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Efficacy of adjunctive therapy using Vizoovet in improving clinical signs of keratoconjunctivitis sicca in dogs: A pilot study

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Abstract

Objective: To assess the clinical safety and efficacy of adjunctive therapy using Vizoovet to ameliorate clinical signs of keratoconjunctivitis sicca (KCS) in dogs.

Animals studied: Twenty client-owned dogs.

Procedures: Canine patients diagnosed with KCS were enrolled in this prospective study. Patients were randomly selected to receive either Vizoovet or GenTeal drops twice daily in addition to twice daily tacrolimus 0.03% solution. Data were collected from only one eye of each patient and included STT-1, IOP, TFBUT, and results of objective clinical scoring performed by pet owners. Statistical significance was set at $P \leq .05$.

Results: In all, 20 dogs (20 eyes) were enrolled in this prospective randomized study. Females (n = 12; 60%) outnumbered males (n = 8; 40%) and all dogs were spayed/neutered. Mean age of all dogs was 10.6 ± 3.79 years. In both treatment groups, the improvement in STT-1 values over the course of the study was significant ($P = .002$). When comparing the STT-1 improvements between groups, no significance was found ($P = .78$). In both groups, the improvement in TFBUT was significant ($P = .0018$). When comparing the TFBUT improvements between groups, no significance was found ($P = .14$). Squinting, rubbing, ocular discharge, and medication administration scores all significantly improved throughout the course of the study; however, they did not differ significantly between groups. Throughout the study, no adverse side effects were noted clinically or by the pet owner in either group.

Conclusions and Clinical Relevance: Adjunctive treatment with Vizoovet was as safe and effective as GenTeal drops at improving clinical signs of dry eye in dogs.

KEYWORDS

aloe vera, canine, chamomile, dry eye, keratoconjunctivitis sicca, propolis

1 | INTRODUCTION

Canine keratoconjunctivitis sicca (KCS) or dry eye is a common ocular condition seen in both primary care and ophthalmology-specific practices with a reported incidence of 1% in North America.[1,2] The disease is characterized by an aqueous tear deficiency resulting in desiccation and inflammation of the conjunctiva and cornea. Attributable clinical signs include blepharospasm, thick mucoid ocular and periocular discharge, conjunctival hyperemia, and corneal changes including fibrosis, pigmentation, vascularization, and possible ulceration. With chronicity, the corneal changes can be sufficient to cause vision loss.

Etiologies of KCS in dogs include congenital alacrima,[2-5] congenital,[6] immune-mediated/idiopathic lacrimal adenitis,[7-10] infectious disease (canine distemper virus),[9,11-13] drug-induced,[2,14-28] surgery-induced,[1,29-31] neurogenic,[32-34] metabolic diseases,[33,35] and as a side effect of radiation treatment.[36-38] By far, the most common etiology is immune-mediated/idiopathic.

Specific dog breeds affected by KCS include English bulldog, West Highland white terrier, pug, Yorkshire terrier, American cocker spaniel, pekingese, miniature schnauzer, English springer spaniel, Boston terrier, Cavalier King Charles spaniel, lhasa apso, bloodhound, and samoyed.[1,4-6,39]

Dry eye is diagnosed using a combination of characteristic clinical signs and low Schirmer tear test-1 (STT-1) values.[2,40] In general, a STT-1 value less than 15 mm/min with appropriate clinical signs is consistent with KCS.[2] Other ancillary diagnostics include fluorescein staining to evaluate for ulceration, tear film break up time (TFBUT),[41] meibometry,[42] ocular thermography,[43] tear ferning,[44] tear film osmolarity,[45] corneal impression cytology,[46] and noncontact infrared meibography.[47]

Treatment of immune-mediated/idiopathic canine dry eye is typically multifactorial and includes tear stimulation, topical lubrication, topical antimicrobial therapy (if corneal ulceration is present), topical mucolytics, and topical anti-inflammatory therapy.[2]

The most common therapies utilized today include cyclosporine 0.2% ointment (Optimmune, Schering-Plough Animal Health), compounded cyclosporine 1%-2%, and tacrolimus 0.02%-0.03%.[2,9,32,39,48-51] These calcineurin inhibitors block T-cell-mediated lacrimal glandular inflammation allowing for improved secretion of tears. Studies have shown tacrolimus to be superior in KCS treatment as compared to cyclosporine.[52,53] Other published, but less commonly utilized, KCS therapies include interferon alpha, pimecrolimus, sirolimus, nerve growth factor, punctal plugs, episcleral cyclosporine implants, mesenchymal stem cells, and parotid duct transposition.[54-63]

Adjunctive treatments should aim to provide lubrication, until natural tear production increases, and decrease the signs of dry eye. Unfortunately, however, topical lubricant therapies for canine KCS have been sparsely studied, although there are a multitude of products available. There are four reports that show significant improvement in clinical signs of dry eye in canine patients receiving topical gel with hyaluronic acid.[64-67] There are also three other studies showing use of fatty acids and antioxidant/anti-inflammatory nutraceuticals to aid in reducing symptoms of KCS.[68-70] To these authors' knowledge, no studies have yet evaluated use of all-natural tear replacement therapies.

The purpose of this study was to evaluate the use of Vizoovet to adjunctively improve the clinical signs of dry eye in dogs.

2 | MATERIALS AND METHODS

Canine patients examined at Eye Care for Animals in Austin, Texas and subsequently diagnosed with presumed immune-mediated/idiopathic keratoconjunctivitis sicca were enrolled in this prospective study. Informed owner consent was obtained prior to data collection. No patients had been treated with tear stimulant or topical lubricant therapy prior to presentation. All patients were examined by a board-certified veterinary ophthalmologist including slit lamp biomicroscopy (Kowa SL-15; Kowa), indirect fundoscopy (Keeler Vantage; Keeler Instruments, Inc), Schirmer tear test-1 (Schirmer tear test strips; Schering-Plough Animal Health, Baton Rouge, LA, USA), rebound tonometry (TonoVet®, Lumic International), and fluorescein staining to evaluate for surface defects and tear film break up time (TFBUT). Diagnosis of keratoconjunctivitis sicca was based on characteristic clinical signs (periocular and ocular mucoid discharge, conjunctival hyperemia, corneal vascularization, corneal fibrosis, ± corneal pigmentation) and STT-1 values of less than 15 mm/min of wetting. Exclusion criteria included presence of corneal ulceration, presence of other ocular diseases that could cause ocular discomfort, and etiologies of dry eye other than immune-mediated/idiopathic (eg, neurogenic or secondary to endocrinopathy). Patients were placed into one of two groups based on computer randomization software (www.random.org). All patients had bilateral KCS except one which had previously underwent enucleation of the right eye for perforating ulcerative keratitis. In patients with bilateral KCS, the eye in which data were collected was also determined by the same randomization software. The eyes in the treatment group received tacrolimus 0.03% ophthalmic solution (Diamondback Drugs) twice daily followed by Vizoovet (Dioptrix, Petnetwork, http://petnetwork.me)* twice daily after a period of 5 minutes. The control group received tacrolimus 0.03% ophthalmic solution twice daily followed by GenTeal tears moderate (Alcon Laboratories, Inc) twice daily after a period of 5 minutes. This topical lubricant therapy was chosen for the control group based on similar viscosity and presumed ocular retention time. Data collected for analysis included STT-1 value, intraocular pressure (IOP), and TFBUT at initial examination (Day 0) and 2-week recheck examination (Day 14). Pet owners were given a data sheet to be filled out in between examination dates. The data sheet (see Table 1) included daily objective observations of squinting, rubbing, ocular discharge, and attitude for medication administration. Observations were to be made at the same time once daily and were given a value of 0-3. Pet owners,

TABLE 1 Pet owner scoring sheet

	Squinting (0-3)	Rubbing (0-3)	Discharge (0-3)	Attitude for giving medications (0-3)
Day 1				
Day 2				
Day 3				
Day 4				
Day 5				
Day 6				
Day 7				
Day 8				
Day 9				
Day 10				
Day 11				
Day 12				
Day 13				
Day 14				
If any abnormal or unusual symptoms are seen, please contact our office immediately and please note what abnormality and the date of occurrence in the section below.				
Comments: ____				
Grading scales and definitions:				
Squinting (excessive blinking or holding the eye closed)				
0 None				
1 Intermittent excessive blinking, mostly holding the eye open				
2 Mostly excessive blinking, may hold eye open when stimulated (ie by giving a treat)				
3 Holding the eye closed all the time				
Rubbing (either at the E-collar or the eye)				
0 None				
1 Occasional rubbing (ie 1-2 times per day)				
2 Moderate rubbing (ie 5-10 times per day)				
3 Rubs all of the time				
Ocular discharge (typically found around the inner corner of the eye)				
0 None				
1 Slight clear to grey mucous				
2 Moderate grey to green mucous				
3 Copious green to yellow mucous				
Attitude when administering medications (eye drops)				
0 Does not react negatively				
1 Tries to squint eye while administering drops				
2 Tries to pull away or vocalizes while administering drops				
3 Becomes aggressive or fearful while administering drops				
Scoring system				
Maximum score of 12; Minimum score of 0. (On any given day)				

the attending ophthalmologist, and those interpreting data were not masked to treatment groups. *[Corrections added on July 8, 2020, after first online publication: the Supplier of Vizoovet has been corrected from "Aventix Animal Health" to "Petnetwork, http://petnetwork.me".]

Statistical analyses were done using a commercially available software program (Stata Version 14.2, StataCorp, www.stata.com). Continuous data were checked for normality using the Shapiro-Wilk's test. Normally distributed data were presented as a mean and standard deviation. Data that were not normally distributed were presented as a median and range. A chi-squared test was performed to evaluate for differences between groups for categorical data. A paired t test was done to look for differences between groups and for differences between the day 0 and day 14 measurements of STT and TFBUT. A t test was performed to look for differences in baseline values between the two groups. A Kruskal-Wallis test was used to look for a difference between the two groups for grading of clinical signs at the baseline measurement. To look for effects over time on clinical signs between groups, a random effects ordered logistic regression was done with the clinical sign as the ordinal dependent variable and the treatment group and day the clinical sign was recorded as independent variables with the patient ID set as the panel ID and the day of the observation as the time variable. Significance was set at $P < .05$.

3 | RESULTS

A total of 20 dogs (20 eyes) were enrolled in this prospective randomized study. Females (n = 12; 60%) outnumbered males (n = 8; 40%) and all dogs were spayed/neutered. There was no difference between number of males and females comparing treatment versus control group ($P = 1.0$). Mean age of all dogs was 10.6 ± 3.79 years (Vizoovet = 10.4 ± 3.37 years; Control = 10.8 ± 4.34 years). There was no difference between the mean age of dogs comparing treatment versus control group ($P = .82$). The median weight of all dogs was 7.15 kg (range = 4.1-27.3 kg) (Vizoovet = 6.65 kg [range = 4.1-23.0 kg]; Control = 8.2 kg [range = 4.5-27.3 kg]). Median weights were not different between groups ($P = .23$). A total of 12 breeds were represented (see Table 2). The most common breed was Shih tzu (n = 4; 20%) followed by Pekingese (n = 3; 15%), Bichon frise (n = 2; 10%), English bulldog (n = 2; 10%), and mixed breed (n = 2; 10%). Data for 20 eyes were included in analysis (right = 11, 55%; left = 9, 45%).

All data points are listed in Table 3. The mean STT-1 value for all eyes at day 0 was 8.65 ± 4.56 mm/min (range = 0-15 mm/min) and at day 14 was 14.7 ± 6.68 mm/min (range = 0-25 mm/min). The overall improvement in STT-1 values was significant ($P < .0001$). The Vizoovet group had a mean STT-1 value at day 0 of 8.5 ± 5.06 mm/min (range = 0-15 mm/min) and 14.8 ± 8.04 mm/min (range = 0-21 mm/min) at day 14. The improvement in STT-1 values was significant ($P = .002$). The control group had a mean STT-1 value at day 0 of 8.8 ± 5.75 mm/min (range = 0-14 mm/min) and 14.6 ± 10.71 mm/min (range = 6-25 mm/min) at day 14. The improvement in STT-1

TABLE 2 Breed distribution

Breed	Number	Percentage (%) of Total
Shih tzu	4	20
Pekingese	3	15
Bichon frise	2	10
English bulldog	2	10
Mixed breed	2	10
Dachshund	1	5
Yorkshire terrier	1	5
Miniature Schnauzer	1	5
Poodle	1	5
Golden retriever	1	5
Pug	1	5
Beagle	1	5

TABLE 3 Data points

	Vizoovet	GenTeal Drops
Mean STT-1 Day 0	8.5 ± 5.06 mm/min	8.8 ± 5.75 mm/min
Mean STT-1 Day 14	14.8 ± 8.04 mm/min	14.6 ± 10.71 mm/min
Mean TFBUT Day 0	3.1 ± 3.78 s	4.0 ± 3.27 s
Mean TFBUT Day 14	12.1 ± 6.49 s	9.4 ± 3.37 s
Squinting Score Day 0	1.3	1.5
Squinting Score Day 14	0.2	0.7
Rubbing Score Day 0	1.2	1.0
Rubbing Score Day 14	0.4	0.6
Ocular discharge Score Day 0	1.9	1.7
Ocular discharge Score Day 14	0.4	0.9
Med Administration Score Day 0	1.2	1.1
Med Administration Score Day 14	0.6	0.5

values was significant ($P = .0004$). Two eyes in the Vizoovet group had no improvement in STT-1 values; however, all eyes in the control group had an improvement. The mean change in STT-1 values in the Vizoovet group was 6.3 ± 3.03 mm/min (range = 0-14 mm/min) and 5.8 ± 3.37 mm/min (range = 2-12 mm/min) in the control group. When comparing the STT-1 improvements between groups, no significance was found ($P = .78$).

The mean TFBUT value for all eyes at day 0 was 3.55 ± 3.47 seconds (range = 0-12 seconds) and at day 14 was 10.75 ± 5.22 seconds (range = 0-21 seconds). The overall improvement in TFBUT values was significant ($P < .0001$). The Vizoovet group had a mean TFBUT value at day 0 of 3.1 ± 3.78 seconds (range = 0-12 seconds) and 12.1 ± 6.49 seconds (range = 0-21 seconds) at day 14. The improvement in TFBUT values was significant ($P = .0018$). The control group had a mean TFBUT value at day 0 of 4.0 ± 3.27 seconds (range = 0-10 seconds) and 9.4 ± 3.37 seconds (range = 4-14 seconds) at day 14. The improvement in TFBUT values was significant ($P = .0011$). One eye in both the Vizoovet group and control group had no improvement in TFBUT values. The mean change in TFBUT values in the Vizoovet group was 9.0 ± 4.34 seconds (range = 0-19 seconds) and 5.4 ± 3.63 seconds (range = 0-10 seconds) in the control group. When comparing the TFBUT improvements between groups, no significance was found ($P = .14$).

Regarding the information collected from pet owners on the at-home scoring sheet, to determine effects of treatment over time, days 1, 7, and 14 were compared. Squinting did not differ at baseline between groups ($P = .59$) and effect of treatment did not differ significantly ($P = .167$). Squinting scores did improve throughout the study both groups ($P < .001$). Rubbing did not differ at baseline between groups ($P = .69$) and effect of treatment did not differ significantly ($P = .842$). Rubbing scores did improve throughout the study in both groups ($P = .0071$). Ocular discharge did not differ at baseline between groups ($P = .54$) and effect of treatment did not differ significantly ($P = .386$). Ocular discharge scores did improve throughout the study in both groups ($P = .0002$). Medication administration difficulty scores did not differ at baseline between groups ($P = .77$) and effect of treatment did not differ significantly ($P = .632$). Medication administration difficulty scores did improve throughout the study ($P = .0428$).

Throughout the study, no adverse side effects were noted clinically or by the pet owner in either group.

4 | DISCUSSION

In today's society, all-natural remedies are becoming very popular in both human and veterinary medicine as part of a well-rounded or holistic approach of treating diseases. In the present study, we evaluated the safety and ability of an all-natural topical lubricant therapy to improve the signs of dry eye. Vizoovet contains three ingredients that are proposed to protect the ocular surface and provide anti-inflammatory activity. The first ingredient is propolis or bee's wax. Compounds found in propolis include phenolic acids, flavonoids, esters, diterpenes, sesquiterpenes, lignans, aromatic aldehydes, alcohols, amino acids, fatty acids, vitamins, and minerals.[71] Studies have shown the health benefits of this compound to include antimicrobial, improved wound healing, antioxidant, and anti-inflammatory.[72-76] The second ingredient is aloe vera which has numerous proposed health benefits including antimicrobial, antioxidant, anti-inflammatory, tissue protection, and wound healing.[77-80] The third ingredient of Vizoovet is chamomile with health benefits including antioxidant, anti-inflammatory, and antimicrobial.[81-83] All of these potential therapeutic benefits would be considered quite helpful in cases of dry eye to improve surface inflammation, protect diseased epithelium, and heal corneal and conjunctival wounds if present.

We compared the safety and efficacy of Vizoovet to a commercially available over-the-counter topical lubricant eye drop. This particular eye drop was chosen as it closely resembled the approximate viscosity of the test product as to not skew results based on ocular retention time.

Published normal STT-1 value in dogs is 23.56 mm/min.[84] In our study, STT-1 values significantly improved in both groups within the 2-week study period being almost 15 mm/min. It has been shown that it can take approximately 6-8 weeks to see full effect of tear stimulation therapy.[51] This is the likely reason that STT-1 values failed to reach normal values. When compared, neither group showed a statistical advantage regarding tear stimulation potential. This likely indicates that the all-natural ingredients in Vizoovet do not have a direct tear stimulant potential.

Normal TFBUT in dogs is 19.7 ± 5 seconds.[85,86] In the present study, TFBUT improved significantly in both the study and control groups. This likely indicates that the active ingredients in the all-natural product do not facilitate improvement in the quality of the tear film, despite their proposed protective and anti-inflammatory effects. Low patient numbers due to the pilot study nature of this project could have inhibited seeing a true statistically significant difference with regard to STT-1 and TFBUT values.

Although likely considered unconventional, we collected data from pet owners regarding specific ocular parameters we felt were important in the treatment of canine KCS patients. Clinical signs we included were squinting, rubbing, ocular discharge, and attitude of the patient with respect to medication administration. Blepharospasm or squinting and self-trauma from rubbing are very common clinical findings in canine dry eye. Ocular discharge is present due to lack of aqueous component of tears and can be quite significant.

Also, patients can be quite averse to medication administration either due to the disease or medication itself. These are not factors that can always be evaluated in the examination room by the attending veterinarian but can be evaluated by pet owners on a daily basis. All of the observations showed significant improvement throughout the course of the study but were not different between groups. Again, this could be due to low patient numbers or that truly there is no different between the test and control products.

Clinical signs of dry eye including degree/type of ocular discharge, conjunctival hyperemia, and corneal abnormalities (ulceration, fibrosis, pigmentation, and vascularization) were not objectively evaluated in this study. Interobserver variations are likely significantly different between practicing ophthalmologists when scoring these variables, and hence, were not included. Photographic documentation of each individual patient could be performed in future studies which could be objectively evaluated. Future studies are warranted to continue to evaluate this all-natural product.

In conclusion, adjunctive therapy with Vizoovet is as safe and effective as GenTeal drops in improving the clinical signs associated with KCS in the dog. Further studies are warranted to determine if there are statistical differences between this product and over-the-counter products with respect to KCS treatment.

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