Impact of propylene glycol-hydroxypropyl guar nanoemulsion eyedrops on mild to moderate dry eye

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Abstract

Aim: To evaluate symptom relief in Argentinian patients with mild to moderate dry eye disease (EOS) treated with propylene glycol-hydroxypropyl guar (PG-HPG) nanoemulsion (Systane™ Complete) eye drops.

Methods: A phase IV single-arm, open-label, prospective, interventional clinical trial was performed in 40 EOS patients. The primary endpoint was the mean difference in the Ocular Surface Disease Index (OSDI) in mild and moderate EOS sufferers after 28 days of treatment. The secondary endpoint was noninvasive tear breakup time (NBUT) in mild and moderate EOS sufferers at 14 and 28 days.

Results: A moderate negative correlation was found between OSDI score and NBUT (Spearman rank correlation rho = -0.26, p-value <0.001). Baseline OSDI score was on average 21.5 points (95% CI 18.8 - 24.1), after 14 days of treatment it was 16.2 (95% CI 13.6 - 18.8), and after 28 days it was 13.4 (95% CI 11.85 - 15.69). When comparing the baseline OSDI and the OSDI at 28 days, the average decrease was 8.06 points (95% CI 6.88 - 9.24, p-value <0.001). At baseline, NBUT was 5.94 seconds (95% CI 1.49 - 10.4), at 14 days it was 7.00 seconds (95% CI 2.74 - 11.3), and at 28 days it was 7.61 seconds (95% CI 3.14 - 12.1). Between baseline and 28 days of treatment, NBUT increased by 1.68 seconds (95% CI 0.79- 2.57, p-value <0.0001).

Conclusion: The PG-HPG nanoemulsion provided symptom relief after instillation four times a day

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for 28 days in an Argentinian population of patients with mild and moderate EOS.
Keywords: dry eye disease, propylene glycol-hydroxypropyl guar nanoemulsion, artificial tears, ocular lubricants, OSDI, NBUT.

Efectos de la nanoemulsión de propilenglicol-hidroxipropil guar en gotas oftálmicas para la sequedad ocular leve a moderada

Resumen

Objetivo: Evaluar el alivio de los síntomas en pacientes argentinos con enfermedad de ojo seco (EOS) de leve a moderada tratados con nanoemulsión de propilenglicol-hidroxipropil guar (PG-HPG) (Systane® Complete) en colirio.
Métodos: Se realizó un ensayo clínico de fase IV, abierto, prospectivo e intervencionista en 40 pacientes con EOS. El criterio de valoración primario fue la diferencia media en el índice de enfermedad de la superficie ocular (OSDI) en pacientes con EOS leve y moderada tras 28 días de tratamiento. El criterio de valoración secundario fue el tiempo de ruptura lagrimal no invasiva (NBUT) en pacientes con EOS leve y moderada a los 14 y 28 días.
Resultados: Se encontró una correlación negativa moderada entre la puntuación OSDI y el NBUT (*Spearman rank correlation* rho = -0,26, p-value <0,001). La puntuación OSDI basal fue de una media de 21,5 puntos (IC 95%: 18,8 - 24,1), tras 14 días de tratamiento fue de 16,2 (IC 95%: 13,6 - 18,8) y tras 28 días fue de 13,4 (IC 95%: 11,85 - 15,69). Al comparar el OSDI basal y el OSDI a los 28 días, la disminución media fue de 8,06 puntos (IC del 95%: 6,88 - 9,24; valor de p <0,001). Al inicio, el NBUT fue de 5,94 segundos (IC del 95%: 1,49 - 10,4), a los 14 días fue de 7,00 segundos (IC del 95%: 2,74 - 11,3) y a los 28 días fue de 7,61 segundos (IC del 95%: 3,14 - 12,1). Entre el inicio y los 28 días de tratamiento, el NBUT aumentó en 1,68 segundos (IC del 95%: 0,79 - 2,57; valor de p <0,0001).
Conclusiones: La nanoemulsión PG-HPG proporcionó alivio de los síntomas tras su instilación cuatro veces al día durante 28 días en una población argentina de pacientes con EOS leve y moderada.
Palabras clave: enfermedad de ojo seco, nanoemulsión de propilenglicol-hidroxipropil guar, lágrimas artificiales, lubricantes oculares, OSDI, NBUT.

Efeitos do colírio de nanoemulsão de propilenoglicol-hidroxipropilguar para olhos secos leves a moderados

Resumo

Objetivo: Avaliar o alívio dos sintomas em pacientes argentinos com doença do olho seco (DED) leve a moderada, tratados com nanoemulsão de propilenoglicol-hidroxipropilguar (PG-HPG) (Systane® Complete) em colírio.
Métodos: Um ensaio clínico de fase IV, aberto, prospectivo e intervencionista foi conduzido em 40 pacientes com DED. O endpoint primário foi a diferença média no índice de doença da superfície ocular (OSDI) em pacientes com DED leve e moderada após 28 dias de tratamento. O desfecho secundário foi o tempo de ruptura não invasiva da lágrima (NBUT) em pacientes com DED leve e moderado aos 14 e 28 dias.
Resultados: Foi encontrada correlação negativa moderada entre o escore OSDI e o NBUT (correlação de classificação de Spearman rho = -0,26, valor p <0,001). A pontuação inicial do OSDI foi em média 21,5 pontos (IC 95%: 18,8 - 24,1), após 14 dias de tratamento foi 16,2 (IC 95%: 13,6 - 18,8) e após 28 dias foi 13,4 (IC 95%: 11,85 - 15,69). Ao comparar o OSDI basal e o OSDI aos 28 dias, a diminuição média foi de 8,06 pontos (IC 95%: 6,88 - 9,24; valor de p <0,001). No início do estudo, o NBUT foi de 5,94 segundos (IC 95%: 1,49 - 10,4), aos 14 dias foi de 7,00 segundos (IC 95%: 2,74 - 11,3) e aos 28 dias foi de 7,61 segundos (IC 95%: 3,14 - 12,1). Entre o início do estudo e 28 dias de tratamento, o NBUT aumentou 1,68 segundos (IC 95%: 0,79 - 2,57; valor de p <0,0001).
Conclusões: A nanoemulsão PG-HPG proporcionou alívio dos sintomas após instilação quatro vezes ao dia durante 28 dias em uma população argentina de pacientes com DED leve e moderada.
Palavras-chave: doença do olho seco, nanoemulsão de propilenoglicol-hidroxipropilguar, lágrimas artificiais, lubrificantes oculares, OSDI, NBUT.

Introduction

The Tear Film and Ocular Surface Society (TFOS) released the findings from the second Dry Eye Workshop (DEWS II), which highlight that the tear film is fundamentally a two-layered structure, composed of a lipid layer atop a muco-aqueous layer[1]. It is suggested that the interactions among the various components of the tear film, including lipids, mucins, proteins, and salts, are crucial for maintaining its homeostasis. Therefore, a lubricant that can address all layers of the tear film is essential[2]. Artificial tear products (ATPs), which aim to replenish and support the natural tear film, continue to be the primary treatment strategy for managing dry eye disease (EOS)[1]. The primary objectives of their use are to alleviate symptoms, stabilize the tear film, and restore ocular surface integrity. Nevertheless, the majority of artificial tear products (ATPs) are formulated to supplement either the lipid layer or the aqueous layer of the tear film.

Traditionally, artificial tears, predominantly based on cellulose derivatives, have shown a short-lived effect on tear film stability due to their limited retention time on the ocular surface. In 2003, Alcon Laboratories introduced an innovative in situ gelling technology, which remains the only lubricant that forms a viscoelastic gel through crosslinking within the ocular pH range[3]. This breakthrough utilized hydroxypropyl-guar (HPG) as a natural polysaccharide gelling agent, marking a significant advancement in dry eye treatment and forming the foundation of the Systane™ family of artificial tear products (Alcon Laboratories, Inc., Fort Worth, TX, USA). HPG is notable for its pH sensitivity and the ability of the borate cross-linker agent to bond to the guar backbone, both within and between polymer chains. Extensive research supports this chemistry and gelation process. Extensive research supports this chemistry and gelation process[4-7]. HPG cross-linking notably increases viscosity, from 10 cp to 10,000 cp, resulting in a "soft", thin gel with bio-adhesive properties that help retain the demulcents on the ocular surface[8]. HPG molecules preferentially adhere to the damaged hydrophobic areas of the epithelium, providing a protective coating that aids in healing and lubrication[5-6, 8]. The non-Newtonian properties of this lubricant cause its viscosity to increase between blinks and decrease during blinks, enhancing its retention on the eye[9].

There is a nanoemulsion lubricant product called Systane™ Complete (Alcon, Inc., Fort Worth, TX, USA), which contains propylene glycol (PG) as the active demulcent with a higher amount of HPG gelling technology than the previous Systane™ Balance formulation, plus a lipid excipient in smaller nano-sized droplets to optimize the lipid surface coverage with a more translucent appearance[10]. Nanoemulsions, which contain droplets sized between 10 and 100 nm, are designed for patients with dry eye resulting from either lipid or aqueous deficiencies.

Although this product is available in the Latin American market, to date, the authors of the present work did not find any studies that evaluated the efficacy of Systane Complete™ in this population, especially in patients with dry eye in the population of Argentina. Because of that, our purpose was to evaluate the potential rapid improvement in symptom relief in Argentinian patients with mild to moderate EOS following a single drop of PG-HPG nanoemulsion, assessed with the Ocular Surface Disease Index (OSDI).

Subjects and methods

A Phase IV, open-label, single-arm, interventional study was conducted in adult patients with EOS of all major subtypes (aqueous-deficient, evaporative, and mixed). The study was evaluated and registered on ethical committee of the Consejo Argentino de Oftalmología. Also, the study was conducted following good clinical practices for research involving human subjects (Argentinian regulation 6677/2010), the Argentinian Ministry of Public Health's guidelines for human research (Resolution 1480/2011), and adhering to the Helsinki Declaration.

The study population consisted of adult patients (between 18 and 70 years old) with a clinical diagnosis of mild to moderate dry eye disease (EOS) or dry eye associated with meibomian gland dys-

function (MGD). Based on initial evaluation, the severity and predominant type of dry eye were identified. A comprehensive ophthalmologic examination was performed. The inclusion criteria include a non-invasive tear film breakup time (TBUT) of les than 10 seconds at screening visit, an OSDI category of mild/moderate dry eye (OSDI score 13-32 at baseline), and 2 weeks washout of any current AT before baseline OSDI score. Included patients were given the OSDI questionnaire to assess symptoms[11], followed by the non-invasive TBUT assessment as a parameter of tear film stability[12]. It's important to note that to evaluate treatment effectiveness, a minimum of four weeks of strict compliance monitoring was necessary (product tolerance and actual frequency of use).

Exclusion criteria include patients with a history of hypersensitivity to the study drug or any of its excipients, or to medications in similar chemical classes. Patients with a history of malignancy in any organ system (except localized basal cell carcinoma of the skin or in situ cervical cancer) within the past 5 years, whether treated or untreated, are also excluded, regardless of evidence of local recurrence or metastases. Those who have used any topical ocular medication containing benzalkonium chloride (BAK) or other substances known to be harmful to the tear film lipid layer within the month preceding the screening visit are excluded. Additionally, patients with a history of ocular abnormalities that could negatively impact safety or efficacy outcomes, uncontrolled active systemic diseases, active ocular infections, recent punctal plug insertion or diathermy procedures within 30 days of the screening visit, and any ophthalmic surgeries, including corneal refractive procedures, are excluded. Subjects using glaucoma medications, those currently using lipid-based artificial tears (ATs), individuals with other concomitant use of eye drops, current contact lens users, those with active inflammation, and patients with inflammatory or autoimmune conditions (e.g., ocular cicatricial pemphigoid, Sjögren's disease) are also excluded. Cases where the Schirmer test I result is higher than 10 mm and those with obstructive meibomian gland dysfunction are likewise excluded.

Considering that the amount of applied fluorescein can influence the result in the invasive TBUT, a noninvasive TBUT was performed, usign a Topcon CA-800 device (Topcon Corporation; Tokyo, Japan). Values less than 10 second are considered anormal.

Our primary endpoint was the mean difference of the OSDI questionnaire in mild and moderate dry eye disease sufferers with 28 days of use four times a day of Systane Complete™ vs baseline (day 0). As complementary information, the mean difference of the OSDI questionnaire in mild and moderate dry eye disease sufferers were evaluated after 14 days of treatment and, noninvasive TBUT (in mild and moderate EOS sufferers) were evaluated on day 14 and 28 during treatment.

At baseline, following patients' consent to participate, a comprehensive ophthalmological examination was conducted. This included assessment of best corrected visual acuity (BCVA), slit lamp examination, applanation tonometry, indirect ophthalmoscopy, noninvasive TBUT, and OSDI questionaire. The medication (Systane Complete™) was delivered to subjects, and they were guided to set four alarms on their cell phones (every four hours), as daily reminders of medication schedule.At day 14, and at day 28, the OSDI questionaire and the noninvasive TBUT were performed. To detect adverse effect or signs of ocular surface intolerance, patients were asked about discomfort in each visit during the study, enphasizing aspects as burning or foreign body sensation after treatmen drops institlation.

A sample size of 40 patients was calculated for the primary endpoint as recommended by TFOS DEWS II Diagnostic Methodology report[12], considering a 10% dropout. This report considers a clinical difference to detect of 4.5 to 7.3 points in the OSDI questionnaire for mild/moderate patients. SD of repeated measures is 6.7 points. Alpha is set to 0.05 and power is set at 80%. Descriptive statistics for baseline characteristics were calculated appropriately according to distribution of each variable (mean and SD or median and IQR).

Mean difference of the OSDI questionnaire between time points (baseline, 14 and 28 days

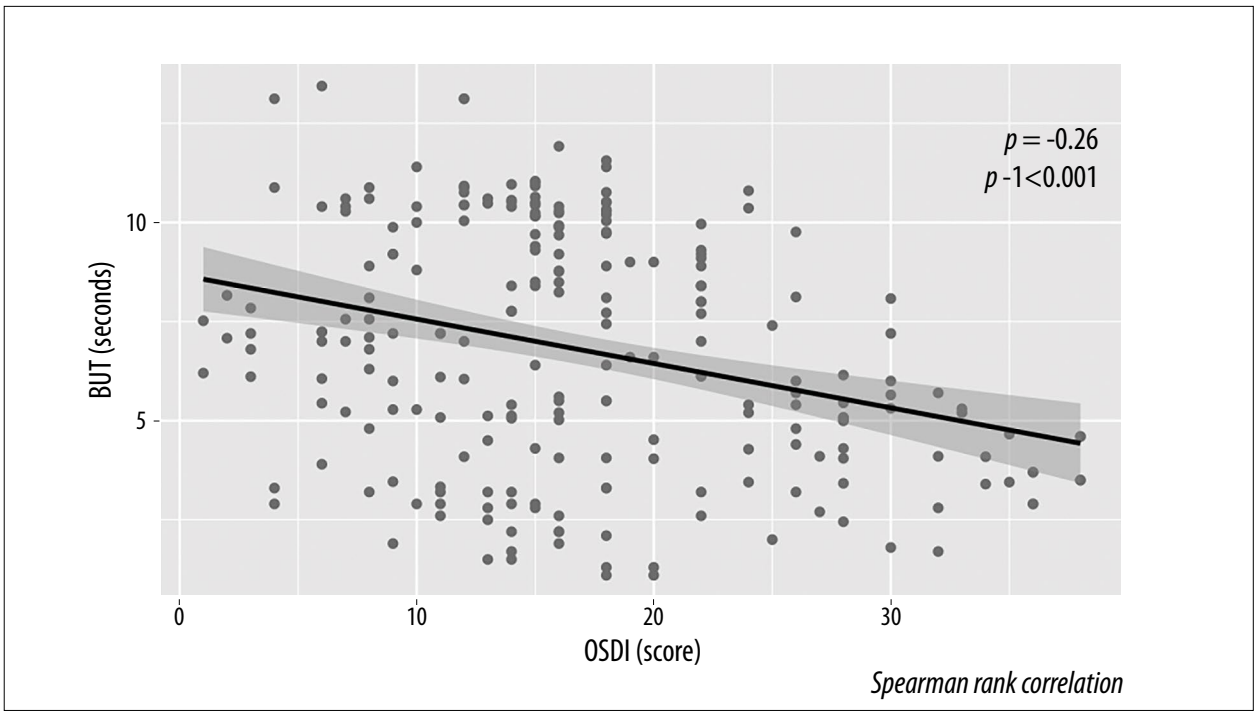

Figure 1. Correlation between OSDI and BUT. Scatter plot showing the relationship between OSDI score and BUT (in seconds). A moderate negative correlation is observed between these two variables: as BUT increases, the score obtained on the OSDI decreases (Spearman rank correlation coefficient -0.26, p-value <0.001).

after use of Systane Complete™ four times a day) will be assessed with mixed model analysis of variance (ANOVA) for repeated measures, which provides inferential statistics. Inferential statistics were calculated by means of 95% confidence intervals and corresponding p-values. Multiple comparisons will be assessed with Tukey and Dunnet methods. All analyses were performed using R 4.2.1. The dataset of this study is available upon request from the corresponding author.

Results

The mean age of the participants was 54.6 ± 9.4 years (85.4% were women). There were no losses to follow-up or missing data. No adverse effects were detected and no patient reported discomfort after eyedrops instilation. A moderate negative correlation was found between OSDI score and NBUT (Spearman rank correlation rho = -0.26, p-value <0.001) (Fig. 1).

The results of the model to evaluate the evolution of the OSDI are shown in Figure 2. Baseline OSDI score was on average 21.5 points (95% CI 18.8 - 24.1), after 14 days of treatment it was 16.2 (95% CI 13.6 - 18.8), and after 28 days it was 13.4 (95% CI 1.85 - 3.69). When comparing the baseline score with the corresponding data after two weeks of treatment, we found an average decrease of 5.29 points (95% CI 4.12- 6.46, p-value <0.001). At day 28, the average decrease was of 2.77 additional points (95% CI 1.85 - 3.69, p-value <0.001). And when comparing the baseline OSDI and the OSDI at 28 days, the average decrease was 8.06 points (95% CI 6.88 - 9.24, p-value <0.001).

The results of the model to evaluate the evolution of the NBUT are shown in Figure 3. At baseline NBUT was 5.94 seconds (95% CI 1.49 - 10.4), at 14 days it was 7.00 seconds (95% CI 2.74 - 11.3), and at 28, 7.61 seconds (95% CI 3.14 - 12.1). Between baseline and 14 days NBUT increased on average 1.06 seconds (95% CI 0.286 - 1.84, p-value <0.0001). And between 14 and 28 days,

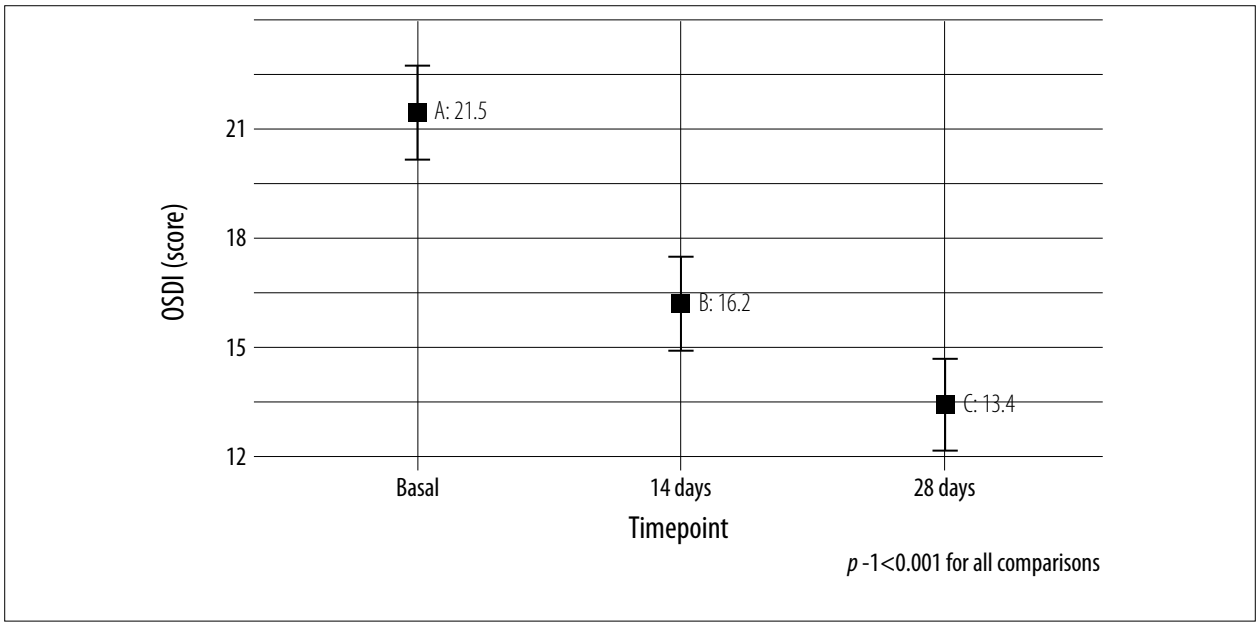

Figure 2. Score in the Ocular Surface Disease Index (OSDI). Estimates from the repeated measures ANOVA mixed model. A decrease in the OSDI score is observed after 14 days and after 28 days of treatment with Systane Complete™ 4 times a day, compared to the baseline score. The mean baseline score was 21.5 points, at 14 days it was 16.2 points (p-value <0.001) and at 28 days it was 13.4 points (p-value <0.001).

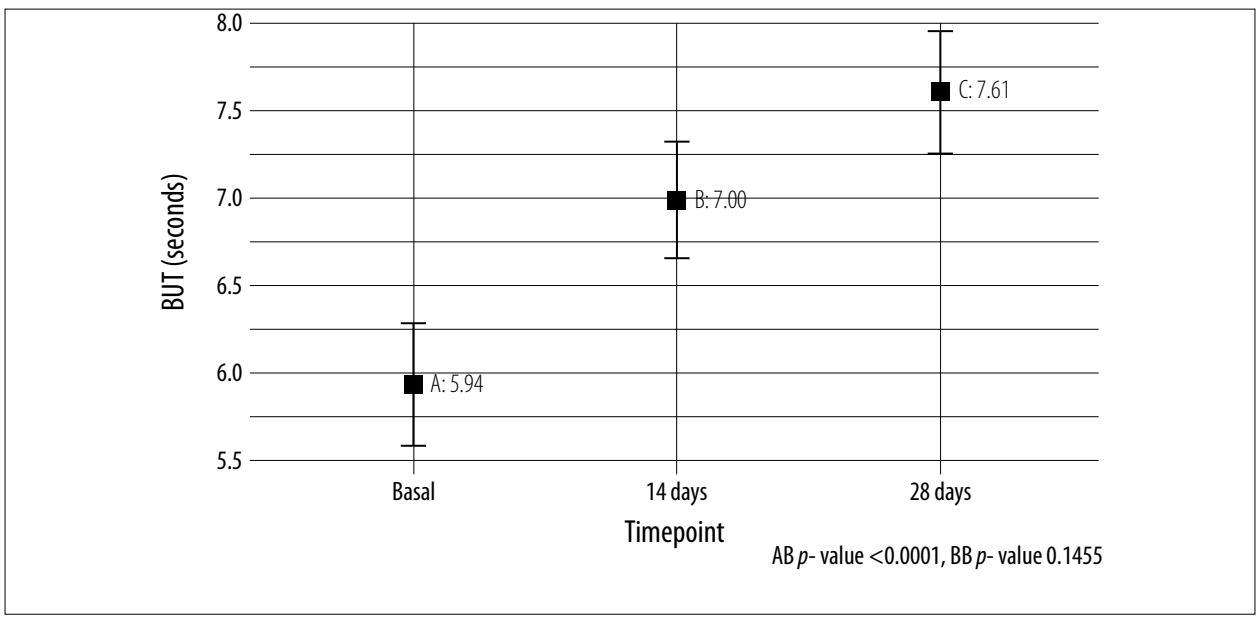

Figure 3. Break-up time (BUT). Estimates from repeated measures ANOVA mixed model. An increase in BUT is observed after 14 days and after 28 days of treatment with Systane Complete™ 4 times a day, compared to baseline BUT. The mean baseline BUT was 5.94 seconds, at 14 days it was 7 seconds (p-value <0.0001), and at 28 days it was 7.61 seconds (p-value 0.1455). Although the increase at day 28 is significant compared to baseline, it is not statistically significant when compared to BUT at 14 days.

the average increase was 0.62 seconds (95% CI -0.156 - 1.39, p-value 0.1455). Between baseline and 28 days of treatment BUT increased 1.68 seconds (95% CI 0.79 - 2.57, p-value <0.0001).

Discussion

EOS is a multifactorial condition affecting the ocular surface and is one of the most common reasons for frequent visits to eye care practitioners, impacting an estimated 30 million people in the US[13-14]. The symptoms and visual disturbances associated with EOS significantly affect patients' daily routines and quality of life. Consequently, alleviating dryness symptoms is crucial. The primary treatment goal for patients with EOS is to enhance ocular comfort by restoring the ocular surface and tear film to their normal state. Artificial tears are typically the first-line treatment, complemented by environmental modifications, dietary changes, patient education, evaluation of exacerbating factors, and systemic medications[15].

The study results showed that the PG-HPG nanoemulsion effectively alleviated symptoms associated with dry eye disease (EOS) across all patient subtypes. This finding aligns with previous research by Yeu *et al.*[10], Srinivasan *et al.*[16], and Bickle *et al.*[17]. The effectiveness of Systane Complete's unique formulation, which includes excipients suitable for patients with mixed EOS, may explain these results. After applying the PG-HPG nanoemulsion, the HPG/borate meshwork becomes activated, creating a protective viscoelastic barrier on the surface epithelium[18]. As the pH stabilizes and sorbitol is diluted, this viscoelastic HPG meshwork continues to crosslink, preserving the protective barrier and serving as a reservoir for the gradual release of lipids into the tear film[18].

The anionic phospholipid DMPG (dimyristoyl phosphatidyl- glycerol) moves to the top of the tear film, where it integrates with existing lipids to fill and stabilize gaps caused by lipid deficiency from MGD. This nanoemulsion formulation restores the complete tear structure, helping to prevent exacerbations of dry eye and promote a healthier ocular surface[16-18].

The PG-HPG nanoemulsion was well tolerated throughout the study, with no adverse effects reported, consistent with findings from other studies[10, 16-17]. The Systane family of lubricant eye drops includes a distinctive antimicrobial polycationic preservative, polyquaternium-1 at 0.001% (Polyquad™, Alcon Laboratories, Inc., Fort Worth, TX, USA)[18]. Although both polyquaternium-1 and benzalkonium chloride are effective antimicrobial agents, polyquaternium-1 is less cytotoxic to the ocular surface compared to benzalkonium chloride[19-20].

Improvement in OSDI and TBUT was evident at 14 and 28 days compared to baseline. While the greatest improvement in TBUT was observed at 14 days, between days 14 and 28, although the tear breakup time shortened, it was not significant. OSDI significantly improved at both 14 and 28 days. This suggests that the treatment with Systane Complete™ was beneficial for symptomps relief, and should be administered for at least 28 days to observe better subjective improvement after the use of lubricating treatment. This oustanding finding was very important. Thus, practitioners may argue that the treatment should be administered at least for a month. Other authors as Srinivasan *et al*[16, 18], and Bickle *et al*[17] obtained similar results.

The present study has limitations in relation to its design, since no comparative groups with other lubricant products and/or a placebo group were considered. On the other hand, it has been a short follow-up period, but due to the improvements observed, it encourages us to propose a study with a continuous use of 3 to 6 months, which will allow us to detect whether the symptoms continue to improve or stabilize over time, also considering the inflammatory basis of this pathology. Precisely because of the same aspect, we are aware that the use of the lubricant is not to cure, but to improve the symptoms suffered by dry eye patients. However, it is the first study performed with this ophthalmic lubrican in an Argentinian sample of EOS patients. This is an original aspect of the presente study, consider-

ing the TFOS epidemiology report, that emphize that EOS patients can have different therapeutic response regarding the geographical location, enviroment and lifestyle[21].

In summary our study demonstrates that the use of Systane Complete™ eyedrops for 28 days, four times a day, resulted in both objective and subjective improvement in argentinian patients with mild to moderate dry eye studied. More studies with large samples with a longer follow-up will be important to confirm the present results.

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