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ORIGINAL REPORT

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Precorneal retention time of ocular lubricants measured with fluorophotometry in healthy dogs

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Abstract

Objective: Determine the precorneal retention time of five different ocular lubricants commonly used in dogs.

Animals Studied: Six healthy Beagle dogs (n = 12 eyes).

Procedures: Five ocular lubricants were studied: Artificial Tears Solution® (1.4% polyvinyl alcohol), I-Drop® Vet Plus (0.25% hyaluronate), Optixcare® Eye Lube Plus (0.25% hyaluronate), Systane® Ultra (0.4% polyethylene glycol 400 and 0.3% propylene glycol), and Artificial Tears Ointment® (mineral oil/white petrolatum). Each lubricant was mixed with 10% sodium fluorescein to achieve 1% fluorescein formulations. Following topical administration of 35 mg in each eye, tear fluid was collected with capillary tubes at selected times (0, 1, 5, 10, 20, 30, 40, 50, 60, 90, 120, 180 min) and fluorescein concentrations were measured with a computerized scanning ocular fluorophotometer.

Results: Tear fluorescence was significantly greater with Artificial Tears Ointment® compared with other lubricant formulations from 1 to 20 min post-administration. Median (range) precorneal retention times were significantly different among the 5 lubricants, ranging from 40 minutes (20–90 min) for Artificial Tears Ointment®, 35 min (20–90 min) for Systane® Ultra, 30 min (10–60 min) for I-Drop® Vet Plus, 25 min (10–60 min) for Optixcare® Eye Lube Plus, and 10 min (10–20 min) for Artificial Tears Solution®. Precorneal retention time was significantly lower for Artificial Tears Solution® compared with the other 4 formulations.

Conclusions: This study established normative data for the retention time of common lubricants on the ocular surface of dogs, which may be used to guide clinicians with their choice of lubricant and frequency of administration.

KEYWORDS

artificial tears, dry eye, Keratoconjunctivitis sicca, lacrimomimetics, tear film, viscosity

1 | INTRODUCTION

Artificial tears, or "lacrimomimetics," are routinely used in human and veterinary patients to lubricate the ocular surface and help manage a variety of clinical conditions. Artificial tears minimize discomfort and relieve symptoms in patients with qualitative and/or quantitative tear film abnormalities (dry eye disease), as shown in humans, dogs, cats, and other species.[1–4] Artificial tears are also used to lubricate the eyes perioperatively,[5] promote corneal wound healing, and reduce irritation from adnexal disorders that may abrade the cornea, among other indications.[6,7]

Numerous brands and types of artificial tears are available on the market for use in animal and human patients. Selection of the appropriate lacrimomimetic for use in humans may be dictated by patient-specific needs,[8] such as hyaluronan-based artificial tears (e.g., Hylocomod®) for mucin-deficient eyes and lipid emulsion eyedrop (e.g., Sooth®) for lipid-deficient eyes, although no consensus exists among clinicians given conflicting results in the literature for human patients.[9] Other selection factors include cost and presence/absence of preservatives,[10] as well as general physiochemical characteristics that affect the kinetics of the formulation on the ocular surface.[11] An artificial tear formulation with a long precorneal retention time is generally desirable, allowing for extended lubrication and reduced frequency of administration.[12] Several strategies exist to enhance precorneal retention time—for instance increasing formulation viscosity or using mucoadhesive polymers to bind to ocular mucins—with much of the work involving preclinical animal models (e.g., rabbits, rodents)[13,14] and clinical studies in humans.[12,15] Although helpful, such findings cannot be directly extrapolated to companion animals owing to important species differences in ocular surface anatomy and physiology.[16]

Using fluorophotometry, the main purpose of the study was to determine the precorneal retention time of five ocular lubricants that are commonly used in clinical practice and have various physicochemical properties, namely (1) Artificial Tears Solution® (1.4% polyvinyl alcohol), a non-viscous eyedrop with lacrimomimetic properties; (2) I-Drop® Vet Plus (0.25% hyaluronate), a viscous eyedrop with mucinomimetic properties; (3) Optixcare® Eye Lube Plus (0.25% hyaluronate), a viscous gel with mucinomimetic properties; (4) Systane® Ultra lubricant eye drops (0.4% polyethylene glycol 400 and 0.3% propylene glycol), a lacrimomimetic that forms a viscoelastic matrix on the ocular surface; and (5) Artificial Tears Ointment® (mineral oil/white petrolatum), a lipid-based lacrimomimetic ointment. The present work was conducted in dogs, as they commonly develop ocular surface disease and represent an excellent large animal model for translational research in humans given the similarities in ocular parameters pertinent to topical ophthalmic drug administration.[16,17–19]

2 | MATERIALS AND METHODS

2.1 | Animals

Six Beagle dogs (three neutered males and three spayed females) were included in the study, all confirmed to be healthy based on physical and ophthalmic examinations by a board-certified veterinary ophthalmologist (LS, RA), including Schirmer tear test-1 (STT-1; Eye Care and Cure Corp; Tucson, Arizona, USA), rebound tonometry (TonoVet; Icare Finland Oy), fluorescein staining of the ocular surface (Bio-Glo; HUB Pharmaceutics LLC), slit-lamp biomicroscopy (SL-17; Kowa Company, Ltd.), and indirect ophthalmoscopy (Keeler Vantage; Keeler Instruments, Inc.). All dogs were 1.0–2.5 years old and weighed 6.0–9.5 kg. The study was approved by the Institutional Animal Care and Use Committee of Iowa State University (protocol # 18–398).

2.2 | Experiment

Five ophthalmic lubricants were evaluated on both eyes of each dog on separate days (≥1 day washout period between formulations): (1) Artificial Tears Solution® (1.4% polyvinyl alcohol; Rugby, Rockville Center); (2) I-Drop® Vet Plus (0.25% hyaluronate; I-Med Pharma Inc.); (3) Optixcare® Eye Lube Plus (0.25% hyaluronate; Aventix Animal Health); (4) Systane® Ultra lubricant eye drops (0.4% polyethylene glycol 400 and 0.3% propylene glycol; Alcon Laboratories Inc.); and (5) Artificial Tears Ointment® (mineral oil/white petrolatum; Rugby, Rockville Center). Each lubricant was mixed in a sterile manner with the assistance of a pharmacist with 10% sodium fluorescein (AK-Fluor®, Akorn Inc.) to achieve 1% fluorescein lubricant formulations. For ophthalmic solutions (Artificial Tears Solution®, Systane® Ultra, I-Drop® Vet Plus), 10% fluorescein was mixed to the solution at a volume ratio of 1:9 to achieve a 1% fluorescein formulation, with vigorous mixing of the eyedropper performed at time of preparation and before topical administration. For the gel (Optixcare®) and ointment formulations (Artificial tears ointment®), 10% fluorescein was mixed to the gel or ointment at a mass ratio of 1:9 to achieve a 1% fluorescein formulation; specifically, the mixing was achieved by placing 10% fluorescein in a 2.5-mL syringe, the gel or ointment formulation in another 2.5-mL syringe, both connected by a Luer-lock to Luer-lock connector, then mixing the contents of both syringes back and forth prior to topical administration.

The amount of fluorescein applied topically was standardized to 35 mg among all lubricants, a process achieved by instilling 35-μL of each 1% ophthalmic solution (Artificial Tears Solution, I-Drop® Vet Plus, Systane® Ultra) with a pipette (Eppendorf Reference® 2, 10–100 μL), or emptying the content of a tuberculin syringe (without the needle) (BD Ultra-Fine needle 30G™; Becton, Dickinson & Company) pre-loaded with 0.035-ml of each 1% gel or ointment formulation (Optixcare® Eye Lube Plus; Artificial Tears Ointment). As an additional precaution, all syringes were weighed before and after administration of the lubricant (Pioneer® PX224 Analytical Balance; Ohaus Corporation) to confirm the amount of fluorescein lubricant applied onto each eye.

Following topical instillation, animals were allowed to blink naturally then the eyelids were held open to collect tear fluid from each eye with a 2-μL capillary glass tube (Drummond Scientific Co.) at the following time points: 0 min (i.e., immediately after instillation and spontaneous blinking), 1, 5, 10, 20, 30, 40, 50, 60, 90, 120, and 180 min. The capillary tube was placed against the central or lateral tear meniscus for ≤5 s to collect tear fluid by capillary action, while great care was taken to minimize the risk of inadvertent ocular irritation and reflex tearing. The length of fluid contained within each capillary tube was measured to the nearest millimeter using a ruler; this value was used to calculate the volume of fluid collected knowing that each 32 mm tube equates to 2 μL. The collected fluid was then expelled into a 2-ml Eppendorf tube that contained 500 μL of phosphate-buffered saline (Gibco® PBS, pH 7.2; Thermo Fisher Scientific), vortexed for 30 s, and transferred to a cuvette for analysis. Fluorescein concentrations were measured (μg/mL) in each sample with a computerized scanning ocular fluorophotometer (Fluorotron Master™; Coherent Radiation) as previously described.[18,19]

2.3 | Data analysis

2.3.1 | Fluorophotometry

Fluorescein concentrations were calculated based on the tear volume collected for each sample, which was measured in μL, and then they were corrected based on a calibration curve established by analyzing a dilution series of known fluorescein concentrations in triplicate (1–10 000 μg/mL). Furthermore, fluorescein values were adjusted in samples for which the weight of lubricant applied topically varied slightly from the expected value of 35 mg. Precorneal retention time was measured in minutes and was demarcated by the moment at which the fluorescence of the tear film sample decreased below 5% of the baseline value.[20]

2.3.2 | Statistical analysis

The normality of the data was assessed with the Shapiro–Wilk test, and results from right and left eyes were compared by means of paired *t* tests. Since no significant differences were noted between eyes ($p \geq .152$), the average of the measurements of the right and left eyes of each dog were used for further analysis. Differences in tear film fluorescence and precorneal retention times among lubricants were assessed with the two-way repeated measures ANOVA test (with post hoc Tukey) and the Kruskal–Wallis test (with post hoc Student–Keuls), respectively. The R software (version 3.6.0) was used to calculate the area under the concentration-time curve (AUC), a parameter that was compared among lubricants using the one-way ANOVA test (with post hoc Tukey). Statistical analyses were performed with SigmaPlot 14.5 (Systat Software). p values <.05 were considered significant for differences in AUC and precorneal retention times, while p values <.01 were considered significant for differences in tear film fluorescence at each time point (Bonferroni correction for repeated measures).

3 | RESULTS

Data not normally distributed are reported as median (range), while data normally distributed is reported as mean ± standard deviation (range).

3.1 | Tear film kinetics

Tear film concentrations (reported in fluorescence) following topical instillation of five different lubricants are depicted in Figure 1. Of note, the ointment appeared to distribute rapidly and homogenously on the ocular surface after topical administration, although tear sampling was subjectively slower and more challenging for the first few timepoints when compared to solution-based lubricants. Fluorescein decay was biphasic in all groups, that is, rapid decline for the first 10 min followed by a slower decline from 10 to 180 min post-instillation. However, the decline was slower in eyes receiving Artificial Tears Ointment compared to other groups. Statistical comparisons of tear film concentrations are reported in Table 1; in particular, tear

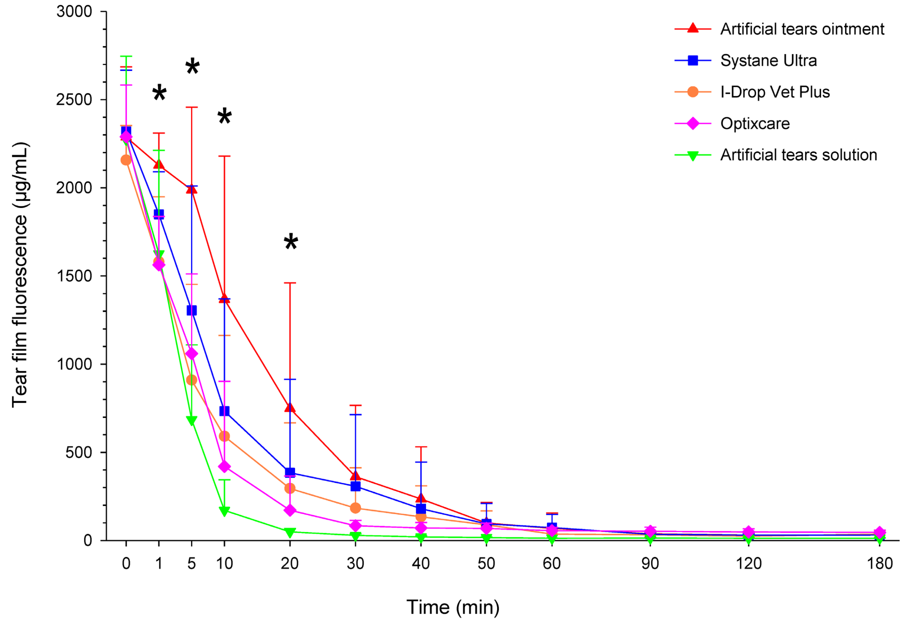

FIGURE 1 Scatter plot depicting the mean ± standard deviation of tear film fluorescence over 180 min after instillation of five ocular lubricants in six healthy Beagle dogs: Artificial Tears Ointment®, Systane® Ultra, I-Drop® Vet Plus, Optixcare® Eye Lube Plus and Artificial Tears Solution®. Statistical differences among groups ($p < .01$) are depicted by asterisks. See Table 1 legend for additional details.

TABLE 1 Results of two-way repeated-measures ANOVA and post hoc Tukey tests comparing tear film fluorescence at selected time points (0–180 min) after instillation of five ocular lubricants in six healthy Beagle dogs: Artificial Tears Ointment® (=Ointment), Systane® Ultra (=Systane), I-Drop® Vet Plus (=I-Drop), Optixcare® Eye Lube Plus (=Optixcare) and Artificial Tears Solution® (= Solution), with statistically significant differences noted at 1, 5, 10, and 20 min.

Time	Statistical analysis
0	$p \geq .846$
1	Ointment > Optixcare ($p = .004$) Ointment > I-Drop ($p = .005$) Ointment > Solution ($p = .009$)
5	Ointment > I-Drop ($p < .001$) Ointment > Optixcare ($p < .001$) Ointment > Systane ($p < .001$) Ointment > Solution ($p < .001$) Systane > Solution ($p = .001$)
10	Ointment > I-Drop ($p < .001$) Ointment > Optixcare ($p < .001$) Ointment > Systane ($p < .001$) Ointment > Solution ($p < .001$) Systane > Solution ($p = .004$)
20	Ointment > Solution ($p < .001$) Ointment > Optixcare ($p = .003$)
30	$p \geq .226$
40	$p \geq .663$
50	$p \geq .986$
60	$p \geq .996$
90	$p \geq .999$
120	$p \geq .999$
180	$p = 1.000$

fluorescence was higher in eyes receiving Artificial Tears Ointment from 1 to 20 min post-instillation, a finding that was statistically significant as compared to Artificial Tears Solution (1, 5, 10, 20 min; $p \leq .009$), Optixcare® (1, 5, 10, 20 min; $p \leq .004$), I-Drop® Vet Plus (1, 5, 10 min; $p \leq .005$), and Systane® Ultra (5, 10 min; $p < .001$).

3.2 | Percent remaining on the ocular surface

Table 2 summarizes the percent lubricant remaining on the ocular surface at 1–180 min post-instillation when compared to baseline (t = 0 min). Mean values dropped from 100% (t = 0 min) to 68.1–94.5% (1 min), 30.2–87.3% (5 min), 7.7–60.1% (10 min), 2.2–34.2% (20 min), 1.3–16.3% (30 min), 1.0–10.1% (40 min), 0.7–4.1% (50 min), 0.6–3.0% (60 s), 0.6–2.3% (90 min), 0.6–2.1% (120 min), and 0.6–2.0% (180 min).

3.3 | Precorneal retention time

Median (range) precorneal retention times were significantly different among the 5 lubricants (p = .036), varying from 40 min (20–90 min) for Artificial Tears Ointment®, 35 min (20–90 min) for Systane® Ultra, 30 min (10–60 min) for I-Drop® Vet Plus, 25 min (10–60 min) for Optixcare® Eye Lube Plus, and 10 min (10–20 min) for Artificial Tears Solution®. Precorneal retention time was significantly lower for Artificial Tears Solution compared with the other 4 formulations ($p \leq .028$). The average half-life precorneal retention times varied from 12.5 min (Artificial Tears Ointment), 7.3 min (Systane® Ultra), 6.2 min (I-Drop® Vet Plus), 5.0 min (Optixcare® Eye Lube Plus) and 3.7 min (Artificial Tears Solution).

4 | DISCUSSION

The present study confirmed the superior ocular lubrication provided by ophthalmic ointments and other viscous formulations when compared to standard artificial tears solution, as shown in other species.[21–24] The petrolatum-mineral oil base of Artificial Tears Ointment® prolongs ocular contact time secondary to the nonpolar properties of the mineral oil, that is readily absorbed by the oily portion of the precorneal tear film, as well as the large size of petrolatum molecules, which are not easily removed by blinking via the nasolacrimal apparatus.[25]

The ingredients of Systane® Ultra enhance precorneal retention time by minimizing tear evaporation and improving adherence of the lubricant to the corneoconjunctival surface. Systane® Ultra is composed of two hydrophilic demulcents (polyethylene glycol/propylene glycol), as well as natural polysaccharide gelling agent (hydroxypropyl guar, or HP guar) buffered with borate and sorbitol. The use of HP guar increases the viscosity of the eye drop and forms a protective viscoelastic matrix on the ocular surface to provide prolonged retention of the active demulcents.[26]

TABLE 2 Mean ± SD (range) percent fluorescein remaining in tears at each time point (1–180 min) compared with t = 0 min in canine eyes receiving five different ocular lubricants. Results are reported in %. See Table 1 legend for additional details.

Time (min)	1	5	10	20	30	40	50	60	90	120	180
Ointment	94.5 ± 12.4 (82.2–116.8)	87.3 ± 18.6 (61.5–117.1)	60.1 ± 34.8 (26.7–98.6)	34.2 ± 35.1 (1.7–89.9)	16.3 ± 18.6 (1.4–45.5)	10.1 ± 11.7 (0.9–26.8)	4.1 ± 4.4 (0.9–11.4)	2.8 ± 3.0 (0.7–8.7)	1.7 ± 0.8 (0.8–3.2)	1.4 ± 0.8 (0.9–3.0)	1.4 ± 0.8 (0.6–2.9)
Systane	80.8 ± 12.8 (63.0–98.5)	58.3 ± 32.5 (11.0–93.0)	32.2 ± 26.6 (5.6–62.0)	15.9 ± 20.4 (0.9–46.8)	12.7 ± 14.8 (0.8–38.5)	7.2 ± 9.3 (1.1–25.3)	3.8 ± 4.1 (0.8–11.6)	3.0 ± 2.7 (0.6–7.7)	1.5 ± 0.4 (1.1–2.1)	1.4 ± 0.4 (1.0–2.1)	1.4 ± 0.7 (1.0–2.7)
I-Drop	73.4 ± 16.4 (44.1–91.5)	41.6 ± 24.4 (13.3–70.9)	27.0 ± 26.3 (1.8–64.9)	13.7 ± 17.5 (1.3–46.7)	8.5 ± 10.7 (1.2–29.0)	6.3 ± 8.3 (1.2–22.9)	4.1 ± 3.7 (1.1–11.0)	1.7 ± 1.6 (0.8–4.9)	1.5 ± 0.8 (0.8–2.7)	1.2 ± 0.5 (0.6–1.8)	1.7 ± 1.0 (0.9–3.5)
Optixcare	68.1 ± 8.2 (60.0–81.4)	47.0 ± 20.4 (25.1–74.5)	18.3 ± 21.5 (4.7–61.3)	7.6 ± 8.6 (2.3–25.1)	3.7 ± 1.4 (2.3–6.0)	3.1 ± 1.3 (1.9–5.5)	3.0 ± 1.3 (1.8–5.1)	2.4 ± 0.8 (1.7–3.6)	2.3 ± 1.0 (1.3–4.2)	2.1 ± 0.8 (1.4–3.7)	2.0 ± 0.7 (1.3–3.2)
Solution	71.5 ± 19.0 (48.4–99.7)	30.2 ± 16.5 (12.6–51.0)	7.7 ± 7.8 (1.0–20.8)	2.2 ± 0.7 (0.9–2.9)	1.3 ± 0.5 (0.6–2.1)	1.0 ± 0.4 (0.5–1.6)	0.7 ± 0.1 (0.6–0.9)	0.6 ± 0.1 (0.4–0.8)	0.6 ± 0.1 (0.5–0.7)	0.6 ± 0.1 (0.5–0.8)	0.6 ± 0.1 (0.5–0.7)

As for products such as I-Drop® Vet Plus and Optixcare® Eye Lube Plus, the presence of hyaluronic acid in the formulation—a glycosaminoglycan with a viscoelastic rheology—helps prolong ocular contact time by reducing washout and enhancing water retention on the ocular surface.[20,27,28]

A biphasic fluorescein decay was observed for all lubricants, as previously reported with other topical formulations applied to canine eyes.[19,29] Notably, the initial decline was slower with the ointment formulation owing to the aforementioned properties (i.e., nonpolar properties of the mineral oil, large size of petrolatum molecules), a finding that likely explained the statistically greater tear film concentrations vs. other lubricants for the first 20 min, and the longer precorneal retention time obtained with the ointment. The median precorneal retention time of ocular lubricants in dogs varied depending on the preparation, and the same trend can be found in human patients in the medical literature.[25,30] The half-life of petrolatum-based ophthalmic ointment is overall similar in humans compared with dogs (9.7 vs. 12.5 min, respectively).[25] Similarly, the precorneal retention times were relatively similar in humans and dogs for Systane® Ultra (32.6 vs. 35 min, respectively) and hyaluron-based artificial tears (28.6 vs. 25–30 min, respectively).[30] These findings validate the use of dogs as a large animal model for ocular surface studies,[16] although interspecies differences including the type of ocular mucin expression[31] and the larger tear volume in dogs[18] should be taken into account.

Precorneal retention time is an important parameter to guide clinical selection for ocular lubricants, that is, which one to use and at what frequency, although other important factors (not evaluated herein) should be taken into consideration. Ophthalmic ointments provide longer precorneal residence times, but may be more challenging to apply than eyedrops, may cause transient blurry vision, and may cause local irritation in selected patients.[21,25,32] On the other hand, Systane® Ultra may have a shorter ocular retention time, but its ingredients were shown to promote ocular surface health by improving tear film quality, reducing meibomian gland dysfunction, and promoting regeneration of damaged corneo-conjunctival epithelium.[26,33] Similarly, hyaluron-based products bind to ocular mucins, stabilizing the tear film for several hours despite the relatively low retention time reported in the present study, and promote corneal wound healing.[34] Evaluation of tear film stability and epithelial regeneration was beyond the scope of the present study but should be assessed in future experiments of ocular lubricants in dogs.

Importantly, the present findings likely underestimated the "true" precorneal retention time of ocular lubricants in canine patients. The experiment mixed the ocular lubricants with sodium fluorescein to estimate tear film levels with fluorophotometry. Although fluorophotometry is often considered superior to other tear assessment methods (e.g., fluorescein clearance test or lacrimal scintigraphy),[35] the use of fluorescein might have reduced the viscosity of formulations,[36] and altered tear film kinetics owing to fluorescein loss through conjunctival permeation.[37] Furthermore, heterogeneous mixing of the fluorescein among the lubricants (owing to different physicochemical properties of the formulations) might have affected tear film kinetics and subsequent precorneal retention time. However, the authors believe the study's mixing methodology using interconnected Luer-lock syringes, provided acceptable formulations for the experiment, as the tear film kinetics of the gel and ointment followed a similar decay pattern as the solution formations (and not an "erratic" sawtooth-like pattern), and the variability in tear film concentrations among dogs was sufficiently low to allow for statistically significant findings to be detected among lubricants, even with a relatively low sample size. Future studies could consider other techniques to assess precorneal retention time, such as spectral domain optical coherence tomography,[38,39] although the methodology would need to be adjusted to provide reliable measurements in awake and potentially "uncooperative" canine subjects.

The study was limited to unanesthetized dogs with normal aqueous tear secretion. Precorneal retention time of Systane® eyedrop was 11% higher in humans with dry eye disease when compared to healthy subjects (36.3 vs. 32.6 min, respectively),[30,40] while ocular residence time of petrolatum-based ointment was 230% higher in human eyes that were kept closed when compared to eyes with normal blinking (half-life 32 vs. 9.7 min, respectively).[25] The same may be true in dogs. On the other hand, precorneal retention time of lubricants may be shorter in canine eyes with reflex tearing owing to an accelerated tear turnover rate.[41] Furthermore, the animals in the present study were relatively young and results may differ in older subjects, as they might retain lubricants for a longer period of time due to potential reductions in tear volume, reflex tearing, and tear turnover rate.[42,43]

In conclusion, the present study established normative data for the retention time of common lubricants on the ocular surface of dogs, which may be used to guide clinicians with their choice of lubricant and frequency of administration.[16] Additional studies are warranted before specific guidelines can be suggested on lubricant type and frequency of administration on tear film quality and corneo-conjunctival health in a variety of diseased eyes and the eyes of animals under anesthesia.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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