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Original Study

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Preliminary evaluation of tear production in dogs hospitalized in an intensive care unit

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Abstract

Objective – To determine the tear production in dogs admitted to an intensive care unit (ICU).
Design – Prospective observational study from November 2010–September 2011.
Setting – Private emergency and referral hospital.
Animals – Thirty healthy control dogs and 30 dogs hospitalized in an ICU for treatment of systemic illness without previously diagnosed ophthalmic disorders and no recent history of anesthesia. Enrollment was based on availability of the ophthalmologist within 24 hours of admission to the ICU.
Interventions – Tear production was measured utilizing Schirmer tear test strips (STT) in healthy control animals as well as in hospitalized canine patients. All patients received an ophthalmic examination by a board-certified veterinary ophthalmologist within 24 hours of admission to the ICU. Lubrication with artificial tear gel every 2–4 hours as needed was implemented after STT was measured.
Measurements and Main Results – Average tear productions in the control and canine ICU populations were 24.5 mm/min and 13.2 mm/min, respectively. This was found to be statistically significant ($P < 0.001$). Furthermore, there was a trend toward a decrease in tear production in patients with kidney disease and a trend toward normal tear production in patients with cardiac disease but the sample size was likely too small to enable detection of a statistically significant difference.
Conclusions – This study demonstrates a decrease in tear production in canine ICU patients. While further study is warranted to determine how different diseases impact tear production, these finding support the implementation of frequent ocular lubrication in all ICU patients.

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Keywords: corneal injury, corneal ulcer, complications, tear film

Introduction

The precorneal tear film is essential to ocular health. It is made up of 3 layers: the lipid, mucin, and aqueous layers. The lipid or outermost layer is produced by the meibomian glands. This layer is responsible for reducing the evaporation of the deeper layers of the tear film. The aqueous, or middle, layer is produced by the lacrimal and third eyelid glands. The aqueous layer is responsible for providing nutrition to the cornea, protection through local immune reactions and removing debris and waste.[1–3] Finally, the mucin, or innermost, layer is produced by the conjunctival goblet cells, and provides a bridging hydrophilic surface across the cornea, over which the aqueous tear film can be evenly distributed.[2]

Tear film deficiencies can be quantitative or qualitative in nature. Quantitative tear film deficiencies result from a decrease in the aqueous layer, whereas qualitative tear film abnormalities arise from abnormalities in the composition or the function of the mucin or lipid tear layers. Any alteration to the layers can lead to an abnormal tear film and may subsequently result in impaired innate ocular defenses and corneal damage may occur.

In veterinary patients, the most common cause of keratoconjunctivits sicca (KCS) is an immune-mediated

Abbreviations

KCS	keratoconjunctivits sicca
STT	Schirmer tear test

From the The Animal Medical Center, New York, NY 10065.

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destruction of the lacrimal gland. Additional causes of decreased tear production include endocrinopathies such as diabetes mellitus, hyperadrenocorticism, and hypothyroidism,[3,4] many routinely used medications, including sulfa drugs, sedatives, and opioids,[4–10] general anesthesia, neurologic deficits, infection, iatrogenic removal of the nictitans gland, other immune-mediated diseases, and trauma.[11–16]

The most commonly utilized method of measuring aqueous tear production in veterinary medicine is the Schirmer tear test (STT).[17,18] There are 2 variations of the STT: STT-1 and STT-2. The STT-1 is performed without the use of topical anesthetics. It measures the volume of tears in the lacrimal lake, the basal secretion of tears and trigeminal-facial reflex tearing. The STT-2 differs in that the cornea and conjunctiva are topically anesthetized and the lower conjunctival fornix is dried with a cotton applicator. This serves as an estimate of basal tear secretion only, removing any contribution from reflex tear production.[19,20] As we are focusing on quantitative tear film deficiency, for the remainder of this study, STT will be used to refer to STT-1. Normal STT values range from 15–25 millimeters (mm) per 60 seconds, and KCS in dogs is generally accepted as being less than 10 mm per minute.[2,3,18] A decrease in tear production has been shown to predispose patients to ocular surface disorders.[21]

While decreased tear production and ocular morbidity during critical illness has been widely documented in human beings,[11,15,22] to the authors' knowledge it has not previously been documented in critically ill veterinary patients. Reported mechanisms of decreased tear production or increased loss in human beings include the following: inadequate eyelid closure,[23] sedation,[23] anesthesia,[23,24] kidney disease,[25] immune disorders,[26] and age.[26] To counter this decrease in tear film, multiple strategies have been developed in human medicine. These range from frequent application of ocular lubrication to mechanical eyelid closure with adhesives and moisture chambers.[11,24] It is possible that these techniques may be adapted to the veterinary setting.

The purpose of this study is to document the tear production of canine patients admitted to an intensive care unit (ICU). We hypothesized that this population will have decreased values when compared with a healthy control group.

Materials and Methods

Two distinct groups of patients were considered eligible for enrollment in this study. The first group (controls) consisted of 30 canine patients that were deemed healthy based on routine physical examination and ophthalmic examination. This group of animals was comprised of staff-owned pets, and dogs that were presented to community practice for routine general health examinations. These pets were not receiving any medications other than heartworm or flea/tick preventive. The second group (patients) consisted of 30 dogs admitted to the ICU for treatment of systemic illness. Patients with preexisting ocular surface disease as evidenced by corneal vascularization, fibrosis, or pigmentation, or those that were anesthetized within the previous 24 hours were excluded from participation. Owner consent was obtained for all patients prior to enrollment.

All controls and patients in the study received an ophthalmic examination by a board-certified veterinary ophthalmologist within 24 hours of admission to the ICU. The examination included slit-lamp biomicroscopy, indirect ophthalmoscopy, and intraocular pressure measurement to ensure that no preexisting ocular conditions were present. Schirmer Tear strips[a] from the same production batch (Lot number 10110823) were utilized in both controls and patients. Only the STT-1 was performed during this study. The notched end of the strip was placed in the lower conjunctival sac at the junction of the middle and the lateral third of the eyelid. The strip remained in place for 60 seconds after which the reading was made in mm. Fluorescein staining was only performed in those patients where defects or irregularities in the corneal surface were noted during slit lamp biomicroscopy. Once all tests were performed, ocular lubrication with an artificial tear gel[b] was employed every 2–4 hours as needed.

Statistical analyses

Schirmer Tear test data were collected for the left (OS) and right (OD) eyes in both controls and patients. Each data set was assessed for normality via the Anderson–Darling test. All data were normally distributed; therefore, parametric tests were used.

Tear production OS and OD within the same patient, in both controls and patients, were assessed using a paired Student's *t*-test. Because no difference was found between OS and OD tear production, these values were averaged as a single data point for the purpose of later analysis.

The level of tear production, in the controls and patients, was assessed using a Student's *t*-test. A P value of <0.05 was considered to be statistically significant. As these populations had unequal variances, a heteroscedastic Student's *t*-test was performed. The mean, standard error, and standard deviation (SD) of the 2 populations were calculated. The mean and SD are represented graphically as a bar chart. A box and whiskers plot was generated to better illustrate the distribution of

the data. A one-way ANOVA was also used to compare kidney disease or cardiac disease patients with control animals.

Gender effects were evaluated using Student's *t*-test and age-effects on tear production were assessed using linear regression. As there were insufficient numbers to discriminate between breed variances, breeds were instead grouped together based on physical characteristics into brachycephalic, mesocephalic, and dolichocephalic categories. Breed effect was assessed using a one-way ANOVA.

Results

Thirty control animals were enrolled in this study. The control population consisted of 16 neutered females, and 14 neutered males. There was no significant effect of sex on tear production. Ages ranged from 0.5 to 11 years with a median of 3.5 years. There was no significant effect of age on tear production noted and no statistical difference was noted between OS and OD tear production. The mean STT in this group was 24.5 mm/min (range: 15–31 mm/min, SD: 3.89 mm/min). Eleven breeds were represented in the control population: mixed breed 14/30, pitbull 4/30, Golden Retriever 3/30, English Bulldog 2/30, and one each of Boston Terrier, Boxer, Rhodesian Ridgeback, Lhasa Apso, German Shepherd, Pug, Greater Swiss Mountain Dog. When grouped into the categories of brachycephalic, mesocephalic, and dolichocephalic, there was no statistically significant effect of breed on tear production.

The patient population (30 dogs) was composed of 14 males (12 castrated, 2 intact) and 16 females (15 spayed, 1 intact). There was no significant effect of sex on tear production in this population. Patient age ranged from 0.5 to 14 years with a median age of 8 years. There was no significant effect of age on tear production noted. The patient group was significantly older ($P < 0.01$) than the controls. No statistical difference was noted between OS and OD tear production in the patient group. Twenty-two breeds were represented including: Yorkshire Terrier ($n = 4$), Shih Tzu ($n = 3$), Great Dane ($n = 2$), Dachshund ($n = 2$), Maltese ($n = 2$), and 1 each of following: Labrador Retriever, Alaskan Kleeklai, Cavalier King Charles Spaniel, Weimaraner, German Shepherd, Wheaton Terrier, Border Collie, Dalmatian, Golden Retriever, Italian Greyhound, American Cocker Spaniel, Brussels Griffon, Doberman Pinscher, Mastiff, Pitbull, Chihuahua, and mixed breed. When categorized into brachycephalic, mesocephalic, and dolichocephalic breeds, no significant difference in tear production was appreciated between the breeds. Of the disease processes represented, 6/30 dogs had kidney disease, 5/30 had cardiac disease or heart failure, 4/30 had gastrointestinal disorders, 4/30 dogs had neurologic disease, 2/30 had metabolic disease (eg, diabetic ketoacidosis, hypoadrenocorticism), 2/30 had neoplastic processes, 2/30 had pneumonia, 2/30 had hematologic abnormalities (eg, anemia, thrombotic disease), and each of the following disorders were represented once: extrahepatic portosystemic shunt, trauma (hit by car) and hypertrophic osteodystrophy. Patient records were examined and previous medical therapy was available for 25/30 animals. Of these 25 patients, 11/25 had recorded that no medications had been given prior to examination, 5/25 patients were receiving gastrointestinal medications (eg, famotidine, metronidazole, maropitant, ondansetron, lactulose, tylosin, metoclopramide), of these 5/25 patients, 3 were also receiving concurrent antimicrobials (eg, amoxicillin-clavulanic acid, marbofloxacin, enrofloxacin, unknown antimicrobial injection) and one was receiving zinc supplementation, a hepatoprotective supplement,[c] and prednisone. Three of 25 records showed that the patient was receiving only flea/tick or heart worm preventive medications, 3/25 patients were receiving cardiac medications (eg, furosemide, pimobendan, enalapril, spironolactone, amlodipine, bisoprolol), and 2/25 patients were receiving joint support (glucosamine) and either metacam or tramadol. There was one additional patient receiving a hepatoprotective supplement[c] and hydroxyzine.

The mean tear production within the patients was 13.2 mm/min (range: 0–28 mm/min, SD: 7.16 mm/min). Three dogs in the patient population had corneal ulceration documented. The STT results in these eyes were 7 mm/min, 23 mm/min, and 4 mm/min, respectively. Patients had significantly decreased tear production when compared to the controls ($P < 0.001$; see Figure 1). These data are also represented using a box and whiskers plot in Figure 2. An example of a patient with markedly decreased tear production is shown in Figure 3.

Post-hoc analysis of kidney and cardiac patients was performed as there was an overrepresentation of these diseases in the patient population. All patients with kidney disease had STT results $\leq$11 mm/min (range: 2–11 mm/min). Conversely, patients with cardiac disease had STT results $\geq$11 mm/min (range: 11–25 mm/min). While both patient groups produced significantly fewer tears than the control animals when analyzed individually ($P < 0.005$) for kidney patients versus control ($P < 0.05$ for cardiac patients versus control), the sample sizes were perhaps too small to establish statistical significance in tear production among diseases.

Tear production was reevaluated in 2 patients at a 2-week postdischarge examination. In both patients, tear production had initially been <7 mm/min. On recheck, the tear production was noted to be increased with 1 patient returning to normal values >20 mm/min

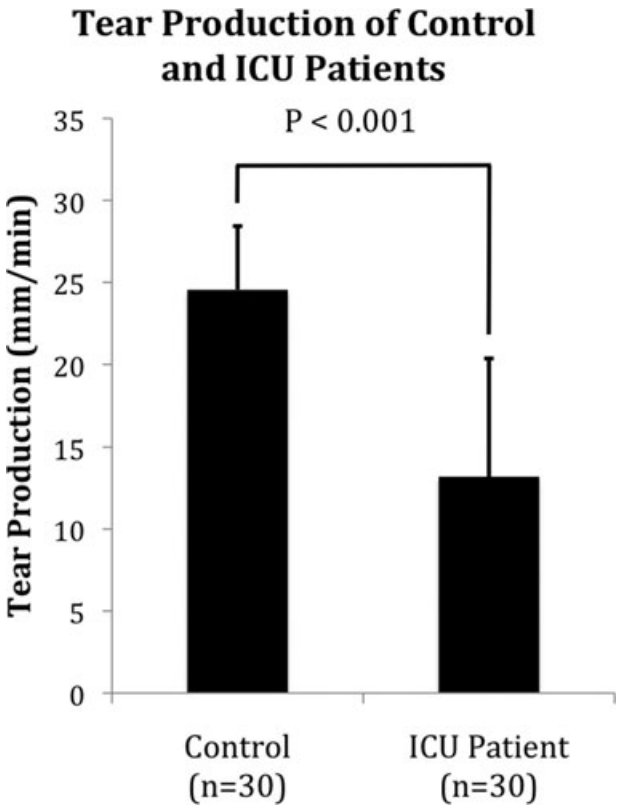

Figure 1: Comparison of tear production between control and ICU canine patients. Bars represent mean tear production in millimeters per minute (mm/min). Error bars represent SD.

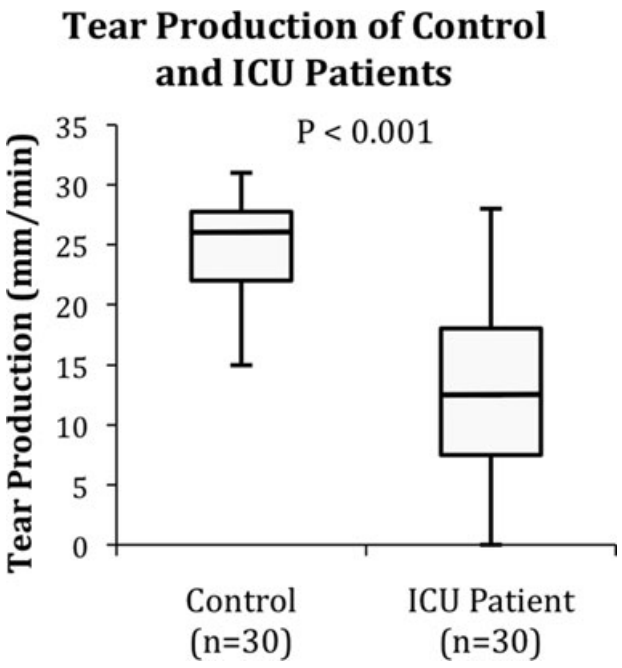

Figure 2: Comparison between control and ICU canine patients. The line within each box plot represents the median tear production for that group. The lower and upper limits of each box plot represents the 25th and 75th percentile of the data, respectively. The bars outside of the box plot represent the minimum and maximum data points.

bilaterally and the second having a normal tear production >20 mm/min in one eye and 11 mm/min in the other eye.

Discussion

This study demonstrated a significant decrease in tear production in a canine ICU patient population. The reason for this decrease may be multifactorial with underlying disorders such as organ dysfunction, as seen in people with kidney disease,[23] endocrinopathies,[3,4] trauma, and neurologic abnormalities as seen with autonomic dysfunction and facial neuropathies[27,28] playing major roles in the underlying pathogenesis. Breed predispositions,[29] although not reflected in the current data, may have also contributed to this tear decrease. While it was beyond the scope of this study to identify the definitive etiology associated with the decreased tear production, this is the first study in the veterinary literature to document that canine patients experience this phenomenon. This study highlights the fact that it is possible to have decreased tear production without significant corneal changes noted on cursory examination, and underscores the possibility that corneal disease is being underrecognized, underdiagnosed, and consequently undertreated.

Corneal disease is a cause of morbidity in any patient population; however, in critically ill patients, ocular changes may go unnoticed until damage to the eyes is severe. As ocular lubrication is minimally invasive, inexpensive, and may help to prevent permanent ocular damage, it seems prudent to implement an ocular health protocol in critically ill dogs. All canine ICU patients, except those that would suffer adverse effects from such an intervention (eg, dyspneic animals), would likely benefit from artificial tear gel instillation every 2–4 hours.

Feline patients were not evaluated in this study, as feline STT values are much more variable than seen in their canine counterparts. The STT values can decrease due to autonomic control during stressful situations.[30] As cats experience many similar disease processes, however, future studies are recommended to determine whether decreased tear production in critical illness occurs in this species.

Limitations of this study include a small sample size that precludes the assessment of contributory factors and risks associated with individual disease processes. Further studies evaluating individual disease processes are warranted to fully evaluate impact on tear production.

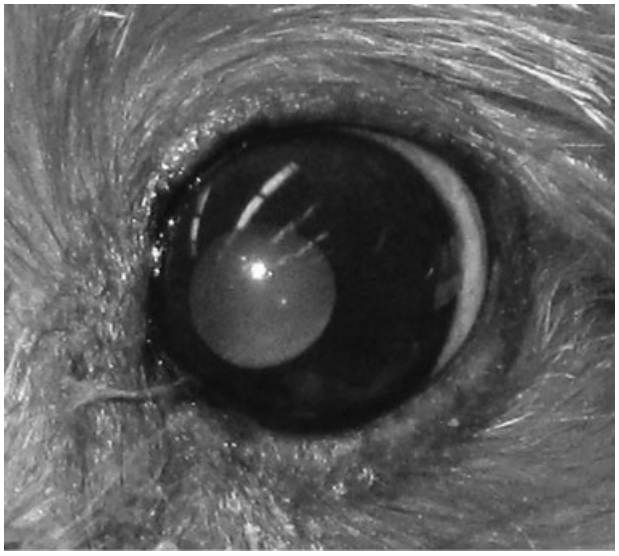

Figure 3: Example of an ICU patient with low tear production. A 6-year-old MI Yorkshire Terrier with grossly normal ocular examination and STT of 2 mm/min OD, 1 mm/min OS.

Another limitation is that the timing of the Schirmer Tear testing was not standardized. It has been previously documented that there is some variation in tear production within an individual animal. A day-to-day variation in tear production of 2 mm/min[31] and a diurnal variation of 0.7 mm/min, with the lowest STT values being noted at 10 am and the highest being noted around 4 pm,[31,32] have been reported. This may have introduced bias into the study as many STTs were obtained in late afternoon or evening. Therefore, the values reported in this study may be elevated due to the time of collection. Additionally, STT has been shown to decrease by approximately 0.4 mm/min for every 1 year of age increase. This confounding factor may have been avoided if the control population had been age-matched to the ICU patients. The presence of corneal ulceration in 3 of the ICU patients may have also added some bias into the study, as reflex tearing occurs in response to corneal damage. As the subset of patients with stain uptake is very small, and would tend to skew the data toward a higher STT result, we considered this to have minimal impact on our conclusions. Additionally, there are several other variables that can impact tear production and tear film distribution, independent of critical illness, that were not investigated during this study. Conditions such as an abnormal palpebral reflex, obtundation, and incomplete eyelid closure can independently impact tear production and tear film distribution. Further investigations involving a more in depth analysis of the tear film and corneal surface including Rose Bengal staining, tear film break-up times and blink rates are indicated. Finally, several medications have been shown to alter tear production.[5–7,9,10] Most dogs in this report had received medications prior to admission into the ICU such as cardiac, gastrointestinal and pain medications. It is possible that these medications may have contributed to the decrease in tear production; however, due to the design of this study, it is not possible to determine their individual contributions.

Conclusions

This study demonstrated a significant decrease in tear production in a canine patient population hospitalized in an ICU. While no significant difference was identified between the tear productions associated with specific disease processes, trends toward decreased tear production in kidney disease and closer to normal tear production in cardiac disease were noted. Further study is warranted to determine the underlying etiologies that impact tear production and evaluation as to whether this is a reversible process. Given the decrease in tear production and potential for secondary corneal ulceration, implementation of a protocol involving frequent ocular lubrication in all canine ICU patients should be considered.

Footnotes

[a] Schirmer Tear Strips, Schering-Plough Animal Health, Kenilworth, NJ.
[b] LubriFresh PM, Major Pharmaceuticals, Livonia, MI.
[c] Denamarin, NutraMax Laboratories, Inc, Edgewood, MD.

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