of the study, dogs were randomly assigned to receive placebo inhalant for the first 2 weeks of the trial (n = 9) or fluticasone propionate therapy (n = 11; Figure 1). Baseline FETCH scores and cough scores did not differ between groups ($P > .05$). However, dogs receiving fluticasone had a greater change in FETCH score compared to placebo ($P = .003$) for those who had

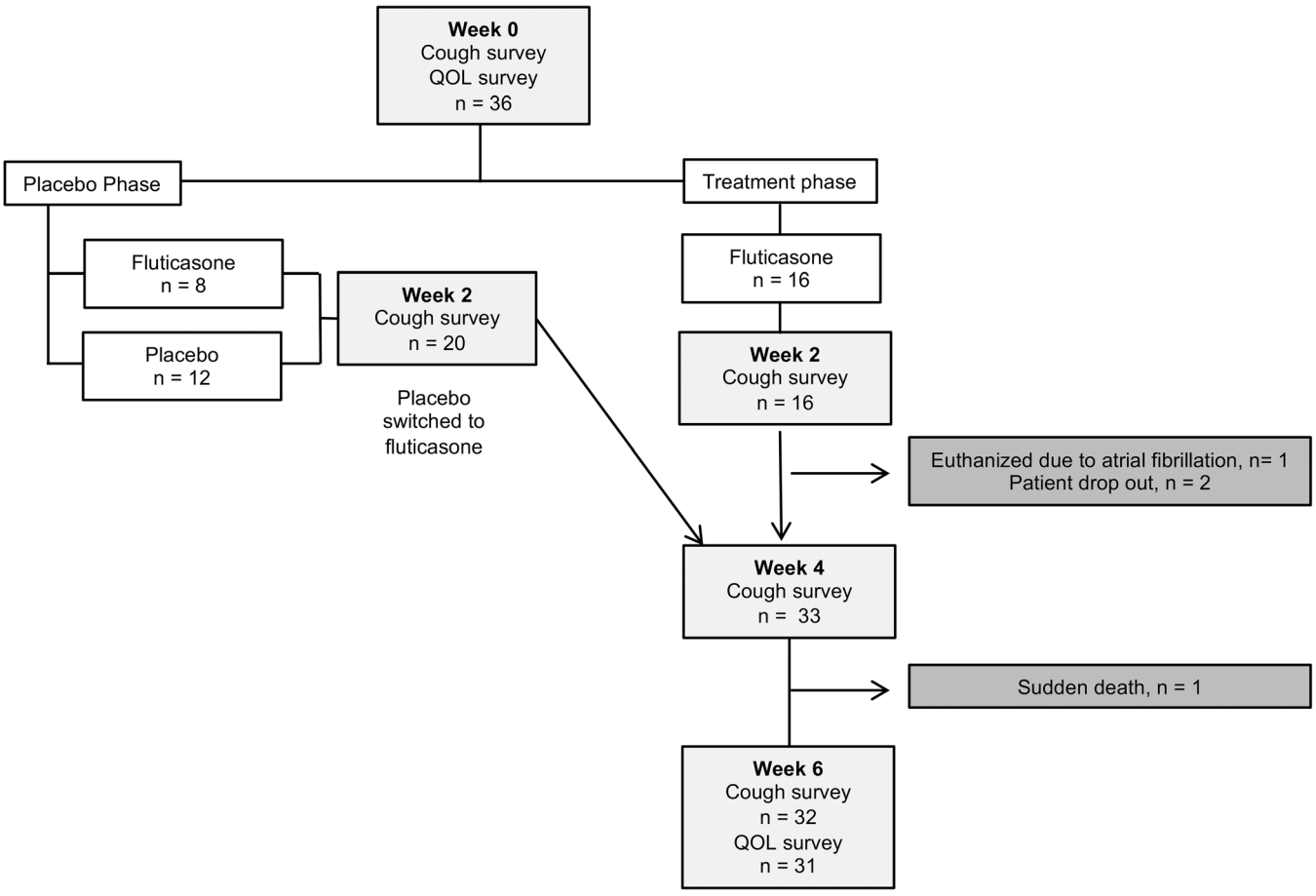

FIGURE 1 Consort diagram. QOL, quality of life.

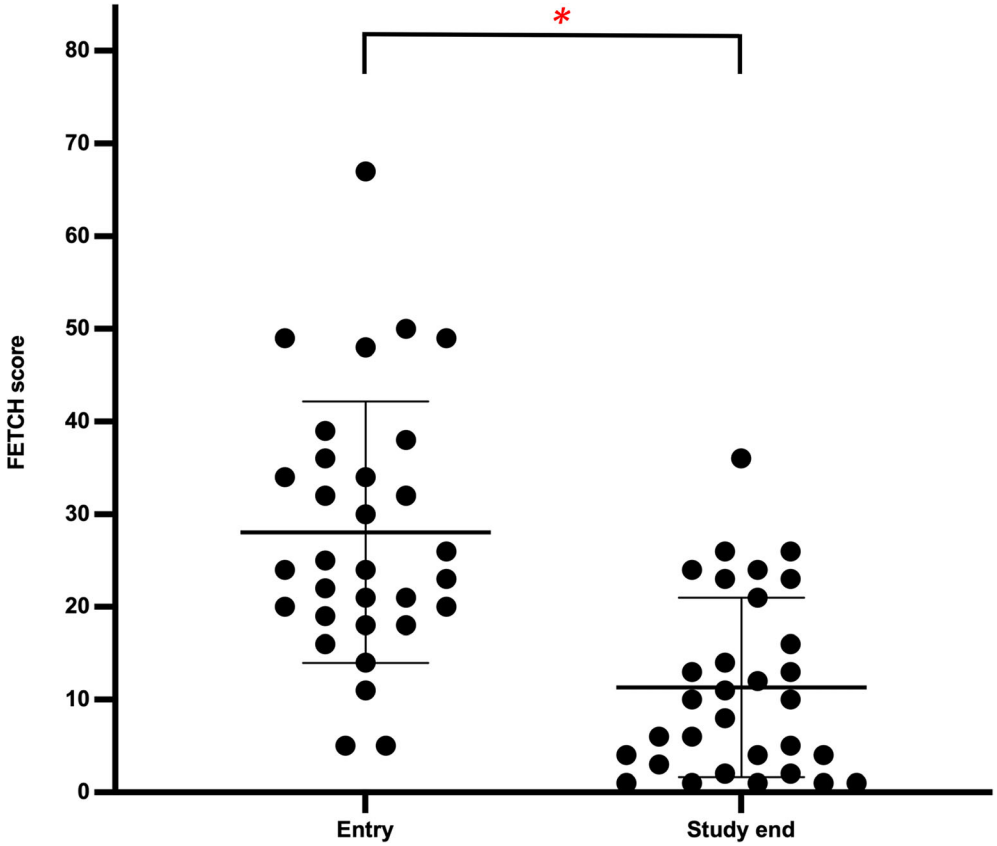

FIGURE 2 Functional evaluation of cardiac health questionnaire (FETCH) score (maximum possible 85) was significantly lower at study end compared to study entry ($P < .0001$). Filled circles represent individual values, lines represent mean ± SD. *$P < .0001$.

completed the study at the time of the interim analysis. Cough scores were also significantly reduced in dogs on fluticasone treatment compared to placebo ($P = .01$, data not shown). All dogs that had received placebo were switched to fluticasone propionate inhalation to complete the trial, and the placebo arm of the study was discontinued.

Cough surveys were completed in 32 dogs and FETCH surveys in 31 dogs at study end. FETCH score at baseline (28.1 ± 14.1) was significantly higher than at study completion (11.3 ± 9.7, $P < .0001$; Figure 2). There was a median 69% (range, 7%-96%) decrease in FETCH scores from the start to the end of study. Individual cough frequency, duration, and severity and total cough scores were significantly higher at baseline than at weeks 2 and 4 of treatment ($P < .0001$; Figure 3). There were no significant differences between scores obtained at weeks 2 and 4. Percent reduction in features of cough is presented in Table 1. There was no significant difference in response to fluticasone therapy for total cough score between dogs that had bronchoscopy performed to confirm a diagnosis compared to those that had a presumptive diagnosis of bronchomalacia made based on physical examination and imaging findings (data not shown).

Median client satisfaction with treatment response was 91 out of 100 (range 56-100) on a VAS, with a higher score representing greater satisfaction. When assessing client satisfaction in regards to weeks of fluticasone treatment, satisfaction was considered significantly improved between weeks 2 and 6 ($P = .03$) but not significantly different between weeks 2 and 4 ($P = .2$). Client satisfaction at the end of study did not differ between dogs that had bronchoscopy and those that did not ($P = .18$; Table 2). Ease of aerosol drug administration significantly improved over the course of the study period ($P = .05$; Figure 4), and only 1 out of the 32 dogs was removed because of poor dog compliance. Ease of administration on the VAS scale was 22.5 out of 100 (range, 0-77) at week 2 compared to 9 out of 100 (range, 0-69) at week 6 with a lower score corresponding to improved ease.

Potential adverse effects of therapy were reported for 16/32 (50%) dogs (Table 3). The most common reported adverse effects were polyphagia (7/32, 22%), polyuria and polydipsia (5/32, 16%), and panting or sleeping more than usual (4/32 each, 13%). Adverse effects did not lead to the cessation of fluticasone in any dog. Adverse effects noted after 2 weeks of placebo were reported in 3 dogs and included increased panting (1), pot belly (1), and polyphagia (1).

Repeat analysis of FETCH and cough scores was performed after removal of 3 dogs that were prescribed ER theophylline and significance was retained. Of the 3 dogs, 2 did not undergo bronchoscopy and 1 did.

4 | DISCUSSION

Fluticasone significantly improved QOL and cough frequency, duration, and severity in dogs with AWC and IAD. While coughing did not fully resolve, total cough scores and individual cough frequency, duration, and severity decreased by a median of at least 50% across this group of dogs although there was variation in response among dogs.

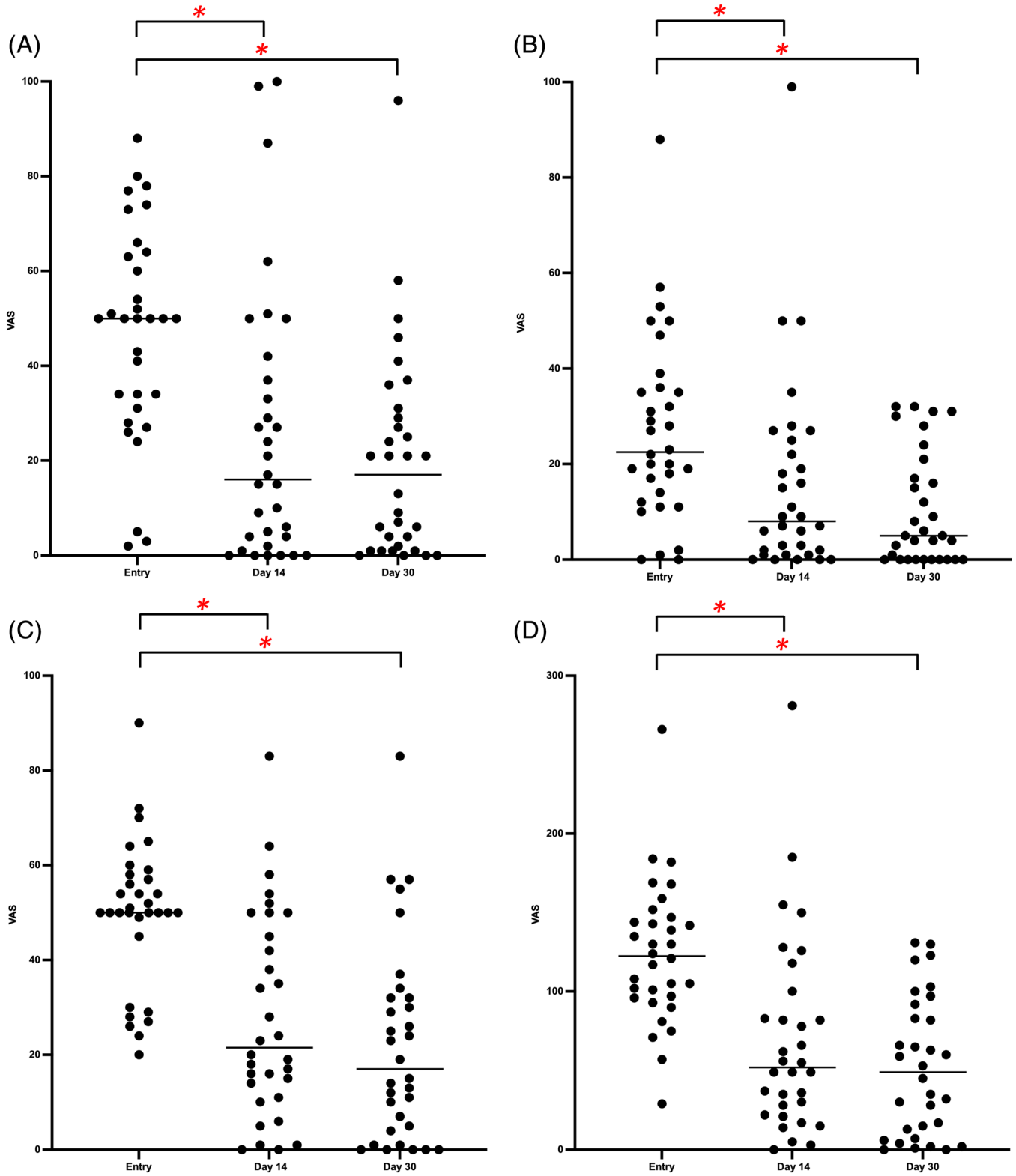

FIGURE 3 Surveys used a visual analog scale (VAS) to evaluate frequency (A), duration (B), and severity (C) of cough as well as total cough scores (D) at study entry and after 14, 30, and 45 days. Values were significantly different ($P < .0001$) between study entry and days 14 and 30 but not between days 14 and 30. *$P < .0001$.

Furthermore, fluticasone effects on cough were achieved within the first 2 weeks of therapy, suggesting little lag time in response to therapy. Anecdotally, response to inhaled medications has been suggested to require at least 2 weeks of treatment but that was not our experience. Cough response at 4 weeks of therapy was similar to that at 2 weeks, leading us to conclude that if an individual dog has not had

TABLE 1 Number (%) of dogs that had >50% improvement in features of cough after 4 weeks of fluticasone by inhalation, including frequency, duration, severity, and total cough score compared to dogs that did not have >50% improvement.

	Percent improvement in cough score Median (range)	Dogs that improved >50%	Dogs that had bronchoscopy performed that did not improve	Dogs that did not have bronchoscopy performed that did not improve
Frequency	66% (−600 to 100)	23/32 (72%)	5/17 (29%)	4/15 (27%)
Duration	59% (−200 to 100)	18/32 (56%)	8/17 (47%)	6/15 (40%)
Severity	59 (−66 to 100)	19/32 (60%)	8/17 (47%)	5/15 (33%)
Total score	69 (−83 to 100)	20/32 (63%)	8/17 (47%)	4/15 (27%)

TABLE 2 Owner satisfaction with dogs during fluticasone propionate therapy.

Duration of Flovent therapy		2 weeks	4 weeks	6 weeks
All dogs	Sample size	n = 32	n = 32	n = 20
	Median (range)	79 (10-100)	83 (26-100)	97 (56–100)
Bronchoscopy	Sample size	n = 17	n = 17	n = 10
	Median (range)	79 (50-100)	78 (26-100)	93 (56-100)
No bronchoscopy	Sample size	n = 15	n = 15	n = 10
	Median (range)	79 (10-100)	93 (61-99)	99 (66-100)

Note: Client satisfaction is presented as a median and range. Client satisfaction is out of a 100-point scale with a higher score corresponding to higher satisfaction.

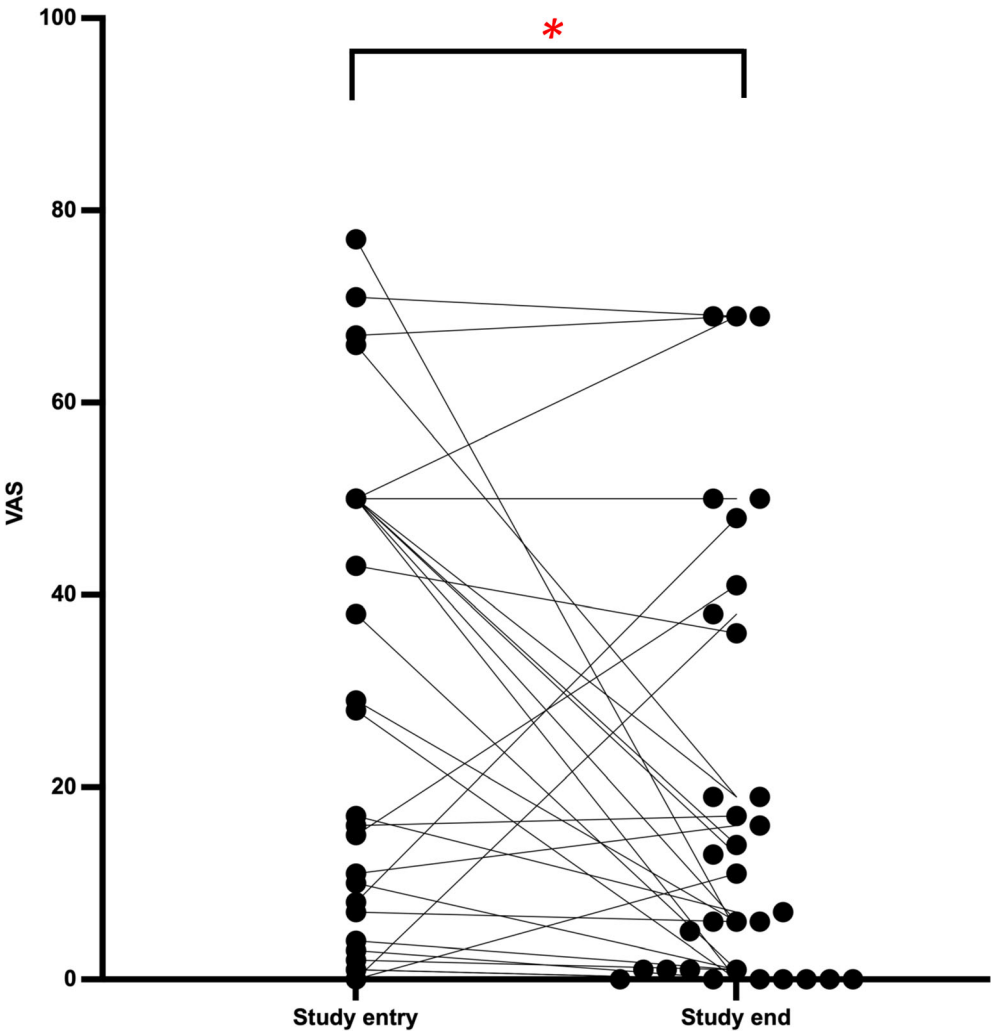

FIGURE 4 Overall ease of drug administration via aerosolization improved from study entry to the end of the study period, $P = .05$. Higher values on the visual analog scale (VAS) correspond to greater difficulty of administration. *$P < .0001$.

TABLE 3 Client-perceived fluticasone adverse effects.

Adverse effects	Proportion of dogs	Percent of dogs
Polyphagia	7/32	22%
Polyuria and polydipsia	5/32	16%
Panting	4/32	13%
Sleeping more	4/32	13%
Thinning of hair coat	3/32	9%
Weight gain	3/32	9%
Pot belly	3/32	9%
Restlessness	2/32	6%

significant cough improvement by 2 weeks, an extended duration of fluticasone is unlikely to yield further benefits. While dosing was arbitrary in this study, we have identified that the 110 mcg/puff dose of fluticasone when prescribed twice a day is effective.

Our power calculation was designed with the intent of characterizing fluticasone efficacy among various subtypes of IAD (ELD, CB), AWC alone, and mixed IAD and AWC. We were unable to achieve this goal because dogs in this study largely had mixed disease, with 88% percent of dogs that underwent bronchoscopy having both AWC and IAD. Only 1 dog had AWC alone, further supporting the observation that AWC commonly is found with inflammation. While AWC is not typically thought of as a primary inflammatory disease, many dogs with AWC have concurrent IAD, raising the question of whether or not these 2 diseases are causal or independent.[28,29]

In our study, dogs empirically diagnosed with AWC in the absence of bronchoscopic confirmation all had concurrent MMVD stage B2 and C. These dogs displayed a similar response to fluticasone compared to dogs that underwent bronchoscopy to confirm the diagnosis, suggesting that these dogs had inflammation accompanying AWC. A previous study documented concurrent IAD and bronchomalacia via bronchoscopy and BAL in dogs with MMVD, regardless of the stage of MMVD.[29] Therefore, we suspect that many of the dogs enrolled with a presumptive diagnosis of AWC might also have had concurrent IAD.

In our study, empiric diagnosis of AWC was based on physical examination and radiographic changes although neither of these variables has a high sensitivity,[2,3,30] and bronchoscopy is still considered the gold standard for AWC diagnosis.[3] Additionally, our cohort of dogs was generally older, smaller, and overweight, which is similar to the description of the cohort of dogs with bronchomalacia in prior studies.[1,28,30,31] We conclude that empiric fluticasone should be considered in dogs with advanced MMVD in which general anesthesia is considered risky and for which there exists a high clinical suspicion for AWC as the cause of chronic non-cardiogenic cough, because there likely is a concurrent inflammatory component. Bronchoscopy is still recommended for definitive diagnosis of complicating conditions in dogs that are suitable anesthetic candidates. Bronchoscopy not only allows for a more definitive diagnosis but also assessment of the remainder of the airways for additional findings, such as mucus and bronchiectasis, that could alter clinical recommendations. For example, clinicians should be cognizant that bronchiectasis could potentially enhance the risk for bronchopneumonia when inhaled corticosteroids are prescribed and may recommend additional therapeutics, such as physiotherapy, when bronchiectasis is identified.

The Chihuahua and Cavalier King Charles Spaniel breeds were overrepresented in our study. Chihuahuas have been well characterized in previous studies evaluating bronchomalacia,[1,29,30] and it is not surprising that they were commonly identified here. While equal numbers of Chihuahuas underwent bronchoscopy as compared to those that did not, the majority of Cavalier King Charles Spaniels had a presumptive diagnosis of AWC and concurrent MMVD, because of the high prevalence of MMVD in this breed.[32] This could have contributed to their over-representation in our study. Furthermore, while the etiology of bronchomalacia has not been fully elucidated and is likely multifactorial, brachycephalic obstructive airway syndrome (BOAS) creating excess negative intrathoracic pressures has been 1 proposed mechanism,[33,34] and Cavalier King Charles Spaniels are considered a brachycephalic breed.[35] Further prospective studies assessing fluticasone efficacy in brachycephalic verses mesocephalic or dolicocephalic dog breeds could be considered to evaluate if differences in skull conformation affect treatment efficacy, as BOAS could be a unique association with AWC.

Fifty percent of owners reported 1 or more potential adverse effects of fluticasone administration, and these were similar to those associated with oral corticosteroids, including polyuria/polydipsia, polyphagia, and panting. Likely, some of these adverse effects were biased as some adverse effects were noted just after finishing 2 weeks of placebo. Unfortunately, our study was not designed to assess the severity of these findings so it is difficult to compare adverse effects of inhaled with oral corticosteroids. A previous retrospective study documented owner-reported signs of hypercortisolism in 5 dogs administered prednisolone orally but the same owners did not note any adverse effects in the same dogs when administered fluticasone.[19] Fluticasone has high local potency in the airways and theoretically reduced systemic adverse effects because of an increased rate of first-pass metabolism and decreased absorption.[36] Despite the theoretically reduced systemic absorption of fluticasone, fluticasone suppression of the HPAA in dogs has been documented, although these earlier studies used twice the dose of fluticasone as compared to that used in this study.[16,37] Our study suggests that clinical signs of hypercortisolism can be seen with a mid-range dose of inhaled administration of fluticasone. Owners reported high satisfaction with fluticasone therapy despite suspected adverse effects; therefore, it seems that owner-perceived benefits of the fluticasone outweighed owner-perceived adverse effects.

Administration of aerosolized medication was considered highly feasible by owners and improved with sustained use, although this was not uniform for all dogs and owners. Aerosolized delivery did require 1 owner training session and often a period of acclimation of 2-3 days, which both owners and veterinarians need to be aware of. This study is the first to date that assesses feasibility of aerosolized medications in dogs and shows that metered-dose inhalers, spacers, and face masks are practical in dogs.

One limitation of this study is that fluticasone therapy was assessed only for 4 weeks, and longer duration assessments are warranted for follow up as relapses can occur.[18] Furthermore, we relied on owner compliance and perception for adverse effects, feasibility, and response to treatment; however, owner perception is also a cornerstone when re-evaluating dogs with chronic cough in the clinic. Of note, additional medications were permitted at the discretion of the clinician out of ethical concerns. Only a small percentage of dogs (9%) had ER theophylline prescribed. Finally, approximately half of our population did not undergo bronchoscopy, and we cannot entirely exclude existence of underlying infection or other causes of cough other than AWC or IAD. Prior studies have documented that IAD rarely occurs with relevant bacterial infection although study results are variable.[5,30,38]

In conclusion, fluticasone was efficacious and feasible in dogs with definitive AWC, definitive IAD, or presumptive AWC with concurrent MMVD. We confirmed that AWC and IAD occurred concurrently in the majority of dogs. Fluticasone therapy led to high owner satisfaction but clinicians should be vigilant of fluticasone-induced hypercortisolism.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest. Trudell Medical International had no role in study design, data collection, or analysis.

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 the University of California, Davis IACUC, Protocol 21 956.

HUMAN ETHICS APPROVAL DECLARATION

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

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SUPPORTING INFORMATION

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

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