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Randomized controlled trial of trehalose: An efficient autophagic bioprotectant in the management of dry eye disease

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Abstract:

PURPOSE: To compare the therapeutic effect of sodium hyaluronate (SH)–trehalose (Trehalube, Microlabs, Bangalore, India, SH 0.1% and trehalose 3%) or SH (0.1% Hylotears, Raymed, Chandigarh, India) alone in patients with dry eye disease (DED).

MATERIALS AND METHODS: Patients were randomized into two groups: SH-trehalose (SH 0.1% and trehalose 3%) or SH (0.1% Hylotears) alone. The Ocular Surface Disease Index (OSDI) questionnaire was used to assess patient's symptoms. Patients were followed up at 4 and 8 weeks, and OSDI score, tear film break-up time (TBUT), tear film height (TFH), Schirmer's test, and conjunctival staining were evaluated at each visit.

RESULTS: A total of 384 patients were included in the study, 192 patients in each arm. The mean age of participants was 37.62 + 14.4 years and 225 were women (56%). The improvement in Schirmer's test was significantly better in the SH-trehalose group at 8 weeks (5.26 + 4.3 mm, 95% confidence interval = 4.6–5.9 mm) compared to the SH group (3.71 + 3.9, 95% confidence interval = 3.15–4.28 mm). The TBUT and TFH showed slight improvement at 4 weeks in both groups, but not at 8 weeks. There were no group differences at all-time points in terms of conjunctival staining and OSDI-based grades of DED.

CONCLUSION: It was found that treating dry eye with SH-trehalose leads to greater improvement in the Schirmer's values and TBUT after 8 weeks of sustained use in patients with DED, and this was more pronounced in those with severe DED.

Keywords:

Clinical trial, dry eye, sodium hyaluronate, trehalose

Introduction

Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tears film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. Dry eye disease (DED) is a common but underdiagnosed disease that affects

between 5% and 50% of the population^[1,2] and significantly impacts patient's vision-related quality of life.^[3] Recent estimates show that there may be 16 million diagnosed cases of DED in the United States alone, with the prevalence being higher in women and in populations above 45 years of age.^[4] With increasing dependence on electronic devices, digital eye strain is very common and contributing to the increasing prevalence of DED.^[5,6] Hence, there is incomplete blinking and there is instability of the tear film.

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The Tear Film and Ocular Surface Society in the Dry Eye Workshop II recently redefined dry eye as a multifactorial disease of the ocular surface where loss of tear film homeostasis including tear film instability and hyperosmolarity leads to ocular surface inflammation and damage.^[7] It also considers evaporative and aqueous deficiency DED as part of a continuum. This report also described best practices for the treatment and management of DED and laid emphasis on differentiating evaporative from aqueous deficiency type of dry eye for selecting the most appropriate management strategy.^[8] However, the multifactorial nature of DED makes it difficult to identify a single cause in any particular patient. A multipronged approach is required for optimizing patient outcomes including treating the tear insufficiency, lid abnormalities, ocular surface inflammation, and other factors such as dietary changes and environmental modifications.^[8,9]

Most management strategies for DED revolve around improving the tear volume with lubricants derived from carboxymethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl guar, sodium hyaluronate (SH), and polyvinyl alcohol or a combination of these. Trehalose is a naturally occurring nonreducing homodisaccharide that has been shown to protect cultured human corneal epithelial cell membranes from oxidative injury, increase autophagy, prevent cell death from desiccation, and preserve the normal cellular morphology, functions of cell membrane, and their proliferative activity.^[10,11] Autophagy is a process which mediates the sequestration, lysosomal delivery, and degradation of proteins and organelles. This leads to an enhancement of FOXO1 activation and contents of various other autophagy-related genes products (LC3, Beclin 1, Sqstm 1, and Atg 5). At molecular level, trehalose functions as a cryoprotective agent by preventing the crystallization of protein hydration water. In combination with lubricants, it has the potential to improve tear film homeostasis and benefit patients suffering from DED.

Trehalose has been previously studied for the management of DED.^[12-15] However, despite a randomized study design in some, most studies have an inadequate sample size or have not followed up patients for a sufficiently long period. Only the study by Chiambaretta *et al.*^[16] evaluated more than 100 patients using a randomized clinical trial and compared SH-trehalose combination and SH alone in the management of DED. To address this, we performed a randomized clinical trial to analyze whether the SH-trehalose combination is superior to SH alone in a cohort of Indian patients in Western Rajasthan with DED.

Materials and Methods

This was a randomized, active-controlled, single-masked, clinical trial approved by the institutional ethics

committee (approval number: AIIMS/IEC/2019-20/1018) and followed the tenets of Declaration of Helsinki and good clinical practice guidelines. Informed consent was obtained from all participants before enrollment. The Clinical Trial Registry of India reference number for the article is CTRI/2020/04/024605.

Participants

Patients between 15 and 74 years of age attending the outpatient services of the ophthalmology department with complaints such as dryness, watering, grittiness, burning, and hyperemia were examined to rule out DED by performing Schirmer's test and tear film break-up time (TBUT) using standardized procedures. Those with a Schirmer's test of <10 mm at the end of 5 min or a TBUT of <10 s were invited to participate in the study. Patients with systemic risk factors for DED such as Sjogren's disease, lupus, and chronic drug intake causing dry eyes such as antidepressants and antihistamines were also included, and specific systemic and drug history were noted. Participants who did not give consent to take part in the study or had a prior ocular surgery or were on any ocular medications including lubricants and antiglaucoma medications were excluded.

Sample size calculation

Given 1:1 randomization, 90% power, and a precision error of 5% to detect a difference of 10% or more in Schirmer's test value at 5 min between eyes receiving SH-trehalose and SH alone, a required sample size of 384 eyes (192 in each group) was calculated.

Randomization, masking, and allocation

Patients were randomized into two treatment groups: SH-trehalose (Trehalube, Microlabs, SH 0.1% and trehalose 3%) or SH (0.1% Hylotears, Raymed) alone. Randomization codes were generated using a computer program (random number assignment protocol) and placed in serially numbered sealed envelopes for allocation. The ophthalmologist (not the principal investigator) who evaluated the patients before recruitment was masked to the type of drug allocated. However, the patient was aware of the drug given. The sealed envelopes were attached to the case files and opened on the day of recruitment by a trained nursing staff. Patients were asked to instill the assigned drops 4 times a day for 8 weeks. Masking was maintained during follow-up visits, so that the examining ophthalmologist performing slit-lamp examination and other clinical tests was unaware of the treatment group.

Clinical assessment

At baseline, after a detailed history, a detailed ophthalmological examination including visual acuity

with refraction if required, intraocular pressure, and anterior and posterior segment examination was done. The Ocular Surface Disease Index (OSDI) questionnaire was used to assess patient's symptoms. The results were recorded on a scale from 0 to 100 as previously defined, with scores 0–12 representing normal, 13–22 representing mild DED, 23–32 representing moderate DED, and >33 representing severe DED.^[17]

The TBUT was measured by applying fluorescein stain to the ocular surface. Slit-lamp examination with a cobalt blue filter was used to investigate the tear film layer. The patient was asked to look straight and the time from the last blink to the appearance of first random dry spot on the cornea was noted. The tear film height (TFH) was measured on the slit lamp before TBUT assessment.

The Schirmer's test was performed without the application of local anesthesia. Schirmer's strips were inserted in the eye over the lower lid margin, at the junction of the middle and outer third. The patient was asked to close the eye, and after 5 min, the wetting of the Schirmer's paper was measured.

The van Bijsterveld conjunctival staining score was measured after staining with rose bengal. The conjunctiva was divided into a superior paralimbal area, inferior paralimbal area, and a peripheral area with a grading scale of 0–3, with 0 meaning no staining and 3 meaning maximum staining, with a maximal score of 9.^[18]

Patients were followed up at 4 and 8 weeks, and the OSDI score, TBUT, TFH, Schirmer's test, and conjunctival staining were evaluated at each visit.

Outcome measures

A change in Schirmer's test values at 8 weeks of follow-up between groups was the primary outcome measure. Changes in the other parameters including TBUT, TFH, and conjunctival staining were assessed as secondary outcome measures.

Statistical analysis

All continuous variables were presented as mean with standard deviation or median with interquartile range, while categorical variables were presented as proportions (*n*, %). The worse eye was selected based on the lower Schirmer's value at baseline and the right eye was chosen in cases where both the right and left had the same values. Parameters from the worse eye were selected for statistical analysis. Group differences in continuous variables were analyzed using the Student's *t*-test or the Wilcoxon's rank-sum test for nonparametric variables. Group differences in categorical variables were analyzed using the Chi-square or the Fisher's exact test for comparing proportions <5%. Repeated measures

ANOVA was used to analyze differences in continuous variables at different time points compared to baseline values. Linear regression analysis was carried out to determine group differences in continuous variables after adjusting for covariates deemed to be confounders.

All data were entered into Microsoft Excel and analyzed using STATA 12.1 I/c (StataCorp, Fort Worth, Texas, USA). *P* < 0.05 was considered statistically significant.

Results

We included a total of 384 patients in the study, 192 patients in each arm. The mean age of participants was 37.62 ± 14.4 years and 225 were women (56%) as depicted in Chart-1. There was no difference in age (36.72 ± 14.8 vs. 36.12 ± 13.6 years, *P* = 0.63) or gender between groups. The right was the worse eye in 276 patients (79%), while the left eye was worse in the remaining 108 (21%). Based on the OSDI scores at baseline, 160 patients (42%) had mild dry eye, 154 (40%) had moderate dry eye, and 50 (13%) had severe dry eye, while a minority (*n* = 20, 5%) were normal.

Table 1 shows comparison of Schirmer's tests at baseline and at 4 and 8 weeks of follow-up in the two groups. There was no difference in the values at baseline and at 4 weeks, but at 8 weeks, the Schirmer's test showed significantly better values in the SH-trehalose group. Similarly, the improvement in Schirmer's test was significantly better in the SH-trehalose group at 8 weeks (5.26 ± 4.3 mm, 95% confidence interval = 4.6–5.9 mm) compared to the SH group (3.71 ± 3.9, 95% confidence interval = 3.15–4.28 mm). The improvement in Schirmer's values was significant at 4 weeks compared to baseline in both groups (repeated measures ANOVA), while the improvement continued only in the SH-trehalose group at 8 weeks (*P* = 0.01), but not in the SH group (*P* = 0.42).

Similar trends were seen in the TBUT at 4 and 8 weeks [Table 2] with significantly greater values in the SH-trehalose group (=3.42 ± 4.3 mm, 95% confidence interval = 2.8–4.1 mm) compared to the SH group (=2.29 ± 4.2 mm, 95% confidence interval = 1.7–2.8 mm).

Table 1: Comparison of Schirmer's test values in the worse eye in eyes receiving trehalose versus standard therapy

Schirmer's test (mm)	Trehalose (n=192)	Standard therapy (n=192)	<i>P</i>
Baseline	6.12±2.7	6.12±2.7	0.99
At 4 weeks	10.26±3.5*	9.81±3.2*	0.15
At 8 weeks	11.36±3.2*	9.82±3.2	<0.001
Difference at 4 weeks	4.14±3.1	3.69±3.4	0.10
Difference at 8 weeks	5.26±4.3	3.71±3.9	<0.001

**P*<0.05 – Repeated measures ANOVA comparing the time points from previous time point

Again, the improvement in TBUT values was significant at 4 weeks compared to baseline in both groups (repeated measures ANOVA), while the improvement continued only in the SH-trehalose group at 8 weeks ($P = 0.02$), but not in the standard treatment group ($P = 0.54$). The TFH [Table 3] showed slight improvement at 4 weeks in both groups, but not at 8 weeks. There were no intergroup differences at any time point.

Conjunctival staining using rose bengal stain is shown in Table 4. There was a significant improvement in the staining pattern in both groups at 4 weeks, with majority showing no staining at this time ($P < 0.001$ in both groups). At 8 weeks, 69% ($n = 264$) showed no staining, 25% ($n = 96$) showed mild staining, and 6% ($n = 24$) continued to show maximum staining. There were no group differences at all-time points in terms of conjunctival staining. The OSDI scores are shown in Table 5. There was a significant improvement, with 204 (53%) patients showing moderate-to-severe dry eye at baseline, which reduced to 96 (25%) at 4 weeks and 20 (5%) at 8 weeks. There were no group differences in the OSDI-based grades of DED.

The magnitude of improvements in Schirmer's values for subgroup of patients with severe dry eye ($n = 50$) at baseline showed that improvement was significantly more in those receiving SH-trehalose ($n = 25$, $=6.4 \pm 3.8$) compared to SH ($n = 25$, $=3.0 \pm 3.4$ mm, $P < 0.001$). Linear regression analysis showed that the Schirmer's test had a 1.54 mm greater improvement (95% confidence interval = 1.7–2.4 mm) in those receiving SH-trehalose compared to standard treatment, despite adjusting for age, gender, and OSDI score at baseline. An analysis including both eyes of every patient was repeated using repeated measures statistics and generalized linear models (results not shown). This did not change any of the results or inferences significantly.

No significant adverse events were noted in either group during the follow-up period.

Discussion

Trehalose is a naturally occurring disaccharide with exceptional bioprotectant properties that has been shown to protect cultured human corneal epithelial cell membranes from oxidative injury, increase autophagy, prevent cell death from desiccation, and preserve the normal cellular morphology, functions of cell membrane, and their proliferative activity. At molecular level, trehalose functions as a cryoprotective agent by preventing the crystallization of protein hydration water. In combination with lubricants, it has the potential to improve tear film homeostasis and benefit patients suffering from DED.

Table 2: Comparison of tear film break-up time in the worse eye in eyes receiving trehalose versus standard therapy

TBUT (s)	Trehalose (n=192)	Standard therapy (n=192)	P
Baseline	6.07±3.4	5.46±3.1	0.09
At 4 weeks	8.03±3.7*	7.73±3.5*	0.48
At 8 weeks	9.50±3.3*	7.76±3.5	<0.001
Difference at 4 weeks	2.26±4.7	1.96±4.3	0.53
Difference at 8 weeks	3.42±4.3	2.29±4.2	0.12

* $P < 0.05$ – Repeated measures ANOVA comparing the time points from previous time point. TBUT=Tear film break-up time

Table 3: Comparison of tear film height in the worse eye in eyes receiving trehalose versus standard therapy

TFH (mm)	Trehalose (n=192)	Standard therapy (n=192)	P
Baseline	0.43±0.2	0.45±0.3	0.44
At 4 weeks	0.49±0.4*	0.46±0.3*	0.73
At 8 weeks	0.49±0.3	0.47±0.2	0.57
Difference at 4 weeks	0.06±0.5	0.07±0.6	0.42
Difference at 8 weeks	0.06±0.4	0.02±0.3	0.99

* $P < 0.05$ – Repeated measures ANOVA comparing the time points from previous time point. TTF=Tear film height

Table 4: Comparison of rose bengal staining grades in the worse eye in eyes receiving trehalose versus standard therapy

RB staining	Trehalose (n=192), n (%)	Standard therapy (n=192), n (%)	P
Baseline			
No stain (0-3)	59 (31)	54 (28)	0.85
Mild stain (4-6)	109 (57)	113 (59)	
Maximum stain (7-9)	24 (12)	24 (13)	
At 4 weeks*			
No stain (0-3)	129 (67)	128 (67)	0.96
Mild stain (4-6)	49 (26)	51 (26)	
Maximum stain (7-9)	14 (7)	13 (7)	
At 8 weeks			
No stain (0-3)	139 (73)	125 (66)	0.25
Mild stain (4-6)	41 (21)	55 (29)	
Maximum stain (7-9)	12 (6)	12 (5)	

* $P < 0.05$ – Chi-square comparing the time points from previous time point

In this randomized, single-masked clinical trial, we found that treating dry eye with SH-trehalose leads to greater improvement in Schirmer's values and TBUT compared to standard treatment with SH alone. However, this benefit was seen only with prolonged therapy up to 8 weeks and was not observed at 4 weeks. The benefit was more pronounced in those with severe dry eye and the benefit persisted even after adjusting for confounders such as age and gender. The improvement in conjunctival staining and grade of DED did not differ between groups at all-time points, suggesting that even though objective parameters show a much better response to trehalose addition, subjective patient improvement is seen in both groups.

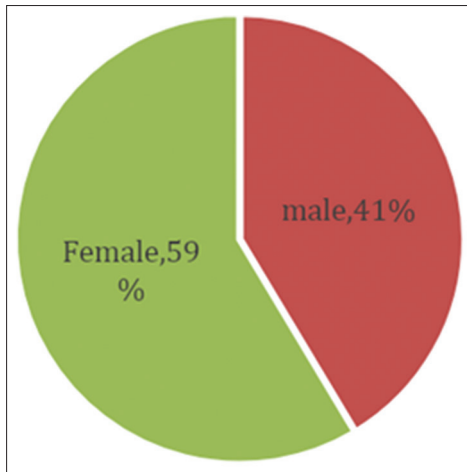


Chart 1: Demographic profile

Table 5: Comparison of ocular surface disease index in the worse eye in eyes receiving trehalose versus standard therapy

OSDI	Trehalose (n=192), n (%)	Standard therapy (n=192), n (%)	P
Baseline			
Normal	10 (5)	10 (5)	0.93
Mild DED	77 (40)	83 (43)	
Moderate DED	80 (42)	74 (39)	
Severe DED	25 (13)	25 (13)	
At 4 weeks*			
Normal	35 (18)	43 (22)	0.27
Mild DED	101 (56)	109 (57)	
Moderate DED	50 (23)	35 (18)	
Severe DED	6 (3)	5 (3)	
At 8 weeks			
Normal	48 (25)	57 (30)	0.38
Mild DED	132 (69)	127 (66)	
Moderate DED	10 (5)	8 (4)	
Severe DED	2 (1)	0	

*P<0.05 – Chi-square comparing the time points from previous time point.
OSDI=Ocular surface disease index, DED=Dry eye disease

Chiambaretta *et al.*^[16] performed a similar randomized study including 53 patients in the SH-trehalose group and 52 in the SH group and followed them up for 84 days. Based on the Oxford dry eye grading scale used as the primary outcome measure at day 35 (5 weeks), the authors reported noninferiority of SH-trehalose over hyaluronic acid (HA) alone. The authors also noted a significant improvement in the OSDI score, with significantly fewer patients in the moderate-to-severe group in the SH-trehalose group. We did not observe beneficial effects of the SH-trehalose combination at the 4 weeks' time point, but did so at the 8 weeks' time point, though we did not investigate at the 5-week time point. These results show that the beneficial influence of trehalose on the desiccating corneal epithelial cells takes more than 1 month to manifest using both subjective and objective parameters. Hence, it is imperative that

therapy be continued beyond 1 month before evaluating its effects.

In another randomized study, Matsuo used a randomized, double-masked, dose-ranging, fellow eye-controlled clinical trial design and enrolled 34 patients with moderate-to-severe dry eye syndrome.^[12] The patients used either 100 or 200 mM trehalose dissolved in saline six times daily in one eye and control saline in the other eye for 4 weeks. The authors reported that the conjunctival staining scores of the ocular surface improved at both 2 weeks and 4 weeks in the eyes with 100 and 200 mM trehalose, compared with eyes with control saline. The TBUT also became significantly longer at 2 weeks and 4 weeks with 100 mM trehalose. This was one of the initial studies to show the beneficial effects of trehalose; however, since the control group was placebo and not an active ingredient, it is difficult to compare our results with this study.

In another randomized study, Doan *et al.*^[14] enrolled 52 eyes with SH-trehalose and 53 with HA alone for 84 days and found that significantly more patients had OSDI <19 at day 84 in the SH-trehalose group (79%) than in the SH group (59%). The authors did not find this difference at day 35, again showing a delayed influence of trehalose on the improvement in patients' symptoms. Pinto-Bonilla *et al.* studied 17 adult patients with moderate-to-severe dry eye syndrome who were randomized to treatment with SH-trehalose or Systane eyedrops containing carboxymethylcellulose, dextran, and glycerin for 7 days. The authors concluded that both medications were equally effective in improvement of the OSDI scores and patients symptoms. We found an improvement in the objective tests, but did not see any improvement in the OSDI grades even at 8 weeks. It is possible that SH is an effective lubricant and, being part of both groups, leads to symptomatic improvement equally. However, we believe that the objective improvements in the Schirmer's and TBUT may translate into fewer applications of SH-trehalose compared to HA alone, though we did not allow an "as required installation" in our protocol and thus were unable to study the graded response in our patients. Furthermore, the tear film stabilizing influence of trehalose may be evident over longer follow-up times.

We have summarized the previous clinical trials using trehalose and presented our results in direct comparison to these [Table 6]. As evidenced by these comparisons, our study included a large sample size compared to other studies. A complete dry eye evaluation was done including the questionnaire and the various dry eye tests to increase the reliability, similar to methodology of previous studies. Our study also focused on the epidemiology, showing that large proportion of the patients had mild-to-moderate disease.

Table 6: Comparison of previous studies on trehalose

Study authors	Study design	Methods and outcome measures	Conclusion
Chiambaretta <i>et al.</i>	Randomized controlled trial SH-trehalose (<i>n</i> =53) versus SH (<i>n</i> =52)	Oxford dry eye grading scale, Schirmer's test, tear break-up time, conjunctival hyperemia, and global performance were assessed at baseline, day 35, and day 84	HA-trehalose is effective and safe, with better patient satisfaction, than existing HA-only eyedrops particularly from the 1 st month of treatment, and offers a therapeutic advancement in the treatment of moderate to severe DED
Matsuo <i>et al.</i>	Randomized double-masked clinical trial. Compared trehalose (100 mM and 200 mM) versus saline (<i>n</i> =34 with moderate to severe dry eye used drug and saline in one eye each)	Symptoms and signs in both eyes were recorded at baseline, 2 weeks, and 4 weeks in terms of fluorescein and rose bengal staining and tear film break-up time	Fluorescein and rose bengal staining scores improved at both 2 weeks and 4 weeks. Tear film break-up time improved with 100 mM trehalose. No ocular adverse events were observed
Doan <i>et al.</i>	Phase III, randomized, controlled, single-blind, multicenter study. Compared HA-trehalose (<i>n</i> =52) versus HA administered for 84 days	Eligible patients had moderate to severe DED with OSDI \geq 18. Here the results of a <i>post hoc</i> analysis of the percentage of patients with OSDI < 19 on day 35 and day 84 are reported	This data supports the addition of trehalose to HA-containing eyedrop solutions to provide better symptomatic relief from moderate to severe DED, based on an OSDI score of < 19 after 84 days of treatment
Current study	Randomized single-masked clinical trial. SH-trehalose (<i>n</i> =192) versus SH (<i>n</i> =192) alone	OSDI score, Schirmer test, tear break-up time, tear film height and rose bengal staining	We found that SH-trehalose lead to greater improvement in the Schirmer's values and TBUT after eight weeks of sustained use in patients with DED, and this was more pronounced in those with moderate to severe DED

OSDI=Ocular surface disease index, DED=Dry eye disease, SH=Sodium hyaluronate HA: Hyaluronic acid

This study showed that trehalose was more effective in moderate-to-severe DED.

The merits of this study are the large sample size, strict adherence to randomization and masking protocols, and a relative long follow-up to study beneficial effects of SH-trehalose. The demerits are the lack of use of more sophisticated tools for tear film assessment and lack of masking of patients, which might influence the subjective OSDI scores.

Conclusion

We found that treating dry eye with SH-trehalose leads to greater improvement in the Schirmer's values and TBUT after 8 weeks of sustained use in patients with DED, and this was more pronounced in those with severe DED. However, this did not translate into better subjective outcomes. More studies with longer follow-up times are required to uncover the continued and enhanced efficacy of the SH-trehalose drops over SH and other routinely used lubricants, especially in patients with severe DED.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

References

1. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, *et al.* TFOS DEWS II Epidemiology Report. *Ocul Surf* 2017;15:334-65.
2. Rouen PA, White ML. Dry eye disease: Prevalence, assessment, and management. *Home Healthc Now* 2018;36:74-83.
3. Li M, Gong L, Chapin WJ, Zhu M. Assessment of vision-related quality of life in dry eye patients. *Invest Ophthalmol Vis Sci* 2012;53:5722-7.
4. Farrand KF, Fridman M, Stillman IÖ, Schaumberg DA. Prevalence of diagnosed dry eye disease in the United States among adults aged 18 years and older. *Am J Ophthalmol* 2017;182:90-8.
5. Sheppard AL, Wolffsohn JS. Digital eye strain: Prevalence, measurement and amelioration. *BMJ Open Ophthalmol* 2018;3:e000146.
6. Courtin R, Pereira B, Naughton G, Chamoux A, Chiambaretta F, Lanhers C, *et al.* Prevalence of dry eye disease in visual display terminal workers: A systematic review and meta-analysis. *BMJ Open* 2016;6:e009675.
7. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, *et al.* TFOS DEWS II Definition and Classification Report. *Ocul Surf* 2017;15:276-83.
8. Jones L, Downie LE, Korb D, Benitez-Del-Castillo JM, Dana R, Deng SX, *et al.* TFOS DEWS II Management and Therapy Report. *Ocul Surf* 2017;15:575-628.
9. Rolando M, Cantera E, Mencucci R, Rubino P, Aragona P. The correct diagnosis and therapeutic management of tear dysfunction: Recommendations of the P.I.C.A.S.S.O. board. *Int Ophthalmol* 2018;38:875-95.

10. Matsuo T. Trehalose protects corneal epithelial cells from death by drying. *Br J Ophthalmol* 2001;85:610-2.
11. Hill-Bator A, Misiuk-Hojlo M, Marycz K, Grzesiak J. Trehalose-based eye drops preserve viability and functionality of cultured human corneal epithelial cells during desiccation. *Biomed Res Int* 2014;2014:292139.
12. Matsuo T, Tsuchida Y, Morimoto N. Trehalose eye drops in the treatment of dry eye syndrome. *Ophthalmology* 2002;109:2024-9.
13. Pinto-Bonilla JC, Del Olmo-Jimeno A, Llovet-Osuna F, Hernández-Galilea E. A randomized crossover study comparing trehalose/hyaluronate eyedrops and standard treatment: Patient satisfaction in the treatment of dry eye syndrome. *Ther Clin Risk Manag* 2015;11:595-603.
14. 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;34:1373-6.
15. 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.
16. Chiambaretta F, Doan S, Labetoulle M, Rocher N, Fekih LE, 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;27:1-9.
17. Grubbs JR Jr., Tolleson-Rinehart S, Huynh K, Davis RM. A review of quality of life measures in dry eye questionnaires. *Cornea* 2014;33:215-8.
18. George MA, Abelson MB, Schaefer K, Mooshian M, Weintraub D. A precise method of using rose Bengal in the evaluation of dry eye and the detection of changes in its severity. *Adv Exp Med Biol* 1994;350:549-52.