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Improving ocular surface comfort in contact lens wearers

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ABSTRACT

Purpose: Contact lens discomfort (CLD) is a major concern that can lead to the decreased or abandoned use of contact lenses. Contact lens users with dry eye disease are more likely to present with CLD. This study was conducted to evaluate the efficacy of a bioprotective preservative free, hypotonic, 0.15% hyaluronic acid (HA)-3% Trehalose artificial tear in managing dry eye symptoms in contact lens wearers.

Methods: A prospective, single-arm, observational pilot study to evaluate the effectiveness of treatment with HA-Trehalose artificial tears in contact lens wearers (N = 33) aged 18–45 years with symptoms of ocular discomfort. Participants used a preservative-free, hypotonic HA-Trehalose artificial tear (1 drop/4 times per day) for 84 days. Participants were assessed using Visual Analogue Scale (VAS) for dry eye symptoms (pain, photophobia, dry eye sensation, blurry vision, foreign body sensation, itching, tingling/burning, and sticky eye feeling), Ocular Surface Disease Index (OSDI), Contact Lens Dry Eye questionnaire (CLDEQ-8), Berkley Dry Eye Flow-Chart (DEFC) on Day 0 and Day 84 and tear break-up time (TBUT), ocular surface staining with fluorescein and lissamine green, tear meniscus evaluation, and visual acuity on Day 0, 35, and 84.

Results: All VAS symptoms (except tingling/burning and sticky eye feeling), OSDI, CLEDQ-8, and DEFC showed statistically significant ($p < 0.05$) improvement from baseline (Day 0) to Day 84. Similarly, corneal (fluorescein) and conjunctival (lissamine green) quality improved during the study ($p < 0.05$ at Day 84 versus baseline). Tear break-up time (TBUT), conjunctival (lissamine green) staining, and tear meniscus decreased but the changes were not statistically significant. Visual acuity did not change during the study. There were no ocular or systemic adverse events.

Conclusions: This study showed that the instillation of a preservative-free, hypotonic, HA-Trehalose artificial tear in contact lenses wearers with dry eye syndrome significantly improved symptoms and reduced associated signs such as corneal and conjunctival staining.

1. Introduction

Contact lenses are effective for the correction of refractive errors and are widely used globally. However, they are associated with various complications, such as contact lens discomfort (CLD), dry eye, allergic conjunctivitis, microbial infections of the ocular surface, or blepharitis and Meibomian gland (MG) dysfunction [1]. Soft contact lenses are the most commonly used. These lenses cover the entire cornea and their diameter extends approximately 2 mm onto the bulbar conjunctiva [2] and so the most common complications related to the use of contact lenses are related to alterations of the cornea.

The materials and maintenance systems for contact lenses have improved, reducing complications related to their use, but contact lenses remain a foreign body placed in the eye and can affect the biochemical and biophysical properties of the tear film [3,4].

CLD is characterized by episodic or persistent adverse ocular sensations related to contact lens use that may occur with or without visual disturbance and which can cause the user to decrease or abandon the use of the contact lenses [5].

Reducing contact lens discontinuation has always been a goal, and a challenge, for contact lens practitioners, and CLD is a major concern. The main reasons for discontinuing contact lens use are discomfort and dryness, which have a prevalence of around 50% for conventional hydroxyethyl methacrylate (HEMA) soft lenses [6] although discontinuation rates are lower in silicone hydrogel lenses wearers [7].

Contact lens wearers with dry eye disease are more likely to present symptoms of CLD. Dry eye disease increases with age, therefore it is likely that suspected CLD in older people may instead be a manifestation of acquired dry eye disease [8]; Nichols et al reported that 52.3% of contact lens wearers identified dry eye symptoms compared to 7.1% of

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emmetropic subjects (who were not contact lens users) [9].

Among the strategies proposed to manage the discomfort associated with contact lens use is the use of artificial tears, which can provide benefits including decreased friction between the contact lens and the tarsal conjunctiva, general ocular lubrication, decreased tear osmolarity, increased tear retention, dilution of inflammatory cytokines, and replacement of tear film components [10,11].

A commercially available, multidose, sterile, preservative-free, hypotonic aqueous solution with neutral pH that contains trehalose and hyaluronic acid (HA) has been demonstrated to be effective in subjects with dry eye symptoms [12]. The combination of trehalose and hyaluronic acid provides protein regeneration and protection [13–16] hydration and lubrication of the ocular surface for a long period of time [17,18] and maximum comfort [19]. The incorporation of such a artificial tear, with the ability to reduce the degree of inflammation and tear evaporation [20] could improve the quality of life of the contact lens wearer.

This study was conducted to evaluate the efficacy of a bioprotective HA-Trehalose artificial tear in managing dry eye symptoms in contact lens wearers.

2. Subjects and methods

2.1. Study design and participants

This was a prospective, single-arm, observational pilot study to evaluate the effectiveness of treatment with HA-Trehalose artificial tear in contact lens wearers with symptoms of ocular discomfort. The study was conducted in accordance with Good Clinical Practice, applicable International Conference on Harmonisation guidance and practices, and in compliance with the ethical principles of the Declaration of Helsinki and local regulations, including independent ethics committee approval of the study protocol before starting the study. The study was explained in detail to each participant and written informed consent was obtained prior to enrolment.

Participants who had used silicon hydrogel (Si-Hy) contact lenses (48% water content, 52% Comfilcon A material, 128 Oxigen Permeability DK, and a 0.75 Modulus MPa) for at least 1 year and between 5 and 7 days per week for a total of 8–14 h per day, and who had an Ocular Surface Disease Index (OSDI) test score > 18 (mild to moderate dry eye symptoms) were eligible for inclusion in the study. Participants continued to use the same type of lens throughout the study. Further inclusion criteria were age ≥ 18 years and normal ophthalmic findings except dry eye disease. The main exclusion criteria were any ocular inflammatory disease except dry eye, confirmed diagnosis of Meibomian gland dysfunction, any active ocular condition with or without topical ocular treatment, ocular infection or trauma within the last 3 months, presence of palpebral or nasolacrimal disorders, and inadequate contact lens fitting as judged by the Investigator. The study was conducted between December 2018 and July 2019.

The study duration was 84 days, with three study visits. Participants were recruited and enrolled into the study at the baseline visit (Visit 1) at Day 0, after a 7 day washout period with sodium chloride drops, only for those who were using other artificial tears, and were supplied with preservative free, hypotonic, HA-Trehalose artificial tears (Thealoz® Duo, Laboratoires Théa, Clermont-Ferrand, France) with 0.15% Hyaluronic Acid and Trehalose 3%, to use for the duration of the study (1 drop/4 times per day). At each visit, the number of drops instilled per day and for how many days per week was recorded. A follow-up visit (Visit 2) was performed at Day 35 and a final visit (Visit 3) at Day 84.

The worst eye from each participant was included in all assessments and was defined as the eye with the lowest TBUT; if TBUT was equal in both eyes, the worst eye was defined as the one with the smallest meniscus; if still equal in both eyes, the worst eye was defined as the one with the highest Oxford score; if still equal in both eyes, the worst eye was defined as the one with the highest van Bijsterveld score; and if still equal in both eyes, the worst eye was defined as the right eye [21].

3. Efficacy assessments

3.1. Visual analogue scale (VAS)

On Day 0 and 84, a VAS was used to measure sensations associated with dry eye symptoms (pain, photophobia, dry eye sensation, blurry vision, foreign body sensation, itching, tingling/burning, and sticky eye feeling) on a scale of 1–10, with the higher score being a more severe sensation. A score below 4 cm is considered desirable for a chronic sensation management [22].

3.2. Ocular surface disease Index

On Day 0 and 84, the OSDI test was used (with contact lenses) to assess dry eye symptoms by quantifying the frequency and vision related impact of symptoms [23]. The ranges of scores described for the tests are: normal = <12; mild = 12–21; moderate = 22–33; and severe = >33. An OSDI score of 18 points or higher was used as an inclusion criterion for the study to ensure that contact lens wearers had dry eye symptoms with a score of at least mild to moderate.

3.3. Contact lens dry eye questionnaire (CLDEQ-8)

On Day 0 and 84, the CLDEQ-8 (an 8-item questionnaire) was used to measure dry eye symptoms specifically related to contact lens wear and to reflect the degree of discomfort they cause. Participants with a score ≥ 12 could benefit from a clinical intervention for the management of ocular symptoms. A change of 3 points between visits was considered clinically significant. The calculation of the final score was made by adding the score of each of the marked responses, the final score ranges from 1 to 37 [24,25].

3.4. Berkley dry eye flow-chart (DEFC)

On Day 0 and 84, the DEFC, consisting of 3 questions, was used to classify subjects into 5 subgroups of dry eye symptoms induced by the use of contact lenses based on the presence or absence of dry eye sensation during the previous week (1 = no dryness; 2 = dryness but no discomfort; 3 = dryness and discomfort, but not enough to interfere with activities or use of contact lenses; 4 = dryness and discomfort enough to sometimes interfere with activities or the use of contact lenses; 5 = dryness and discomfort enough to frequently or always interfere with activities or the use of contact lenses) [24,26].

3.5. Tear break-up time (TBUT)

On Day 0, 35, and 84, tear fluorescein break up time was measured using a stopwatch. Sodium fluorescein (3 μL of concentration 20 mg/mL) was instilled into the upper bulbar conjunctiva. The TBUT was assessed after three complete blinks and measured when the first disruption of the tear film appeared. Three readings were taken and the average was used as its value. The slit-lamp magnification was set at 10×, the background illumination intensity was kept constant with the cobalt blue light and a Wratten 12 yellow filter [27].

3.6. Ocular surface staining with fluorescein and lissamine green

On Day 0, 35, and 84, corneal integrity was assessed by vital staining with sodium fluorescein after instillation of 3 μL sodium fluorescein on the ocular surface. After allowing the subject to blink for 20–30 s, the degree of corneal staining was analyzed using the Oxford scale [28]. This scale scores the degree of corneal deterioration from Grade 0 to 5, with Grade 0 being unaffected and Grade 5 being the greatest corneal deterioration.

On Day 0, 35, and 84, conjunctival integrity was evaluated with lissamine green dye. The Van Bijstervald scale was used as a grading scale for damage in 3 conjunctival regions: temporal bulbar conjunctiva, corneal area, and nasal bulbar conjunctiva. Each was graded from 0 to 3, with a maximal overall score of 9 for each eye [29].

3.7. Tear meniscus evaluation

Subjective evaluation of the tear meniscus was done on Day 0, 35, and 84. The quality of the meniscus was graded by the modified Grade 1–4 scale [30] (1 = intact [visible, regular meniscus, and absence of detritus]; 2 = slightly decreased [less visible, regular meniscus, and absence of detritus]; Grade 3 = markedly diminished or discontinuous [meniscus very diminished, irregular and/or presence of detritus]; Grade 4 = absent [absence of meniscus]). Grade 1 and 2 represented a healthy meniscus and Grade 3 and 4 represented an abnormal meniscus.

3.8. Visual acuity

LogMar Visual Acuity (ETDRS) was measured on Day 0, 35, and 84 by the procedure developed by Early Treatment Diabetic Retinopathy Study (ETDRS) using the best optical compensation and at a distance of 4 m. The results were expressed in decimal logarithm [31].

3.9. Safety assessments

3.9.1. Adverse events

Participants were asked to report any adverse events at each visit, and visual acuity was recorded as a safety evaluation.

3.10. Statistical analysis

Statistical analyses were conducted using SPSS v.22.0 (IBM Corporation. Released 2013. IBM SPSS Statistics for Macintosh. Version 22.0) to evaluate data from the study eye. The distribution of the data was analyzed using Shapiro-Wilk W and Kolmogorov Smirnov tests [32] and not all the variables were normally distributed. Mean changes of the quantitative outcomes were compared with the Student's *t*-test or analysis of variance (ANOVA) rank non-parametric test, and a P-value $<$ 0.05 was considered statistically significant.

In addition, the binomial test, McNemar-Bowker, was used to analyze the qualitative results, p-value $<$ 0.05 was considered statistically significant.

Effect size (Cohen's d) was used to calculate the standardized difference between mean values, using the mean change score (before and after treatment) divided by the standard deviation (SD) of the same measure before treatment. Changes were categorized as trivial (d $<$ 0.2), small (d = 0.2 to $<$ 0.5), moderate (d = 0.5 to $<$ 0.8), or large (d $\geq$ 0.8) [33].

As this was a pilot study, no sample size calculation was performed.

4. Results

4.1. Participants

Thirty-three subjects (27 women and 6 men) (ie, a total of 33 eyes) were included and completed the study according to the protocol. Two participants required a washout period with sodium chloride drops instilled 4 times daily for 7 days due to previous use of artificial tear. There were no study drug discontinuations. The mean ± SD age was 24.06 ± 5.68 years (range 18–45 years).

To obtain the results, the visit on Day 0 (baseline) and Day 84 were compared, using the visit on Day 35 as a follow-up.

4.2. Efficacy assessments

There was a statistically significant improvement in each VAS assessment from Day 0 to Day 84 except for tingling/burning and sticky eye feeling (Table 1).

The VAS assessment with the largest improvement from Day 0 to Day 84 was dry eye sensation (reduction of 28.40 ± 24.48), followed by blurry vision (reduction of 15.37 ± 26.28), photophobia (11.56 ± 31.90), and foreign body sensation (9.92 ± 31.97). Smaller reductions, but still statistically significant, were seen for itching (5.30 ± 24.35) and pain (3.03 ± 16.47). The reductions for tingling/burning (2.95 ± 24.27) and sticky eye feeling (2.42 ± 20.99), which did not reach statistical significance, were slightly less than for pain. Large and moderate effect size values were obtained, respectively, for the variables dry eye sensation (ES = 1.16) and blurry vision (ES = 0.58).

There was a statistically significant improvement in dry eye symptoms from baseline to Day 84 evaluated with OSDI, CLDEQ-8, and DEFC. The effect size was large (ES $\geq$ 0.8) for these three symptomatology tests.

After 84 days of treatment, mean ± SD OSDI score decreased significantly from 32.06 ± 12.19 to 17.99 ± 11.14 (mean ± SD reduction. 14.07 ± 13.59); 85% of participants experienced an OSDI score reduction, and 57.6% showed an OSDI score of 18 or less at Day 84. The Effect Size (Cohen's d) (1.04) showed a large effect of HA-Trehalose artificial tear on OSDI score, after application of treatment (Fig. 1).

Similarly, mean ± SD CLDEQ-8 score decreased significantly from 19.33 ± 4.32 to 12.84 ± 4.06 (mean ± SD reduction: 6.48 ± 5.03) (Fig. 2) and the Effect Size (Cohen's d) (1.29) showed a large effect of HA-Trehalose artificial tear.

Mean ± SD DEFC score decreased significantly from 3.66 ± 0.77 to 2.42 ± 1.25 (mean ± SD reduction: 1.24 ± 1.25), and the Effect Size (Cohenśs d) (0.99) showed a large effect of HA-Trehalose artificial tear (Fig. 3).

Related to the clinical signs and the quality of the tear film, corneal (fluorescein) staining, improved significantly (p $<$ 0.05) from baseline to Day 84, with a moderate effect size. However, there were no significant changes in tear meniscus, conjunctival (lissamine green) staining, and TBUT (Table 2).

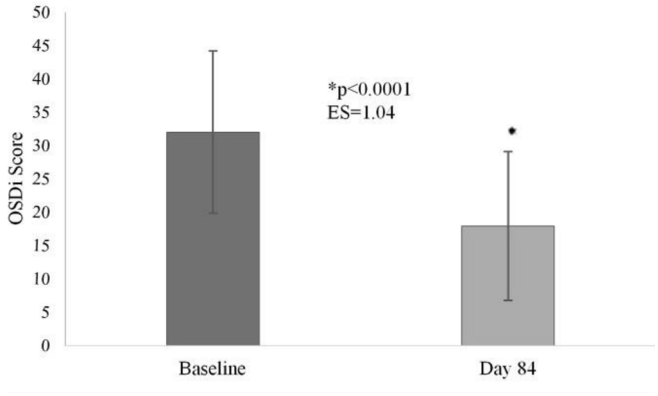
4.3. Safety assessments

No ocular or systemic adverse events were reported by any participant. There was no change in visual acuity (logMAR), which was 0.06 ±

Table 1
VAS scores at baseline and after 84 days treatment with HA-Trehalose artificial tear.

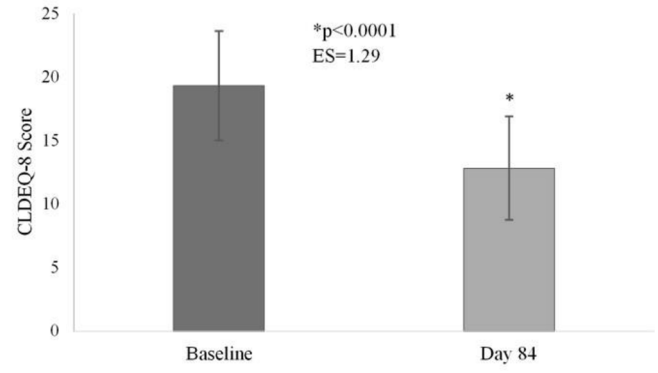
	Baseline	Day 84	P-value	Effect Size
VAS (0–100)				
Pain	14.92 ± 18.88	11.89 ± 19.76	0.05*	0.18
Photophobia	32.80 ± 28.40	21.24 ± 29.26	0.005*	0.36
Dry eye sensation	64.62 ± 21.38	36.21 ± 25.17	<0.0001*	1.16
Blurry vision	35.22 ± 28.09	19.84 ± 18.03	<0.0001*	0.58
Foreign body sensation	35.22 ± 28.09	25.30 ± 29.68	0.005*	0.31
Itching	32.57 ± 25.16	27.27 ± 25.22	0.02*	0.22
Tingling/burning	20.75 ± 24.15	17.80 ± 26.34	0.24	0.12
Sticky eye feeling	20.75 ± 22.53	18.33 ± 21.54	0.43	0.12

Data are mean ± SD, p-value and Effect Size (Cohen's d).
*Statistically significant difference using Student's *t*-test.



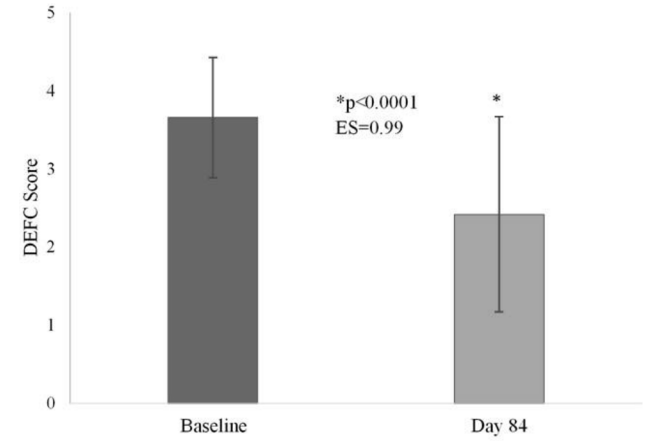
*p-value<0.0001; ES, Effect Size (Cohen's d)

Fig. 1. OSDI score at baseline and Day 84.



*p-value<0.0001; ES, Effect Size (Cohen's d)

Fig. 2. CLDEQ-8 score at baseline and Day 84.



*p-value<0.0001; ES, Effect Size (Cohen's d)

Fig. 3. DEFC score at baseline and Day 84.

0.10 at both baseline and Day 84.

5. Discussion

It is estimated that up to half of contact lens users experience discomfort directly related to their use, affecting millions of users around the world. Symptoms are typically related to eye discomfort such as ocular dryness, irritation, fatigue, burning or foreign body sensation. In addition to these symptoms, associated signs such as decreased TBUT, corneal and conjunctival staining and decreased tear meniscus, among others, have also been found [6]. These factors are secondary to the development of dry eye, which is linked to contact lens use [34]. In order to mitigate the development of dry eye or its associated symptoms, the use of tear supplements and wetting agents has been proposed and can be useful as a treatment to reduce discomfort in patients with dry eye [35]. In this pilot study, preservative-free HA-Trehalose artificial tear supplement has been used to demonstrate reduced signs and symptoms of CLD in contact lens wearers.

Table 2
TBUT, fluorescein staining, lissamine green staining, and tear meniscus evaluation at baseline and after 84 days with HA-Trehalose artificial tear.

	Baseline	Day 84	Baseline-Day 84	P-value	Effect size
TBUT (s)	3.64 ± 1.76	3.33 ± 1.57	−0.30 ± 1.51	0.924	0.20
Corneal staining (Fluorescein) (0–5)	0.92 ± 1.05	0.41 ± 0.48	−0.52 ± 0.96	<0.001*	0.55
Conjunctival staining (Lisamine green) (0–9)	2.52 ± 1.52	2.06 ± 1.34	−0.45 ± 1.50	0.165	0.30
Tear meniscus (0–3)	1.79 ± 0.55	1.76 ± 0.44	−0.03 ± 0.49	0.845	0.06

Data are mean ± SD, p-value and Effect size (Cohen's d).
*Statistically significant using adjusted LS Means P-Value for ANOVA rank transformed differences (TBUT, corneal staining, conjunctival staining) and McNemar-Bowker test (Tear meniscus).

There was an improvement from baseline to Day 84 in all symptomatology tests, with VAS, OSDI, CLDEQ-8, and DEFC showing a statistically significant decrease in the degree of symptoms after 84 days of using HA-Trehalose artificial tear. From the VAS assessments, the two symptoms that improved the most were dry eye sensation and blurry vision, followed by foreign body sensation, photophobia and itching. The only symptoms evaluated in the VAS test that did not show statistically significant reduction differences during the study were tingling/burning and sticky eye feeling, although these symptoms were reduced with respect to the baseline visit. It is noted that these two symptoms were not frequently reported, making it more difficult to achieve statistical significance for small changes over time. These symptomatology results are in agreement with previous data published by Fariselli et al. [20], which showed a reduction in subjective symptoms measured by VAS. The beneficial effect of this artificial tear in terms of the subjective assessment of the participants is important as it reduces CLD. The CLDEQ-8 test confirmed this finding, being significantly improved at Day 84, and the DEFC test, which reflects the degree to which symptoms interfere with daily activities, was also significantly improved at the end of the study, as the subjects had at least one degree of reduction. Similarly, the OSDI test results showed a statistically significant reduction, which agrees with previous OSDI results in moderate to severe dry eye patients treated with HA-trehalose drops published by Chiambaretta et al (OSDI was 45.5 ± 17.2 at baseline and reduced by 30.2 ± 18.7 at D84) [36] and Doan et al (OSDI was 45.5 ± 17.2 at baseline and reduced to 15.50 ± 13.96 at D84) [37].

Furthermore, HA-Trehalose artificial tear improved ocular surface signs related to dry eye. Most of the measured signs were reduced after the instillation of this artificial tear. A statistically significant decrease was observed in corneal staining (fluorescein) and a reduction, although not statistically significant, was also observed in conjunctival staining (lissamine green). The reductions in corneal and conjunctival staining support those described by Fariselli et al. [20] and Chiambaretta et al. [36], in which the ocular surface signs related to dry eye disease improved and a restoration of the ocular surface occurred after instillation of an HA-Trehalose solution.

TBUT results at baseline (3.64 ± 1.76) were consistent with those

described before in subjects diagnosed with dry eye disease [38]. The effect size (ES) obtained for this measure was 0.20, which corresponds to a small change between results, so it was not considered clinically relevant. The reduction in TBUT between baseline to Day 84 was not consistent with previous results in which TBUT increased by 2–3 s after treatment with HA-Trehalose drops [20,36]. However, the worsening reported in the present study did not seem to affect the integrity of the ocular surface, which had reduced staining, nor did it affect the symptoms presented by the participants, which also decreased in incidence during the study. This could be due to the fact that the reduction in TBUT leads to a decrease in the interblink interval, so that the tear film would be regulated [39]. This reduction in TBUT, therefore, does not appear to the clinically relevant, although a study of longer duration and also more subjects is needed to further analyze the evolution of TBUT over time.

The tear meniscus remained unchanged and remained within normal parameters for contact lens wearers during the study.

Overall, the results from the present pilot study are in accordance with what was described at the Tear Film and Ocular Surface Society International Workshop on Contact Lens Discomfort, which states that the use of artificial tears or wetting agents improve the signs and symptoms of dry eye and therefore the discomfort with contact lenses [35]. The results demonstrated potential efficacy of the artificial tear HA-Trehalose to improve the comfort of contact lens use, which would justify the design of a properly designed long-term study. Nevertheless, some limitations should also be taken into account when interpreting the results of the study. The small sample size, short duration, and particularly the uncontrolled design limit the results, which should be confirmed in the future through a larger, randomized controlled trial. However, the present study showed promising results and justifies further research.

6. Conclusions

In conclusion, the data obtained in the present pilot study showed that the instillation of a preservative-free, hypotonic, HA-Trehalose artificial tear supplement (Thealoz® Duo) in subjects wearing contact lenses with dry eye syndrome significantly improved symptoms and reduced associated signs such as corneal and conjunctival staining. Furthermore, no adverse effects related to the instillation of this artificial tear were found. These promising results should be confirmed in a randomized controlled trial.

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Data availability

Data will be made available upon reasonable request to the Corresponding Author, with permission from Laboratoires Thea.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Lim CHL, Stapleton F, Mehta JS. Review of contact lens–related complications. Eye Contact Lens 2018;44:S1–10. https://doi.org/10.1097/ICL.0000000000000481.
[2] Villani E, Canton V, Magnani F, Viola F, Nucci P, Ratiglia R. The aging meibomian gland: an in vivo confocal study. Investig Opthalmology Vis Sci 2013;54(7):4735. https://doi.org/10.1167/iovs.13-11914.
[3] Craig JP, Willcox MDP, Argüeso P, Maissa C, Stahl U, Tomlinson A, et al. The TFOS International Workshop on Contact Lens Discomfort: Report of the contact lens interactions with the tear film subcommittee. Investig Ophthalmol Vis Sci 2013;54. https://doi.org/10.1167/iovs.13-13235.
[4] Lemp MA, Bielory L. Contact lenses and associated anterior segment disorders: dry eye disease, blepharitis, and allergy. Immunol Allergy Clin North Am 2008;28(1):105–17. https://doi.org/10.1016/j.iac.2007.11.002.
[5] Nichols KK, Redfern RL, Jacob JT, Nelson JD, Fonn D, Forstot SL, et al. The TFOS International Workshop on Contact Lens Discomfort: Report of the definition and classification subcommittee. Investig Ophthalmol Vis Sci 2013;54. https://doi.org/10.1167/iovs.13-13074.
[6] Pucker AD, Tichenor AA. A review of contact lens dropout. Clin Optom 2020;12:85–94. https://doi.org/10.2147/OPTO.S198637.
[7] Guillon M. Are silicone hydrogel contact lenses more comfortable than hydrogel contact lenses? Eye Contact Lens 2013;39:86–92. https://doi.org/10.1097/ICL.0b013e31827cb99f.
[8] Dumbleton K, Caffery B, Dogru M, Hickson-Curran S, Kern J, Kojima T, et al. The TFOS International Workshop on Contact Lens Discomfort: Report of the subcommittee on epidemiology. Investig Ophthalmol Vis Sci 2013;54. https://doi.org/10.1167/iovs.13-13125.
[9] Nichols JJ, Ziegler C, Mitchell GL, Nichols KK. Self-reported dry eye disease across refractive modalities. Investig Ophthalmol Vis Sci 2005;46:1911–4. https://doi.org/10.1167/iovs.04-1294.
[10] Downie LE, Craig JP. Tear film evaluation and management in soft contact lens wear: a systematic approach. Clin Exp Optom 2017;100(5):438–58. https://doi.org/10.1111/cxo.12597.
[11] Jones L, Brennan NA, González-Méijome J, Lally J, Maldonado-Codina C, Schmidt TA, et al. The TFOS International Workshop on Contact Lens Discomfort: Report of the contact lens materials, design, and care subcommittee. Investig Ophthalmol Vis Sci 2013;54. https://doi.org/10.1167/iovs.13-13215.
[12] Fondi K, Wozniak PA, Schmidl D, Bata AM, Witkowska KJ, Popa-Cherecheanu A, et al. Effect of hyaluronic acid/trehalose in two different formulations on signs and symptoms in patients with moderate to severe dry eye disease. J Ophthalmol 2018;2018:1–7. https://doi.org/10.1155/2018/4691417.
[13] Baudouin C, Aragona P, Messmer EM, Tomlinson A, Calonge M, Boboridis KG, et al. Role of hyperosmolarity in the pathogenesis and management of dry eye disease: Proceedings of the ocean group meeting. Ocul Surf 2013;11:246–58. https://doi.org/10.1016/j.jtos.2013.07.003.
[14] Jain NK, Roy I. Effect of trehalose on protein structure. Protein Sci 2009;18:24–36. https://doi.org/10.1002/pro.3.
[15] Čejková J, Čejka Č, Luyckx J. Trehalose treatment accelerates the healing of UVB-irradiated corneas. Comparative immunohistochemical studies on corneal cryostat sections and corneal impression cytology. Histol Histopathol 2012;27:1029–40. https://doi.org/10.14670/HH-27.1029.
[16] Li J, Roubeix C, Wang Y, Shi S, Liu G, Baudouin C, et al. Therapeutic efficacy of trehalose eye drops for treatment of murine dry eye induced by an intelligently controlled environmental system. Mol Vis 2012;18:317–29.
[17] Nakamura M, Hikida M, Nakano T, Ito S, Hamano T, Kinoshita S. Characterization of water retentive properties of hyaluronan. Cornea 1993;12(5):433–6. https://doi.org/10.1097/00003226-199309000-00010.
[18] Snibson GR, Greaves JL, Soper NDW, Tiffany JM,Wilson CG, Bron AJ. Ocular surface residence times of artificial tear soluctions. Cornea 1992;11:288-293. https://doi.org/0.1097/00003226-199207000-00003.
[19] Wozniak PA, Schmidl D, Bata AM, Fondi K, Witkowska KJ, Aranha dos Santos V, et al. Effect of different lubricant eye gels on tear film thickness as measured with ultrahigh-resolution optical coherence tomography. Acta Ophthalmol 2017;95(4):e307–13. https://doi.org/10.1111/aos.2017.95.issue-410.1111/aos.13342.
[20] Fariselli C, Giannaccare G, Fresina M, Versura P. Trehalose/hyaluronate eyedrop effects on ocular surface inflammatory markers and mucin expression in dry eye patients. Clin Ophthalmol 2018;12:1293–300. https://doi.org/10.2147/OPTH.S174290.
[21] Novack GD, Asbell P, Barabino S, Bergamini MVW, Ciolino JB, Foulks GN, et al. TFOS DEWS II clinical trial design report. Ocul Surf 2017;15(3):629–49. https://doi.org/10.1016/j.jtos.2017.05.009.
[22] Burckhardt CS, Jones KD. Adult measures of pain: The McGill Pain Questionnaire (MPQ), Rheumatoid Arthritis Pain Scale (RAPS), Short-Form McGill Pain Questionnaire (SF-MPQ), Verbal Descriptive Scale (VDS), Visual Analog Scale (VAS), and West Haven-Yale Multidisciplinary Pain Inven. Arthritis Rheum 2003;49:S96–104. https://doi.org/10.1002/art.11440.
[23] Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the ocular surface disease index. Arch Ophthalmol 2000;118:615. https://doi.org/10.1001/archopht.118.5.615.
[24] Chalmers RL, Begley CG, Moody K, Hickson-Curran SB. Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8) and opinion of contact lens performance. Optom Vis Sci 2012;89:1435–42. https://doi.org/10.1097/OPX.0b013e318269c90d.
[25] Koh S, Chalmers R, Kabata D, Shintani A, Nishida K. Translation and validation of the 8-item Contact Lens Dry Eye Questionnaire (CLDEQ-8) among Japanese soft contact lens wearers: The J-CLDEQ-8. Contact Lens Anterior Eye 2019;42(5):533–9. https://doi.org/10.1016/j.clae.2019.03.002.

[26] Tran N, Graham AD, Lin MC. Contact lens & anterior eye ethnic differences in dry eye symptoms: effects of corneal staining and length of contact lens wear. Contact Lens Anterior Eye 2013;36:281–8. https://doi.org/10.1016/j.clae.2013.06.001.
[27] Bron AJ, Abelson MB, Ousler G, Pearce E, Tomlinson A, Yokoi N. Methodologies to diagnose and monitor dry eye disease: Report of the Diagnostic Methodology Subcommittee of the International Dry Eye Workshop. Ocul Surf 2007;5:108–52. https://doi.org/https://doi.org/10.1016/s1542-0124(12)70083-6.
[28] Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. Cornea 2003;22(7):640–50.
[29] van Bijsterveld OP. Diagnostic tests in the Sicca syndrome. Arch Ophthalmol 1969;82(1):10–4.
[30] Khurana AK, Chaudhary R, Ahluwalia BK, Gupta S. Tear film profile in dry eye. Acta Ophthalmol 1991;69(1):79–86. https://doi.org/10.1111/j.1755-3768.1991.tb01997.x.
[31] Ferris FL, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. Am J Ophthalmol 1982;94:91–6. https://doi.org/https://doi.org/10.1016/0002-9394(82)90197-0.
[32] Razali N, Wah Y. Power comparisons of shapiro-wilk, kolmogorov-smirnov, lilliefors and anderson-darling tests. J Stat Model Anal 2011;2:21–33.
[33] Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. Med Care 1989;27(Supplement):S178–89.
[34] Markoulli M, Optometry SK-C, 2017 U. Contact lens wear and dry eyes: challenges and solutions. Clin Optom 2017;9:41. https://doi.org/https://dx.doi.org/10.2147%2FOPTO.S111130.
[35] Nichols JJ, Willcox MD, Bron AJ, Belmonte C, Ciolino JB, Craig JP, et al. The TFOS international workshop on contact lens discomfort: executive summary. Invest Ophthalmol Vis Sci 2013;54:TFOS7–13. https://doi.org/https://doi.org/10.1167/iovs.13-13212.
[36] Chiambaretta F, Doan S, Labetoulle M, Rocher N, El Fekih L, Messaoud R, et al. A randomized, controlled study of the efficacy and safety of a new eyedrop formulation for moderate to severe dry eye syndrome. Eur J Ophthalmol 2017;27(1):1–9. https://doi.org/10.5301/ejo.5000836.
[37] Doan S, Bremond-Gignac D, Chiambaretta F. Comparison of the effect of a hyaluronate–trehalose solution to hyaluronate alone on Ocular Surface Disease Index in patients with moderate to severe dry eye disease. Curr Med Res Opin 2018;34(8):1373–6. https://doi.org/10.1080/03007995.2018.1434496.
[38] Le Q, Zhou X, Ge L,Wu L, Hong J, Xu J. Impact of dry eye syndrome on vision-related quality of life in a non-clinic-based general population. BMC Ophthalmol 2012;12:22. https://doi.org/https://doi.org/10.1186/1471-2415-12-22.
[39] Ousler GW, Hagberg KW, Schindelar M, Welch D, Abelson MB. The ocular protection index. Cornea 2008;27:509–13. https://doi.org/10.1097/ICO.0b013e31816583f6.