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Comparison study of two different topical lubricants on tear meniscus and tear osmolarity in dry eye

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ABSTRACT

Purpose: To compare the effect of single-drop administration of two different ophthalmic solutions on tear meniscus and tear osmolarity in patients with mild to moderate dry eye disease.
Methods: This prospective study comprised of 122 patients with mild to moderate dry eye disease. These patients received a single dose of either unpreserved trehalose 3%, hyaluronic acid 0.15%, carbomer 0.25% (TH−HA, Thealoz Duo Gel) (Group 1) or hyaluronic acid 0.3% (HA) (Group 2) gel-based lubricants. Tear meniscus (height and depth) were measured using anterior segment optic coherence tomography (AS − OCT) at baseline and 10, 60, 120, and 240 min. after instillation. Tear osmolarity, Schirmer I test, tear break-up time (TBUT), gel properties, and patient comfort were evaluated 240 min. after instillation.
Results: Tear meniscus height (TMH) and tear meniscus depth (TMD) showed a significant increase with both lubricants compared to the baseline ($p < 0.001$). This effect remained significant for up to 60 min. and 120 min. for the TH−HA and HA 0.3% solutions, respectively ($p < 0.05$, for both). Mean comfort duration was 115.1 ± 20.1 min. in Group 1 and 148.3 ± 49.0 min in Group 2 ($p < 0.001$). Tear osmolarity, Schirmer I test, and TBUT were similar between the baseline and 240 min. for each group.
Conclusions: The results of this study demonstrate that 0.3% HA remains on the ocular surface for longer than TH-HA. The longer ocular residency time also seems to correlate with a longer patient comfort duration.

1. Introduction

Dry eye disease (DED) is highly prevalent throughout the world and is associated with tear instability, visual problems, and a reduction in the quality of life [1]. DED is a multifactorial disorder of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by hyperosmolarity, inflammation, tear film instability, and neurosensory abnormalities, as described in the Tear Film and Ocular Surface Society's Dry Eye Workshop (TFOS DEWS) II Report [2]. The presence of any one of three specified signs: a reduced non-invasive tear break-up time; elevated or a large interocular disparity in osmolarity; and ocular surface staining (of the cornea, conjunctiva or lid margin) in either eye, refers to the loss of homeostasis and confirms the diagnosis of DED [3].

DED directly affects the tear film and ocular surface. For that reason, objective methods are important for defining its severity and management protocol. Recently, a new method for the non-invasive measurement of tear meniscus based on optical coherence tomography has been developed. Anterior segment optical coherence tomography (AS − OCT) provides high resolution images of the cornea and anterior segment [4]. AS − OCT can also be used for tear meniscus assessment. Previous studies have shown that tear meniscus height correlates well with objective signs, as well as with subjective symptoms of DED [5,6].

DED management is complicated due to the multifactorial etiology of DED, and no single treatment regimen has been found that is suitable for all patients. According to TFOS DEWS II treatment begins with conventional lubricants for early-stage disease, with progression to more advanced therapies for more severe forms of DED [7]. Artificial tears have some specific properties for relieving the symptoms and signs of the patients: viscosity, lubricity, lipid content, electrolyte composition, and osmoprotective effects [8,9]. Ocular residence time on the ocular surface is a feature of viscosity and describes the duration of effect of the artificial tears. Although artificial tears are a mainstay of DED management, frequent instillation is a common problem. This is due to the short residence time of lubricants on the ocular surface [10,11]. Increased viscosity will increase ocular residence time [12,13].

Hyaluronic acid (HA) is a natural lubricant and has excellent water-retaining properties, which makes it well-suited for use in artificial

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tears [14]. HA has unique viscoelastic properties that are also helpful in the repair of corneal epithelial defects. Hyaluronate has been shown to accelerate the proliferation of human corneal epithelial cells and upregulate the expression of repair cytokines, thereby reducing apoptosis and downregulating the expression of inflammatory cytokines; in addition, it promotes the repair of ocular damage [15]. HA has a relatively longer residence time on the ocular surface, due to its water-entrapping and mucoadhesive properties, which leads it to be widely used in ophthalmic products [16]. The viscosity of HA is related to its concentration. Thus, with a higher concentration, ocular residence time will be increased, producing a longer period of improved patient-comfort [17]. Trehalose and carbomer are also used in artificial tears and have additional effects on the comfort of the patients. Trehalose, a natural disaccharide, is able to stabilize bilipid membranes and labile proteins. It has a protective effect against desiccation and oxidative insult [18]. Carbomer has a longer residence time by binding with mucin to prolong adhesion of the tear substitute [19], and is mostly found in gel-type formulations.

Some recent studies have used Anterior Surface Ocular Coherence Tomography (AS − OCT) to characterize the effect of various eye drops on the tear film. Carracedo et al. found that the residence time of HA drops was positively correlated with HAconcentration [20]. Wozniak et al. showed that a combination of trehalose 3% + HA 0.15% led to a significantly longer increase in tear film thickness than HA 0.2% only [21]. Schimidl et al. observed that trehalose 3% + HA 0.15% had a longer residence time than HA 0.15% [22].

Trehalose combined with HA is a new and promising agent for the treatment of long-term DED patients. In clinical practice, HA formulations mostly have an HA 0.15% concentration. For this study, two commercially available artificial tears: trehalose (unpreserved trehalose 3% + hyaluronic acid 0.15%) (TH-HA) and (HA 0.3%) were compared with the aim of evaluating the effect of a single drop instillation on tear film meniscus height and depth, on tear osmolarity, ocular residency time, and on patient comfort, in patients with mild to moderate DED. The osmoprotective effect of both gel-based topical lubricants was also investigated.

2. Materials and methods

This study, which was prospective, randomized, single-masked, and observer-blinded, was performed in adherence to the tenets of the Declaration of Helsinki. The local ethics committee approved the methodology. Written informed consent was obtained from all of the subjects. Subjects were included, who were at least 18 years of age, diagnosed with primary Sjogren's syndrome (PSS), history of DED for at least 3 months, tear break-up time (TBUT) ≤10 s or Schirmer I test ≤10 mm, OSDI score ≥13 points, and normal ophthalmic findings except DED. The eye with the lower TBUT was selected as the study eye. If TBUT was identical for both eyes, the eye with the lower Schirmer I test was selected. If Schirmer I test results were identical for both eyes, the right eye was chosen for study purposes. Exclusion criteria were: history of smoking, history of any other ocular disease or surgery, conjunctivochalasis, atopy, severe dry eye (totally unresponsive to topical artificial tear treatment), pregnancy, allergic disease, presence of systemic disease except PSS (diabetes, hypertension, renal or hepatic dysfunction), systemic or local use of one of the following medications: glucocorticosteroids, cyclosporine A, antibiotics, NSAIDs.

A pre-study screening was administered to each patient two weeks before starting the test day to screen for inclusion/exclusion. Selected patients were randomized into two test groups: Group 1 (TH−HA) (Thealoz Duo Gel®, Laboratoires Théa, Clermont Ferrand, France), and Group 2 (HA 0.3%) (Vismed Gel®, TRB Chemedica, UK). Patients were asked to stop the use of any artificial tears 12 h before the start of the study. All measurements were completed over one day.

On the test day, measurements of tear meniscus height (TMH), tear meniscus depth (TMD), tear osmolarity, Schirmer I test, tear break-up time (TBUT) and ocular surface disease index (OSDI) questionnaire were evaluated as part of a full ophthalmological examination. The results from these measurements provided a baseline for later comparisons. One drop of lubricant (Vismed Gel or Thealoz Duo Gel) were then administered by single ophthalmologist, according to which test group they were assigned to. Measurements of TMH and TMD were repeated 10, 30, 60, 120, and 240 min. after instillation. After 240 min., patient satisfaction (subjective evaluation of ocular comfort with 5 questions), tear osmolarity, Schirmer I, and TBUT were evaluated. Patient satisfaction was evaluated on gel properties on-eye by asking about: sticky (presence/absence), viscosity (presence/absence), blurring effect (presence/absence), burning or stinging (presence/absence) and relief of symptoms (mild/moderate/severe). The comfort duration of the drops was also recorded.

Tear osmolarity was measured with the Tear Lab Osmolarity system (TearLab, San Diego, CA, USA). The Tear Lab system consists of a test microchip reader unit, a microchip holder, and an osmolarity test microchip, which is clipped onto the top of the holder. The tip of the test microchip is placed next to the inferior, lateral tear film meniscus, along the lower eyelid, where it can absorb the correct amount of fluid (50 nanolitres). Once the holder is docked with the reader unit, the system reader calculates and displays the osmolarity measurement in mOsm/litre on an LCD screen.

The Schirmer I test was applied to the lower a third of the lateral bulbar conjunctiva without topical anesthesia. The patient was asked to look away from the paper strip and to blink normally. The results were evaluated by measuring the length of wetting of the paper strip after 5 min. Results were recorded in millimeters (mm).

The TBUT test was recorded using sodium fluorescein strip gently touched in upper conjunctiva to stain the tear film and observed under cobalt blue light using a slit-lamp biomicroscope. The patient was asked to look straight-ahead and to blink once, and then to refrain from blinking for as long as possible. The TBUT was recorded as the time in seconds from the final blink until the appearance of the first break in the fluorescein under cobalt blue illumination. The test was repeated 3 times and the average recorded.

OSDI is a questionnaire of 12 items that evaluates the symptoms of eye-related irritation and the effect on visual acuity. The OSDI questionnaire validated in Turkish was used [23]. The total OSDI score of each patient was calculated as: OSDI score = (Total score of all answered questions x100) / (Total number of questions answered x4). Mild to moderate DED was evaluated according to OSDI score. An OSDI score between 13 and 22 points was evaluated as mild, the one between 23 and 32 points as moderate. OSDI score above 32 points were excluded from the study.

2.1. Tear Meniscus measurement with OCT

OCT measurements were performed using Swept Source OCT (SS − OCT, DRI OCT Triton, Topcon, Tokyo, Japan). The lower tear meniscus height and depth measurements were provided using the SS-anterior segment OCT single vertical scan mode. In follow-up measurements, the scan was applied to the same region of the eyelid just below the corneal vertex, centered on the inferior cornea and the lower eyelid. The patient was asked to blink normally during the imaging procedure while looking at a fixed target within the device. Images were obtained within the first second immediately after a blink. A built-in caliper was used for measuring the tear meniscus height and depth in micrometers. The line at which the meniscus intersected with the cornea (superiorly) and the eyelid (inferiorly) was the tear meniscus height (TMH). The line from TMH to inferior fornix was tear meniscus depth (TMD). (Fig. 1)

2.2. Statistical analyses

SPSS 20.0 was used for statistical analysis. The Shapiro-Wilk test

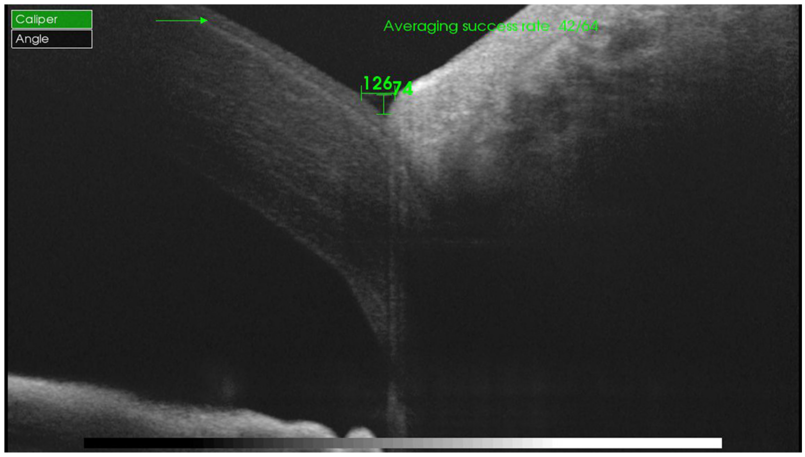

Fig. 1. Images showing the tear meniscus height (TMH) and depth (TMD) measurements by swept source optical coherence tomography (SS − OCT).

was used to test for normality of the data. Descriptive statistics included mean ± SD or median (min–max) for the continuous variables, whereas the number of cases and percentages were calculated for the categorical variables. For non-normally distributed data, the significance of the difference between groups was calculated using the Mann–Whitney U test. The difference within dependent samples was assessed using the Wilcoxon sign test. The Spearman correlation coefficient was used to analyze the statistical significance between quantitative tear meniscus parameters and patient satisfaction values. A P value of less than 0.05 was considered as statistically significant.

3. Results

Fifty-six patients using TH–HA (Group 1) and 66 patients using HA 0.3% (Group 2) were included in the study. No age or gender-related significant difference was detected between study groups ($p > 0.05$). Demographic data and baseline clinical characteristics are presented in Table 1. No significant differences were detected between the groups at baseline.

The mean baseline TMH was 237.4 ± 85.6 and 242.8 ± 75.3 μm in Groups 1 and 2, respectively. Both lubricants provided significant increases in TMH and TMD at 10 min after administration. ($p < 0.001$) (Table 2 and 3). The highest TMH and TMD values were reached after 10 min. When compared with baseline, the increase in TMH, and TMD remained significant at 60 min after tear drop instillation in both groups. At 120 min, a significant increase in TMH and TMD was only detected in Group 2. Differences in time-based percentages are displayed in Figs. 2 and 3 (10 min.: $p = 0.005$; 60 min.: $p = 0.013$, 120 min.: $p = 0.014$). At 240 min after instillation of the drops, TMH and TMD were decreased significantly in both groups. TBUT, tear osmolarity and Schirmer I test showed no significant change at 240 min in both groups compared to baseline ($p > 0.05$).

Table 1
Demographic data and baseline clinical characteristics of the groups.

	Group 1 (n = 56)	Group 2 (n = 66)	P-Value
Age, yrs	52.5 ± 13.2	53.4 ± 11.4	0.40
Gender (M/F)	10/46	8/58	0.37
OSDI score	21.4 ± 6.2	20.8 ± 5.9	0.82
TBUT, s	3.0 ± 2.5	3.4 ± 2.5	0.31
Schirmer I test, mm/ 5 mins	3.3 ± 2.5	4.7 ± 3.4	0.17
Tear Osmolarity, mOsm/L	309.3 ± 12.5	307.6 ± 8.5	0.59
Tear Meniscus Height, μm	237.4 ± 85.6	242.8 ± 75.3	0.65
Tear Meniscus Depth, μm	164.4 ± 55.5	159.3 ± 55.1	0.49

Values are mean ± standard deviation of baseline examination. OSDI: Ocular Surface Disease Index, TBUT: tear break-up time.

Table 2
Tear meniscus height (TMH) measurements at each follow-up.

TMH (μm, mean ± SD)	Group 1	Group 2	P value
Baseline	237.4 ± 85.6	242.8 ± 75.3	0.65
10 min.	377.2 ± 141.6	415.6 ± 92.2	0.007
60 min.	269.0 ± 91.4	286.6 ± 61.1	0.45
120 min.	251.9 ± 78.1	248.3 ± 69.4	0.112
240 min.	246.5 ± 76.3	241.7 ± 44.7	0.125

Table 3
Tear meniscus depth (TMD) measurements at each follow-up.

TMD (μm, mean ± SD)	Group 1	Group 2	P value
Baseline	164.4 ± 55.5	159.3 ± 55.1	0.49
10 min.	220.0 ± 70.9	235.4 ± 37.8	0.008
60 min.	174.4 ± 61.6	187.7 ± 36.4	0.009
120 min.	170.5 ± 54.9	173.8 ± 52.6	0.225
240 min.	162.7 ± 49.4	167.8 ± 32.3	0.06

At the end of 240 min patient satisfaction, including gel properties, was evaluated, and no significant difference was detected between the groups (Table 4). Mean comfort duration was 115.1 ± 20.1 min in Group 1 and 148.3 ± 49.0 min in Group 2. This difference between the comfort durations of the patients was significant ($p < 0.001$).

4. Discussion

This study investigated the differences between two gel-based artificial tears in patients with mild to moderate DED. Tear meniscus depth and height were measured at baseline and at defined time points after a single drop instillation. The change in tear film meniscus during this study provided information about the corneal residency time of the two different eye drops. Other clinical measures for DED, such as determination of tear film break-up time (TBUT), Schirmer I test, tear osmolarity, and subjective assessments were also performed. Although some parameters (TBUT, Schirmer I, tear osmolarity) did not show a statistically significant difference between the two treatments, HA 0.3% was superior to TH- HA by means of long corneal residency time and high patient comfort.

HA has an important role in relieving dry eye symptoms, probably due to its viscoelasticity [24,25]. The viscoelastic properties of HA allows stabilization of the pre-corneal tear film and an increase in the corneal residency of the agent. HA is capable of entrapping water and spreading over the ocular surface by means of molecular coherence within the formulation [26]. In this way, the HA solution becomes less elastic and more viscous between the blinks. Therefore, HA solutions

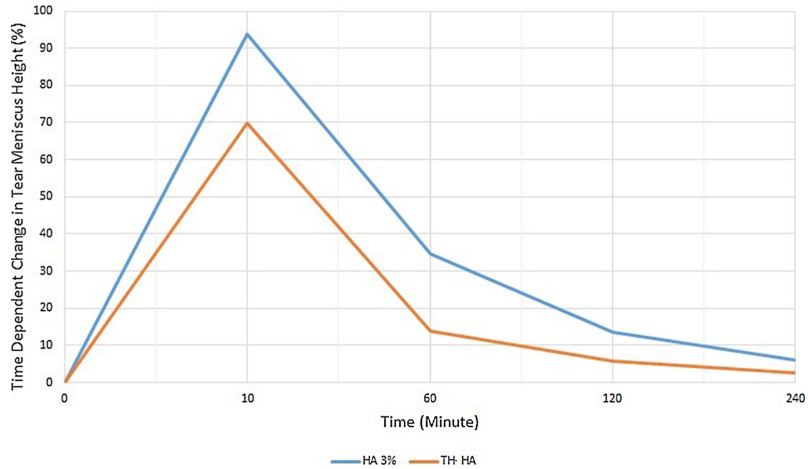

Fig. 2. Time dependent change (%) of tear meniscus height.

retard the evaporation of the water on the ocular surface and cover the surface as a shell by adherence to mucin [27,28].

Trehalose is a sugar which can be synthesized by bacteria, fungi, plants and invertebrate animals. It is also labeled as a bioprotectant and osmoprotectant agent. In a desiccation setting, trehalose stabilizes the cell membrane lipid bilayer; thereby inhibiting cell damage. In addition, trehalose promotes hydration of corneal epithelial cells and heals the ocular surface by suppressing apoptosis [29,30]. Trehalose with HA helps epithelization through faster healing, and longer corneal residency time, to improve TBUT [31,32].

Although ocular residency time of an artificial drop is important in terms of drug pharmacokinetics, few studies have examined this issue. Radioactive labeling of drugs is a known technique for measuring the ocular residency time [10]. Snibson et al. demonstrated mean ocular surface residence times for HA 0.3% and HA 0.2% of 23.5 and 11.1 min., respectively [16]. Anterior segment OCT technology has enabled non-invasive assessment of tear meniscus height and depth associated with ocular residency. In our study, we compared two different gel-based artificial tears in terms of ocular residency time by AS – OCT. We found a 93.85% increase in TMH at 10 min. with administration of HA 0.3% vs a 69.7% increase with TH–HA. The TMH at 10 min. was higher compared to baseline values for both drop formulations and this effect lasted for 120 min. in HA 0.3% vs 60 min. in TH—HA. Schmidl et al. reported that TH–HA applied patients had a longer residency time than HA 0.15% [33]. Whereas, using HA 0.3% in the current study led to a high TMH in favor of HA. Wozniak et al. compared a single dose of trehalose 3%, hyaluronic acid 0.15%, carbomer 0.25% gel (TH); hyaluronic acid 0.2% gel (HA); and polyethylene glycol 0.4% + propylene glycol 0.3% gel (PP) in mild to moderate dry eye disease in terms of ocular residency and patient comfort [21]. They found that tear film thickness (TFT) increased significantly and kept this pronounced difference at 10 and 30 min. compared to baseline, whereas only the TH group displayed a significant increase at 60 and 120 min.. They could not explain the reason for this effect, but they postulated that interaction of trehalose with lipid membranes involving the surrounding hydration shell might generate this superiority of TH—HA to other artificial drops included in the study. In this study, enhancing the concentration of HA to 0.3% may match the effect of TH–HA, consisting of 0.15% hyaluronic acid. The reason for an increased residence time of HA 0.3% may be related to

Table 4
Patient satisfaction with the drops.

Parameters	Group 1	Group 2	P-Value
The eye gel is sticky	24/56	26/66	0.69
The eye gel is viscous	12/56	6/66	0.06
The eye gel is blurring vision	5/56	4/66	0.54
The eye gel burns/ stings	0/56	0/66	1
The eye gel relieves the symptoms			
Mild	9/56	8/66	0.48
Moderate	9/56	9/66	0.51
Severe	38/56	49/66	0.45

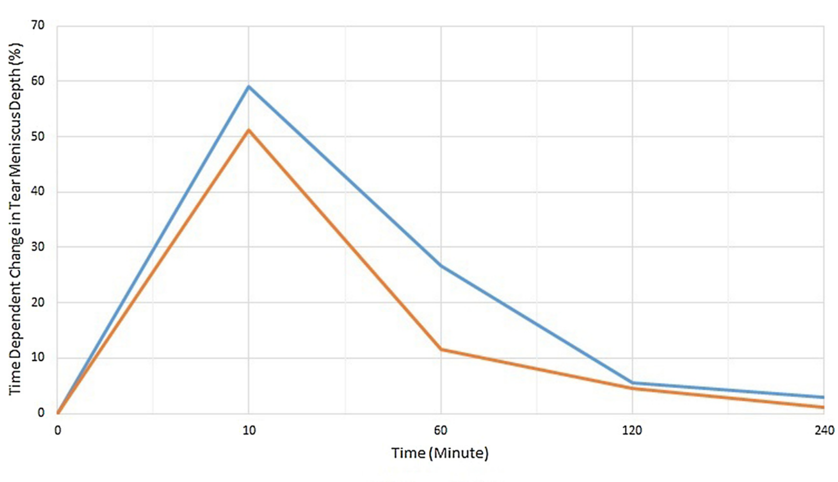

Fig. 3. Time dependent change (%) of tear meniscus depth.

spreading characteristics, pseudoplasticity and muco-adhesion of the agent [12]. Previous studies have showed that solutions with higher concentrations of HA stay on the eye for longer, and will therefore increase the thickness and stability of the tear film [16,34].

Patients were assessed based on their satisfaction of the drop after 240 min., but no significant difference was detected between the two groups. However, the comfort duration of patients using HA 0.3% was longer than patients with TH—HA. According to the TFOS DEWS II report, tear film thickness (TFT) is one of the dry eye sub-classification methods [35]. OCT thus gives the possibility of non-invasive measurements of both the upper and lower menisci in terms of height, area, and curvature of the surface. Although none of these parameters correspond to central TFT, lower TMH reflects the volume of muco-aqueous tears [36,37]. When the TMH increases, dry eye symptoms reduce [3]. Therefore, maintaining a high TMH might be associated with increased comfort time. A rising tendency for TBUT and Schirmer I was noted, but neither artificial drop changed significantly after 240 min., compared to the baseline.

High osmolarity is a known factor in the disease process of dry eye [2]. In this study, no significant change in tear osmolarity was noted between the baseline and 240 min. values. This result might be related to the single application of the lubricant during measurements and/or the delayed time of measurement after instillation. Frequent administration of these artificial tears would be expected to lower osmolarity level over time.

The major limitations of this study were the small sample size, short-term follow-up time, inability to check the response after a long period administration of the lubricants, and lack of control group due to artificial tears' unknown safety on non-dry eye subjects.

In conclusion, our results demonstrate that 0.3% HA lasts longer on the ocular surface than TH-HA. In addition, a longer ocular residency time leads to improvement in duration of comfort. However, before concluding that HA 0.3% is superior to TH-HA, further randomized prospective studies with a larger sample size and with follow up over a longer period of time are required.

Declaration of Competing Interest

The authors report no conflicts of interest. The authors are responsible for the content and writing of the paper.

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