Abstract:

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Methods: Eight disposable soft lens wearers equally divided between habitual users of OptiFree Express Lasting Comfort No Rub™ formula (Alcon Labs) or ReNu® MultiPlus™ (Bausch & Lomb) were enrolled in this crossover study. The habitual lens care product was designated the first crossover period. Subjects completed a visual analog scale rating of mid and end-of-day comfort, underwent slit lamp examination for staining, and had corneal sensitivity measured by Cochet-Bonnet esthesiometry before and after being
switched to the alternative lens care product. The lens care product being used was masked from the investigator.

Results: Subjects habitually using OptiFree Express reported higher comfort ratings than subjects using ReNu MultiPlus. On crossover, subjects who initially used ReNu MultiPlus experienced similar comfort when using OptiFree Express; however, OptiFree Express users experienced a substantial drop in comfort when switched to ReNu MultiPlus. Esthesiometry demonstrated significant differences in average sensitivity in favor of OptiFree Express ($P = .0041$). Statistical trends supported observed increases in corneal sensitivity when crossing to OptiFree Express and decreased corneal sensitivity when crossing to ReNu MultiPlus. ReNu MultiPlus was also associated with slightly greater levels of corneal staining.

Conclusion: ReNu MultiPlus, a biguanide-based contact lens care product was associated with decreased comfort during both mid and end-of-day periods. ReNu MultiPlus was also associated with significant reduction in relative corneal sensitivity compared to Polyquad-based OptiFree Express. Disturbance to normal corneal sensitivity may play a role in contact lens related dry eye and discomfort. Further investigation is warranted.
H. Dwight Cavanagh, MD, PhD, Editor
Eye & Contact Lens: Science and Clinical Practice

Dear Dwight:

I am hereby submitting my manuscript entitled “Contact Lens Care Product Effects on Corneal Sensitivity and Patient Comfort” for consideration. I look forward to your comments. Thank you.

Art
Contact Lens Care Products Effects on Corneal Sensitivity and Patient Comfort

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Introduction

Hydrophilic contact lenses and contact lens care products have improved dramatically since their introduction in the early 1960s. However, patient discomfort and dropout continues to plague the contact lens industry. In 2004, almost as many patients discontinued contact lens wear as were newly fitted with contact lenses – a trend that continues unabated.

Patients wearing hydrophilic lenses often experience contact lens related discomfort as dryness.\(^1,2\) For the majority, discomfort tends to worsen over the course of the day, peaking in the evening hours.\(^3\) Lens related discomfort may be sufficiently severe to prompt premature lens removal and reduce maximum wearing time. Proposed etiologies for contact lens related discomfort include metabolic depression of corneal function, bulk water loss from hydrophilic lenses, alterations in lens surface wettability and damage to the lid wiper surfaces of the tarsal conjunctiva.\(^4,5,6,7\)

Preservative systems and disinfectants are frequently cited as potential causes of contact lens related discomfort and dissatisfaction.\(^8\) Intrinsic toxicity of lens care products may be a contributing factor; however, ocular surface disturbance caused by solution toxicity can be obscured by the difficulty of in vivo measurement combined with the cornea’s propensity for rapid healing. The
The role of lens care system constituents that condition lens surfaces to enhance and prolong surface wetting has recently garnered renewed attention and may prove an important factor in sustained contact lens comfort.\textsuperscript{10,11,12} However, overall patient comfort with contact lens wear is likely related to a variety of factors – many of them still obscure.

The importance of normal corneal neural function in maintaining homeostasis of the ocular surface and tear film has recently been described in great detail.\textsuperscript{13} Disrupted neural function and diminished corneal sensitivity has been shown to adversely influence tear film integrity and ocular surface health.\textsuperscript{14} Transient and occasionally longer-term dry eye is a common complaint after LASIK due to disruption of the corneal neural plexus.\textsuperscript{15}

Corneal hypoesthesia is a well recognized complication of contact lens wear. Hypoesthesia is accepted as an essential part of the adaptation mechanism in rigid lens wearers and also occurs with soft contact lens wear.\textsuperscript{16,17,18,19,20} Despite the association of contact lens wear and corneal hypoesthesia and the established link between hypoesthesia and dry eye, the relation of contact lens related hypoesthesia and dry eye has not been previously investigated.
Hypoesthesia observed with contact lens wear may be related to the lenses or to other factors. Prior reports of biguanide associated corneal toxicity described significant superficial corneal staining unaccompanied by discomfort or photophobia when polyhexamethylene biguanide (PHMB) based ReNu® MultiPlus™ was used in conjunction with Purevision silicone hydrogel lenses worn on a daily wear schedule. Given the amount of corneal involvement in these reports, the lack of patient discomfort was remarkable. A possible explanation is that ReNu MultiPlus or some component of the solution, impaired corneal sensation in addition to being associated with the observed corneal staining.

To explore the possible relation between different contact lens care products and corneal sensitivity a pilot study was conducted. Variables examined included visual analog-based subjective daytime and end of day comfort ratings, corneal fluorescein staining, and corneal esthesiometry measurements.

**Materials and Methods**

A crossover study was conducted to assess subjective comfort ratings, superficial corneal staining and corneal sensitivity among experienced disposable soft contact lens wearers who habitually used either OptiFree Express Lasting Comfort No Rub™ Formula or ReNu® MultiPlus™. A crossover design was chosen to minimize influence of extraneous variables. To reduce study cost and
complexity the habitual care product was treated as the first treatment period. The solution being tested was masked from the investigator.

Key enrollment criteria included absence of ocular disease, prior successful full-time soft disposable (2-week, daily wear, minimum of 8 hours of lens wear per day) contact lens wear of at least one year duration and habitual use of either of the two test products: OptiFree Express Lasting Comfort No Rub Formula or ReNu MultiPlus

Subjects were randomly selected from the patient population of a suburban specialty contact lens practice. Those who met the entrance criteria were invited to participate as subjects. As incentive, participants received two boxes of disposable lenses at the completion of the study. All study-related examinations were provided without additional cost.

All participants were required to sign an informed consent, complete a visual analog scale based questionnaire evaluating habitual mid and end-of-day comfort (0-100 scale), provide a brief history of their contact lens wear experience, submit to slit lamp examination with and without sodium fluorescein and allow measurement of corneal sensitivity using a Cochet-Bonnet esthesiometer. The Cochet-Bonnet esthesiometer uses a nylon monofilament to quantify relative corneal sensitivity measured on a 0-6 scale. Higher numbers represent greater
lengths of exposed monofilament and less force applied to the cornea. Higher numbers represent greater amounts of relative corneal sensitivity. All measurements were taken at the corneal center.

Eight patients (16 eyes) were enrolled. Habitual care product use was evenly divided between the two test products: four patients used OptiFree Express and four patients, ReNu MultiPlus. Since the patient’s habitual lens care product was used for the first crossover period the study commenced immediately upon the subject’s agreement to participate. Corneal sensitivity was measured precisely ten minutes after lens removal to ensure consistency of data. In addition, all study encounters occurred during the afternoon to eliminate diurnal effects and minimize confounding due to length of lens wear.

At the completion of the initial evaluation, a new set of contact lenses was dispensed and sufficient supply of the crossover test product provided to the subject. Participants were instructed to use the test product exclusively for the two weeks prior to the second evaluation. At the second visit, subjects were evaluated as previously described.

Changes in corneal sensitivity occurring after crossover were subjected to statistical analysis using an unpaired t-test and overall average sensitivity
measures of the two products during both test periods were analyzed using ANOVA.

**Results**

Subjects completed a visual analog-based scale (VAS) rating of lens comfort at the beginning of each examination. Two time periods were assessed: mid-day (from 1-6 PM) and end of day (from 6 PM until lens removal). The mean mid-day comfort score reported by all subjects (habitual and crossover) using ReNu Multi Plus was 75.0 compared to 88.75 for those using OptiFree Express (Table 1). By the end of day, comfort ratings dropped appreciably to 57.5 for ReNu users and a similar amount, to 67.5 for patients using OptiFree Express.

When grouped by habitual lens care product, ReNu users reported mid-day comfort scores of 88.8 dropping to 62.5 by end of day. In contrast, OptiFree users reported average mid-day comfort scores of 92.5 and 75.0 by end of day. (Table 1) There was a 4 point comfort advantage for habitual OptiFree users during the mid day period and a more substantial 12.5 point difference by end of day. Subjects who switched from ReNu to OptiFree reported similar levels of comfort 88.75 vs. 85.0 mid-day and 62.5 vs. 60.0 end of day, respectively. OptiFree users who switched to ReNu reported average comfort scores decreasing from 92.5 to 61.25 mid-day and 75.0 to 52.5 during the end of day period, respectively.
Corneal staining was rated on a 0 to 4 scale with 0 being absent staining, 1 trace staining and 4 severe staining. Staining was not quantified by specific area of the cornea hence staining ratings represent averages for the entire corneal surface. Average OU staining for all subjects while using ReNu MultiPlus was 0.69 compared to 0.06 for OptiFree (Table 2). Staining in subjects who habitually used ReNu averaged 0.875 OU while OptiFree users had an average grade of 0.125 OU. When subjects switched care products, those switching to OptiFree dropped from 0.875 to 0.125, a decrease of 0.75, while habitual OptiFree Express users switching to ReNu MultiPlus increased from 0 staining to an average of 0.5 (Table 2).

Corneal sensitivity differences between the two test products were found during both periods of the study. Subjects who habitually used ReNu MultiPlus had average scores of 5.00 OD and 4.81 OS (Table 3). Habitual OptiFree Express users had scores of 5.44 and 5.81 OD and OS (Table 4). Scores of both eyes combined were 4.91 for habitual ReNu users (Table 3) vs. 5.63 for patients using OptiFree Express (Table 4).

Esthesiometery scores for all subjects (habitual and test groups) using ReNu MultiPlus were 4.81 OD and 4.84 OS while scores for OptiFree Express users were OD 5.69 and OS 5.75 (Table 5). The average sensitivity score for both
eyes combined was 4.83 for ReNu compared to 5.72 for OptiFree users. Analysis of variance demonstrated significant differences ($P = .0041$) in average sensitivity measures of all subjects using OptiFree vs. those using ReNu.

Patients switching from ReNu to OptiFree Express showed increased corneal sensitivity averaging nearly a full point OU (4.91 compared to 5.81) $P = .068$. Similarly patients switching from OptiFree Express to ReNu MultiPlus experienced a sensitivity loss of nearly a full point OU (4.75 compared to 5.63) $P = 0.107$. While not statistically significant, these suggestive trends were reflective of the small sample size (n of 4 in each group) used in this pilot study.

**Discussion**

The inability of clinicians to accurately and reliably measure subjective contact lens experience or to quantify objective measures that correlate with comfort and patient satisfaction represents a significant clinical dilemma. Without such measures, it is impossible to scientifically analyze the etiology of patient discomfort or accurately evaluate lens and lens care product performance in “real world” situations.

Visual analog scales (VAS) have been used extensively to measure subjective response to a variety of situations and stimuli. They have been validated for use within eyecare and provide a quantifiable measure of subjective patient
experience. 23 Despite their ease of application, VAS have not been used extensively in clinical settings other than for FDA clinical or post-approval marketing studies usually sponsored by industry.

Although this pilot study involved a limited patient population, results from VAS testing demonstrated a substantial difference in comfort ratings between patients using OptiFree Express Lasting Comfort No-Rub formula and those using ReNu MultiPlus. Although all patients reported being satisfied with their lenses and care regimens during initial survey, VAS-comfort scores reflected considerable discomfort that worsened as the day progressed. Decreases in lens comfort during the afternoon and evening have been previously reported. The differences observed in the current study validate the sensitivity of VAS-comfort measurements for detecting clinically significant changes.24

Mean comfort scores showed ReNu users experienced essentially no comfort difference after switching from ReNu to OptiFree Express. However, OptiFree users experienced a surprising and clinically significant 20 to 30 point (0-100 scale) comfort loss after switching to ReNu MultiPlus. Among all subjects, there was an average 10 point comfort difference between OptiFree Express and ReNu MultiPlus, with OptiFree ranking higher than ReNu in this study.
End of day discomfort is a likely factor in patient dissatisfaction and dropout. Test data confirmed the trend towards decreased comfort at the end of the day with an approximate 20-point difference between afternoon and end of day comfort. Patients, including those participating in this pilot study, typically describe this discomfort as dryness.

Current thinking regarding the etiology of dry eye recognizes the importance of properly functioning corneal sensory nerves and an intact neuronal loop in maintaining ocular surface homeostasis and lacrimal function. This same mechanism may play a role in contact lens wear, and might be a factor contributing to the dry eye symptoms and related discomfort that many patients experience.

Decreased corneal sensitivity associated with contact lens wear has been described previously. Other reports have suggested that some lens care products may be responsible for increased levels of end of day dryness and overall discomfort. This is the first report to link a biguanide preserved lens care product with decreased relative corneal sensitivity and a concurrent increase in subjective lens discomfort.

As described previously, a relation between corneal staining and preservative toxicity has been suggested. Two previous studies reported significant corneal
staining in patients who wore Bausch & Lomb Purevision contact lenses and used ReNu MultiPlus Solution on a daily basis.\textsuperscript{21,22} The surface chemistry of the PureVision lens may facilitate high levels of biguanide accumulation from repeated soaking during daily disinfection cycles and the subsequent release of these ingredients onto corneas when the lenses are worn.\textsuperscript{26} Despite staining severity expected to cause discomfort and/or photophobia, subjects in these studies remained asymptomatic.

In this study, subjects who used ReNu habitually and during the test period showed mild superficial corneal staining. However, as with the aforementioned studies, subjects did not complain of discomfort. Possible biguanide related disturbance to corneal nerve function or transmission may explain the lack of symptoms.

Given the critical role of an intact neural loop and normal corneal sensation, a neurotoxic or neuropathic disrupting corneal sensory nerve function also affords a possible explanation for lens related dry eye symptoms. A temporary decrease in corneal sensation might significantly reduce lens awareness and discomfort caused by epithelial disturbance. Longer periods of hypoesthesia could possibly impact lacrimal system homeostasis and result in dry eye related symptoms. Prolonged hypoesthesia might ultimately lead to symptoms severe enough to prompt discontinuation of lens wear.


**Conclusion**

Contact lens discomfort is a problem for a significant percentage of the soft lens wearing population. It ultimately leads to patient dropout and may have serious short and long-term practice ramifications. Understanding the fundamental causes of lens discomfort has been complicated by clinicians’ inability to correlate patient subjective experience with physical findings. This pilot study explored comfort, corneal sensitivity and ocular surface integrity in subjects using two leading lens care products.

In this study subjects using biguanide based ReNu MultiPlus were less comfortable during and at end-of-day than patients who used Polyquad-based OptiFree Express Lasting Comfort No-Rub Formula. Subjects who used ReNu also had significantly lower corneal sensitivity scores than patients who used OptiFree Express. Whether this effect is related to the biguanide PHMB, is specific to the ReNu MultiPlus formulation or due to other factors remains unclear and will require further investigation.

We recognize that the presence of an intact neural loop is essential for the maintenance of a healthy ocular surface. This study suggests that lens care products may disrupt normal ocular surface sensory neural function and thus
may play an important and heretofore unrecognized role in lens related dry eye symptoms and discomfort. Decreases in corneal sensitivity may also explain why patients with clinically significant acute corneal staining remain relatively comfortable despite objectively worrisome physical findings.

It is important to recognize that this is only a preliminary study involving a small sample of experienced contact lens wearers and explores only a small part of what is most likely a complex multifactorial problem. The etiology of the observed findings remains unclear. Additional research with larger patient populations and more stringent controls is necessary to confirm these findings and to more fully assess possible etiology and correlation between patient comfort, corneal staining and lens care product-related corneal desensitization.
References

Table 1. Comfort scores for the two test products measured using a visual analog scale (0-100). (100 = greatest comfort). Habitual and crossover comfort ratings, mean and OU scores are displayed.

<table>
<thead>
<tr>
<th></th>
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<th>ReNu End of Day</th>
<th>OFX Mid-Day</th>
<th>OFX End of Day</th>
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<td>57.5</td>
<td>88.75</td>
<td>67.5</td>
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Table 1. Comfort scores for the two test products measured using a visual analog scale (0-100). (100 = greatest comfort). Habitual and crossover comfort ratings, mean and OU scores are displayed.
Table 2. Mean superficial punctate keratopathy scores (0 = none, 1 = trace, 4 = severe).

<table>
<thead>
<tr>
<th></th>
<th>ReNu SPK OD</th>
<th>ReNu SPK OS</th>
<th>OFX SPK OD</th>
<th>OFX SPK OS</th>
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<tr>
<td>Habitual ReNu Use</td>
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<tr>
<td>Mean all Subjects</td>
<td>0.63</td>
<td>0.75</td>
<td>0.13</td>
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Mean All Subjects OU: 0.69 (Habitual ReNu Use), 0.06 (Habitual OptiFree Use)
<table>
<thead>
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<th>ReNu OD</th>
<th>ReNu OS</th>
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<th>OFX OS</th>
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</tr>
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<td>6.00</td>
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<td>6.00</td>
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<tr>
<td><strong>Mean</strong></td>
<td><strong>5.00</strong></td>
<td><strong>4.81</strong></td>
<td><strong>5.94</strong></td>
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**Mean OU** | **4.91** | **5.81**

Table 3. Mean Cochet-Bonet corneal sensitivity scores for right, left and both eyes in subjects who habitually used ReNu MultiPlus
Table 4. Mean Cochet-Bonet corneal sensitivity scores for right, left and both eyes in subjects who habitually used OptiFree Express Lasting Comfort Formula

<table>
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<td>5.81</td>
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Mean OU 5.63 4.75
Table 5. Mean Cochet-Bonet corneal sensitivity scores by lens care product used. Scale 1-6. 1 = lowest measured sensitivity, 6 = highest sensitivity.

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<tr>
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Habitual ReNu Use  Habitual OptiFree Use