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# Effects of Daily Irrigation on Corneal Epithelial Permeability and Adverse Events With Silicone Hydrogel Contact Lens Continuous Wear

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**PURPOSE.** To determine whether daily irrigation with sterile saline solution during silicone hydrogel (SiH) contact lens continuous wear (CW) can mitigate increases in corneal epithelial permeability ( $P_{dc}$ ) and reduce the risk of adverse events.

**METHODS.** In this study, 161 non-contact lens wearers were fit with SiH contact lenses and randomized to either a treatment ( $n = 81$ ) or control ( $n = 80$ ) group for 30-day CW. Subjects in the treatment group irrigated every morning and whenever dryness symptoms occurred; subjects in the control group did not. Mixed effects models were employed to assess the changes in  $P_{dc}$ , and survival analysis methods were employed to estimate the risk for adverse events.

**RESULTS.** Epithelial permeability increased over 30-day CW with SiH lenses ( $P = 0.001$ ). Risk of inflammatory (odds ratio [OR] = 1.94) and lens-induced (OR = 1.90) adverse events increased with irrigation; these events also occurred sooner, on average, in the irrigation group. Although the overall risk for Asians was higher than for non-Asians, irrigation had no significant impact on risk among Asians, but significantly increased risk among non-Asians.

**CONCLUSIONS.** Thirty-day CW results in a measurable increase in epithelial permeability. Risk of inflammatory and lens-induced adverse events also increase over time during CW. Daily irrigation with sterile saline solution did not mitigate increases in epithelial permeability or decrease risk of adverse events.

**Keywords:** continuous contact lens wear, irrigation, corneal epithelial permeability, fluorometry, daily contact lens wear, adverse events, survival analysis

The corneal epithelium has an essential role in the innate defense mechanism of the protective ocular barrier.<sup>1-4</sup> It has been shown that corneal epithelial permeability can be increased by continuous wear (CW) of silicone hydrogel (SiH) contact lenses, in spite of the elimination of hypoxia with newer hyper-O<sub>2</sub> transmissible materials.<sup>5</sup> It also has been shown that rigid gas-permeable lenses permit faster recovery of corneal epithelial barrier function upon awakening from overnight wear than do soft lenses,<sup>5</sup> which is likely due to the greater rate of postcontact lens tear flushing achieved with rigid lenses.<sup>6-8</sup> It has been hypothesized that reduced tear mixing beneath a soft contact lens can cause unwanted substances (e.g., debris, metabolic byproducts) to agitate against the corneal epithelium during blinking after awakening from overnight lens wear. It also is possible that stagnation of the tears trapped beneath the lens could result in accumulation of inflammatory cells, which could trigger an inflammatory cascade. Although to our knowledge there has been no definitive study to date linking changes in epithelial barrier function to changes in ocular surface health, several studies have suggested that overnight wear of soft lenses with relatively poor tear exchange is associated with increased epithelial permeability,<sup>5</sup> and with increased incidence of contact lens-related adverse events.<sup>9-13</sup>

Presumably, the CW modality poses the greatest risk to ocular surface integrity. Could corneal epithelial barrier function be restored more quickly during CW by daily irrigation of the eyes with a sterile ophthalmic solution immediately upon awakening,

coupled with gentle nudging of the lens to dislodge it in order to increase postlens tear thickness, thereby permitting improved postlens tear exchange?<sup>14</sup> Could daily irrigation and gentle nudging of the lens each morning contribute to a lower risk of adverse events during CW? Enhanced tear mixing aids the flushing of postlens debris, including mucus, corneal epithelial cells, and neutrophils, which have been associated with an inflammatory response following SiH CW.<sup>15-18</sup>

In this study, we recruited subjects for 30-day CW with SiH contact lenses, and randomly assigned each subject to either a daily regimen of morning ocular irrigation with lenses on the eye or a standard CW modality without daily irrigation. Corneal epithelial permeability ( $P_{dc}$ ) measurements were taken by fluorometry at baseline, after 1 night of overnight wear, and after approximately 30 days of CW. After the initial 30-day CW period, subjects elected either to continue CW with their assigned treatment or to revert to daily wear with no irrigation, and then were followed for approximately 1 year to assess the longer-term risk of adverse events.

## METHODS

### Subjects

Subjects between the ages of 18 and 39 years were recruited from the University of California, Berkeley campus and surrounding community. Screening took place at an orientation

visit during which informed consent was obtained after a detailed explanation of the study goals, procedures, and potential risks of participation. A questionnaire was administered at the orientation visit to collect demographic information, ocular health history, and medical history pertaining to ocular and systemic illnesses, and use of medications. Qualified participants had no history of contact lens wear for a minimum of one year, had spectacle prescriptions between  $-1.00$  diopter sphere (DS) and  $-10.00$  DS with less than  $0.75$  diopters (D) of astigmatism, had no history of ocular surgery or serious injury, had no corneal scarring, and were free of any ocular disease or systemic disease with ocular manifestation. Potential enrollees who reported frequent swimming, smoking, or use of medications with ocular surface side effects also were excluded. This study adhered to the tenets of the Declaration of Helsinki, was approved by institutional review board (University of California, Berkeley, Committee for Protection of Human Subjects), and was Health Insurance Portability and Accountability Act (HIPAA)-compliant.

### Study Protocol

The study design was prospective, controlled, and randomized, with parallel treatment and control arms. Stratified block randomization was employed to ensure approximately equal proportions of subjects in the treatment (irrigation) and control (no irrigation) study groups, for both Asian and non-Asian subgroups, throughout the course of the study. The Asian subgroup consisted of subjects self-reporting as Chinese, Japanese, Vietnamese, Taiwanese, Cambodian, Korean, or Pacific Islander. The non-Asian subgroup included Caucasian, Hispanic, Middle-Eastern, and Indian subjects. The eye to be measured first with fluorometry also was block-randomized within each study group to control for potential biases due to unknown systematic machine or subject differences between right and left eye measurements, instrument drift over the course of the study, or changes in observers or observer criteria.

### Measurements and Procedures

Subjects were fitted with either Focus Night & Day or Air Optix Night & Day Aqua (CIBA Vision Corp., Duluth, GA) SiH contact lenses (lotrafilcon A,  $13.8$  mm diameter,  $8.4$  mm or  $8.6$  mm base curve radius,  $24\%$  H<sub>2</sub>O,  $175$  Dk/t). Subjects randomized to the treatment group also were instructed to irrigate with preservative-free Unisol 4 Saline Solution (Alcon Laboratories, Inc., Fort Worth, TX) daily upon awakening and any time they experienced dryness sensation during CW.

Subjects who passed the initial screening and elected to participate underwent a comprehensive ocular health examination, including a slit-lamp examination with sodium fluorescein dye illuminated with cobalt blue light and viewed with a Wratten #12 yellow barrier filter. Subjects meeting all initial eligibility criteria then were fit with trial contact lenses. The subsequent visit required the subject to arrive within 2 hours of awakening, and began with a brief white light examination of the cornea to ensure continued ocular surface integrity, followed by  $P_{dc}$  measurement. After fluorometry measurements were completed, a more thorough slit-lamp examination with sodium fluorescein was conducted to screen for the presence of central corneal staining, which could potentially bias  $P_{dc}$  measurements. Punctate staining in the central cornea and 4 peripheral quadrants was graded according to the Mandell grading system,<sup>19</sup> and subjects with greater than grade 1 central staining were excluded from the analysis.

Subjects then were dispensed contact lenses for daily wear adaptation, and returned for a 7-day progress check and a

sodium fluorescein examination. Subjects were dispensed new contact lenses for CW and then returned after 1 night of overnight wear for lens assessment,  $P_{dc}$  measurement, and a sodium fluorescein examination. Subjects who successfully adapted to overnight wear then were randomized to the treatment or control group for 30-day CW, after which final  $P_{dc}$  measurements and ocular surface examinations were conducted. After the initial 30-day CW period, subjects were given the option to continue the CW regimen as randomized or revert to daily wear with no irrigation, and then were followed for approximately 1 year to assess the longer-term risk of adverse events.

For  $P_{dc}$  measurements, an automated scanning fluorometer (Fluorotron Master; Ocumetrics, Mountain View, CA) was used to measure the rate of sodium fluorescein penetration into the central cornea using a single-drop technique, in which  $2$   $\mu$ L of  $0.35\%$  sodium fluorescein are instilled on the superior bulbar conjunctiva via micropipette, and the decay in fluorescence is measured over a period of approximately 30 minutes, alternating between eyes every 2 minutes. Details of the fluorometry procedure and estimation of  $P_{dc}$  from the fluorescence decay readings have been reported previously.<sup>20</sup>

### Statistical Methods

After an extensive exploratory analysis, a multivariable linear mixed-effects modeling approach was used to assess the effect of irrigation on  $P_{dc}$  while accounting for repeated measures across visits and between fellow eyes, and adjusting for the possible influence of other covariates, including age, sex, ethnicity, and time awake before measurement. Epithelial permeability was analyzed on the natural logarithm scale to better approximate normality. Additive and interaction terms were examined, and models were compared by log-likelihood for nested models and by Akaike's Information Criterion for nonnested models. The final model was chosen based on F-test  $P$  values, consideration of effect sizes, and examination of residual and other diagnostic plots.

The risk of an adverse event during SiH contact lens CW cannot be assessed accurately by a naïve estimate (e.g., number of adverse events/number of subjects enrolled) because such estimates fail to take into account censoring of the data. Subjects who enter into the study either may suffer an adverse event, become disqualified, voluntarily discontinue, become lost to follow-up, or complete the study successfully without an adverse event. These subjects all contribute varying amounts of time at-risk for an adverse event. Survival analysis methods take censoring into account, provide unbiased estimates of the probability of survival in CW without an adverse event, and can provide risk estimates adjusted for the influence of the main explanatory variable (presence or absence of irrigation) as well as demographic and other covariates, and their interactions. We used the Kaplan-Meier nonparametric estimator of the survival function to compare survival probability free of an adverse event between treatment and control groups, as well as between Asians and non-Asians, males and females, and age categories ( $<21$  years,  $\geq 21$  years). In addition, we compared survival curves between subjects who remained in CW after the initial 30-day CW period and the subgroup who elected to revert to a daily wear schedule. The Kaplan-Meier method assumes that censoring and survival times are independent, and that the survival probability is constant within the intervals between successive adverse events. Cox proportional hazards (CPH) models allowed us to estimate the odds ratios (OR) for an adverse event associated with any linear combination of these explanatory variables, and their interactions, as well as with age treated as a continuous covariate. The significance of multivariate CPH

TABLE 1. Disposition of Subjects at End of Study

	Total	Treatment	Control
N of subjects enrolled	161	81	80
N of subjects completed	147	74	73
N of subjects DO/DQ	14	7	7
Adverse events	9	6	3
Superior epithelial arcuate lesion	1	1	0
Contact lens-associated red eye	2	2	0
Extensive corneal staining	1	0	1
Conjunctivitis	2	1	1
Corneal abrasion	2	1	1
Corneal ulcer	1	1	0
Other DO/DQ	5	1	4
Inadequate best VA	1	0	1
Discomfort/dryness	2	0	2
Lost to follow-up	2	1	1

DO, dropped out (voluntarily); DQ, disqualified (by clinician).

models was tested using the Wald test, and the proportional hazards assumption was checked by examining log-log and Schoenfeld residual plots.

RESULTS

Part 1: Subject Characteristics

A total of 401 potential subjects responded to recruitment efforts, were given an orientation to the study, and were screened for eligibility. Of these, 161 met all inclusion criteria, were able to adapt successfully to overnight lens wear, and were randomized to either the control (no irrigation,  $n = 80$ ) or treatment (irrigation,  $n = 81$ ) group. Of these, 147 successfully completed the first phase of the study: 74 in the treatment group and 73 in the control group. The reasons for the 14 randomized subjects (7 in each group) failing to complete the first phase of the study are detailed in Table 1.<sup>21</sup> A total of 91 subjects agreed to take part in the second phase of the study, with 56% of subjects continuing the same CW protocol (with or without irrigation, as randomized), and 44% electing to revert to daily wear with no irrigation.

Our 161 CW subjects averaged (SD) 21.6 (3.9) years of age, ranging from 18 to 38 years. There were 81 female and 80 male subjects, with 48% of Asian descent and 52% being non-Asian. These demographics closely matched those of the University of California, Berkeley campus community from which subjects were recruited.<sup>22</sup> There were no significant differences between the treatment and control groups in age distribution, sex proportions, or ethnic makeup.

Part 2: Corneal Epithelial Permeability

Overall descriptive statistics for raw  $P_{dc}$ , and  $\ln(P_{dc})$ , stratified on visit, are shown in Table 2. The distribution of  $P_{dc}$  itself

TABLE 2. Descriptive Statistics for Raw  $P_{dc}$  (nm/s) and Natural Logarithm-Transformed  $P_{dc}$ , Stratified on Visit

	$P_{dc}$			$\ln, P_{dc}$		
	Median	Mean	SD	Median	Mean	SD
Baseline	0.0874	0.0974	0.0596	-2.4378	-2.5144	0.6686
1 Night ONW	0.0995	0.1092	0.0595	-2.3076	-2.3904	0.6831
30-Day CW	0.1076	0.1258	0.0842	-2.2293	-2.2757	0.6850

Measurements on the two eyes of each subject are combined.

tends to be right-skewed, and after examining model fits, the distribution of residual errors was found to deviate from normal, which violates the model assumptions; therefore, the natural logarithm transformation was applied to the raw  $P_{dc}$  values, and all subsequent analyses were performed using  $\ln(P_{dc})$ .

The means and 95% confidence intervals (CIs) for  $\ln(P_{dc})$ , stratified on study group and eye, showed a general increasing trend in  $\ln(P_{dc})$  from baseline (no lens) to 1 night of overnight contact lens wear, to 30-day CW (Fig. 1). Univariate analyses suggested that  $\ln(P_{dc})$  is not related to age or sex, although it should be kept in mind that the age range of subjects was limited due to the university-based study population from which we drew our subject sample. Univariate analyses did suggest that  $\ln(P_{dc})$  could be related to ethnicity and to time awake before  $P_{dc}$  measurement, findings that agree with previous studies (Refs. 5, 23-25 and Tierney WS, et al. IOVS 2008;49:ARVO E-Abstract 2554).

The optimal multivariate model (Table 3) shows that, on average,  $\ln(P_{dc})$  increased significantly from baseline after 1 night of overnight wear, and increased further after 30-day CW ( $P = 0.001$ ), that  $\ln(P_{dc})$  is significantly higher for Asian subjects overall ( $P < 0.001$ ), and that  $\ln(P_{dc})$  significantly decreased with increasing time awake before measurement ( $P = 0.001$ ). With the significant factors of visit, ethnicity, and time awake taken into account, there was some suggestion of an overall increase in  $\ln(P_{dc})$  with irrigation; however, it was not significant at the 0.05 level ( $P = 0.104$ ). Age and sex were not significantly related to  $\ln(P_{dc})$  in our final multivariate model.

Part 3: Adverse Events

Overall, daily irrigation during SiH contact lens CW does have an effect on the incidence of adverse events, but in an unexpected direction. Furthermore, Asians and non-Asians may differ in their ocular responses to daily irrigation, and in the nature of the adverse events to which they are susceptible (Table 4). In the nonirrigating control group, Asian subjects had a greater number of all types of adverse events than did non-Asians, with approximately 47% of Asian subjects having at least one adverse event, compared to approximately 16% of non-Asians ( $P = 0.002$ ). In the irrigating treatment group, the differences between ethnic groups in the numbers of adverse events were much smaller, and were not significantly different in the univariate analysis. Details of all adverse events encountered in the 2 study groups, stratified on ethnicity, are shown in Figure 2. The most common problems included contact lens-associated red eye, superior epithelial arcuate lesions, extensive corneal staining, and infiltrates.

The Kaplan-Meier survival curves depicted in Figure 3 show that the probability of remaining free of an adverse event over time is significantly lower in the irrigating treatment group ( $P = 0.026$ ). The mean time to first adverse event was 305 days in the nonirrigating control group, compared to 221 days in the irrigating treatment group ( $P = 0.024$ ). Univariate CPH models

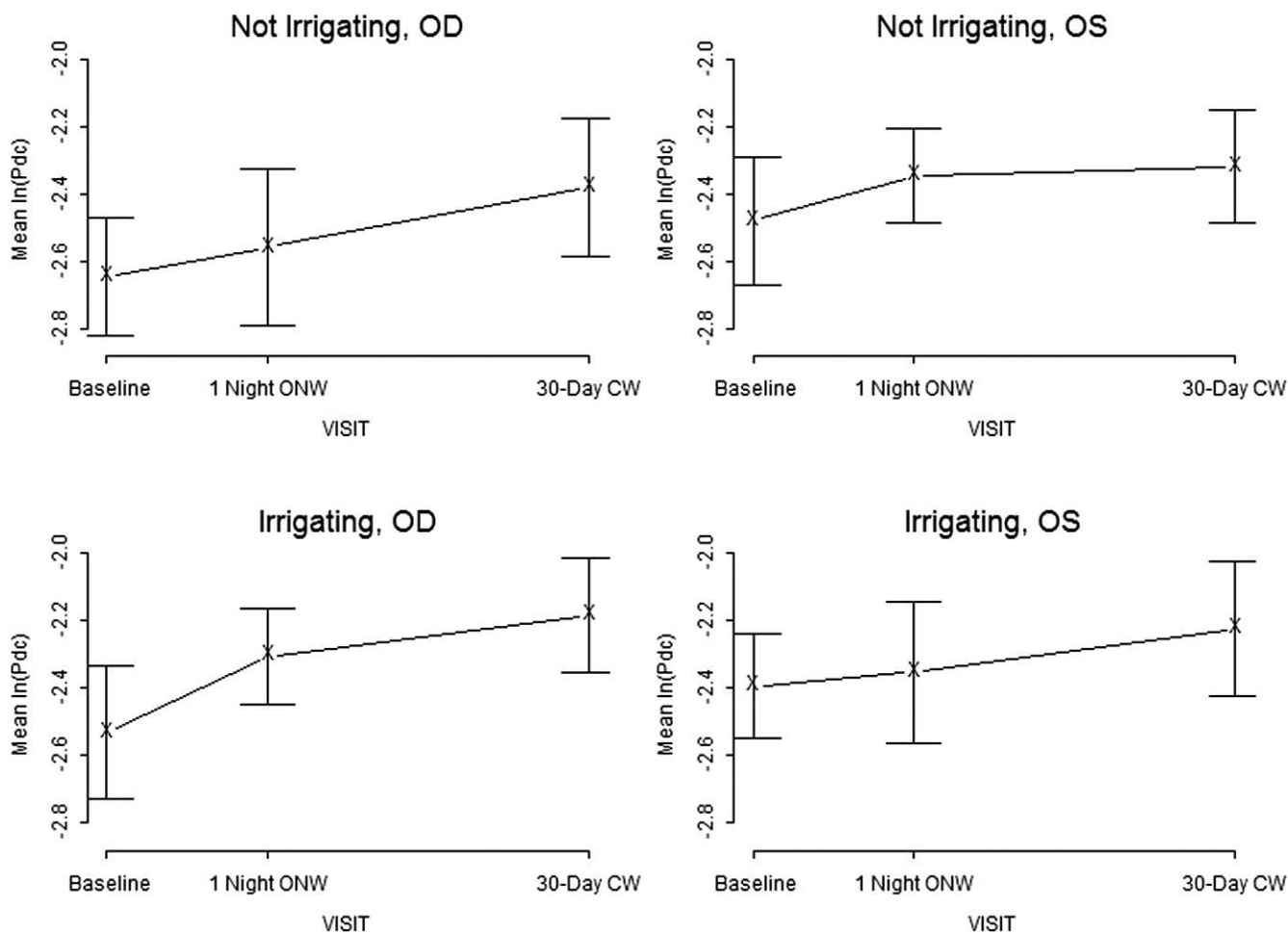


FIGURE 1. Natural logarithm-transformed epithelial permeability. Shown are means and 95% CIs at baseline (no lens), after 1 night of overnight wear (ONW), and after 30-day CW, stratified on eye and irrigation group.

estimate the OR (95% CI) for any adverse event with irrigation versus nonirrigation to be 1.81 (1.07, 3.04).

Among Asian subjects, there were slightly fewer adverse events with irrigation compared with nonirrigation; however, among non-Asian subjects there were far more adverse events with irrigation. For overall adverse events, the best multivariate CPH model included a term for ethnic group, and an interaction between ethnicity and irrigation status (overall model  $P = 0.006$ ). According to this model, there was significantly less risk for non-Asians on average ( $P = 0.030$ ), but a significantly increased risk for non-Asians who irrigated ( $P = 0.001$ ), which was not the case for Asians who irrigated ( $P$

$= 0.780$ ). The OR (95% CI) for overall adverse event risk associated with non-Asian race was 0.41 (0.18, 0.92), with irrigation among non-Asians 4.45 (1.91, 10.37), and with irrigation among Asians 0.90 (0.43, 1.89).

For adverse events overall, there were no significant associations with age (either as a continuous variable or binary category), sex, or contact lens wearing progression (i.e., remaining in CW after the initial 30 days, or switching to daily wear).

We also examined descriptive statistics and survival models separately for different types of adverse events, including contact lens-related, inflammatory, and mechanically-induced events.<sup>13,16,26</sup>

Univariate tests suggested that a significantly greater percentage of Asians had inflammatory adverse events in the control group (28.6% vs. 4.1% for non-Asians,  $P = 0.002$ ), but not in the treatment group (17.9% vs. 28.6% for non-Asians,  $P = 0.383$ ). Although the mean number of days free of an inflammatory event was lower in the treatment group (298 days) compared with the control group (367 days), after taking censoring into account the difference was not significant ( $P = 0.067$ ), nor was there a significantly higher risk of an inflammatory event in the treatment group (OR [95% CI] = 1.94 [0.95, 3.93]). A form of multivariate model identical to that for overall adverse events proved best for inflammatory adverse events as well (overall model  $P < 0.001$ ), with significantly less risk for non-Asians on average ( $P = 0.020$ ), but a significantly increased risk for non-Asians who irrigated ( $P =$

TABLE 3. Multivariate Mixed Effects Models of  $\ln(P_{dc})$

Parameter	Parameter Estimate	P Value
Intercept	-2.035	<0.0001
Visit: 1 night	-0.1144	0.0013
Visit: 30 nights	0.0789	
Irrigation	0.1084	0.104
Ethnicity	-0.2098	0.0001
Time awake	-0.0027	0.0008

After taking into account changes over visits, ethnicity, and time awake before measurement, the effect of irrigation on  $\ln(P_{dc})$  is not significant. The intercept represents the estimate of  $\ln(P_{dc})$  at baseline, immediately upon awakening, with no irrigation, in (arbitrarily) the Asian group.

TABLE 4. Numbers of Adverse Events (AE), Stratified on Type of AE, Ethnic Group, and Irrigation Status at Time of Onset

	Irrigating					Not Irrigating				
	Asian, n = 28		Non-Asian, n = 35		P Value	Asian, n = 49		Non-Asian, n = 49		P Value
	n With AE	% With AE	n With AE	% With AE		n With AE	% With AE	n With AE	% With AE	
All AEs	10	35.71	17	48.57	0.4425	23	46.94	8	16.33	0.0021
Lens-induced AEs	8	28.57	14	40.00	0.4290	16	32.65	8	16.33	0.0990
Inflammatory AEs	5	17.86	10	28.57	0.3829	14	28.57	2	4.08	0.0018
Mechanical AEs	7	25.00	5	14.29	0.3426	12	24.49	6	12.24	0.1913

Fisher's exact test *P* values for comparing Asians and non-Asians are shown.

0.003), which was not the case for Asians who irrigated ( $P = 0.560$ ). The OR (95% CI) for inflammatory adverse event risk associated with non-Asian race was 0.17 (0.04, 0.76), with irrigation among non-Asians being 10.31 (2.25, 47.17), and with irrigation among Asians being 0.74 (0.26, 2.06).

There were a similar number of lens-induced adverse events in the treatment ( $n = 22$  events) and control ( $n = 24$  events) groups; however, the mean number of days free of a lens-induced adverse event was significantly less in the treatment group (252 vs. 337 days,  $P = 0.028$ ). For lens-induced adverse events, the best CPH model contained only a single covariate for irrigation status, with irrigation associated with an increased risk of lens-induced adverse events ( $P = 0.030$ ). The OR (95% CI) for lens-induced events associated with irrigating was 1.90 (1.06, 3.41).

There were no significant differences between treatment and control groups, or between Asians and non-Asians, in terms of mechanical adverse events. There was a greater percentage of Asian subjects with mechanical adverse events in the treatment (25.0% vs. 14.3% for non-Asians,  $P = 0.343$ ) and control (24.5% vs. 12.2% for non-Asians,  $P = 0.191$ ) groups, although these differences were not significant. The mean number of days free of a mechanical adverse event was 319 days in the treatment group and 366 days in the control group ( $P = 0.415$ ), and the OR (95% CI) for a mechanical adverse event with irrigation was 1.36 (0.65, 2.84). In examining multivariate CPH models, we found that neither irrigation status, ethnicity, nor any other covariate or their interactions was significantly associated with increased risk of mechanical adverse events.

## DISCUSSION

To summarize briefly the main results of this study: (1)  $P_{dc}$  increased during 30-day CW, with or without irrigation; after adjusting for the significant effects of visit, time awake before measurement, and ethnicity,  $P_{dc}$  was estimated to have increased with irrigation, although not significantly so at the  $\alpha = 0.05$  level ( $P = 0.104$ ). (2) Risk of inflammatory and lens-induced adverse events increased with irrigation; these events also occurred sooner, on average, in the irrigation group. (3) Although the overall risk of inflammatory adverse events for Asians was significantly higher than for non-Asians, irrigation had no significant impact on risk among Asians, but significantly increased risk among non-Asians.

Some results of this study correspond to the findings of several previous studies. Epithelial permeability increased significantly from baseline (no lens) during 30-day CW, confirming that CW with soft lenses negatively affects corneal epithelial barrier function, despite high levels of lens oxygen transmissibility.<sup>5</sup> It is thought that because SiH lenses permit only a relatively thin postlens tear film<sup>14,27-29</sup> and have relatively poor tear exchange,<sup>7,8,14,29</sup> the tears beneath the

lens are not refreshed during sleep and have accumulated a sufficient amount of debris that, upon awakening and commencement of blinking, a chemical and a mechanical irritation to the cornea ensues. Also in agreement with previous studies, we found that Asians had significantly higher  $P_{dc}$  on average, compared with non-Asians, which is likely due to differences in ocular anatomy and physiology (Refs. 5, 23-25 and Tierney WS, et al. *IOVS* 2008;49:ARVO E-Abstract 2554).

Our study results also suggested that daily irrigation with nonpreserved saline solution upon awakening during CW does not contribute to a less compromised  $P_{dc}$ . In fact, while the difference in  $P_{dc}$  between the irrigation and nonirrigation groups was not significant, there was an observable trend of increased  $P_{dc}$  over the course of 30-day CW in the irrigation group as well as in the nonirrigation group. One possible explanation is that our assumption that the combination of ocular irrigation and nudging of the lens would increase the postlens tear film thickness and enhance tear mixing might not be correct, at least not to the degree that would result in improved  $P_{dc}$ . A second possible explanation is that the lack of improvement in  $P_{dc}$  with irrigation during CW may be attributed primarily to epithelial cytotoxicity associated with the ingredients contained in the irrigant solution, particularly the boric acid buffers, while other factors, such as bottle tip contamination of the irrigants, or mechanical trauma to the cornea induced by subjects' aggressive irrigation or lens nudging technique also could be possible contributors. Several prior in vitro studies have demonstrated that the boric acid buffer contained in unpreserved saline solutions and multipurpose disinfecting solutions (MPDS) can contribute to significantly disrupted tight junctions between corneal epithelial cells and, therefore, to compromised epithelial barrier function. Imayasu et al.<sup>30</sup> conducted an experiment using a monolayer of corneal epithelial cells exposed to an assortment of MPDSs, and found significantly compromised corneal epithelial cell tight junctions in only the cell cultures treated with MPDSs that contained a boric acid buffer. Tanti et al.<sup>31</sup> took these findings a step further with the comparison of borate-based MPDSs to MPDSs containing a phosphate buffer. The investigators added SiH contact lenses soaked in these various MPDSs overnight to monolayers of corneal epithelial cells and later compared cell viabilities between groups. They found a significant increase in cytotoxicity and a decrease in cell integrin expression with borate-based MPDSs when compared to phosphate-buffered MPDSs.<sup>31</sup> The in vivo ramifications of these findings are important to consider, especially as a contact lens may initially retain cytotoxic components and slowly release them over wearing time. It is possible that the adverse effects of the borate buffer outweighed the potential benefits of irrigation in our study, resulting in corneal epithelial barrier function that was no better than that of subjects who did not irrigate at all. Future studies will examine the in vivo effects of phosphate-based versus borate-based buffer solutions, as well as other types of

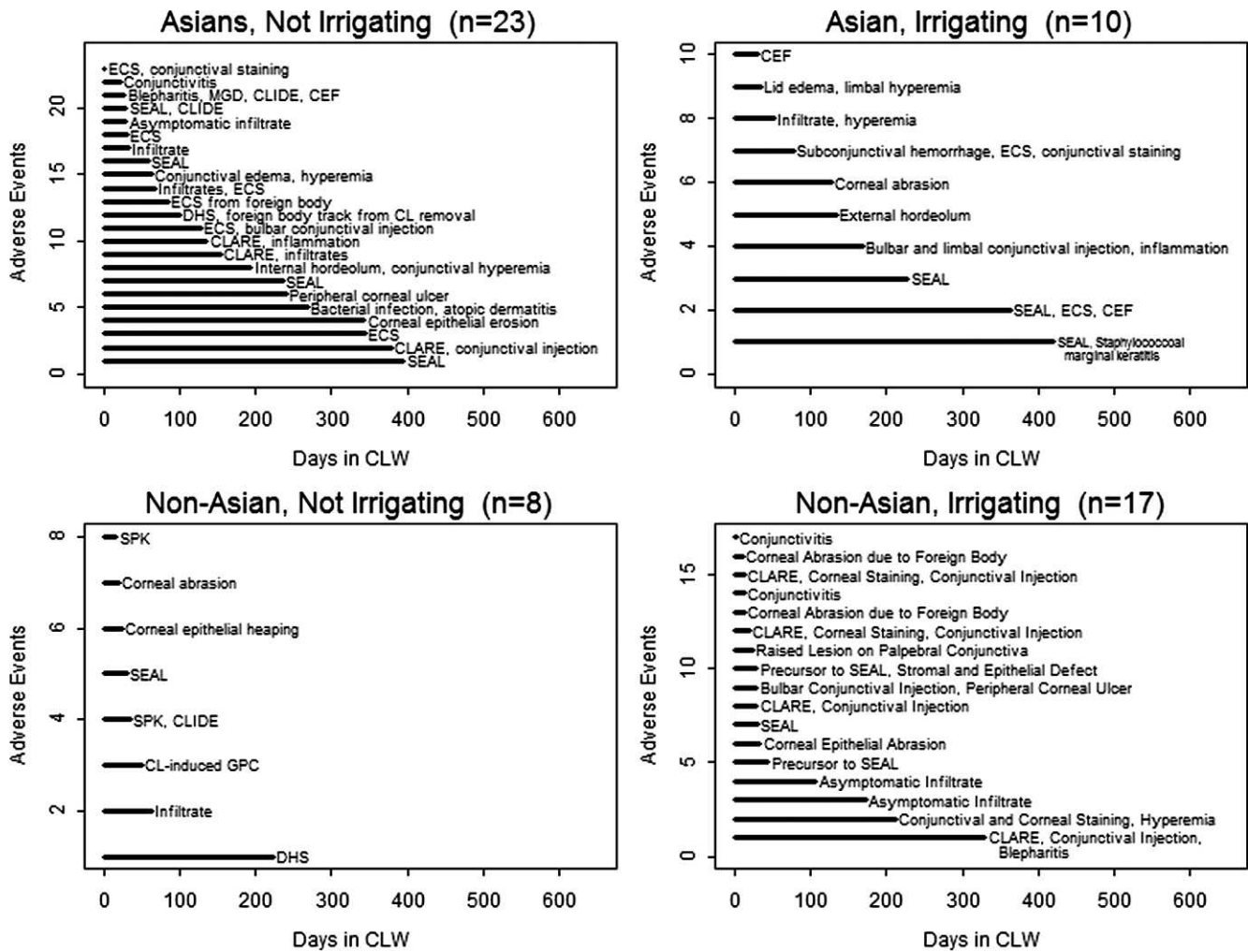


FIGURE 2. Details of the adverse events observed in subjects who did and did not irrigate up until time of onset, for Asians and non-Asians, along with the elapsed days in contact lens wear from baseline to time of onset.

ocular saline solutions, on  $P_{dc}$  measurements. Better understanding of the effects of retained ophthalmic topical solutions also may be important for scleral lens fitting as practitioners often opt to fill the concavity of a scleral lens with saline solution before insertion.

In addition to finding no improvement in  $P_{dc}$  with irrigation, we also found that irrigation was associated with an increased risk of inflammatory and lens-induced adverse events, and with a shorter mean time-to-event. It seems reasonable to hypothesize that a disruption of corneal epithelial barrier function could facilitate the onset of subsequent adverse events. In a post hoc analysis, we found that increased risk of lens-induced adverse events was significantly associated with higher baseline  $\ln(P_{dc})$ , with a CPH model  $P$  value of  $<0.001$  after taking into account the presence/absence of irrigation ( $P = 0.026$ ). The mean baseline  $\ln(P_{dc})$  among subjects who did not have a lens-induced adverse event was  $-2.353 \ln(\text{nm/s})$ , and among those who did have a lens-induced adverse event it was  $-2.029 \ln(\text{nm/s})$ , which difference was significant by  $t$ -test ( $P = 0.001$ ). We also examined the  $\ln(P_{dc})$  taken as close as possible in time before the onset of a lens-induced adverse event, for the 123 subjects who had had a  $P_{dc}$  measurement within 7 days before the event, and found it also to be significantly related to increased risk ( $P = 0.012$ ). Although these results are suggestive, this study did not permit us to examine rigorously the relationship

between  $P_{dc}$  and subsequent adverse events. In the first place, the time elapsed from baseline  $P_{dc}$  measurement to the onset of an adverse event differed among subjects and often was weeks or months, so that a causal link between the two would be somewhat speculative. Furthermore, it was not possible to obtain  $P_{dc}$  readings immediately before the onset of an adverse event for many subjects due to our study design, clinical considerations in performing an invasive measurement if an adverse event were suspected (e.g., through a subject's recounting of symptoms), and the fact that some adverse events had a relatively sudden onset and were assessed by our clinicians at unscheduled visits, so that  $P_{dc}$  before the event could not be obtained. Finally, the etiology of many adverse events in contact lens wear is multifaceted and complex, so that disentangling a causal effect of compromised  $P_{dc}$  from various contact lens, systemic, environmental, and behavioral factors would be very problematic. To our knowledge, no direct study of the potential relationship between corneal epithelial barrier function and subsequent adverse events has been possible to date. We currently are considering alternative study designs that may help to address this question.

The risk of inflammatory adverse events was higher in Asians than in non-Asians in the control group where daily irrigation was not applied. In contrast, applications of daily irrigation provide some level of protection to minimize insult caused by the physical presence of a contact lens on the Asian

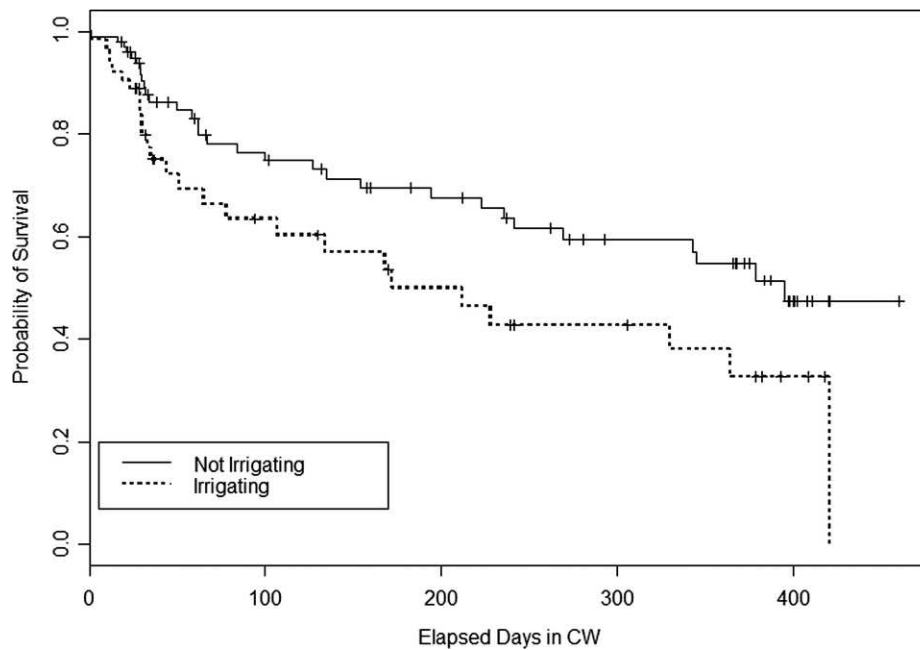


FIGURE 3. Kaplan-Meier survival curves depicting the probability of remaining free of an adverse event, for subjects who did and did not irrigate up until time of adverse event or censoring.

eye, while daily irrigation in non-Asian eyes caused these eyes to respond adversely to the practice. Why would different ethnic groups respond to the application of daily irrigation so differently (assuming there was minimal difference in compliance)? Why does daily irrigation seem to behave as a protective factor for one group, but not the other? Asians (on average) have a higher baseline  $P_{dc}$  to begin with,<sup>25</sup> and have other ocular surface characteristics that are different from non-Asians. Recently, we reported that cytokine concentrations vary significantly by ethnicity before and after overnight sleep (Lin MC, et al. *IOVS* 2013;54:ARVO E-Abstract 5403). Additionally, differences between Asians and non-Asians in the composition and physical properties of tears have been reported.<sup>33-38</sup> Such differences in inherent ocular surface integrity between these two racial/ethnic groups may be responsible, in part, for the known differences in ocular response to contact lens wear in general, and to daily irrigation during CW as described in this study. Future studies are needed to elucidate further the mechanisms that enable different homeostatic states at the ocular surface in different ethnic groups.

It is possible that the similar incidence of adverse events between non-Asians who irrigated and Asians who did not irrigate may be attributable to anatomic and physiologic differences, making irrigation more or less beneficial for each respective group. On average, Asians have smaller palpebral aperture sizes and tauter eyelid structures, and subsequently, a thinner postlens tear film with presumably reduced postlens tear flushing as compared with non-Asians.<sup>38</sup> In this study, irrigation would be most beneficial in the Asian group, inducing sufficient postlens tear turnover to replace stagnant tears, but with minimal corneal exposure to the potentially toxic effects of borate buffer. In contrast, laxer lids and larger aperture eyes on average among non-Asians allow for a thicker postlens tear film and possibly a larger inflow of the borate-buffered solution, and, thus, greater exposure of the cornea to toxicity. Thus, in the case of the Asian group, the relatively low level of tear flushing was sufficient to reduce unwanted substances under the lens but not sufficient to induce solution

toxicity; in the case of the non-Asian group, the prolonged exposure to greater volumes of the irrigation solution may have induced more toxicity and negated any possible benefits of irrigation.

In summary, this study has shown that 30-day CW results in a measurable increase in epithelial permeability. Risk of inflammatory and lens-induced adverse events also increase with CW. Daily irrigation with sterile saline solution did not mitigate increases in epithelial permeability or significantly decrease risk of adverse events in our subjects, and in fact, in our non-Asian subjects daily irrigation appears to have increased the risk of inflammatory adverse events. The results of this study suggested that chronic exposure of topical ophthalmic solution (including sterile saline) during CW should be recommended with caution as irrigation solutions cannot be considered a replacement of natural tears. Further study is needed to determine the best strategies to maximize postlens tear mixing and minimize ocular surface inflammation in wearers of soft contact lenses.

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