Temporal effects of intramuscular administration of medetomidine hydrochloride or xylazine hydrochloride to healthy dogs on tear flow measured by use of a Schirmer tear test I

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Received March 30, 2015.
Accepted June 10, 2015.

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OBJECTIVE
To determine the temporal effects on tear flow measurements obtained by use of a Schirmer tear test (STT) I after IM administration of various doses of medetomidine or xylazine to healthy dogs.

ANIMALS
5 healthy purpose-bred male Beagles.

PROCEDURES
Each dog received IM injections of 2.0 mL of physiologic saline (0.9% NaCl) solution (control treatment); 0.1% medetomidine hydrochloride (5, 10, 20, and 40 μg/kg), and 2.0% xylazine hydrochloride (0.5, 1.0, 2.0, and 4.0 mg/kg). Treatments were injected into the semimembranosus muscles; there was at least a 1-week interval between successive injections. Order of treatments was determined via a randomized Latin square crossover design. The STT I was performed on both eyes before (baseline) and 0.25, 0.50, 0.75, 1, 2, 3, 4, 5, 6, 7, 8, and 24 hours after each injection.

RESULTS
STT I values decreased significantly within 45 minutes after injection of medetomidine or xylazine, which was followed by gradual recovery. The lowest mean STT I value was < 10 mm/min for all sedation treatments, except when dogs received 5 μg of medetomidine/kg. Linear regression of the area under the curve for the 8 hours after administration yielded significant effects for all sedation treatments.

CONCLUSIONS AND CLINICAL RELEVANCE
IM administration of medetomidine or xylazine to dogs reduced tear flow in a dose-related manner. Artificial tear solution or ophthalmic ointment should be used to protect the ocular surface when these drugs are administered to dogs. (*Am J Vet Res* 2016;77:346–350)

Tears play important roles in the ocular surface immune system and metabolic processes on the avascular portion of the cornea. They ensure a smooth optical surface by lubricating the cornea, conjunctiva, and nictitating membrane.[1] Insufficient quantity or quality (or both) of tears decreases lubrication and increases frictional irritation of the ocular surface, which can cause keratoconjunctivitis sicca.[2]

Anesthetic or sedative drugs reduce tear volume in several species.[2–7] In particular, α_2-adrenoceptor agonists alone and in combination with other drugs affect tear production during sedation in cats,[5] horses,[8] and dogs.[9,10] For example, 10 to 15 μg of medetomidine/kg significantly lowers STT I values in dogs.[9] Furthermore, 2.0 mg of xylazine/kg significantly reduces STT I values at 15 and 25 minutes after IM administration to cats.[5] In contrast, 0.5 mg of xylazine/kg has no effect on STT I values at 15 to 25 minutes after IM administration to dogs.[4] Therefore, the conclusions for previous studies are limited by differences in drug doses and durations of observation.

The purpose of the study reported here was to determine the temporal effects of various doses of medetomidine and xylazine administered IM to healthy dogs on tear flow measurements obtained by use of an STT I. We hypothesized that both medetomidine and xylazine would affect tear flow of dogs in a dose- or time-dependent manner.

ABBREVIATIONS
AUC Area under the curve
STT Schirmer tear test

Materials and Methods

Animals

Five healthy purpose-bred male Beagles were included in the study. Mean ± SD age was 6.6 ± 0.8 years, and mean body weight was 14.3 ± 3.5 kg. Dogs were maintained under uniform conditions in an institutional animal laboratory. No abnormalities were detected during routine physical and ophthalmic ex-

aminations, including observation of the globe and eyelids, testing with an STT I, assessment of corneal and eyelid reflexes, vision testing, assessment of direct and indirect pupillary light reflexes, slit-lamp biomicroscopy, direct ophthalmoscopy, and intraocular pressure measurement, performed before the study. All dogs were deemed as American Society of Anesthesiologists physical status 1.[11] All procedures were approved by the Animal Care and Use Committee of Kurashiki University of Science and the Arts.

Procedures

Each dog received 9 injections during the study. All dogs were allowed to acclimate to the experimental room for 12 hours before injections were administered. In addition, food was withheld from all dogs for 12 hours before each injection.

Injections were administered in the semimembranosus muscles. Dogs received 2.0 mL of physiologic saline (0.9% NaCl) solution (control treatment); 0.1% medetomidine hydrochloride (5, 10, 20, and 40 µg/kg); and 2.0% xylazine hydrochloride (0.5, 1.0, 2.0, and 4.0 mg/kg). There was an interval of at least 1 week between successive injections. Order of treatments was determined via a randomized Latin square crossover design.

STT I measurements

Tear flow was measured by use of an STT I before (baseline) and 0.25, 0.50, 0.75, 1, 2, 3, 4, 5, 6, 7, 8, and 24 hours after each injection. The baseline measurement was obtained at 9 AM for all treatments. All dogs remained in the experimental room for 24 hours without any further treatment, including administration of a reversal agent, regardless of whether they still appeared sedated at > 8 hours after injection of medetomidine or xylazine.

Both eyes were tested by use of STT strips.[a] The end of each strip was placed inside the lateral aspect of the lower eyelid. After 60 seconds, the distance that was wet on the strip was recorded as the STT I value. For each experiment, STT strips with the same lot number were used for all 13 measurements. To standardize the body position at each measurement, all dogs were positioned in right lateral recumbency with the eyelids relaxed during each measurement of the STT I value.

Statistical analysis

All data were analyzed with statistical software.[b] The Friedman test for repeated measures was used to evaluate temporal effects for each treatment. When a significant difference was found, the Dunn test was used to compare the baseline mean value with the mean at each time point. Differences between the left and right eyes at every time point for each treatment were examined with the Wilcoxon matched-pairs signed-rank test. Data were reported as mean ± SEM. Significance for all tests was set at $P < 0.05$.

The AUC of STT I values from baseline to 8 hours was calculated. Data were plotted against the dose of medetomidine or xylazine, and simple linear regression analysis was performed. The effect of a drug on STT I values was considered dose related when linear analysis yielded a significant relationship.

Results

There were no significant differences in STT I values between the right and left eyes for any treatment. Furthermore, there was no significant change in STT I values over time for the control treatment. For all sedation treatments, STT I values of both eyes decreased significantly within 45 minutes after injection, which was followed by a gradual recovery **(Figures 1 and 2)**.

A significant decrease in mean ± SEM STT I values was detected in the left eye at 0.75 hours (12.4 ± 1.8 mm/min) and right eye at 0.5, 0.75, and 1 hour (mean, 14.0 ± 1.1 mm/min, 14.0 ± 2.1 mm/min, and 14.6 ± 1.7 mm/min, respectively) after administration of 5 µg of medetomidine/kg. Mean ± SEM STT I values decreased significantly in the left eye at 0.5, 0.75, and 1 hour (9.2 ± 2.7 mm/min, 7.2 ± 1.7 mm/min, and

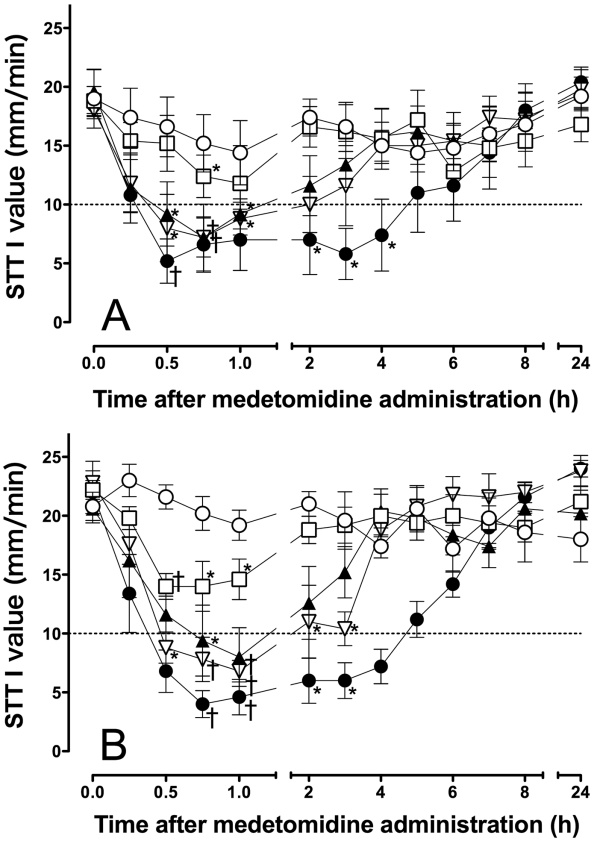

Figure 1—Mean ± SEM STT I values of the left (A) and right (B) eyes of 5 clinically normal dogs before (baseline; time 0) and after IM administration of 2.0 mL of physiologic saline (0.9% NaCl) solution (control treatment [white circles]) and various doses of medetomidine hydrochloride (5 µg/kg [white squares], 10 µg/kg [black triangles], 20 µg/kg [inverted white triangles], and 40 µg/kg [black circles]). Notice the amount of time that STT I values are < 10 mm/min (horizontal dotted line). *,†Within a treatment, value differs significantly (*$P < 0.05$; †$P < 0.01$) from the baseline value.

9.2 ± 1.3 mm/min, respectively) and in the right eye at 0.75 and 1 hour (9.4 ± 3.0 mm/min and 8.0 ± 2.5 mm/min, respectively) after administration of 10 µg of medetomidine/kg. Mean ± SEM STT I values decreased significantly in the left eye at 0.5, 0.75, and 1 hour (8.0 ± 2.9 mm/min, 7.2 ± 2.8 mm/min, and 8.8 ± 1.4 mm/min, respectively) and in the right eye at 0.5, 0.75, 1, 2, and 3 hours (8.8 ± 1.3 mm/min, 7.8 ± 1.9 mm/min, 6.8 ± 0.9, 11.0 ± 3.1 mm/min, and 10.4 ± 1.4 mm/min, respectively) after administration of 20 µg of medetomidine/kg. Mean ± SEM STT I values decreased significantly in the left eye at 0.5, 2, 3, and 4 hours (5.2 ± 1.9 mm/min, 7.0 ± 3.0 mm/min, 5.8 ± 2.2 mm/min, and 7.4 ± 3.1 mm/min, respectively) and in the right eye at 0.75, 1, 2, and 3 hours (4.0 ± 1.1 mm/min, 4.6 ± 1.5 mm/min, 6.0 ± 2.0 mm/min, and 6.0 ± 1.5 mm/min, respectively) after administration of 40 µg of medetomidine/kg.

Mean STT I value of both eyes was never < 10 mm/min after injection of 5 µg of medetomidine/kg. However, the mean STT I value was < 10 mm/min for 30 minutes in the left eye and 15 minutes in the right eye after injection of 10 µg of medetomidine/kg, for 30 minutes in both eyes after injection of 20 µg of medetomidine/kg, and for 210 minutes in both eyes after injection of 40 µg of medetomidine/kg.

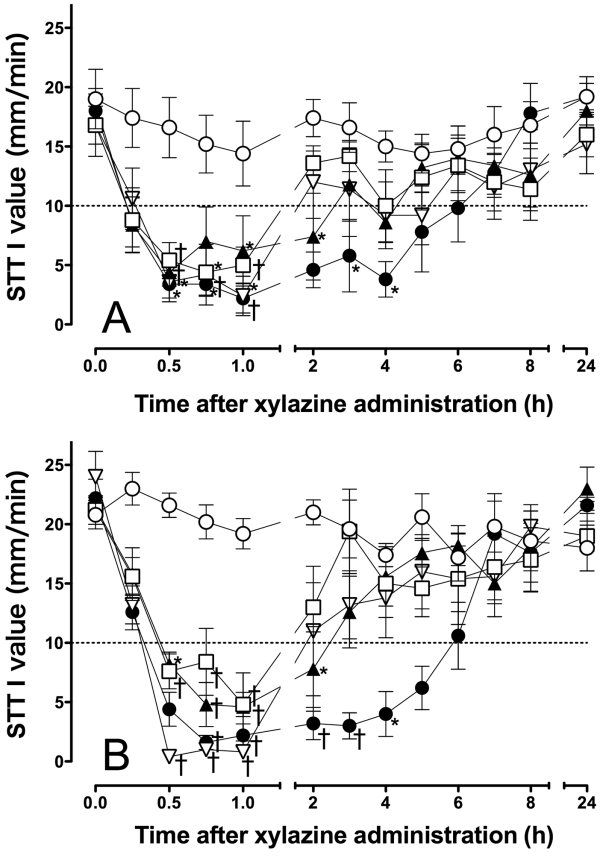

Figure 2—Mean ± SEM STT I values of the left (A) and right (B) eyes of 5 clinically normal dogs before (baseline; time 0) and after IM administration of 2.0 mL of physiologic saline solution (control treatment [white circles]) and various doses of xylazine hydrochloride (0.5 mg/kg [white squares], 1.0 mg/kg [black triangles], 2.0 mg/kg [inverted white triangles], and 4.0 mg/kg [black circles]). ***See*** Figure 1 for remainder of key.

After injection of 0.5 mg of xylazine/kg, mean ± SEM STT I values decreased significantly at 0.5, 0.75, and 1 hour in both eyes (left eye: 5.4 ± 1.5 mm/min, 4.4 ± 2.0 mm/min, and 5.0 ± 1.5 mm/min, respectively; right eye: 7.6 ± 1.5 mm/min, 8.4 ± 2.8 mm/min, and 4.8 ± 1.0 mm/min, respectively). Significant decreases in mean ± SEM STT I values were also detected in the left eye at 0.5, 1, and 2 hours (4.4 ± 1.2 mm/min, 6.2 ± 3.0 mm/min, and 7.4 ± 3.7 mm/min, respectively) and in the right eye at 0.5, 0.75, 1, and 2 hours (8.2 ± 1.0 mm/min, 4.8 ± 1.9 mm/min, 4.6 ± 2.9 mm/min, and 7.8 ± 3.6 mm/min, respectively) after injection of 1.0 mg of xylazine/kg. After injection of 2.0 mg of xylazine/kg, both eyes had significant decreases in mean ± SEM STT I values at 0.5, 0.75, and 1 hour (left eye: 3.6 ± 1.7 mm/min, 4.2 ± 2.6 mm/min, and 2.4 ± 1.7 mm/min, respectively; right eye: 0.4 ± 0.2 mm/min, 1.0 ± 0.5 mm/min, and 0.8 ± 0.2 mm/min, respectively). Mean ± SEM STT I values decreased significantly in the left eye at 0.5, 0.75, 1, 3, and 4 hours (3.4 ± 1.2 mm/min, 3.4 ± 0.9 mm/min, 2.2 ± 1.2 mm/min, 5.8 ± 3.1 mm/min, and 3.8 ± 1.5 mm/min, respectively) and in the right eye at 0.75, 1, 2, 3, and 4 hours (1.6 ± 0.6 mm/min, 2.2 ± 1.0 mm/min, 3.2 ± 1.4 mm/min, 3.0 ± 1.1 mm/min, and 4.0 ± 1.9 mm/min, respectively) after injection of 4.0 mg of xylazine/kg.

In contrast to results for the medetomidine treatments, all the xylazine treatments resulted in mean STT I values < 10 mm/min. The mean STT I value was < 10 mm/min for 45 minutes in the left eye and 30 minutes in the right eye after injection of 0.5 mg of xylazine/kg. The mean STT I value was < 10 mm/min in the left and right eyes for 105 and 90 minutes, respectively, after injection of 1.0 mg of xylazine/kg. Mean STT I values < 10 mm/min were recorded in both eyes for 30 minutes after injection of 2.0 mg of xylazine/kg. Mean STT I values < 10 mm/min were detected in the left eye for 345 minutes and in the right eye for 270 minutes after injection of 4.0 mg of xylazine/kg.

Linear regression analysis of AUC data of both eyes for the 8-hour period after injection revealed significant effects for all medetomidine treatments **(Figure 3)**. It also yielded significant effects for the xylazine treatments for the left ($P = 0.014$) and right ($P < 0.001$) eyes. The AUC values of both eyes were significantly lower after injection of 40 µg of medetomidine/kg, compared with values for the control treatment. Furthermore, AUC values were significantly lower, compared with those of the control group, in the right eye after injection of 2.0 mg of xylazine/kg ($P = 0.020$) and 4.0 mg of xylazine/kg ($P = 0.003$) and in the left eye after injection of 4.0 mg of xylazine/kg ($P = 0.020$).

Discussion

The present study was conducted to evaluate the effects of various doses of medetomidine and

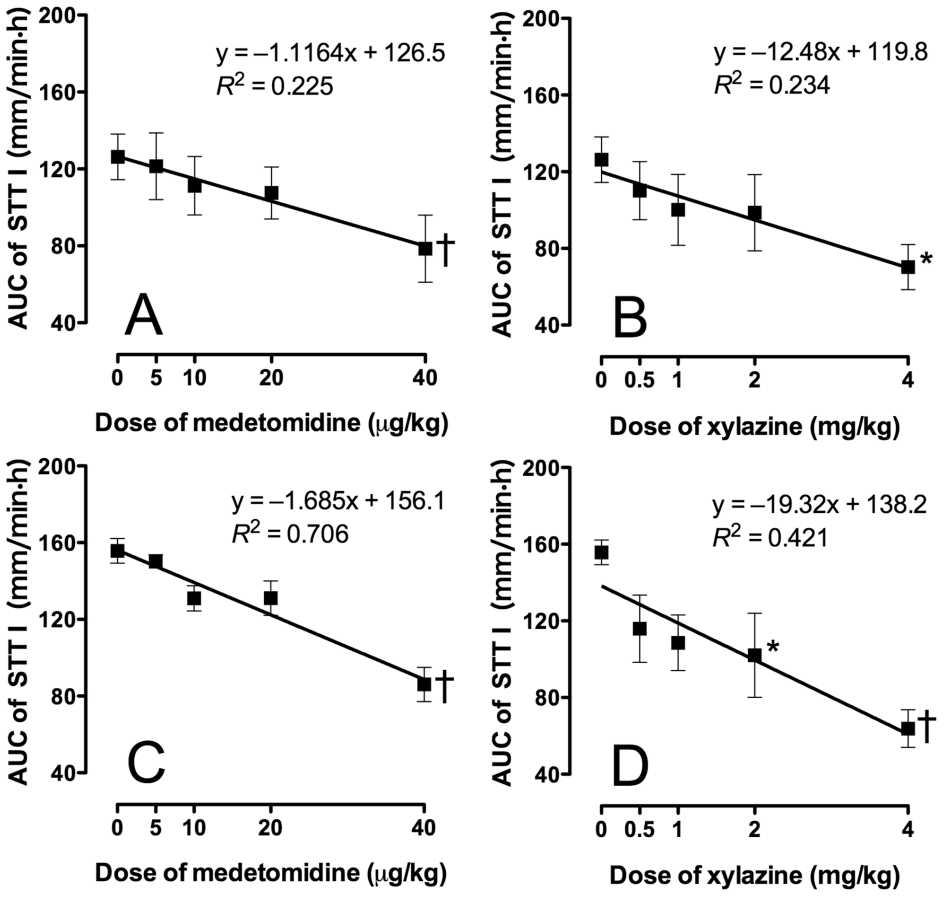

Figure 3—Mean ± SEM AUC of STT I values of the left (A and B) and right (C and D) eyes of 5 clinically normal dogs during the 8-hour period after IM administration of various doses of medetomidine hydrochloride (A and C) or xylazine hydrochloride (B and D). *†Value differs significantly (*P < 0.05; †P < 0.01) from the value for the control treatment (IM administration of 2.0 mL of physiologic saline solution).

xylazine administered IM to healthy dogs on tear flow measured by use of the STT I. All doses of the drugs significantly decreased STT I values within 45 minutes after injection. In agreement with results of another study,[4] the dose of 0.5 mg of xylazine/kg did not significantly decrease STT I values at 0.25 hours after administration. However, STT I values at 0.5 hours after injection of 0.5 mg of xylazine/kg were lower than those before administration. Therefore, injection of 0.5 mg of xylazine/kg affected tear flow only begining 30 minutes after IM administration.

Results of linear regression analysis suggested that both medetomidine and xylazine reduced tear flow in a dose-related manner. Higher doses typically induced a more prolonged decrease in STT I values. The duration of a significant decrease in STT I values was 3 to 4 hours after injection of 40 μg of medetomidine/kg and 4 hours after injection of 4.0 mg of xylazine/kg, although a significant reduction was detected beginning 30 minutes after injection of 5 μg of medetomidine/kg and 0.5 mg of xylazine/kg. These findings can be explained by the possibility that the dose of these α_2-adrenoceptor agonists influenced the duration, rather than the degree, of the effect on tear flow.

The selectivity of medetomidine for α_2-adrenoceptors is approximately 10 times as high as that of xylazine, and medetomidine is an imidazoline receptor agonist, whereas xylazine is not.[12,13] However, both drugs similarly decreased STT I values in eyes of dogs in the study reported here. In addition, it was reported in another study[9] that the medetomidine-induced decrease in STT I values for eyes of dogs is reversed by administration of atipamezole, an α_2-adrenoceptor antagonist. These findings suggest that reduced tear flow subsequent to administration of medetomidine or xylazine is via α_2-adrenoceptor action and excludes effects on α_1-adrenoceptors or imidazoline receptors. The α_2-adrenoceptor is a presynaptic receptor at the terminus of adrenergic nerve fibers.[14] Adrenergic nerve fibers innervate the lacrimal glands of mice.[15] Of relevance to the present study, such innervation has not yet been identified in dogs.[10]

The decrease in tear flow induced by medetomidine and xylazine may be attributed to suppression of reflex tear production through increased antinociception, inhibitory effects on the lacrimal glands at the cellular level, reduced blood flow in the lacrimal glands caused by α_2-adrenoceptor agonist–induced vasoconstriction, or a combination of these factors.[9,10] However, medetomidine caused a greater decrease in tear production than did xylazine, a drug with similar vasoactive effects.[4,10] In the present study, both medetomidine and xylazine significantly decreased STT I values at 30 minutes after IM administration to dogs. This result suggested that reduced blood flow in the lacrimal glands caused by α_2-adrenoceptor–mediated vasoconstriction was the mechanism underlying the effect on tear flow for medetomidine as well as xylazine.

The STT I value for clinically normal dogs is reportedly > 15 mm/min. The mean ± SD STT I value was 18.89 ± 2.62 mm/min in 1 study.[16] A sustained decrease in tear production leads to irritation of the ocular surface, and STT I values < 10 mm/min can

result in keratoconjunctivitis sicca.[1] In the present study, all sedation treatments, except 5 µg of medetomidine/kg, yielded STT I values < 10 mm/min with a duration of 0.25 to 5 hours. The duration of such low STT I values was 15 to 30 minutes for injection of 10 and 20 µg of medetomidine/kg, 3.5 hours for injection of 40 µg of medetomidine/kg, 30 to 45 minutes for injection of 0.5 mg of xylazine/kg, 1.5 to 1.75 hours for injection of 1.0 mg of xylazine/kg, 30 minutes for injection of 2.0 mg of xylazine/kg, and 4.5 to 5.75 hours for injection of 4.0 mg of xylazine/kg. These results indicated that artificial tear solution or ophthalmic ointment should be used to protect the ocular surface in dogs receiving an IM injection of > 10 µg of medetomidine/kg or 0.5 mg of xylazine/kg.

Dogs treated with 15 µg of medetomidine/kg have a significant sustained decrease in STT I values for 1 hour after anesthesia.[10] In the present study, STT I values did not return to the reference range simultaneously with recovery from sedation. Importantly, regardless of the dose of sedative administered, STT I values in some dogs did not return to the reference range despite recovery from sedation. Therefore, practitioners should observe the ocular surface and evaluate tear flow in dogs sedated with medetomidine (alone or in combination) during anesthesia and also after recovery from anesthesia.

Body position does not affect results of tear flow measurement in dogs.[7] No significant differences in STT I values between the left and right eyes were detected for dogs positioned in right lateral recumbency in the present study, which supports the findings of that previous study.[7]

The STT value is considered an indicator of tear production.[2,4–8,10,17–19] However, it does not distinguish tear production by the lacrimal glands from tear secretion via the ducts. Therefore, in the study reported here, it is possible that tear secretion decreased because of ductal constriction but tear production remained unaltered. This is an important point for investigation of the mechanism of decreased tear flow induced by α_2-adrenoceptor agonists and a limitation of the present study.

For the study reported here, IM administration of medetomidine and xylazine decreased tear flow in eyes of dogs in a dose-related manner. Values of STT I < 10 mm/min were detected after administration of all doses of medetomidine and xylazine, except 5 µg of medetomidine/kg. The underlying mechanism may be α_2-adrenoceptor–induced reduction in tear production or tear secretion in dogs.

Footnotes

a. ColorBar Schirmer tear test, Eagle Vision Inc, Memphis, Tenn.
b. GraphPad Prism, version 6, GraphPad Software Inc, La Jolla, Calif.

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