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Effects of Lens-Care Solutions on Hydrogel Lens Performance

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SIGNIFICANCE: Lens care multipurpose solutions (MPSs) can have varying effects on contact lens (CL) surface properties and the corneal epithelium.

PURPOSE: The aim of this study was to investigate the short-term effects of newer MPS on CL comfort and dryness, prelens tear-film stability, and ocular-surface health. *In vitro* study was also performed to assess the effect of MPSs on CL surface properties.

METHODS: Acuvue 2 CLs were soaked in control solution, Clear Care (CC), or test solutions: PureMoist, Biotrue, RevitaLens (RL), or saline solution (SS). Over four visits, subjects were exposed to control solution in one eye and to test solution in the contralateral eye for 2 hours using presoaked CLs. Contact lens comfort and dryness, ocular-surface health assessment, prelens noninvasive tear breakup time, and corneal epithelial permeability measured with fluorometry were assessed. Captive-sessile bubble technique evaluated CL wettability and viscous drag *in vitro*.

RESULTS: At 10 minutes, mean comfort \pm SD with PureMoist (76 ± 22) was lower than CC (86 ± 15 , $P = .02$), Biotrue (92 ± 9 , $P < .005$), RL (90 ± 13 , $P < .005$), and SS (90 ± 14 , $P < .005$). No other difference in comfort or dryness was noted. RevitaLens was associated with greater corneal epithelial permeability than CC ($P = .020$) and increased corneal staining compared with all MPSs ($P < .005$ for all). RevitaLens was also associated with longer prelens noninvasive tear breakup than CC ($P < .005$). *In vitro* results agreed with clinical findings of tear-film stability as RL reduced viscous drag. Contact lens surface wettability was enhanced by all MPSs in comparison to SS.

CONCLUSIONS: Differences of MPSs on the ocular surface were found *in vivo* and *in vitro*. RL caused the greatest corneal epithelium disruption but also associated with higher tear-film stability. The effect of MPSs on CL surface properties *in vitro* seems to reflect how MPSs altered prelens tear stability.

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Current multipurpose lens care solutions contain combinations of preservatives for disinfection, buffers to maintain pH, chelating agents to remove proteins, surfactants to remove lipid deposits, and wetting agents to improve comfort.¹ However, even with today's advances, the combination of these chemicals has been shown *in vitro* to induce corneal epithelial cytotoxicity, which leads to reduced cell viability, disrupted corneal epithelial tight junctions, and diminished defense against pathogens.^{2–5} *In vitro* studies also suggest that multipurpose solution may affect tear-film stability by altering lens-surface properties, which may influence contact lens comfort and dryness.^{6–9} Understanding how these *in vitro* observations translate *in vivo* may hold important implications for contact lens wearers.

In order to evaluate clinical performance of multipurpose solutions, it is important to first consider how it influences the corneal epithelium. The state of the cornea is most commonly assessed by slit-lamp biomicroscopy, focusing on the level of corneal staining observed after sodium fluorescein instillation. Studies using slit-lamp assessment have found that certain multipurpose solutions are predisposed to induce corneal staining, which may reflect increased inflammation and potentially influence wear comfort.^{10–13} However, this method is subjective, shown to have significant inter-observer variability and, most importantly, lacks the sensitivity to detect cellular-level changes.^{14,15} An alternate method of assessing corneal integrity is by using scanning fluorometry, which

measures the permeability of the corneal epithelium to fluorescein and is commonly accepted as a means to quantitate epithelial barrier function.^{14,16} The clinical significance of corneal epithelial permeability was suggested by Lin et al.,¹⁷ who demonstrated that greater corneal epithelial permeability during overnight contact lens wear was associated with increased risk of inflammatory and contact lens-induced adverse events.

Previous clinical studies have demonstrated that certain formulations among the older generation of multipurpose solutions can have a greater impact on corneal epithelial permeability, but similar investigations on the newer generation of multipurpose solutions (Biotrue, Opti-Free PureMoist, RevitaLens, and Clear Care) have not been done.^{18,19} Currently, there has been only one *in vitro* study on newer multipurpose solutions using cultured human corneal epithelial cells, which found that Biotrue had the least impact on cell viability and epithelial barrier function.²⁰ Nevertheless, *in vitro* models are unable to simulate the complex system involving interactions among various ocular-surface parameters; therefore, an *in vivo* study is warranted.³

In addition to ensuring that multipurpose solution is not adversely affecting corneal health, it is also important to consider how multipurpose solution affects contact lens comfort and dryness. Thus, it would be vital to understand if multipurpose solution influences prelens tear-film stability, as it is considered to play a critical role in lens-wear comfort.²¹ To understand this better, our

group previously used captive-sessile bubble technique for examining tear-lipid film—as it helps mediate prelens tear-film stability—and found that the newer generation of multipurpose solution could bind irreversibly to the tear-lipid film, making it less viscous and elastic.⁶ It was noted that Opti-Free PureMoist and RevitaLens caused more alterations to the tear-lipid-film interfacial properties, whereas Biotrue and Clear Care caused less pronounced and more reversible changes.⁶ This result suggests that multipurpose solutions could potentially alter prelens tear-film stability, but a clinical study is needed to elucidate the implications of our findings. In addition, as prelens tear-film stability depends on complex interactions of tear film and the contact lens surface, it would be important to conduct additional *in vitro* experiments to determine if multipurpose solutions alter contact lens surface properties.

Therefore, the goal of this study was twofold. First, a clinical study was conducted to investigate the short-term effect of newer multipurpose solutions on comfort, dryness, prelens tear-film stability, corneal epithelial permeability, and ocular-surface health. Second, *in vitro* experiments were done to ascertain the influence of multipurpose solutions on the properties of the contact lens surface.

MATERIALS AND METHODS

Part I: Clinical Study

Study Design

This was a prospective, double-masked, randomized, contralateral, crossover study. Eyes were exposed to each solution using a hydrogel contact lens material, and comparisons of comfort, dryness, prelens tear-film stability, ocular-surface health, and corneal epithelial permeability were performed. The study consisted of five visits; visit 1 was the baseline visit, and visits 2 to 5 involved solution exposure. Visits 1 and 2 were scheduled at least 1 day apart. Visits 2 to 5 were scheduled at least 1 week apart to ensure a sufficient washout period from contact lens and solution exposure.²²

For the entirety of the study, the same eye served as the control eye and was exposed only to the control solution. The test eye was exposed to each test solution in a randomized order. A stratified block randomization was used to determine the control eye, which eye would be measured first for noninvasive tear breakup time and corneal epithelial permeability, and the order of solution exposure. The randomization was stratified by ethnicity (East Asian and non-Asian). Subjects and technicians were masked from which solution the subject would be exposed to at each visit. To ensure proper clinician masking as contact lenses were stored in their manufacturer-provided cases, two clinicians were employed for this study. The first clinician inserted the contact lens, and the second, masked from the solution, assessed contact lens fit and ocular-surface health. Subjects completed all visits with the same technician and clinicians in order to minimize interobserver variability.

Study Population

Subjects were recruited from the University of California, Berkeley, and the surrounding community. Subjects taking systemic or ocular medication, or with a history of systemic or ocular disease or surgery, were excluded from the study. Only non-contact lens wearers, defined as individuals who had never worn contact lenses before or had discontinued contact lens wear more than 1 year prior to study participation, were recruited for this study. Habitual contact

lens wearers were excluded in order to minimize any confounding effects from their contact lens wear.

Subjects aged 18 to 39 years were eligible for the study and consisted of individuals who were of either East Asian or non-Asian descent. These two groups were chosen because Lin et al.²³ demonstrated that Asian subjects had increased corneal epithelial disruption and reported discomfort after multipurpose solution exposure when compared with non-Asian subjects. An interethnic difference in the subjective and objective response to contact lenses has also been reported.^{24–27} Individuals were considered to be East Asian if they were of Chinese, Taiwanese, Japanese, or Korean descent or a mixture of these ethnicities. Individuals were considered to be non-Asians if they were of European white, Latin American, or Spanish descent or a mixture thereof. Informed consent, with a complete description of the goals, risks, benefits, and procedures of the study, was obtained from all participants. This study observed the tenets of the Declaration of Helsinki and was approved by the University of California, Berkeley, Committee for Protection of Human Subjects.

Instrumentation and Measurements

Subjects were asked to complete a set of 100-point visual analog scales to rate comfort (0 = “poor and intolerable,” 100 = “excellent and cannot be felt”) and dryness (0 = “no sensation of dryness,” 100 = “extremely dry and intolerable”) for each eye. To account for possible errors while filling the 100-point visual analog scales, a staff member (who was not directly related to the study) reviewed the questionnaire to ensure that there were no obvious errors (e.g., excellent comfort with extremely dry). If an obvious error was noted, the staff member was instructed to ask the subject, in a nonleading manner, to double-check the erroneous answers. Forms processing application (Hewlett Packard TeleForm; Hewlett Packard, Palo Alto, CA) was used to measure and record subjects' response on the visual analog scale.

Anterior ocular-surface health was evaluated with slit-lamp biomicroscopy (SL120; Carl Zeiss Meditec Inc., Jena, Germany) under white light to ensure there was no evidence of active or preexisting ocular pathology (e.g., corneal scars, infiltrates, corneal epithelial irritation). Bulbar and limbal redness, corneal and conjunctival staining, palpebral redness, and roughness were assessed using the original Cornea and Contact Lens Research Unit grading scale. Corneal and conjunctival staining was assessed with sodium fluorescein (BioGlo Fluorescein Strips; HUB Pharmaceuticals, LLC, Rancho Cucamonga, CA) under cobalt blue illumination and viewed using a 530-nm yellow barrier filter.

Noninvasive tear breakup time was measured using the Medmont e300 corneal topographer (Medmont International Pty Ltd, Victoria, Australia), with the end point consisting of the first visible disruption noted on the placido mires or upon a blink. Noninvasive tear breakup time was measured three times per eye, alternating eyes between measurements, with a 1-minute break between each measurement. The Medmont e300 was also used to take corneal topography, and subjects were disqualified if there was more than a 1.00-diopter inter-eye difference in the horizontal or vertical meridian. This was to ensure that both eyes would have similar lens fits, thus minimizing any effect of lens fit on the study results.²⁴

A scanning fluorometer (Fluorotron Master, Ocumetrics, Mountain View, California) was used to measure tear film and stromal fluorescence to determine corneal epithelial permeability. Four

baseline measurements per eye were taken to determine autofluorescence. Two microliter of 0.35% topical sodium fluorescein were instilled on the ocular surface and 10 scans per eye were recorded over a 20-minute period. Each eye was then irrigated to remove residual tear-film fluorescein and four values per eye of stromal fluorescence were measured. Corneal epithelial permeability was calculated by dividing the baseline-corrected post-irrigation stromal fluorescence by the time integral of the tear-film fluorescence. The complete protocol for measuring corneal epithelial permeability has been published elsewhere.¹⁶ Measurements were done at the same time of day to account for diurnal variation and at least 2 hours awake to control for fluctuations in corneal epithelial permeability after awakening.²⁸ Following measurements on the scanning fluorometer, corneal staining using sodium fluorescein was assessed. If more than five punctate corneal staining spots were observed in the central cornea (3 to 4 mm), the measurement was considered invalid as excessive central staining could potentially bias estimates of corneal epithelial permeability.²⁹

Study Lenses and Care Regimens

The characteristics of the five lens care solutions used in the study are detailed in Table 1. Clear Care was the control solution in the study, as it has been shown to induce minimal effects on the ocular-surface integrity.^{12,30-33} Test solutions were PureMoist, Biotrue, RevitaLens and saline solution from Cleanoz. Although saline solution is not a multipurpose solution, it was included in the study to serve as a reference point to compare to other multipurpose solutions as it lacks preservative, buffer, surfactant or any additional agent.

A conventional hydroxyethylmethacrylate-based soft contact lens (Acuvue 2, Etafilcon A, Johnson & Johnson, New Brunswick, New Jersey) was used as a vehicle to deliver the solutions onto the ocular surface. We wanted the ocular surface to receive maximal exposure to multipurpose solution, which could be achieved with the Acuvue 2 lens due to its high water content.^{7,34} A single lens power (-0.50 diopters [D]) and base curve (8.3) were used to standardize volume of solution introduced to the eye. Contact lenses were prepared by soaking them in the solution, which was replaced daily, for 6 to 14 days (the varying days reflected when subjects were available for their next visit). This allowed adequate time to extract the blister pack solution and saturate the lens matrix with the lens-care solution.⁷ Manufacturer-provided lens cases were used with each solution to reflect real-world use and to minimize binding of preservatives to cases.¹⁹ Staff members prepared the study lenses while wearing sterile nitrile gloves to minimize contamination during lens handling. Subjects wore the contact lens and were exposed to each solution for 2 hours. This time was chosen because Garofalo et al.³⁵ had shown that maximum

solution-induced corneal staining occurred approximately after 2 hours. Subjects were allowed to wear their habitual spectacles over the contact lenses.

Study Protocol

Prior to the first visit, each subject was screened for eligibility. Ocular-surface disease index, visual analog scale, and Likert scale for comfort and dryness were administered to assess baseline ocular comfort. Subjects who indicated a strong baseline preference (on a 5-point Likert scale) in comfort and dryness for one eye or the other were disqualified. This was to ensure that any intereye difference in comfort and dryness would be primarily due to multipurpose solutions. In addition, anterior ocular health was assessed with slit-lamp biomicroscopy under white light to ensure a normal ocular surface, and corneal topography was done to confirm that subjects met study inclusion-criteria eligibility.

On the first visit, baseline values, without contact lens wear, were measured for each subject. Precorneal noninvasive tear breakup time was measured and was followed by a baseline measurement on corneal epithelial permeability with scanning fluorometry. Corneal staining was then assessed with slit-lamp biomicroscopy using sodium fluorescein. Visits 2 to 5 started with an anterior ocular health assessment with slit-lamp biomicroscopy without fluorescein to ensure a normal ocular surface, which was followed by precorneal noninvasive tear breakup time measurements. Presoaked contact lenses were inserted and allowed to settle for 10 minutes before subjects were asked to rate contact lens comfort and dryness. After 2 hours of lens wear, the subjects were again asked to rate contact lens comfort and dryness. A slit-lamp examination was then performed to assess contact lens wettability, surface quality, postblink movement, tightness, centration, and overall fit acceptance. Lens performance was assessed with a diffuser and eyepiece graticule under eight times' magnification. Wettability and surface quality were graded on a scale of 0 to 4. Movement was recorded to the nearest 0.1 mm. Lens tightness was assessed by digital push-up test and rated on a continuous scale from 0% to 100%. The methods for contact lens assessment are described in detail in Truong et al.²⁴ Prelens noninvasive tear breakup time was measured in each eye, and then contact lenses were removed and discarded. Thereafter, corneal epithelial permeability was measured with scanning fluorometry, and corneal staining was assessed with slit-lamp biomicroscopy using sodium fluorescein.

Part II: *In Vitro* Study: Lens-Surface Wettability, Friction-Drag Evaluations, and Protein Uptake

Lens preparation for *in vitro* wettability evaluations was identical to the one used for the clinical portion of this study. Modified sessile-captive bubble/drop configuration was used in a dynamic-cycling

TABLE 1. Preservatives and buffers in the five lens care solutions used in this study

Brand	Manufacturer	Preservative	Buffer
Clear Care	Alcon (Fort Worth, TX)	None	Phosphonic acid
Opti-Free PureMoist	Alcon (Fort Worth, TX)	Polyquad-1 0.001% and Aldox 0.0006%	Boric acid and sodium citrate
Biotrue	Bausch + Lomb (Rochester, NY)	Polyquad-1 0.0001% and Dymed 0.00013%	Boric acid and sodium borate
RevitaLens OcuTec	Abbott Medical Optics (Santa Ana, CA)	Polyquad-1 0.0003% and alexidine hydrochloride 0.00016%	Boric acid, sodium borate, and sodium citrate
Cleanoz 0.9% saline solution	UbiMed (Los Angeles, CA)	None	None

regimen.^{6,36} The details of the instrumentation: bubble/drop, lens holder designs, and sessile bubble methodology, can be found elsewhere.^{6,36} The magnification 1 mm = 140 pixels was used for detection of moving contact-line position and advancing-receding contact angles determination, with an accuracy of ± 0.01 mm and $\pm 1.0^\circ$, respectively. The lens and bubble/drop holders were immersed in either saline solution or dilute 1:10 multipurpose solution. For friction-drag measurements, a mineral oil drop was used instead of air bubble; contact angle and drop-edge positions were measured while the oil drop was expanded to cover approximately 50% of the entire lens surface. The initial drop volume, volumetric flow rate, and the gap between lens surface and drop holder were kept identical in all experiments to ensure equivalent dilatation rates for expanding interfaces between oil drop and contact lens.

Total model proteins uptake by Acuvue 2 lenses was quantified using colorimetric bicinchoninic acid protein assay. The protocol for protein uptake quantification was described elsewhere.^{6,36} Enhanced protocol (60°C, 30 hours) was used for Acuvue 2 lenses soaked for 2 hours in individual model protein solutions and regular protocol (35°C, 30 minutes) for lenses soaked in a three-model proteins mixture. An advantage of this method is that it is suitable for quantification of total protein uptake directly on contact lenses treated with bicinchoninic acid protein assay working reagent without any preliminary extraction.⁶ Calibrations were performed using hen egg white lysozyme, β -lactoglobulin, and mixture of lysozyme, β -lactoglobulin, and bovine mucin (weight ratio 2:1:0.1) solutions in buffered saline (all proteins were used as received from Sigma-Aldrich, St. Louis, MO). Spectrophotometry was used to determine light absorbance at wavelength = 562 nm (UCB2000 spectrophotometer; Ocean Optics, Dunedin, Florida). Each lens was placed in a separate scintillation vial containing 2 mL of bicinchoninic acid protein assay working reagent. The vials with lenses were agitated in thermostatic shaker at a speed of 100 to 120 revolutions/min for 30 minutes (1 hour) at temperature 35°C (60°C), then cooled down to room temperature. Light absorbance was measured in the same bottle using a DipTip optic dipping probe (World Precision Instruments, Sarasota, FL) under a 10-mm light path. Two blank lenses, one directly from blister and another presoaked in designated multipurpose solution or model tear electrolyte solution, were concurrently treated in the same way and used for background readings. The background values were subtracted from the readings of protein-soaked lenses, and total protein uptake was then calculated using calibration curves. Typically, 300 to 500 readings were taken for each sample; repeatability of signal was within ± 10 arbitrary units with an SD of ± 0.2 $\mu\text{g}/\text{sample}$. All *in vitro* measurements were computerized and were independent of observer variability.

Statistical Methods

A thorough exploratory and descriptive preliminary analysis was conducted by assessing bivariate plots and univariate models to examine for possible significant associations between explanatory and outcome variables, which guided how multivariate modeling was used. Upon reviewing residual plots in the models, values of prelens noninvasive tear breakup time, corneal epithelial permeability, and changes in corneal epithelial permeability (ratio of corneal epithelial permeability after solution exposure to baseline) were natural log transformed to better approximate normality in order to meet key assumptions for statistical modeling. The results were reported after back transformation. Student *t* test was used to compare control-solution pairs (e.g., Clear Care vs. PureMoist), with $P < .05$ considered as statistically significant. The P value

was adjusted using Tukey adjustment to avoid type I error when multiple comparisons were done to ascertain if there was a difference between test solutions (PureMoist, Biotrue, RevitaLens, saline solution). Multivariate mixed-effects modeling was used to account for repeated measures and to evaluate for any relationships between the different outcomes (comfort, dryness, prelens noninvasive tear breakup time, corneal epithelial permeability, ocular health) and multipurpose solutions, taking into consideration the effect from various factors such as demographics and contact lens fitting parameters. Mixed-effects model also accounted for the random effects from both subjects who had multiple measurements and the sequences of solutions. In the models, multipurpose solution was set as a primary fixed explanatory variable, which was composed of five distinct values (PureMoist, Clear Care, Biotrue, RevitaLens, and saline solution). A stepwise procedure was involved with reduced multivariate model selection procedure. Being alert with spurious relationship, a reevaluation of the factor was done in multivariate model to control the effects from other variables. The statistics of means and SDs reported in the table and plots were calculated from the raw data rather than the model estimates.

RESULTS

Subjects

A sample of 54 subjects was initially enrolled in the study following the screening visit. Fourteen subjects discontinued prior to study completion: one subject was disqualified because of excessive corneal staining following baseline corneal epithelial permeability measurements upon multiple attempts, one was disqualified because of unacceptable lens fit, nine discontinued because of scheduling conflicts, and three were lost to follow-up. A total of 40 subjects (24 female and 16 male subjects) with a mean age of 22 (SD, 3) years (range, 18 to 34 years) completed all five visits of the study. Ethnicities were evenly distributed between East Asian ($n = 20$) and non-Asian ($n = 20$) with baseline values listed in Appendix Table 1, <http://links.lww.com/OPX/A306>. Mean horizontal corneal curvature was 43.0 (SD, 1.4) D (range, 38.7 to 46.3 D), and mean vertical corneal curvature was 44.1 (SD, 1.3)D (range, 40.4 to 47.2 D).

Comfort and Dryness

Fig. 1 shows the mean comfort at 10 minutes and 2 hours for each control-test solution pair. After 10 minutes of wear, the only significant difference in comfort when assessing the control-test solution pairs was that PureMoist (76 ± 22) was less comfortable than Clear Care (86 ± 15 , $P < .005$). PureMoist was also less comfortable than the other test solutions: Biotrue (92 ± 9 , $P = .005$), RevitaLens (90 ± 13 , $P = .005$), and saline solution (90 ± 14 , $P = .005$). After 2 hours of wear, there was no difference in comfort when assessing the control-test solution pairs and when comparing the test solutions to each other. The only difference noted between the 10-minute and 2-hour comfort rating was PureMoist (76 ± 22 vs. 89 ± 17 , respectively; $P = .009$). There was no difference in dryness when assessing the control-test solution pairs and when comparing the test solutions to each other at 10 minutes and 2 hours. There was no difference between the 10-minute and 2-hour dryness rating for all solutions. No difference in comfort and dryness was noted in the intervisit response to Clear Care exposure. No significant difference in contact lens fit characteristics

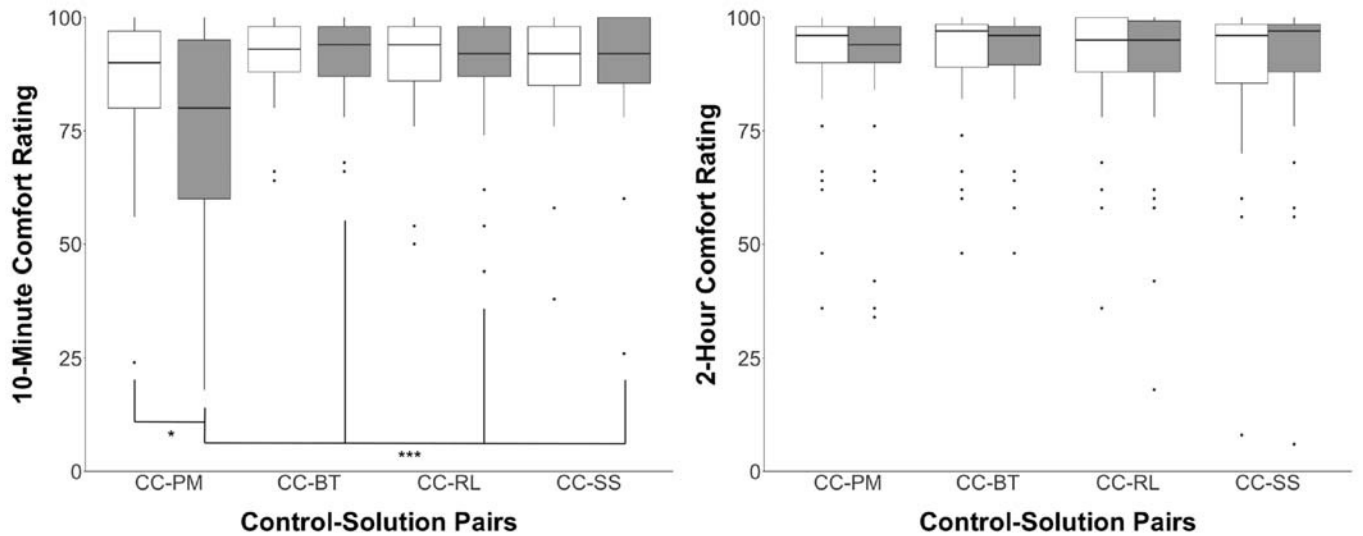


FIGURE 1. Box plot showing 10-minute (left) and 2-hour (right) contact lens comfort rating for each control-test solution pair, with a higher number representing greater comfort. For each control-test solution pair, the white box represents the control solution (Clear Care [CC]), and the gray box represents the test solution (PureMoist [PM], Biotrue [BT], RevitaLens [RL], or saline solution [SS]). * $P = .004$, *** $P = .005$.

was noted among multipurpose solutions. Appendix Table 2, <http://links.lww.com/OPX/A307> provides a summary of the *in vivo* data.

Multivariable mixed-effects analysis was performed on comfort and dryness with solutions as the fixed explanatory variable. Decreased comfort at 10 minutes was associated with exposure to PureMoist when compared with Clear Care, Biotrue, RevitaLens, and saline solution ($P < .005$). Decreased comfort was also associated with more dryness at 10 minutes ($P < .005$), as well as at 2 hours ($P < .005$). In the statistical models, comfort and dryness were not associated with lens fit characteristics, corneal staining, prelens noninvasive tear breakup time, corneal epithelial permeability, ethnicity, and gender.

Tear-Film Stability

Mean precorneal noninvasive tear breakup time was 7.0 ± 0.7 seconds. RevitaLens (4.2 ± 0.6 seconds) had a significantly longer prelens noninvasive tear breakup time than Clear Care (3.2 ± 0.4 seconds, $P < .005$). No difference was noted with the other test solutions. A normalized prelens noninvasive tear breakup time value was determined by taking the ratio of prelens noninvasive tear breakup time to precorneal noninvasive tear breakup time. This was done to better understand how the interaction of the multipurpose solution on the contact lens surface altered the baseline tear-film stability (without lens wear) for each subject. The normalized data showed the same trend, where tear-film stability was longer with RevitaLens compared with Clear Care ($P = .009$) (Fig. 2). No difference in normalized prelens noninvasive tear breakup time was noted in the intervisit response to Clear Care exposure. Multivariable analysis showed that a longer prelens noninvasive tear breakup time was correlated with exposure to RevitaLens when compared with Clear Care ($P < .005$) and saline solution ($P = .033$).

Corneal Epithelial Permeability

Effect on corneal epithelial permeability after solution exposure was measured in terms of absolute values and as the percent change in corneal epithelial permeability after multipurpose

solution exposure compared with the baseline corneal epithelial permeability. A total of five eyes (1 saline solution, 2 Biotrue, 2 RevitaLens) were excluded from analysis because of excessive corneal staining that was noted after corneal epithelial permeability measurement. Mean baseline corneal epithelial permeability was 0.027 (95% confidence interval, 0.024 to 0.031). Mean corneal epithelial permeability following multipurpose solution exposure was 0.025 (95% confidence interval, 0.020 to

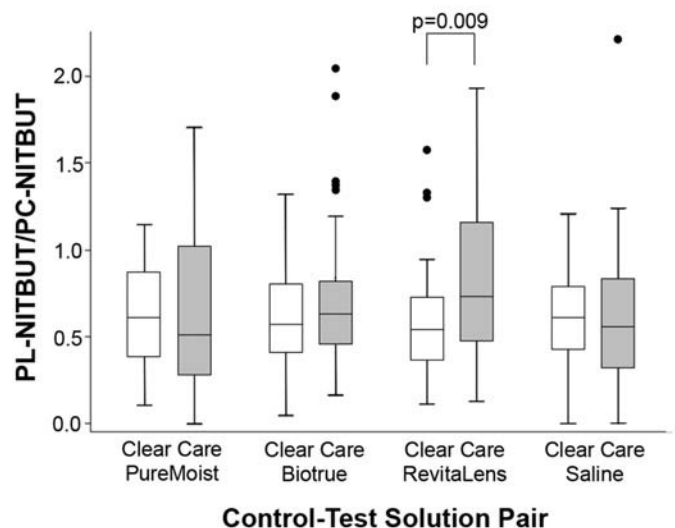


FIGURE 2. Box plot of the normalized prelens noninvasive tear breakup time, which is defined as the ratio of the prelens noninvasive tear breakup time (PL-NITBUT) and the precorneal noninvasive tear breakup time (PC-NITBUT), for each control-test solution pair. For each control-test solution pair, the white box represents the control solution (Clear Care), and the gray box represents the test solution (PureMoist, Biotrue, RevitaLens, and saline solution).

0.031) for PureMoist, 0.025 (95% confidence interval, 0.022 to 0.029) for Biotrue, 0.032 (95% confidence interval, 0.027 to 0.038) for RevitaLens, 0.026 (95% confidence interval, 0.022 to 0.031) for saline solution, and 0.025 (95% confidence interval, 0.020 to 0.031) for Clear Care. Among control-test solution pairs, RevitaLens had a significantly higher corneal epithelial permeability following multipurpose solution exposure than Clear Care ($P = .018$). No difference was noted with the other control-test solution pairs, and no difference was noted when the test solutions were compared with each other.

The percent change of corneal epithelial permeability from baseline was defined as the natural log of corneal epithelial permeability following multipurpose solution exposure/baseline corneal epithelial permeability. Positive percent change indicates increased corneal permeability compared with baseline, and negative change indicates decreased permeability from baseline. The mean percent change was -7% (95% confidence interval, -29 to 21%) for PureMoist, -6% (95% confidence interval, -26 to 20%) for Biotrue, 28% (95% confidence interval, 3 to 60%) for RevitaLens, -5% (95% confidence interval, -30 to 22%) for saline solution, and -13% (95% confidence interval, -31 to 11%) for Clear Care (Fig. 3). The only solution that resulted in increased corneal permeability was RevitaLens, and it was also the only test solution to be significantly higher than Clear Care ($P = .016$). No difference was noted when the test solutions were compared with each other. No difference in corneal epithelial permeability was noted in the intervisit response to Clear Care exposure. Multivariable analysis, after the effect of awake hours was controlled, found that a higher corneal epithelial permeability following multipurpose solution exposure was correlated with exposure to RevitaLens when compared with Clear Care ($P = .020$).

Ocular Surface Health

Aggregate scores for the type, depth, and extent of corneal staining were compiled by adding the score from all five grading regions (superior, inferior, temporal, nasal, and central) in the cornea

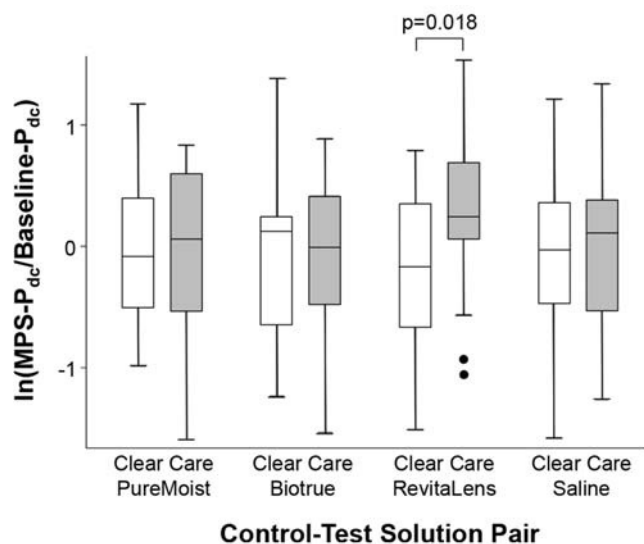


FIGURE 3. Box plot of percent change of corneal epithelial permeability after multipurpose solution exposure ($MPS-P_{dc}$) relative to baseline corneal epithelial permeability ($Baseline-P_{dc}$) for each control-test solution pair.

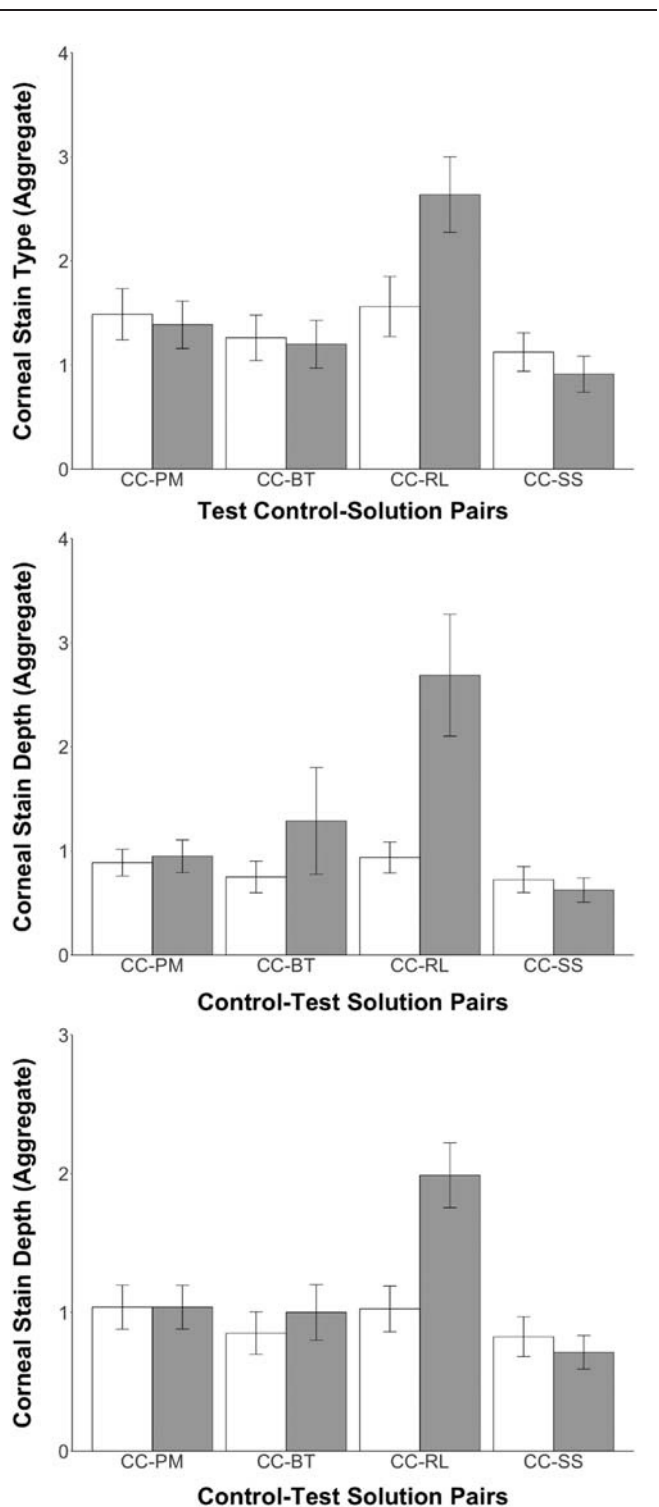


FIGURE 4. Bar graph of the aggregate scores for the type (top), depth (middle), and extent (bottom) of corneal staining for each control-test solution pair. For each control-test solution pair, the control solution (Clear Care [CC]) is in light gray, and the test solution (PureMoist [PM], Biotrue [BT], RevitaLens [RL], or saline solution [SS]) is in dark gray. For corneal staining type, RL had greater staining type compared with CC ($P = .02$) and with other test solutions ($P < .005$). For corneal staining depth and extent, RL had greater staining depth and extent compared with CC and with other test solutions ($P < .005$).

(Fig. 4). RevitaLens (2.7 ± 2.3) had a significantly greater type of staining than Clear Care (1.6 ± 1.8 , $P = .02$), PureMoist (1.4 ± 1.4 , $P < .005$), Biotrue (1.2 ± 1.5 , $P < .005$), and saline solution (0.9 ± 1.1 , $P < .005$). RevitaLens (2.7 ± 3.7) also had a significantly greater extent of staining than Clear Care (0.9 ± 0.9 , $P < .005$), PureMoist (1.0 ± 1.0 , $P = .005$), and saline solution (0.6 ± 0.7 , $P < .005$) and was borderline significant to Biotrue (1.3 ± 3.2 , $P = .07$). RevitaLens (2.0 ± 1.5) had a significantly greater depth of staining than Clear Care (1.0 ± 1.0 , $P < .005$), PureMoist (1.0 ± 1.0 , $P < .005$), Biotrue (1.0 ± 1.3 , $P < .005$), and saline solution (0.7 ± 0.8 , $P < .005$). There seemed to be an overall trend where saline solution had a lower degree in the type, extent, and depth of corneal staining than Clear Care, PureMoist, and Biotrue, although this was not found to be statistically significant

(P values ranging from .07 to .32). No other difference in corneal staining was noted when comparing the other solutions. No difference in corneal staining was noted in the intervisit response to Clear Care exposure. Quadrant-specific analysis revealed corneal staining type was significantly greater inferiorly ($P = .007$) and nasally ($P = .04$) with RevitaLens. For all solutions, no difference was noted in bulbar and limbal redness, conjunctival staining, and palpebral redness and roughness.

In Vitro Contact Lens Surface Properties after Multipurpose Solution Exposure

Fig. 5 shows the advancing water contact angle, surface tension, adhesion tension, and relative rate of mineral oil drop-edge propagation (defined as the propagation rate on contact lens

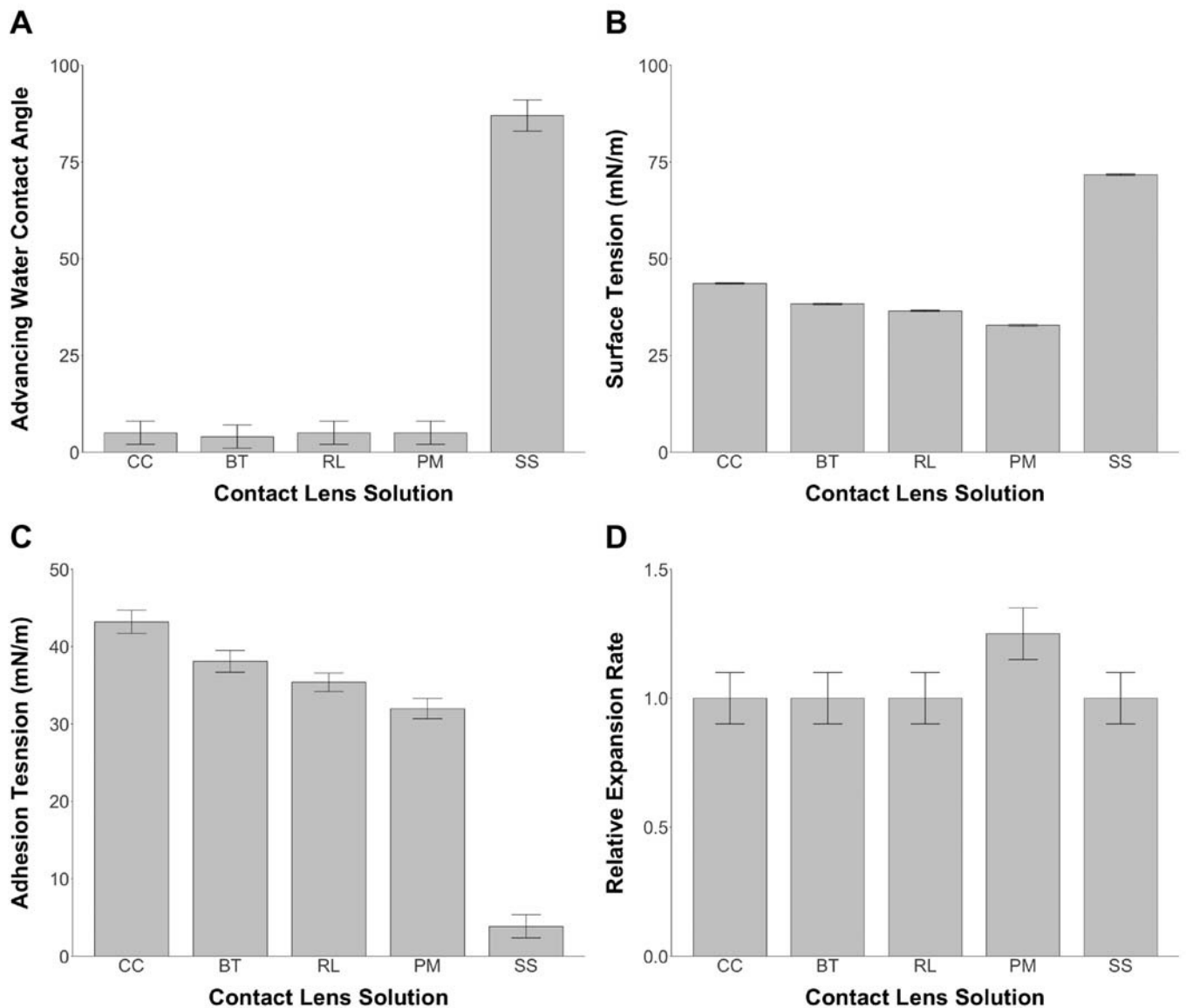


FIGURE 5. Bar graphs of the *in vitro* results for (A) water contact angle, (B) surface tension, (C) adhesion tension, and (D) relative expansion rate for multipurpose solutions (Clear Care [CC], PureMoist [PM], Biotrue [BT], RevitaLens [RL], or saline solution [SS]). Surface tension and adhesion tension are expressed in units of mN/m. Saline solution had greater water contact angle and surface tension and less adhesion tension compared with the other multipurpose solutions ($P < .005$ for all). PureMoist had a greater relative expansion rate than the other multipurpose solutions ($P = .013$). The error bars represent SDs of measurements.

soaked in multipurpose solutions divided by the propagation rate on contact lens soaked in blister pack solution) of the tested multipurpose solutions on the Acuvue 2 lens surface. Saline solution was found to have a significantly higher water contact angle (87 ± 4 degrees) and surface tension (71.1 ± 0.2 mN/m) compared with Clear Care (5 ± 3 degrees, 43.6 ± 0.2 mN/m; $P < .005$ for both), Biotrue (4 ± 3 degrees, 38.3 ± 0.2 mN/m; $P < .005$ for both), RevitaLens (5 ± 3 degrees, 36.5 ± 0.2 mN/m; $P < .005$ for both), and PureMoist (5 ± 3 degrees, 32.8 ± 0.2 mN/m; $P < .005$ for both). Saline solution was also found to have a significantly lower adhesion tension (3.9 ± 1.5 mN/m) compared with Clear Care (43.2 ± 1.5 mN/m, $P < .005$), Biotrue (38.1 ± 1.4 mN/m, $P < .005$), RevitaLens (35.4 ± 1.2 mN/m, $P < .005$), and PureMoist (32.1 ± 1.3 mN/m, $P < .005$). The water contact angle, adhesion tension, and surface tension of Clear Care, Biotrue, RevitaLens, and PureMoist were close to the blister pack solution (4 degrees, 44.2 mN/m, and 44.6 mN/m, respectively). Biotrue, PureMoist, Clear Care, and saline solution did not significantly change the relative rate of mineral oil drop-edge propagation, but RevitaLens had a 25 to 30% increased propagation rate ($P = .013$), indicating reduction of viscous/friction drag between lens surface and the mineral oil drop. Appendix Tables 3, <http://links.lww.com/OPX/A308>, and 4, <http://links.lww.com/OPX/A309>, provide a summary of the *in vitro* data.

The results of model protein uptake *in vitro* by Acuvue 2 lenses presoaked in different multipurpose solutions are summarized in Fig. 6. After accounting for *P* value adjustment in multiple comparison statistical testing, there was no significant difference among

multipurpose solutions in the uptake of the three-protein mix, lysozyme, and lactoglobulin by the presoaked contact lenses.

DISCUSSION

Multipurpose solution manufacturers are faced with a challenge in designing a solution that is biocompatible with the ocular surface but is also capable of disinfecting, cleaning, improving wettability, and preventing contact lens surface deposits.¹ Manufacturers have made progress, but our study suggests that there are variances among new generations of multipurpose solutions, which may hold important implications for comfort and ocular-surface integrity in contact lens wearers.

In this study, the only difference in comfort among multipurpose solution was the greater discomfort noted in PureMoist after 10-minute exposure that was not seen after 2 hours, likely due to most of the leaching-out of the contact lens and subsequently draining with tear flow. It is important to note that the differences in discomfort observed in this study not only demonstrate statistical significance but also are clinically significant. Papas et al.³⁷ previously reported that a 7- to 8-point difference on a 100-point questionnaire was considered to be a just-noticeable difference in terms of subject preference. Therefore, the 10-point comfort difference for the 10-minute exposure between PureMoist and Clear Care and the 13-point comfort difference between the 10-minute and 2-hour exposure to Clear Care represent a tangible difference for patients. The lack of difference in contact lens comfort and dryness

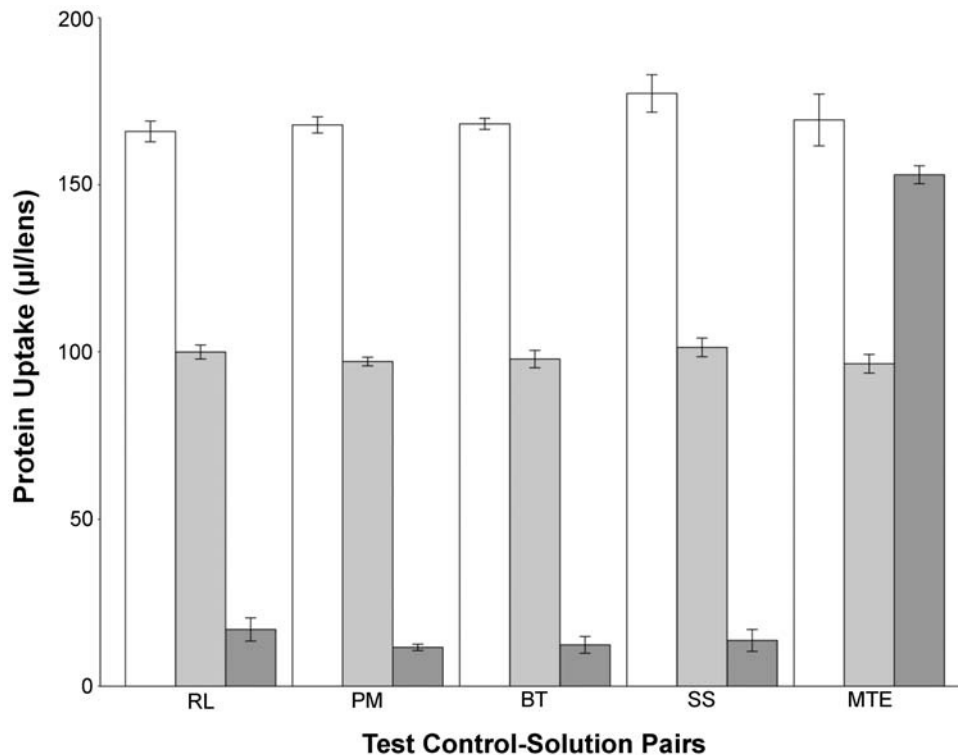


FIGURE 6. Bar graph of the protein uptake (in $\mu\text{g}/\text{lens}$) in three-protein mix (white bar), lysozyme (light gray bar), and lactoglobulin (dark gray bar) for multipurpose solutions (PureMoist [PM], Biotrue [BT], RevitaLens [RL], or saline solution [SS]) and model tear electrolyte solution (MTE). The error bars represent SDs of measurements.

at 2 hours among multipurpose solutions may have been due to only minor differences noted in prelens noninvasive tear breakup time. Nevertheless, the initial difference in comfort may be due to multipurpose solution ingredients that the eye considers irritant, with preservatives a likely culprit.^{38,39} Compared with the other multipurpose solutions, PureMoist contains the highest concentration of Polyquad (polyquaternium 1) and a relatively high concentration of Aldox (myristamidopropyl dimethylamine). Tilia et al.³⁸ reported there were more burning and stinging upon insertion with lens presoaked in Polyquad-Aldox compared with Polyquad-alexidine. Willcox et al.³⁹ also reported burning and stinging with Polyquad-Aldox. However, a study on long-term use of multipurpose solution by Young et al.⁴⁰ found that polyhexamethylene biguanide-containing systems were associated with greater discomfort than Polyquad-containing systems. It is difficult to know the exact reason for the discrepancy in comfort during short- and long-term use, but it warrants further investigation because it may provide information on how the ocular surface adapts to chemical irritants.

As a way to improve comfort, manufacturers have included additional compounds to their formulations to minimize discomfort and dryness. Therefore, it was surprising that saline solution, which contains no chemicals besides sodium chloride, had comparable comfort and dryness to the other solutions. Saline solution has pH value of 6.7, which is in contrast to the pH of the other multipurpose solutions: 7.8 for PureMoist, 7.3 for Biotrue, 7.7 for RevitaLens, and 6.7 for Clear Care.^{9,41} Furthermore, even though saline solution has the same pH as Clear Care, Clear Care and the other multipurpose solutions contain buffers, which act to control pH fluctuations during lens storage and lens wear. The pH of the ocular surface has been measured from 7.14 to 7.82 using a pH microelectrode.^{9,41} Based on this, saline solution should have been viewed as less comfortable because it was more acidic, below the lower limit of natural human-tear pH range, and lacked a buffer to manage fluctuations in pH. It is possible that any mild irritation caused by acidic nonbuffered saline was equivalent to the chemical irritation of buffered multipurpose solutions. This finding warrants further research into the relative contribution of pH and chemical components on ocular-surface comfort. In addition, this finding should not prompt advocacy for the off-label use of saline solution as a contact lens care solution because it would undoubtedly increase the risk of infections and other adverse events. Instead, it argues that it may be possible for manufacturers to lower the concentration of certain compounds in multipurpose solution without compromising comfort.

An example of the potential issues can be seen with buffers, which help in controlling and maintaining constant pH; studies suggest that some of them may contribute to increased disruption of corneal epithelial tight junctions.^{2,42} Boric acid buffer has been identified as the most disruptive based on studies done by Imayasu et al.,^{2,42} which found that it contributed to higher cytotoxicity and a diminished resistance against *Pseudomonas aeruginosa* when compared with a phosphate buffer. Other studies have been unable to show the same association.^{20,43} It is interesting to note that our findings showed that only one of the three multipurpose solutions containing boric acid buffer (RevitaLens) showed increased corneal epithelial permeability and corneal staining compared with Clear Care, which has a phosphate buffer. This is in agreement with Dassanayake et al.,⁴⁴ who also found increased corneal staining with RevitaLens.

Because RevitaLens does not contain boric acid as a buffer, the pharmacokinetic properties of alexidine may be responsible for the

observed increase in corneal epithelial permeability and corneal staining.⁴⁴ The propensity of preservatives that enter and accumulate in contact lens matrix is based on their respective charges and the preservative's molecular size relative to the contact lens pore size.^{7,9,45} Etafilcon A (Acuvue 2) is an ionic polyhydroxyethylmethacrylate hydrogel lens (Federal Drug Administration group IV) that contains polymethacrylic acid, which has negatively charged anionic groups on the lens surface that attract water and other positively charged solution components. The major preservatives in the studied multipurpose solutions are all cationic (as are the surface-active additives in these multipurpose solutions) and will have a propensity to adhere to the Acuvue 2 lens surface because of electrostatic attraction.³⁶ In this case, the major factor that influences pharmacokinetics may be attributed to the molecular weight of the preservative, with alexidine having a significantly lower molecular weight (582 g/M) than Polyquad-1 (810 g/M) and polyaminopropyl biguanide (2670 g/M). As a result, alexidine likely has a greater proclivity to be absorbed and then released by the contact lens compared with the other preservatives. As the contact lenses in this study were soaked for approximately 7 days, it is probably the speed and amount of preservative released into an eye that contributed to increased corneal compromise with RevitaLens. There is a strong possibility that this effect is different with silicone hydrogel lenses because they have more compact polymer matrix with lower water content, have smaller pore sizes, and are mostly nonionic.⁴⁶

Although there was not a significant difference in corneal staining between saline solution and the other multipurpose solutions (besides RevitaLens) in short-term use, there was an overall trend suggesting that saline solution contributed to less epithelial change of the cornea. It is possible that a longer exposure would lead to a larger difference in corneal staining between saline solution and the other multipurpose solutions. This may hold an important implication for patients who use inhalation saline solution (similar to the Cleanoz saline solution) off-label as a scleral lens insertion solution. Another factor to consider is the state of corneal health in the study cohort. It is conceivable that the possible adverse effects of chemicals present in ophthalmic solutions (e.g., buffered saline solution) are likely not an issue for patients who have a healthy cornea but could be a potential issue for patients with existing cornea pathology (e.g., keratoconus, pellucid marginal degeneration), especially with the increased length of solution exposure during scleral lens wear. A long-term study is warranted to confirm the possible benefits (e.g., better ocular-surface comfort and health) from the lack of chemicals in saline solution use during soft and scleral lens wear. This could potentially help inform manufacturers in the potential benefits of decreasing the concentration of certain components in multipurpose solutions.

Even though this study found a correlation between the increased corneal staining and corneal epithelial permeability noted with RevitaLens, it is important to delineate the difference between corneal staining and corneal epithelial permeability because there is still conflicting evidence regarding their relationship and their implications on ocular health.^{18,19,47} Epithelial barrier function evaluated by fluorometry measures the amount of fluorescein that penetrates through the epithelium and remains after all excess fluorescein is washed.¹⁶ There are multiple proposed explanations of epithelial corneal staining visualized with sodium fluorescein, namely, (1) fluorescein pooling in areas of epithelial erosions, (2) paracellular movement of fluorescein due to damaged tight junctions, (3) transcellular diffusion due to damaged surface glycocalyx followed by movement through gap junctions,

(4) solution-induced corneal staining, and (5) preservative-associated transient hyperfluorescence.^{48,49} Although the exact relationship between corneal epithelial permeability and corneal staining is not completely understood, there is still compelling evidence to suggest that less corneal disruption (in terms of either corneal epithelial permeability or corneal staining) is attributed to a lower rate of complications during contact lens wear.^{17,48,50}

Although RevitaLens was linked with the greatest level of corneal epithelial compromise, the stabilizing polymers and other components found in RevitaLens were associated with improved tear-film stability. In some ways, this contradicts the study done by González-Méijome et al.,⁵¹ which argued that tear-film stability may be more dependent on the characteristics of an individual's tear film than on multipurpose solutions. It should be noted that their study used a different instrument (Keeler Tearscope) to assess prelens noninvasive tear breakup time; they used a silicone hydrogel contact lenses, and most important, it was measured after 10 hours of contact lens wear. It is likely that the effects of multipurpose solutions on tear-film stability predominantly occur during the initial period of contact lens wear, whereas tear-film composition plays an increasingly important role over time as the solution leaches out of the contact lens. In a cohort of young and healthy individuals, the 1- to 2-second difference noted in prelens noninvasive tear breakup time between lens care solutions is likely not clinically significant. Nevertheless, the effect of a 1- to 2-second difference may be more profound among symptomatic contact lens wearers or for those with a compromised ocular surface from meibomian gland dysfunction or aqueous deficiency.

Interestingly, our results seem to differ from our previous *in vitro* study that found that PureMoist and RevitaLens, compared with

Clear Care and Biotrue, caused the greater changes in interfacial rheological properties of tear-lipid layer, making tear-film destabilization more likely.⁶ It is important to note that prelens tear-film stability is defined by the interactions between the tear film as a whole, not just by the lipid layer, and our additional *in vitro* investigation suggests that multipurpose solutions may alter contact lens surface properties. The results indicate that the change in tear-film stability is unlikely to occur because of water-advancing angle, surface tension, and adhesion tension variations but could be due to the effect of multipurpose solutions on reducing friction drag, which was assessed by relative expansion rate. We developed the friction-drag evaluation of mineral oil over a contact lens as an *in vitro* model to mimic the spreading process of the lipid film on top of a thin aqueous layer of solution on a contact lens. Our results determined that RevitaLens showed the lowest viscous drag between mineral oil drop and the surface of the Acuvue 2 lens, which may translate into the improved prelens noninvasive tear breakup time observed with RevitaLens. Therefore, measuring relative oil-drop expansion rates over the surface of a contact lens immersed into different aqueous media *in vitro* might be used to characterize prelens tear-film stability and possibly to predict contact lens performance *in vivo*.

We assessed the effects of lens-care solutions by delivering the maximum volume of solution to the ocular surface using a single polyhydroxyethylmethacrylate-based hydrogel lens type and found that differences existed among multipurpose solutions studied. A study assessing longer exposure time may be important in order to determine the effects of prolonged exposure. As the use of newer multipurpose solutions has become more common, this study provides insights to help clinicians offer evidence-based recommendations to their patients.

ARTICLE INFORMATION

Supplemental Digital Content: Appendix Table A1, the baseline values of the subjects in the study, is available at <http://links.lww.com/OPX/A306>. Appendix Table A2, results from the *in vivo* portion of the study with the multipurpose solutions (Clear Care, PureMoist, Biotrue, RevitaLens, or saline solution [SS]), is available at <http://links.lww.com/OPX/A307>. Each trial represents a control-test solution pairs (e.g., Clear Care vs. PureMoist); the order of the trial for each subject was based on a randomization table. Appendix Table A3, results from the *in vitro* portion of the study examining the influence of the multipurpose solutions on the contact lens surface in terms of surface tension, advancing water contact angle, adhesion tension, and expansion rate, is available at <http://links.lww.com/OPX/A308>. Surface tension and adhesion tension were measured in terms of millinewton per meter. Appendix Table A4, results from the *in vitro* portion of the study examining how multipurpose solutions and model tear electrolyte solution affect protein uptake, which was measured as microgram per lens, is available at <http://links.lww.com/OPX/A309>.

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