The Impact of Soft Contact Lens Attributes on Symptoms Associated With Digital Eye Strain in Symptomatic Soft Contact Lens Wearers

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TITLE: The impact of soft contact lens surface and optics on symptoms associated with digital eye strain in symptomatic soft contact lens wearers

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INVESTIGATION SITE: Indiana University

STUDY OVERVIEW

Eye fatigue is a growing concern for the vision community. In large part, this eye fatigue is thought to be exasperated by digital device use, which permeates most all of everyone's lives including work and play. Upwards of three-quarters of the general population may express symptoms of eye fatigue, yet may not know that it is not normal, or that there may be methods to reduce or eliminate eye fatigue. Despite its prevalence, the ocular causes of eye fatigue or unknown and may be related to the cornea/contact lens surface, the accommodative system, the convergence system, overall postural/muscle fatigue, or a combination of these or other causes. The current study aims to systematically investigate the incremental benefits in ameliorating eye fatigue provided by (a) an optimized contact lens spherical prescription, (b) a lens with highly wettable surface, and (c) a lens with optics to aid the accommodative and convergence systems (in addition to a highly wettable lens surface).

PROTOCOL SYNOPSIS

KEY OBJECTIVE	1. Subject-reported eye fatigue (0-100 rating scale)
KEY ENDPOINTS	Superiority (change) of subject-reported rating >8 rating units
STUDY DESIGN	The proposed study design is a subject masked, 2 x 2 randomized, crossover (with a baseline reference) comparing the difference in fatigue rating relative to baseline, where the baseline the is the response for subject habitual lenses, with optimized power, worn on their typical (e.g. 2 week, 1 month) replacement schedule. The study design is balanced for residuals with four sources of variation: lens, sequence group, period and participant. To adjust for individual differences prior to study entrance, difference scores will be used as response variables in the analyses. The same number of participants will be randomized to each of two possible lens sequence groups: {A, B}, {B, A}. Baseline will be evaluated prior to any testing of A and B. Specifically, A and B are: Baseline = Subject habitual lenses, with optimized power, habitual replacement A = DAILIES TOTAL 1 sphere (DT1) B = DAILITES TOTAL 1 MULTIFOCAL (DT1 MF) Subjects will be randomized into two equal groups of those that have each of the two sequences ({A, B}, {B, A}) (balanced Latin Square design).
STATISTICAL CONSIDERATIONS	
Sample size	N=42
Hypothesis	1. Subject-reported eye fatigue difference scores (lens A – baseline) comparing the change in response for lens A to baseline are <0 (i.e. fatigue rating was improved with lens A over baseline). This hypothesis tests if a lens with enhanced surface (DT1) provides better fatigue ratings than a typical lens without an optimized surface (optimized habitual). 2. Subject-reported eye fatigue difference scores (lens B – baseline) comparing the change in response for lens B to baseline are <0 (i.e. fatigue rating was improved with lens B over baseline). This hypothesis tests if a lens with enhanced surface and enhanced optics (DT1 MF) provides better fatigue ratings than a typical lens without an enhanced surface or enhanced optics (optimized habitual). 3. Subject-reported eye fatigue difference scores (lens B – lens A) comparing the difference in response for lens B to lens A are <0 (i.e. fatigue rating was improved with lens B over lens A). This hypothesis tests if a lens with enhanced surface AND enhanced optics (DT1 MF) provides better fatigue ratings than a lens with only enhanced surface (DT1) characteristics.

Data analysis	SAS PROC MIXED (or R LMER) to fit linear mixed effects model to the normalized ratings data.
TEST COMPARATOR PRODUCTS	Baseline = Subject habitual lenses, with optimized power, habitual replacement A = DAILIES TOTAL 1 sphere B = DAILITES TOTAL 1 MULTIFOCAL
INCLUSION/EXCLUSION CRITERIA	1. Self-reported "eye fatigue" at least once per week attributable to digital device use with baseline. 2. Uses a digital device (phone, tablet, computer, etc) at least 4 hours per day 3. Mobile digital device with active data and text plan, able to receive email and text messages 4. Habitual 2-week or monthly silicone single vision hydrogel soft contact lens use; habitually wearing lenses for 6 or more hours per day for 5 or more days per week for the past 30 days 5. Habitual soft contact lens prescription optimized over-refraction within ±0.25 D 6. 18-35 years of age 7. No history of issues of eye alignment or binocularity by self-report 8. No doctor diagnosed, self-reported accommodative or binocular vision issues 9. No doctor diagnosed, self-reported ocular surface disease or dry eye requiring regular, ongoing treatment 10. The subject must appear able and willing to adhere to the instructions set forth in this clinical protocol. 11. Vertex corrected refractive cylinder must be -0.75 or less. 12. Visual acuity best correctable to 20/25 or better for each eye 13. The subject must read and sign the Informed Consent form. 14. No active conditions that may prevent soft contact lens wear. 15. Not habitual wearer of any of the test lenses. 16. Photopic pupil size >=4 mm (normal room illumination ~100 cd/m2)
OFF LABEL	No.
CLINICAL SUPPLIES REQUESTED FROM ALCON	DAILIES TOTAL 1 sphere DAILITES TOTAL 1 MULTIFOCAL
RESULTS DISSEMINATION	Work will be presented at least one international meeting, such as Global Specialty Lens Symposium or ARVO. The work will also be prepared for submission for peer-reviewed publication (e.g. Optometry and Vision Science). Trade publications may also be prepared at Sponsor's request and expense.
CONFLICT OF INTERST	None.

PROPOSAL SUMMARY

STUDY DURATION	1 year

DURATION OF IRB APPROVAL	1 year
GCP TRAINING	Received; 2016-01-12
TYPE OF STUDY	Single center
FUNDING FROM OTHER SOURCES	None.

RATIONALE AND SIGNIFICANCE:

According to a recent survey by the Vision Council, nearly 90% of Americans use digital devices for more than 2 hours per day, with average use around 8 hours. Results from this same survey indicate that as many as 65% of Americans experience symptoms of eye fatigue as a result of digital device use (Vision Council 2016). Recent work by our group (Kollbaum ARVO 2016) indicates that in another typical population 76% of the population suffer from symptoms of eye fatigue, and frequency of reported eye fatigue was similar whether individuals wore soft contact lenses or not. However, of those that wore soft contact lenses, they were more likely to describe their eye fatigue as a feeling of "dryness", whereas non-soft contact lens wearers were more likely to describe their eye fatigue as a feeling of "strain". Despite these differences, however, this result indicates that soft contact lenses are not generally the cause of eye fatigue reported (e.g. reported eye fatigue is more than just contact lens related dryness), and if not the cause, could they be the treatment? Recent work by our group (Kollbaum ARVO 2016) has also identified that sufferers of eyestrain most frequently use descriptors of straining, dryness, and tiredness. This work also found that the sufferers of eyestrain can consistently differentiate and group the symptoms of eyestrain into 3 clusters of global (e.g. headache), surface (e.g. dryness), and optical (e.g. blurring) sensations. This result provides confidence that the "affects" of eyestrain are known and that they are the main components of eyestrain. With this knowledge, work on identifying the potentially multifaceted cause and possible treatments can then occur in a systematic way. For instance, DAILIES TOTAL 1 is a lens with unique surface characteristics that are hypothesized to minimize symptoms of dryness. Accordingly, can it ameliorate reported symptoms of eye fatigue, specifically the surface symptom components of eyestrain? Alternatively, could the optical manipulations provided by DAILIES TOTAL 1 Multifocal ameliorate both the surface and optical sensations sufferers experience?

Furthermore, a recent double-masked, randomized, bilateral cross-over study of pre-presbyopic subjects (Orsborn GSLS 2016) indicates that when two lenses of the same material are compared, one with typical single vision optics and one with optimized optics to decrease accommodative need, individuals report no change in the surface or dryness component of their eye fatigue, but do report a decrease in the optical components of eye fatigue (such as straining). Accordingly, DAILIES TOTAL 1 multifocal, as a single use lens with optimized surface qualities and optimized optics, may be a lens capable of ameliorating eye reported eye fatigue by acting on both the surface and optical sensations that are believed to be the largest components of eye fatigue (Kollbaum 2016).

The current proposal briefly outlines potential strategies to systematically investigate the questions highlighted above. If the results are favorable, the results may serve to help practitioners understand how the DAILIES TOTAL 1 family of products may help ameliorate symptoms of digital eye fatigue.

AIM: To quantify the real-time subject-reported fatigue in symptomatic, non-daily replacement silicone hydrogel soft contact lens wearers and the change in symptomology associated with change to DAILIES TOTAL 1 (sphere), DAILIES TOTAL 1 multifocal (LO Add), relative to normal replacement of habitual lens.

1. No diagnosis of dry eye or ocular surface disease
2. Corneal plane cylinder less than or equal to 0.75 D
3. No diagnosis of any accommodative or convergence problem

METHODS:

STUDY DESIGN: The proposed study design is a subject masked, 2 x 2 randomized, crossover (with a reference) comparing the difference in fatigue rating relative to baseline, where the baseline the is the response for subject habitual lenses, with optimized power, worn on their typical (e.g. 2 week, 1 month) replacement schedule. The study design is balanced for residuals with four sources of variation: lens, sequence group, period and participant. To adjust for individual differences prior to study entrance, difference scores will be used as response variables in the analyses. The same number of participants will be randomized to each of two possible lens sequence groups: {A, B}, or {B, A}. Baseline will be evaluated prior to any testing of A and B. Specifically, A and B are:

Baseline = Subject habitual lenses, with optimized power, habitual replacement
A = DAILIES TOTAL 1 sphere
B = DAILITES TOTAL 1 MULTIFOCAL

Note: To be included in the study, subject-reported eye fatigue at least once per week with baseline (optimized habitual lens, habitual replacement schedule) is required.

Subjects will be randomized into two equal groups of those that have each of the two sequences ({A, B}, {B, A}) (balanced Latin Square design).

At first visit additional baseline, demographic data, and data will be collected. Over refraction will be performed to determine the optimal habitual prescription. Subjects will then be dispensed a new pair of their habitual lenses to be worn on their same replacement cycle. Subjects will, however, not be told that they were given new lenses, but rather to think that these lenses are the same as the ones they brought in. Daily patient-reported outcome measures will be collected for 7 days ±3 days) of wear.

At the follow-up visit, the subject will be rescreened to assure they still meet the enrollment criteria. If so, in-office measures will be performed. The subject will then be randomized to DT1 sphere or DT1 MF Lo add. Each lens will be worn daily for 7 (±3) days. After 7 (±3) days in-office measures will be collected, and the next lens dispensed. There will be 4 visits in all.

Visit 1 = baseline/dispense new optimal habitual on normal replacement schedule
Visit 2 = follow-up habitual/dispense pair 1
Visit 3 = follow-up pair 1/dispense pair 2
Visit 4 = follow-up pair 2/exit

SUBJECTS

Enrollment criteria:

1. Self-reported “eye fatigue” at least once per week WITH OPTIMIZED HABITUAL LENS attributable to digital device use
2. Uses a digital device (phone, tablet, computer, etc) at least 4 hours per day
3. Mobile digital device with active data and text plan, able to receive email and text messages
4. Habitual 2-week or monthly silicone single vision hydrogel soft contact lens use; habitually wearing lenses for 6 or more hours per day for 5 or more days per week for the past 30 days
5. Habitual soft contact lens prescription optimized over-refraction within ±0.25 D
6. 18-35 years of age
7. No history of issues of eye alignment or binocularity by self-report
8. No doctor diagnosed, self-reported accommodative or binocular vision issues

9. No doctor diagnosed, self-reported ocular surface disease or dry eye requiring regular, ongoing treatment
10. The subject must appear able and willing to adhere to the instructions set forth in this clinical protocol.
11. Vertex corrected refractive cylinder must be -0.75 or less.
12. Visual acuity best correctable to 20/25 or better for each eye
13. The subject must read and sign the Informed Consent form.
14. No active conditions that may prevent soft contact lens wear.
15. Not habitual wearer of any of the test lenses.
16. Photopic pupil size >=4 mm (normal room illumination ~100 cd/m2)

SAMPLE SIZE DETERMINATION

The comparison of interest is DT1 sphere and DT1 MF Lo add, so the sample size calculation was based on detecting a difference between these 2 lenses.

1. The proposed study design is a 2 x 2 crossover design balanced for residuals with four sources of variation: lens, sequence group, period and participant. The same number of participants will be randomized to each of two possible lens sequence groups: {A, B}, {B, A}. Because each lens is preceded by every other lens exactly twice we can check for lens carryover effects; if the carryover effect is the same for each lens type, these effects cancel when comparing differences in lens means.
2. The primary outcome measures are difference in subjective ratings for the current trial lenses normalized to the ratings made at baseline wearing habitual lenses, i.e., ratings will be assessed using an integer scale of 0-100 with semantic anchoring and the rating at baseline will be subtracted from the rating made with each one of the three trial lenses.
3. Ideally, the sample size analysis would incorporate 'known' estimates of the mean, variance and (autoregressive) covariance of subjective ratings for the habitual and each of the three study lenses measured in a comparable experimental design to the proposed three-arm crossover study. Here, we rely on ratings data from previous CORL studies to inform the power analysis. Specifically, we have typically observed (1) individual differences in baseline ratings with habitual lenses, (2) period effects such that ratings that are, on average, lower and also more variable at follow-up assessments, and (3) moderate to strong within-participant correlations in ratings assessed with different study lenses. A limitation of the previous data is that that we have typically observed non-significant LENS*PERIOD interactions in the fitted linear mixed regression models. So, for the current analysis, we base the effect size for the *a priori* power analysis on a desired (i.e., clinically relevant) pairwise difference of 9 units in subjective rating. Previous data suggests that the expected variability (σ) in ratings during follow-up assessments is ~15-19 rating units with correlations ranging from 0.50-0.60.
4. To arrive at the initial (unadjusted) sample size estimate, we performed a power analysis for a within-participants comparison of the mean difference in the normalized ratings (i.e., change re: rating at baseline wearing pristine habitual lens) for two study lenses. Specifically, although we will initially fit linear mixed effects models to the data and obtain least-squares estimates of the pairwise mean differences in rating, we can the required sample size to power a *paired-samples t test* for normal (continuous) mean difference

Note that the paired-sample t test assumes normally distributed data and requires N ≥ 2. The test statistics are

$$t = N^{1/2}\left(\frac{\bar{d}-\mu_0}{s_d}\right) \sim t(N-1,\delta) \text{ or, equivalently, } t^2 \sim F(1,N-1,\delta^2)$$

where $\bar{d}$ and s_d are the sample mean and standard deviation of the differences, and

$$\delta = N^{1/2}\left(\frac{\mu_{diff}-\mu_0}{\sigma_{diff}}\right) \text{ and } \sigma_{diff} = (\sigma_1^2 + \sigma_2^2 - 2\rho\sigma_1\sigma_2)^{1/2}$$

represent the non-centrality parameter and standard deviation of the paired difference scores, respectively.

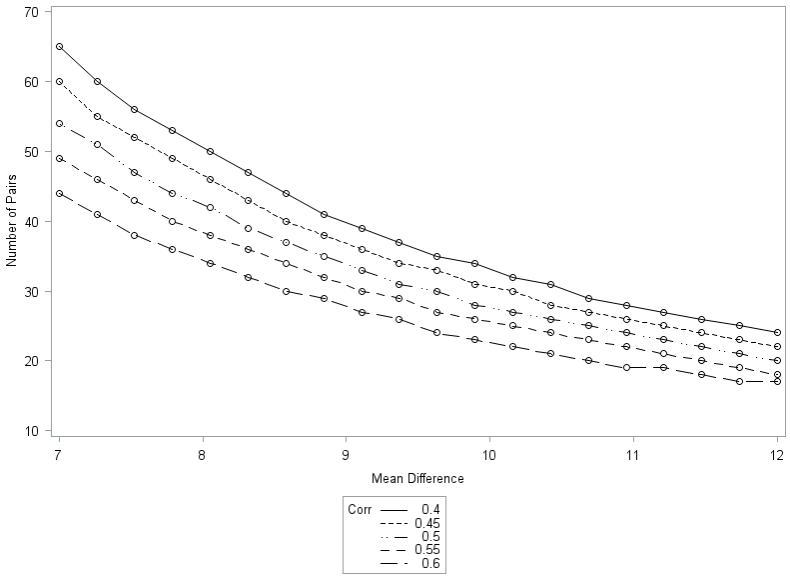
5. Our calculation assumed a standard deviation of 18 rating units. With equal variances, the estimated $\sigma_{diff} = (\sigma_1^2 + \sigma_2^2 - 2\rho\sigma_1\sigma_2)^{1/2} = 18\sqrt{2*(1-\rho)}$. We varied both the sample mean between 7 and 12 units in steps of 1 unit and the within-participant correlation between 0.40 and 0.60 in steps of 0.05 to compute the number of pairs of observations needed to achieve a minimum of 80% power at significance level of α=0.05 and a non-directional test (Ho ≠ 0 mean difference)**. Table 1 and Figure 1** show the results under this scenario. In **Table 1**, rows corresponding to a mean rating difference of 9 units are enclosed in the box. For correlation of 0.50, the estimated number of participants required to detect a moderate effect size of 9/18=0.50 is 34. Because we want to balance the design for residuals, a total sample size of N=36 (unadjusted for dropout) is needed to assign 6 participants to each sequence group. To detect the same effect size with slightly weaker correlations the sample size should be increased to N=42. **Figure 1** shows that rating differences ≥ 9 units could be detected for correlations ≥ 0.40 with sample of 40 or fewer participants.

Table 1

	Computed N Pairs			
Index	Mean Difference	Correlation	Actual Power	N Pairs
1	7	0.40	0.805	65
2	7	0.45	0.807	60
3	7	0.50	0.801	54
4	7	0.55	0.803	49
5	7	0.60	0.805	44
6	8	0.40	0.803	50
7	8	0.45	0.803	46
8	8	0.50	0.803	42
9	8	0.55	0.803	38
10	8	0.60	0.803	34
11	9	0.40	0.804	40
12	9	0.45	0.806	37
13	9	0.50	0.808	34
14	9	0.55	0.810	31
15	9	0.60	0.814	28
16	10	0.40	0.806	33
17	10	0.45	0.801	30
18	10	0.50	0.809	28
19	10	0.55	0.802	25
20	10	0.60	0.812	23
21	11	0.40	0.812	28

22	11	0.45	0.815	26
23	11	0.50	0.818	24
24	11	0.55	0.802	21
25	11	0.60	0.804	19
26	12	0.40	0.815	24
27	12	0.45	0.811	22
28	12	0.50	0.807	20
29	12	0.55	0.802	18
30	12	0.60	0.822	17

Figure 1



Based on this, we aim to enroll 44 subjects, so as to complete 42 throughout the study duration.

LENSES

The spherical power of all corrections will be monocularly, distance vision optimized. Specifically, lens powers may not be the same for all types of lenses, due to power-targeting during manufacture, on-eye flexure, etc. Optimization entails providing the lens for each eye that monocularly provides an objective improvement in acuity and up to -0.25 D more for any patient-reported quality improvement. All lenses will be over-labeled, so as to, as best as possible, preserve masking (less blister pack shape). Of note, subjects will not be able to tell the difference between DT1 and DT1 MF (Lo add) because of the same blister shape, but may be able to tell a difference between these and habitual.

OUTCOME MEASURES

Primary:

1. Subject-reported eye fatigue (0-100 rating scale, 0=optimal)

STATISTICAL ANALYSIS

Our primary analysis will use SAS PROC MIXED (or R LMER) to fit linear mixed effects model to the normalized change from baseline ratings data. Because the proposed design is balanced for residuals we could fit the data using PROC GLM if there are no missing data to obtain identical parameter estimates. A separate model will be fit to the data for each rating scale tested. All four sources of variation (lens, sequence group, period and participant) will be included as class variables. We will also test for a carryover effect by including a character-valued variable whose value represents the lens worn in the previous period ('0' assigned to the carryover variable for the first period). Thus, the initial models used to analyze the data include effects for sequence group, lens, period and the overall carryover. Participant-within-sequence group will be included as a random effect. Although LSMEANS due to lens will not be estimable in these models, differences between trial lenses are if we assume the carryover effect is the same for each lens type. Evidence of a significant Lens-by-Period interaction will be handled by running separate analyses within each period using, for example, a *two-sample independent samples t-test.*

The analysis will not specifically make p-value adjustment for multiple testing as the comparisons are planned in advance. The omnibus in an (M)ANOVA or parameter estimates for a factor in a Linear Mixed-Effects regression model provide the protection against "family-wise" error, i.e., once the omnibus test (or saturated model) detects an effect at say alpha=0.05, doing subsequent pairwise comparisons on different levels of the factor(s) can no longer generate a false alarm (Type I error)!

Having said that, as a follow-up, exploratory technique, we may also use Dunnett's method for performing all pairwise comparisons of the means and other margins across levels of our categorical variables (e.g., lens) after model estimation. This method adjusts the p-values and confidence intervals for multiple comparisons involving a fixed reference category (i.e., the control lens).

PUBLICATION PLAN: Work will be presented at least one international meeting, such as Global Specialty Lens Symposium or ARVO. The work will also be prepared for submission for peer-reviewed publication (e.g. Optometry and Vision Science). Trade publications may also be prepared at Sponsor's request and expense.

TIMELINE: (estimated)

Contract approval: unknown, estimate 1 month

Human subjects approval: 1 month, concurrent to above

Project setup: 1.5 month, concurrent to above

Recruitment: 1 month

Data collection: 3 months

Data analysis: 3 months

Report writing: 3 months