Short-Term Effects of Overnight Orthokeratology on Corneal Epithelial Permeability and Biomechanical Properties

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Purpose. To investigate the effects of 30 nights of overnight orthokeratology (OOK) on corneal epithelial permeability (P_{dc}) and corneal biomechanical properties.

Methods. BE Retainer and Paragon CRT lenses were used. Visits were scheduled approximately 4 hours after awakening at baseline and after 1, 5, 10, 14, and 30 days of treatment. P_{dc} was measured at baseline and at day 30, whereas corneal biomechanical properties and visual acuities (VAs) were measured at all visits.

Results. Thirty-nine neophytes and soft contact lens wearers completed the study. There was no difference in P_{dc} between baseline (ln[P_{dc}] [95% confidence interval (CI)] = −2.65 [−2.80 to −2.50]) and day 30 (ln[P_{dc}][CI] = −2.68 [−2.85 to −2.50]) ($P = 0.88$). Corneal hysteresis (CH) and corneal resistance factor (CRF) reduced significantly from baseline (CH [CI] = 10.89 [10.59–11.19] mm Hg and CRF [CI] = 10.35 [9.99–10.72] mm Hg) to day 30 (CH [CI] = 10.59 [10.31–10.87] mm Hg and CRF [CI] = 9.58 [9.26–9.89] mm Hg) ($P = 0.001$ for CH and $P < 0.001$ for CRF). Posttreatment VA did not reach baseline targets, and the difference was worse with low-contrast letters. Asian individuals ($n = 18$) had significantly worse VA than non-Asian individuals ($n = 21$) under most conditions through day 5, and the difference extended through day 14 with low-contrast letters under mesopic conditions. The percentage of participants who achieved 20/20 uncorrected was 17% Asian and 40% non-Asian individuals after day 1 and reached 69% Asian and 83% non-Asian individuals at day 30.

Conclusions. Thirty nights of OOK did not alter P_{dc} when measured 4 hours after awakening. OOK caused CH and CRF to decrease, but the changes were not clinically significant compared with diseased and postsurgical cases. Asian individuals, who had lower baseline CH in this study, responded slower to OOK based on early uncorrected VA and overrefraction measurements.

Keywords: orthokeratology, corneal epithelial permeability, corneal hysteresis, higher-order aberrations

Overnight orthokeratology (OOK) has garnered much interest in the past decade, in large part because of its potential role in controlling myopia progression. Until recently, not much had been reported of incidence or prevalence of ocular complications or ocular surface integrity associated with OOK, except for case reports of *Pseudomonas aeruginosa* and *Acanthamoeba* infections associated with this treatment.[1–9] Recent studies that compared OOK lens wearers to both nonlens wearers and 30-day continuous-wear silicone hydrogel lens wearers reported that, after 12 months, the greatest increases in tear film concentrations of inflammatory mediators (IL-6, IL-8, matrix metalloproteinase-9 [MMP-9], and epidermal growth factor) were in the OOK group.[10,11] Of most interest is MMP-9, which is believed to be responsible for the desquamation of differentiated apical corneal epithelial cells that express the tight junction protein, occludin.[12] Because the corneal epithelial barrier is a composite of epithelial superficial cells and tight junctions, increased MMP-9 activity on the ocular surface would disrupt the epithelial barrier function (EBF), which protects the eye against hydrophilic molecules, macromolecules, and pathogens.[12,13] Additionally, these corneal epithelial superficial cells that make up the epithelial barrier have been observed to increase significantly in visibility, height, and width in the central cornea in OOK patients when viewed by confocal microscopy.[14] Together, the increased levels of MMP-9 in the tear film and physical alterations to the corneal epithelial superficial cells suggest that the integrity of the EBF may be compromised in OOK patients over time. Scanning fluorophotometry has been used to assess the integrity of the EBF in vivo by measuring the penetration rate of sodium fluorescein through the cornea, also known as corneal epithelial permeability (P_{dc}). Studies have found that P_{dc} is positively correlated to the amount of contact lens–induced hypoxia and presence of preservatives in contact lens care solution.[15–22] To date, no study has reported the effects of OOK on P_{dc} in vivo while controlling for oxygen transmissibility (Dk/t) and solution preservatives.

Other potential indicators of corneal health are corneal biomechanical properties measured with the Ocular Response Analyzer (Reichert Technologies, Depew, NY). Corneal hyster-

Table 1. OOK Contact Lens Characteristics

Design	Lens	Material	Lens CT, mm	Dk, ISO/Fatt	Dk/t
BE Retainer	Equalens II	Oprifocon A	0.22	85	39
	Boston XO2	Hexafocon B	0.22	141	64
Paragon CRT	Equalens II	Oprifocon A	0.167–0.169	85	50.3–50.9
	Menicon Z	Tisilfocon A	0.167–0.169	160	94.7–95.8

CT, center thickness.

esis (CH), which is defined by Reichert Technologies as a measure of viscous damping of the corneal tissue or the energy absorption capability of the cornea, and corneal resistance factor (CRF), which is the viscoelastic resistance to an applied force, have been closely studied in the areas of refractive surgery, glaucoma, and keratoconus research. Studies have largely shown that CH and CRF for the normal eye is, on average, higher than in postoperative and diseased eyes.[23–40] Because the shape of post-OOK corneas are similar to corneas after refractive surgery, it is important to establish the biomechanical properties for this population. No study has reported the changes in biomechanical properties with OOK beyond 3 hours of lens wear.

In this study, we aimed to investigate the effects of 30 nights of OOK on the ocular surface by measuring changes in corneal epithelial permeability and biomechanical properties at baseline and over the course of 30 nights of OOK treatment. We also examined the effects of different Dk/t levels on both P_{dc} and biomechanical properties.

Materials and Methods

Subjects

The current study followed the tenets of the Declaration of Helsinki 1975, as revised in 2000. The study protocol was approved by the Committee for the Protection of Human Subjects (CPHS), which serves as the institutional review board for the University of California, Berkeley. Subjects were recruited from the campus of the University of California, Berkeley. Key qualifying factors included the following: neophytes or experienced soft contact lens wearers, between the ages of 18 and 39 years, no history of rigid gas permeable lens wear, myopia between –0.50 diopters (D) and –6.00 D, a maximum of –1.75 D astigmatism, a difference of less than 1.00 D between corneal toricity and refractive astigmatism, good ocular health with no contraindications for rigid gas permeable contact lens wear, and no corneal scars. Experienced soft contact lens wearers were required to discontinue lens wear for at least 2 weeks prior to the first baseline measurements.

Study Materials

BE Retainer (Precision Technology Services, Vancouver, Canada) and Paragon CRT (Paragon Vision Sciences, Inc., Mesa, AZ) orthokeratology lenses in a variety of Dk/t were used (Table 1). Preservative-free solutions were used with the study lenses: Optimum by Lobob (Lobob Laboratories, Inc., Mountain View, CA) for cleaning, disinfecting, and storing, and Refresh Plus (Allergan, Inc., Irvine, CA) to assist in releasing bound lenses, when needed.

Instrumentation

The Medmont E-300 corneal topographer (Medmont, Melbourne, Australia) and Medmont Studio Version 4 software were used to assess baseline corneal topography and to monitor changes over the course of the treatment period. The Fluorotron Master (Ocumetrics, Mountain View, CA) was used to perform P_{dc} measurements. The Ocular Response Analyzer (ORA) (Reichert Technologies) was used to measure corneal biomechanical properties. The Bausch & Lomb Orbscan II Topographer (Bausch & Lomb, Rochester, NY) was used to measure corneal thickness along the entire cornea. A computerized visual acuity testing system (M&S Technologies Smart System II [SSII]; M&S Technologies, Skokie, IL) was used to measure high- (100%) and low-contrast (10%) visual acuity under photopic (20.31 cd/m^2) and mesopic (0.375 cd/m^2) lighting conditions.

Schedule of Visits

Patients were screened with a comprehensive eye examination, and those who qualified based on the inclusion and exclusion criteria were asked to discontinue any contact lens wear for 2 weeks before returning for baseline measurements. After baseline measurements were collected, subjects were randomized to Dk/t lens groups by minimization and fitted into OOK lenses according to each manufacturer's recommendations. Once an optimal fit was achieved, custom lenses were ordered while subjects underwent a minimum of a 1-week washout. Patients were followed after 1, 5, 10, 14, and 30 nights of OOK treatment with custom lenses. All key study measurements were taken at least 4 hours after awakening or lens removal.

Corneal Epithelial Permeability

Fluorotron Master (Ocumetrics) was used to measure P_{dc} by counting and summing photons along its optical path within the central 4 mm of the cornea. Because the scanning fluorophotometer (Fluorotron Master; Ocumetrics) has no spatial resolution, it is incapable of discerning if elevated signals are from penetrated fluorescein dye in the cornea or from residual dye trapped on the ocular surface. As a result, scanning fluorophotometry is best used to assess subclinical change to epithelial integrity, or P_{dc}, that is not measureable by commonly available methods (e.g., slit-lamp examination, pachometry) and should be performed on pristine corneas. The presence of corneal epithelial dysfunction (i.e., superficial punctate keratitis as seen in dry eye and other ocular surface diseases) would yield an inaccurate permeability coefficient with scanning fluorophotometry and should be measured using slit lamp fluorophotometry instead.[41]

At baseline and after 30 nights of OOK treatment, a masked observer performed a detailed slit lamp examination using both white light and cobalt blue light with a yellow filter. The presence of corneal staining with fluorescein was graded on a 1 to 4 scale, where punctate staining of fewer than 5 points was grade 1; 5 to 10 points as grade 2; 11 to 25 points as grade 3; and more than 26 points as grade 4. Subjects exhibiting more than five punctate stains in the central cornea were

Table 2. P_{dc} Showed No Significant Change Between Baseline and After 30 Days of Treatment, Demonstrated by the $\ln(P_{dc})$ Data

	P_{dc} Mean (95% CI);	$\ln(P_{dc})$ Mean (95% CI)
Baseline	0.080 (0.069–0.091)	−2.65 (−2.80 to −2.50)
Posttreatment, day 30	0.081 (0.070–0.091)	−2.68 (−2.85 to −2.50)
P value (baseline − posttreatment)	NA	0.876

P values derived from mixed-effect modeling.

Table 3. P_{dc} and $\ln(P_{dc})$ for Asian and Non-Asian Individuals at Baseline and After 30 Days of OOK Treatment

	P_{dc} Mean (95% CI)		$\ln(P_{dc})$ Mean (95% CI)		
	Asian	Non-Asian	Asian	Non-Asian	*P* Value
Baseline	0.084 (0.069–0.099)	0.077 (0.061–0.093)	−2.52 (−2.73 to −2.31)	−2.77 (−2.98 to −2.56)	0.09
Posttreatment, day 30	0.092 (0.074–0.109)	0.071 (0.060–0.083)	−2.54 (−2.83 to −2.25)	−2.80 (−3.00 to −2.59)	0.14

P values derived from mixed-effect modeling.

Table 4. Comparison of Baseline and Posttreatment CH, CRF, and CCT

	CH, mm Hg, Mean (95% CI)	CRF, mm Hg, Mean (95% CI)	CCT, µm, Mean (95% CI)
Baseline	10.89 (10.59–11.19)	10.35 (9.99–10.72)	567 (559–576)
Posttreatment, day 30	10.59 (10.31–10.87)	9.58 (9.26–9.89)	564 (555–573)
% change	−2.52 (−3.90 to −1.14)	−7.14 (−8.69 to −5.58)	−1.03 (−1.37 to −0.68)
P value	0.001	<0.001	<0.001

Although the decreases in CH, CRF, and CCT after 30 nights of treatment were statistically significant, it is unclear if the magnitudes of change are clinically significant. *P* values derived from mixed-effect modeling.

excluded from the analysis to avoid an overestimate of the P_{dc}.[22,42]

Corneal Biomechanical Properties

CH and corneal resistance factor (CRF) were measured at baseline and after 1, 5, 10, 14, and 30 nights of treatment. A total of four repeatable measurements were collected in each eye at each visit and averaged for analysis.

Visual Acuity

Best-corrected visual acuity (BCVA) was measured at baseline and all posttreatment visits. Baseline measurements included high-contrast (100%) and low-contrast (10%) targets under photopic conditions (20.31 cd/m^2). Posttreatment measurements also included the same measurements under mesopic conditions (0.375 cd/m^2).

Statistical Methods

Corneal epithelial permeability was converted to a natural logarithmic scale ($\ln[P_{dc}]$) for analysis in order to approximate normal distribution and stabilize between- and within-subject variability.[43–45] The distribution of $\ln(P_{dc})$ was examined by the Kolmogorov-Smirnov test before parametric test was applied to avoid erroneous and inefficient inference.

Pearson correlation was performed to reveal the strength of correlation between CH and central corneal thickness (CCT). The analysis of treatment and ethnicity effects was performed using multivariate mixed-effect model. The model was selected due to its capability to account for the potential correlation between the fellow eyes. The choice of appropriate covariance structure was based on Akaike's Information Criterion (AIC) and Schwarz's Bayesian Criterion (SBC). The mixed-effect model was produced using SAS (version 9.3) PROC MIXED procedure (SAS Institute, Inc., Cary, NC). In post hoc multiple visits comparison, the *P* values were adjusted using Bonferroni correction method.

Results

Study Participants

Thirty-nine subjects (18 males, 21 females) successfully completed the study. The mean ± SD age was 22.5 ± 4.8 years, ranging between 18 and 36 years. Fifteen subjects (38.5%) were neophytes, who did not have any contact lens wear experience for at least 12 months prior to study participation, and 24 subjects (61.5%) were experienced soft contact lens wearers. Asian individuals accounted for 46% of the subjects, and non-Asian individuals made up 54% of the study group. All subjects were randomly assigned to one of four different OOK lens groups based on a minimization scheme.

Corneal Epithelial Permeability

Of the 39 subjects who completed the study, no study participant repeated P_{dc} measurements due to excessive punctate staining discovered after P_{dc} measurements were captured; therefore, no P_{dc} data collected were eliminated from analysis. There was no significant difference in P_{dc} between baseline and 30 nights of treatment (Table 2). Baseline P_{dc} was higher in Asian individuals compared with non-Asian individuals with marginal significance (Table 3; $P = 0.09$). After 30 nights of treatment, P_{dc} in Asian individuals was also higher than in non-Asian individuals but not significant ($P = 0.14$).

Table 5. Significant Differences in Uncorrected Spherical Refraction, High-Contrast BCVA, and low-contrast BCVA Under Photopic Conditions Between Baseline and After 30 Days of Treatment Were Found

	Baseline	30 Days	*P* Value
Refractive error/SOR, D			
Sphere	−2.28 ± 0.98	+0.03 ± 0.58	<0.001
Cylinder	−0.25 ± 0.37	−0.23 ± 0.34	0.563
Photopic BCVA, logMAR			
High contrast	−0.07 ± 0.06	−0.04 ± 0.11	0.009
Low contrast	0.11 ± 0.11	0.18 ± 0.16	<0.001

Uncorrected cylindrical refraction did not change with treatment. Data are mean ± SD.

Corneal Biomechanical Properties

The data for CH and CRF are presented in Table 4. The four repeated measurements collected per eye at each visit were averaged to generate one mean value per eye per visit. The resultant means presented in Table 4 were derived directly from the averages of 78 eyes of 39 patients. The *P* values were obtained from mixed-effect models with a time indicator variable differentiating baseline and posttreatment as fixed effects and the within-subject correlation as random. CH and CRF measured by the ORA reduced significantly from baseline to 30 nights of treatment. CCT measured with the Orbscan II also significantly decreased after 30 nights of OOK treatment and had reached statistical significance by day 10 ($P = 0.01$, mixed-effect repeated measures analysis of variance). At day 30, the overall corneal thickness was 1.03% less than at baseline. A positive correlation was detected between CH and CCT at both baseline ($r = 0.67$, $P < 0.001$) and day 30 ($r = 0.64$, $P < 0.001$).

When the results were stratified by Dk/t at each visit, all Dk/t groups showed a decreasing trend in CH except for the BE-high Dk/t group (Fig. 1). The BE-low group experienced the most significant and consistent decrease in CH ($P < 0.001$) during the treatment period, with significance achieved at day 5 ($P = 0.015$). CRF decreased significantly across all 4 Dk/t groups, and their downward trends were similar to one another.

In general, Asian individuals had lower mean biomechanical property values (mean CH [CI] = 10.49 [10.03–10.96] mm Hg, mean CRF [CI] = 9.76 [9.27–10.25] mm Hg) than non-Asian individuals (mean CH [CI] = 11.23 [10.84–11.61] mm Hg, CRF = 10.86 [10.37–11.36] mm Hg) at baseline ($P = 0.08$ for CH and $P = 0.03$ for CRF). After 30 nights of OOK treatment, the difference in CRF between the Asian and non-Asian groups became only moderately significant ($P = 0.09$).

Visual Acuity

The mean refractive error and BCVA under photopic conditions at baseline and after 30 nights of OOK treatment for the study participants are summarized in Table 5. After 30 nights of treatment, there was a significant change in refractive spherical power ($P < 0.001$) but not in refractive cylindrical power ($P = 0.563$). Additionally, baseline BCVA was not achieved after 30 nights of treatment. As shown in Table 5, the posttreatment mean high-contrast BCVA was approximately 1 to 2 letters worse (not clinically significant) ($P = 0.009$) and low-contrast BCVA was approximately 3 to 4 letters worse than baseline (clinically significant) ($P < 0.001$) under photopic conditions. No baseline visual acuity measurements were taken under mesopic conditions.

When stratified by ethnicity, there was no significant difference in baseline photopic BCVA (Table 6). However, after treatment, there were differences in uncorrected visual acuities between Asian and non-Asian individuals within the first 14 days of treatment (Fig. 2), with Asian individuals presenting with worse acuities when differences were present. Under photopic/high-contrast conditions, marginal significance was found at day 1 ($P = 0.067$). Under photopic/low-contrast conditions, differences were found at day 1 ($P = 0.020$) and day 5 ($P = 0.064$). Under mesopic/high-contrast conditions, a difference was found at day 5 ($P = 0.039$). Finally, under low contrast/low illumination, differences were found at day 1 ($P = 0.068$), day 5 ($P = 0.073$), and day 14 ($P = 0.006$). On a similar note, spherical overrefraction (photopic/high contrast) was higher in the Asian group at day 1 ($P = 0.065$), day 5 ($P = 0.021$), and day 10 ($P = 0.026$) (Fig. 3). The percentage of participants who achieved 20/20 uncorrected was 17% Asian individuals and 40% non-Asian individuals after day 1 and reached 69% Asian individuals and 83% non-Asian individuals after day 30. Multivariate analysis over the 30-day study period revealed that uncorrected visual acuities were closely associated with baseline refractive error, baseline visual acuities under photopic/high-contrast conditions, and corneal response measured by the Medmont Corneal Topographer, but not with ethnicity.

Discussion

This study found that, after 30 nights of OOK treatment, the corneal epithelial barrier function was unchanged and the corneal biomechanical properties, CH and CRF, decreased significantly from baseline when measured approximately 4 hours after lens removal. These results suggest that, by each evening before lens insertion, the integrity of both the corneal epithelial tight junctions and the occludin-expressing corneal

Table 6. Comparison of Baseline Refractive Error and BCVA Between Asian and Non-Asian Individuals Shows No Difference Between the Groups

	Asians	Non-Asians	*P* Value
Refractive error, D			
Sphere, mean ± SD	−2.40 ± 0.95	−2.17 ± 1.01	0.457
Sphere range	−0.50 to −5.25	−0.75 to −4.75	
Cylinder, mean ± SD	−0.20 ± 0.36	−0.29 ± 0.39	0.817
Cylinder range	−0.25 to −0.75	−0.25 to −1.25	
Delta K, mean ± SD	0.81 ± 0.67	0.60 ± 0.59	0.149
Photopic BCVA, logMAR			
High contrast, mean ± SD	−0.066 ± 0.065	−0.080 ± 0.047	0.256
Low contrast, mean ± SD	0.126 ± 0.097	0.095 ± 0.122	0.226

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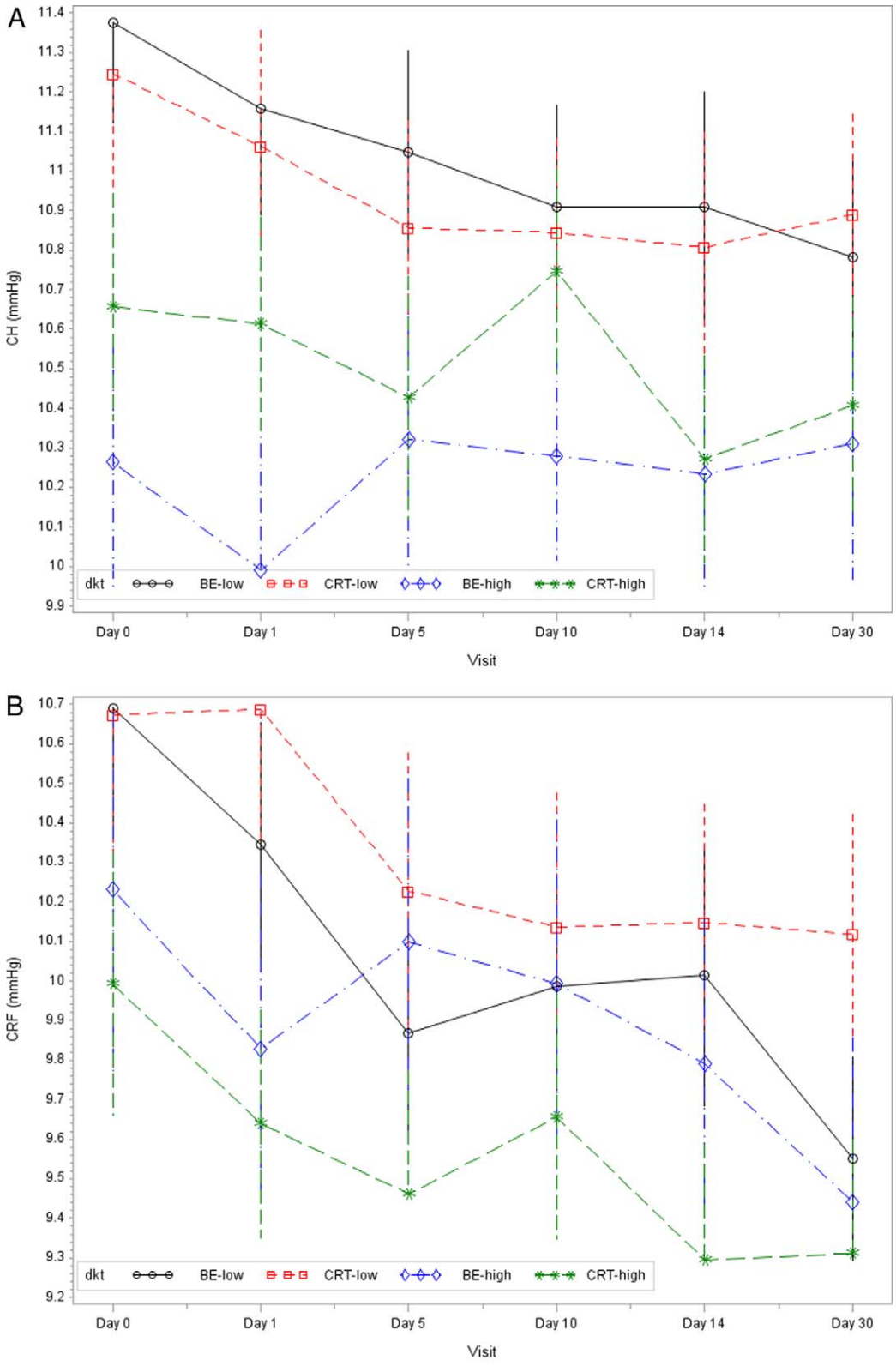

Figure 1. Comparison of CH (**A**) and CRF (**B**) changes over 30 nights of OOK treatment among the Dk/t groups. *Needles* indicate SEMs.

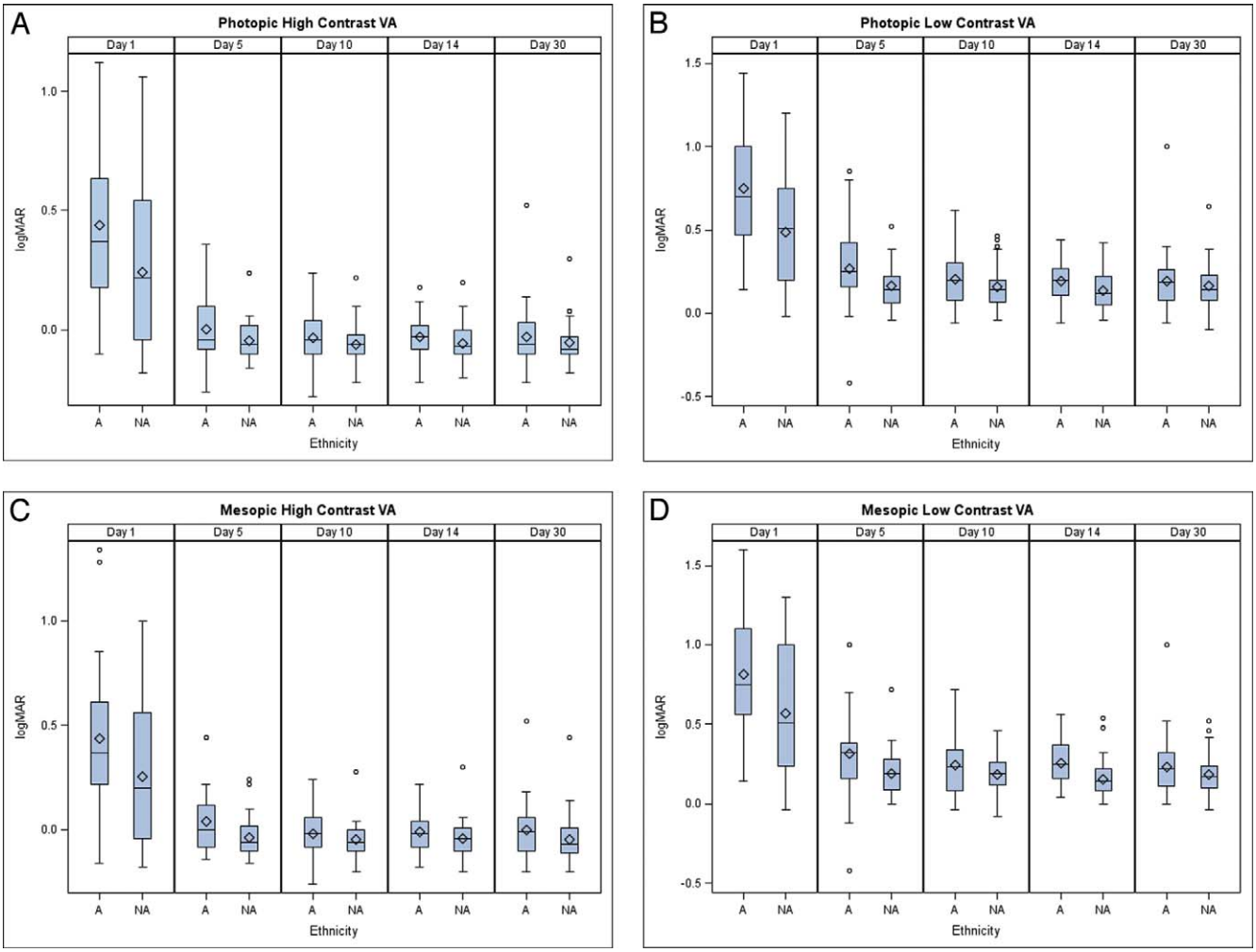

Figure 2. Box plots representing average visual acuity (logarithm of the minimum angle of resolution [logMAR]) over time for each ethnic group, with low- and high-contrast letters under photopic and mesopic conditions (**A–D**). Uncorrected visual acuity disparities between Asian and non-Asian demographics under all conditions were greatest after one night of treatment and became statistically insignificant by day 10, except for under the mesopic low-contrast lighting condition. ◇ (*inside* each *box*) = mean; — (*inside* each *box*) = median; *whiskers* extending from each *box* represent the minimum and maximum of the data within 1.5 intraquartile range. The *circles* represent data points that were outside the 1.5 intraquartile range.

epithelial cells are similar to baseline despite the changes in corneal morphology and biomechanics from OOK treatment.

The P_{dc} results contradict our hypothesis that OOK treatment would compromise the corneal epithelial barrier. Evidence that MMP-9 reduces the expression of the tight junction protein, occludin, and that elevated levels of MMP-9 can be found in the tear film of OOK patients[10–12] suggest that the corneal epithelial barrier would be altered and that P_{dc} would increase with treatment. The discrepancy between our hypothesis and results may be due to the time at which the P_{dc} measurements were collected in our study (at least 4 hours after awakening). It has been shown that MMP-9 levels are approximately 200 times higher in the morning immediately upon awakening than at midday (approximately 3–5 hours after awakening).[46] Also, it has been shown that after 30 days of continuous wear of hyper-Dk rigid gas permeable (RGP) lenses, morning P_{dc} measured immediately upon eye opening was significantly greater compared to baseline, but the P_{dc} measured after 4 hours of awakening was no different from baseline.[18] Therefore, diurnal variability of both MMP-9 and P_{dc} imply that time is of the essence when collecting these measurements and when assessing ocular surface integrity. Our study did not measure posttreatment P_{dc} immediately upon eye opening, so it is unclear if and to what degree the corneal epithelial barrier may have been compromised overnight with treatment. Further studies exploring the impact of OOK on morning ocular surface integrity is warranted.

Our study found significant changes in corneal biomechanical properties, CH and CRF, after 30 nights of OOK treatment. To better understand the implications of these changes, consider memory foam used to make pillows and mattresses. An applied pressure deforms the material, but upon release of the force, the material does not immediately return to its original shape in the way that a stretched rubber band would. The cornea is a viscoelastic material that responds to an applied pressure similar to memory foam. CH is defined as the energy absorption capability of the cornea, so the more energy that is absorbed from the applied pressure (high CH), the slower the cornea will rebound to its original shape. CRF is defined as the overall resistance of the cornea, so the higher the CRF, the more difficult it is to deform the corneal tissue from its baseline state.

Participants in this study experienced a 2.5% decrease in CH ($P < 0.05$) and 7.1% decrease in CRF ($P < 0.05$) after 30 nights

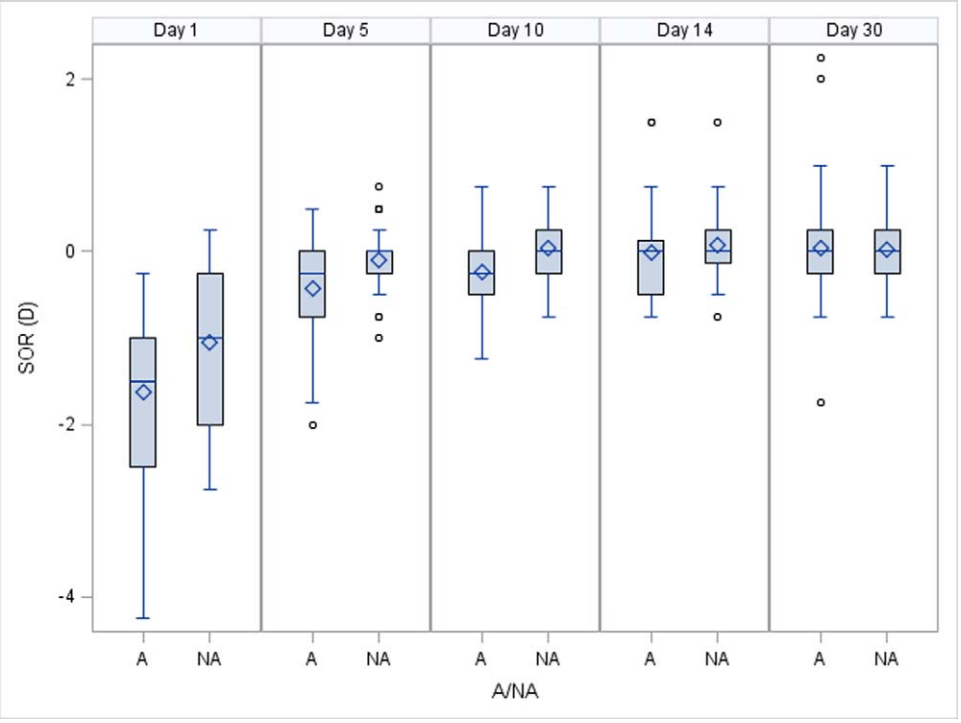

FIGURE 3. Box plot representing spherical overrefraction (SOR) by duration of treatment, stratified by ethnic groups. A comparison of SORs between the Asian and non-Asian groups after 1, 5, 10, 14, and 30 days of treatment showed significant differences between the groups through day 10 only. ◇ (*inside* each *box*) = mean; — (*inside* each *box*) = median; *whiskers* extending from each box represent the minimum and maximum of the data within 1.5 intraquartile range. The *circles* represent data points that were outside the 1.5 intraquartile range.

of OOK treatment, suggesting that the cornea developed a tendency to rebound slightly faster and became less resistant to an applied force after treatment. Although the changes are statistically significant, they may not be clinically significant, as the threshold of clinical significance for biomechanical properties has not been well defined. For comparison, refractive surgery results in a decrease between 14.3% and 20.9% of CH and between 19.9% and 30.9% of CRF,[40,47–49] which are markedly more than seen in this study with OOK. Clearly, the changes to CH and CRF resulting from OOK are not as dramatic as seen from refractive surgery or in disease, and this is further supported by no apparent change in the CH and CCT correlation before and after treatment. By 30 nights of treatment, there continued to be a decreasing trend in CH. A longitudinal study would be beneficial to determine the timeline and degree to which CH changes and if any of the changes are permanent. Also, CH and CRF appear to be affected by the lens Dk/t in this study, where the BE-low group (Dk/t = 39) experienced the greatest percent change in CH and CRF compared with the other three higher Dk/t groups. However, the multivariate modeling revealed that CH is significantly associated with duration of OOK treatment, CRF, IOPcc, and IOPg, and that lens Dk/t was not a significant factor.

The analysis of visual acuity resulted in some interesting findings in this study. First, baseline BCVA was not achieved after 30 nights of OOK treatment, particularly with low-contrast letters, and this can be explained by previously published reports that corneal refractive therapy induces increased amounts of higher-order aberrations (HOAs) and decreased contrast sensitivity function, resulting in slightly reduced acuities.[50–55] This study also found that, in general, uncorrected visual acuity was worse in Asian individuals than in non-Asian individuals within the first 5 days of treatment under most testing conditions, and the difference between the two groups under mesopic/low-contrast conditions was significant through day 14. The differences in the first 5 days can be attributed to residual uncorrected refractive error, which was significantly different between ethnic groups (Fig. 3), because BCVA was not statistically significant between the groups in that period ($P > 0.10$). Although multivariate analysis showed ethnicity not to be a significant factor, it is important to note that the analysis was performed for the full 30-day study period but that univariate analysis showed differences mostly within the first 5 days of treatment. The inferiority of the Asian group's uncorrected visual acuity under mesopic/low-contrast conditions through day 14 can be explained by previous findings that Asian individuals (Chinese, Malaysian, and Korean), overall, have higher amounts of HOAs than Caucasians and Indians[56–64] and that HOAs, in general, are significantly higher under scotopic than photopic conditions.[65] Although no single study directly compared different ethnicities, the collective results of several independent studies do suggest that Asian individuals have higher HOAs than other ethnic groups.

Finally, it is interesting to note that Asian individuals were slower than non-Asian individuals to achieve visual stability (measured at least 4 hours after lens removal at each visit) with OOK treatment, suggesting that the Asian corneas either did not achieve the same correction overnight as their non-Asian counterparts or that the Asian corneas were quicker to rebound after lens removal during the first 5 days of treatment. A pilot study that explored the relationship between CH and OOK effect found that higher baseline values of CH meant slower effect and slower recovery when CH was measured after 3 hours of OOK lens wear and again 3 hours after lens removal.[66] This implies that perhaps the Asian group, that had lower CH at baseline with marginal significance ($P = 0.08$) may have had faster effect overnight but also faster recovery, resulting in the discrepancy in uncorrected visual acuities. It is interesting, however, that by day 10, the effects were nearly

the same when measured 4 hours after lens removal. Future studies should explore how CH impacts corneal reshaping and rate of effect during OOK treatment, particularly in the first 10 days of treatment.

Although a number of adverse events have been reported in children with OOK treatment, this study did not yield any results to suggest that OOK puts patients at greater risk for adverse events compared with other lens types or modalities when managed properly. The integrity of the corneal epithelial barrier was equivalent to baseline by 4 hours after lens removal, and changes in corneal biomechanical properties did not appear to be clinically significant. This positive outcome may be attributed to good tear turnover with RGP lenses[67] overnight and lens removal upon awakening, allowing the ocular surface to normalize throughout the day. One recent study found that morning lens replacement during "continuous wear" resulted in fewer adverse events than with evening lens replacement or no lens replacement at all during the 30-day wearing period.[68] Therefore, when treating patients with OOK, it is imperative to discuss the proper lens care and handling procedures to minimize the risk of adverse events.

In summary, this study found no difference in afternoon corneal epithelial permeability (at least 4 hours after lens removal) between baseline and post-30 nights of OOK treatment, suggesting that the integrity of the superficial epithelial cells and tight junctions normalize by the next wearing period. Corneal biomechanical properties decreased with treatment but to a two to four times lesser degree than seen in postrefractive surgical cases and may be most impacted by lower Dk/t OOK lenses. Finally, there appears to be a relationship between corneal biomechanical properties and time to achieve target vision with OOK, but this requires further exploration.

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