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A preliminary investigation into the effects of ocular lubricants on higher order aberrations in normal and dry eye subjects

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ABSTRACT

Purpose: To study the effects of ocular lubricants on higher order aberrations in normal and self-diagnosed dry eyes.
Methods: Unpreserved hypromellose drops, Tears Again™ liposome spray and a combination of both were administered to the right eye of 24 normal and 24 dry eye subjects following classification according to a 5 point questionnaire. Total ocular higher order aberrations, coma, spherical aberration and Strehl ratios for higher order aberrations were measured using the Nidek OPD-Scan III (Nidek Technologies, Gamagori, Japan) at baseline, immediately after application and after 60 min. The aberration data were analyzed over a 5 mm natural pupil using Zernike polynomials. Each intervention was assessed on a separate day and comfort levels were recorded before and after application. Corneal staining was assessed and product preference recorded after the final measurement for each intervention.
Results: Hypromellose drops caused an increase in total higher order aberrations ($p = <0.01$ in normal and dry eyes) and a reduction in Strehl ratio (normal eyes: $p = <0.01$, dry eyes $p = 0.01$) immediately after instillation. There were no significant differences between normal and self-diagnosed dry eyes for response to intervention and no improvement in visual quality or reduction in higher order aberrations after 60 min. Differences in comfort levels failed to reach statistical significance.
Conclusion: Combining treatments does not offer any benefit over individual treatments in self-diagnosed dry eyes and no individual intervention reached statistical significance. Symptomatic subjects with dry eye and no corneal staining reported an improvement in comfort after using lubricants.

1. Introduction

Dry eye is a complex condition with an inflammatory component, characterized by changes to the ocular surface which relate to increased tear osmolarity and a reduced quantity or quality of tears. The Dry Eye Workshop (DEWS) defined dry eye as 'a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface, accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.' The key additions to their 1995 definition were the inclusion of symptoms of visual disturbance, osmolarity and inflammation [1,2]. The average tear film thickness has recently been estimated at 3 μm [3], which if reduced, can result in symptoms of discomfort, changes in corneal sensitivity and a reduction of visual quality [1], where local variations in power produce higher order aberrations and degradation of the image [4,5].

Changes in tear osmolarity can be measured by tests such as the TearLab system (Ocusense Inc., San Diego, CA, US), although the symptoms of discomfort can also be assessed subjectively by questionnaire or history and symptoms [1]. Sodium fluorescein is widely referred to as a 'vital dye,' although this is has been challenged as the mechanism of staining is not fully understood [6]. Standardized grading of corneal and conjunctival fluorescein staining have given this dye broad applicability as a dry-eye diagnostic test, particularly as an assessment tool in clinical studies of dry eye. Nichols reported retrospectively on a group of 447 patients with dry eye in a clinic based sample and found symptom assessment (82.8%), fluorescein staining (55.5%) and tear break up time (40.7%) to be the most frequently used tests in cases with a dry eye diagnosis [7].

Symptoms of dry eye are often exacerbated by environmental conditions e.g. low humidity [8] and tasks requiring concentration, e.g. computer use [9,10]. The importance of symptoms is underlined by their inclusion in the definition of dry eye [1]; however, lack of correlation between signs and symptoms of dry eye limits the usefulness of data obtained in this way to assess severity [11–13]. Validated questionnaires have been used successfully as a method of screening for potential dry eye [14].

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Artificial tears are the first line treatment for dry eye, but the exact mechanism of these products is difficult to identify as these preparations do not recreate the function of the tear film, but do seem to have a lubrication effect [15]. Preservatives in artificial tears have been shown to be detrimental to the ocular surface e.g. short term exposure to benzalkonium chloride has been shown to decrease goblet cell density in humans [16] and cause tear film instability [17], conjunctival squamous metaplasia and apoptosis [18], disruption of the corneal epithelium barrier [19], and have possible proinflammatory effects [20]. Unpreserved drops or alternative, less toxic preservatives are therefore preferable for the treatment of dry eye. Liposome sprays have been shown to increase lipid layer thickness and improve tear film stability in normal eyes for approximately 60 min following application to a closed eye [21]. The delivery system offers an advantage in that it does not require preservatives and is easy to apply. A reduction in aqueous volume has been shown to affect the spreading ability and stability of the lipid layer [22], introducing the possibility that a lubricant drop could theoretically enhance the performance of a lipid spray in dry eyes.

Historically, the use of invasive techniques to evaluate the tear film may have compromised the results, which has led to the recommendation of 'minimally invasive techniques' for the diagnosis and monitoring of dry eye [14,23]. The use of wavefront sensing aberrometers has been shown to be suitable for evaluating the optical qualities of the tear film [24] and assessing the effects of artificial tears [25].

The purpose of this study was to examine the immediate effects of unpreserved hypromellose 0.3% (w/v) artificial tears (Lumecare®, Medicom Healthcare Ltd., Hampshire, UK) a liposome spray (Tears Again®, Optima Pharmazeutische GmbH) and the treatments combined, on patient-reported ocular comfort, higher order aberrations and Strehl ratio in normal and self-diagnosed dry eye subjects.

2. Methods

2.1. Subjects

The study was approved by the institutional ethics committee and the research followed the tenets of the Declaration of Helsinki. The nature of the study was explained to the participants and written, informed consent was obtained. A group of 24 normals (12 female, 12 male) with a mean age of 24.2 (SD 8, median 21) years and dry eye subjects (15 female, 9 male) with a mean age of 25.7 (SD 7, median 22) years were recruited. The inclusion criterion for dry eye was a score of $\geq$6 according to the Chalmers 5-item questionnaire [26]. The mean dry eye questionnaire score for the normal group was 2.7 (median 2, SD 2.3). The mean dry eye questionnaire score for the dry group was 10.7 (median 12, SD 3.2) (Fig. 1). The exclusion criteria were: diagnosis of dry eye or any eye disease including ocular allergy, medication affecting the ocular surface, refractive surgery, contact lens wear and use of any eye drops within 24 h prior to the study.

The measurements were conducted in a stable, air-conditioned environment of 21° and 24% humidity. Subjects remained in this environment between measurements, during which time they performed tasks requiring high levels of concentration.

2.2. Methods

The subjects were assessed for all interventions administered to the right eye only on three different days within a two week period. The interventions were one drop of unpreserved hypromellose, one spray of liposome solution and the drop and spray combined. Unpreserved drops were selected as common preservatives e.g. benzalkonium chloride have a detergent effect [27] and the potential effect of this detergent on the liposome spray was unknown. Allocation of treatment order was decided for each subject using randomization tables. Comfort levels for the right eyes were rated on a scale of 1–10, where 10 represents the most comfortable at baseline and after 1 h. The subjects were seated with their chin on the chin-rest of the aberrometer when all lubricants were applied to enable the investigator to measure aberrations 5 s after intervention. Aberrometry was performed 2 s after a blink (aberrations are stable for up to 4 s after a blink [28]) at baseline, 5 s after treatment and 1 h after treatment using the Nidek OPD-Scan III, an aberrometer/corneal topography workstation. The aberrometer works on the principle of scanning slit retinoscopy/skiascopy, measuring the time delay between the central and peripheral fundus reflexes. The difference in power across the pupil is used to generate the wavefront and autorefraction data [29] from which Zernike-based maps can be derived. The total eye wavefront error, total spherical aberration and total coma-like aberrations were recorded over a pupil diameter of 5 mm, as this was the smallest natural pupil size in this cohort. Coma and spherical aberrations have been shown to be the most significant higher-order aberrations [30]. Magnitudes of the coefficients of Zernike polynomials were represented as the root mean square (RMS, in micrometers). The Strehl ratio for higher order aberrations was also recorded as a predictor of the image optical quality at the fovea, higher values indicating improved image quality [31]. A slit-lamp examination was performed after the final aberrometry reading to assess corneal staining using fluorescein sodium. The hypothesis for this study was that the combination of aqueous drops and a liposomal spray would result in the most stable and improved optical surface in the dry eye group after 60 min. The normal group was expected to exhibit minimal change after 60 min.

2.3. Data analysis

The power calculation was conducted using G*Power 3.1 [32] (ANOVA repeated measures within factor) and 24 subjects were recruited to achieve a medium effect with 80% power and an alpha level of 0.05. Statistical analysis was performed with SPSS v20.0 (SPSS Inc., Chicago, USA). The ranked data was analyzed using Friedman's ANOVA, with post hoc Bonferroni corrected Wilcoxon signed-rank tests. Normally distributed continuous data underwent parametric statistical analysis. Normality was confirmed for the data sets using Kolmogarov–Smirnoff. Analysis of variance (ANOVA) or 2 tailed independent *t*-tests were used to analyze the data. When ANOVA results were significant, *post hoc* Bonferroni corrected *t*-tests were used to control for type 1 error. A *P* value less than 0.05 was considered significant.

3. Results

The comfort scores revealed the largest improvement after the combination treatment; $\chi^2(2) = 6.240$, $p = 0.04$ (Mean improvement in normal eyes 0.7 ± 0.2 and dry eyes 1.4 ± 1.1), followed by spray (Mean improvement in normal eyes 0.6 ± 0.2 and dry eyes 1.3 ± 1.3) then drops (Mean improvement in normal eyes 0.4 ± 0.2 and dry eyes 1.2 ± 1.1). The scores had larger standard deviations in the dry group, although post hoc comparisons between specific interventions and eye types did not reach statistical significance and the comfort scores did not support the treatment preferences (Fig. 1 and Table 1).

The baseline total higher order aberrations, coma and spherical aberrations between the normal and dry groups were investigated to determine if there was a change in values across the visits before