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Corneal Sensitivity in Tear Dysfunction and its Correlation with Clinical Parameters and Blink Rate

Effie Z. Rahman[1], **Peter K. Lam**[1], **Chia-Kai Chu**[1], **Quianta Moore**[1], and **Stephen C. Pflugfelder**[1]

[1]Department of Ophthalmology, Baylor College of Medicine, Houston, TX

Abstract

Purpose—To compare corneal sensitivity in tear dysfunction due to a variety of causes using contact and non-contact esthesiometers and to evaluate correlations between corneal sensitivity, blink rate and clinical parameters.

Design—Comparative observational case series.

Methods—Ten normal and 33 subjects with tear dysfunction [meibomian gland disease (n = 11), aqueous tear deficiency (n = 10) - without (n = 7) and with (n = 3) Sjögren syndrome (SS) and conjunctivochalasis (n = 12)] were evaluated. Corneal sensitivity was measured with Cochet-Bonnet and air jet esthesiometers and blink rate by electromyelography. Eye irritation symptoms, tear meniscus height, tear break-up time (TBUT), and corneal and conjunctival dye staining were measured. Between group means were compared and correlations calculated.

Results—Compared with control (Cochet-Bonnet 5.45 mm, air esthesiometer 3.62 mg), mean sensory thresholds were significantly higher in aqueous tear deficiency using either Cochet-Bonnet (3.6 mm; P = 0.003) or air (11.7 mg; P = 0.046) esthesiometers, but were not significantly different in the other groups. Reduced corneal sensitivity significantly correlated with more rapid TBUT and blink rate, and greater irritation and ocular surface dye staining with one or both esthesiometers. Mean blink rates were significantly higher in both aqueous tear deficiency and

Corresponding Author: Stephen C. Pflugfelder, MD, Cullen Eye Institute, Baylor College of Medicine, 6565 Fannin, NC 205, Phone: (713) 798-4732, Fax: (713) 798-1457, stevenp@bcm.edu.

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conjunctivochalasis compared with control. Among all subjects, blink rate positively correlated with ocular surface staining and irritation and inversely correlated with TBUT.

Conclusion—Amongst conditions causing tear dysfunction, reduced corneal sensitivity is associated with greater irritation, tear instability, ocular surface disease and blink rate. Rapid blinking is associated with worse ocular surface disease and tear stability.

Keywords

dry eye; corneal sensitivity; blink rate; esthesiometer; ocular surface disease; tear dysfunction

INTRODUCTION

Tear dysfunction is a prevalent disorder caused by decreased tear production, excessive evaporation or an altered distribution.[1] Patients with tear dysfunction often experience irritation symptoms such as dryness, foreign body sensation, and burning[2–4] however, paradoxically certain patients with moderate to severe ocular surface disease have a paucity of irritation symptoms.[5–15] Patients with tear dysfunction may also complain of blurred and fluctuating vision, photophobia and frequent blinking. Increased frequency of blinking has been previously noted in patients with tear dysfunction;[16] however, the factors contributing to the increased blink rate have not been established and may be influenced by the source of tear dysfunction. Studies evaluating tear dysfunction following LASIK have reported a decrease in blink rate.[15] Although LASIK is known to cause corneal hyposensitivity which is often transient, no reduction in corneal sensitivity was found in one study, while hyperesthesia was measured in subjects with concurrent dry eye disease after LASIK.[3,15,17]

Tear instability and epithelial disease can disrupt corneal epithelial barrier function, which can affect corneal sensitivity and nerve morphology.[2,5,6,18,19] Studies measuring corneal sensitivity in dry eye by contact and non-contact methods have reported conflicting results with either increased, decreased or no change in sensitivity.[2–12, 15,17, 20–22] However, none of these previously reported studies stratified dry eye subjects by cause of tear dysfunction. Because corneal epithelial disease is more severe in aqueous tear deficiency than in meibomian gland disease and conjunctivochalasis,[13,14] we hypothesized there may be differences in corneal sensitivity and blink rate between these subsets of tear dysfunction that may be related to severity of ocular surface epithelial disease. To our knowledge, corneal sensitivity and blink rate have not been compared between these distinct subsets of tear dysfunction. Evaluating corneal sensitivities amongst different subsets of tear dysfunction may prove to be important for stratifying patients for clinical trials, for determining the cause for ocular irritation/pain symptoms and perhaps for making treatment recommendations. Furthermore the relationship between sensitivities and blink rate may provide insight into the mechanisms for increased blinking in dry eye. Testing corneal sensitivity in defined subsets of tear dysfunction may help to explain the conflicting results of previous studies that have reported both corneal hyposensitivity and hypersensitivity findings.

The objective of this study was to compare corneal sensitivity using contact and non-contact methods in three common subtypes of tear dysfunction (aqueous tear deficiency, meibomian

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gland disease and conjunctivochalasis). The relationship between corneal sensitivity and irritation symptoms, blink rate, and clinical parameters was also assessed.

METHODS

Study oversight

The institutional review board (IRB) at Baylor College of Medicine approved the study protocol to conduct clinical assessments in a prospective manner in which normal, non-dry eye subjects and those with tear dysfunction were enrolled for research participation after written informed consent. No retrospective IRB approval was necessary. Our study complies with the Health Insurance Portability and Accountability Act.

Study design

Data for this comparative observational case series was collected from April 2012 – June 2014 at the Alkek Eye Center at Baylor College of Medicine, Houston, TX. Subjects underwent a standardized tear and ocular surface evaluation in the following order that included anterior segment optical coherence tomography (OCT) as a measure of tear production and volume, respectively, fluorescein tear break-up time (TBUT) as a measure of tear stability, and corneal fluorescein and conjunctival lissamine green dye staining as measures of ocular surface epithelial cell health. Corneal and conjunctival dye staining with fluorescein and lissamine green, respectively, were performed and graded as previously reported.[13] Severity of eye irritation symptoms was measured using validated questionnaires, including the ocular surface disease index (OSDI) and a 5 question visual analog scale (VAS). After standard clinical tests were performed, corneal sensitivity was measured by both Cochet-Bonnet and air jet esthesiometers, and blink rate was measured using electromyography (EMG) with signals detected by the NeuroSky™ MindBand Bluetooth device (NeuroSky, Silicon Valley, CA). Data from only one eye (with the worst corneal fluorescein staining) for each subject, and the right eye for normal control subjects was included in the data analysis.

Subjects

Thirty-three subjects with tear dysfunction were classified into the following groups: aqueous tear deficiency, meibomian gland disease and conjunctivochalasis according to criteria listed in Table 1. The classifications were based on an ocular surface disease index (OSDI) score > 20, tear break-up time (TBUT) < 7 seconds, tear meniscus height measured by optical coherence tomography (OCT), and the presence (or absence) of meibomian gland disease and conjunctivochalasis.[13]

Normal control subjects had an OSDI score ≤ 20, no history of contact lens or eye drop use, or prior ocular surgery. They also had a TBUT ≥ 8 seconds, and absence of fluorescein and lissamine green staining, meibomian gland disease and conjunctivochalasis on biomicroscopic examination.

Subjects were excluded if they had prior LASIK or corneal transplantation surgery, cataract surgery in the past year, punctal occlusion with plugs or cautery, a history of contact lens

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wear, use of topical medications other than preservative-free artificial tears, or chronic use of systemic medications known to reduce tear production. In addition, subjects were excluded if they had active ocular surface or corneal inflammation, infection, or eyelid disorders causing exposure of the ocular surface. Seventy-one patients were excluded due to these criteria.

Subjects were recruited from patients presenting to the corneal service at the Alkek Eye Center and employees of Baylor College of Medicine.

Optical Coherence Tomography

OCT measurement of the height of the lower tear meniscus was performed as described previously.[13] All subjects underwent cross-sectional imaging of the lower tear meniscus prior to the instillation of drops or measurement of clinical parameters.

Fluorescein tear break up time and corneal fluorescein staining

TBUT was measured by instilling fluorescein into the lower fornix with a fluorescein strip (BioGlo, HUB, Rancho Cucamonga, CA) wet with preservative-free saline (Unisol; Alcon, Fort Worth, Texas). The patient was allowed to blink at a spontaneous rate, and the elapsed time from the last blink to the appearance of the first break in the continuous layer of fluorescein, as observed under cobalt blue light through a yellow filter, was measured in seconds. Three separate measurements were taken as previously described.[13] Corneal fluorescein staining was graded 0 to 6 in each of 5 zones (inferior, nasal, temporal, central and superior) 1 minute after fluorescein instillation, as previously reported.[13]

Conjunctival Lissamine Staining

The ocular surface was examined under white light illumination 1 minute after touching the inferior tarsal conjunctiva with a lissamine green strip (Green Glo 1.5mg Lissamine green (HUB Pharmaceuticals LL Rarncho Cucamonga, CA) wet with preservative-free saline. Staining was graded on a scale of 0 to 3 in the exposed nasal and temporal bulbar conjunctiva with a total maximum score of 6 as previously reported.[13]

Corneal Sensitivity

Corneal sensitivity was measured by both Cochet-Bonnet and by air esthesiometer. A Cochet-Bonnet esthesiometer with a 0.12 mm nylon monofilament touched the center of the corneal surface at a perpendicular angle under illumination. Both eyes of each patient were tested. Patients were asked to indicate when they perceived touch. The longest length of 6.0 cm was utilized first, which corresponds to greater sensitivity. The thread length was decreased by 1.0 cm increments and the measurement repeated until sensation was felt, and it was then increased by 0.5 mm to obtain a final reading to the closest 0.5 mm.

An air esthesiometer was used to evaluate corneal sensation with a non-contact method. Briefly, the prototype esthesiometer (Figure 1) is comprised of a cylinder of medical grade compressed air that is connected via a unidirectional pressure regulator adjusted to 3 psi and inline filter to the OK International DX-255 Basic Digital Fluid Dispenser (OK International, Garden Grove, CA), which outputs the air stimulus at a given pressure over a

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period of two seconds when its foot pedal is depressed. The air then travels to a hose line in which the final flow of gas is adjusted with a flow meter and supplied to a 200 μL pipette tip with an internal diameter of 0.457 mm, that is attached to the end of the hose and secured on a calibrated movable mount that is attached to a stand that can be directly mounted on a Haag-Streit slit lamp (Köniz, Switzerland). The mount housing has 4 red LEDs centered around the pipette tip to aid in aligning the outflow stream with the center of the subject's cornea. During stimulation, the air stimulus was triggered by a foot pedal pressed by the investigator. The average temperature of the air released by the tip was 28°C.

To measure corneal sensitivity, subjects were seated in front of the esthesiometer tip that was positioned 5 mm away from the center of the cornea using a knob on the movable mount. The air-stimulus was applied by tapping the foot pedal that triggered an audible click by the air valve, indicating the onset of the 2-second pulse stimulus. Subjects were informed the air stimulus might be perceived as a "breeze-like" sensation beforehand. The force of the air stimulus was controlled by a knob turned in 45 degree increments and was turned each time the stimulus was not detected. Subjects were asked to report the presence or absence of sensation and to describe the sensation immediately after hearing the audible click. Subjects were instructed to blink between clicks, and the lowest detectable stimulus that elicited a response was recorded as the mechanical threshold. When a response was detected, the experimenter dialed back the knob by 45 degrees to lower the stimulus intensity and confirm the number of turns necessary to elicit the threshold stimulus. The force of the air stimulus was measured in mass (grams).

Blink Rate Measurement

Blink rate was measured using electromyography (EMG) signals detected by the NeuroSky(TM) MindBand Bluetooth device (NeuroSky, Silicon Valley, CA). The MindBand was placed on the subject's forehead and the dry electrodes on the MindBand measured the changing electrical potential of the orbicularis muscles during blinks.

The threshold for detecting a blink was set prior to recording the patient's average blink rate per minute and was adjusted for each individual. Subjects were asked to look straight ahead, in a relaxed manner, without any additional activity for 5 minutes. Patients were asked to avoid speaking, moving extremities, or making facial expressions. Excessive movements during the measurement period were excluded from the data analysis, and only blink rates from minutes 2–4 were used for calculations. Blinks were measured and recorded as blinks/minute. The blink count readings were verified by manual blink counting for each patient.

Testing was performed in the following order: measurement of tear meniscus height by OCT, blink rate measurement, corneal sensitivity by air esthesiometer, tear break-up time, corneal fluorescein and conjunctival lissamine green staining, and, corneal sensitivity by Cochet-Bonnet.

Data analysis

The data was analyzed using GraphPad (Prism 6.0, La Jolla, CA). Normality distribution of data sets was determined using the D'Agostino-Pearson normality omnibus test. Many, but not all of our parameters were normally distributed, thus both parametric (Pearson's

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correlation coefficient and ANOVA), and non-parametric tests (Spearman's rank correlation coefficient, Mann-Whitney, and the Kruskal-Wallis test) were performed. Because the results of parametric and non-parametric tests were similar, the mean values of corneal sensitivity, blink rate, and clinical parameters were compared between tear dysfunction subtypes and control group using ANOVA. All data sets included measurements from interval scales, so the Pearson correlation coefficient (R) was calculated to assess the relationship between corneal sensitivity and irritation symptoms, blink rate, and clinical parameters within the entire tear dysfunction group and within each subtype. A P value of ≤ 0.05 was considered to be statistically significant.

RESULTS

Study population

The demographic features for control and tear dysfunction subjects are presented in Table 2. Age ranged from 30 to 85 years (61.82 ± 12.77 [mean ± SD]) in the 33 tear dysfunction subjects, and 25 to 79 years (47.4 ± 21.69 [mean ± SD]) in the 10 control subjects. There was a statistically significant difference in age between all tear dysfunction (61.82 years) and control (47.4 years) subjects (P = 0.006), and between conjunctivochalasis (66.92 years) and controls (47.4 years) (P = 0.004). There was no difference in age between either meibomian gland disease or aqueous tear deficiency and the control group and there was no statistically significant difference in mean age between the tear dysfunction groups.

Mean value comparisons for corneal sensitivity

For each group, the mean and standard deviation values for corneal sensitivity measured with both methods, clinical parameters of tear function, ocular surface disease and blink rate are shown in Table 3. When compared with the mean corneal sensitivity threshold in the control group using the Cochet-Bonnet (5.450mm; 95% confidence interval (CI) = 4.86 mm to 6.04 mm), there was a significantly higher threshold in the aqueous tear deficiency group (3.6mm; CI = 2.42 mm to 4.78 mm; P < 0.003). When compared with the mean threshold in the control subjects using the air esthesiometer (3.62 mg), there was also a significantly higher threshold in the aqueous tear deficiency group (11.7 mg; CI = 2.18 mg to 21.2 mg; P = 0.046).

Correlation between Cochet-Bonnet and air jet esthesiometers

A significant correlation between our prototype air esthesiometer and the Cochet-Bonnet was found for dry eye subjects (r = −0.512; CI = −0.730 mm to −0.199 mm; P < 0.001). In addition, there was significant correlation between our air esthesiometer and the Cochet-Bonnet for all subjects (r = −0.545; CI = −0.721 mm to −0.275 mm; P < 0.001) (Figure 2).

Mean values comparison for blink rate

When compared with mean blink rate in the control group (14 blinks/min; CI = 9.02 blinks/min – 19.0 blinks/min), significantly higher mean blink rates were measured in both the aqueous tear deficiency group (37.18 blinks/min; CI = 22.5 blinks/min to 51.9 blinks/min; P = 0.001) and conjunctivochalasis group (27.44 blinks/min; CI = 16.5 blinks/min to 38.3 blinks/min; P = 0.01). There was no significant difference in blink rate between

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meibomian gland disease (18 blinks/min; CI = 1.52 blinks/min to 34.4 blinks/min; P = 0.250) and control.

Correlations between corneal sensitivity, blink rate, and clinical parameters

The correlations between corneal sensitivity, blink rate, and clinical parameters are presented in Tables 4 and 5. Reduced corneal sensitivity with the Cochet-Bonnet esthesiometer was significantly correlated with more rapid TBUT, ocular surface dye staining and blink rate, while reduced sensitivity with the air esthesiometer correlated with more rapid TBUT, irritation symptoms measured by the OSDI and blink rate. In addition, there was a significant correlation between the air jet esthesiometer and TBUT, OSDI, and blink rate in all subjects. Moreover, there was a significant positive correlation (P = 0.043) between the air jet esthesiometer and OSDI in the mebomian gland disease subset.

Mean value comparisons of corneal sensitivity measured with both methods, clinical parameters of tear function and blink rate between each subtype of tear dysfunction are shown in Table 3. When comparing mean corneal sensitivity threshold using the Cochet-Bonnet, there was a significantly higher threshold in the aqueous tear deficiency group compared to the conjuctivochalasis group (p = 0.004) or the meibomian gland disease group (p < 0.001). The aqueous tear deficiency group had significantly higher corneal staining than the conjuctivochalasis group (p = 0.006). The aqueous tear deficiency group also had significantly higher conjuctival lissamine green staining compared to either the meibomian gland disease group (p = 0.002) or conjuctivochalasis group (p = 0.007). There were no significant differences between each subtype of tear dysfunction groups for TBUT, OSDI, and blink rate.

Correlation of blink rate with clinical parameters

In all subjects, blink rate positively correlated with corneal staining score (R = +0.448; CI = 0.177 to 0.689; P = 0.005), conjunctival staining score (R = +0.561; CI = 0.263 to 0.761; P < .001), and irritation score measured with the OSDI questionnaire (R = +0.393; CI = 0.031 to 0.664; P = 0.018), and inversely correlated with TBUT (R = −0.424; CI = −0.673 to −0.086; P = 0.008) as shown in Table 5.

DISCUSSION

In this study, we found corneal sensitivity to be reduced in the aqueous tear deficiency subset. Reduced corneal sensitivity was associated with greater eye irritation symptoms, tear instability, ocular surface disease, and blink rate. Previously published studies that evaluated corneal sensitivity in patients with dry eye have reported conflicting results (Supplemental Material at AJO.com - Supplemental Table 1).[2–12,15, 17,20] Eleven studies have shown subjects with dry eye symptoms to have hypoesthesia;[5–15] however, three other studies have reported the opposite. [2–4] Additionally, Chen and Simpson reported no difference in corneal sensitivity in soft contact lens wearers with and without symptoms of dry eye[20] and Tuisku and associates found no difference in corneal sensitivity between LASIK patients who complained of dye eye symptoms and normal controls.[17] Several studies regarding corneal sensitivity in association with changes in the subbasal nerve plexus reported corneal

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hyposensitivity,[8–12] and one described improvement in sensitivity following cyclosporine therapy.[12] In our study, the aqueous tear deficiency group demonstrated corneal hyposensitivity with both the Cochet-Bonnet contact esthesiometer and the non-contact air esthesiometer. In contrast, the meibomian gland disease and conjunctivochalasis groups had corneal sensitivity thresholds similar to control subjects. The aqueous tear deficiency group had a lower tear meniscus height and higher corneal and conjunctival staining than the meibomian gland disease and conjunctivochalasis groups, which may contribute to the differences in corneal sensitivity observed between the different subtypes of tear dysfunction. The decreased corneal sensitivity found in the aqueous tear deficiency group was associated with increased corneal and conjunctival dye staining, which is consistent with other studies.[5,21] It appears that many of the previously published studies that evaluated corneal sensitivity in dry eyes did not use stringent criteria to distinguish between different subtypes of tear dysfunction, classifying subjects as dry eye,[4,17] LASIK,[3,10,11] Sjögren syndrome (SS),[2, 5–7,13] rheumatoid arthritis[12] and rarely aqueous tear deficiency[15] (Supplemental Table 1). Our finding of decreased corneal sensitivity only in the aqueous tear deficiency group that was defined by a low OCT-measured tear volume may be one possible explanation for the conflicting corneal sensitivity findings previously reported. Certain studies, particularly those evaluating patients with SS,[2, 5–7, 13] most likely evaluated primarily aqueous tear deficiency patients, while others may have had included subjects with meibomian gland disease and conjunctivochalasis. Specifically, because only a few studies distinguished between SS and non-SS patients,[2, 5–7, 12–15] we can only be certain that those particular studies evaluating SS consisted of an aqueous tear deficiency population. From the fourteen studies that have reported corneal sensitivity findings in dry eye disease (Supplemental Table 1), only the studies by Benítez-Del-Castillo and associates and by Toker and Asfuroglu enrolled approximately 50% or more SS patients who were found to have corneal hyposensitivity. [6,12] These findings are consistent with our study and support the hypothesis that greater and more chronic corneal epithelial disease may lead to degeneration of corneal nerve endings and reduced corneal sensitivity. Indeed, reduced density of the subbasal nerve plexus has been found in aqueous tear deficiency with and without SS.[9,10,23]

Another possibility is that chronic inflammation induced by tear dysfunction and epithelial disease may contribute to corneal nerve degeneration and reduced sensitivity. [4,22] It remains to be determined if corneal sensitivity is normal or even increased in subjects with marked corneal epithelial disease from recent onset aqueous tear deficiency before the nerve endings degenerate.

The contradictory reports could also be due to differences in methods used to measure corneal sensitivity and in criteria used to define dry eye patients. Because the Belmonte air esthesiometer is not commercially available, we designed our own air esthesiometer. Although our prototype air esthesiometer has certain differences from the Belmonte gas esthesiometer, both esthesiometers deliver the same type of controlled air jet stimulus. Differences between the instruments include the internal diameter of the air outlet that is 0.457 mm in our model and reported to be 0.8 mm in the Belmonte instrument and the ability to change temperature of the air stimulus in the Belmonte instrument. [22] Our instrument also had LED lights around the outlet that assisted in delivering the stimulus to

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the center of the cornea. We found a significant correlation between our prototype air esthesiometer and the Cochet-Bonnet esthesiometer in subjects with tear dysfunction and in all subjects (Figure 2). This finding suggests that use of contact or non-contact esthesiometers may not be the cause for the conflicting results of previously reported studies evaluating corneal sensitivity in dry eye (Supplemental Table 1). The use of both contact and non-contact methods to measure corneal sensitivity is a unique feature of our study.

Our use of OCT tear meniscus height as an indirect measure of tear volume enabled us to accurately measure the amount of tears in the inferior tear meniscus and is another unique feature of our study. [24–26] This allowed for better classification of the tear dysfunction groups into aqueous sufficient or aqueous deficient. Together with the clinical examination, it also identified conjunctivochalasis. The previously repeated studies did not measure tear meniscus height by OCT. Our findings suggest that using OCT to identify patients with aqueous tear deficiency may identify those at risk for developing corneal hypoesthesia.

Interestingly, our study showed that decreased corneal sensitivity was associated with increased ocular surface irritation symptoms with the air esthesiometer, but not with the Cochet-Bonnet. Although both the Cochet-Bonnet and non-invasive air esthesiometer stimulate mechanoreceptors, the air esthesiometer may stimulate other receptors, such as polymodal and cold thermoreceptors whose hyposensitivity may be responsible for the inverse correlation between corneal sensitivity and irritation symptoms that was only seen with the air esthesiometer.[4, 22] In contrast, a previously reported study that used a non-contact air esthesiometer noted increased corneal sensitivity that correlated with increased ocular surface symptoms.[3] Our results seem counterintuitive, as we would expect patients with reduced corneal sensitivity to report less severe eye irritation symptoms than those with normal or increased sensitivities. The basis for our findings remains to be determined. As suggested by previous studies, hyposensitivity and hypersensitivity may be indicators of different stages of dry eye disease, which may help explain the paradoxical finding.[4, 22] Cold thermoreceptors in the cornea have been found to stimulate basal tear secretion in mice and their stimulation from the normal temperature oscillations during interblink intervals in healthy eyes under normal environmental conditions has been hypothesized to give a sensation of ocular comfort or wetness. [27] Reduced sensitivity of these nociceptors to the stimulus delivered by our air esthesiometer that is cooler than the normal cornea temperature of 34°C could lessen the physiological stimulation of tear secretion and possibly contribute to the increased discomfort reported by these subjects.

Similar to previously reported studies, blink rate was found to be increased in aqueous deficient dry eye and we also noted it to be increased in conjunctivochalasis, where central inferior tear meniscus height has previously been found to be normal. [28] Another interesting finding was that reduced corneal sensitivity by both contact and non-contact methods was associated with more frequent blinking. Increased blink rate was positively correlated with severity of irritation symptoms, corneal fluorescein staining and inversely with TBUT.

Our finding that decreased corneal sensitivity correlated with increased blink rate in tear dysfunction is surprising. A study by Toda and associates measured corneal sensitivities and blink rates in 64 patients following LASIK surgery. They discovered that the majority of

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their patients displayed hyposensitivity at 1 and 3 months with a return to baseline sensitivities by 6 months; however, blink rate in these patients was significantly decreased from 3 months onward. [15] In addition, Collins and associates studied the relationship between corneal sensitivity and blink rate in 9 patients by measuring blink rate both before and after use of a topical corneal anesthetic. [29] They found a significant decrease in blink rate after the anesthetic was applied. Based on these findings, we would have expected a decreased blink rate in the aqueous tear deficiency group. However; it is possible that increased blink rate is triggered by factors other than corneal sensation. One potential trigger for increased blink rate is rapid TBUT. In addition to triggering nerve stimulation in areas of tear disruption, tear break up may also increase light scattering and cause patients with tear dysfunction to blink more frequently to improve their quality of vision. Al-Abdulmunem and others suggested that there might be both cortical control and ocular surface control mechanisms driving blinking with the latter predominating in dry eye patients. [30, 31]

In conclusion, our study demonstrates the importance of classifying tear dysfunction groups into subsets, which is often neglected in studies correlating clinical parameters in tear dysfunction. Our study demonstrates that there are significant differences in corneal sensitivity and blink rate between meibomian gland disease, aqueous tear deficiency, and conjunctivochalasis. Therefore, it does not seem appropriate to group these disorders into a generic dry eye category when studying these parameters. Although our findings of decreased corneal sensitivity with increased symptoms and increased blink rate is a surprising discovery, our study is the first to not only distinguish between tear dysfunction subcategories in order to eliminate confounding disease processes, but also to set stringent criteria in regards to measuring corneal sensitivity with both contact and non-contact methods in both eyes, evaluate tear meniscus height by OCT, and incorporate blink rate into our study design. Future studies using larger sample sizes and our tear dysfunction classifications may determine the effects of treatment. These studies may establish how corneal sensitivity changes over time amongst these subsets, and how these changes correspond to blink rate. Our findings have helped set the framework for further research into the causes for eye irritation and increased blink rate in tear dysfunction conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Biographies

Effie Z. Rahman received her BA in Biochemistry/Cell Biology, Psychology, and Ecology/Evolutionary Biology at Rice University. She is currently a fourth year medical student at Baylor College of Medicine with plans to pursue a career in academic ophthalmology.

Peter K. Lam, MD, received his medical degree from Baylor College of Medicine, Houston, Texas. He currently serves as a resident in the Transitional Year Department at UCLA-Harbor Medical Center, Torrance, California. After his internship, Dr. Lam will continue to pursue his ophthalmology residency at Louisiana State University, Shreveport, Louisiana.

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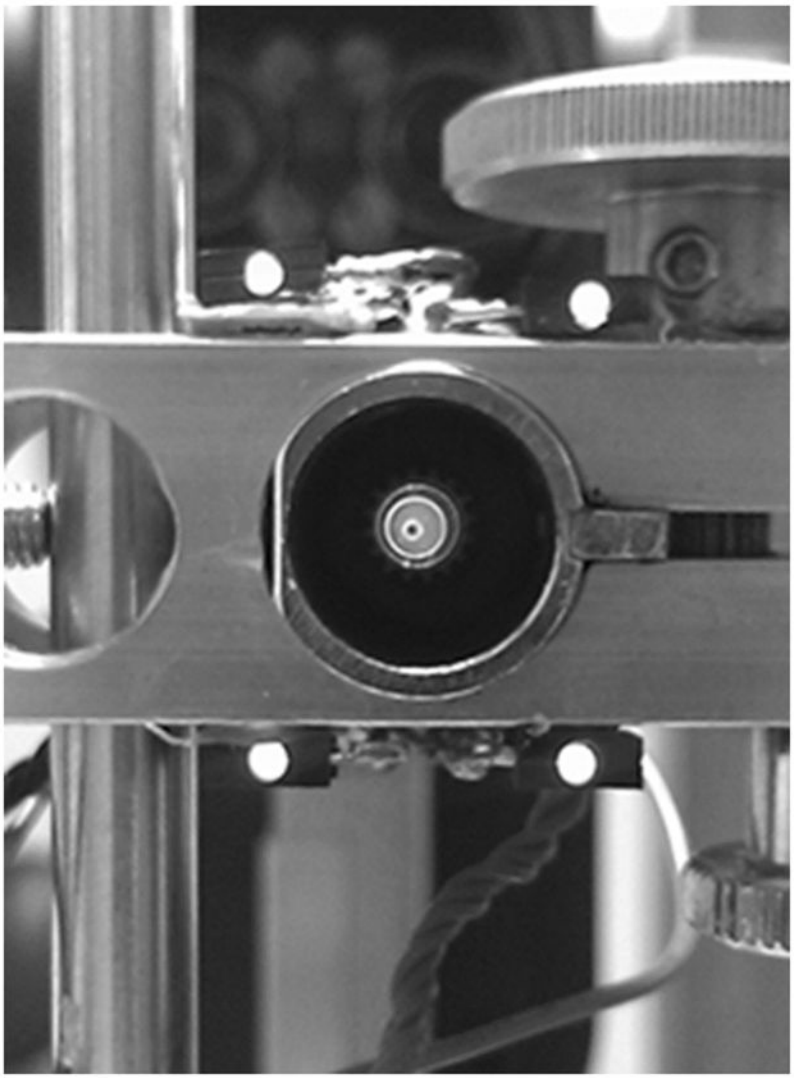

Figure 1.

Components of the air jet esthesiometer used to determine corneal sensitivity in patients with tear dysfunction and in normal controls.

The air esthesiometer is comprised of a cylinder of medical grade compressed air that is connected to an industrial pump that outputs an air stimulus at a given pressure over two seconds when its foot pedal is depressed (left). The air then travels to a hose containing a flow meter that is connected to a pipette tip that is secured on a calibrated movable mount that is attached to a stand directly mounted to a slit lamp (middle). The mount housing has 4 red light-emitting diodes centered around the pipette tip to aid in aligning the outflow stream with the center of the subject's cornea (right).

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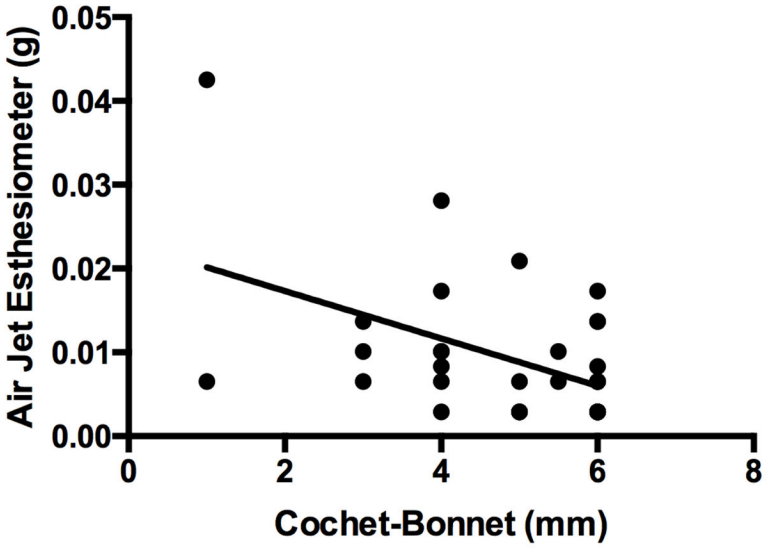

Figure 2.

Correlation between corneal sensitivity measures with both air jet and Cochet-Bonnet aesthesiometers in patients with tear dysfunction and in normal controls.

Correlation between the air esthesiometer and Cochet-Bonnet was evaluated in all subject and a significant correlation was found to exist ($r = -0.545$; CI = −0.721 mm to −0.275 mm; $P < 0.001$).

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Table 1

Criteria used to Define Tear Dysfunction Subsets and Normal Controls

Group	OSDI[a]	TBUT[b] ≤ 7 sec	Meibomian Gland Disease	TMH[c] (μm)
Meibomian Gland Disease	> 20	+	+	> 220
Aqueous Tear Deficiency	> 20	+	−	< 220
Conjunctivochalasis	> 20	+	−	CC
Normal	≤ 20	−	−	> 220

[a] OSDI = ocular surface disease index;

[b] TBUT = tear break up time;

[c] TMH = tear meniscus height in microns measured by optical coherence tomography

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Table 2

Demographic Characteristics in Patients with Tear Dysfunction and Normal Controls

Groups	N (Subjects)	Age, mean ± SD[a]	Age range
Normal	10	47.40 ± 21.69	25–79
All Tear Dysfunction	33	61.82 ± 12.77	30–85
Meibomian Gland Disease	11	60.09 ± 11.73	45–85
Aqueous Tear Deficiency	10	57.60 ± 17.56	30–80
Conjunctivochalasis	12	66.92 ± 6.65	54–77

[a]SD = Standard Deviation

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Table 3

Summary of Mean Values of Clinical Ocular Surface Parameters, Corneal Sensitivity, and Blink Rate in Patients with Tear Dysfunction and Normal Controls

Group	Cochet-Bonnet	AJE[a] (g)	TBUT[b] (sec)	K FL[c]	C LG[d]	OCT TMH[e] (mm)	OSDI[f]	Blink Rate (blinks/min)
Normal	5.45 0.832	0.004 ± 0.004	9.8 ± 0.633	0	0	330.2 ± 161.7	14.25 ± 4.713	14 ± 6.481
All Tear Dysfunction	4.906 ± 1.45	0.008 ± 0.009	3.632 ± 2.06*	3.303 ± 4.405	2.455 ± 2.209*	309.3 ± 323.4	34.53 ± 10.65*	28.37 ± 16.88
Meibomian Gland Disease	5.7 ± 0.538¶	0.006 ± 0.008	3.455 ± 1.214*	3.636 ± 5.065	1.455 ± 1.695¶	289.5 ± 57.56	34.0 ± 11.09*	18 ± 15.61
Aqueous Tear Deficiency	3.6 ± 1.647*§¥**	0.012 ± 0.013*	3.044 ± 1.676*	6 ± 4.714*§	4.3 ± 1.889*§¥**	171.5 ± 40.98*	30.20 ± 6.779*	37.18 ± 17.58*
Conjunctivo chalasis	5.333 ± 1.073¶	0.007 ± 0.006	4.286 ± 2.809*	0.75 ± 1.055¶	1.833 ± 2.038¶	486.8 ± 559.7	39.0 ± 12.08*	27.44 ± 14.19*

Values are mean ± standard deviation (SD).

P values are compared using ANOVA with Tukey post hoc test.

* Denotes statistically significance difference ($p \leq 0.05$) compared to normal;

** denotes statistical significance compared to all subjects;

¥ denotes statistical significance compared to meibomian gland disease;

¶ denotes statistical significance compared to aqueous tear deficiency;

§ denotes statistical significance compared to conjunctivochalasis.

[a] AJE = Air Jet Esthesiometer;

[b] TBUT = tear break up time;

[c] K FL = corneal fluorescein;

[d] C LG = conjunctival lissamine green;

[e] OCT TMH = optical coherence tomography tear meniscus height;

[f] OSDI = Ocular Surface Disease Index

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Table 4

Correlations between Cochet-Bonnet Corneal Sensitivity, Clinical Parameters, and Blink Rate in Patients with Tear Dysfunction

	All Subjects	All Tear Dysfunction	Meibomian Gland Disease	Aqueous Tear Deficiency	Conjunctivochalasis
	R value	R value	R value	R value	R value
Cochet-Bonnet vs TBUT[a]	0.279*	0.248	0.695*	0.508	−0.052
Cochet-Bonnet vs K Fl[b]	−0.466¶	−0.460¥	−0.364	−0.429	−0.642*
Cochet-Bonnet vs C LG[c]	−0.437¥	−0.427¥	−0.384	0.007	−0.180
Cochet-Bonnet vs OCT TMH[d]	0.135	0.213	0.271	−0.491	0.156
Cochet-Bonnet vs OSDI[e]	−0.133	−0.049	−0.402	0.197	−0.711¥
Cochet-Bonnet vs Blink Rate	−0.424¥	−0.346	−0.583	−0.272	0.236
Cochet-Bonnet vs Age	−0.207	−0.019	−0.244	−0.238	−0.059

[a] TBUT = tear break-up time;

[b] K Fl = corneal fluorescein;

[c] C LG = conjunctival lissamine green;

[d] OCT TMH = optical coherence tomography Tear Meniscus Height;

[e] OSDI = ocular surface disease index

* Denotes statistically significance ($p \leq 0.05$);

¥ denotes statistical significance ($p \leq 0.01$);

¶ denotes statistical significance ($p \leq 0.001$).

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Table 5

Correlations Between Blink Rate and Clinical Parameters in Patients with Tear Dysfunction

	All Subjects	All Tear Dysfunction	Meibomian Gland Disease	Aqueous Tear Deficiency	Conjunctivochalasis
	R value	R value	R value	R value	R value
Blink Rate vs TBUT[a]	−0.424¥	−0.147	0.251	0.148	−0.459
Blink Rate vs K FL[b]	0.448¥	0.350*	0.150	0.364	0.240
Blink Rate vs C LG[c]	0.561¶	0.452*	0.138	0.407	0.494
Blink Rate vs OCT TMH[d]	−0.040	−0.055	−0.317	0.240	0.001
Blink Rate vs OSDI[e]	0.393*	0.212	0.777*	0.585	0.073
Blink Rate vs Age	0.063	−0.229	0.415	−0.475	−0.304

[a] TBUT = tear break-up time;

[b] K Fl = corneal fluorescein;

[c] C LG = conjunctival lissamine green;

[d] OCT TMH = optical coherence tomography Tear Meniscus Height;

[e] OSDI = ocular surface disease index.

* Denotes statistically significance ($p \leq 0.05$);

¥ denotes statistical significance ($p \leq 0.01$);

¶ denotes statistical significance ($p \leq 0.001$).