Changes in Symptoms of Midday Fogging with a Novel Scleral Contact Lens Filling Solution

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SIGNIFICANCE: Midday fogging of scleral contact lenses requires frequent lens removal and reapplication for a large portion of lens wearers. Using a lens filling solution that mimics the composition of tears is hypothesized to have an impact on the production of material trapped under a scleral lens.

PURPOSE: The purposes of this open-label study were to assess the safety of a scleral lens filling solution, which closely approximates the ionic concentration and pH of human tears, and to assess signs and symptoms of midday fogging with this formulation and with subjects’ habitual sodium chloride solutions.

METHODS: Existing scleral lens wearers with midday fogging (N = 22) were examined and completed surveys of symptoms. Subjects filled the concavity of their current lenses with test solution and were assessed immediately and approximately 4 hours later for safety monitoring. Test solution was dispensed and used for 5 to 9 days when subjects were reexamined and repeated the surveys. Biomicroscopy and anterior optical coherence tomography images were used to assess midday fogging objectively.

RESULTS: The median (interquartile range) Ocular Surface Disease Index score decreased from 27.1 (21.7) U when using habitual filling solution to 9.1 (20.1) U when using the test solution (P = .006). Current Symptoms Survey findings with the test solution compared with habitual solution resulted in statistically significant decreases in burning/stinging (P = .04), grittiness/foreign body sensation (P = .01), dryness (P = .002), blurry/fluctuating vision (P = .002), and overall pain/discomfort (P = .006). Objective assessment of corneal staining and fogging revealed decreases that were not statistically significant in this small sample size.

CONCLUSIONS: This study establishes the safety and subject tolerance of a scleral lens filling solution that mimics the ionic composition of human tears. Significant improvements in subjective ratings, although likely biased in this unmasked trial, suggest that further studies of the effectiveness of this solution in reducing midday fogging are warranted.

Modern scleral lenses, which vault the cornea of the eye and have great benefit in correcting irregular astigmatism, have seen a surge in use over the past two decades with the availability of highly oxygen-permeable lenses. Many patients report improved vision and comfort with scleral lenses compared with previous lens modalities; however, many wearers report having to remove their lenses during the day because of clouding of vision, a phenomenon referred to most commonly as midday fogging. The vaulting nature of scleral lenses requires solution, typically saline, to be placed into the concavity of the lens before it is applied to the ocular surface, creating a post-lens fluid reservoir. This relatively large reservoir is not active in tear exchange in the same manner as occurs with a small diameter corneal contact lens, leading to the possibility of various substances becoming trapped behind the lens. A survey of scleral lens wearers conducted by the Scleral lenses in Current Ophthalmic Practice Evaluation group found that 26.1% of patients wearing scleral lenses (n = 264) reported midday fogging.

A study by Carracedo et al. showed an increase in the turbidity of the post-lens tear layer of patients with keratoconus wearing scleral lenses that had been filled with a saline containing preservative over a span of 6 to 9 hours after lens insertion. Schornack and Nau found that the optical density of the post-lens tear reservoir doubled when evaluating normal eyes wearing scleral lenses after 2 hours of wear. A study by Walker et al. evaluated post-lens tear samples with and without fogging. Analysis suggested that lipid was present in those samples classified as turbid (Walker et al. Global Specialty Lens Symposium 2014). A recent study found the presence of leukocytes to be greater in scleral lens wearers who experience midday fogging, hypothesizing that this finding is related to hypoxia or inflammation in these patients.

In addition, there is no consensus on what is considered an ideal scleral lens fit by practitioners, with conflicting studies showing reduced midday fogging when scleral lenses are fit to match the exact scleral curvature, and other studies finding that lenses fit less tightly and therefore promoting tear exchange had longer periods of wear without midday fogging (McKinney et al. IOVS 2013;54: ARVO E-Abstract 5483).
A study by Rismondo et al.9 determined that sodium, potassium, calcium, magnesium, and chloride ions are all present in human tears. Bachman and Wilson10 examined the amount of light scattered from the epithelial surface of an excised rabbit cornea with an in vitro specular microscope while the epithelium was bathed in different solutions. Corneas bathed in a solution of only sodium chloride resulted in more surface light scatter, and therefore greater cell sloughing than those corneas bathed in a buffered solution containing sodium, potassium, calcium, magnesium, and chloride ions. Given that the composition of the filling solution typically trapped under a scleral lens consists of sodium chloride ions, the results of the just-described study suggest that saline could be increasing corneal cell sloughing, with the resulting cellular debris causing potentially significant midday fogging. The increased sloughing of epithelial cells with typical saline formulations may be further exacerbated by the vaulting properties of a scleral lens. Studies have shown that, without the eyelid pressure of a normal blink across the ocular surface, normal epithelial cell exfoliation cannot occur, trapping this debris under the lens.11–13

In this study, a novel solution that has been designed to mimic the composition of the tears and the pH of the normal ocular surface was tested for safety.14 Although the study design is not masked, assessments were made to evaluate the impact of this solution on signs and symptoms of midday fogging.

### METHODS

This open-label study (ClinicalTrials.gov identifier, NCT03380624) conformed to the tenets of the Declaration of Helsinki and was conducted under the approval of the Institutional Review Board of the Ohio State University. All subjects provided written consent before the start of the study. The open-label design was necessary in order to assess clinical ocular compatibility and the test solution was compared to the control, habitual scleral lens insertion solution (sodium chloride) used by the subject for all assessments including signs and symptoms of midday fogging.

Table 1 lists the formulation for the test solution, which is designed to be physiologically similar to the pH and electrolyte composition of the tear film. The study was conducted in two parts. The first cohort of patients (n = 11) used the nonpreserved test solution as prescribed and prepared by a compounding pharmacy in 3-mL dose containers. The second cohort of patients used the same nonpreserved formulation as prepared by a commercial compliant Blow-Fill-Seal manufacturer (ASept Pak Inc., Malone, NY) in 10-mL dose containers. Twenty-two unique individuals completed the study, with eight subjects participating in both cohorts. Of the data collected for subjects who repeated the study, only the first study visit was analyzed for outcome measure results.

The primary safety outcome measure was slit lamp examination of the ocular anterior segment. Secondary outcome measures were subjective assessment of ocular symptoms using the Ocular Surface Disease Index and Current Symptoms Survey. The Ocular Surface Disease Index survey was used to grade overall ocular surface symptoms in both eyes, and the Current Symptoms Survey assessed each eye separately using a visual analog scale in which subjects marked a location on a horizontal line, which corresponded to the level of each of the following symptoms: burning or stinging, grittiness or foreign body sensation, dryness, blurriness or fluctuating vision, and overall ocular pain or discomfort. These subjective assessments were completed with the habitual scleral solution at the baseline visit and were assessed again after using the test solution at the final study visit.

Clinical grading of midday fogging by slit-lamp biomicroscope and anterior optical coherence tomography was performed for an objective measures of midday fogging after a grading system of the amount of particulate present with the following scale: 0, none; 1, trace; 2, easily noticeable; 3, moderate; 4, heavy; and 5, dense. Optical coherence tomography instrumentation used in this study was a Visante OCT (Carl Zeiss Meditec, Dublin, CA) and a higher-resolution Cirrus OCT (Carl Zeiss Meditec, Dublin, CA). A procedure was developed such that all optical coherence tomography images were collected and masked before being viewed by graders. Two graders assessed the optical coherence tomography images and graded them on a scale of 0 to 5 on the density of particulate visible between the posterior surface of the scleral lens and ocular surface. Any images that received different grades from the graders were then put through an adjudication process to determine a final grade. The graded images were then unmasked for statistical analysis.

### Study Design

This study consisted of two visits on the first study day to assess the first exposure to the test solution and an additional study visit 7 to 9 days after daily use of the test solution (Fig. 1). To participate, subjects were screened to determine if they experienced foggy or cloudy vision, had to remove their scleral lenses during the day to see better, or had been told by their eye doctor that fogging was present when wearing their lenses. Potential subjects were required to have been wearing a scleral lens with a stable fit for at least 3 months. Initial study visits were scheduled at a time in which participants could wear their lenses for at least 4 hours continuously before being examined. After consenting to participate in the study, subjects were asked to answer questions regarding their habitual solution and habitual scleral lens wear. All subjects reported using a nonpreserved saline solution containing sodium chloride. Subjects completed the Ocular Surface Disease Index survey and Current Symptoms Survey surveys, visual acuity was measured, subjects were examined with a slit-lamp biomicroscope to assess lens fit and ocular health and to grade the presence of fogging, and optical coherence tomography images were collected. The ocular surface was examined again after the lenses were removed.

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**TABLE 1. Unit dose vials sterile fill (% wt/volume)**

| Component                  | % wt/volume |
|----------------------------|-------------|
| Sodium chloride            | 0.73        |
| Calcium chloride           | 0.0068      |
| Potassium chloride         | 0.051       |
| Sodium phosphate dibasic   | 0.3530      |
| Magnesium chloride         | 0.0023      |
| Purified water             |             |
| pH                         | 7.2–7.6     |

Osmolarity by freezing point or vapor pressure 300 to 325 mOsmol/L.
The initial exposure to the test solution, filling the concavity of the scleral lens and applying the lens to the eye, was monitored in the office with a slit-lamp biomicroscope after the solution was used. There were no adverse events, and all subjects were released and instructed to return in approximately 4 hours or sooner if fogging occurred. Upon the return of the subject, visual acuity was measured, and a slit-lamp biomicroscopic assessment of the ocular health, lens fit, and fogging was completed. There were no adverse events, and each subject was dispensed enough vials of test solution to fill their lenses for the next 5 to 9 days, with extra solution if needed. All used and unused solution bottles were to be kept and returned at the final study visit.

The final study visit was scheduled 5 to 9 days after the initial test solution visit. This visit was scheduled at approximately the same time of day as the first visit for comparison of fogging when using the different solutions with the same lens wear time. Subjects completed the Ocular Surface Disease Index survey and Current Symptoms Survey based on their symptoms while using the test solution during the study and were also allowed to make comments about their experience with the test solution. Visual acuity was measured; subjects were examined with a slit-lamp biomicroscope to assess lens fit, ocular health, and the presence of fogging; and optical coherence tomography images were collected. Lenses were removed, and the ocular surface was examined without lenses.

Statistical Analysis
Statistical analysis included paired t tests of objective assessments of logMAR visual acuity, corneal staining, and grading of fogging by examiner and by masked optical coherence tomography grading. The majority of the symptom survey responses were not normally distributed (Anderson-Darling); therefore, subjective grading of Ocular Surface Disease Index and Current Symptoms Survey symptoms was analyzed with the Wilcoxon signed rank test. Agreement between masked graders of optical coherence tomography was assessed with Fleiss κ statistics.

RESULTS
Twenty-two unique individuals (8 female, 14 male) completed the study, with eight subjects participating in both cohorts. Twenty subjects were wearing scleral lenses because of a diagnosis of keratoconus. One subject wore scleral lenses for diagnoses of both
keratoconus and keratoconjunctivitis sicca. One subject wore scleral lenses because of a diagnosis of exposure keratopathy secondary to lagophthalmos and had a history of photorefractive keratectomy in both eyes. For all assessments, unless otherwise noted, data compared were for the right eye unless the subject wore only a scleral lens in the left eye. When overall study data were discussed, those subjects who repeated the study were assessed using the data collected at their first visit.

**FIGURE 2.** Median and interquartile range of symptoms assessed when using the habitual and test solution. Symptoms were measured with the OSDI (A) and CSS to assess for burning/stinging (B), grittiness/foreign body sensation (C), overall pain/discomfort (D), blurry/fluctuating vision (E), and dryness (F). The CSS assesses each symptom on a visual analog scale from 0 to 100. Each fenced box plot displays the median and interquartile ranges for survey responses. The solid center line represents the median, with the upper and lower edges of the box representing the 75th and 25th percentiles, respectively. The upper and lower whiskers represent the upper and lower extremes. CSS = Current Symptoms Survey; OSDI = Ocular Surface Disease Index.
Part 1 Results

In the initial safety and feasibility portion of the study, 11 subjects (6 male/5 female adults) completed the study. Nine subjects wore scleral lenses in both eyes, and two subjects wore a scleral lens in one eye. No subjects returned early for complaints of fogging for their same day assessment or their final study visit. Assessment of superficial punctate keratitis was the same or less for all subjects when assessed after use of the test solution compared with their habitual solution. Mean high contrast visual acuity when using the habitual and test solutions was not statistically different in this small group. Results of symptom assessments were not normally distributed and were analyzed with Wilcoxon signed rank testing. Comparisons of Current Symptoms Survey assessments with the habitual solution and the test solution revealed statistically significant improvements in grittiness/foreign body sensation ($P = .04$) and blurry/fluctuating vision ($P = .04$). Symptoms of burning/stinging ($P = .05$), dryness ($P = .06$), and pain/overall discomfort ($P = .05$) approached significance. The Ocular Surface Disease Index was completed by 10 of the 11 subjects. The median (interquartile range) Ocular Surface Disease Index score when using the habitual filling solution was 25.0 (23.1) U compared with 7.3 (16.8) U for subjects when using the test filling solution, with a statistically significant median change of 10.41 ($P = .01$). No subjects experienced any adverse events, and it was determined feasible to proceed with using commercially produced vials for further testing.

Overall Study Results

The following analysis of 22 unique participants includes the initial 11 subjects who used the test solution as prepared by a compounding pharmacy and 11 additional subjects who used the same nonpreserved formulation as prepared by a commercial Blow-Fill-Seal manufacturer.

Visual Acuity and Ocular Surface

High-contrast visual acuity measured while subjects were using their habitual saline solution was not statistically different from high-contrast acuity when using the test solution. Ocular surface assessments of staining revealed a numerical decrease in mean (standard deviation) staining when using the test solution 0.5 (0.8) compared with the habitual saline 0.7 (0.8), although the change was not statistically significant ($P = .09$). Eleven subjects had a lower staining grade when assessed after use of the test solution. Eight subjects had no change in staining when comparing use of the habitual and test solutions. Three subjects had a higher staining grade when assessed after use of the test solution. All changes assessed were less than two grades of difference in corneal staining.

Symptoms

Subjects assessed symptoms with the Current Symptoms Survey by grading each eye individually. For analysis, the right eye of each subject was used unless only the left eye wore a scleral lens. Scores for symptoms did not yield normal distributions; therefore, nonparametric statistical analysis was used to compare subjective symptom scores when using habitual solution with symptoms when using the test solution. Box plots showing the median and interquartile range of these symptom grades can be found in Fig. 2. Wilcoxon signed rank testing of the median values revealed statistically significant differences in the symptoms for burning/stinging ($P = .04$), grittiness/foreign body sensation ($P = .01$), dryness ($P = .002$), blurry/fluctuating vision ($P = .002$), and overall pain/discomfort ($P = .006$). Similarly, the median (interquartile range) Ocular Surface Disease Index score with use of habitual solution was 27.1 (21.7) compared with test solution 9.1 (20.1), revealing a statistically significant difference in scores between the two solutions ($P = .006$). Median scores with interquartile ranges and median changes in symptoms with the habitual and test solutions can be found in Table 2. The eight subjects who repeated the study showed similar improvements in median changes in Ocular Surface Disease Index and all Current Symptoms Survey symptoms assessed when they completed the study with the second cohort.

Assessment of Fogging by Examiner

Examiner grading of particulate present during slit-lamp biomicroscope examination found 1 subject had an improvement from 4 to 1, 7 subjects improved by one grade level, 10 subjects had the same level of grading with both solutions, and 4 subjects had worsening of fogging by one grade level when comparing findings with the habitual solution to those with the test solution. The mean (standard deviation) fogging grade when using the habitual solution was 1.9 (0.9), and the average fogging grade when using the test solution was 1.6 (0.8). This decrease in fogging when assessed by slit lamp was not statistically significant ($P = .2$).

Assessment of Fogging with Optical Coherence Tomography

Grading of the two sets of optical coherence tomography images showed agreement of 41.14% ($P < .0001$, Fleiss $\kappa$) for two graders when evaluating the images collected using the Visante OCT and 30.88% ($P = .01$, Fleiss $\kappa$) when grading those of the Cirrus OCT. Any images that were not graded identically were adjudicated by having both graders view the projected images simultaneously. Discussion between the graders then resulted in a consensus grade.

| TABLE 2. Median (interquartile range) of subjective assessments of symptoms associated midday fogging with scleral lens wear |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | OSDI             | CSS: burning/stinging | CSS: grittiness/foreign body sensation | CSS: dryness | CSS: blurry/fluctuating vision | CSS: overall pain/discomfort |
| Medial score (IQR) with habitual saline | 27.1 (21.7) | 1.5 (8.8) | 3.5 (16.5) | 15.3 (40.4) | 15.8 (45.9) | 3.0 (20.3) |
| Medial score (IQR) with test solution | 9.1 (20.1) | 0.8 (4.4) | 1.0 (6.0) | 1.5 (10.6) | 4.0 (10.4) | 0.0 (2.0) |
| Median change in score | 7.3 ($P = .006^*$) | 1.3 ($P = .04^*$) | 2.3 ($P = .005^*$) | 16.0 ($P = .001^*$) | 15.5 ($P = .001^*$) | 4.4 ($P = .004^*$) |

*Statistically significant change in symptom when using test scleral lens filling solution compared with habitual filling solution as assessed by Wilcoxon signed rank test. CSS = Current Symptoms Survey; IQR = interquartile range; OSDI = Ocular Surface Disease Index.
Mean (standard deviation) graded Visante OCT image was 2.5 (1.5) for the habitual solution compared with 2.2 (1.4) for the test solution, which was not a statistically significant difference ($P = .3$). Because the Cirrus OCT was introduced after part 1 of the study was completed, the data analysis used all subject visits completed in the second portion of the study. Comparison of fogging with the habitual solution and the test solution revealed no significant difference between the average fogging measured using the Cirrus OCT ($P = .9$). Examples of graded images can be seen in Fig. 3.

DISCUSSION

Determining safety to the ocular surface can be challenging in a population that is already compromised because of disease. Scleral lens wearers, by nature, are often suffering from ocular disorders associated with inflammation, such as keratoconus or dry eye, in which corneal staining can be a regular phenomenon. In this study, corneal assessments of staining made after use of the habitual

![FIGURE 3. Examples of anterior optical coherence tomography (OCT) images collected and graded for midday fogging based on particulate visible between the posterior surface of the lens and the ocular surface. Yellow vertical line marks the area assessed. Note that subjects in this study were scleral lens wearers with ocular disease including keratoconus and ocular surface disorder wearing their habitual lenses. The fit of these lenses varies based on both the fitter and the ocular contour, which is typical of clinical practice.](image_url)
saline used to fill a lens were compared with the staining following use of the test solution for approximately the same period. The decrease in mean staining score, although not statistically significant, implies that safety to the cornea with this formulation is at least equal to that of the products currently on the market. This was not surprising because the addition of calcium, magnesium, potassium, and phosphate ions to the typical sodium and chloride ions more closely matches the composition of human tears than sodium chloride alone.

The open-label study design was necessary for first exposure testing of the solution. As a result, it is possible that bias was introduced for the assessments of symptoms by patients. Objective testing with slit lamp assessment grading of masked optical coherence tomography images was completed to minimize this shortcoming.

Assessment of fogging by both slit-lamp biomicroscopy and optical coherence tomography did not show statistically significant changes when comparing the particulate viewed behind the lens when using habitual solution to that when using the test solution, although there was a small average numerical decrease found with all methods of measuring fogging. This is not entirely surprising because there are multiple proposed causes of midday fogging, which likely are contributing to the particulate under the lens. Although it was hoped that a change in the solution between a scleral lens and the ocular surface could lessen the measured amount of trapped particulate, other factors may play an additional role in this phenomenon, including lens fit and tear exchange. This study did not evaluate tear exchange and did not involve any changes in lens fit of the participants and hoped to keep these contributors to midday fogging constant by using existing scleral lens wearers. It is possible that changes in measurable particulate with the test solution would be more apparent if other contributing factors for midday fogging were minimized before assessing changes with the test solution.

Although the open-label design of this study must be considered when evaluating the subjective findings of the study, it was hoped that using a linear visual analog scale, rather than a numerical scale, would lessen the bias, which often accompanies an unmasked trial. Previous studies of ocular comfort have determined that a visual analog scale change between 7 and 8 U corresponds to the just-noticeable difference in symptoms, with changes at or above this level considered clinically significant. The decrease of more than 16 U on the dryness symptom scale therefore is large enough to warrant further studies of symptoms in a future masked trial.

Similar consideration of bias must be given when assessing the Ocular Surface Disease Index findings in this study. The mean ± standard deviation Ocular Surface Disease Index score for subjects when using their habitual sodium chloride scleral filling solution was 26.2 ± 17.3, which is categorized as a moderate ocular surface disease score. Miller et al. found that those subjects who were categorized at baseline with moderate Ocular Surface Disease Index scores (23 to 32 points) required an Ocular Surface Disease Index change of 4.5 to 7.3 for a meaningful improvement in symptoms. The improvement in Ocular Surface Disease Index score to 16.9 ± 18.9 when using the test scleral filling solution both exceeds the minimal clinically important difference and changes the category of dry eye from moderate to mild. In a masked study, this change in Ocular Surface Disease Index score would be considered both statistically significant and clinically significant. These findings are promising but must be tempered by the likely effect of bias in this study because of the lack of masking.

Assessments of the particulate under a scleral lens in midday fogging were completed using multiple methods, and the protocol developed for this grading process is likely to be useful in future studies of midday fogging. Although the change in particulate assessed in this small population was not statistically significant when comparing the two solution formulations, the numerical decrease in this value is promising. Surveys to assess symptoms of midday fogging showed promising results, although the authors acknowledge that the open-label design of this study does introduce the possibility of bias into the subject responses.