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ORIGINAL RESEARCH

Influence of Environmental Factors with Clinical Signs and Symptoms in the Management of Dry Eye Disease

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Background: This research aims to investigate the influence of environmental factors on the treatment efficacy of ocular lubricants in patients from urban areas with dry eye disease (DED).

Methods: A phase IV clinical trial, which included 173 patients from major cities in Mexico, was randomly assigned to use ocular lubricants four times a day for 30 days. Ocular Surface Disease Index (OSDI), noninvasive tear film break-up time (NIBUT), ocular staining, and conjunctival hyperemia (CH) among other factors like weather, and air pollution as covariates were analysed.

Results: After 30 days, OSDI score decreased by 14.8 points (p<0.001), and NIBUT increased by 2.9 seconds (p< 0.001), with longer values observed in patients recruited in autumn and winter (additional 1.8 seconds, p< 0.05) compared to those recruited in spring. Patients living in cities with cooler weather and high humidity, but low air quality had higher OSDI and conjunctival stain scores of up to 4.4 and 0.3 points, respectively, as compared to those living in cities with similar pollution and humidity levels but with higher temperatures (p-values= 0.019 and 0.050). Patients with moderate CH had an increase of up to 0.8 points in their corneal stain score (p< 0.010). We also found that ozone levels were related to the predicted changes in OSDI and NIBUT.

Conclusion: This study demonstrated the impact of environmental factors on the signs and symptoms of DED and suggests that patients residing in cities with inadequately controlled air pollution can benefit from using ocular lubricants to alleviate their symptoms.

Trial Registration: Trial is registered at clinicaltrials.gov (NCT04702776).

Keywords: Dry eye disease, dry eye symptoms, dry eye signs, environmental factors, ocular lubricants

Introduction

Dry eye disease (DED) is a chronic inflammatory, multifactorial disease that is caused by numerous factors such as environment, systemic and ocular allergies, aging, smoking, contact lens use, female sex, and postmenopausal estrogen therapy, among others. These factors can lead to instability of the tear film, which is a hallmark of all forms of DED.[1,2] Tear film instability can result in increased tear osmolarity.[3] The Tear Film and Ocular Surface Society's (TFOS) Dry Eye Workshop II (DEWS II) has highlighted these aspects as important factors in the diagnosis and management of DED.[4–6] The symptoms in DED are often nonspecific and commonly include redness, burning, stinging, foreign body sensation, pruritus, tenderness, and photophobia.[1,7,8] However, the heterogeneity of these symptoms and the lack of correlation between the clinical signs and symptoms have led to this disease being underdiagnosed and undertreated.[9,10]

DED can have a negative impact on the psychological well-being of those who suffer from it. Furthermore, a negative association between DED and work environment, as well as its corresponding socioeconomic implications, has been reported.[11] Symptoms tend to worsen in workplaces where electronic devices are heavily used, due to demanding visual tasks and poor indoor air quality. As a result, work productivity and performance can be harmfully affected.[8,12] Smartphone

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use, disrupted tear film stability, shorter tear break-up time (TBUT), and corneal staining are accompanied by normal Schirmer test values and oxidative stress indices in the tears and at the ocular surface.[13–15] Studies have reported that artificially controlled environments in buildings, vehicles, and airplanes, air pollution in urban and metropolitan areas, air-borne allergens, temperature, relative humidity, and behavioral factors (exposure to smoke, medications, chemicals, etc.) are commonly associated with the risk of several systemic and ocular conditions like DED.[8,15–18]

The relevance of our research lies in the study's population, which comprises patients from major cities in Mexico. These cities share several characteristics, such as inadequately controlled air pollution, high population density, and heavy traffic indexes,[19] all environmental factors that have been associated with exacerbated DED symptomatology.[8,17] Air pollution in Latin American countries is not being adequately controlled. Major urban areas of the most densely populated territories, such as Mexico City metropolitan area (MCMA), have poor air quality that exceeds the health safety levels recommended by the World Health Organization (WHO). Since high ozone levels and lower humidity levels have been associated with DED, people residing in these cities can have an exacerbated risk of increasing their DED symptoms.[18] Additionally, changes in environmental factors associated with typical seasonal variations may cause occasional ocular surface disease or temporary dry eye complaints (seasonal DED).[20–22] The environment comprises a broad range of factors (such as sunlight, temperature, humidity, different types of pollutants, etc.) in constant and direct contact with the ocular surface.[4,6,8,15]

Ocular lubricants are the most used therapeutic tool for DED, regardless of its cause. There are different types of ocular lubricants available, including those that contain sodium hyaluronate (SH).[23–25] Studies suggest that high molecular weight (HMW) SH is more effective in treating DED than its low molecular weight (LMW) counterpart. HMW-SH also has protective properties against corneal epithelial cell apoptosis caused by benzalkonium chloride toxicity, ultraviolet light radiation, and chemical burns. It also has anti-inflammatory properties and can reduce pain sensation.[26] Some examples of such widely used lubricants in Mexico and Latin America are Lagricel® Ofteno (0.4% HMW-SH, Laboratorios Sophia, S.A. de C.V., Zapopan, Jalisco, Mexico), Humylub® Ofteno PF (0.1% HMW-SH/0.18% chondroitin sulfate [CS], Laboratorios Sophia, S.A. de C.V., Zapopan, Jalisco, Mexico), and Hyabak® (0.15% LMW-SH, Théa Laboratoires, Clermont-Ferrand, France), all of them with proven success in the management of DED.[10,25,27]

Based on previous research,[8,15,16,18,20] we hypothesized that patients with DED who live in urban areas will experience clinical signs and symptoms related to conjunctival hyperemia, shorter TBUT, conjunctival and corneal staining. For people residing in such areas, using ocular lubricants can help alleviate their symptoms and maintain clinical parameters even when the levels of atmospheric pollutants are higher, or weather conditions are adverse, as shown in Figure 1.

This study aims to investigate the influence of environmental factors like weather and air pollution, as well as symptoms and clinical signs, on the treatment efficacy of SH-based ocular lubricants in mild-to-moderate DED patients from major cities in Mexico.

Materials and Methods

This study was a phase IV randomized, open-label, clinical trial conducted at six sites in Mexico: three in Guadalajara metropolitan area (GMA), two in Monterrey metropolitan area (MMA), and one in MCMA. The trial was registered on clinicaltrials.gov as NCT04702776. The study's protocol and informed consent form were reviewed and approved by an ethics committee at each site (see Acknowledgments section for more information). The trial also followed the Declaration of Helsinki and complied with Good Clinical Practice Standards. Every participant provided their informed consent before joining and the recruitment process was carried out between October 2021 and May 2023. It is worth noting that at the time of recruiting, there were no lockdown measures in place due to the COVID-19 pandemic.

As per the TFOS DEWS II criteria, patients were diagnosed with DED according to an ocular surface disease index (OSDI) score of 13 or more and at least one of the following: more than five dots of corneal staining (with fluorescein stain), more than nine dots of conjunctival staining (with lissamine green stain), or a noninvasive tear film break-up time (NIBUT) value of less than 10 seconds.[4,11,28–30] Moreover, only mild-to-moderate DED patients were included, since the exclusion criteria listed cases in which patients required management of DED with treatments described in step 2 or above, according to the TFOS DEWS II. All patients included in the study had a diagnosis of DED upon joining. While

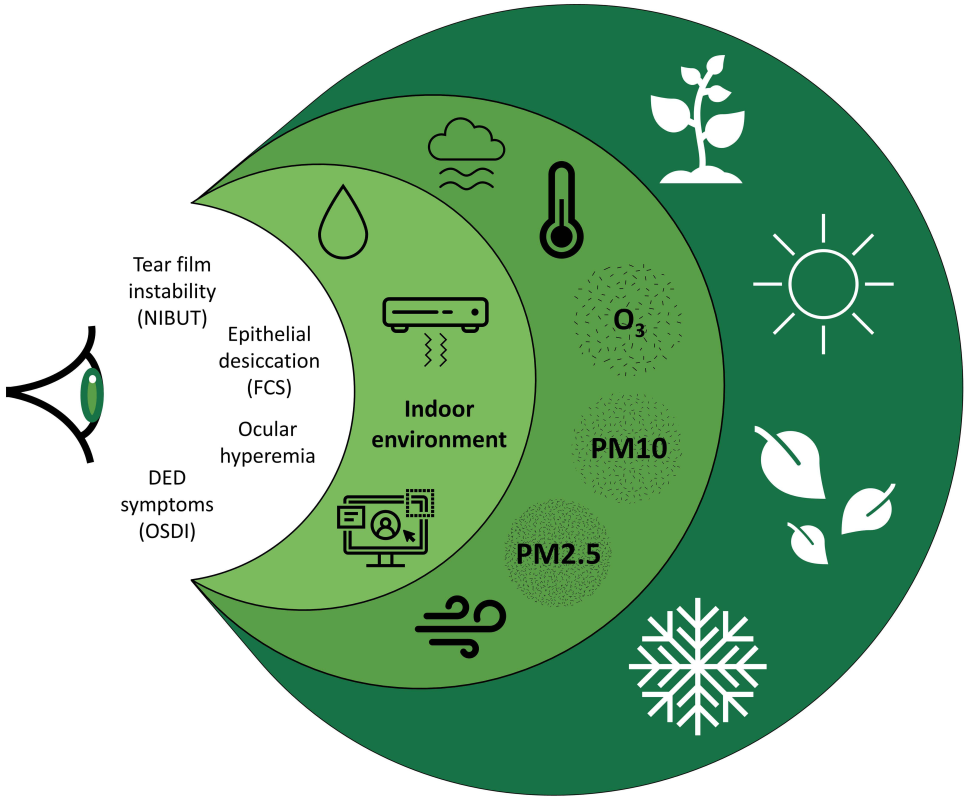

Figure 1 Patients residing in urban areas with mild to moderate dry eye experience clinical signs and symptoms associated with conjunctival hyperemia, shorter tear break-up time, conjunctival and corneal staining, and environmental factors such as temperature, humidity, air pollutants, and the use of electronic devices. For those living in such areas, using ocular lubricants can help alleviate their symptoms and maintain clinical parameters, even when the levels of atmospheric pollutants are higher.

they could have a history of using ocular lubricants, during the current study they were only allowed to use the assigned eye drops. Patient data records were chosen based on specific criteria outlined in Table S1.

Baseline data included age, sex, body mass index (BMI), medical and ophthalmic history, concomitant drug use, OSDI score, NIBUT, conjunctival and corneal staining with lissamine green and with fluorescein stains (LGCS and FCS), conjunctival hyperemia (CH), best corrected visual acuity (BCVA), and the incidence of chemosis. The analysis of this study considers the city of residence, weather conditions (temperature and relative humidity), recruitment season, and maximum index of air pollution contaminants (ozone, particulate matter with diameters less than 10 and 2.5µm [PM10, and PM2.5, respectively]) as environmental factors. The urban areas considered were the larger metropolitan regions of Mexico: MCMA, MMA, and GMA. To gather the necessary climatological data, the historical monthly weather reports for each city (smn.conagua.gob.mx) and the historical data of air particles from the respective air quality monitoring report (www.aire.cdmx.gob.mx [MCMA], http://inecc.gob.mx [GMA], and http://aire.nl.gob.mx [MMA]) were used.

Randomization and Evaluations

All included patients were randomly assigned to receive preservative-free ocular lubricant eye drops four times a day for 30 days in both eyes. The goal was to determine if HMW-SH would be more effective in managing the symptoms of DED in the study population. The first group received 0.4% HMW-SH (Lagricel® Ofteno [LCO], n=54), the second group received 0.1% HMW-SH/0.18% CS (Humylub® Ofteno [HLO], n=58), and the third group received 0.15% LMW-SH (Hyabak® [HBK], n=61). The trial was open label, meaning that patients, researchers, and other sponsoring team members were aware of the treatment assignments. However, to minimize bias, patients were randomly assigned to treatment groups using computer software. Follow-up visits were conducted on days 17–19 and 31–33 after randomization (day 0). A safety call was made 7 days after the final visit (38–40 ± 1 day). At each visit, the patients were evaluated for OSDI, BCVA, anterior biomicroscopy, NIBUT, FCS, LGCS, fundoscopy under mydriasis, and were questioned about the incidence of adverse events (AE).

Outcomes

The OSDI is a questionnaire consisting of 12 items used to evaluate a patient's subjective experience of DED symptoms and classify the effects they have on vision-related function in order to grade the severity of the disease.[29] NIBUT was measured using Oculus Keratograph 5M.[31,32] Changes in LGCS and FCS scores were evaluated after applying the dye on the ocular surface and observing the resulting staining pattern. The rate of conjunctival hyperemia was evaluated according to the Efron grading scale.[33,34] The BCVA in LogMAR was considered a safety parameter due to potential alterations caused by DED. Additionally, the presence of chemosis and the incidence of AE were registered. As the measurements obtained from both eyes are generally related, only one data point per subject was selected from the eye with the worst NIBUT value among all ophthalmology variables. In cases where NIBUT values were the same for both eyes, the data from the right eye was considered. Patient adherence to the assigned eye drops was monitored to ensure the quality of research and treatment acceptance.

Statistical Analysis

Statistical analysis was performed using the R statistical software (The R Foundation for Statistical Computing; http://www.R-project.org). Sample size calculation was based on a 35% reduction estimate in OSDI scores after one month of treatment with similar ocular lubricants.[25] To achieve a statistical power of 80% with a significance level of 0.05, a sample size of at least 50 subjects in each group was needed.[35] Descriptive statistics, including means, frequencies, standard deviations (SD), and ranges were used to organize, summarize, and present all data unless otherwise stated. Spearman correlation coefficient was used to determine the relationship between factors of interest. To assess the changes in OSDI, NIBUT, LGCS, and FCS, a multivariable logistic regression model with a generalized estimating equation (GEE) was used. Categorical variables were analyzed using p × q contingency tables, and Pearson's Chi-square test was used to manage the differences. The statistical significance was based on a *p*-value of less than 5%.

Results

Description of Patients

The study included 173 adult patients belonging to the intent-to-treat population (ITT). Among these patients, 42.2% were from MCMA, 45.7% were from GMA, and 12.1% were from MMA. Twelve patients discontinued the study, with eight of them doing so because of major protocol deviations. The remaining four discontinued the study due to adverse events, including one corneal abrasion and three probable COVID-19 infections. Therefore, 161 patients completed the entire protocol without deviations up to day 31–33. Their mean age ± SD was 30.7 ± 10.8 years (range 18 to 71 years) and 56.6% of the sample was female. Seventy-six (43.9%) of enrolled patients were users of at least one concomitant drug, such as hormonal contraceptives (65.7%), non-steroidal anti-inflammatory drugs (11.4%), antihistamines and antibiotics in the same proportion (3.8%), and others (15.3%). Baseline and demographic characteristics are presented in Table 1.

Associations Between Factors

Several correlations were observed in the data during the baseline visit. A strong positive correlation was found between patient's sex and the use of concomitant drugs (r=0.68, $p<0.001$). Additionally, there was a weak positive relationship observed between sex and BMI (r=0.27, $p< 0.001$). Furthermore, a moderate positive correlation was found between LGCS and FCS scores (r=0.47, $p< 0.001$). Weak positive relationships were observed between the FCS score and both OSDI score and NIBUT value (r-values = 0.22 and 0.23, *p*-values = 0.003 and 0.002). Weak relationships were also found between OSDI and the maximum temperature, ozone levels, and PM2.5 (r-values = 0.24, −0.23, and 0.22, *p*-values = 0.002, 0.002, and 0.003, respectively). CH was significantly correlated with the minimum relative humidity (r0.20, p=0.009), maximum temperature (r= −0.38, $p< 0.001$, and ozone levels (r=0.21, p=0.005). All the significant correlations are displayed in Figure S1.

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Table 1 Summary of Baseline Description of Randomized Patients (N=173)

Variable		Value
Sex, Male / Female (%)		75 (43.4) / 98 (56.6)
Age, years ± SD		30.7 ± 10.8
BMI, kg/m^2 ± SD		25.2 ± 3.9
Users of concomitant medications, n (%)		76 (43.9)
City of residence	MCMA, n (%)	73 (42.2)
	GMA, n (%)	79 (45.7)
	MMA, n (%)	21 (12.1)
Distribution of patients by season	Spring, n (%)	49 (28.3)
	Summer, n (%)	38 (22.0)
	Autumn, n (%)	29 (16.8)
	Winter, n (%)	57 (32.9)
OSDI score ± SD		26.2 ± 5.2
NIBUT, seconds ± SD		4.7 ± 3.1
LGCS, score ± SD		0.7 ± 0.7
FCS, score ± SD		0.7 ± 0.7
Conjunctival hyperemia, normal (%)		59 (34.1)
Chemosis, n (%)		0 (0)
BCVA, LogMAR ± SD		0.03 ± 0.12

Abbreviations: BCVA, best-corrected visual acuity; BMI, body mass index; FCS, fluorescein corneal staining; GMA, Guadalajara metropolitan area; LGCS, lissamine green conjunctival staining; MCMA, Mexico City metropolitan area; MMA, Monterrey metropolitan area; NIBUT, noninvasive tear film break-up time; OSDI, ocular surface disease index; SD, standard deviation.

Adherence Reporting

The administration of lubricants was consistent across all groups, with up to 90% compliance. By day 15, the compliance rates were 95.5 ± 7.6%, 94.4 ± 12.6%, and 93.8 ± 14.4% for LCO, HLO, and HBK, respectively. On day 30, the compliance rates were 93.6 ± 9.4%, 95.5 ± 5.6%, and 94.7 ± 9.8% for the same groups. There were no significant differences in adherence at any of the time points evaluated (p-values= 0.740 and 0.530).

Influence of Environmental Factors and Clinical Signs on Ocular Symptoms

The GEE model for the OSDI change (adjusted for visit day, city, ozone, maximum temperature [22–34°C], NIBUT, CH, and LGCS as covariables) shows a significant score reduction on days 15 and 30 (−10.6 and −14.8, $p< 0.001$). The patients located in the GMA and MMA versus those in MCMA had a relative increase of 3.9 and 4.4 in OSDI scores (p-values= 0.005 and 0.019). The maximum temperature significantly increased the OSDI score by 0.5 points for each grade ($p< 0.050$). Finally, for patients with a CH graded as moderate, the effect observed in OSDI score was an increase of 4.6 points ($p= 0.030$) versus those with normal CH. The model's analysis of variance (ANOVA-Wald) showed differences for factors visits ($p< 0.001$), city ($p< 0.001$), maximum temperature ($p< 0.050$), and CH ($p< 0.010$). Figure 2 displays the effect of maximum temperature over the expected change in OSDI score.

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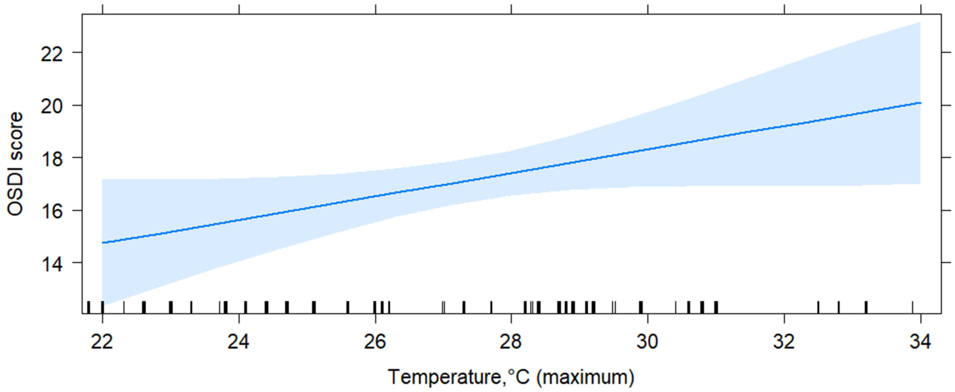

Figure 2 Main effect plot for ocular surface disease index score with 95% confidence intervals. The GEE model results indicate that the effect of maximum temperature over the expected OSDI scores was significant (p<0.05).

Based on the weather and air pollutant levels in the city of residence, there were differences in the reduction of OSDI scores, as shown in Table 2 and Figure S2. However, we found no significant differences between the effectiveness of HMW-SH and LMW-SH in terms of reducing the OSDI score. At the final visit, OSDI scores were 10.1 ± 8.3, 12.2 ± 10.6, and 8.6 ± 7.3 for LCO, HLO, and HBK, respectively.

Influence of Environmental Factors on Clinical Signs

The GEE model for NIBUT (adjusted for visit, season, minimum temperature [6–18°C], ozone, OSDI, and FCS, as covariables), showed a significant increase on days 15 and 30 by 2.4 and 2.9 seconds, respectively (p< 0.001). Patients recruited in the autumn and the winter seasons had a significant increase of 1.8 seconds in NIBUT values (p< 0.010) versus those recruited in spring. Temperature significantly increased the NIBUT value by 0.3 seconds for each grade (p< 0.010). A significant reduction in NIBUT of −0.06 seconds was predicted in those patients with high OSDI scores versus those with lower scores (p< 0.050). Lastly, the model's ANOVA showed differences for the factors time (p< 0.001), minimum temperature (p< 0.050), ozone (p<0.050), and OSDI (p< 0.050). Figure 3 displays the effect of minimum temperatures over the predicted change in NIBUT values.

Table 2 Environmental Factors and OSDI Score

City	Visit	Max-Temp °C	Min-Temp °C	Max-RH %	Min-RH %	Ozone	NO_2	PM10	PM2.5	OSDI Score
MCMA	Basal	25.7 ± 2.0	12.4 ± 1.9	70.2 ± 17.8	23.5 ± 11.1	106.0 ± 28.8	57.1 ± 15.2	147 ± 69.2	54.0 ± 24.5	25.8 ± 5.1
	Day 15	25.5 ± 2.0	12.7 ± 1.5	75.7 ± 14.8	26.7 ± 10.2	97.9 ± 26.7	54.1 ± 17.2	120 ± 54.5	42.6 ± 16.4	9.0 ± 6.1
	Final	25.6 ± 2.4	12.6 ± 1.9	70.4 ± 15.6	24.4 ± 12.2	104.0 ± 32.3	58.8 ± 19.6	142 ± 74.3	41.9 ± 15.7	5.3 ± 4.2
GMA	Basal	29.9 ± 1.2	13.1 ± 1.9	71.7 ± 17.6	19.2 ± 14.7	72.3 ± 25.1	38.8 ± 6.9	110 ± 24.4	81.8 ± 31.8	27.8 ± 4.4
	Day 15	30.2 ± 1.2	13.2 ± 2.9	67.3 ± 18.8	19.1 ± 14.3	65.2 ± 20.7	ID	98.5 ± 30.8	87.5 ± 31.7	18.6 ± 7.5
	Final	30.4 ± 1.4	13.7 ± 2.6	67.3 ± 19.0	19.2 ± 14.6	73.1 ± 24.4	ID	104 ± 32.1	73.6 ± 28.2	13.5 ± 8.3
MMA	Basal	25.4 ± 3.0	9.6 ± 3.7	82.9 ± 19.8	33.2 ± 18.1	97.4 ± 10.5	64.0 ± 14.6	143 ± 41.6	39.0 ± 13.4	21.8 ± 5.8
	Day 15	26.3 ± 2.6	10.0 ± 2.7	88.2 ± 20.2	35.6 ± 21.5	94.3 ± 13.7	64.2 ± 13.6	156 ± 31.3	40.8 ± 12.5	20.6 ± 13.8
	Final	27.1 ± 3.5	11.1 ± 3.6	72.6 ± 30.6	32.6 ± 25.9	87.4 ± 15.6	56.8 ± 12.5	144 ± 24.9	37.8 ± 3.9	14.6 ± 14.1

Notes: Climate data of historical monthly weather reports from https://smn.conagua.gob.mx. The maximum levels in each registered day were used for ozone in ppb, NO_2 in ppb, PM10 in μg/m,[3] and PM2.5 in μg/m.[3] Data of air particles from http://www.aire.cdmx.gob.mx (MCMA), http://inecc.gob.mx (GMA), and http://aire.nl.gob.mx (MMA). After the basal visit, all patients used an SH-based ocular lubricant until their final visit. Mean value ± SD for all data.

Abbreviations: GMA, Guadalajara metropolitan area; ID, insufficient data; MCMA, Mexico City metropolitan area; MMA, Monterrey metropolitan area; NO_2, nitrogen dioxide; RH, relative humidity; OSDI, ocular surface disease index; ppb, parts per billion; SH, sodium hyaluronate; SD, standard deviation.

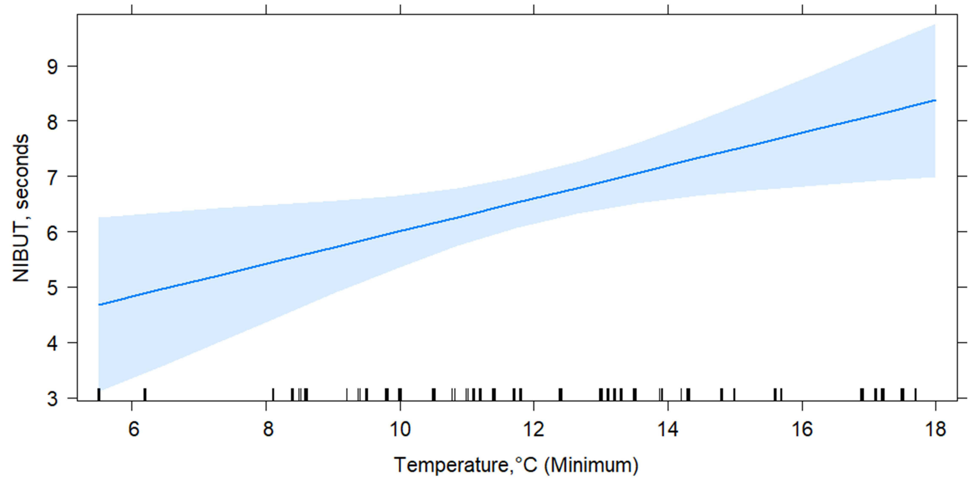

Figure 3 Main effect plot for noninvasive tear film break-up time in seconds with 95% confidence intervals. The GEE model results indicate that the effect of minimum temperature over the expected NIBUT value was significant (p<0.001).

For LGCS, the analysis (adjusted for city, OSDI, and CH as covariables) indicated an increased estimate in staining score on those patients located in the cities of GMA and MMA versus those in MCMA of 0.3 points (p-values= 0.001 and 0.050, respectively). Patients with high OSDI scores also showed an increase of 0.01 points (p= 0.005). Finally, for patients with a CH grading labeled as mild-to-moderate, the effect observed in LGCS scores was an increase of 0.5 (p< 0.001) and 0.7 points (p< 0.010), respectively. The ANOVA model showed differences for the factors city (p< 0.010), CH (p< 0.001), and OSDI (p< 0.010), while weather, air pollution particles, and season did not show any significant effects on LGCS changes.

The GEE model for FCS, adjusted by visit, age, maximum temperature [22–34°C], and CH as covariables showed significant reductions at day 15 (−0.2, p= 0.007) and 30 (−0.3, p< 0.001). Regarding age, a small but significantly increased effect is expected in older patients (0.01, p< 0.010). Temperature significantly increased the FCS by 0.03 score for each grade (p< 0.001). Furthermore, for patients with a CH grading considered mild-to-moderate, the effect observed in FCS score was an increase of 0.3 (p< 0.001) and 0.8 points (p< 0.010). The ANOVA model showed differences for factors visit (p< 0.001), age (p< 0.001), maximum temperature (p< 0.050), and CH (p< 0.001). Figure 4 displays the effect of maximum temperature over the predicted change in FCS score. All the GEE models are displayed in Tables S2–S5.

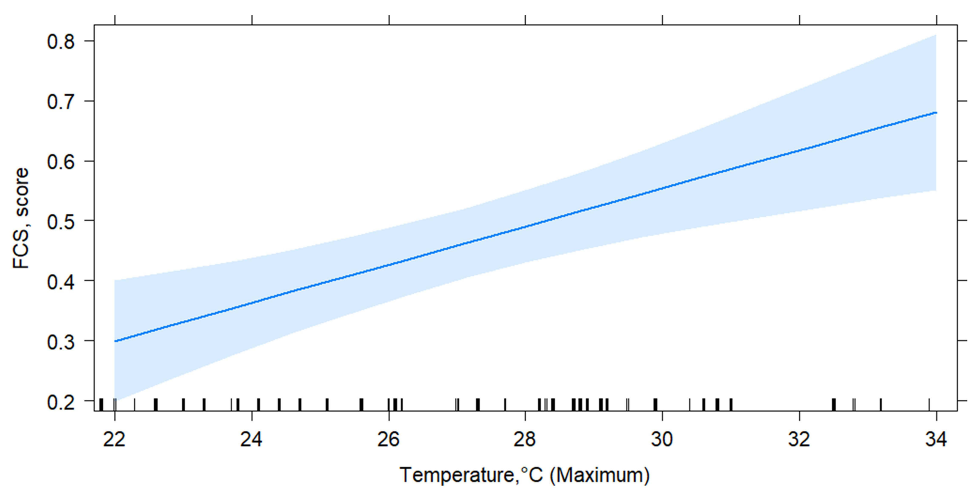

Figure 4 Main effect plot for fluorescein corneal staining score with 95% confidence intervals. The GEE model results indicate that the effect of maximum temperature over the expected FCS score was significant (p<0.001).

Safety Parameters

The BCVA (LogMAR) did not change significantly from baseline to final visit in any of the visits (p=0.390). Regarding chemosis, no patients presented it before or after the treatment. Finally, a total of seventeen patients presented at least one unexpected and drug related AE (9.8%, ITT population), all of which were classified as mild. Regarding AE causality evaluation, 35% were possible and 65% probable, without differences among treatment groups (p= 0.400). The most common class of reported AE was ocular discharge (20%), followed by ocular pain (10%), without significant differences among groups (p= 0.200).

Discussion

DED is characterized by unstable tear film, unbalanced osmolarity, and inflammation of the ocular surface.[36] DED is often diagnosed by conducting in-clinic tests that assess the structure and function of the eye. These tests evaluated tear stability (TBUT) and production (Schirmer test), along with changes in structural integrity (corneal and conjunctival staining).[1,37,38] Additionally, the structure of the cornea is assessed through confocal microscopy.[1,8] Furthermore, several studies have explored the environmental factors that can lead to DED, including adverse environmental exposures, behavioral factors, and medications.[4,6,8,15] In a recent review by Heilenbach et al, it was found that living in rural areas is linked to various age-related eye diseases, while people living in urban areas settings had a higher risk of DED and uveitis.[39] Um et al, also reported similar findings, with individuals in metropolitan cities demonstrating a higher risk of experience DED.[40] Furthermore, studies comparing people living in urban areas and rural environments have stated that the increased ozone levels and reduced humidity in urban environments are associated with DED even after adjustment for sex and other systemic diseases.[6] These findings imply that since exposure to certain environmental factors predominant in urbanized areas predispose to DED, then patients who are not subject to these conditions will more likely present less symptoms or signs related to this disease. The objective of our study was to demonstrate the link between the effect of environmental factors and the symptoms experienced by individuals suffering from DED, particularly those residing in urban areas with low air quality levels.

After using SH-based ocular lubricants for a month, patients showed significant improvement in their eye comfort. OSDI score decreased by 14.8 points, FCS score decreased by 0.3 points, and NIBUT increased by 2.9 seconds. The improvement was directly linked to the duration of eye drop usage. Additionally, the results show that patients living in cities with cooler weather, high humidity, and low air quality such as MMA have OSDI scores up to 4.4 points higher than those who live in cities with similar pollution and humidity levels, but with higher temperatures like MCMA. During hot seasons, the OSDI and the FCS scores tend to increase by 0.5 points and 0.03 points, respectively, for each grade. On the other hand, in cooler seasons such as autumn and winter, NIBUT values tend to be longer by 1.0 to 1.8 seconds compared to the dry and hot days. Patients who suffer from moderate conjunctival hyperemia showed an increase of 4.6 points in OSDI score, as well as a 0.5 to 0.8 points increase in corneal and conjunctival staining, in comparison to those who have normal grading. Additionally, the study found that ozone levels were related to the predicted changes in OSDI and NIBUT.

Several studies have supported the association of increased ground-level ozone, NO_2, and PM2.5 concentrations and increased ocular discomfort, irritation, and symptoms of DED, as well as lower TBUT and meibomian gland dysfunction, while increased PM10 concentration aggravated tear film stability.[18,41–43] The air contaminant levels that exceed the health and safety recommendations by the WHO reported during the recruitment period of the current study in MCMA, GMA, and MMA were ozone (~170 ppb), NO_2 (~107 ppb), PM10 (~360 µg/m^3), and PM2.5 (~399 µg/m^3). In MCMA, atmospheric blocking caused ozone contingencies. This scenario is present in cities surrounded by mountains with high levels of ozone precursors (such as MMA).[44] In addition, studies in ozone levels in Mexico have focused mainly on the MCMA, with less consideration on other large metropolitan areas such as GMA and MMA, where the maximum Mexican air quality standards are frequently exceeded.[45] Increased FCS scores were associated with higher PM2.5, PM10, ozone, SO_2, and NO_2 exposures.[46] Our research did not indicate a direct impact of any air particle on FCS or LGCS scores. However, we did observe a significant increase in FCS score by 0.03 score for each grade of rising maximum temperature levels during the hot seasons. Weather, air pollution particles, and seasonal variations did not show any significant effects on the predicted changes in LGCS.

In our study, the GMA and MMA patients showed higher total OSDI scores than the Mexico City group, by 3.9 and 4.4 points, respectively. For people with DED who live in these areas, it is important to use eye lubricants frequently to relieve symptoms and maintain clinical parameters, as supported by the current study.

We found no evidence to suggest that HMW-SH is more effective at reducing DED symptoms than its counterpart LMW-SH after one month of usage. Previous studies have shown that eye drops administered four times per day for a month have been effective in tests such as TBUT, conjunctival and corneal stains, and OSDI.[10,47–49] However, according to Semp and et al, it may take up to four months for clinical signs to change.[26] It is possible that a longer follow-up period for patients using HMW-SH eye drops may reveal additional beneficial effects. However, the severity of the symptoms of DED decreased significantly over time with the use of the SH-based ocular lubricants.

Since outdoor ambient temperature, artificially controlled environments in buildings, and indoor workplaces are not always well controlled, changes in ambient temperature could affect the tear film behavior.[12,50] Low relative humidity is associated with increased ocular irritation, alteration of the precorneal tear film, and significantly impacts tear film evaporation regardless of the presence of DED;[51] these effects may be exacerbated during the use electronic devices.[6] A significant difference in Schirmer-1 tests and TBUT has been reported in normal subjects living in places characterized by a dry and warm climate compared with those living in cold places.[50] Exposure to a dry environment can also increase the FCS. In the current study, patients recruited in cooler seasons showed a significant reduction of 0.3 points in FCS score versus those recruited in hot seasons, which is consistent with the findings of previous studies.[12]

Extremely high or low temperatures in outdoor and indoor environments can affect ocular surface homeostasis and directly or indirectly precipitate DED symptoms.[6] Song et al reported significantly higher ocular symptoms, ocular staining scores, and tear osmolarity with lower temperatures (6.0 ± 7.3°C). A 1°C increase in temperature led to a significant decrease in the mentioned parameters,[51] with similar findings in previous studies.[50,52] The present study shows that for patients recruited in summer and autumn, we can expect longer NIBUT values compared to those recruited in spring, up to 2.9 seconds. The highest ozone mixing ratios observed in industrial areas (such as the MMA and MCMA) are observed in spring, with minimum values in winter, which could explain these results.[45]

In contrast, temperatures near 40°C can change the properties of meibomian gland lipids and disrupt the tear film,[6,50] which could explain the findings among MMA's population. The MMA is surrounded by mountains that give it a dramatic backdrop but also trap air flow, exacerbating atmospheric pollution, with warm, wet summers and cool, dry winters. Patients living in MMA and GMA showed an increase of up to 0.3 points in their LGCS scores. These cities have warmer temperatures than MCMA. Also, the peak value of ozone for the GMA in winter and spring occurs an hour or so earlier than for the MMA and MCMA,[45] when population mobility to workplaces is higher, which is consistent with the increase of OSDI scores by 3.9 points observed on those patients.

Allergens can affect the lipid and mucin layers, leading to a tear film instability and an allergic state creates an inflammatory environment in the ocular surface which also contributes to worsening of DED symptoms.[53] These factors may vary with the seasons, as suggested by previous studies. Although general environmental characteristics may be commonly shared during specific seasons, it is important to consider geographic and demographic variations for seasonal DED. Previous studies have found an increased prevalence of DED during the winter months, potentially due to low humidity, and during the spring due to higher airborne pollen concentrations.[21,22] Studies suggest that dry eye complaints are most associated with the summer and winter seasons. Wind has been identified as the most frequently reported environmental factor impacting DED symptoms in the European population,[20] which is consistent with the findings of our study.

The study conducted by Sullivan et al previously found no consistent relationship between the common signs and symptoms of DED.[54] Our study, on the other hand, revealed only weak correlations among corneal and conjunctival staining and OSDI scores, NIBUT and conjunctival hyperemia. However, we did find correlations between OSDI and maximum temperature, ozone and PM2.5 levels. Additionally, CH was correlated with minimum relative humidity, maximum temperature, and ozone levels. These findings suggest that symptoms alone are insufficient for the diagnosis and management of DED, as there was a lack of correlation among patients' characteristics, symptoms, and clinical signs. It is important to consider a range of factors, including environmental factors, when diagnosing and managing DED.

It has been reported that people working in air-conditioned buildings tend to have a higher level of CH. The severity of CH is also higher for those who work at computers for more than 4 hours a day.[55] Our study also shows that CH is related with FCS score. Patients from urban cities with moderate CH had an increase of 0.8 points in their conjunctival and corneal stains, and their OSDI score increased by 4.6 points.

Finally, in relation to safety evaluations, BCVA did not change significantly from baseline to final visit in any of the visits, and it is worth noting that no patients presented chemosis at any point during the study. Regarding the assessment of AE, less than 10% of the patients experienced at least one non-related AE, and all these events were classified as mild. The most common related AEs reported were ocular discharge and ocular pain, which are expected AE of ocular lubricants in general.[10,20,25] These events were mild and short-lived (lasting less than 5 minutes after application) and did not require any additional treatment. Overall, the benefits of using these eye drops outweigh the risk associated with their use.

One limitation of this study is the evaluation of subjective experience of DED symptoms by the OSDI questionnaire. One principal disadvantage of the OSDI is its limited account of the effects of DED on vision-related functioning as opposed to severity alone; however, it has proven to be a valuable patient-reported subjective outcome measure in clinical trials.[56–58] The lack of more details about the specific working conditions of our patient population, the time they spent commuting to work, and the exact amount of time of electronic device used could also be considered as a limitation. Lastly, the absence of a control group or placebo would limit the observed changes in the OSDI and signs over the month of treatment, due to the treatment effect of the SH-based ocular lubricants. However, taking into consideration previous studies, where the efficacy of SH eye drops in the management of DED has been demonstrated,[10,25,27] we did not consider a placebo group necessary for this study.

In conclusion, our study demonstrated the impact of environmental factors on the clinical signs and symptoms of mild-to-moderate DED. Patients who live in densely populated cities with high heavy traffic, and poorly controlled air pollution can benefit from using ocular lubricants to improve their symptoms. While we are unable to confirm if HMW-SH would be more effective in managing the symptoms of DED in our study population, we found that SH-based ocular lubricants were effective in improving symptomatology after one month of use.

Abbreviations

AE, adverse events; CH, conjunctival hyperemia; DED, dry eye disease; FCS, fluorescein corneal staining; GMA, Guadalajara metropolitan area; HMW, high molecular weight; LGCS, lissamine green conjunctival staining; LMW, low molecular weight; MCMA, Mexico City metropolitan area; MMA, Monterrey metropolitan area; NIBUT, noninvasive tear film break-up time; OSDI, ocular surface disease index; SH, sodium hyaluronate.

Data Sharing Statement

The dataset generated during and/or analyzed for the current study is available in the Open Science Framework (https://osf.io) repository as DOI10.17605/OSF.IO/J389E.

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Phase IV Clinical Study to Compare the Efficacy of the Ophthalmic Solution Humylub Ofteno® PF with Hyabak® and Lagricel Ofteno® PF as Treatment for Dry Eye (NCT04702776) was conducted in six centers in Mexico (MCMA, GMA, and MMA). The study protocol and informed consent form were approved by their respective Institutional Review Boards as follows: Comité de Ética en Investigación del Hospital la Misión, Monterrey, Nuevo León, México; Comité de Ética en Investigación de la Clínica de Enfermedades Crónicas y de Procedimientos Especiales, Morelia, Michoacán, México; Comité de Ética en Investigación de la Asociación para Evitar la Ceguera en México IAP, Ciudad de México,

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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