Original Article

Short-term effect of non-preserved cationic oil-in-water ophthalmic emulsion on tear meniscus parameters of healthy individuals in a prospective, controlled pilot study

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ABSTRACT

Background: This study investigated the effect of instilling a single drop of non-preserved cationic oil-in-water ophthalmic emulsion (Cationorm®) on the lower (LTM) and upper tear meniscus (UTM) parameters of normal eyes.

Methods: In this prospective, single-center, non-randomized, controlled pilot study, optical coherence tomography was used to estimate the UTM and LTM height, depth, and cross-sectional area in participants without a history of dry eye disease. In the right eye (study eye), we instilled one drop of Cationorm® in the lower conjunctival sac. Scans of the tear menisci were acquired at baseline, before the instillation, and at 5, 15, and 30 min thereafter. Control scans of the left eye (control eye) were obtained at the same timepoints. The tear meniscus parameters of the study eye were compared with the control eye at each timepoint.

Results: Twenty subjects (11 male and 9 female; mean ± standard deviation of age: 37.8 ± 10.9 years) were included in the study. Compared to the control eye, instillation of a single drop of Cationorm® resulted in significantly higher LTM parameter values and a higher UTM cross-sectional area up to 30 min after instillation (all $P < 0.05$). The UTM height and depth were significantly greater in the study eye than in the control eye up to 5 min ($P < 0.001$ and 0.007, respectively) and 15-min ($P = 0.045$, and 0.002, respectively) after Cationorm® instillation. In the study eye, Cationorm® resulted in a significant increase in LTM parameter values up to 30 min post-instillation (all $P < 0.001$). The UTM height was significantly greater up to 15 min post-instillation than at baseline. The UTM depth and area increased significantly from baseline to 5 min after instillation ($P = 0.043$, and 0.002, respectively).

Conclusions: Cationorm® seems to have a prolonged residence time on the ocular surface of healthy subjects as indicated by LTM parameters and to a lesser extent by UTM parameters.

KEY WORDS

ophthalmic emulsion, cationorm, upper tear meniscus, lower tear meniscus, spectral domain-optical coherence tomography, SD-OCT, residence time

INTRODUCTION

As stated in the definition of the Tear Film and Ocular Surface Society's Dry Eye Workshop II "*Dry eye is a multifactorial disease of the ocular surface, characterized by a loss of homeostasis of the tear film, and accompanied by*

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ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" [1]. In dry eye disease (DED), tear film hyperosmolarity and instability coexist and reinforce each other, creating a vicious cycle of disease and leading to a gradual increase in ocular surface inflammation [1].

Artificial tears are the first treatment measures for DED [2]. There are several different types of artificial tears, each of which has various constituents. Some of these solutions target a specific layer of the tear film, whereas others have been developed to restore more than one layer. Both preserved and non-preserved artificial tears are available. There are further differences among preserved formulations, depending on the *in vivo* behavior of various preservative compounds [3].

Cationorm® (Santen, Evry, France) is a recent addition to the list of therapeutic choices for the treatment of DED. This solution targets all the layers of the tear film by primarily enhancing the lipid layer, which consequently stabilizes the whole tear film [4]. Cationorm® is an innovative artificial tear preparation, as it is a non-preserved, cationic, oil-in-water ophthalmic emulsion, based on the patented novel Novasorb® nanotechnology, which was developed to improve the bioavailability of ocular drugs as compared to the conventional aqueous solutions [5].

The tear menisci hold the biggest part of the tear volume. Tears are spread from the menisci to the ocular surface with each blink. Tear meniscus dimensions measured by means of spectral domain-optical coherence tomography (SD-OCT) have previously been used as a means of indirect estimation of the tear film volume and stability [6, 7]. This pilot study aimed to investigate the residence time of Cationorm® artificial tears on the ocular surface following instillation of a single drop in healthy subjects, by evaluating the lower (LTM) and upper tear meniscus (UTM) parameters.

METHODS

This was a prospective, single-center, non-randomized, controlled pilot study, that was approved by the institutional review board of the University Hospital of Patras and was performed in adherence with the tenets of the Declaration of Helsinki. All the study procedures were first explained to study participants, after which written informed consent was obtained from each participant.

We included subjects who were ≥ 18 years of age and in good general health with no history of previous ocular disease, any ocular surgery, any systemic diseases or medications, and who did not report DED-related symptoms. Before inclusion in the study, all subjects underwent a slit-lamp examination with fluorescein and lissamine green dye staining, as well as a tear film break-up time test, to exclude ocular surface abnormalities and confirm their eligibility for the study. None of the subjects had used contact lenses or reported instillation of any eye drops for at least 15 days prior to their examination. Pregnant or lactating women were excluded from the study.

A single drop of Cationorm® was instilled in the lower conjunctival sac of the right eye (study eye) of each subject. No drops were instilled in the left eye, which served as the control eye. Tear meniscus scans were acquired with OCT, as previously described [8]. More precisely, cross-sectional images were taken with the SD-OCT RTVue-100 (Optovue Inc, Fremont, CA, USA, software version A6 [9,0,27]) with the anterior segment wide-angle lens (CAM-L). Scans were obtained vertically, with the guide at the 6 o'clock position, with the inferior and superior tear menisci centered on the lower and upper cornea and eyelid, respectively. Scans were acquired at baseline, prior to instillation of Cationorm® and at 5, 15, and 30 min after instillation of the drop in the right eye (Figure 1). Control scans of the left eye were taken at the same timepoints.

Examinations of all study participants were conducted in the same room with the same environmental conditions (mean ± standard deviation [SD] of room temperature and relative humidity: 26 ± 3°C and 45 ± 4%, respectively), in mesopic conditions, and at the same time of day, to avoid diurnal fluctuations in tear meniscus parameters [9]. At each timepoint, three scans were obtained and the mean value of the three measurements was used for statistical analysis. Each OCT scan was obtained approximately 2-3 s after a blink. The same examiner imaged both the UTM and LTM of both eyes in all subjects. If there were any artifacts, the scan was repeated until an artifact-free image was obtained. Afterwards, the RTVue-100 image analysis and caliper software was used to determine the tear meniscus height, depth and cross-sectional area.

The primary outcomes were the LTM parameters in the study eye as compared to those of the control eye at 5 min after Cationorm® instillation. The secondary outcomes were the changes of the parameters in the LTM and UTM after Cationorm® instillation. The comparisons of the LTM parameters between the study and control eye at 15 and 30 min and the comparisons of the UTM parameters between the study and control eye up to 30 min after Cationorm® instillation were also secondary outcome measures.

Statistical analysis was performed using the IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, Chicago, IL, USA). The investigator who conducted the statistical analysis was masked to study groups

to reduce a possible source of bias. All the evaluated variables were expressed as mean ± SD. Normality of data distribution was evaluated using the Kolmogorov-Smirnov test.

The paired-sample Student's *t*-test was performed to compare parametric data between the study and control eyes, while the Wilcoxon non-parametric test was used for comparisons of non-parametric values between these eyes. Repeated-measures analysis of variance (ANOVA) test was used to compare parametric values, with Bonferroni post-hoc tests, within groups. Friedman's test was applied to compare non-parametric values, with the Wilcoxon test used for post-hoc comparisons. For all statistical analyses performed, differences assumed statistically significant at $P < 0.05$. Bonferroni correction was used to avoid type I errors. The alpha-level of 0.05 was corrected for multiple comparisons involving the three outcome measures, resulting in an adjusted alpha of 0.017 (0.05/3) [10].

A power analysis was performed using GPower software (version 3.1), based on the results of a previous study [11]. The minimum sample size was calculated as at least 14 participants, with the significance level being set to < 0.05 and statistical power of 0.95.

RESULTS

Twenty subjects (11 male and 9 female) were included in the study. The mean ± SD of age of the participants was 37.8 ± 10.9 years. Tables 1 and 2 show the LTM and UTM parameters in the study and control eyes at baseline and at 5, 15, and 30 min after Cationorm® instillation.

At baseline, there were no statistically significant differences in the tear meniscus parameters between the two eyes (all $P > 0.05$) (Tables 1 and 2). Compared to the control eye, a single drop of Cationorm® resulted in statistically significantly higher LTM parameter values, and a larger UTM area, up to 30 min after instillation ($P < 0.05$ at all timepoints post-instillation) (Tables 1 and 2). The UTM height and depth were significantly greater in the study eye than in the control eye at 5 and 15 min after Cationorm® instillation (both $P < 0.05$ at 5- and at 15 min post-instillation) (Table 2). In the study eye, Cationorm® resulted in a statistically significant ($P < 0.001$) increase in the LTM parameter values, up to 30 min post-instillation as compared to pre-instillation values (Table 1). The UTM height was significantly greater up to 15 min after instillation than at baseline ($P = 0.01$). The UTM depth and area was significantly increased at 5 min after instillation as compared to baseline ($P = 0.043$, and 0.002, respectively) (Table 2).

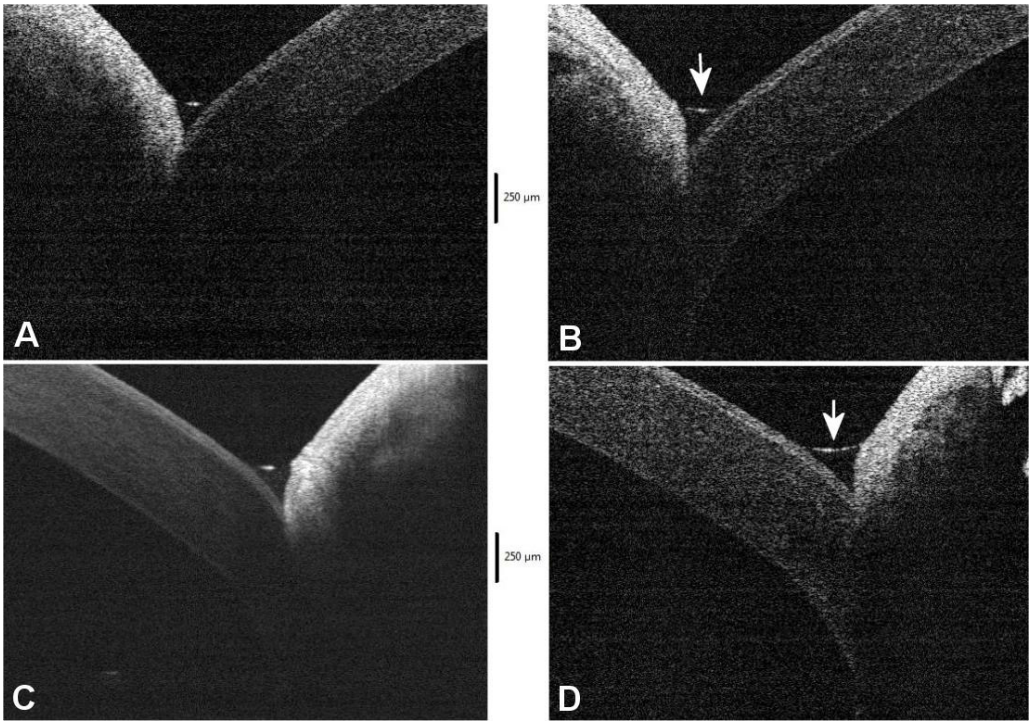

Figure 1. Cross-sectional optical coherence tomography image of lower (A, B) and upper tear menisci (C, D) of the study eye prior (A, C) to and 5 min (B, D) after the instillation of one drop of Cationorm®, respectively. The tear menisci appear hyper-reflective at 5 min after the instillation (arrows).

Table 1. Lower tear meniscus (LTM) parameters in the study eye at baseline and at 5, 15 and 30 min after Cationorm® instillation, as well as in the control eye at the corresponding timepoints

Variable	Baseline	5 min	15 min	30 min	*P-value*
LTM height (µm)					
Study eye, Mean ± SD	246.6 ± 40	381.1 ± 138.2*	328.9 ± 121.4**	275.9 ± 49.1	**< 0.001**†
Control eye, Mean ± SD	257.3 ± 45.5	275.3 ± 59.9	244.6 ± 38.3	243.4 ± 43.2	0.179†
P-value‡	0.341	**0.004**	**0.009**	**0.006**	
LTM depth (µm)					
Study eye, Mean ± SD	137.2 ± 33.0	180 ± 62.1***	179.1 ± 55.4*	166.7 ± 51.5****	**< 0.001**†
Control eye, Mean ± SD	143.6 ± 24.5	144.2 ± 34.6	140.4 ± 30.3	134.6 ± 29.9	0.258†
P-value	0.221§	**0.024**‡	**0.002**‡	**0.002**§	
LTM area (10^{-3} mm^2)					
Study eye, Mean ± SD	17.8 ± 6.6	39.6 ± 28*	32.7 ± 23*****	27.6 ± 13.1***	**< 0.001**†
Control eye, Mean ± SD	18.1 ± 6.2	19.1 ± 5.9	17.4 ± 5.7	16.9 ± 5.9	0.158¶
P-value	0.824§	**0.001**‡	**0.002**‡	**< 0.001**§	

Abbreviations: µm, micrometer; SD, standard deviation; mm^2, square millimeter. Note: Study eye, right eye (instillation of a single drop Cationorm® artificial tears); Control eye, left eye (no drops were instilled); † Between-timepoints comparisons with the Freidman test (**P* < 0.001, ** *P* = 0.004, *** *P* = 0.001, **** *P* = 0.008, ***** *P* = 0.002 compared to baseline; post-hoc Wilcoxon test). ‡ Wilcoxon test and §paired sample t-test for comparisons between the study and control eye at each timepoint. ¶ Between-timepoints comparisons with repeated-measures ANOVA. *P*-values in bold are statistically significant.**

Table 2. Upper tear meniscus (UTM) parameters in the study eye at baseline and at 5, 15 and 30 min after Cationorm® instillation, as well as in the control eye at the corresponding timepoints

Variable	Baseline	5 min	15 min	30 min	*P-value*
UTM height (µm)					
Study eye, Mean ± SD	194 ± 36.7	273.4 ± 63.5*	223.1 ± 37.9**	223.3 ± 54.8	**< 0.001**
Control eye, Mean ± SD	202.3 ± 27.3	206 ± 42.45	196.8 ± 42.6	206.8 ± 41.9	0.751
P-value†	0.269	**< 0.001**	**0.045**	0.158	
UTM depth (µm)					
Study eye, Mean ± SD	137.7 ± 41.4	173.5 ± 41.6***	146.1 ± 31.7	141.7 ± 39.7	**0.004**
Control eye, Mean ± SD	129.4 ± 43.3	134.1 ± 52.5	120.9 ± 37.8	123.8 ± 27.4	0.442
P-value†	0.298	**0.007**	**0.002**	0.072	
UTM area (10^{-3} mm^2)					
Study eye, Mean ± SD	14.7 ± 6	26.3 ± 10.5****	16.9 ± 5.5	18 ± 8.3	**0.001**
Control eye, Mean ± SD	13.9 ± 5.3	14.9 ± 7.5	13.1 ± 5.4	13.9 ± 5.9	0.563
P-value†	0.519	**0.001**	**0.017**	**0.045**	

Abbreviations: µm, micrometer; SD, standard deviation; mm^2, square millimeter. Note: Study eye, right eye (instillation of a single drop Cationorm® artificial tears); Control eye, left eye (no drops were instilled); † Between-timepoints comparisons with repeated-measures ANOVA (* *P* < 0.001, ** *P* = 0.01, * *P* = 0.043, and **** *P* = 0.002, compared to baseline). ‡ Paired samples t-test for comparisons between study and control eyes at each timepoint. *P*-values in bold are statistically significant.**

DISCUSSION

We conducted a prospective, single-center, non-randomized, controlled, pilot clinical study to evaluate the short-term effect of a single drop of Cationorm® on the tear meniscus parameters of normal eyes. We utilized a noninvasive, quantitative method for evaluating tear meniscus parameters (SD-OCT RTVue-100 with an anterior segment wide-angle lens). We found that a single drop of Cationorm® resulted in a significant increase in the tear meniscus parameters of normal eyes up to 30 min after instillation. The beneficial effect of Cationorm® was more prolonged and evident on the LTM parameters.

The LTM and UTM parameters provide an objective, noninvasive method for assessment of DED. Specifically, they correlate significantly with the symptoms of DED, tear break-up time, and Schirmer's test results [8, 12]. DED is a common ocular condition that can deteriorate the quality of life of affected individuals [13]. Two types of DED have been described, according to the cause initiating the pathological process. The first type is dry eye due to insufficient production of the aqueous phase of the tear film, and the second type is dry eye due to increased evaporation of tears. The difficulty of defining DED, along with a lack of consensus on the diagnostic

criteria and the poor standardization of diagnostic tests, are factors that make DED diagnosis and estimation of its prevalence challenging [14].

Choosing treatment for DED is as complex as the pathophysiology of the disease. There are increasingly numerous management options. The choice of the appropriate treatment depends on the initial cause of the disease and the severity of the related signs and symptoms. Some treatment approaches target symptomatic relief, whereas others aim to tackle the underlying pathological process [15]. The administration of tear substitutes remains the primary DED management. There is a great diversity of available products, and their differences are intensely researched. Various other medical and surgical treatment methods are used, some of which are designed to tackle DED due to specific causes, while others are used only in cases of severe disease [16].

Cationorm® is a new preparation of artificial tears. It is a non-preserved, cationic, oil-in-water ophthalmic emulsion that is based on the patented novel Novasorb® nanotechnology [5]. The principle of Novasorb® technology is the delivery of polar and non-polar lipids and surfactants to the ocular surface [17]. This allows restoration of the possibly damaged lipid layer of the tear film, given that the majority of dry eye cases initially involve evaporative or mixed causes. Furthermore, deficiencies of the lipid layer are likely to occur at some point during the progression of DED, due to aqueous deficiency. Novasorb® technology also aims to achieve a prolonged precorneal residence time by exploiting the beneficial electrostatic interaction between the positively charged oil droplets of the cationic nanoemulsion and the negatively charged mucin layer that covers the epithelial cells of the cornea and the conjunctiva [4]. A third important characteristic of Novasorb® technology is that the cationic emulsion demonstrates superior spreading on the ocular surface in comparison with conventional eye drops [5]. This might be of particular importance for Novasorb®-based artificial tears. Lastly, cetalkonium chloride, the polar lipid contained in Novasorb®-based cationic nanoemulsions, has been shown to alter the expression of proinflammatory cytokines *in vitro,* indicating a possible *in vivo* anti-inflammatory effect on the ocular surface [17].

A clinical study evaluated the effect of Retaine, the trade name of Cationorm® in the United States, on patients with DED and found that 1-2 drops of the emulsion, instilled twice daily for 2 weeks, resulted in a significant reduction in the mean tear break-up area, in corneal fluorescein staining, and in all dry eye symptoms, with a significant improvement in the quality of life [4].

Cationorm® has also been found to be safe and generally well-tolerated, as it was demonstrated to have no negative impact on best corrected visual acuity or intraocular pressure. Treatment-related adverse effects have been described, of which the majority were mild and of ocular nature, although they led to discontinuation of the therapy in some cases [18, 19]. In an experimental study, a 3-day overdose treatment with Cationorm® in abraded rabbit corneas was shown to be well tolerated [20].

Our study had certain strengths and limitations. The prospective design of the study and the head-to-head comparison with control eyes is a strength. Furthermore, the investigator that conducted the statistical analysis was masked, reducing a possible source of bias. However, the study was limited in that the tear meniscus parameters were measured manually, using the computer caliper measurement tool, and we cannot exclude possible bias during these measurements. Furthermore, we did not conduct complementary diagnostic tests to evaluate the effect of Cationorm® on any other ocular surface parameters, such as osmolality, Schirmer's test, or tear break-up time evaluation. Finally, we propose enrollment of a larger group of participants, using random allocation, in future studies to provide more powerful analysis with more solid conclusions. Likewise, further studies focusing on the impact of Cationorm® on tear meniscus variables and on the ocular surface of eyes in patients with DED are required.

CONCLUSIONS

In our study, the tear meniscus parameters were used as a tool for the quantification of tear volume changes after Cationorm® installation. According to our results, instilling a single drop of Cationorm® exerted a positive impact on tear meniscus variables of normal eyes for up to 30 min after administration. The results of this study could indicate that Cationorm® may also contribute to the restoration of the tear film and ocular surface homeostasis in DED.

ETHICS DECLARATIONS

Ethical approval: This study was approved by the institutional review board of the University Hospital of Patras and was performed in adherence with the tenets of the Declaration of Helsinki. All the study procedures were explained to and written informed consent was obtained from all the participants.

Conflict of interests: None.

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