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Effect of different artificial tears on tear film parameters in dry eye disease

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SIGNIFICANCE: Artificial tears remain the cornerstone for managing dry eye disease. The current study's real-world efficacy test of carboxymethylcellulose (CMC), polyethylene glycol (PEG) 400, or sodium hyaluronate (SH)–based lubricants highlights their similar effects on noninvasive tear film parameters over the short term. However, patients reported better relief with SH-based lubricants.

PURPOSE: This study aimed to compare the short-term impact of different artificial tear formulations on tear film in moderate dry eye disease patients.

METHODS: A prospective, double-masked, controlled study randomly allocated moderate dry eye disease patients into five groups of artificial tears: 0.5% CMC, 1% CMC, 0.1% SH-trehalose, 0.4% PEG 400–0.3% propylene glycol (PG), and 0.1% SH–0.4% PEG 400–0.3% PG. Noninvasive tear breakup time (NIBUT), tear meniscus height, and bulbar redness (Keratograph 5M; OCULUS Optikgeräte, Wetzlar, Germany) were assessed (in a controlled environment chamber 68 to 70°F; 35% relative humidity) at baseline and every 15 minutes for 1 hour after a drop instillation in the left eye. The right eye was an internal control. At 1 hour, subjects were asked for a change in subjective symptomatology (scales 0 to 4). A linear mixed-effect model was used for analysis.

RESULTS: Each artificial tear group had 20 patients (100 patients). All groups had similar dry eye disease types and durations, baseline ocular surface disease index scores, and tear film parameters. All artificial tears showed significant improvement in NIBUT values at all time points from baseline compared with contralateral eyes. The change in NIBUT values was similar between different artificial tears at all time points. Bulbar redness scores and tear meniscus height showed no significant change in either eye with time or artificial tears. All patients reported improvement in dry eye disease symptomatology, with significant differences observed between 1% CMC and SH-PEG-PG ($p=0.01$), 0.5% CMC and SH-PEG-PG ($p<0.0001$), and 0.5% CMC and 0.1% SH-trehalose ($p=0.01$), where SH-based tear drops performed better.

CONCLUSIONS: Tear film stability improves following a single drop of CMC, SH, and PEG-based artificial tears, although these artificial tears do not differ in their short-term effect.

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Artificial tears are commonly prescribed for dry eye disease and many ophthalmic disorders in ophthalmic practice.[1–3] The artificial tears market has many over-the-counter lubricants, the first line of therapy for dry eye disease patients. Commonly used artificial tears are carboxymethylcellulose (CMC) or sodium hyaluronate (SH)–based formulations. Existing clinical studies or trials on both types have shown a positive response in subjective improvement and tear film stability, with few studies reporting a significant difference between the CMC- and SH-based artificial tears.[4–12] Despite many trials, there are no evidence-based guidelines for optimal artificial tears and dosing frequency for different dry eye disease subtypes and severity.[2] The physician's subjectivity in selecting an artificial tear is compounded by unpredictable patient responses despite similar dry eye disease signs, as there is a weak correlation between dry eye signs and symptoms.[2,13] A study evaluated the dynamic change in tear film parameters following the instillation of a single drop of artificial tear.[14] Assessment of tear volume and tear meniscus height (measured using ocular coherence tomography [OCT]) changes over 1 hour in 20 healthy individuals revealed significant increases happening at 5 minutes following different artificial tears (0.5% CMC, 1% CMC, 0.4% polyethylene glycol [PEG] 400–0.3% propylene glycol [PG]) or normal saline instillation, but changes returned to baseline after 20 minutes.[14] No differences were seen between artificial tears after 5 minutes. It is unclear how a short-term change in tear volume maintains the tear film over the day, as many studies prescribe artificial tears four or six times daily. Sodium hyaluronate–based formulations were introduced for high molecular weight, viscosity, and increased retention time.[15,16] Numerous studies have shown the beneficial effects of SH-based artificial tears on tear breakup time, corneal staining, and dry eye disease symptoms, with few exceptions.[2,7,15] However, their comparison with other artificial tears has been studied less. The effect on tear film stability was similar with 0.5% CMC or 0.1% SH use in mild to moderate dry eye disease patients following 56 to 84 days of use.[4,9] A randomized comparative study revealed Systane Hydration (SH–hydroxypropyl guar) to be similar to 0.15% SH alone in corneal staining, tear breakup time, and symptom improvement.[6] A comparison of different CMC-, SH-, and PEG-based artificial tears on tear film parameters has not been performed. *In vitro* comparison of SH-, hydroxypropylmethylcellulose (HPMC), and CMC-based ocular lubricants revealed SH to have better water retention and prevent

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drying of human corneal epithelial cells.[17] Does retention time differ between SH- versus CMC- versus PEG-based formulations? The current study investigated the short-term effects of different artificial tears on tear film and whether these commercially available distinct artificial tear formulations affect it differently.

METHODS

The institutional ethical committee approved this prospective, double-masked, cross-sectional study and adhered to the tenets of the declarations of Helsinki. Study subjects include consecutive dry eye disease patients presenting to our clinic. Dry eye disease was diagnosed if all three were present—an Ocular Surface Disease Index (OSDI) value >22 (for moderate dry eye disease), Schirmer <10 mm or noninvasive tear breakup time value <7 seconds at least in one eye, and positive corneal fluorescein staining. Dry eye disease was classified into subtypes—aqueous deficient dry eye (noninvasive tear breakup time <7 seconds, Schirmer >10 mm, positive staining, and OSDI >22) and evaporative dry eye (Schirmer <10 mm, positive staining, and OSDI >22). Excluded were patients with a recent history of ocular surgery (in the past 6 months), history of refractive surgery, corneal scarring, corneal vascularization, limbal stem cell deficiency, cicatricial dry eye disease, epithelial defect, contact lens users, absolute zero Schirmer values, and pregnant or lactating mothers. Patients were randomly assigned into the five artificial tear groups comprising 20 subjects each.

Ocular lubricants

This study used different commercially available artificial tears representing eye drops commonly used in authors' practice. The tested topical artificial tears were Teardrops (0.5% CMC; Sun Pharma, Assam, India), Refresh Liquigel (1% CMC; Allergan Pharma, Madhya Pradesh, India), Trehalube (0.1% SH-trehalose [TH]; Microlabs, South Sikkim, India), Systane Ultra (0.4% PEG 400-0.3% PG; Alcon, Singapore), and Systane Hydration (0.1%SH-0.4% PEG 400-0.3% PG, Alcon, Singapore; see Appendix Table A1, available at http://links.lww.com/OPX/A766). These artificial tears differ in their active as well as inactive ingredients. A drop of freshly opened artificial tear was instilled only into the left eye by the same observer (MBA) who was aware of the drop type. The patient and examiner (MM) who performed tear film evaluations were masked. The right eye served as an internal control to account for inherent tear dynamics changes reflected in tear film parameters.

Tear film evaluation

All subjects had their routine slit-lamp examination and dry eye workup, including the Schirmer I test (without anesthesia), OSDI, and tear film evaluation. Willing patients were called on another day for drop testing. All patients were instructed not to use artificial tears on the test day. Evaluation of noninvasive tear breakup time, tear meniscus height, and bulbar redness score was performed on Keratograph 5M (OCULUS Optikgeräte, Wetzlar, Germany) using standard protocol in a controlled environment chamber (internal dimension, 6′ × 5′ × 8′; 68 to 70°F; 35 ± 5% relative humidity; display LCD 200 lux) at baseline and 15, 30, 45, and 60 minutes after the single drop instillation. The participants were in the controlled chamber for 15 minutes before the drops were instilled. Noninvasive tear breakup time represents the average noninvasive tear breakup time of three readings. A masked observer performed all evaluations (MM). All tests were performed between the daytime of 10 AM to 2 PM. After 1 hour, subjects were asked if they felt any subjective improvement on a 5-point scale (0 to 4; 0, no change; 1, <25% improvement; 2, 25 to 50% improvement; 3, 50 to 75% improvement; 4, >75% improvement) in the left eye. Noninvasive tear breakup time was tested first, followed by tear meniscus height. The order of the eye to be tested first for noninvasive tear breakup time was random.

Statistical analysis

Statistical analysis was performed using R software (R-4.4.2, R Foundation for Statistical Computing, Vienna, Austria). The nlme package was used to fit the linear mixed-effects models, and the multcomp package was utilized for the post hoc comparisons and Bonferroni correction. Baseline comparisons between the five groups were performed using an analysis of variance (ANOVA) test for each variable of interest with the lm() function used to fit linear models and the aov() function to perform ANOVA (Table 1). To ensure comprehensive model validation, each model was evaluated against specific diagnostic criteria, including residual normality, homoscedasticity, independence of residuals, and goodness of fit. If a model failed any diagnostic checks, corrective actions in the form of data transformation were applied. The changes in tear meniscus

TABLE 1. Demographic data and baseline tear film parameters of all groups

Variables	Teardrops	Refresh Liquigel	Systane Ultra	Systane Hydration	Trehalube	*p**
Mean age (y)†	34.3 (10.6)	38.6 (13.7)	39.6 (16.8)	40.4 (12.9)	48.3 (10.8)	0.002
OSDI score†	28.43 (4.45)	27.82 (4.84)	42.08 (43.85)	28.83 (6.28)	28.75 (8.50)	0.14
Duration of DED (mo)†	10.4 (23.4)	13.6 (28.4)	20.5 (33.9)	19.3 (34.5)	11.1 (14.1)	0.73
Type of DED ADDE:EDE	6:14	6:14	8:12	7:13	4:16	0.87
CFS (OD)†	1 (0.22)	1 (0.31)	1.1 (0.55)	1 (0)	1 (0.31)	0.28
CFS (OS)†	1 (0)	1 (0.31)	1.23 (0.49)	1 (0)	1 (0.31)	0.05
Baseline tear film parameters†						
Schirmer I (OD) (mm)	24.63 (11.08)	19.78 (11.14)	18.46 (11.47)	14.78 (12.58)	15 (10.16)	0.003
Schirmer I (OS) (mm)	24.27 (11.89)	22.78 (12.64)	23.55 (11.95)	17.85 (12.89)	16.8 (10.58)	0.04
TMH (OD) (mm)	0.28 (0.11)	0.25 (0.067)	0.25 (0.08)	0.29 (0.19)	0.28 (0.09)	0.43
TMH (OS) (mm)	0.25 (0.08)	0.24 (0.073)	0.26 (0.07)	0.27 (0.08)	0.26 (0.09)	0.09
NIBUT (OD) (s)	5.33 (1.79)	4.5 (1.78)	4.67 (1.75)	3.99 (1.43)	4.10 (2.01)	0.19
NIBUT (OS) (s)	4.39 (1.35)	5.02 (1.77)	4.86 (1.71)	3.85 (1.43)	4.26 (1.49)	0.06
Bulbar redness (OD)	1.16 (0.43)	1.15 (0.53)	0.92 (0.42)	1.19 (0.66)	1.11 (0.61)	0.21
Bulbar redness (OS)	1.2 (0.48)	1.12 (0.44)	1.08 (0.51)	1.17 (0.63)	1.24 (0.57)	0.74

**P* values are calculated using a one-way ANOVA test. †Values are represented as mean (SD). CFS = corneal fluorescein staining score (Oxford staining score); DED = dry eye disease; NIBUT = noninvasive tear breakup time; OD = right eye; OS = left eye; TMH = tear meniscus height.

TABLE 2. Changes in noninvasive tear breakup time and tear meniscus height with and without different lubricants instillation

	Baseline	15 min	*p**	30 min	*p**	45 min	*p**	60 min	*p**
NIBUT control eye, mean (SD)									
Teardrops	4.50 (1.79)	4.48 (1.33)	>0.99	4.22 (1.81)	>0.99	4.44 (1.51)	>0.99	4.29 (1.43)	1.0
Refresh Liquigel	4.50 (1.78)	5.81 (4.48)	0.48	5.74 (4.91)	0.57	4.79 (2.61)	>0.99	5.58 (3.41)	0.80
Systane Ultra	4.67 (1.75)	4.98 (4.05)	>0.99	5.28 (3.43)	>0.99	4.67 (2.47)	>0.99	5.18 (2.53)	1.0
Systane Hydration	3.99 (1.43)	4.11 (1.26)	>0.99	3.92 (1.35)	>0.99	4.25 (1.36)	>0.99	4.60 (1.64)	0.48
Trehalube	4.10 (2.01)	3.88 (1.62)	>0.99	4.67 (1.76)	>0.99	4.28 (1.74)	>0.99	3.83 (1.60)	1.0
NIBUT study eye, mean (SD)									
Teardrops	4.39 (1.35)	13.94 (5.02)	<0.001	13.66 (5.79)	<0.001	15.11 (4.73)	<0.001	14.45 (4.61)	<0.001
Refresh Liquigel	5.02 (1.77)	11.93 (5.54)	<0.001	12.81 (5.54)	<0.001	12.16 (6.05)	<0.001	11.35 (5.97)	<0.001
Systane Ultra	4.86 (1.71)	12.67 (4.33)	<0.001	12.57 (3.98)	<0.001	12.30 (5.06)	<0.001	11.37 (5.41)	<0.001
Systane Hydration	3.85 (1.43)	3.85 (1.43)	<0.001	9.89 (5.26)	<0.001	9.17 (4.83)	<0.001	8.81 (4.79)	<0.001
Trehalube	4.26 (1.49)	9.99 (6.62)	<0.001	13.95 (6.74)	<0.001	14.17 (7.25)	<0.001	12.99 (6.66)	<0.001
TMH control eye, mean (SD)									
Teardrops	0.28 (0.11)	0.23 (0.08)	0.03	0.28 (0.09)	>0.99	0.27 (0.08)	0.13	0.25 (0.09)	0.56
Refresh Liquigel	0.25 (0.07)	0.24 (0.06)	>0.99	0.25 (0.08)	>0.99	0.24 (0.07)	>0.99	0.23 (0.07)	0.87
Systane Ultra	0.25 (0.08)	0.26 (0.06)	>0.99	0.29 (0.09)	0.15	0.25 (0.08)	>0.99	0.26 (0.07)	>0.99
Systane Hydration	0.29 (0.19)	0.25 (0.09)	0.32	0.25 (0.08)	0.49	0.24 (0.08)	0.15	0.22 (0.06)	0.03
Trehalube	0.28 (0.09)	0.28 (0.08)	>0.99	0.25 (0.10)	>0.99	0.29 (0.09)	>0.99	0.26 (0.10)	>0.99
TMH study eye, mean (SD)									
Teardrops	0.25 (0.08)	0.28 (0.10)	>0.99	0.26 (0.08)	>0.99	0.26 (0.08)	>0.99	0.24 (0.08)	>0.99
Refresh Liquigel	0.24 (0.07)	0.29 (0.10)	0.03	0.26 (0.08)	0.63	0.24 (0.06)	>0.99	0.24 (0.07)	>0.99
Systane Ultra	0.26 (0.07)	0.27 (0.09)	>0.99	0.28 (0.06)	>0.99	0.27 (0.07)	>0.99	0.26 (0.08)	>0.99
Systane Hydration	0.27 (0.08)	0.26 (0.07)	>0.99	0.26 (0.08)	>0.99	0.26 (0.74)	>0.99	0.24 (0.68)	>0.99
Trehalube	0.26 (0.09)	0.31 (0.09)	>0.99	0.24 (0.11)	>0.99	0.28 (0.69)	0.32	0.28 (0.07)	>0.99

**p* Values denote the differences from the baseline and have been calculated using the linear mixed-effect model. NIBUT = noninvasive tear breakup time; TMH = tear meniscus height.

height, noninvasive tear breakup time, or bulbar redness at different time points from the baseline in the study and control eye were compared using the linear mixed-effects model (Tables 2, 3) with post hoc pairwise comparisons. Different artificial tears formulations (Table 4) were also compared using a linear mixed-effect model to determine the difference in the change in the tear film parameters in the study eye, i.e., left eye only. Generalized linear hypothesis testing (glht) was used for post hoc pairwise comparisons between different artificial tears formulations (Table 4) and time points (Tables 2, 3; Dunnett method). Bonferroni correction was applied to adjust the p values to control for multiple comparisons. This ensured that the probability of making a type I error was controlled across multiple tests. For comparing the subjective improvement grades, ordinal logistic regression analysis (using the polr function from the MASS package in R) was performed, followed by Tukey post hoc analysis with Bonferroni correction for pairwise comparisons. A p value of <0.05 was taken as statistically significant.

TABLE 3. Changes in bulbar redness score with and without different lubricants instillation

	Baseline	15 min	*p**	30 min	*p**	45 min	*p**	60 min	*p**
Bulbar redness, control eye, mean (SD)									
Teardrops	1.16 (0.43)	1.22 (0.48)		1.29 (0.54)		1.16 (0.47)		1.18 (0.42)	
Refresh Liquigel	1.15 (0.53)	1.13 (0.59)	>0.99	1.16 (0.66)	>0.99	1.11 (0.57)	>0.99	1.18 (0.59)	>0.99
Systane Ultra	0.92 (0.42)	1.01 (0.43)	0.11	0.99 (0.45)	0.20	1.03 (0.39)	0.13	0.98 (0.39)	0.45
Systane Hydration	1.19 (0.66)	1.22 (0.67)	>0.99	1.30 (0.63)	0.19	1.33 (0.66)	0.05	1.33 (0.66)	0.05
Trehalube	1.11 (0.61)	1.19 (0.59)	>0.99	1.18 (0.53)	>0.99	1.23 (0.49)	>0.99	1.23 (0.54)	>0.99
Bulbar redness, study eye, mean (SD)									
Teardrops	1.2 (0.48)	1.20 (0.49)	>0.99	1.20 (0.56)	>0.99	1.20 (0.50)	>0.99	1.09 (0.42)	>0.99
Refresh Liquigel	1.12 (0.44)	1.07 (0.60)	>0.99	1.06 (0.53)	>0.99	1.05 (0.59)	>0.99	0.97 (0.39)	0.09
Systane Ultra	1.08 (0.51)	1.07 (0.52)	>0.99	1.00 (0.43)	0.70	1.02 (0.41)	>0.99	1.02 (0.42)	>0.99
Systane Hydration	1.17 (0.63)	1.24 (0.68)	0.49	1.22 (0.63)	0.90	1.24 (0.66)	0.49	1.25 (0.68)	0.25
Trehalube	1.24 (0.57)	1.07 (0.34)	0.64	1.17 (0.32)	0.90	1.17 (0.37)	0.81	1.19 (0.36)	0.72

**p* Values denote the differences from the baseline and calculated using linear mixed-effect model.

TABLE 4. Comparison of change in NIBUT values between different artificial tears at different time points

	Difference in NIBUT values	p^*
Time = 0		
Systane Hydration − Refresh Liquigel	−1.17	0.19
Systane Ultra − Refresh Liquigel	−0.17	>0.99
Teardrops − Refresh Liquigel	−0.37	>0.99
Trehalube − Refresh Liquigel	−1.09	0.30
Systane Ultra − Systane Hydration	1.00	0.44
Teardrops − Systane Hydration	0.81	>0.99
Trehalube − Systane Hydration	0.09	>0.99
Teardrops − Systane Ultra	−0.20	>0.99
Trehalube − Systane Ultra	−0.92	0.65
Trehalube − Teardrops	−0.72	>0.99
15 min		
Systane Hydration − Refresh Liquigel	−2.04	>0.99
Systane Ultra − Refresh Liquigel	0.74	>0.99
Teardrops − Refresh Liquigel	0.98	>0.99
Trehalube − Refresh Liquigel	−2.17	>0.99
Systane Ultra − Systane Hydration	2.78	>0.99
Teardrops − Systane Hydration	3.02	0.80
Trehalube − Systane Hydration	−0.13	>0.99
Teardrops − Systane Ultra	0.24	>0.99
Trehalube − Systane Ultra	−2.91	0.92
Trehalube − Teardrops	−3.15	0.69
30 min		
Systane Hydration − Refresh Liquigel	−3.39	0.59
Systane Ultra − Refresh Liquigel	−0.25	>0.99
Teardrops − Refresh Liquigel	0.63	>0.99
Trehalube − Refresh Liquigel	−0.64	>0.99
Systane Ultra − Systane Hydration	3.15	0.79
Teardrops − Systane Hydration	4.03	0.25
Trehalube − Systane Hydration	2.75	>0.99
Teardrops − Systane Ultra	0.88	>0.99
Trehalube − Systane Ultra	−0.40	>0.99
Trehalube − Teardrops	−1.27	>0.99
45 min		
Systane Hydration − Refresh Liquigel	−2.98	0.99
Systane Ultra − Refresh Liquigel	0.14	>0.99
Teardrops − Refresh Liquigel	1.49	>0.99
Trehalube − Refresh Liquigel	1.00	>0.99
Systane Ultra − Systane Hydration	3.12	0.84
Teardrops − Systane Hydration	4.47	0.14
Trehalube − Systane Hydration	3.99	0.28
Teardrops − Systane Ultra	1.34	>0.99
Trehalube − Systane Ultra	0.86	>0.99
Trehalube − Teardrops	−0.48	>0.99
60 min		
Systane Hydration − Refresh Liquigel	−2.54	>0.99
Systane Ultra − Refresh Liquigel	0.03	>0.99
Teardrops − Refresh Liquigel	1.85	>0.99
Trehalube − Refresh Liquigel	0.86	>0.99
Systane Ultra − Systane Hydration	2.56	>0.99
Teardrops − Systane Hydration	4.39	0.14
Trehalube − Systane Hydration	3.39	0.56
Teardrops − Systane Ultra	1.83	>0.99
Trehalube − Systane Ultra	0.83	>0.99
Trehalube − Teardrops	−0.99	>0.99

*p Values were calculated using a linear mixed-effect model. NIBUT = noninvasive tear breakup time.

RESULTS

Demographics and clinical details

Table 1 summarizes all groups' clinical details and baseline tear film parameters. Five groups denote five different tested artificial tears. All five groups had similar sex distribution, OSDI scores, dry eye disease duration, and dry eye disease subtypes. The baseline tear film parameters comparison showed no differences in groups except for Schirmer values, although all groups had more than 10-mm mean Schirmer values (Table 1). In the results below, the ingredients SH, PEG 400, and PG represent 0.1% SH, 0.4% PEG 400, and 0.3% PG.

Subjective improvement

Patients in each group reported different grades of improvement in dry eye symptoms (Fig. 1; $p<0.01$; one-way ANOVA test). 0.5% CMC improved symptoms by 25% in seven patients, and 25 to 50% and 50 to 75% in six patients each, whereas 1% CMC had grade 2 improvement in 1 patient and grade 3 improvement in 13 dry eye disease patients. Different number of patients reported improvement with SH-TH (one grade 1, no grade 2, and nine grade 3), PEG 400–PG (seven grade 1, five grade 2, and 10 grade 3), and SH–PEG 400–PG drops (one grade 1, six grade 2, and six grade 3). More than 75% improvement in symptoms was reported with all drops—0.5% CMC (n = 1), 1% CMC (n = 5), SH-TH (n = 4), PEG 400–PG (n = 4), and SH–PEG 400–PG (n = 1) drop. Post hoc analysis revealed significant differences between 0.5% CMC and SH–PEG 400–PG ($p<0.0001$; −3.13 log-odds difference; Systane Hydration better), 0.5% CMC and SH-TH ($p=0.01$; 2.2 log-odds difference; Trehalube better), and 1% CMC and SH–PEG 400–PG ($p=0.01$; 1.92 log-odds difference; Systane Hydration better). Other post hoc comparisons did not differ significantly regarding the subjective improvement.

Noninvasive tear breakup time

There were no differences between the baseline values of the study eye and the control eye in any of the groups. Following a drop instillation, all artificial tears significantly improved noninvasive tear breakup time values ($p<0.001$) at 15, 30, 45, and 60 minutes from baseline (Table 2; Fig. 1). The control eye (no drops instilled) showed no significant change in noninvasive tear breakup time values from baseline (Table 2). The study and control eye comparison also revealed significant improvement in noninvasive tear breakup time at all time points following artificial tear drop instillation ($p<0.001$ for all artificial tears). Between the artificial tear drops, there was no difference in the noninvasive tear breakup time changes across different time points from baseline (Table 4).

Tear meniscus height

Tear meniscus height values showed no significant change within or between the eyes (i.e., with or without artificial tear drop) for any artificial tears at 15, 30, 45, and 60 minutes from baseline (Table 2; Fig. 1). Study and control eyes had similar values at baseline in all groups. All groups had baseline mean tear meniscus height values of more than 0.25 mm.

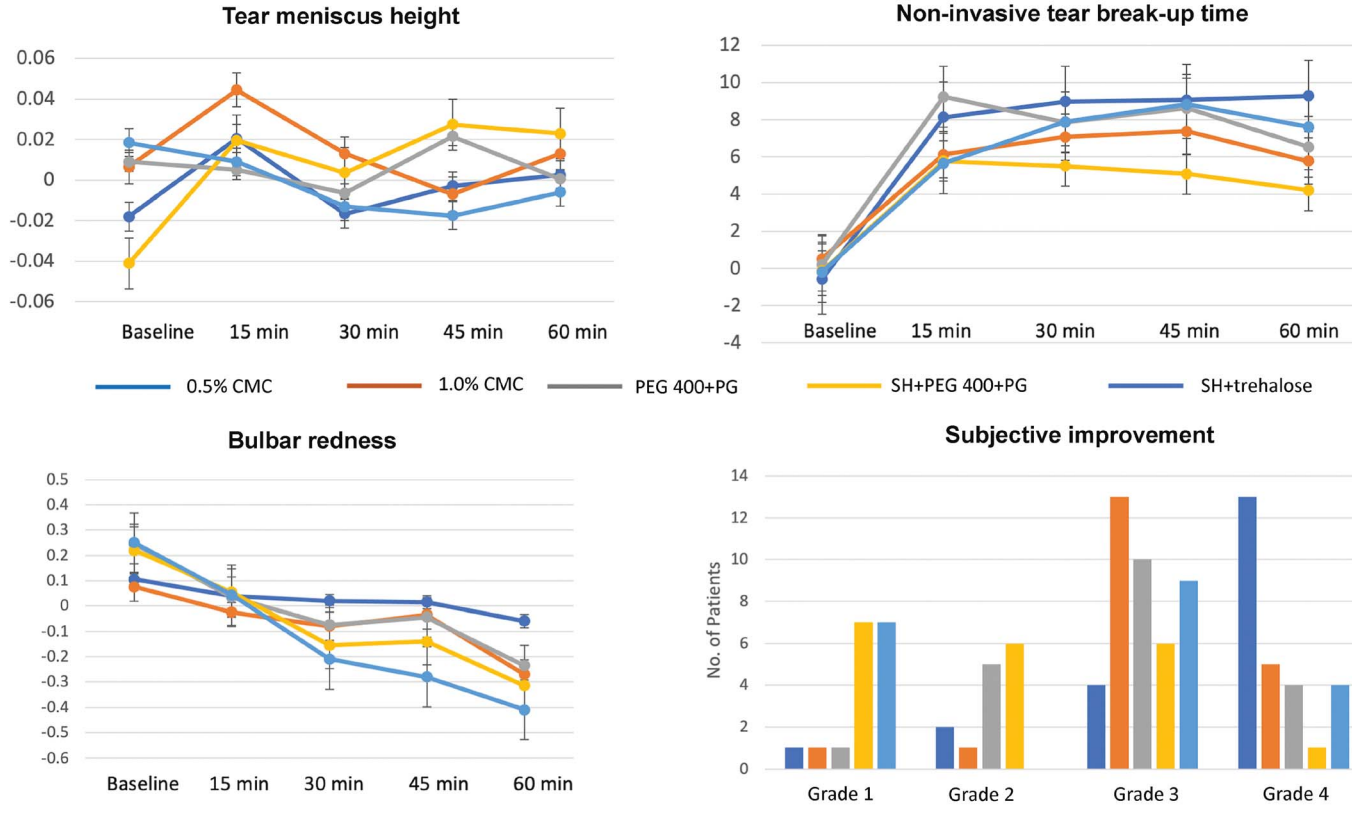

FIGURE 1. Graphs show the differences in TMH, NIBUT, and bulbar redness scores between treated and control eyes at different time points using five artificial tear formulations. The plotted values are mean ± confidence intervals. Artificial tears are as follows: 0.5% CMC (Teardrops), 1% CMC (Refresh Liquigel), 0.4%PEG400+0.3%PG (Systane Ultra), 0.1%SH+0.4%PEG400+0.3%PG (Systane Hydration), and 0.1%SH-TH (Trehalube). NIBUT = noninvasive tear breakup time; TMH = tear meniscus height.

Bulbar redness

Bulbar redness showed no significant change within or between the eyes (i.e., with or without drop) for any artificial tears at 15, 30, 45, and 60 minutes from baseline (Table 3; Fig. 1). The baseline scores of bulbar redness were similar in all groups.

DISCUSSION

The current study evaluated the tear film changes following the instillation of a single drop of artificial tear in subjects with moderate dry eye disease over a defined period. The dynamic changes in tear volume and stability indicate the ocular surface residence time of different artificial tears and their real-world efficacy in improving tear film parameters. Noninvasive tear breakup time values were significantly improved with all artificial tears and maintained until 1 hour of drop instillation. However, none of the artificial tear formulations were superior to the other in terms of noninvasive tear breakup time changes at any time from baseline. This implies that the short-term effect of SH-containing drops is similar to that of CMC-based formulations at 1 hour of instillation. There might be a difference in their long-term effects, which needs to be studied further. Tear meniscus height and bulbar redness scores showed no change in the study or the control eye with time. Surprisingly, tear meniscus height did not show significant change, which could indicate the spread of artificial tears over the ocular surface rather than residing in the tear menisci along the lid margins. Subjectively, patients felt better with SH-based formulations than CMC-based eye drops, with no subjective difference between SH with or without TH.

The efficacy of artificial tears is tested *in vitro* on contact lens–based systems, corneal or conjunctival epithelial cell lines, and animal models.[1,17] Studies examining their effects in dry eye disease patients have mainly looked at improved dry eye symptomatology and/or corneal staining or tear breakup time.[3] Many such studies are industry-sponsored and open label, where a single lubricant or a maximum of two lubricants are commonly evaluated. Hence, comparative studies involving different formulations are missing, which would be needed to select an ocular lubricant for a dry eye disease patient. However, the consensus is that gel formulations do better than CMC or PEG alone. In the category of CMC and PEG, Systane and Refresh Tears have been studied extensively[6]; current study compared these old formulations with recently introduced SH or SH-TH combinations. The formulations used in the current study had SH with TH and SH added to Systane Ultra–containing HP guar gelling technology. A randomized, blinded trial of 0.5% CMC versus 0.1% SH revealed no differences in tear breakup time, corneal staining, or subjective symptoms between the two at 4 and 8 weeks.[4] The current study also observed no difference in noninvasive tear breakup time values between SH- and CMC-based formulations despite similar baseline noninvasive tear breakup time values. The current study did not observe any significant change in noninvasive tear breakup time of the control eye (received no artificial tears); hence, the change was solely due to an artificial tear drop. Hence, these novel artificial tear formulations should be tested in large cohorts to ascertain differences. The tested artificial tear formulations differ in viscosity and active and inactive ingredients. The viscosity of ocular artificial tears affects tear film stability, which has been tested *in vitro* and *in vivo*.[14,18] A study examined the dynamic distribution of Refresh Tears, Systane, Refresh Liquigel, and isotonic saline drops in 40 eyes of 20 healthy individuals.[14] All drops improved the upper and lower tear meniscus height, radius, and curvature. However, the improvement lasted for 20 minutes only. Systane and Refresh Liquigel improved tear meniscus height more than isotonic saline and Refresh tears for 5 minutes.[14] These drops had different viscosities, with Refresh Liquigel having maximum viscosity. All artificial tear formulations were better than no drops or normal saline, similar to this study, where the artificial tears receiving the study eye were better than the control eye. The current study measured tear meniscus height after 15 minutes and found no difference with any formulations. Hence, the effects on tear meniscus height may occur in the initial few minutes. The SH-based formulations with or without glycerine had higher noninvasive tear breakup time values than CMC- or PEG-based artificial tears in the *in vitro* model.[18] The *in vitro* model was a contact lens or collagen shield placed over the simulated cornea of an OcuBlink system. The current study results differ from the *in vitro* study, where SH- and CMC-based artificial tears improved noninvasive tear breakup time similarly. The difference could be attributed to human eyes and dry eye disease patients having different tear film behavior than *in vitro* systems.

Sodium hyaluronate– or glycerine-based formulations show more reduction in tear osmolarity than plain CMC. Short-term application of preservative-free artificial tears reduced tear osmolarity within 15 minutes compared with the control group.[10] However, none of the groups had elevated tear osmolarity at baseline (all <308 mOsm/L). The current study did not look at tear osmolarity to avoid tear volume/menisci disturbances due to TearLab testing on the tear meniscus height and noninvasive tear breakup time values. The next question is if adding TH creates a difference compared with SH alone. Sodium hyaluronate's viscoelastic and mucoadhesive properties prolong its retention time on the ocular surface. Trehalose stabilizes lipids in the cell membrane and promotes corneal epithelial cell healing by inhibiting apoptosis. A similar study looked at two artificial tears—SH 0.3% versus SH 0.15%–TH in 122 moderate dry eye disease patients—and found that both artificial tears improved tear meniscus height (measured using OCT) at 1 hour.[8] However, only the SH 0.3%–TH combination maintained the improvement at 2 hours from the drop instillation. Tear breakup time, tear osmolarity, and Schirmer I values were similar to baseline levels with both formulations at 2 hours. The tear meniscus height improvement differs from our findings, as no significant change was observed in tear meniscus height at 1 hour from baseline. The current study used Keratograph 5M for tear meniscus height measurement, which could be the underlying reason. Comparison of TH 3%, SH 0.15%, carbomer 0.25%, SH 0.2% gel, and PEG-PG combination in mild to moderate dry eye disease revealed an increase in tear film thickness at 10 and 30 minutes with all artificial tears; however, only the TH group maintained the increase until 1 and 2 hours.[19] The combination (SH 0.15%–TH 3%) has shown improvement in dry eye disease symptoms and signs in post-menopausal women with dry eye disease as well.[20] The major limitation of all these studies is single-arm and open-label studies. It is unclear if one artificial tear supersedes the other. A systematic review of different artificial tears on rose bengal staining revealed no significant difference between various formulations (traditional [HPMC, polyvinylalcohol (PVA)], carbomer based, and SH based).[1] When artificial tears were tested individually, SH-based formulations were better than traditional or carbomer-based ATs. Short-term (90 minutes) and long-term use (3 weeks) of an artificial tear-containing carbomer, hyaluronic acid, glycerol, and medium-chain triglycerides showed a significant increase in noninvasive tear breakup time, tear lipid layer pattern, and OSDI values.[21] A randomized double-masked study compared the changes in tear film thickness (measured using OCT) following a single dose of TH-SH versus 0.15% SH in 60 patients with moderate dry eye disease.[22] Trehalose-SH combination maintained the increase in tear film thickness for 240 minutes compared with 40 minutes with SH alone. The current study measured different tear film parameters using Keratograph 5M than OCT-based tear film thickness, which could explain why no difference was found in SH-TH– versus SH-based artificial tears in the current study.

The current study looked at noninvasive tear breakup time, tear meniscus height, and bulbar redness only and not a change in corneal staining to avoid fluorescein dye affecting tear parameters. *In vitro* models cannot predict the changes in human eyes. Hence, the current study evaluated the impact of a single dose on tear film volume and stability over 1 hour using noninvasive tests. One of the study's strengths is that it includes 0.5% CMC-, PEG-, and SH-based formulations in real-time settings. Although clinical measurement of noninvasive tear breakup time values is stated to be affected by patient and environmental factors, no change in the control eye reflects the stable environment of the controlled environment chamber used for the current experiment. The limitations of this study are the small sample size and lack of long-term response after drop instillation. One should interpret the current study findings considering the differences in the active and inactive ingredients in the tested lubricants.

The real-world efficacy of artificial tears in dry eye disease patients varies in moderate dry eye disease, where SH-based, PEG-based, and CMC-based artificial tears work similarly concerning their effect on noninvasive tear breakup time. All artificial tears improve tear film stability for 1 hour following a single dose. The addition of TH seems to have no additional short-term effect on tear film stability, although its molecular effects might differ and need further study.

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