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Short-Term Changes in Tear Lipid Layer Thickness After Instillation of Lipid Containing Eye Drops

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Purpose: Lipid-containing eye drops is increasingly popular in eye clinics to treat dry eye. Tear lipid layer thickness (LLT) changes after instillation of lipid eye drops have not been characterized. We aim to evaluate these changes of LLT using a noninvasive interferometry-based method.

Methods: This prospective clinical study was conducted on staff and patients from Singapore National Eye Centre with ad hoc recruitment. Noninvasive tear break up time was measured using the Keratographer 5M. LLTs were measured using a tear interferometer machine before and at 1, 5, and 15 minutes after instillation of lipid-containing drops, either Cationorm unidose or Artelac Lipids. Fluorescein clearance (tear clearance rate) and Schirmer tests were conducted. The tear clearance rate of fluorescein dye was based on the visual examination of the color of a Schirmer strip after 5 minutes, compared against color standards.

Results: This study included a total of 84 participants aged $\geq$21 years. Many were female (92.8%) and Chinese (89.2%). A tear clearance rate of 1/16 was most common (35.7%), whereas 1/128 and 1/32 were uncommon (3.57% each). Schirmer results were 6.5 $\pm$ 8.1 mm, and noninvasive tear break up times were 8.12 $\pm$ 6.25 mm. Participants with baseline LLT $<$60 nm had greater changes in LLT after Cationorm instillation, compared with those with an LLT of $>$60 nm. LLT changes over 15 minutes were not associated with tear clearance rate. Similar results were obtained when using Artelac Lipids.

Conclusions: Our results showed that participants' initial LLT affected their responsiveness to lipid-containing eye drops more than other factors.

Translational Relevance: Doctors may choose to measure the baseline LLT of patients before deciding whether to prescribe lipid eye drops to patients.

Introduction

Dry eye is a chronic multifactorial disease of the tear and ocular surface, characterized by tear instability. This problem is increasing and has a major impact on visual function and quality of life, with symptoms that adversely hinder a patient's ability to carry out daily activities, such as driving and reading.[1]

A large proportion of patients with dry eye either self-treat or are managed by their general practitioner. The cost of treating dry eye annually is high and can cause great economic burden.[2,3] Dry eye is also far more prevalent than previously thought, and has significant economic implications, including costs associated with increased health care use, missed school and work, leisure and quality-of-life issues, and decreased work productivity.[4,5] Studies that have shown that increased dry eye symptoms were associated with decreasing quality-of-life report that the association was generally weak.[6]

Tear instability and evaporative losses are major components of dry eye that incur morbidity, but can be

Table 1. List of Clinical Characteristics of Participants

Characteristic	Cationorm ($n = 28$)	Artelac ($n = 30$)
Age (years)	59.4 ± 15.0, 63 (21–83)	50.9 ± 20.6, 54 (22–85)
Female gender	92.9 (26)	66.7 (20)
Symptom score (SPEED)[a]	11.7 ± 6.4, 11 (0–23)	7.0 ± 8.5, 4 (0–27)
NITBUT (seconds)	8.1 ± 6.2 5.9 (1.7–22.2)	6.4 ± 4.5, 5.5 (0.0–24.0)
Tear clearance rate	0.06 ± 0.05, 0.25 (0.004–0.063)	0.011 ± 0.006, 0.008 (0.004–0.031)
Schirmer (mm)	6.52 ± 8.15, 4.5 (0–42.5)	11.3 ± 6.0, 9.5 (5–27)
Baseline lipid layer thickness (nm)	67.1 ± 23.6, 65 (29–100)	55.4 ± 17.7, 57 (27–100)

NITBUT, noninvasive tear break up times; SPEED, Standard Procedure for Evaluation of Eye Dryness.
[a]Standard patient evaluation of eye dryness (symptom questionnaire).
Values are mean ± standard deviation, median (minimum–maximum), or number (%).

addressed with eye drops that increase tear stability (by decreasing tear evaporation or promoting tear structure stability).[7–11] In addition, tear stability is clinically relevant because it affects clinical decisions related to contact lens use.[12]

The tear film lipid layer plays a key role in tear surface tension and is important for tear stability as well as ocular surface homeostasis. Lipid eye drops are getting more popular in clinical practice.[13] A previous study has demonstrated that a single drop of artificial tear can change the thickness of the preocular tear.[14] Other studies have shown that the tear lipid thickness measured by interferometry could be increased by instillation of one drop of lipid-containing eye drops.[15–17]

The factors that determine the increase and subsequent return to normal lipid layer thickness (LLT) after instillation of these eye drops are unknown. It is also not known whether the changes in LLT are correlated with tear clearance rates. We aim to evaluate these changes of LLT after a single drop of lipid-containing eye drop up to 15 minutes, using a noninvasive interferometry-based method, and examine the clinical factors that may influence these changes.

Methods

Study Design and Participants

This clinical study was conducted at the Singapore Eye Research Institute, Singapore. The study was approved by the Institutional Review Board of Singapore Health Services, and complied with the Tenets of Declaration of Helsinki for human research. Written informed consent had been obtained from all participants. We recruited 84 participants (62.5% women and mean age 61.0 ± 13.8 years) from the eye clinics in the Singapore National Eye Centre (Table 1).

Eligibility

Inclusion criteria were adults >21 years of age who were willing to undergo the study procedures. Exclusion criteria were patients who were presented to the clinic for an acute eye problem such as visual loss or painful eye. Patients with significant corneal staining were also excluded. Patients must not have any use of eye drops for ≥2 hours before undergoing the study procedures. We did not select specific types of patients because our study was to determine LLT changes after instillation of lipid-containing eye drops in a small and homogenous group of participants, not the therapeutic efficacy of eye drops in dry eye.

Study Procedures

Intervention

Two types of lipid-containing eye drops, Artelac and Cationorm, were used for two separate groups of participants. We chose to use Artelac and Cationorm in this study because these two eye drops were the most commonly used and available lipid-containing eye drops in Singapore at that time. The choice of Cationorm or Artelac eye drops in participants was random and not based on any clinical decision.

The examination of the right eye of participants in the study was a monocular one. Before the instillation of eye drops, the baseline LLT was measured using the LipiView machine. One drop of the eye drops was then instilled into the participant's right eye and the LLT of participants was measured 1, 5, and 15 minutes after instillation of the eye drop. We chose our time points based on a preliminary study involving testing a separate and smaller group of participants ($n = 3$)

with Artelac where the timeline for measurements was 0, 1, 15, 20, 45, and 60 minutes. From this study, we observed that there was no further significant change in LLT after 15 minutes. We added the 5-minute time point in our study because there were significant differences between the LLT of both the baseline LLT of <60 nm and >60 nm groups of participants from our pilot study. Therefore, the following time points were chosen: 0, 1, 5, and 15 minutes, with 15 minutes as our last study time point.

Participants had to take note of the precautions such as no rubbing of eyes and no blinking forcefully. This is because deliberate, forceful blinking was found to significantly increase the LLT of the tear film. The magnitude of increase was found to be correlated with the baseline LLT values; individuals with baseline LLT values of 75 to 150 nm demonstrated a mean increase in LLT of 33 nm after forceful blinking, whereas subjects with baseline LLT values of ≤60 nm experienced a mean increase of 19 nm. Forceful blinks increased the LLT by >15 nm owing to expression of meibum from meibomian gland dysfunction.[18]

Questionnaire

All participants underwent symptom evaluation by the Standard Procedure for Evaluation of Eye Dryness (SPEED) questionnaire, a previously validated way to assess dry eye symptoms.[19–21]

Keratograph 5

We tested the noninvasive tear break up times (NITBUT) of participants with the K5. The first NITBUT image acquired in the right eye was used for further analysis.[22–25] Briefly, participants were told to blink a few times and then close their eyes. When they opened their eyes again, they were instructed to look at a fixation light. A certain time interval set by the machine, which was not alterable by user (maximum of 24–25 seconds). After that time interval had passed, the examination would cease, regardless of whether a NITBUT reading was obtained. If an NITBUT reading had been obtained from the machine and the patient subsequently blinked (before 20 seconds), the procedure was not repeated. Failure to keep the eyelids open for 20 seconds might be due to excessive irritation when the participants were keeping their eyes open, which could be related to tear stability issues. Repeated testing might further affect tear stability and subsequent results. On such occasions, the zones that had not yet broken up would be assigned as 25 seconds. The study data for first break up NITBUT displayed by the commercial software were first analyzed.

Lipiview

Tear film lipid thickness was evaluated with the Lipiview interferometry (TearScience, Morrisville, NC) as previously described.[26] The mean thickness was derived using an interferometric method over the inferior portion of the cornea, based on an imaging procedure acquired over a 30-second duration. Each color interferometric unit of lipid thickness corresponds to 1 nm. Any value provided as ≥100 would be analyzed as 100.

Statistical Analysis

We conducted linear regression for both types of eye drops. Parametric unpaired *t*-tests were used to compare the LLT between any two groups that were defined by categorical variables. Spearman correlation coefficients were calculated for analyses involving two continuous variables. The significance threshold (alpha level) was set at 0.05. Analysis was performed on Stata13.1 (StataCorp, College Station, TX).

The LLT was plotted at different times, for the two groups of participants using Cationorm or Artelac and at each time point after instillation (1, 5, or 15 minutes) the LLTs were compared using the unpaired *t*-test. Because there were three comparisons, to adjust for multiple testing, the level of statistical significance was 0.05/3 or 0.0167. The actual *P* value calculated before any adjustment was provided.

To examine the significance of LLT changes at each time point, the paired *t*-tests were performed separately for participants with a baseline of ≤60 nm or >60 nm.

We calculated the maximum difference between the highest LLT reached at any of the four time points of the 25-minute duration and the baseline LLT. This was named as the maximum increase. We also calculated the maximum decrease, which is the difference between the highest LLT reached during this 15-minute period and the LLT at the time point immediately after. These two variables were used for the calculation of the Spearman correlation coefficients. Other variables that were involved in analyses were age, SPEED questionnaire score, NITBUT, Schirmer score, tear clearance rate, drug type (eye drop), and baseline LLT.

Results

Clinical Characteristics of Participants

The clinical and demographic characteristics of the study participants are shown in Table 1. The mean LLTs were 67 and 51 nm in the Cationorm and Artelac studies, respectively. The mean SPEED

scores, which documented the severity and frequency of dry eye symptoms, were 9.2 ± 6.3 and 7.0 ± 8.5. The mean first break up times provided by K5 were 8.1 and 9.6 seconds in the Catiornorm and Artelac studies, respectively. Overall, 64.3% of Cationorm participants, 33.3% of Artelac participants and 0% of participants from the pilot study (Artelac) had systemic diseases such as hypertension. Only one of the participants had diabetes mellitus.

Changes of LLT With Time

A single lipid-containing eye drop was instilled, either Artelac or Cationorm, in different participants. The overall LLT did not show any significant change with time (data not shown) with either Artelac or Cationorm eye drops. For the participants instilled with Cationorm, LLT of those with baseline <60 nm increased steeply from time of instillation to 1 minute, before increasing more gently to 15 minutes. It is interesting that the LLT increased to >60 nm sometime after 5 minutes. The LLT of those with a baseline of >60 nm decreased slightly at 1 minute, before increasing to above the initial baseline LLT at the end of 15 minutes. There were significant differences between these two groups at 1 minute ($P = 0.0011$), 5 minutes ($P = 0.0019$) and 15 minutes ($P = 0.0066$) (Figure A). A similar trend occurred after the instillation of Artelac eye drop, except that for those with a baseline LLT of <160 nm, LLT had already increased to >60 nm by 1 minute, and may demonstrate a reducing LLT as early as 15 minutes. The differences in LLT between the groups were borderline significant at 5 minutes ($P = 0.026$) and significant at 15 minutes ($P = 0.0095$) (Figure B). The maximum increase of LLT within the 15 minutes was moderately and inversely correlated to the baseline LLT of participants who had Cationorm ($r = -0.47$) (Figure C) or Artelac ($r = -0.54$) (Figure D). Both correlations were significant ($P = 0.01$ and $P = 0.003$, respectively).

In the pilot study, another 26 younger participants underwent similar treatment with Artelac. This study had a similar trend of LLT change, except perhaps the participants with a baseline LLT of >60 nm showed negligible change in LLT or did not show any LLT change at all (Supplementary Fig. S1). When we combined the data (Supplementary Fig. S2) of the patients in the main study with those in the pilot study who received Artelac ($n = 56$), we observed a similar trend as in the patients in the main study. The patients in the preliminary study did not have tear clearance rate and SPEED performed; thus, they could not be combined with the main study for subsequent analyses.

Associations of the Amount of Maximum Increase of LLT With Other Variables

A linear regression model was conducted on several variables: baseline LLT, time after instillation, Schirmer, tear clearance rate, NITBUT, age, and SPEED scores (dry eye symptoms). Upon analysis, it was found that the baseline LLT is the main factor associated with the amount of LLT increase, and a lower baseline LLT was associated with a subsequent increase in the LLT (Tables 2 and 3). The increase in the LLT was not significantly affected by the tear clearance rate or the parameters related to dry eye such as SPEED or NITBUT. Because the type of eye drop (whether Artelac or Cationorm) was not a significant covariate, the maximum increase in the LLT was similar for both types of eye drops. When the regression was performed for the participants with Artelac eye drops instilled alone (Supplementary Table S1) or with Cationorm eye drops instilled alone (Supplementary Table S2), similar results were obtained.

In addition to these linear regressions, we also performed regression with LLT as the dependent variable (outcome), using patient identification number to control for repeated measurements, and time (as the covariate to determine time-related change), in addition to these parameters. When this analysis was performed for patients who had Artelac eye drops instilled, we observed that there was a significant time effect, as well as interparticipant variation in LLT. Furthermore, the most significant factor that was associated with the observed LLT was the baseline LLT (Supplementary Table S3). A similar trend was observed when we repeated the analysis for participants with Cationorm eye drops (Supplementary Table S4). When a combined analysis was performed for participants with Cationorm or Artelac eye drops instilled, a similar trend was again observed (Supplementary Table S5). The effect of the type of eye drop (Cationorm or Artelac) did not reach significance ($P > 0.05$), suggesting that the LLT did not behave differently after adjusting for the other factors.

Associations of the Maximum Decrease (or Slope) With Other Variables

When this regression analysis was performed with the maximum decrease in the LLT after reaching its highest point, none of the covariates were found to be statistically significant. However, not all participants had a decrease in the LLT, because many participants who had Cationorm eye drops instilled achieved their highest LLT only at 15 minutes.

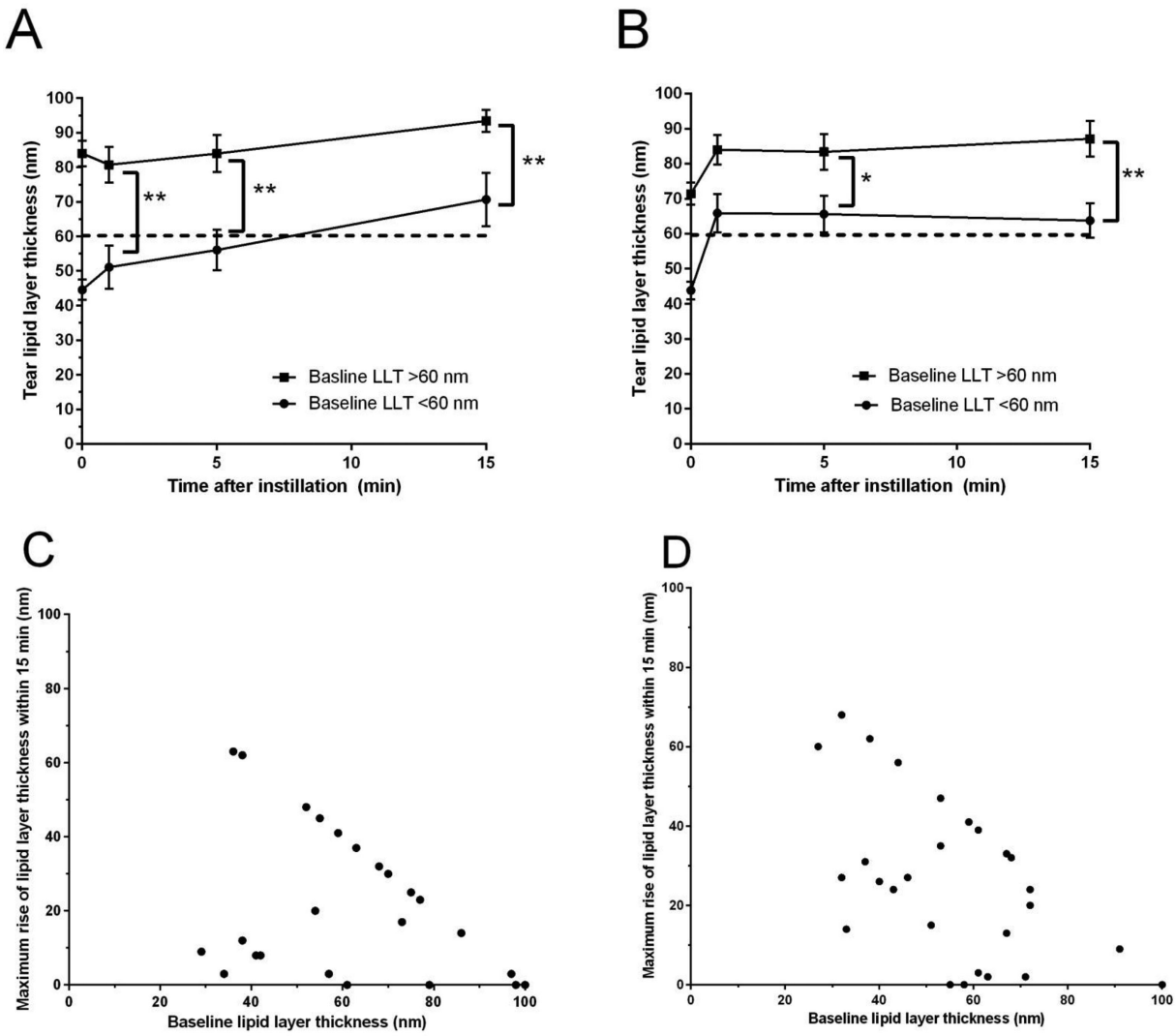

Figure. Lipid layer thickness (LLT) after instillation of one drop of Cationorm (A) or Artelac (B). Scatter diagram showing correlation of baseline LLT with maximum increase of LLT within 15 minutes after one drop of (C**)** Cationorm or (D) Artelac. Symbol, mean LLT; error bar, standard error of the mean. The *P* value was calculated by two-tailed unpaired *t*-tests between the two groups at each time point, without adjusting for multiple comparisons.*0.05 > *P* > 0.01; **0.01 > *P* > 0.001; ***$P < 0.001$. The changes from baseline were calculated using paired *t*-tests (*P* values not shown in figure for simplicity). After instillation of Cationorm eye drops. (A) For participants with a baseline LLT of >60 nm, the subsequent LLTs were not significantly altered ($P > 0.05$) at any time point. For participants with a baseline of LLT ≤60 nm, the LLT at 1 minute and 5 minutes were not significantly increased ($P > 0.05$), but at 15 minutes, it was significantly increased ($0.01 < P < 0.05$). After instillation of Artelac eye drops. (B) At all time points, the baseline LLT was >60 nm and the LLTs were significantly higher than baseline ($0.01 < P < 0.05$). For a baseline LLT of <60 nm, the LLTs were significantly increased at 1 minute ($P < 0.001$), at 5 minutes ($P < 0.01$), and at 15 minutes ($P < 0.01$).

Discussion

In this study, we found the LLT to change significantly after the instillation of lipid-containing drops.

The profile of change is affected by the type of lipid containing eye drop.

The increase of LLT was more rapid at 1 minute in the case of Artelac, but LLT started to decrease after 5 minutes. For Cationorm, the increase of the LLT is more gradual and more sustained. It is still unknown how long it will take for the LLT to decrease (some time after 15 minutes). The only variable that is associated with a greater increase of LLT was a low baseline LLT.

Previous studies have shown that oil-containing drops, and not other kinds of eye drops, increase tear LLT. Soothe (also called Artelac eye drops) improved LLT by 107%, which was more than Systane eye drops

Table 2. Linear Regression of the Maximum Increase in the LLT as a Dependent Variable With Other Clinical Variables as Covariates

Covariates	Coefficient	Standard Error	*P* Value
Baseline LLT	−0.54	0.13	<0.001***
Tear clearance rate	39.6	69.8	0.573
NITBUT	−0.35	0.49	0.478
Schirmer (mm)	0.40	0.36	0.275
Symptom score (SPEED)[a]	0.26	0.32	0.431
Drug type[b]	2.69	6.14	0.663
Age (years)	0.10	0.15	0.516

LLT, lipid layer thickness; NITBUT, noninvasive tear break up times; SPEED, Standard Procedure for Evaluation of Eye Dryness.
[a]Standard patient evaluation of eye dryness (symptom questionnaire).
[b]Whether the participants received one drop of Cationorm or Artelac.
***Value is significant.

(which does not contain lipids in the formulation) and only induced a 16% change at 15 minutes after instillation. There was minimal or no detectable increase in LLT in 57.5% ($n = 23$) of subjects after one drop of Systane, and a *decrease* in LLT occurs in 7.5% ($n = 3$) subjects. Unlike our report, this study only recruited participants with a baseline LLT of <75 nm.[17]

A similar study using Systane Ultra and Sooth XP showed that LLT 15 minutes after the instillation of Systane Ultra was not statistically significant when compared with the baseline LLT, whereas an LLT of 15 minutes after instillation of Soothe XP was statistically significant ($P < .001$). Unlike our report, eligibility was then determined by a LLT of <75 nm at baseline and the inability to increase the LLT by ≥15 nm with three blinks, as determined by interferometric methods. The study also had an evaluation of meibomian gland drop out with meibography, which was not conducted in our report.[15]

In another study, an increased LLT was observed 1 hour after Tears Again (liposome) spray formulation compared with normal saline.[27] Refresh Endura eye drops, which is anionic emulsion containing castor oil, glycerine carbomer, induced an increase in the LLT at 1 to 15 minutes after instillation compared with Soothe.[16] We did not evaluate the Tear Again and Refresh Endura in our study.

The differences in the effect of Artelac and Cationorm on the LLT over 15 minutes could be due to the differences in the compositions of the eye drops. Artelac is an anionic emulsion containing medium chain triglycerides and carbomer, which could potentially interact with lipids in the tear film, whereas Cationorm is a cationic emulsion containing 1% mineral oil with cetalkonium chloride. The cetalkonium chloride is positively charged, and can interact with negatively charged corneal epithelial cell membranes. This may then release lipids into the superficial lipid layer slowly over time (last longer).

The strength of this study includes a uniform protocol and testing under relatively uniform conditions. We did not do the study within a controlled environment chamber with fixed humidity and temperature, but all measurements were performed in the same room with central air conditioning. A limitation was that we only performed one baseline measurement per participant. However, the changes detected in our study were largely beyond the limits of repeatability and reproducibility, so they were likely to be reliable.[26] Using the LipiView instrument, the observation of lipid thickness is only possible over the area of 2.5 mm height and 5.0 mm width in the lower part of the cornea.[17] Although the intervention has led to clinically measurable differences of the participants' LLTs, any other measurable variables such as NITBUT during the short time could not be included. We did not repeat measurement of NITBUT after instillation of eye drop, and hence we do not know the functional effect of LLT changes, but this is not within the aim of the study. The analysis reason why NITBUT was not measured repeatedly at short intervals was because that would affect blinking and increase stress and may affect the LLT. Furthermore, analysis on baseline NITBUT showed that NITBUT does not significantly affect the subsequent change in LLT in the studied eyes. Current measurement of NITBUT required alteration of normal blinks and may affect subsequent LLT measurements. We did not include cases of dry eye with significant corneal staining within lower zone of the cornea because this affects the test–retest variability of LLT in our experiment. We also did not have enough males in the study to evaluate the potential contribution

Table 3. Characteristics of Participants With Lower LLT (<60 nm) or Higher LLT (≥60 nm)

	Cationorm			Artelac		
Characteristic	Baseline LLT <60 nm	Baseline LLT ≥60 nm	*P* Value	Baseline LLT <60 nm	Baseline LLT >60 nm	*P* Value
No. of participants	12	16		13	17	
Age (years)						
Mean ± SD	52.9 ± 18	63.4 ± 10.8	0.064	45.9 ± 20.6	55.2 ± 19.3	0.23
Median (minimum–maximum)	59.5 (21–73)	65.5 (45–83)		40 (22–85)	57 (22–83)	
Female gender, % (N)	83.3 (10)	100 (16)	0.17	62.5 (10)	62.9 (9)	1.0
Symptom score (SPEED)[a]						
Mean ± SD	9.8 ± 8.0	12.9 ± 5.0	0.220	8.8 ± 9.5	5.2 ± 7.0	2.26
Median (minimum–maximum)	8 (0–22)	12 (5–23)		5 (0–27)	2 (0–24)	
Noninvasive break up time (seconds)						
Mean ± SD	11.8 ± 7.4	5.34 ± 3.24	0.004	5.3 ± 2.7	5.5 ± 4.3	0.93
Median (minimum–maximum)	9.5 (3.06–22.18)	4.4 (1.72–15.36)		5.5 (0.0–10.2)	4.5 (4–16.8)	
Tear clearance rate						
Mean ± SD	0.047 ± 0.044	0.7 ± 0.058	0.26	0.009 ± 0.005	0.013 ± 0.007	0.17
Median (minimum–maximum)	0.04 (0.004–0.125)	0.0625 (0.0078–0.625)		0.008 (0.004–0.016)	0.016 (0.004–0.031)	
Schirmer (mm)						
Mean ± SD	8.88 ± 11.6	4.75 ± 3.64	0.19	12.1 ± 6.3	10.3 ± 5.9	0.42
Median (minimum–maximum)	5.5 (1–42.5)	4.5 (0–15)		11.5 (5–25)	8 (5–27)	
Baseline LLT (nm)						
Mean ± SD	44.6 ± 10.2	84 ± 14.74,	<0.001	43.8 ± 10.1	71.4 ± 11.4	<0.001
Median (minimum–maximum)	41.5 (29–59)	82.5 (61–100)		43.5 (27–59)	67.5 (61–100)	

[a]Standard patient evaluation of eye dryness (symptom questionnaire). LLT, lipid layer thickness; SPEED, Standard Procedure for Evaluation of Eye Dryness.

of gender to the LLT profiles. Additionally, we did not compare the LLT of the right treated eye with the LLT of the left untreated eye of the participants because the time points of measuring LLT (0, 1, 5, and 15 minutes) were too close to each other to measure both the LLTs one after the other. The LipiView machine can only measure the tear LLT of one eye at a time, taking ≤30 seconds for acquisition. This procedure would cause difficulty, especially in the 0- and 1-minute readings.

The clinical implication of our results is that we may want to use LLT as a way to select patients who can benefit from the lipid-containing eye drops. Patients who want to have a quicker response may want to select Artelac whereas those who want to instill eye drops less frequently may want to choose Cationorm.

In conclusion, we confirmed that LLT can be altered after lipid containing eye drops, and the most important factor determining this response is the baseline LLT of participants. Different types of lipids may alter LLT in a distinct way.

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