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Original Article

Improvement of dryness symptoms at the end of the day with artificial tear

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ABSTRACT

Purpose: This study aimed to evaluate the efficacy of Systane COMPLETE Preservative-Free in improving symptoms of occasional dryness, particularly towards the end of the day.
Methods: A multicentric longitudinal prospective study was conducted. Participants were required to have an Ocular Surface Disease Index (OSDI) score between 13 and 32 (mild-to-moderate symptoms of dryness). Subjects used Systane COMPLETE Preservative-Free four times a day (upon waking, at midday, in the afternoon, and two hours before bedtime) for one month. Weekly questionnaires were administered, and a review was conducted at the beginning and end of the study. The Wilcoxon signed-rank test was used to compare OSDI, DEQ-5, Efron scale scores, and corneal staining using the Oxford scale. Correlations between environmental variables and symptom scores were also analyzed.
Results: This sample included 19 men and 67 women with a mean age of 42.6 ± 13.2. Statistically significant improvements were observed in both questionnaires (OSDI and DEQ-5) across all visits ($p < 0.01$) reducing the score to less than half, particularly with a decrease in symptoms at the final visit after artificial tear use (DEQ-5). The DEQ-5 questionnaire score at the initial visit correlates (Spearman's Rho) with limbal hyperemia ($\rho = 0.24$; $p = 0.02$), and conjunctival staining ($\rho = 0.28$; $p < 0.01$). The OSDI questionnaire score correlates with conjunctival staining ($\rho = 0.38$; $p = 0.03$). Moreover, the DEQ-5 questionnaire score showed correlations with several environmental factors ($\rho = 0.23-0.33$; $p < 0.04$).
Conclusions: Systane COMPLETE Preservative-Free has proven effective in improving moderate ocular dryness symptoms, as measured by the OSDI questionnaire, as well as end-of-day dryness, as assessed by the DEQ-5.

Introduction

In recent years, the number of subjects experiencing dry eye symptoms without a formal diagnosis of dry eye disease has been increasing.[1,2] In the United States, approximately 38 million individuals suffer from these symptoms of ocular dryness.[3] This condition is more prevalent in women, particularly following the onset of menopause, and its incidence rises with age in both sexes.[2] However, an increase in prevalence in youngers individual has also been observed. Evidence suggests that this type of ocular dryness may be associated with environmental pollution, being more common in cities with high levels of air pollution.[2,3] Furthermore, the widespread use of digital devices is also linked to dry eye symptoms, either due to excessive evaporation of the tear film's aqueous layer caused by reduced blink frequency or as a secondary effect of air conditioning or heating systems.[4] Additionally, the decrease in blink rate can lead to a reduction in the lipid layer, alongside other factors that may interfere with this lipid phase of the tear film.[5] Although these symptoms do not always correlate with observable clinical changes on the ocular surface.[6]

On the other hand, chronic blepharitis affects between 37 % and 47 % of subjects who visit an ophthalmologist for dry eye symptoms.[7] Posterior blepharitis, characterized by inflammation of the eyelids, is commonly caused by Meibomian Gland Dysfunction, which disrupts the lipid composition of the tear film and leads to evaporation of the aqueous layer and thus the ocular surface dryness.[8] The primary treatment for blepharitis includes eyelid hygiene, along with the application of heat and massage to the eyelids to facilitate Meibomian gland secretion and help restore the lipid layer of the tear film.[9] Additionally, for subjects experiencing dryness symptoms, a common first-line treatment involves the use of artificial tears, which are indicated for the temporary relief of irritation or discomfort on the ocular surface.[10,11]

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Mild-to-moderate symptoms of ocular dryness can interfere with daily activities, affecting subjects' quality of life and functional abilities, even in those without ocular pathology or significant clinical signs.[3] These symptoms can be exacerbated not only by prolonged use of digital devices but also by factors such as allergies, contact lens wear, air conditioning exposure, and environmental or climatic pollution. However, these symptoms are often temporary and disappear when the activity or factor ends, although sometimes these symptoms worsen at the end of the day.[5,12] Furthermore, it is advisable to assess symptoms and signs early in their onset to manage dryness effectively. Validated questionnaires, such as the Ocular Surface Disease Index (OSDI) and the Dry Eye Questionnaire (DEQ-5), can be highly useful in evaluating dryness and visual comfort, especially at the end of the day. These tools complement examinations by providing a quantitative measure of symptomatology.[13,14]

Artificial tears have been shown to enhance the stability of the tear film, reduce ocular surface stress, and improve contrast sensitivity and optical quality because get a more uniform tear film, thereby enhancing subjects' quality of life.[11] Artificial tears are available in single-dose and multi-dose formats, with the latter traditionally requiring preservatives to maintain sterility and extend their useful life.[10,11] Benzalkonium chloride (BAK) is a commonly used preservative in ophthalmology, although it is also recognised as one of the most toxic.[15] In response to the adverse effects associated with preservatives such as BAK, less cytotoxic alternatives have been developed, including Polyquad® (Alcon Laboratories, Inc.Fort Worth, TX, USA), Purite® (Bio-Cide International Inc., Norman, OK, USA), and GenAqua® (Novartis Ophthalmics, East Hanover, NJ, USA).[16] These advancements have also led to the design of specialised vials that prevent microbial contamination, enabling the development of preservative-free multi-dose formulations, such as Systane COMPLETE Preservative-Free (Alcon Laboratories, Inc.Fort Worth, TX, USA).[11]

Systane COMPLETE Preservative-Free is recommended for the treatment of evaporative, aqueous-deficient, and mixed forms of dry eye.[10,11,16] This preservative-free lipid-based formulation supports the maintenance of tear film homeostasis and stability.[17] The primary aim of this study was to evaluate the efficacy of Systane COMPLETE Preservative Free in improving symptoms of occasional dryness, particularly towards the end of the day.

Methods

Study design

A multicenter longitudinal prospective study has been carried out on subjects treated at General Optica centers throughout Spain. The study was approved by the Human Science Ethics Committee (PI 23−3237) of Valladolid East-Area (Hospital Clinic, Castilla y Leon Public Health System-SACYL). All subjects were treated in accordance with the Declaration of Helsinki and the European Data Protection Regulation (2016/679 Regulation of the European Parliament and the Council of 27th of April 2018 General Data Protection Regulation).

All investigators received the necessary training on the study protocol to minimize the impact of variability between professionals. Participants were recruited from 10 optometric centers among individuals attending for a visual examination who reported symptoms of dryness during the anamnesis. Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, a total of 93 subjects were required to identify as statistically significant a difference of 1 unit or greater in the questionnaire's score. The standard deviation was assumed to be 3.2, and a dropout rate of 10 % was anticipated.

Subjects aged between 18 and 65 years were included in the study. All participants provided written informed consent prior to enrolment, agreeing to adhere to the scheduled visit timeline and to comply with the artificial tear instillation regimen, which consisted of four applications per day, as instructed. Participants were required to have an Ocular Surface Disease Index (OSDI) score between 13 and 32 to ensure they exhibited mild-to-moderate symptoms of dryness.

Subjects who had undergone ocular surgery within the past year were excluded from the study, as were those who had used contact lenses, artificial tears, and/or ocular medication within the past month. Participants with diagnosed ocular conditions such as dry eye syndrome, glaucoma, age-related macular degeneration (AMD), or other retinal dystrophies were also excluded. Additionally, participants were excluded if they scored 3 or higher on any ocular surface clinical sign, based on the Efron scale, or if they exhibited corneal staining (assessed with sodium fluorescein) exceeding grade 1 on the Oxford scale. These patients were considered to have unhealthy eyes and to require ophthalmologic management.

Procedure

During the first visit, all participants received all the information related to the study. Clinical data of age, gender, visual acuity (VA) and refractive error, a complete slit lamp examination (EFRON and Oxford scale) and OSDI and DEQ-5 questionnaires were collected in the initial visit to ensure that subjects met the inclusion criteria. Additionally, the number of hours participants spent outdoors and in front of screens each day was recorded during the clinical record. All subjects who met the study criteria signed the informed consent form after receiving a detailed explanation and having any questions addressed. Participants were instructed to use Systane COMPLETE Preservative-Free four times per day in each eye, upon waking, at midday, in the afternoon and the final application recommended to be performed two hours before bedtime (at least three hours apart). During the study period, no other artificial tears or eye medication could be used.

One week after the initial visit, participants were contacted by telephone to confirm adherence to the instructions and the OSDI and DEQ-5 questionnaires were repeated. The same questionnaires were administered by telephone again the following week, and two weeks later (one month after the first visit), participants attended a follow-up appointment, during which the same tests and questionnaires conducted during the initial visit were repeated. Adherence was verified by checking the amount remaining in the second bottle of artificial tears (Fig. 1)

Material

The OSDI questionnaire classifies the level of ocular dryness suffered by the subject. It has twelve questions grouped into three categories or subscales: ocular symptoms, vision-related function and environmental triggers. It offers five possible answers (0: never; 1: sometimes, 2: half the time, 3: most of the time, 4: all the time; and not available). The total score of the test is obtained with the addition of all the answers, multiplied the result by 25 and divided this result by the number of questions answered. Subjects are considered symptomatic starting from 13 points. The normal score is between 0 and 12 and a distinction is made mild between 13 to 22 points, moderate between 23 and 32 points and severe (33 to 100 points) dry-eye disease. In addition, the OSDI questionnaire has been shown to have sensitivity and specificity enough to distinguish between normal subjects and subjects with dry eye, in combination with other tests such as DEQ-5.

The 5-Item Dry Eye Questionnaire (DEQ-5) is a validated tool consisting of five questions that assess three common symptoms associated with dry eye (eye discomfort, eye dryness, and watery eyes). In this test, participants are asked how frequently they have experienced these symptoms over the past month (never, rarely, sometimes, frequently, or constantly) and the intensity of these symptoms at the end of the day, two hours before bedtime (never experience it, not intense at all, or very intense). The DEQ-5 is scored on a scale from 0 to 22 points, with individuals being classified as symptomatic if they score 6 points or higher.

In this multicentric study, researchers used the Efron scale as a reference, which consists of a scale of clinical signs from zero to four. This 0

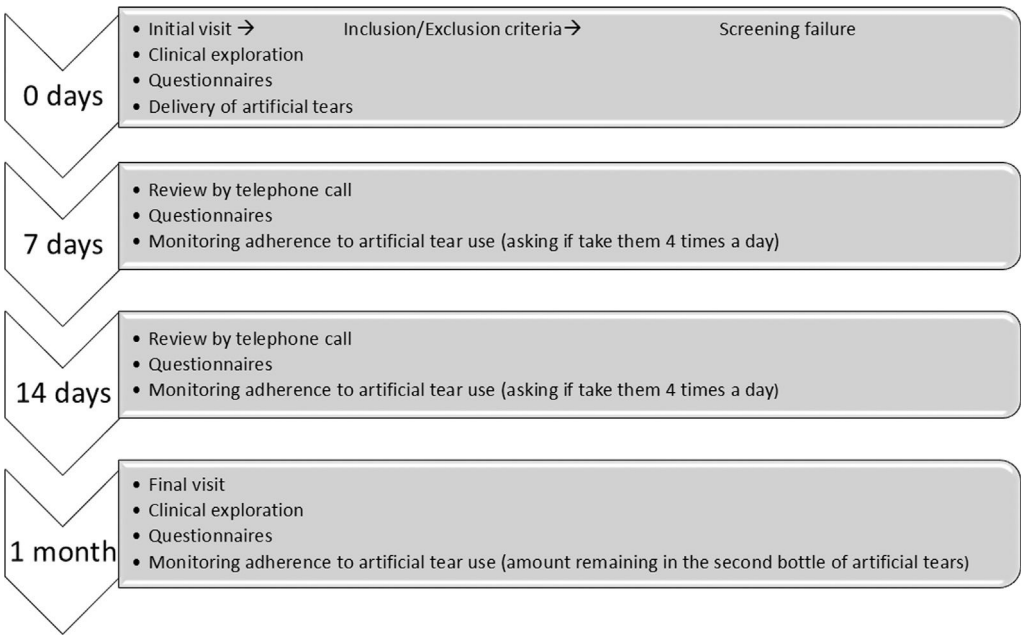

Fig. 1. Study visits diagram.

to 4 scale uses images to describe the severity of complications that may occur on the ocular surface. In this study, conjunctival and limbal hyperemia, blepharitis, meibomian gland dysfunction, and corneal and conjunctival staining were evaluated. Besides, the Oxford grading scale was used too. This scale divides corneal staining into six groups based on severity, from 0 (absent) to 5 (severe). The examiner compares the overall appearance of the subject's corneal staining to a reference figure, simulating the staining pattern found in dry eye disease.

Besides, environmental data were requested from the Spanish State Meteorological Agency (AEMET) and from the Ministry for the Ecological Transition and the Demographic Challenge of Spain (MITECO), using the data from the station closest to each center. Data collected were: temperature (daily mean, maximum and minimum, °C), humidity (relative humidity, %), wind (kilometers per hour, Km/h), solar radiation (kJ/m²), rainfall (tenths of a millimetres), sulfur dioxide (SO_2 in μg/m³), ozone (O_3 in μg/m³), nitrogen oxide (NO in μg/m³), nitrogen dioxide (NO_2 in μg/m³), particulate matter <10 μm (PM_{10} in μg/m³), particulate matter <2.5 μm ($PM_{2.5}$ in μg/m³). The initial visits took place from February to July and the final visits from March to August, associated with the environmental data of the day (24-hour average) on which the subject made these visits with the clinical data collected on that day.

Data analysis

Statistical analysis was performed using the SPSS 26.0 (SPSS, Chicago, IL, USA) statistical package for Windows. The non-parametric data distribution was verified with the Kolmogorov-Smirnov test ($P < 0.05$ indicated that the data were non-parametrically distributed). The results are presented as the mean ± standard deviation (SD) and range (minimum-maximum). The Wilcoxon signed-rank test was used to compare the VA, OSDI, DEQ-5, and Efron scale score values and corneal staining evaluated with the Oxford scale. The variations in these clinical parameters were analyzed depending on age, comparing pre- and post-value in this grouping. $P < 0.05$ was considered significant. Correlations with Spearman's Rho (ρ) were also performed between the clinical variables and the environmental variables on the day of the study visit (initial and final visit). As well $P < 0.05$ was considered significant.

Results

One hundred and one subjects were included in this study. A total of 86 participants completed both the initial and final visits and 78 participants completed all four follow-up visits. There were 15 dropouts, some due to non-compliance with scheduled visits or mild discomfort associated with the artificial tears used, with no clinical signs observed (no corneal or conjunctival staining). In a few cases, difficulty in reaching participants to administer the questionnaire for one and two weeks also contributed to the final balance. This sample is composed of 19 men and 67 women with a mean age of 42.6 ± 13.2, a maximum age of 65 and a minimum age of 19 years old. The average refraction for the right eye was −0.44±1.80 D with an average astigmatism of −0.59±0.94 D with 25 myopes, 15 hyperopes, and 46 emmetropes.

Questionnaires or subjective outcomes

Regarding the primary endpoint (OSDI) and the secondary endpoint (DEQ-5), as dryness at the end of the day, analysis of questionnaire data a statistically significant improvement ($p < 0.01$) was found between all visits to both questionnaires with a decrease in initial and final scores of 15 points for OSDI and 6 points for DEQ-5 as shown in Table 1. Besides, the questionnaires show a statistically significant correlation across all visits ($p < 0.01$; Spearman Rho), especially when symptoms decrease at the last visit after the use of artificial tears. Moreover, the DEQ-5 questionnaire score at the initial visit correlates with limbal hyperemia ($\rho = 0.24$; $p = 0.02$), and conjunctival staining ($\rho = 0.28$; $p < 0.01$). OSDI score questionnaire correlates with conjunctival staining ($\rho = 0.38$; $p = 0.03$).

The questionnaire scores by age group are shown in Table 1. In younger subjects, the differences between DEQ-5 and OSDI scores are statistically significant between all visits $p < 0.01$. However, in the case of older subjects, there are statistically significant differences between all visits $p < 0.01$ except between the third and fourth visit ($p = 0.24$) for the DEQ-5 questionnaire. The differences are statistically significant between all visits except the second and the last one by the OSDI questionnaire. The correlation between the questionnaires is statistically significant in both groups but more variable than in the analysis of the total sample.

Table 1
The means with standard deviation scores of the questionnaires with the range and the sample sizes for each visit are shown by age grouping.

Questionnaire	Initial visit (n = 101)	7-day visit (n = 91)	14-day visit (n = 81)	Final visit (n = 86)	p
Global Data					
OSDI	23.16 ± 6.17 (13 to 31.8)	13.69 ± 9.82 (0 to 47.7)	10.62 ± 9.74 (0 to 52.1)	8.18 ± 7.39 (0 to 37.5)	**<0.01**
DEQ-5	10.10 ± 3.78 (1 to 18)	6.44 ± 3.79 (0 to 16)	5.18 ± 3.75 (0 to 14)	4.01 ± 3.12 (0 to 11)	**<0.01**
ρ	0.42 (**$p < 0.01$**)	0.55 (**$p < 0.01$**)	0.64 (**$p < 0.01$**)	0.78 (**$p < 0.01$**)	-
Under 45 years of age (n = 49)					
OSDI	23.70 ± 6.30	15.88 ± 10.31	12.96 ± 11.36	9.29 ± 8.27	**0.01**
DEQ-5	9.92 ± 3.58	7.00 ± 3.68	5.74 ± 3.36	4.16 ± 3.05	**0.01**
ρ	0.48 (**$p < 0.01$**)	0.72 (**<0.01**)	0.57 (**<0.01**)	0.57 (**<0.01**)	
Over 45 years old (n = 52)					
OSDI	22.64 ± 6.06	11.54 ± 8.90	8.23 ± 7.12	7.03 ± 6.21	**0.01**
DEQ-5	10.27 ± 3.98	5.84 ± 3.85	4.54 ± 4.11	3.86 ± 3.21	**0.01**
ρ	0.40 (**$p < 0.01$**)	0.84 (**<0.01**)	0.54 (**<0.01**)	0.74 (**<0.01**)	

The comparison of these values was performed with the Wilcoxon rank test and the correlation with Spearman Rho. Initial visit: 0 day; Final visit: 1 month.

Clinical signs or objective outcomes

Table 2 shows the values obtained on the Efron scale and corneal staining with the Oxford scale. The scores of all analyzed parameters of the Efron (except corneal staining, $p = 0.12$) and corneal staining with the Oxford scale decreased statistically significantly ($p < 0.02$) after one month of artificial tears use as shown in Table 2.

Analyzing these data in a dichotomous parameter with cross-tabs, considering the score 0 as adequate and the others as altered, the following was obtained a statistically significant difference in the conjunctival hyperemia ($p < 0.01$) with 22 subjects with zero score in the initial visit and 39 in the final visit; likewise with the limbal hyperemia ($p < 0.01$) where a score of zero is given initially to 32 subjects and in the final visit to 56 subjects, and in the Blepharitis ($p < 0.01$) improving from 62 to 73 subjects with a score of zero; as well as meibomian glands ($p < 0.01$) with an increase to 60 zero score in the initial visit and 72 zero score in the final visit; in the conjunctival staining the improvement ($p < 0.01$) with 38 subjects to 57 in the final visit calculated with exact Fisher test. However, there were no improvements in corneal staining ($p = 0.07$) with the Efron scale but there was a statistically significant improvement in corneal staining with the Oxford scale ($p < 0.01$) with 54 to 68 subjects with zero scores. In addition, the data were divided into two age groups, from 18 to 45 years of age and from 46 to 65 years of age in Table 2.

The results of the slit-lamp examination divided according to age are shown in table 2. All indicators improved statistically significantly except corneal staining on both scales, the Efron and Oxford scales in the group over 45 years. Analyzing these data in a dichotomous parameter with cross-tabs (Fisher exact test), considering the score 0 as adequate and the others as altered, the following was obtained a statistically significant difference in conjunctival hyperemia ($p < 0.02$), blepharitis ($p < 0.01$), meibomian glands ($p < 0.01$), conjunctival staining ($p < 0.01$), in both groups, limbal hyperemia ($p = 0.01$) and corneal staining with Oxford scale value in young people (under 45 years).

Environmental factors

As for the other data collected, there is a correlation $\rho = 0.26$; $p = 0.01$, with the initial OSDI score and the hours the subject stays outdoors. However, there is no correlation between the initial OSDI score with the hours of screen use and in the case of the DEQ-5, the initial score does not correlate with either time $p > 0.3$. The average outdoor hours were 3.5 h and the average time with screens was 6.5 h. No difference in habits, hours with screens or outdoors does not change statistically significantly in the month of the study $p > 0.52$.

The concentrations of environmental factors recorded during the initial and final visit were compared. No statistically significant differences

Table 2
Scores (mean, standard deviation, and range) of the Efron and Oxford scales for the initial (0 day) and final (1 month) visit data by age grouping.

Visit	Conj H	Limb H	Bleph	MG	S. corneal	S. conj	Oxford
Global Data							
Initial Visit 0 day	0.99 ± 0.73	0.74 ± 0.66	0.37 ± 0.65	0.35 ± 0.61	0.15 ± 0.42	0.71 ± 0.74	0.32 ± 0.47
Final Visit 1 month	0.59 ± 0.58	0.36 ± 0.51	0.15 ± 0.39	0.18 ± 0.47	0.06 ± 0.28	0.33 ± 0.52	0.21 ± 0.41
P	**< 0.01**	**< 0.01**	**< 0.01**	**< 0.01**	0.12	**< 0.01**	**0.02**
Under 45 years of age (n = 49)							
Initial visit 0 day	0.96 ± 0.74	0.73 ± 0.64	0.32 ± 0.66	0.34 ± 0.60	0.13 ± 0.33	0.60 ± 0.70	0.29 ± 0.46
Final visit 1 month	0.45 ± 0.50	0.34 ± 0.53	0.14 ± 0.41	0.18 ± 0.45	0.00 ± 0.00	0.36 ± 0.57	0.16 ± 0.37
P	**<0.01**	**<0.01**	**0.02**	**<0.01**	**0.03**	**<0.01**	**0.01**
Over 45 years old (n = 52)							
Initial visit 0 day	1.02 ± 0.74	0.75 ± 0.69	0.41 ± 0.64	0.37 ± 0.64	0.18 ± 0.49	0.82 ± 0.76	0.35 ± 0.48
Final visit 1 month	0.74 ± 0.63	0.38 ± 0.49	0.17 ± 0.38	0.18 ± 0.50	0.13 ± 0.40	0.30 ± 0.46	0.26 ± 0.44
P	**0.02**	**<0.01**	**<0.01**	**<0.01**	0.58	**<0.01**	0.25

The comparison of the initial and final visit was performed with the Wilcoxon rank test.
H: hyperemia; Conj: conjunctival; limb: limbal; Bleph: blepharitis; MG: meibomian glands; S: staining; Oxford: corneal staining with Oxford scale.

Table 3
Correlations between questionnaire scores (OSDI and DEQ-5) and environmental factors at the initial and final visits.

	Initial visit (0 day))			Final visit (1 month)		
	DEQ-5	OSDI	Env Fact OSDI	DEQ-5	OSDI	Env Fact OSDI
SO_2	ρ = **0.33**	ρ = 0.22	ρ = **0.31**	ρ = **0.28**	ρ = 0.03	ρ = 0.11
(μg/m³)	p = **0.02**	p = 0.06	p < **0.01**	p = **0.02**	p = 0.82	p = 0.39
O_3	ρ = 0.02	ρ = −0.01	ρ = −0.10	ρ = **−0.33**	ρ = **−0.28**	ρ = **−0.30**
(μg/m³)	p = 0.85	p = 0.99	p = 0.42	p < **0.01**	p = **0.03**	p = **0.03**
NO	ρ = 0.11	ρ = 0.02	ρ = 0.07	ρ = **0.25**	ρ = 0.16	ρ = 0.20
(μg/m³)	p = 0.26	p = 0.88	p = 0.51	p = **0.03**	p = 0.15	p = 0.08
NO_2	ρ = 0.18	ρ = 0.15	ρ = 0.03	ρ = **0.23**	ρ = 0.09	ρ = 0.11
(μg/m³)	p = 0.07	p = 0.15	p = 0.78	p = **0.04**	p = 0.43	p = 0.39
Wind	ρ = −0.12	ρ = −0.10	ρ = −0.19	ρ = **−0.25**	ρ = −0.17	ρ = −0.21
(Km/h)	p = 0.22	p = 0.32	p = 0.05	p = **0.02**	p = 0.12	p = 0.07

Env: Environmental; Fact: Factors. P: Spearman Rho.

were found in daily maximum temperature (p = 0.07), wind (p = 0.57), solar radiation (p = 0.16), rainfall (p = 0.05), SO_2 (p = 0.45), PM_{10} (p = 0.19), $PM_{2.5}$ (p = 0.65). However, some environmental factor did show statistically significant difference between visits: relative humidity (p < 0.01; initial visit: 67.22 ± 14.47 % versus final visit: 63.26±13.06 %), mean temperature (p < 0.01; initial visit: 15.73 ± 5.71 °C versus final visit: 17.40±6.63 °C), minimum temperature (p < 0.01; initial visit: 10.68±5.76 °C versus final visit: 12.37 ± 6.90 °C), O_3 (p < 0.01; initial visit: 66.82 ± 16.68 μg/m³ versus final visit: 67.33 ± 21.82 μg/m³), NO (p < 0.01; initial visit: 9.70 ± 13.82 μg/m³ versus final visit: 5.21 ± 5.02 μg/m³, NO_2 (p = 0.02; initial visit: 16.82 ± 11.00 μg/m³ versus final visit: 13.69 ± 9.23 μg/m³).

Correlations between clinical outcomes and environmental conditions on the day of the examination were also analyzed. At the initial visit, statistically significant correlations (p < 0.02) were observed between the DEQ-5 score and SO_2, as well as the environmental subscale of the OSDI, while no correlation was found with the overall OSDI score (p = 0.06). At the final visit, several correlations were identified, particularly in the DEQ-5 score, with SO_2, O_3, NO, NO_2, and wind speed (p < 0.04), as shown in Table 3. Furthermore, many statistically significant correlations were found between the Efron scale with the environmental factors (Table 4), although these correlations differed between the initial that in the final visits, probably by the different environmental factors of each day. No correlations were found with temperature and PM_{10}.

Discussion

Ocular dryness is an increasingly common issue, associated with multiple causes and triggering factors. Although symptoms are not always present, they may be linked to certain activities or situations involving adverse environmental conditions. Inflammation, tear film instability, loss of homeostasis, and ocular surface stress can result in significant damage to the ocular surface.[12] If these factors persist regularly, the alteration of the ocular surface could become irreversible, highlighting the importance of implementing preventive treatment from the onset of initial symptoms.[18]

An increased rate of tear evaporation, whether due to Meibomian gland dysfunction, a reduction in the frequency or quality of blinking, or other factors identified by the TFOS, leads to tear hyperosmolarity.[12] This causes epithelial damage, which activates inflammatory pathways, destabilizes the tear film, and results in ocular discomfort, typically manifesting as dryness.[19] Treatment aims to restore homeostasis to both the ocular surface and the tear film.[12] For this reason, hypotonic artificial tears have been developed to reduce tear osmolarity and re-establish osmotic balance. A recent study by Kim et al.[20] demonstrated that such tears improve tear film stability and help preserve the integrity of the ocular surface.

Several studies have demonstrated the efficacy of nanoemulsion artificial tears containing propylene glycol/hydroxypropyl-guar in alleviating dry eye symptoms by enhancing the lipid layer of the tear film and significantly improving symptoms.[17,21] These drops have shown benefits for subjects with aqueous-deficient dry eye, evaporative dry eye, or a combination of both (mixed dry eye), relieving discomfort associated with dryness, such as pain, burning, stinging, and eye fatigue.[17,22]

Questionnaires or subjective outcomes

In this study, the specific cause of ocular dryness was not identified; however, subjects exhibited mild dryness according to the results of the OSDI test, with occasional symptoms. Systane COMPLETE Preservative-Free artificial tears have proven effective in reducing symptoms, as shown in both questionnaires, with scores decreasing by half (p < 0.01). They also contributed to the improvement of many mild ocular surface alterations (p < 0.02). However, the study's follow-up period lasted only four weeks. Furthermore, it should be noted that, without data from a control group for comparison, the results in this case could be overestimated, as the questionnaire scores decreased by more than half of their initial value. However, these outcomes seem to be consistent with those reported in other studies. In the study conducted by Duncan et al.,[23] it was concluded that the use of Systane COMPLETE can significantly improve the quality of life of symptomatic digital device users when administered approximately four times per day. Similarly, Pucker et al.[10,24] found that Systane COMPLETE safely and significantly enhances comfort in symptomatic contact lens users. However, this study did not demonstrate significant improvements in ocular signs such as tear break-up time, Schirmer's test, or corneal staining compared to baseline or the control group after two weeks of follow-up in contrast to the results of this study. Additionally, Pucker et al.[25] conducted a study with 20 participants, concluding that the use of Systane Hydration in digital device users provides effective relief from symptoms associated with ocular dryness, significantly improving their quality of life.

Clinical signs or objective outcomes

The absence of clinical signs, particularly when symptoms are intermittent, could represent an optimal time to detect and address the condition, making it possible to reverse its progression. For this reason, questionnaires can be highly useful tools for identifying occasional symptoms that subjects may consider normal.[13,14,26] While artificial tears can be a valuable therapeutic tool, it is also essential to analyze the underlying causes of ocular dryness. Environmental factors, such as

Table 4
Correlations between environmental factors and values obtained on the Efron scale.

	Hum. (%)	Wind (km/h)	Radia. (kJ/m²)	Rainfall (tenths mm)	SO_2 (μg/m³)	O_3 (μg/m³)	NO (μg/m³)	NO_2 (μg/m³)	$PM_{2.5}$ (μg/m³)	Hum. (%)	Wind (km/h)	Radia. (kJ/m²)	Rainfall (tenths mm)	SO_2 (μg/m³)	O_3 (μg/m³)	NO (μg/m³)	NO_2 (μg/m³)	$PM_{2.5}$ (μg/m³)
Mean ± SD (Min-Max)	67.2 ± 4.4 (33–92)	23.6 ± 12.6 (5–57)	516.1± 327.3 (0–1163)	10.0 ± 39.3 (3–331)	3.5 ± 2.2 (1–11.45)	66.8 ± 16.7 (12–98)	9.7 ± 13.8 (1–58)	16.8 ± 11.0 (2.2–62.6)	7.2 ± 3.0 (2.7–13.3)	63.2 ± 13.0 (20–88)	24.7 ± 12.5 (8–62)	487.76± 303.18 (0–1168)	18.2 ± 61.9 (0–386)	3.7 ± 2.2 (1–9.2)	67.3 ± 21.8 (10.5–116.8)	5.2 ± 5.0 (1–21.45)	13.7 ± 9.2 (2.3–36.6)	5.9 ± 2.8 (3.5–11.3)
	Efron Initial visit (0 day)									EFRON Final visit (1 month)								
Hyperemia Conj.	**−0.26**	0.00	0.21	−0.17	−0.13	0.17	−0.12	−0.15	−0.43	−0.01	−0.01	−0.16	0.07	0.09	0.24	−0.09	0.03	**−0.63**
	0.01	0.99	0.10	0.10	0.27	0.19	0.26	0.16	0.07	0.94	0.94	0.24	0.56	0.44	0.06	0.45	0.81	**0.02**
Hyperemia Limbal	**−0.28**	−0.14	**0.25**	**−0.28**	0.05	0.21	−0.06	−0.10	−0.30	0.06	−0.06	0.05	0.08	0.04	−0.04	−0.12	−0.04	0.18
	<0.01	0.16	**0.04**	**<0.01**	0.65	0.10	0.57	0.35	0.21	0.59	0.60	0.72	0.49	0.75	0.77	0.31	0.74	0.55
Meibomian	**−0.30**	**−0.33**	−0.05	−0.14	**0.45**	−0.08	0.10	0.09	−0.14	−0.12	**−0.34**	0.14	0.17	**0.41**	−0.15	0.18	0.15	0.22
Gland	**<0.01**	**<0.01**	0.71	0.18	**<0.01**	0.56	0.32	0.38	0.58	0.29	**<0.01**	0.30	0.12	**<0.01**	0.25	0.12	0.21	0.46
Blepharitis	−0.11	**−0.47**	−0.10	−0.13	**0.41**	−0.25	**0.28**	**0.23**	−0.20	−0.06	**−0.37**	0.16	0.08	**0.38**	−0.21	0.01	0.05	0.02
	0.28	**<0.01**	0.45	0.22	**<0.01**	0.05	**<0.01**	**0.02**	0.43	0.60	**<0.01**	0.15	0.47	**<0.01**	0.10	0.97	0.64	0.94
Corneal staining	0.17	−0.05	−0.10	−0.03	−0.02	−0.21	0.19	0.19	−0.44	**0.22**	−0.02	**−0.31**	0.01	−0.17	−0.04	−0.03	−0.03	-
	0.10	0.66	0.44	0.79	0.90	0.11	0.07	0.07	0.06	**0.04**	0.84	**<0.02**	0.98	0.16	0.79	0.82	0.80	
Conj. staining	−0.17	−0.10	−0.07	−0.19	0.01	−0.13	0.10	0.11	−0.30	−0.16	**−0.31**	**0.36**	−0.20	0.17	0.12	0.05	0.10	−0.33
	0.09	0.31	0.59	0.06	0.91	0.31	0.35	0.27	0.21	0.14	**<0.01**	**<0.01**	0.07	0.16	0.38	0.68	0.41	0.27
Oxford	−0.07	0.17	0.24	**−0.25**	−0.22	0.10	−0.14	−0.11	−0.04	0.05	0.13	**−0.28**	−0.18	−0.24	**0.29**	**−0.25**	**−0.23**	0.08
Corneal St.	0.51	0.09	0.06	**0.01**	0.06	0.43	0.19	0.30	0.87	0.97	0.24	**0.04**	0.09	0.05	**0.03**	**0.02**	**0.04**	0.80

Hum: Humidity; Radia: Radiation; Conj: Conjunctival; St:staining; -: Very little data was collected on $PM_{2.5}$. The top line shows the Spearman's rho value (ρ) and the bottom line shows the p-value.

humidity and temperature, may act as precursors to hyperosmolarity.[18,27]

Environmental factors

Environmental factors play a significant role in ocular dryness.[18,28,29] Notable among these are relative humidity, wind, air pollution, and allergens.[29] Additionally, other studies have highlighted the influence of temperature.[18,28] Low relative humidity has been shown to increase tear evaporation, exacerbating ocular dryness symptoms, while low ambient temperatures can also intensify these effects. Furthermore, both extremely high and low temperatures negatively impact the homeostasis of the tear film.[18]

At the baseline visit, prior to the administration of artificial tears, correlations between questionnaire scores and environmental factors were generally low. This may be explained by the fact that symptom scores at that stage are more closely linked to tear film instability and its direct effects on the ocular surface than to external environmental influences.

After one month of treatment with artificial tears, questionnaire scores decreased by approximately 50 %, likely due to the improved tear film stability provided by the treatment. At this moment, with a stabilized ocular surface and scores on both questionnaires within the normal range, a greater number of correlations with environmental factors appear,[30] particularly in the DEQ-5 questionnaire, which focuses on symptoms occurring at the end of the day.

As environmental conditions vary significantly across geographic regions and seasons, these findings should be interpreted with caution and validated through additional studies. Nevertheless, several environmental parameters such as SO_2, O_3, NO, NO_2, and wind, appear to be consistently associated with ocular surface alterations and symptom severity, as shown in Tables 3 and 4. Moreover, some correlations were negative, particularly for wind, rainfall, and humidity, whereas others (e.g., O_3, NO, NO_2, $PM_{2.5}$). This could be related to rainfall. Rainfall increases the humidity of the environment and usually improves the dryness symptomatology. However, thunderstorms can generate ozone from oxygen in the air.

The results of this study align with an emerging line of research exploring how environmental conditions influence dry eye symptoms. The TFOS Lifestyle Report (2023) reviews this issue by considering factors such as temperature, humidity, wind, and atmospheric pollutants (O_3, NO_2, SO_2), and their potential impact on the ocular surface.[30]

Although there are solid biological foundations, such as increased tear evaporation in dry environments or inflammatory disruption caused by pollutants, the report itself warns that the current evidence remains limited, with most studies being cross-sectional and lacking adequate control of confounding variables. Associations have been described between exposure to pollutants like NO_2 and SO_2 and non-specific ocular symptoms, as well as models suggesting the role of low humidity and wind in tear film instability. However, prospective and methodologically robust studies are still needed to confirm these findings, particularly in mild or early-stage dry eye.[28,30,18]

In this context, these findings provide additional evidence by showing an increase in the correlations between environmental variables and symptoms after the use of artificial tears, suggesting that greater tear film stability may enhance the visibility of environmental effects. This phenomenon was particularly evident in the DEQ-5 questionnaire, which specifically includes items assessing symptom intensity at the end of the day, a time when cumulative environmental exposure may have a greater clinical impact.

Nonetheless, this study is not without its limitations. The primary limitation is the absence of a control group and the short follow-up period of one month. It would be very interesting to corroborate these results in a future study with a control group and a follow-up period of at least three months. Additionally, the number of women included in the study is significantly higher than that of men. While ocular dryness

symptoms are more prevalent in women than in men, with a ratio of 2:1, this distribution does not align with the sample composition in this study. These limitations restrict the generalizability of the results. Regarding environmental factors, the sample size may be small for this type of analysis; however, the results have been consistent with those of other studies, despite this not being a controlled study of environmental factors. Therefore, these findings should be interpreted with caution.

In conclusion, Systane COMPLETE Preservative-Free has proven effective in improving moderate ocular dryness symptoms, as measured by the OSDI questionnaire, as well as end-of-day dryness, as assessed by the DEQ-5. Furthermore, it also improved mild signs of dryness, as quantified using the Efron scale.

Declaration of competing interest

None of the authors have any conflict of interest. Partially funded by an Alcon Investigator Initiated Trial (IIT#75026881). The data will be made available on reasonable request to the corresponding author. The study was approved by the Human Science Ethics Committee (PI 23-3237) of Valladolid East-Area (Hospital Clinic, Castilla y Leon Public Health System-SACYL). All participants provided written informed consent prior to enrolment.

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