Scientific Research Publishing

Open Journal of Ophthalmology, 2017, 7, 103-116
http://www.scirp.org/journal/ojoph
ISSN Online: 2165-7416
ISSN Print: 2165-7408

Comparison of the Clinical Efficacy of Four Different Liposomal Sprays for the Treatment of Dry Eye

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How to cite this paper: Hueck, A. and Wehrmann, R. (2017) Comparison of the Clinical Efficacy of Four Different Liposomal Sprays for the Treatment of Dry Eye. *Open Journal of Ophthalmology*, **7**, 103-116.
https://doi.org/10.4236/ojoph.2017.72015

Received: March 14, 2017
Accepted: May 15, 2017
Published: May 18, 2017

Abstract

Purpose: To compare the clinical efficacy of four different liposomal sprays for dry eye treatment. *Methods*: Prospective randomized consecutive intraindividual comparison enrolling 166 patients (age, 18 - 93 years). Patients were randomly assigned to one of 4 groups, receiving one spray in their right eye and another one in their left eye: Ocuvers Hyaluron (OH) (87 eyes) and Ocuvers Lipostamin (OL) (80 eyes) (Innomedis AG), and Tears Again (TA) (80 eyes) and Tears Again Sensitive (TAS) (85 eyes) (Optima Pharmaceutical). Symptomatology was evaluated with the OSDI (Ocular Surface Disease Index) questionnaire. Subjective comfort, tear break up time (TBUT), redness, tear meniscus, application comfort and smell were evaluated during a 30-minute follow-up. *Results*: Smell for TA and TAS was significantly fattier compared to OH and OL ($p < 0.001$). After application of TA, patients reported significantly more burning sensations compared to the rest of the sprays ($p < 0.001$). At 10 minutes, subjective comfort ($p \leq 0.027$) and TBUT ($p \leq 0.004$) were significantly better with OH and OL compared to TA and TAS. At 30 minutes, the same trends were observed, with also significantly less ocular redness with OL compared to the rest ($p = 0.043$). Significant correlations were found between baseline OSDI and changes in ocular redness at 10 ($r = -0.287$, $p = 0.011$) and 30 minutes ($r = -0.237$, $p = 0.037$) after the application of OL. *Conclusions*: The four evaluated liposome sprays may be useful for dry eye treatment, with higher subjective comfort and less dry eye signs using the Ocuvers sprays. The use of OL may be a better treatment option for severe dry eye.

Keywords

Liposomal Spray, Dry Eye, Ocuvers, Tears Again, Tear Break Up Time, Redness, Smell

1. Introduction

Dry eye syndrome (DES) is an ocular condition characterized, according to the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007), by the presence of symptoms, ocular surface lesions, tear instability and tear hyperosmolarity [1]. It has a variable prevalence that ranges from 0.39% to 30% in patients older than 50 years [2] [3] [4] [5]. Age and gender have been defined as two of the most relevant risk factors for DES [4]. Several options of treatment have been developed and tested for this ocular condition, such as artificial tears, lipid-containing lubricants, inserts, anti-inflammatory or immunosuppressant drops, antibiotics, dietary omega-3 essential fatty acids, autologous serum, intense-pulsed-light (IPL), punctual plugs, moisture-retaining eyeglasses, hydrophilic bandage contact lenses or secretagogues [6]. Liposomal sprays are another option for treatment of DES [7]. These sprays contain phospholipid liposomes to overcome the disturbance of the lipid phase which is present in around 80% of patients with DES [7]. Several studies have confirmed the efficacy of this type of sprays, with significant improvements in eyelid edge parallel conjunctival folds (LIPCOF), tear break-up time (TBUT), Schirmer I test outcome, and symptoms [7]-[12]. Different liposomal spray formulations have been developed and commercially released. However, only one study has compared the clinical effect of some of them [10]. Specifically, Pult *et al.* [10] demonstrated that OptrexActiMist (AM, Optima-Pharma, Germany) (same formulation as Tears Again) was significantly better in terms of ocular comfort and tear film stability improvement than TearMist and DryEyesMist sprays. The aim of the current study was to compare the clinical effect of four different liposomal sprays for DES treatment in terms of subjective comfort, ocular redness, and TBUT as well as in terms of application comfort and smell in a sample of patients with different levels of dry eye symptomatology.

2. Patients and Methods

2.1. Patients

Patients with a diagnosis of dry eye were randomized to one of the following four groups: Ocuvers Hyaluron (OH) (Innomedis AG, Germany) vs. Tears Again (TA) (Optima Pharmaceutical GmbH, Germany), OH vs. Tears Again Sensitive (TAS) (Optima Pharmaceutical GmbH, Germany), Ocuvers Lipostamin (OL) (Innomedis AG, Germany) vs. TA and OL vs. TAS. Patients were randomly assigned to the spray they receive in the right eye which was defined to be the first eye to be treated. The various labels of the four sprays are listed in **Table 1**.

Symptomatology was evaluated with the OSDI (Ocular Surface Disease Index) questionnaire which is a valid and reliable instrument for measuring the severity of dry eye disease, and possesses the necessary psychometric properties to be used in clinical research [13]. It consists of 12 questions about common symptoms in the dry eye disease and a scoring system for obtaining an overall index for being used as an indicator of the severity of the disease [13]. Included in the

Table 1. Different labels of the four tear spray products used in the study.

Original Product	Available Other Labels
Ocuvers spay hyaluron	Okuzell Lipidspray
Ocuvers spray lipostamin	-
Tears Again	LipoNit Polyeye Comfort Optrex Actispray 2 in 1 for dry eyes
Tears Again Sensitive	LipoNit Sensitive Optrex Actisrpay 2 in 1 for tired eyes Omnimed Lidspray Omnitears Lidspray

study were subjects with different level of dry eye symptoms (OSDI grades 1, 2, 3 or 4) and a signed informed consent. Exclusion criteria included the use of an artificial tear or other eye drop on the day of examination, any degenerative ocular pathology and ocular inflammation. The study received Ethics Committee approval and was carried out in accordance with the tenets of the Declaration of Helsinki.

2.2. Examination Protocol

An OSDI assessment was performed in all patients. The following subjective parameters were evaluated: subjective comfort, using a scale from 0 (very bad) to 100 (excellent), application comfort, using a scale from 0 (not burning at all) to 100 (strongly burning), and smell (scale from 0—no smell to 5—extremely fatty smell). The following objective parameters were measured with keratography (Oculus Keratograph 5M, Oculus GmbH, Wetzlar, Germany): non-invasive tear break up time (TBUT), including the first measure of three consecutive measurements and the average, general conjunctival redness using a scale from 1 (slight) to 3 (strong) as well as the mean value of bulbar and nasal redness, and tear meniscus (evaluated as mild, normal, moderate and severe). The variables were assessed before (subjective comfort, TBUT, tear meniscus, redness) and/or during (subjective comfort, application comfort, smell) the application of the spray as well as 10 and 30 minutes after its application.

2.3. Liposome Sprays

OH spray is composed of a phospholipid complex, sodium-hyaluronate, and an isotonic borate-buffered solution (pH: 7.2). OL spray has the same composition except sodium-hyaluronate which is replaced by several natural plant extracts: capparis spinose, helychrysum italicum, euphrasia officinalis, and glyccyrrhiza glabra. TA spray is composed of the following elements: 2-phenoxyethanol, phospholipid (from soy bean), retinol sodium chloride, alpha-tocopherol, and ethanol, whereas TAS has a modified composition including phospholipid (from soy bean), sodium chloride and ethanol, but also retinol palmitate, dexpanthenol, and DL-alpha-tocopherol.

2.4. Statistical Analysis

Sample size was calculated with G*Power 3.1.9.2. For the primary endpoint, a TBUT difference of 4 sec between pre-application and post-application of the spray was chosen. The standard deviation was expected to be 8 sec at both application times. For an alpha of 0.05 and a power of 0.95 a sample size of 47 eyes per comparison has been calculated.

Statistical analyses were performed with a commercially available software package (SPSS for Mac, Version 20.0; IBM Corporation, Armonk, NY, USA). Normality of data samples was evaluated by means of the Kolmogorov-Smirnov test. When parametric analysis was possible, the 1-way analysis of variance (ANOVA) with Bonferroni post-hoc analysis was used for comparisons between spray groups, whereas the Kruskal-Wallis test was applied to assess the significance of such differences when parametric analysis was not possible. The Mann-Whitney test with the Bonferroni's adjustment was used for the post-hoc analysis of the Kruskal-Wallis test outcome. For all statistical tests, a p-value of less than 0.05 was considered as statistically significant.

3. Results

A total of 332 eyes from 166 patients with an age range from 18 to 93 years was included in the study (mean age: 64.3 years). The sample included 87 eyes (26.2%) using OH, 80 eyes (24.1%) using TA, 85 eyes (25.6%) using TAS, and 80 eyes (24.1%) using OL. Table 2 shows a comparative analysis of the clinical data obtained before/during the application of the spray in each group. As shown, statistically significant differences were found between groups in spray application comfort and smell ($p < 0.001$) which were both measured during application. Specifically, the smell of TA and TAS was significantly fattier than the smell of OH and OL ($p < 0.001$). Whereas patients rated the smell of OH and OL between "no smell" and "hardly perceivable smell" the rating of TA and TAS was in average between "moderate" and "very intense fatty smell". Likewise, comfort immediately after application was significantly better (less burning) using OH compared to TA ($p < 0.01$) and TAS ($p = 0.026$), and using OL compared to TA ($p < 0.001$).

Ten minutes after the application of the spray, there were statistically significant differences between spray groups in subjective comfort, TBUT, spray application comfort and smell ($p < 0.001$) (Table 3 and Figure 1). Specifically, subjective comfort was significantly better and TBUT significantly higher with OH and OL compared to TA and TAS ($p \leq 0.027$). Likewise, smell was reported to be significantly less fatty for OH and OL compared to TA and TAS ($p < 0.001$) and application comfort was significantly better with OH and OL compared to TA ($p < 0.001$) (Table 3 and Figure 1). Thirty minutes after the application of the spray, statistically significant differences were found between spray groups in all clinical variables evaluated ($p \leq 0.047$) (Table 4 and Figure 1), with similar results than those found at 10 minutes after application. No significant differences were found in the distribution of tear meniscus outcomes before the

Table 2. Clinical data obtained before/during application of the spray. Abbreviations: TBUT, tear break up time; OH, Ocuvers Hyaluron; TA, Tears Again; TAS, Tears Again Sensitive; OL, Ocuvers Lipostamin.

Mean (SD) Median (Range)	OH	OL	TA	TAS	p-value
Age (years)	65.7 (16.9) 69.0 (19 to 93)	63.1 (17.5) 68.0 (18 to 93)	64.5 (18.1) 69.5 (19 to 93)	64.0 (16.3) 69.0 (18 to 90)	0.754
OSDI	16.7 (16.2) 13.0 (0 to 63)	14.7 (16.7) 8.0 (0 to 73)	17.5 (17.8) 12.5 (0 to 73)	14.0 (15.1) 8.0 (0 to 69)	0.412
Subjective comfort	63.4 (21.8) 60.0 (20 to 100)	69.8 (24.9) 70.0 (0 to 100)	66.2 (23.5) 70.0 (0 to 100)	68.0 (23.5) 70.0 (20 to 100)	0.200
Ocular redness	0.4 (0.6) 0.0 (0 to 2)	0.3 (0.5) 0.0 (0 to 1)	0.4 (0.5) 0.0 (0 to 2)	0.3 (0.5) 0.0 (0 to 1)	0.860
Bulbar and nasal conjunctival redness	1.3 (0.6) 1.2 (0.0 to 2.5)	1.2 (0.5) 1.2 (0.2 to 2.2)	1.2 (0.6) 1.1 (0.0 to 2.5)	1.2 (0.5) 1.2 (0.0 to 2.4)	0.781
TBUT 1st measurement (seconds)	7.6 (5.8) 5.5 (1.2 to 25.0)	6.4 (5.3) 4.6 (0.8 to 25.0)	7.3 (5.7) 5.0 (1.2 to 24.0)	6.7 (5.7) 4.6 (1.2 to 25.0)	0.413
TBUT average (seconds)	10.4 (5.7) 9.6 (2.2 to 25.0)	8.7 (5.3) 7.3 (1.9 to 25.0)	10.4 (6.2) 8.4 (2.3 to 24.0)	10.0 (5.9) 8.3 (1.3 to 25.0)	0.156
Smell	0.3 (0.6) 0.0 (0 to 3)	0.5 (0.8) 0.0 (0 to 3)	3.3 (1.7) 4.0 (0 to 5)	2.9 (1.5) 3.0 (0 to 5)	<0.001 OH-TA < 0.001 OH-TAS < 0.001 OL-TA < 0.001 OL-TAS < 0.001
Application comfort	0.1 (1.1) 0.0 (0 to 10)	0.5 (2.7) 0.0 (0 to 20)	13.6 (20.7) 0.0 (0 to 80)	2.0 (7.4) 0.0 (0 to 40)	<0.001 OH-TA < 0.001 OH-TAS 0.026 OL-TA < 0.001 OL-TAS 0.210

application of the liposomal sprays (p = 0.065) and at 10 minutes after the application of the spray (p = 0.138) (Figure 2). However, a significantly higher proportion of eyes with high tear meniscus was observed at 30 minutes after the application of the spray in the OH and OL groups (p = 0.037) (Figure 2).

When changes in ocular comfort at 10 and 30 minutes after spray application were compared in the four spray groups, statistically significant differences were found between groups in the change in ocular comfort, conjunctival redness, and TBUT (p < 0.001). All these parameters improved significantly more with OH and OL compared to TA or TAS (p ≤ 0.031), except for one comparison (difference in change of ocular redness (p = 0.095) and first measurement of TBUT (p = 0.137) between OH and TAS at 10 minutes) (Table 5).

Finally, Table 6 summarizes the correlation between the changes in subjective comfort, redness and TBUT (10 and 30 minutes after application) and the baseline OSDI value. Statistically significant positive correlations between baseline OSDI

Table 3. Clinical data obtained 10 minutes after application of the spray. Abbreviations: TBUT, tear break up time; OH, Ocuvers Hyaluron; TA, Tears Again; TAS, Tears Again Sensitive; OL, Ocuvers Lipostamin.

Mean (SD) Median (Range)	OH	OL	TA	TAS	p-value
Subjective comfort	80.7 (17.2) 80.0 (20 to 100)	86.0 (16.0) 90.0 (20 to 100)	59.4 (22.9) 60.0 (5 to 100)	73.5 (21.6) 70.0 (20 to 100)	<0.001 OH-TA < 0.001 OH-TAS 0.027 OL-TA < 0.001 OL-TAS < 0.001
Ocular redness	0.4 (0.5) 0.0 (0 to 1)	0.3 (0.5) 0.0 (0 to 1)	0.4 (0.5) 0.0 (0 to 2)	0.3 (0.5) 0.0 (0 to 1)	0.354
Bulbar and nasal conjunctival redness	1.2 (0.5) 1.1 (0.0 to 2.2)	1.2 (0.5) 1.1 (0.2 to 2.2)	1.3 (0.6) 1.3 (0.0 to 2.5)	1.3 (0.5) 1.2 (0.3 to 2.3)	0.267
TBUT 1st measurement (seconds)	9.5 (6.6) 8.2 (1.7 to 25.0)	8.9 (5.5) 8.4 (1.2 to 24.0)	6.3 (5.2) 4.5 (0.8 to 24.0)	7.1 (5.8) 4.8 (1.2 to 25.0)	<0.001 OH-TA < 0.001 OH-TAS 0.004 OL-TA < 0.001 OL-TAS 0.002
TBUT average (seconds)	13.3 (5.7) 12.2 (2.5 to 25.0)	12.3 (5.2) 11.2 (2.5 to 24.0)	9.4 (5.5) 8.6 (2.0 to 24.0)	10.2 (5.9) 10.9 (2.4 to 25.0)	<0.001 OH-TA < 0.001 OH-TAS < 0.001 OL-TA < 0.001 OL-TAS 0.002
Smell	0.1 (0.4) 0.0 (0 to 2)	0.1 (0.5) 0.0 (0 to 2)	2.6 (1.6) 3.0 (0 to 5)	2.0 (1.5) 2.0 (0 to 5)	<0.001 OH-TA < 0.001 OH-TAS < 0.001 OL-TA < 0.001 OL-TAS < 0.001
Application comfort	0.8 (6.5) 0.0 (0 to 60)	0.6 (5.6) 0.0 (0 to 50)	6.9 (15.4) 0.0 (0 to 60)	0.8 (3.5) 0.0 (0 to 20)	<0.001 OH-TA < 0.001 OH-TAS 0.241 OL-TA < 0.001 OL-TAS 0.119

and ocular comfort changes after the application of the spray were found in all groups, although correlations were poor ($0.227 \leq r \leq -0.356$, $p \leq 0.037$). Likewise, statistically significant negative correlations were found between baseline OSDI and the changes in ocular redness at 10 minutes ($r = -0.287$, $p = 0.011$) and 30 minutes ($r = -0.237$, $p = 0.037$) after the application of the OL spray (Table 6).

4. Discussion

In the current study, an improvement in subjective comfort, meniscus evaluation and TBUT as well as some level of reduction in bulbar and nasal conjunctival redness were observed after the use of the four liposomal sprays evaluated.

Table 4. Clinical data obtained 30 minutes after application of the spray. Abbreviations: TBUT, tear break up time; OH, Ocuvers Hyaluron; TA, Tears Again; TAS, Tears Again Sensitive; OL, Ocuvers Lipostamin.

Mean (SD) Median (Range)	OH	OL	TA	TAS	p-value
Subjective comfort	82.2 (16.9) 80.0 (20 to 100)	86.9 (16.3) 90.0 (20 to 100)	62.0 (21.7) 60 (20 to 100)	73.4 (22.4) 70.0 (20 to 100)	<0.001 OH-TA < 0.001 OH-TAS 0.010 OL-TA < 0.001 OL-TAS < 0.001
Ocular redness	0.4 (0.5) 0.0 (0 to 1)	0.2 (0.4) 0.0 (0 to 1)	0.4 (0.5) 0.0 (0 to 2)	0.4 (0.5) 0.0 (0 to 1)	0.043 OH-TA 0.214 OH-TAS 0.784 OL-TA 0.005 OL-TAS 0.052
Bulbar and nasal conjunctival redness	1.1 (0.5) 1.1 (0.0 to 2.1)	1.1 (0.5) 1.1 (0.2 to 2.1)	1.3 (0.6) 1.2 (0.3 to 2.5)	1.2 (0.5) 1.2 (0.3 to 2.2)	0.047 OH-TA 0.079 OH-TAS 0.241 OL-TA 0.012 OL-TAS 0.045
TBUT 1st measurement (seconds)	12.1 (6.9) 9.5 (2.2 to 25.0)	11.4 (6.9) 9.4 (2.1 to 24.0)	6.5 (5.8) 4.4 (2.0 to 25.0)	7.2 (5.7) 5.4 (1.2 to 25.0)	<0.001 OH-TA < 0.001 OH-TAS < 0.001 OL-TA < 0.001 OL-TAS < 0.001
TBUT average (seconds)	15.0 (5.7) 14.1 (2.7 to 25.0)	14.3 (5.7) 13.1 (3.5 to 24.0)	9.1 (5.5) 8.2 (2.0 to 25.0)	9.6 (5.5) 8.8 (2.0 to 25.0)	<0.001 OH-TA < 0.001 OH-TAS < 0.001 OL-TA < 0.001 OL-TAS < 0.001
Smell	0.0 (0.2) 0.0 (0 to 1)	0.1 (0.3) 0.0 (0 to 2)	1.8 (1.6) 1.5 (0 to 5)	1.3 (1.4) 1.0 (0 to 5)	<0.001 OH-TA < 0.001 OH-TAS < 0.001 OL-TA < 0.001 OL-TAS < 0.001
Application comfort	0.0 (0.0) 0.0 (0 to 0)	0.6 (5.6) 0.0 (0 to 50)	6.3 (14.7) 0.0 (0 to 60)	0.6 (3.2) 0.0 (0 to 20)	<0.001 OH-TA < 0.001 OH-TAS 0.078 OL-TA < 0.001 OL-TAS 0.352

This is consistent with the results of previous studies evaluating the outcomes obtained with different types of liposomal sprays for dry eye [10] [11]. Pult *et al.* [10] demonstrated in a comparative study that the use of TA improved comfort by a mean factor of 1.5 in a sample of 80 subjects and increased significantly the TBUT. In contrast, in another study McGinnigle *et al.* [9] failed to find significant differences in subjective comfort using TA. In our sample, TA and TAS provided a significantly lower increase in subjective comfort compared to OH and OL. One of the main factors contributing to this may be differences in pH among the different formulations evaluated, with the best outcome in terms of

Table 5. Changes obtained in the analyzed sample at 10 and 30 minutes after the application of each spray in subjective comfort, redness and break-up time. Abbreviations: TBUT, tear break up time; OH, Ocuvers Hyaluron; TA, Tears Again; TAS, Tears Again Sensitive; OL, Ocuvers Lipostamin.

Mean (SD) Median (Range)	OH	OL	TA	TAS	p-value
10 *Minutes after the Application of the Spray*					
Subjective comfort	17.2 (19.2) 20.0 (−40 to 80)	16.2 (18.8) 20.0 (−30 to 80)	−6.8 (22.7) 0.0 (−85 to 50)	5.5 (18.0) 0.0 (−50 to 40)	<0.001 OH-TA < 0.001 OH-TAS < 0.001 OL-TA < 0.001 OL-TAS < 0.001
Ocular redness	−0.04 (0.27) 0.00 (−1 to 1)	−0.04 (0.19) 0.00 (−1 to 0)	0.08 (0.26) 0.00 (0 to 1)	0.02 (0.15) 0.00 (0 to 1)	0.005 OH-TA 0.011 OH-TAS 0.095 OL-TA 0.003 OL-TAS 0.025
Bulbar and nasal conjunctival redness	−0.08 (0.19) −0.05 (−0.60 to 0.50)	−0.07 (0.29) −0.10 (−0.90 to 1.99)	0.12 (0.21) 0.00 (−0.50 to 0.70)	0.02 (0.16) 0.00 (−0.40 to 0.90)	<0.001 OH-TA < 0.001 OH-TAS < 0.001 OL-TA < 0.001 OL-TAS < 0.001
TBUT 1st measurement (seconds)	1.9 (6.7) 1.3 (−19.6 to 21.3)	2.7 (5.9) 2.7 (−22.1 to 23.2)	−1.0 (6.1) −0.1 (−21.4 to 19.8)	0.5 (6.5) 0.6 (−20.4 to 19.8)	<0.001 OH-TA 0.002 OH-TAS 0.137 OL-TA < 0.001 OL-TAS 0.008
TBUT average (seconds)	2.8 (5.8) 3.1 (−16.0 to 17.6)	3.8 (5.5) 4.2 (−14.4 to 19.3)	−1.0 (6.8) −1.0 (−21.4 to 18.6)	0.2 (6.8) 0.1 (−17.3 to 17.7)	<0.001 OH-TA < 0.001 OH-TAS 0.005 OL-TA < 0.001 OL-TAS < 0.001
30 *Minutes after the Application of the Spray*					
Subjective comfort	18.7 (19.6) 20.0 (−40 to 80)	17.1 (19.2) 20.0 (−30 to 80)	−4.2 (21.4) 0.0 (−50 to 70)	5.4 (17.7) 0.0 (−50 to 40)	<0.001 OH-TA < 0.001 OH-TAS < 0.001 OL-TA < 0.001 OL-TAS < 0.001
Ocular redness	−0.06 (0.34) 0.00 (−1 to 1)	−0.09 (0.29) 0.00 (−1 to 0)	0.11 (0.35) 0.00 (−1 to 1)	0.04 (0.19) 0.00 (0 to 1)	<0.001 OH-TA 0.002 OH-TAS 0.031 OL-TA < 0.001 OL-TAS 0.001
Bulbar and nasal conjunctival redness	−0.14 (0.22) −0.10 (−0.60 to 0.80)	−0.14 (0.25) −0.10 (−0.60 to 1.29)	0.10 (0.31) 0.00 (−0.90 to 1.10)	0.00 (0.18) 0.00 (−0.50 to 0.90)	<0.001 OH-TA < 0.001 OH-TAS < 0.001 OL-TA < 0.001 OL-TAS < 0.001

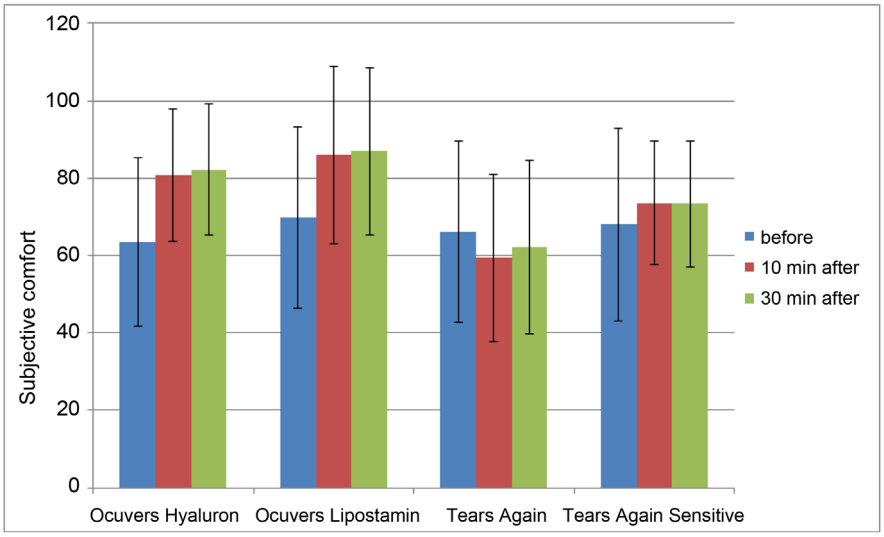
Continued

TBUT 1st measurement (seconds)	4.4 (7.1) 4.2 (−20.4 to 20.0)	5.0 (6.4) 3.6 (−4.1 to 20.9)	−0.5 (6.0) 0.1 (−18.0 to 20.3)	0.6 (5.4) 0.4 (−15.5 to 18.2)	<0.001 OH-TA < 0.001 OH-TAS < 0.001 OL-TA < 0.001 OL-TAS < 0.001
TBUT average (seconds)	4.6 (6.0) 4.4 (−16.9 to 20.0)	5.7 (6.2) 5.3 (−10.9 to 19.8)	−1.1 (5.9) −0.4 (−16.1 to 18.6)	−0.1 (5.7) 0.0 (−11.9 to 17.7)	<0.001 OH-TA < 0.001 OH-TAS < 0.001 OL-TA < 0.001 OL-TAS < 0.001

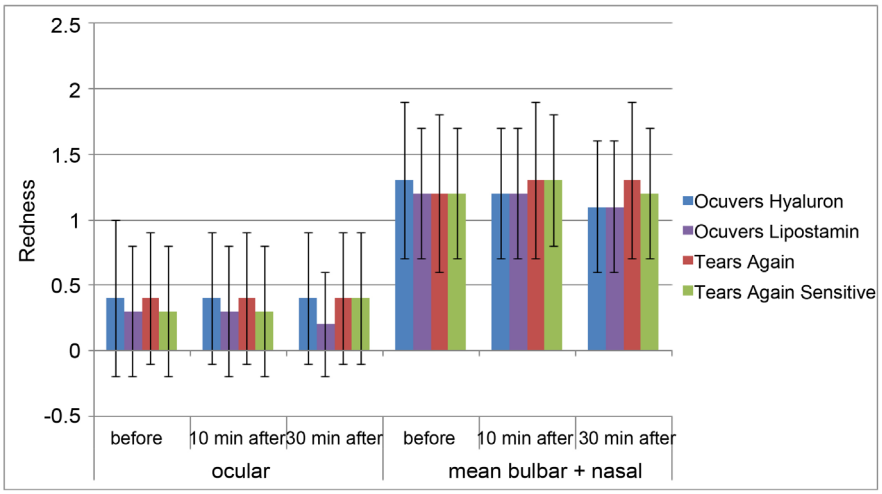
Table 6. Correlations between changes in the parameters evaluated and the baseline OSDI score. Abbreviations: TBUT, tear break up time; OH, Ocuvers Hyaluron; TA, Tears Again; TAS, Tears Again Sensitive; OL, Ocuvers Lipostamin.

Coefficient of correlation p-value	OH	OL	TA	TAS
Change subjective comfort				
10 minutes	0.328	0.278	0.236	0.227
	0.002	0.013	0.035	0.037
30 minutes	0.356	0.251	0.285	0.172
	0.001	0.025	0.010	0.114
Change ocular redness				
10 minutes	−0.154	−0.287	0.047	0.103
	0.158	0.011	0.676	0.349
30 minutes	−0.085	−0.237	−0.011	−0.009
	0.441	0.037	0.921	0.933
Change bulbar and nasal conjunctival redness				
10 minutes	−0.163	−0.119	0.134	−0.132
	0.133	0.299	0.236	0.233
30 minutes	−0.332	0.002	0.096	−0.086
	0.002	0.983	0.402	0.436
Change TBUT 1st measurement (seconds)				
10 minutes	0.133	0.115	0.038	0.096
	0.218	0.311	0.741	0.387
30 minutes	0.060	−0.131	0.047	−0.124
	0.588	0.271	0.690	0.285
Change TBUT average (seconds)				
10 minutes	0.073	0.165	0.038	0.193
	0.503	0.145	0.741	0.078
30 minutes	0.136	0.044	−0.006	−0.045
	0.216	0.716	0.957	0.698

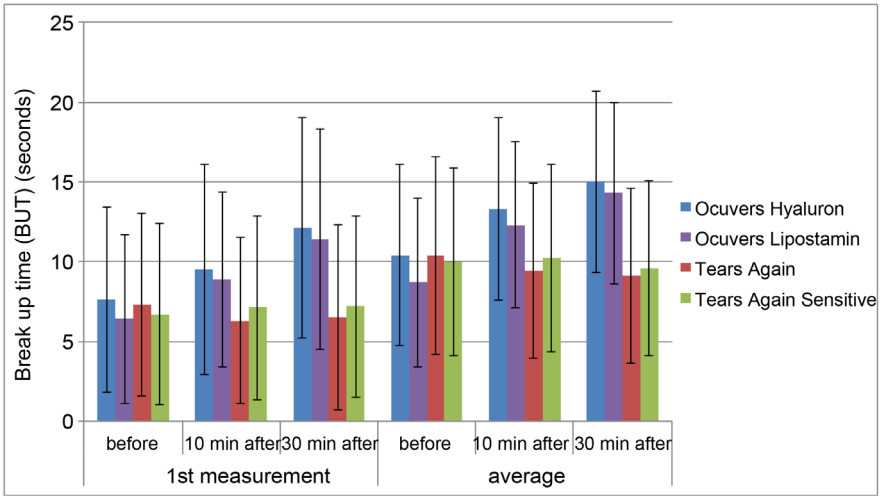
ocular comfort for those with pH closest to the physiological pH of tears [14]. Likewise, differences in viscosity or changes induced in tear viscosity due to the application of the spray may have also contributed to differences in ocular comfort between groups [15]. More studies about the composition and behaviour of liposomal sprays in healthy and dry eye subjects should be conducted in order to better understand the mechanism of action of liposomal sprays. The significantly higher improvement in ocular comfort with OH and OL compared to TA and



(a)



(b)



(c)

Figure 1. Distribution of subjective comfort (a) redness (b) and non-invasive tear break-up time (c) outcomes before, 10 minutes after and 30 minutes after the application of each liposome spray.

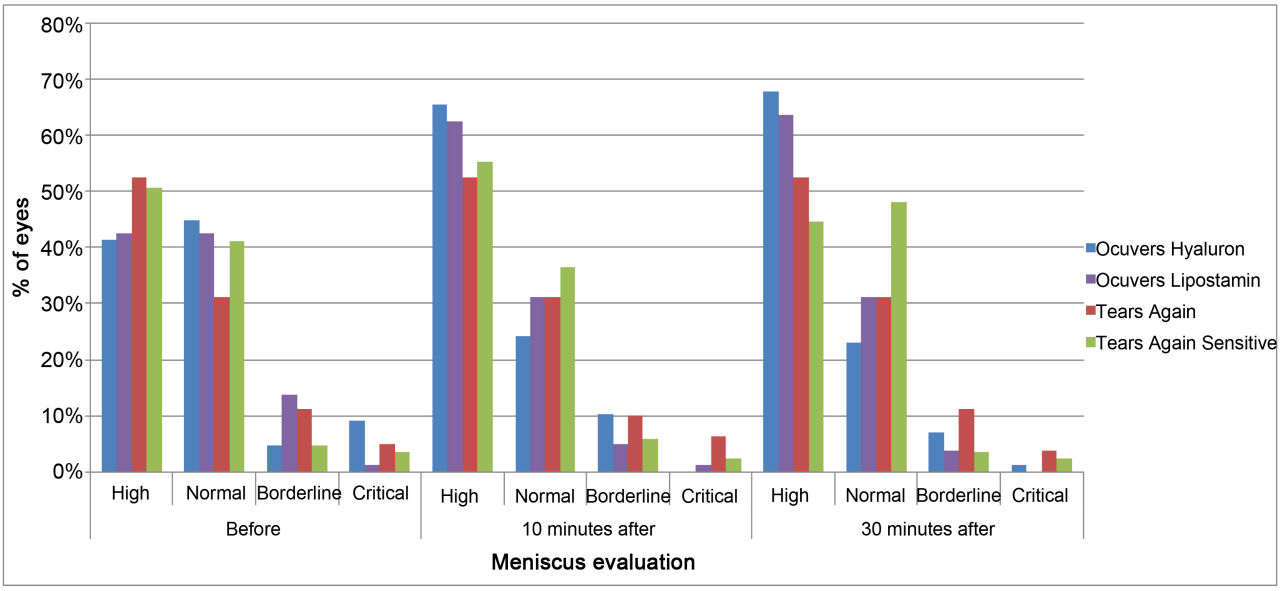


Figure 2. Distribution of the meniscus evaluation outcomes before, 10 minutes after and 30 minutes after the application of each liposome spray.

TAS found in our sample was also consistent with the more significant improvement observed in conjunctival redness, TBUT and tear meniscus. Therefore, OH and OL induced a more significant stabilization of the tear film and consequently a more stable ocular surface.

As OSDI has been demonstrated to be a valid and reliable instrument for measuring the severity of dry eye [13] the correlation between this parameter and changes occurring in different clinical parameters has been investigated to confirm, if the improvement using the evaluated liposomal sprays was better in those eyes with severe dry eye symptomatology. This correlation analysis has shown that OSDI was positively correlated only with changes in ocular comfort, except for the change in comfort at 30 minutes after the application of TAS. This confirms that the evaluated sprays induced a more significant effect on ocular comfort in those eyes with more symptoms. Although all correlations were poor, the strongest correlations were found with OH and OL. Furthermore, a significant negative correlation was found between the change in ocular redness and OSDI using OL. This means that more reduction of conjunctival redness was achieved in those eyes with higher OSDI or more symptomatology of dry eye. Therefore, OL seems to be the best option of the four sprays for reducing conjunctival redness in severe dry eye. The better performance in terms of ocular redness of this specific spray compared to the rest may be related to its different composition. Göbbels and Gross [16] demonstrated in a comparative study that dry eye treatment with eye drops containing dexpanthenol, a component which is present in TAS, led to a favorable and -compared to dexpanthenol-free eye drops-superior improvement of disturbances of corneal epithelium permeability. Likewise, the inclusion of plant extracts in OL may have contributed to the clinical effect observed for this spray. There are several studies confirming the

benefit of treating dry eyes with specific plants extracts, such as improving clinical signs, decreasing inflammation, and ameliorating oxidative stress markers [17] [18] [19] [20] [21]. Possibly, the plant extracts in OL might explain the more effective reduction in conjunctival redness in eyes with severe dry eye in which a significant inflammatory process is present. This should be confirmed in future experimental research, examining the exact impact of these extracts on the ocular surface and how they affect the potential inflammatory process associated to dry eye symptoms.

Besides the evaluation of clinical outcomes, other aspects related to the four sprays have been analysed, such as comfort during application itself and smell. Significant differences between sprays have been detected in these variables, with less initial burning sensation after the application of OH or OL and the worst response with TA. This is consistent with previous studies evaluating the clinical effect of TA and reporting an initial burning sensation after the application of this spray [7]. The initial sensation with OH and OL was good, with minimal level of burning. Smell was significantly fattier with TA and TAS compared to OH and OL. None of the OH and OL patients reported a strong or very strong fatty smell, in contrast to 36.5% and 57.5% of the TA and TAS patients, respectively. This seems to be related to the composition of these liposomal sprays.

5. Conclusion

The four liposomal sprays evaluated are useful for the treatment of dry eye symptoms, with higher improvement in subjective comfort, ocular redness, TBUT, and tear meniscus using OH or OL. The most prominent differences between the Ocuvers and Tears Again sprays were found for TBUT and smell with highly significant better TBUT and less fatty smell of the Ocuvers products. The use of OL seems to be more appropriate in cases of severe dry eye symptomatology, allowing a more significant reduction of ocular redness, possibly due to a more effective reduction of the associated inflammatory process. Likewise, the initial burning sensation after the application of the spray is significantly higher with the use of TA and therefore might be not recommendable in cases with severe symptoms and disturbances. As patient compliance to treatments is strongly related to subjective sensation and tolerability, the better subjective comfort, application comfort and smell of the OH and OL sprays should lead to a better adherence to treatment plans, resulting in a better clinical outcome. It seems that the latest developments in dry eye therapy, which OH and OL are based on, provide a better tolerability and efficacy compared to earlier generations of sprays.

Disclosure

No financial interest in any product mentioned in the manuscript.

Conflict of Interest

No conflict of interest.

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