Contact Lens & Anterior Eye xxx (2010) xxx–xxx

Contents lists available at ScienceDirect

Contact Lens & Anterior Eye

journal homepage: www.elsevier.com/locate/clae

Tear osmolarity measurement using the TearLab™ Osmolarity System in the assessment of dry eye treatment effectiveness☆

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Lubricant eye drop
Tear osmolarity
Dry eye

ABSTRACT

Purpose: To evaluate the efficacy of three commercially available lubricant eye drops for the treatment of mild, dry, irritated eyes.
Methods: Randomized, investigator-masked evaluation of 60 patients in which 20 patients used carboxymethylcellulose sodium (CMC), 0.5% (Cellufresh®, Allergan Inc., Irvine, CA) (group 1); 20 patients used a drop containing polyethylene glycol 400, 2.5% and sodium hyaluronate (Blink® Intensive Tears, Abbott Medical Optics Inc., Santa Ana, CA) (group 2); and 20 patients used HP Guar 0.18% (Systane®, Alcon Laboratories Inc., Ft. Worth, TX) (group 3). Study visits were at baseline and 1 month. Tests performed at both visits included Schirmer, tear-film break-up time (TBUT), visual acuity, fluorescein staining, tear osmolarity and wavefront aberrometry. Osmolarity testing was performed prior to instillation of the lubricant eye drops and then a final time 5 min after instillation of the drop at both day 1 and day 30. Tear osmolarity was performed only in the right eye and only one time before and after instillation of lubricant eye drops.
Results: At day 1 the mean reduction in osmolarity 5 min after instillation of the lubricant eye drop was, -5.0 ± 1.9 in group 1, -9.0 ± 4.2 in group 2 and -5.0 ± 2.2 in group 3. At day 30 the mean reduction in osmolarity 5 min after instillation of the lubricant eye drop was, -5.6 ± 2.3 mOsm/L in group 1; -9.9 ± 2.8 mOsm/L in group 2 and -4.5 ± 1.8 mOsm/L in group 3. The differences were statistically significant between groups 1 and 2, and 2 and 3. There was a reduction of osmolarity from day 1 to day 30 but the differences were not statistically significant. We feel that after a 30-day treatment with the lubricant eye drops, the lower osmolarity values could indicate that the tear film is progressing towards a more normal osmolarity value. A future study could examine the tear osmolarity value after 60 or 90 days of usage. LogMAR best-corrected visual acuity (BCVA) results showed an improvement in group 2 compared with baseline with no change in BCVA in groups 1 and 3. There was no statistically significant change from day 1 to 1 month in TBUT, while the Schirmer test showed an improvement in all groups at 1 month.
Conclusions: Assessment of tear osmolarity provides the most objective, measurable test for determining improvement in dry eye patients. The instillation of any artificial tear or lubricant eye drop should decrease the tear-film osmolarity. The results found that polyethylene glycol 400, 0.25% and sodium hyaluronate (Blink® Intensive Tears) significantly improved tear osmolarity compared with carboxymethylcellulose sodium (CMC), 0.5% (Cellufresh®) and HP Guar 0.18% (Systane®) after instillation.

1. Introduction

Lubricant eye drops are the accepted treatment when a patient presents with signs or symptoms of dry eye disease before more invasive treatments are employed [1]. However, as noted in the 2007 Dry Eye Workshop (DEWS) report, there has been a lack of evidence on the efficacy of many of the active ingredients used in these tears. In the DEWS Management and Therapy chapter, the authors note that this is likely the result of currently available tests or because it is not clear if the active ingredients are intended to lubricate, replace tears, improve tear osmolarity or lessen ocular surface inflammation [1]. Two points are clear from this report: there is a need for more sensitive clinical tests to assess if lubricant eye drops improve the ocular surface health and that lubricant eye drops should have active ingredients that do more than lubricate.

☆ Financial disclosure: This study was funded by an unrestricted educational grant by Abbott Medical Optics.
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doi:10.1016/j.clae.2010.01.003

Hyaluronic acid (HA) has a long history of use in ophthalmic surgery since its introduction in the 1970s as a vitreous replacement and then later as a surgical tool in cataract surgery [2,3]. Evidence also shows that HA has the ability to increase the stability of the tear film, promote corneal healing and strengthen the mucous layer of the tear film [4–7].

One of the challenges in managing dry eye disease patients has long been in objectively measuring the effectiveness of a chosen treatment. Signs and symptoms often do not match with results of tests, including tear-film break-up time, Schirmer tear test or ocular surface (cornea and conjunctival) staining [1,8–10]. As a result, there is an ongoing search for tests that can objectively diagnose dry eye disease, as well as assess treatment effectiveness. Recent studies have looked at optical coherence tomography [11], tear stress tests [12], fluorescein dye tracking with a xeroscope [13] and wavefront aberrometry [14] as methods for objectively assessing the efficacy of various lubricant eye drops solutions [15–17].

In our study presented here, we elected to use a new diagnostic test for assessment of tear osmolarity. The TearLab™ Osmolarity System (TearLab™ Corp., San Diego, CA) is described as a "lab-on-a-chip" system that uses a 50 nL tear sample in order to measure the osmolarity of the tear. The system is non-invasive, user friendly and provides a result in less than 1 min. The TearLab™ System utilizes a hand-held pen that features a non-invasive tear collection interface to decrease sampling time to less than a second. The test card is used as a measurement system as well as a tear collection device. Once the sample is collected, the pen initiates measurement and is docked onto the TearLab™ Reader, which displays a quantitative measurement from the test card analysis. The test is quick, easy to administer and the system does not require calibration [18].

As indicated in the DEWS report, osmolarity is considered to be one of the most objective assessments for dry eye disease [1]. In addition, standard dry eye assessment tests of Schirmer, tear-film break-up time (TBUT), corneal and conjunctival fluorescein staining, as well as visual acuity assessment and wavefront aberrometry were performed in order to provide a comparison for measurement of treatment effectiveness.

2. Methods

This study was a randomized, investigator-masked study involving three types of lubricant eye drops and 60 patients divided into three treatment groups: 20 patients received a carboxymethylcellulose sodium drop (CMC), 0.5% (Cellufresh®, Allergan Inc., Irvine, CA) (Group 1); 20 patients received a drop containing polyethylene glycol 400, 0.25% and sodium hyaluronate (Blink® Intensive Tears, Abbott Medical Optics Inc., Santa Ana, CA) (group 2); and 20 patients used HP Guar 0.18% (Systane®, Alcon Laboratories Inc., Ft. Worth, TX) (group 3). A sample size of 60 subjects is a customary size for this type of study. The protocol was evaluated and approved by the medical experts of the Center of Ocular Pharmacology of the University of Pisa (Italy) and by the local research ethical committee.

The Ocular Surface Disease Index 2 (OSDI-II) scale was used to select patients: only patients with an OSDI-2 value between 30 and 60 and with a Schirmer test <7 mm after 5 min were included in this study. Patients with non-dry eye ocular pathology who were undergoing treatment with topical or systemic medications for other types of ocular pathologies were excluded from this study. For patients already in treatment using lubricant eye drops, a washout period of 10 days was used.

The study involved measurements at a baseline visit and then again at 30 days with patients instilling the assigned tears up to four times per day. Measurements were performed before instillation of the lubricant eye drops and then again 5 min after instillation.

The lubricant eye drops were instilled at the beginning of each evaluation period (time = 0 days and time = 30 days), only after the initial measurement of the tear-film osmolarity, and prior to all other clinical tests for measuring the characteristics of the tear film and cornea-conjunctiva.

The measurements were performed in a specific order to ensure that the ocular surface had recovered from the previous test. Tear osmolarity was performed first followed by Schirmer tear testing, wavefront aberrometry, TBUT, fluorescein staining of the cornea and conjunctiva and then visual acuity assessment. The interval between Schirmer test and TBUT was 5 min and the interval between the instillation of fluorescein and assessment of corneal and conjunctival staining was 2 min. Schirmer's test, wavefront aberrometry, TBUT, fluorescein staining of the cornea and conjunctiva and visual acuity assessment testing were done before artificial tear instillation.

2.1. Testing protocols

2.1.1. Tear osmolarity measurement

Tear osmolarity was measured using an in vitro diagnostic device (TearLab™ Osmolarity System, TearLab™ Corp., San Diego, CA) designed to take a 50 nL sample of tears. As noted previously, the test was performed prior to instillation of the lubricant eye drops and then a final time 5 min after instillation of the drop. Tear osmolarity was performed only in the right eye and only once before and after instillation of lubricant eye drops. The manufacturer of the TearLab™ states that no additional calibration is required for the TearLab™ as it is calibrated at the factory. We did, however, ensure that the system was functioning normally once per day as per the product manual instruction guide using monodose saline with an osmolarity value of 300 mOsm/L. The system comes with an electronic systems check test card which is inserted in the saline solution to gather a sample and produce a measurement. If the measurement is within normal values, then it is functioning properly. The TearLab™ manufacturers state that the instrument has a CV% (coefficient of variation) of approximately 1.5% which results in an analytical standard variation of ±5 mOsmol/L [18].

Data not included in this study, obtained from a small patient sample (five healthy subjects), demonstrated repeatable osmolarity values when a sample was taken from the same eye and measured three times within a period of 15 min. These measurements were consistent with the CV% value noted by the manufacturer [18].

Furthermore, at 30 days, the values demonstrate both the effect of the therapy at 30 days, before the instillation of the lubricant eye drops, and the effect of therapy at 30 days, after the instillation of the lubricant eye drops.

2.1.2. Schirmer tear test

This was performed without anesthesia with a testing time of 5 min.

2.1.3. Corneal wavefront aberrometry

The corneal wavefront aberrometry was evaluated using a CSO™ corneal topography system (CSO, Florence, Italy). The CSO™ topography system measures 6144 points on the anterior corneal surface. This is performed by projecting 24 Placido rings onto the cornea and then capturing the images of these rings using a high-resolution camera. The CSO™ corneal topographer/aberrometer converts the corneal elevation profile into corneal wavefront data using the Zernicke polynomials, taking into account that deviations in the topography are directly proportional to wavefront

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deviations on the anterior surface of the cornea. Higher order aberration values are expressed as root-mean-square (RMS) values in micrometers. Only this parameter was used in this study. Measurements were made before instillation of drops and then 5 min after instillation at both visits.

2.1.4. Tear-film break-up time

To perform the TBUT test, one drop of saline solution was placed on a fluorescein strip (Fluoralfa Strips™, Alfa Intes, Casoria, Italy) and the dye placed on the eye prior to receiving the lubricant eye drops and then 5 min after instillation. For each test, the time was counted in seconds to the first break-up. The test was performed three times and then averaged to provide the final measurement.

2.1.5. Fluorescein staining

To perform the conjunctival and corneal staining, one drop of saline solution was placed on a fluorescein strip (Fluoralfa Strips™, Alfa Intes, Casoria, Italy) and then instilled in the eye. The coloration was scaled from 0 (no staining) to 4 (complete surface of the eye stained) both before instillation of the lubricant eye drops and then 5 min after instillation.

2.1.6. Visual acuity

Visual acuity was evaluated using a LogMAR chart (3 m testing distance) before and after instillation of the lubricant eye drops (time 0 and 30 days). All the measurements were made in the same lighting conditions.

The room where all tests were performed was kept at a temperature of 24 °C with a relative humidity of 20% and an atmospheric pressure of 1016 mbar (hPa). The ambient room lighting remained constant and habitual.

2.2. Statistical analysis

We used the Tukey *P*-value test to analyze the data. To analyze the results of the TBUT, Schirmer, staining, wavefront analysis and visual acuity, the eye with a worse value (i.e. smaller value) at baseline was used. If the values were the same for both eyes, the study eye was randomly selected. To understand how frequently study subjects were using lubricant eye drops at baseline we used the Kruskal–Wallis test.

3. Results

3.1. Tear osmolarity

Table 1 provides a summary of the osmolarity results and between-group *P* values at day 1 and day 30. At day 1, there was a statistically significant difference in reduction of osmolarity between groups 1 and 2 and groups 2 and 3. The difference between groups 1 and 3 was not statistically significant. At day 30, the difference in reduction of osmolarity was statistically significant between groups 1 and 2 and between groups 2 and 3. Again, the difference between groups 1 and 3 was not statistically significant.

The mean change in osmolarity from day 1 to day 30 before and after instillation of the lubricant eye drop is demonstrated in Table 2. Although there were statistical differences in osmolarity at day 1 and day 30 before and after drop instillation the differences from day 1 to day 30 were not statistically significant.

3.2. Wavefront aberrometry

There were no statistical differences between the three groups when we compared day 30 wavefront aberrometry with the day 0 result, although improvements were seen in each group. Table 3 describes the improvement in aberrometry results between the two visits for each group and the *P*-value comparison between the three groups.

3.3. Tear break-up time (TBUT)

All groups demonstrated an improvement with TBUT testing. There was no significant difference between the three groups (Table 4).

Table 4 indicates that the three lubricant eye drops increase the TBUT but the differences were not statistically significant. It should be noted that the baseline TBUT for Cellufresh® is worse (i.e.

Table 1
Summary of osmolarity results.

Treatment	Day 1			Day 30		
Statistics	Before drop	After drop	Change	Before drop	After drop	Change
Cellufresh®						
N	20	20	20	20	20	20
Mean (SD)	320.6 (2.0)	315.6 (2.3)	−5.0 (1.9)	318.0 (1.3)	312.4 (2.2)	−5.6 (2.3)
95% CI	319.6, 321.5	314.5, 316.6	−5.9, −4.1	317.4, 318.6	311.4, 313.4	−6.7, −4.5
Median	320.0	316.0	−5.0	318.0	312.0	−6.5
Min., Max.	318.0, 326.0	309.0, 319.0	−10.0, −2.0	315.0, 320.0	309.0, 317.0	−10.0, −2.0
Blink®						
N	20	20	20	20	20	20
Mean (SD)	320.9 (3.4)	311.9 (2.8)	−9.0 (4.2)	316.8 (2.5)	306.9 (2.3)	−9.9 (2.8)
95% CI	319.3, 322.5	310.6, 313.2	−11.0, −7.0	315.6, 318.0	305.8, 308.0	−11.2, −8.6
Median	320.0	312.0	−8.0	317.0	307.0	−9.5
Min., Max.	316.0, 330.0	306.0, 317.0	−22.0, −5.0	311.0, 321.0	303.0, 311.0	−15.0, −5.0
Systane®						
N	20	20	20	20	20	20
Mean (SD)	321.9 (2.7)	316.9 (2.3)	−5.0 (2.2)	317.1 (1.6)	312.6 (2.6)	−4.5 (1.8)
95% CI	320.6, 323.1	315.8, 317.9	−6.0, −4.0	316.3, 317.8	311.3, 313.8	−5.4, −3.6
Median	322.0	317.0	−5.0	317.0	312.5	−4.0
Min., Max.	318.0, 327.0	312.0, 322.0	−10.0, −2.0	314.0, 320.0	308.0, 318.0	−9.0, −2.0
Tukey *P*-value						
Blink® vs. Systane®	0.5244	<.0001	0.0002	0.9030	<.0001	<.0001
Blink® vs. Cellufresh®	0.9151	<.0001	0.0002	0.1059	<.0001	<.0001
Systane® vs. Cellufresh®	0.3028	0.2310	1.0000	0.2389	0.9779	0.3111

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Table 2
Change in osmolarity from day 1 to day 30.

Treatment	Day 30–day 1[a]		
Statistics	Before drop	After drop	Change
Cellufresh®			
N	20	20	20
Mean (SD)	−2.6 (2.4)	−3.2 (2.9)	−0.6 (3.5)
95% CI	−3.6, −1.5	−4.5, −1.8	−2.2, 1.0
Median	−2.0	−3.0	−1.0
Min., Max.	−9.0, 2.0	−8.0, 5.0	−8.0, 7.0
Blink®			
N	20	20	20
Mean (SD)	−4.1 (2.9)	−5.0 (2.9)	−0.9 (4.3)
95% CI	−5.4, −2.8	−6.4, −3.6	−2.9, 1.1
Median	−3.5	−4.5	−1.0
Min., Max.	−10.0, 0.0	−12.0, 1.0	−8.0, 11.0
Systane®			
N	20	20	20
Mean (SD)	−4.8 (2.9)	−4.3 (2.8)	0.5 (2.2)
95% CI	−6.1, −3.5	−5.6, −3.0	−0.5, 1.5
Median	−5.0	−4.0	0.0
Min., Max.	−9.0, 0.0	−11.0, −1.0	−3.0, 5.0
Tukey *P*-value			
Blink® vs. Systane®	0.6926	0.7207	0.4120
Blink® vs. Cellufresh®	0.1740	0.1109	0.9594
Systane® vs. Cellufresh®	0.0288	0.4173	0.5762

[a] Before drop = before drop at day 30 - before drop at day 1. After drop = 5 min after drop at day 30 - 5 min after drop at day 1. Change = change from "Before" to "After" at day 30 - change from "Before" to "After" at day 1.

smaller) than that for Blink® if we use a *P*-value of 0.05 as a cut-off. Therefore, the change in TBUT may be misleading.

3.4. Schirmer tear test

All groups showed an improvement from day 0 to day 30. There was also no statistically significant difference between the three groups with Schirmer test (Table 5). The baseline of Schirmer for Blink® is worse (i.e. smaller) than that for Cellufresh®. This is the opposite of the TBUT finding.

Table 3
Aberrometry based on eyes with worse (higher) aberrometry value at day 1.

Treatment	Aberrometry		
Statistics	Day 1	Day 30	Day 30–day 1[a]
Cellufresh®			
N	20	20	20
Mean (SD)	0.79 (0.31)	0.55 (0.25)	−0.25 (0.30)
95% CI	0.65, 0.94	0.43, 0.66	−0.39, −0.10
Median	0.79	0.52	−0.13
Min., Max.	0.36, 1.44	0.26, 1.08	−1.14, 0.02
Blink®			
N	20	20	20
Mean (SD)	0.88 (0.36)	0.64 (0.21)	−0.24 (0.29)
95% CI	0.72, 1.05	0.54, 0.74	−0.38, −0.11
Median	0.89	0.70	−0.20
Min., Max.	0.38, 1.44	0.32, 0.97	−0.84, 0.33
Systane®			
N	20	20	20
Mean (SD)	0.82 (0.30)	0.66 (0.24)	−0.16 (0.29)
95% CI	0.67, 0.96	0.55, 0.77	−0.29, −0.03
Median	0.85	0.63	−0.17
Min., Max.	0.38, 1.45	0.36, 1.22	−0.99, 0.42
Tukey *P*-value			
Blink® vs. Systane®	0.7887	0.9704	0.6364
Blink® vs. Cellufresh®	0.6508	0.4219	0.9999
Systane® vs. Cellufresh®	0.9715	0.3004	0.6296

For each subject, the eye with a worse aberrometry (i.e. larger value) at baseline was used in the analyses. If the values were the same for both eyes, the study eye was randomly selected. All measurements were taken before instillation of the artificial tears.

[a] A negative value means improvement.

Table 4
Tear break-up time (TBUT) based on eyes with worse (smaller) TBUT value at day 1.

Treatment	Tear break-up time (s)		
Statistics	Day 1	Day 30	Day 30–day 1[a]
Cellufresh®			
N	20	20	20
Mean (SD)	6.0 (0.9)	7.2 (1.1)	1.3 (1.1)
95% CI	5.5, 6.4	6.7, 7.7	0.7, 1.8
Median	6.0	7.0	1.0
Min., Max.	4.0, 8.0	6.0, 10.0	−1.0, 4.0
Blink®			
N	20	20	20
Mean (SD)	51.8 (6.6)	38.5 (5.8)	−13.3 (6.8)
95% CI	48.7, 54.9	35.8, 41.2	−16.5, −10.2
Median	52.3	37.9	−14.3
Min., Max.	40.2, 64.6	25.6, 52.6	−24.8, 2.2
Systane®			
N	20	20	20
Mean (SD)	6.2 (1.0)	7.8 (1.0)	1.6 (1.0)
95% CI	5.8, 6.6	7.4, 8.2	1.1, 2.1
Median	6.0	8.0	1.0
Min., Max.	4.0, 8.0	6.0, 10.0	0.0, 3.0
Tukey *P*-value			
Blink® vs. Systane®	0.2207	0.9083	0.5635
Blink® vs. Cellufresh®	0.0378	0.1008	1.0000
Systane® vs. Cellufresh®	0.6792	0.2245	0.5635

For each subject, the eye with a worse TBUT (i.e. smaller value) at baseline was used in the analyses. If the values were the same for both eyes, the study eye was randomly selected.

[a] A positive value means improvement. All measurements were taken before instillation of the artificial tears.

Table 5
Schirmer test based on eyes with worse (smaller) Schirmer test value at day 1.

Treatment	Schirmer test (mm)		
Statistics	Day 1	Day 30	Day 30–day 1[a]
Cellufresh®			
N	20	20	20
Mean (SD)	6.4 (1.7)	7.2 (2.2)	0.9 (2.8)
95% CI	5.5, 7.2	6.2, 8.2	−0.4, 2.1
Median	6.5	7.5	0.0
Min., Max.	3.0, 10.0	5.0, 12.0	−5.0, 7.0
Blink®			
N	20	20	20
Mean (SD)	5.0 (1.6)	7.4 (1.7)	2.5 (1.7)
95% CI	4.2, 5.7	6.6, 8.2	1.7, 3.2
Median	5.0	8.0	2.5
Min., Max.	3.0, 8.0	5.0, 10.0	0.0, 7.0
Systane®			
N	20	20	20
Mean (SD)	6.1 (1.8)	6.6 (1.7)	0.6 (1.8)
95% CI	5.2, 6.9	5.8, 7.4	−0.3, 1.4
Median	7.0	6.5	0.0
Min., Max.	3.0, 9.0	5.0, 10.0	−2.0, 5.0
Tukey *P*-value			
Blink® vs. Systane®	0.1101	0.3786	0.0178
Blink® vs. Cellufresh®	0.0308	0.9400	0.0537
Systane® vs. Cellufresh®	0.8425	0.5762	0.8966

For each subject, the eye with a worse Schimer test (i.e. smaller value) at baseline was used in the analyses. If the values were the same for both eyes, the study eye was randomly selected.

[a] A positive value means improvement. All measurements were taken before instillation of the artificial tears.

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Table 6
Ocular surface staining (cornea and conjunctival) based on eyes with worse (higher) staining grade at day 1.

Treatment	Staining			
Grade	Day 1	Day 30	Change[a]	
Cellufresh®				
N	20	20	*N*	20
Grade 0	16 (80%)	19 (95%)	Improved 1 Grade	3 (15%)
Grade 1	4 (20%)	1 (5%)	No change	17 (85%)
			Worsen 1 Grade	0 (0%)
Blink®				
N	20	20	*N*	20
Grade 0	11 (55%)	18 (90%)	Improved 1 Grade	7 (35%)
Grade 1	9 (45%)	2 (10%)	No change	13 (65%)
			Worsen 1 Grade	0 (0%)
Systane®				
N	20	20	*N*	20
Grade 0	9 (45%)	18 (90%)	Improved 1 Grade	9 (45%)
Grade 1	11 (55%)	2 (10%)	No change	11 (55%)
			Worsen 1 Grade	0 (0%)
Wilcoxon Rank-Sum *P*-value				
Blink® vs. Systane®	0.7524	1.0000	Blink® vs. Systane®	0.7475
Blink® vs. Cellufresh®	0.1760	1.0000	Blink® vs. Cellufresh®	0.2733
Systane® vs. Cellufresh®	0.0484	1.0000	Systane® vs. Cellufresh®	0.0824

For each subject, the eye with a worse staining grade (i.e. larger value) at baseline was used in the analyses. If the values were the same for both eyes, the study eye was randomly selected.
[a] A grade reduction means improvement. All measurements were taken before instillation of the artificial tears.

3.5. Fluorescein staining

Table 6 shows the results for the change in ocular surface staining from day 0 to day 30 in all groups. There were no statistical differences between the three groups.

Table 7
Best-corrected visual acuity (BCVA; LogMAR) based on eyes with worse BCVA change at day 30.

Treatment	BCVA (LogMAR and line change)		
Statistics	Day 1	Day 30	Line change[a]
Cellufresh®			
N	20	20	20
Mean (SD)	0.02 (0.04)	0.01 (0.03)	0.0 (0.1)
95% CI	−0.00, 0.04	−0.00, 0.03	−0.0, 0.1
Median	0.00	0.00	0.0
Min., Max.	0.00, 0.16	0.00, 0.10	0.0, 0.6
Blink®			
N	20	20	20
Mean (SD)	0.02 (0.04)	0.01 (0.03)	0.1 (0.2)
95% CI	0.00, 0.04	0.00, 0.03	−0.0, 0.2
Median	0.00	0.00	0.0
Min., Max.	0.00, 0.10	0.00, 0.10	0.0, 0.6
Systane®			
N	20	19	19
Mean (SD)	0.02 (0.04)	0.02 (0.04)	0.0 (0.0)
95% CI	0.01, 0.04	0.01, 0.04	–
Median	0.00	0.00	0.0
Min., Max.	0.00, 0.10	0.00, 0.10	0.0, 0.0
Tukey *P*-value			
Blink® vs. Systane®	0.9964	0.6651	0.2138
Blink® vs. Cellufresh®	0.9140	0.9950	0.5895
Systane® vs. Cellufresh®	0.8786	0.6061	0.7474

For each subject, the eye with a worse BCVA change (i.e. smaller BCVA line increase or larger BCVA decrease) at day 30 was used in the analyses. If the BCVA change was the same for both eyes, the study eye was randomly selected. All measurements were taken before instillation of the artificial tears.
[a] A positive value means improvement.

3.6. Best-corrected visual acuity

There was a slight, but not statistically significant improvement in group 2 from day 0 to day 30 when best-corrected visual acuity results were compared. In the two other groups, there was no change between the two visits (Table 7).

4. Discussion

Current methods of diagnosing dry eye disease have a number of limitations. This is primarily due to the fact that these tests look at physical endpoints or parameters that are signs of late-stage disease. In addition, the basis for efficacy of commonly used diagnostic tests, such as the Schirmer tear test or Rose Bengal staining, may actually show higher rates of sensitivity and specificity because the sample population is typically selected because it has previously demonstrated dry eye disease symptoms [1]. In addition, because dry eye disease is multifactorial, there is a strong likelihood of variability of results from study to study. For these reasons, the DEWS subcommittee on Diagnostic Methodology concluded that were was no gold standard for diagnosis of dry eye disease.

Recognizing this, we concluded from the literature that both the Schirmer test and corneal staining had positive predictive values (PPVs) of 31%, while tear-film break-up had a PPV of 25%. The test with the highest PPV was tear osmolarity. In his meta-analysis on tear osmolarity, Tomlinson found that this test had a PPV of 87% [19].

While tear osmolarity has proven to be the most accurate method for diagnosing and following dry eye disease patients, the challenge has been to conduct the test quickly and efficiently [20,21]. Until recently, the test was typically performed in a clinical laboratory setting and required large samples of tears; this was often a challenge in patients with severe dry eye. However, these difficulties diminished when in 2008 the TearLab™ Osmolarity System became commercially available in Europe. The system is designed to be used in an eye care practitioner's office, has great ease-of-use and requires a very small volume of tears: 50 nL.

Please cite this article in press as: Benelli U, et al. Tear osmolarity measurement using the TearLab™ Osmolarity System in the assessment of dry eye treatment effectiveness. Contact Lens Anterior Eye (2010), doi:10.1016/j.clae.2010.01.003

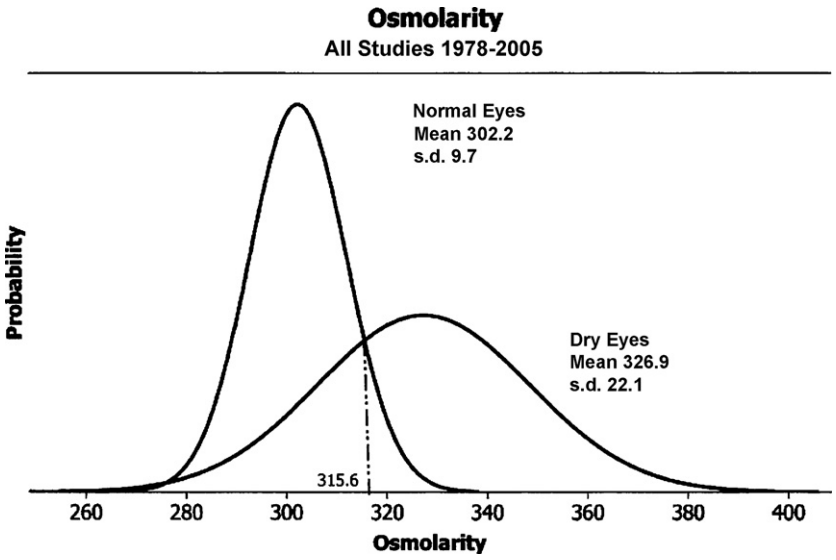

Fig. 1. The tear osmolarity measurements of normal vs. dry eyes based on the meta-analysis performed by Tomlinson [19].

We elected to include the TearLab™ system in this study to determine if it was able to provide a more sensitive assessment of the performance of the lubricant eye drops used in this study. By comparing the results from the other diagnostic tests performed in this study, it becomes clear that tear osmolarity is able to measure more subtle changes in the condition of the ocular surface than Schirmer, TBUT or corneal staining.

In this study, only the tear osmolarity testing showed any demonstrable difference or improvement between day 0 and day 30. In each group, there was a statistical improvement in the osmolarity over the course of the study. There were no differences, however, seen between the three groups in the traditional dry eye diagnostic tests: Schirmer, TBUT or ocular surface (cornea and bulbar conjunctiva) staining.

It is common sense that the instillation of any lubricant eye drop or saline solution would decrease the osmolarity of the tear film. In this study, we found that some lubricant eye drops decrease the osmolarity more than others after instillation. The subjects receiving the polyethylene glycol 400, 0.25% and sodium hyaluronate (Blink® Intensive Tears, Abbott Medical Optics Inc., Santa Ana, CA) demonstrated the greatest improvement with a mean reduction of 9.0 mOsm/L after instillation on the first visit and 9.9 mOsm/L after instillation 30 days after beginning the treatment. This might be due to the higher hypotonicity of the Blink® Intensive tears (Blink® intensive tears, 174 mOsm/L; Systane®, 288 mOsm/L; Cellufresh®, 312 mOsm/L) and the clinically proven, longer lasting effect of sodium hyaluronate [2]. This is demonstrated by the change over the course of the study in the osmolarity values in the Blink® group (Table 1). Prior to treatment, this group had a mean osmolarity of 320.9 mOsm/L, which improved to 306.9 mOsm/L on the last visit. When these results are compared with the osmolarity curve proposed by Tomlinson in his meta-analysis, it becomes clear that the patients in this group returned to a normal osmolarity measurement over the course of this study (Fig. 1) [19]. The Systane® group passed from an osmolarity of 321.9 mOsm/L at the beginning of the study to 312.6 mOsm/L at the end. The Cellufresh® group went from 320.6 mOsm/L to 312 mOsm/L.

The DEWS report authors concluded that the measurement of tear osmolarity is probably the single most important objective test in the diagnosis of dry eye disease. In fact, tear hyperosmolarity may reasonably be regarded as the signature feature that characterizes the condition of "ocular surface dryness". Based upon the categorization of dry eye disease proposed in the DEWS report (Table 8) [1,22], and Tomlinson's meta-analysis for tear osmolarity measurements of normal vs. dry eyes (Fig. 1), [19] clinical

Table 8
Dry eye severity grading scheme.

Dr eye severity level	1	2	3	4*
Discomfort, severity & frequency	Mild and/or episodic; occurs under environmental stress	Moderate episodic or chronic, stress or no stress	Severe frequent or constant without stress	Severe and/or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity-limiting episodic	Annoying, chronic and/or constant, limiting activity	Constant and/or possibly disabling
Conjunctival injection	None to mild	None to mild	+/−	+/++
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Corneal staining (severity/location)	None to mild	Variable	Marked central	Severe punctate erosions
Corneal/tear signs	None to mild	Mild debris, ↓ meniscus	Filamentary keratitis, mucus clumping, ↑ tear debris	Filamentary keratitis, mucus clumping, ↑ tear debris, ulceration
Lid/meibomian glands	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinization, symblepharon
TFBUT (sec)	Variable	≤10	≤5	Immediate
Schirmer score (mm/5 min)	Variable	≤10	≤5	≤2

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treatment decisions for dry eye patients can be made. Importantly, the recommended diagnostic cut-off of ≥316 mOsm/L has been well validated, particularly by Tomlinson [19].

We believe the conclusion to be made from this study is that tear osmolarity testing has the potential to become the gold standard in the diagnosis and management of dry eye disease. In addition, the study results also show that there is a definite, statistically validated benefit to treating patients with a PEG 400 and sodium hyaluronate eye drop in order to improve the ocular surface while alleviating patient symptoms.

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