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Response of the ageing eye to first day of modern material contact lens wear

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Abstract:	ABSTRACT Objectives: To investigate the ocular surface of an aged population wearing a daily disposable contact lens over their first day of wear. Methods: Forty eyes from forty presbyopic subjects were fitted a daily CL (Delefilcon A). Tear osmolarity, tear meniscus area (TMA) and ocular surface aberrations (total higher order root means square (RMS)) were assessed at baseline (t0), at 20 minutes (t1) and after 8 hours (t2) of wear. Fluorescein corneal and conjunctival staining and tear break up time (TBUT) were performed at t0 and t2. Results: No statistically significant changes were found between t0, t1 and t2 for TMA, and between t0 and t2 for fluorescein corneal and conjunctival staining. TBUT worsened by the end of the day from 10.4±0.4 seconds t0 to 9.0±0.3 seconds t2 ($P < 0.05$). Osmolarity showed significant changes between t0 306.9±2.3 mOsm/L and t1 312.4±2.4 mOsmol/L ($P = 0.02$), but returned to baseline values at 8 hours (310.40±2.26 mOsm/L; $P = 0.09$). Total higher order root means square (RMS) showed significant changes between t0 0.38±0.02 µm and t1 0.61±0.04 µm ($P \leq 0.001$) and between t0 and t2 0.64±0.41 µm ($P \leq 0.001$). Conclusions: Delefilcon A may induce measures changes (osmolarity and TBUT values) in a presbyopic population, however TMA and vital staining were maintained at the baseline level over the day. Keywords: Contact lenses, multifocal, presbyopia, osmolarity

Response of the ageing eye to first day of modern material contact lens wear

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ABSTRACT

Objectives: To investigate the ocular surface of an aged population wearing a daily disposable contact lens over their first day of wear.

Methods: Forty eyes from forty presbyopic subjects were fitted a daily CL (Delefilcon A). Tear osmolarity, tear meniscus area (TMA) and ocular surface aberrations (total higher order root means square (RMS) were assessed at baseline (t_0), at 20 minutes (t_1) and after 8 hours (t_2) of wear. Fluorescein corneal and conjunctival staining and tear break up time (TBUT) were performed at t_0 and t_2.

Results: No statistically significant changes were found between t_0, t_1 and t_2 for TMA, and between t_0 and t_2 for fluorescein corneal and conjunctival staining. TBUT worsened by the end of the day from 10.4±0.4 seconds t_0 to 9.0±0.3 seconds t_2 ($P < 0.05$). Osmolarity showed significant changes between t_0 306.9±2.3 mOsm/L and t_1 312.4±2.4 mOsmol/L ($P = 0.02$), but returned to baseline values at 8 hours (310.40±2.26 mOsm/L; $P = 0.09$). Total higher order root means square (RMS) showed significant changes between t_0 0.38±0.02 µm and t_1 0.61±0.04 µm ($P \leq 0.001$) and between t_0 and t_2 0.64±0.41 µm ($P \leq 0.001$).

Conclusions: Delefilcon A may induce measures changes (osmolarity and TBUT values) in a presbyopic population, however TMA and vital staining were maintained at the baseline level over the day.

Keywords: Contact lenses, multifocal, presbyopia, osmolarity

INTRODUCTION

The lacrimal functional unit is a system composed of the ocular surface, its secretory glands (lacrymal glands, meibomian glands, conjunctival goblet cells), the nerves that connect them[1] and the nasolacrimal passage[2]. A healthy ocular surface is maintained by proper tear production and drainage; any perturbation in this balance may lead to dryness of the ocular surface and eventually to Dry Eye Disease (DED)[3].

Increasing age leads to several changes to the tear film (TF) and the ocular surface[4], which include: a reduced tear volume[4,5] (lacrimal gland dysfunction, decrease in lacrimal gland mass) which is thought to increase tear osmolarity and compromise TF stability[5]; reduced reflex tear secretion and breakup time (TBUT)[6]; and to decline the function of goblet and meibomian glands cells[7].

Given the increase in life expectancy, an increase in the prevalence of dry eye in the population is also expected[4]. Nonetheless, information regarding the prevalence of DED in the elderly is quite equivocal[8-11]. Several consequences of the normal aging process could explain why the elderly population could be more prone to dry eye; this includes raised oxidative stress, hormonal changes, inflammatory systemic conditions[4], lid laxity and the use of systemic and topical medication[4,12]. DED has been considered as a significant concern in the aging contact lens (CL) wearing population[1,13]. Bennet et al. highlighted that a comprehensive anterior segment exam is an essential prerequisite to CL fitting, due to the higher prevalence of the anterior segment conjunctival degenerative processes that may disrupt the TF layer[14]. When a CL is fitted on a patient's eye, the TF is separated into pre- and post-lens TF. In addition to the changes in composition, pre-lens TF (PLTF) stability is reduced due to the thinning of the lipid layer and the tear volume on the anterior surface of the CL is also diminished, both events leading to an increased evaporation rate and dewetting compared to normal TF[15]. CL discomfort has been identified as the primary reason for CL discontinuation[15,16,17,18]. CL material (silicone hydrogel[19]), parameters (lower sphere power[16]) and wearing schedule (daily disposable[19]) have been reported as the main aspects associated with CL dropouts[19]. According to a recent survey[19], increased age is the main factor impacting retention rate, with multifocal CL fittings presenting the lowest continuation of use (57%) in comparison with other CL designs for the same age range population; poor achieved vision was identified as a key factor in multifocal CL wearers that stopped wearing contact lenses. Besides, Patel et al. suggest that the presbyopic population might be more susceptible to dryness-related comfort problems[20], mainly due to decreased TF stability, eventually leading to CL discomfort and dropout.

The purpose of this study was to assess the performance of a new daily disposable CL material on the ocular surface of a presbyopic population. To the best of our knowledge, this is the first study reporting the clinical outcomes of a water gradient daily CL material in a presbyopic population over their first day of CL wear. To achieve that goal, TF and ocular surface parameters were investigated along a day of CL wear.

MATERIAL AND METHODS

Forty subjects, neophyte CL wearers, were recruited. This prospective, nonrandomized study was approved by the Institutional Ethics Committee of the University of Valencia. Informed consent was obtained for all subjects enrolled in the study. The clinical study adhered to the tenets of the Declaration of Helsinki.

Each of the subjects underwent a comprehensive ophthalmic examination, which included (in the following sequence): visual acuity, monocular and binocular refraction, anterior segment slit lamp biomicroscopy, osmolarity, measurement of the inferior tear meniscus area (TMA), topographic examination and TBUT assessment using fluorescein.

The room temperature was controlled and maintained between 20 and 25 degrees Celsius; the room humidity was maintained between 35 to 40%. The same investigator carried out all measurements and subsequent data analysis. Inclusion criteria were spherical equivalent refractive error between +6.00 to -10.00D, astigmatism ≤0.75D, monocular corrected distance visual acuity of 0.0 logMAR or better and normal binocularity. Patients who experienced any anterior segment pathology, previous corneal surgery, corneal abnormalities, DED or any general health condition were excluded from the study.

Slit Lamp Examination

Anterior ocular assessment was performed by biomicroscopy and included bulbar conjunctiva and cornea evaluation at a magnification of 10x to 32x for the presence of active inflammation and structural changes/abnormalities of the corneal layers.

Anterior chamber and iris were evaluated for inflammation, eyelids for crusts and/or collarettes. Fifteen minutes after material insertion, contact lens fit quality was evaluated for centration, coverage, movement as well as push-up recovery speed.

Tear Osmolarity

Tear film osmolarity was measured using a laboratory-on-a-chip system (TearLab™ Corp, San Diego, CA) in order to collect (using passive capillary action) and analyze the electrical impedance of a minimal (50 nL) tear sample from the infero-lateral tear meniscus. According to Foulks and al. osmolarity values below 308mOsm/L should be considered as normal[21]. Readings between 308 and 325 mOsm/L are representative of mild-to-moderate dry eye, and values above 325mOsm/L indicate the severe state of the disease[21].

Inferior Tear Meniscus Area

Details of the anterior segment optical coherence tomography (AS-OCT) imaging technology have been described previously[22,23]. The SL SCAN-1 (Topcon, Japan) is a spectral-domain OCT integrated into a slit lamp which uses an 840 nm superluminescent diode and provides 5000 A-scans/s with an axial resolution of 8-9 µm and a lateral resolution <20 µm. This device allows images of the inferior tear meniscus to be obtained using the B-scan mode by scanning at the 6 o'clock ocular position with a cross line centered on the inferior lid edge. Measurements of the inferior tear meniscus area

(TMA), defined as the triangular area formed by the anterior corneal boundary, anterior boundary of the lower eyelid and anterior borderline of the tear meniscus, were performed manually using image analysis software imageJ (http://imagej.nih.gov/ij/).

Aberrations Analysis

The corneal front surface wavefront aberrations derived from the Placido-based corneal topographer Atlas 9000 (software v3.0.0.39; Carl Zeiss Meditec, Jena, Germany) over a 6 mm central zone was assessed with a non-dilated pupil and repeated three times between 4-6 seconds after a blink[24,25]. The choice not to control pupil diameter was deliberate, as this study intended to assess the effect of this multifocal CL material in normal conditions of illumination, under the condition patients are usually assessed. Since the device used to quantify aberrometry is a Placido disk-based topographer, it uses the first Purkinje image which is formed on the PLTF, to calculate topographic and aberrometric values. Image capture was timed for the same time post blink for each subject, as it has been found that TF stability is achieved approximately 6 seconds after a blink, and overall aberrations tend to rise for about 10 seconds after a blink[25].

Tear Film Breakup Time and Corneal-Conjunctival Staining Score

TBUT was measured subjectively with a slit lamp (equipped with a blue filter) by inserting into the lower fornix a fluorescein strip moistened with one drop of a non-preserved saline solution. The strip was then removed and the patient asked to blink three times and look forward during the procedure. The average of three consecutive TBUT measurements (time between the last blink and the appearance of the first random dry spot on the corneal surface, manually timed) was then calculated. Corneal staining was evaluated after TBUT under blue illumination, 3.0 minutes after fluorescein instillation. Corneal and conjunctival subjective assessment followed the grading scheme from Efron's scale (grades from 0-4) observed with 16x slit lamp magnification.

Eligible patients (based on inclusion and exclusion criteria) were fitted binocularly with multifocal CLs (Delefilcon A, Dailies Total1® Multifocal). According to manufacturers' information, Delefilcon A is a silicone-hydrogel material with a silicone core water content of 33% and a hydrogel surface water content above 80 %. Its Dk/t is 159 @ -3.00D at a central thickness of 0.09 mm. Power ranges from +6.00 to -10.00 (in 0.25 steps) with a base curve of 8.5 mm. All baseline measures were repeated at 20 minutes and 8 hours after CL insertion.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Science software (Version17.0, SPSS, Inc., Chicago, IL, USA). Only right eye data was analyzed to avoid bias due to the similarities between the eyes of an individual. Friedman's nonparametric statistical test was used to detect differences over time of TMA, osmolarity and aberrations as they were not normally distributed. The Sign test was used to compare related intergroups for ordinal parameters (conjunctival and corneal staining), whereas a related samples average *t* test was used in the intergroup parameters with normal distribution (TBUT). Differences were considered statistically significant at $p \leq 0.05$.

RESULTS

The average age of the participants was 50.0±4.4 years, ranging between 41 and 60 years old. Mean spherical equivalent refractive error was +1.11±0.35 D and ranged from -4.25 to +2.50 D. From the 40 eyes included, 18 were myopic (mean spherical equivalent error -2.80±0.72D) and 22 hypermetropic (+0.90±0.24D). Mean values and standard deviations of the parameters assessed at each visit over the day are presented in table 1. Osmolarity showed significant changes between baseline (306.93±2.32 mOsm/L) and 20 minutes (312.43±2.42 mOsm/L) (P=0.02) (Figure 1). No statistically significant changes were found between baseline (306.93±2.32 mOsm/L) and 8 hours (310.40±2.26 mOsm/L) (P=0.09). TMA values diminished across the day (from 0.020±0.003 mm^2 to 0.017±0.03 mm^2) (P=0.061), but was not statistically significant.

Figure 2 displays aberrometric root mean square (RMS) data before CL adaptation at 20 minutes and 8 hours after CL insertion. Ocular surface higher order RMS aberrations showed a statistically significant increase between baseline (0.38±0.21 µm) and 20 minutes (0.61±0.44 µm) (P≤0.001) and between baseline and 8 hours (0.64±0.41 µm) (P≤0.001). No statistically significant changes were found between 20 minutes (0.61±0.44 µm) and 8 hours (0.64±0.41 µm) (P=0.711). TBUT worsened by the end of the day from 10.4±0.4 seconds at baseline to 9.0±0.3 seconds after 8 hours of CL wear (P<0.05) (Figure3). No statistically significant differences were found between the measurements at baseline, and after 8 hours of CL wear regarding fluorescein corneal (P=0.727) and conjunctival staining (P=0.092).

DISCUSSION

A healthy tear film is a key factor in order to maintain a functional and efficient ocular surface. Ocular dryness and discomfort represent the main complaints in CL wearers[16-18,26]; CL discomfort (CLD) (24%) and dryness (20%) being the primary reasons for discontinuation[16,17,19]. According to Dumbleton et al., "discomfort" is the most frequently cited reason for CL dropout[17], but its precise meaning to the individuals is more complex to assess. Indeed, the terms dry eye and CL discomfort closely interlace, since a patient that presents signs and symptoms of dry eye has more propensity to have CL discomfort when fitted with CLs[27].

Tear hyperosmolarity is a key mechanism of ocular surface inflammation leading to dry eye clinical features[28,29]. Environment, CL materials and parameters, and TF factors such as stability have been described as triggers for the rise of osmolarity[30-32]. TF stability is altered by CL wear regardless of the lens type as CLs induce changes in TF structure, creating a PLTF and a postlens TF, that is, new interfaces within the ocular environment[15]. PLTF is mainly responsible for the hydration and wettability of the CL front surface, facilitating the interaction with palpebral conjunctiva, by reducing friction forces and hence providing a smooth optical surface[33,34]. PLTF instability can be found in hydrogel high water content and thin CLs, leading to a rise of osmolarity, since it has been suggested that this type of lens can dehydrate easily partly due to its elevated water content[31,35].

Previous studies demonstrated that refractive index (RI) of a CL material and its water content are closely related, showing the interest of evaluating RI to assess lens water content[36].Delefilcon A provides a water gradient and a surface water content corresponding to a high-water content hydrogel material, and as such, it may be expected to induce a rise in osmolarity values when fitted, due to partial dehydration of the outermost part of the CL material. This hypothesis seems robust since in Schafer et al. study, an index change was found to occur on the CL surface after 15 minutes of lens wear, shifting from a high-water content RI to a level compatible with a low water content material RI[37]. However, Iskander et al.[38] found that this water gradient material provided a better end of the day TF surface quality (TFSQ) than a high-water content hydrogel material. This finding implies that the rate of superficial dehydration of this material is lower than other CLs[38].

Previous studies of existing, largely young, CL wearers reported significant rises in tear osmolarity in CL wearers during the time of use[39-41]. Iskeleli et al. found that monthly hydrogel soft CLs induced a raise in osmolarity values between 1-2 hours after insertion[40]. Sarac et al. evaluated osmolarity with daily wear silicone-hydrogel CLs over the course of a day and found a rise in tear osmolarity after 4 hours of CL wear, followed by an insignificant reduction in osmolarity values at the end of the day[41]. These results are in agreement with the present study. Indeed, statistically significant differences have been found between baseline and 20 minutes showing that an increase in osmolarity values occurs even sooner than evaluated before; while over the course of the day a reduction in tear osmolarity values could be observed, although not statistically significant, but consistent with the findings of Sarac and al[41].

According to Nichols et al. the on-eye CL sits in and not on the TF[34]; CLs are many times thicker than the TF so its insertion is expected to induce perturbation to the ocular surface as noted earlier[42]. Furthermore, CL interaction with the eyelid and cornea can modify tear composition and electrolytes levels, as shown by Tighe and al.[43]. The hypothesis explored in the present study was that CL initially disturbs the newly formed PLTF (by inducing reflex tearing), leading to decreased TF stability and increased evaporation, resulting in elevated tear osmolarity values at 20 minutes. Besides, it is speculated that increases in osmolarity at 20 minutes might also be partly due to both an ocular surface response to CL insertion, and an individual tear interaction with the CL material.

At the end of the day (i.e after 8 hours of CL wear), osmolarity values were lower than those obtained at 20 minutes, but did not reach the baseline level. Furthermore, both values obtained at 20 minutes and after 8 hours of CL wear were higher than the cut-off value of 308mOsm/L, which, according to Foulks, can be considered as a mild form of dry eye[21].

It is important to emphasize that no significant changes were found regarding corneal or conjunctival staining by the end of the day, which means that even if osmolarity was above cut-off values, it was not clinically significant since there was no significant cellular damage. Osmolarity values did not change over the time of wear, which may imply that CL surface properties remain rather stable during the 8 hours of CL wear and provide enough oxygen transmission and lubrication to the ocular surface in order not to induce any additional staining. However, if the osmolarity changes occur in a similar pattern over longer-term wear, corneal integrity could well be compromised.

It is known that tear hyperosmolarity induces epithelial cell hyperosomolarity[44-46], leading to intracelular activation involving MAP Kinase and NFκB pathways and therefore liberation of pro-inflammatory cytokines, which eventually induce epithelial cell apoptosis[44-46]. Further investigation is needed in order to assess the rise in osmolarity values from baseline and the duration of this elevation that could trigger an inflammatory response from the ocular surface, leading to cellular apoptosis and the corresponding positive vital dye staining.

Tear meniscus can be defined as the accumulation of tears between the lid margin and the bulbar conjunctiva; it is present on both superior and inferior eyelids[47,48]. It is believed that tear meniscus contains 75%-90% of the total volume of the TF [47], which makes it a useful clinical parameter to assess TF volume and its possible changes over time. AS-OCT is a useful device for *in vivo* non-invasive quantification of tear meniscus parameters, with[48,49] or without CLs[50,51]. Czajkowski et al. showed that AS-OCT presents sensitivity and specificity for dry eye diagnosis of 86.1% and 85.3% for TMA and a strong positive correlation to tear meniscus height ($r=0.763$, $p<0.0001$), making this device a valuable tool for diagnosis and follow-up of patients with dry eye disease[52].

In the present study, TMA values did not show significant changes across the day. It suggests that short-term CL wear may have limited impact on tear meniscus parameters in a non-dry eye presbyopic population, which is in agreement with Wang et al. work on the influence of CL wear on upper and lower meniscus in a normal young adult population[53]. Chen et al. evaluated CL wearers with self-reported dryness, asymptomatic wearers and asymptomatic non lens wearers[51]. No significant statistical changes were found between baseline and after 30 minutes for the asymptomatic wearers, which is in agreement with the results obtained in this study. According to our results, it seems very likely that CL insertion induces reflex lacrimation responsible for an immediate increase of tear volume and decreased TF stability, but it tends to return back to normal values by 20 minutes after CL lens insertion. PLTF quality mainly relies on surface wettability and the water content of CL materials[54,55]. In this study, no difference was found at the end of the day in comparison to baseline, even if TMA diminished over the day, which suggests that PLTF surface quality remained stable over time. Higher-order aberrations are believed to contribute up to seven percent of retinal image quality[56,57]. The main difference between a perfect wavefront and the one displayed by the human eye mainly is due to higher order aberrations, more precisely third order coma-like and fourth-order spherical aberrations[58-60]. It is known that the effect of coma and spherical aberrations is pupil dependent, the greater the pupil size, the greater the aberrations and the depreciation of the final retinal image[61].

In this study, the CL geometric characteristics were a front and back surface aspheric center-near multifocal design, which is expected to induce a certain amount of spherical aberration[62]. Moreover, decentration of a CL on the eye due to eye movement or to the lag in the replacement of the CL after blink are expected to induce coma-like aberrations proportional to the amount of decentration from the visual axis[61,63,64]. For these reasons it was decided to only assess ocular surface high order RMS of coma-like and spherical aberration in this study. Data were converted into RMS values for spherical aberrations and coma combined[61,65] in order to follow-up changes of the total RMS over time and to assess the influence of the CL insertion over this parameter.

A statistical significant increase in ocular surface higher order RMS was found between baseline and 20 minutes, i.e from the CL insertion. In the majority of participants, the set of ocular surface higher order RMS increased 20 minutes after CL insertion, but remained stable over the day; no significant difference was found between 20 minutes and 8 hours of CL wear. This could be explained by the behaviour of the lens on the eye, remaining stable throughout the day, and the time the lens took to centre after a blink, which was approximately the same at 20 minutes and 8 hours, thus obtaining similar aberrations values for all participants.

Tear quality, stability and dynamics play a key role in optical performance of CLs [25,66,67]. Indeed, local variation of PLTF thickness influences the amount of ocular aberrations being measured[68]. DED, according to its severity, is also known to induce a significant rise in aberrations, so the fact that corneal high order RMS remained rather stable during the day may imply that the pre-lens TFSQ and dynamics were minimally impacted over the course of the day.

TBUT is one of the clinical methods used to assess compromised tear film stability [69]. In the present study, a significant decrease in TBUT was found between baseline and 8 hours of wear. This decrease in TF stability was an expected outcome, since TF structure is altered by CL (increased evaporation and perturbation in TF spreading[15-18]). Since measurement was carried out just after CL removal, it was expected that complete recovery of the TF would not yet have been achieved at that moment. So, even if a statistical decrease in TBUT was evidenced, it is unlikely to have any clinical significance. Fluorescein dye is not the first option to assess TF stability (since its efficiency relies on a controlled amount of fluorescein instilled and on the practitioner's experience to detect the first dry spot on corneal surface), as objective, non-invasive methods are now available[70]. The topographer used in the current study was the Atlas 9000, even if based on Placido disks, does not include in the software an automatic delimitation of the BUT.

Instead the TFOS DEWS II standardized methodology for use of fluorescein to assess subjectively tear film stability was adopted[70] using a single investigator applicating the strip onto the inferior conjunctiva to ensure minimal variability and give reproducible results. The subjective assessment of TBUT and vital staining, as discussed before, could be limitations of the study along with the time between visits that was not masked to the investigator and could have influenced the results. Duration of wear might be another limitation of the current study as previous works reported a longer average time of wear with up to 25% of the patients wearing their lenses up to 16 hours[71,72]. The duration evaluated in this study is more in agreement with a recreational wear including hobbies or social activities[73,74], which gives valuable information, but does not represent a typical day for usual CL wearers.

CONCLUSIONS

This study reports the clinical performance of a water gradient daily disposable soft CL on the ocular surface and the TF in a neophyte presbyopic population over their first 8 hours of wear. CL insertion induces an initial decrease in TF stability observed by osmolarity values rising after 20 minutes of wear, but it did not impact tear meniscus metrics and seemed to be transitory, as a decrease, without reaching baseline values, occurred by the end of the wearing period. Ocular surface aberrations remained largely stable from CL insertion, demonstrating an even repartition of TF over the CL material surface.

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Table 1: Comparison of the objective measurements of the non-previous CL wearers at the initial visit (t_0), 20 minutes (t_1) and 8 hours (t_2) after CL insertion (mean ± SD). TMA: tear meniscus area; TBUT: tear break-up time.

FIGURE LEGENDS

Figure 1. Box-plot of osmolarity at baseline, 20 minutes and 8 hours of Cl wear. Medians are shown for each plot, quartiles are shown as boxes, ranges as whiskers and outliers as dots.

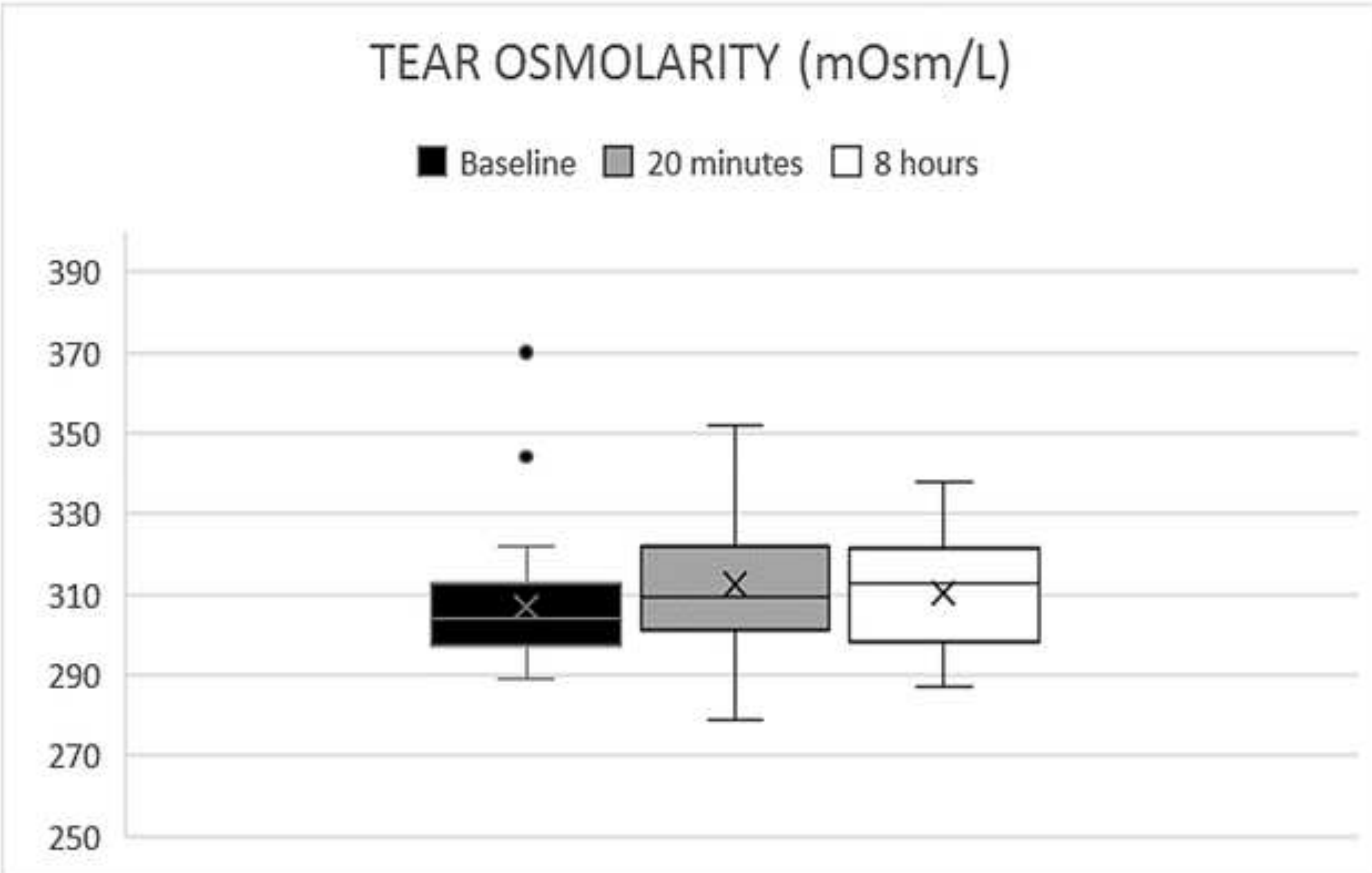
Figure 2. Box-plot of RMS at baseline, 20 minutes and 8 hours of Cl wear. Medians are shown for each plot, quartiles are shown as boxes, ranges as whiskers and outliers as dots.

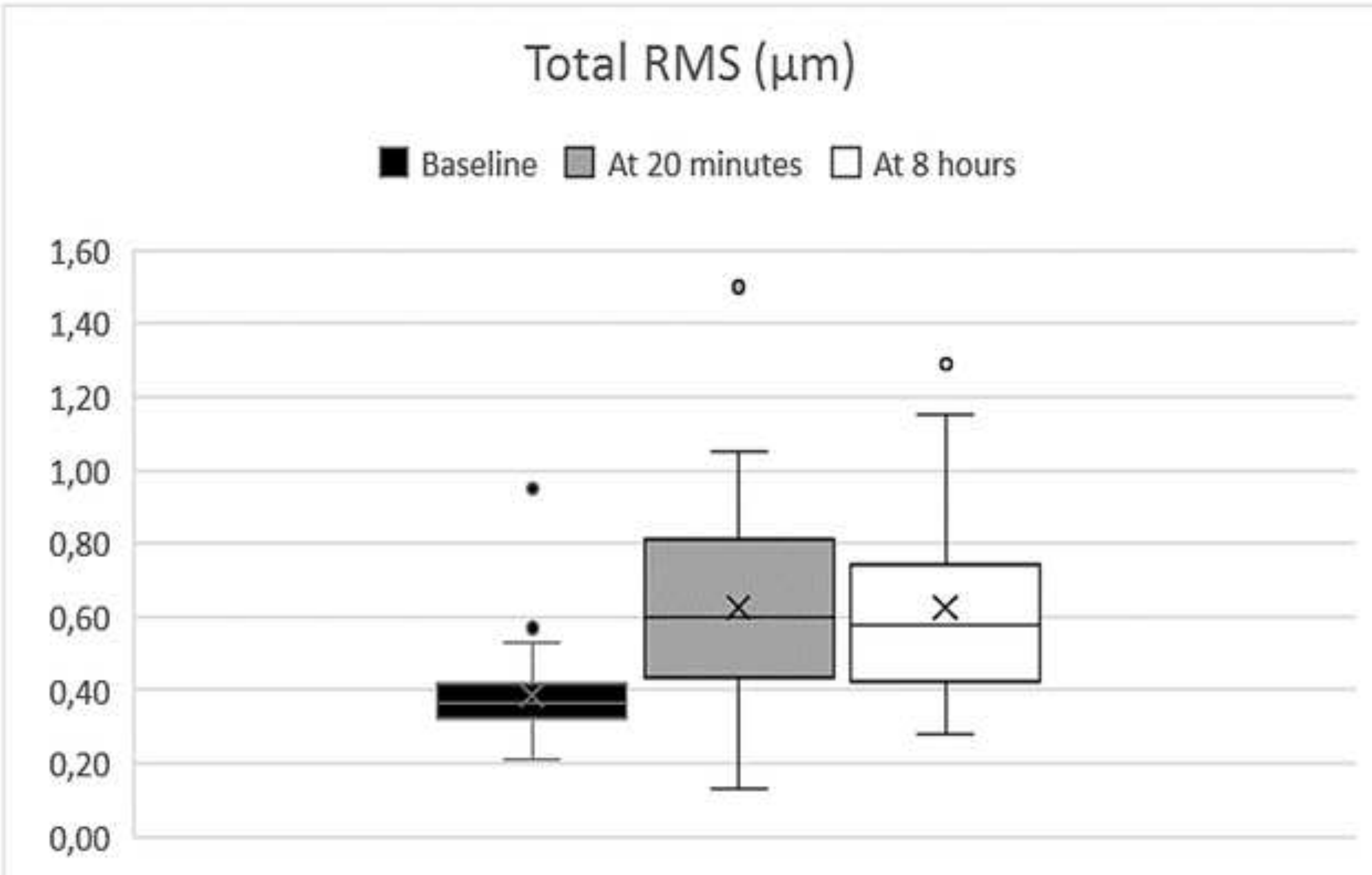
Figure 3. Box-plot of TBUT at baseline, 20 minutes and 8 hours of Cl wear. Medians are shown for each plot, quartiles are shown as boxes, ranges as whiskers and outliers as dots.

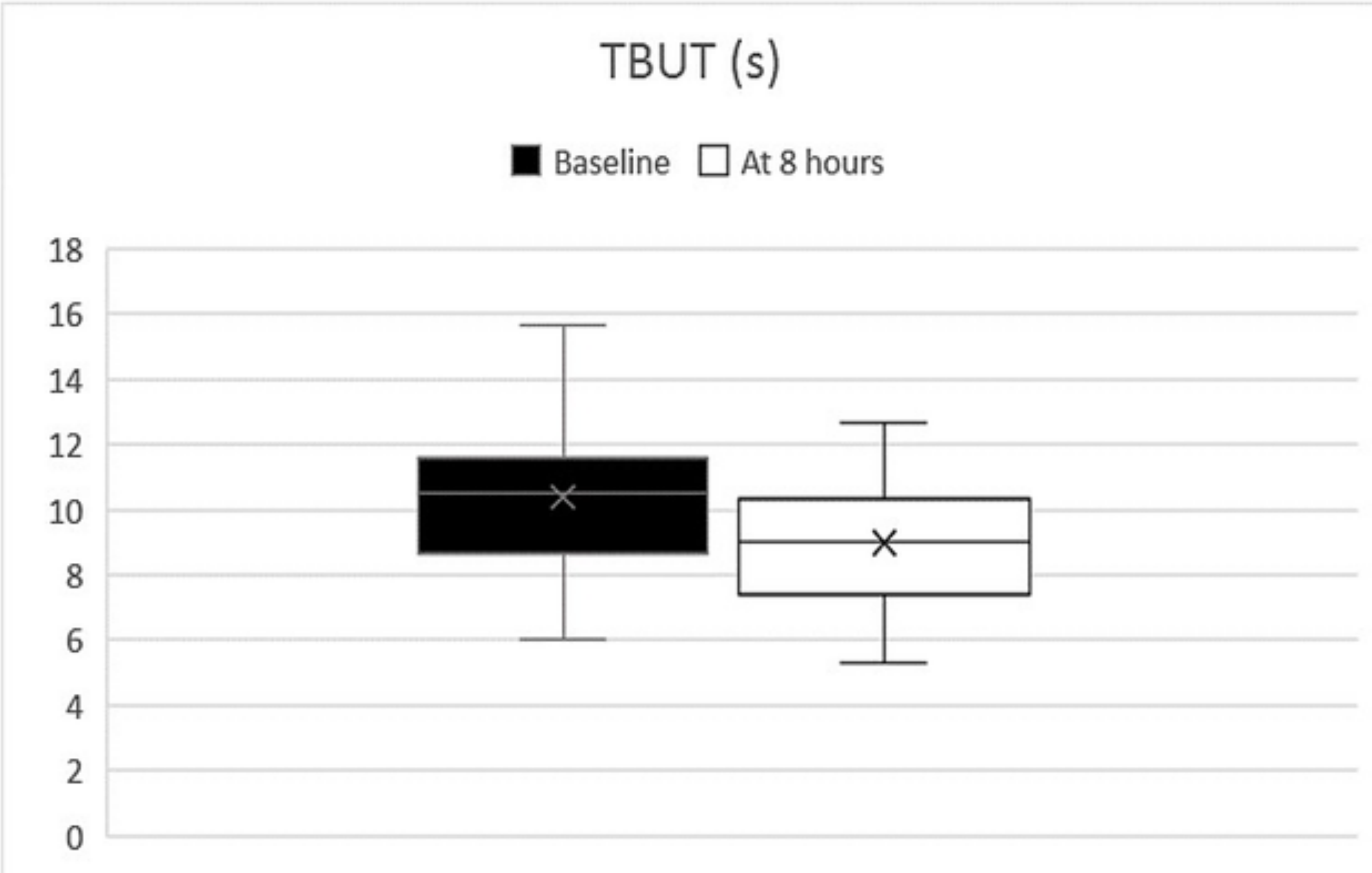
TABLES

Table 1: Comparison of the objective measurements of the non-previous CL wearers at the initial visit (t_0), 20 minutes (t_1) and 8 hours (t_2) after CL insertion (mean ± SD). TMA: tear meniscus area; TBUT: tear break-up time.

	Baseline (t_0)	**At 20 minutes (t_1)**	**At 8 hours (t_2)**	**P value**
Aberrations (µm)	0.38 ± 0.21	0.61 ± 0.04	0.64 ± 0.41	(t_0)/ (t_1) P< 0.01 (t_0)/(t_2) P< 0.01 (t_1)/(t_2) P=0.71
Osmolarity (mOsm/L)	306.93 ± 2.32	312.43 ± 2.42	310.40 ± 2.26	(t_0)/ (t_1) P=0.02 (t_0)/(t_2) P=0.09 (t_1)/(t_2) P=0.71
TMA (mm^2)	0.020 ± 0.003	0.019 ± 0.002	0.017 ± 0.003	P=0.061
TBUT (s)	10.4 ± 0.4	-	9.0 ± 0.3	P <0.01


TEAR OSMOLARITY (mOsm/L)
Baseline
20 minutes
8 hours
390
370
350
330
310
290
270
250


Total RMS (µm)
Baseline
At 20 minutes
At 8 hours
1,60
1,40
1,20
1,00
0,80
0,60
0,40
0,20
0,00


TBUT (s)
Baseline
At 8 hours
18
16
14
12
10
8
6
4
2
0