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Evaluation of the effects on conjunctival tissues of Optive eyedrops over one month usage

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ABSTRACT

The objective was to compare the effect on conjunctival tissues of the repeated use, over a one-month period, of Optive compared to Hylocomod eyedrops by a population of dry eye sufferers. The rationale for the study was that among dry eye sufferers who attend eye care practices for symptomatic relief, a large number present with conjunctival anomalies evidenced by tissue staining and that conjunctival recovery is essential to their successful long term management. The hypothesis tested was that the decrease in conjunctival staining with Optive is at least as good, and possibly greater, than that with Hylocomod. The cohort population was made up of 47 subjects (11 male and 26 female) aged 42 ± 16 years with at least mild dry eye symptoms and conjunctival and/or corneal staining. The population included contact lens wearers (n = 26) and non-wearers (n = 21). The subjects were randomly allocated to use one of the two study products; they were instructed to use the products as often as needed but at least three times a day. Conjunctival staining was rated on forced choice scales and measured objectively using digital photographs and image analysis. The findings showed that, whereas the staining at the start of the investigation was similar (p = 0.318–0.664), staining after one month of use was significantly less with Optive than Hylocomod (p = 0.028–0.002). The results demonstrated that the regular use of Optive over one month was significantly superior to Hylocomod in improving conjunctival status by producing a greater reduction in the staining of dry eye sufferers.

1. Introduction

Keratoconjunctivitis sicca (KCS), also known as dry eye disease, has been recently defined internationally by the Dry Eye Workshop (DEWS) under the hospices of the Tear Film and Ocular Surface (TFOS) Society as "a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface" [1].

The evaluation of the conjunctiva is highly relevant to ocular symptomatology and the examination of dry eye patients [2]. Conjunctival anomalies such as reduced goblet cells density, squamous cell metaplasia, nuclear changes and keratinisation have been observed in pathological dry eye [3] and localised changes to the conjunctiva are believed to be associated to ocular symptoms [2].

The systematic rating of symptoms is an important part of the profiling of dry eye sufferers to that effect a number of questionnaires have been developed. One such questionnaire the Ocular Surface Disease Index (OSDI) is now used extensively both in clinical investigations and routine practice. The questionnaire, which has been validated [4,5], produces a global score from the 12 questions asked. The score can range from 0 to 100; prior clinical evaluation has established ranges of severity based upon the calculated scores (Normal = 0–12; Mild = 13–22; Moderate = 23–32; and Severe = 33–100).

Several studies have reported on the value of lissamine green staining in assessing dry eye patients [2,3,6–8]. Among these, a large study of 100 dry eye patients and 100 controls found that severe lissamine green staining only occurred in dry eye patients (87% vs. 0%) [6]. Further, the presence of lissamine green staining was reported in people complaining of dry eye symptoms associated with poor air quality [9]. In this latter investigation, staining results also correlated with ocular irritation. Among contact lens wearers, a study involving 25 contact lens wearers, whereby sodium fluorescein was used to evaluate the cornea and lissamine green to evaluate the conjunctiva, reported conjunctival lissamine green staining in 84% of cases but a far less prominent sodium fluorescein corneal staining, occurring only in 40% of the contact lens wearers tested [10]. Lissamine green vital stain has

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been reported to be promoted by disruption of cell to cell junction, cell death or degeneration, while sodium fluorescein staining manifests only whenever there is a disruption of cell to cell junction to allow fluorescein to accumulate in the intercellular spaces [11–13]. Lissamine green in a 1% concentration has been shown to be of similar staining efficacy than rose bengal 1% but without the associated discomfort reported with rose bengal [14].

A normal ocular surface is essential in maintaining a stable tear film. The aqueous layer is maintained at the ocular surface via its interaction with the mucin gel-like structures that covers the corneal and conjunctival epithelia. Any disruption of the ocular surface is preceded by a damage to the overlying mucin gel, hence the importance of monitoring epithelial anomalies. In the case of the conjunctiva lissamine green is preferred to sodium fluorescein because the latter at times remains stagnant within the conjunctival folds creating false staining and/or masking real staining.

The investigation aimed to quantify the effects of the repeated use of Optive eyedrops and Hylocomod eyedrops on the ocular surface characteristics, in a population complaining of at least mild dry eye symptoms. Optive (manufactured by Allergan Ltd.), preserved by Purite, contains carmellose sodium and glycerine as lubricants and also compatible solute technology to moisturise the ocular surface and protect cells from osmotic stress [15]. Hylocomod (manufactured by Ursapharm) is preservative free and contains hyaluronic acid as a lubricant to moisturise the ocular surface. The investigation also evaluated the changes in ocular symptoms associated with the instillation of study products.

2. Methods

The test eyedrops were Optive eyedrops manufactured by Allergan and the control eyedrops were Hylocomod eyedrops manufactured by Ursapharm (Table 1). Both eyedrops are CE marked products. The subjects were required to use the study eyedrops as needed but at least three times a day. The eyedrops were used on a dispensing basis for a continuous period of one month. Prior to the dispensing visit, the subjects found suitable (Table 2) were dispensed with buffered unpreserved saline (Minims from Chauvin Pharmaceuticals Ltd.) to use at least three times a day for a period of approximately two weeks to establish a common baseline. The subjects' symptomatology, assessed by the Ocular Surface Disease Index (OSDI) questionnaire, needed to achieve a score of 13 (slight dryness) or greater.

The study was a randomized, bilateral, single masked, group comparison dispensing study of one-month duration. The subjects were randomly allocated to use the test or control eyedrops. The investigators who carried out the subjective rating of the effects on the ocular tissues were masked as to the identity of the study product used by the subject and the investigator assistants who carried out the measurement of the staining photographs was masked as to the identity of the study product and the visit status.

The subjects attended an initial enrolment visit to obtain their informed consent and evaluate their suitability to take part in the investigation. If they fulfilled the investigation inclusion and exclusion criteria, the subjects were dispensed with unpreserved single dose saline eyedrops to use for approximately two weeks. The two weeks running period with unpreserved saline was to establish a common baseline for the dry status of the subjects at the final study enrolment decision. After approximately two weeks of using saline eyedrops the subjects' suitability to take part was re-assessed. If still suitable, the subjects were then required to attend for one dispensing visit and two follow-up visits, one after one week and another after four weeks of study product usage as applicable (Fig. 1). The study was approved by an independent ethics committee prior to the enrolment of the subjects.

The effects of the study products on the conjunctival tissues were evaluated with lissamine green and sodium fluorescein stains separately for the limbal and bulbar regions. Lissamine green dye sodium fluorescein dye strips were used; unpreserved saline (Sauflon Pharmaceuticals Ltd.) was the agent to wet the strips. Lissamine green was observed with a broad beam diffuse white light and sodium fluorescein with a cobalt blue filter in the lighting

Table 1
Study eyedrops—ingredients.

Optive ingredients	Function
Sodium carboxymethylcellulose (0.5%)	Lubricant
Glycerine (0.9%)	Lubricant
Purite® (0.01%)	Preservative
L-Carnitine	Osmoprotectant
Erythritol	Osmoprotectant
Hylocomod ingredients	**Function**
Sodium hyaluronate (0.1%)	Lubricant
Citrate	Buffer
Sorbitol	Osmotic agent
Water	Solvent

Table 2
Inclusion and exclusion criteria.

Inclusion criteria
- Age 18 years or more.
- Emmetrope or ametrope corrected with spectacles or soft contact lenses.
- Mild to severe dry eye symptoms defined as achieving a OSDI score between 13 and 100.
- Mild to moderate conjunctival staining in each eye (Grades 2–3 with lissamine green staining in at least one quadrant)

and/or

Mild to moderate corneal staining in each eye (Grades 3–7 with sodium fluorescein staining in at least one quadrant).
- Best visual acuity of 6/9 or better in each eye.
- Willingness to adhere to the instructions set in the clinical protocol.
- Signature of the subject informed consent form.

Exclusion criteria
- Previous usage of Hylocomod eyedrops.
- Previous usage of Optive eyedrops.
- Systemic or ocular allergies.
- Systemic disease which might have an ocular component.
- Autoimmune disease which might have an ocular component.
- Use of systemic medication which might have ocular side effects.
- Any ocular infection.
- Use of ocular medication.
- Significant ocular tissue anomaly.
- Pregnancy, lactation or intended pregnancy.
- Diabetes.
- Infectious diseases (e.g. hepatitis and tuberculosis).
- Contagious immunosuppressive diseases (e.g. HIV).
- Any medical condition that might be prejudicial to the study.

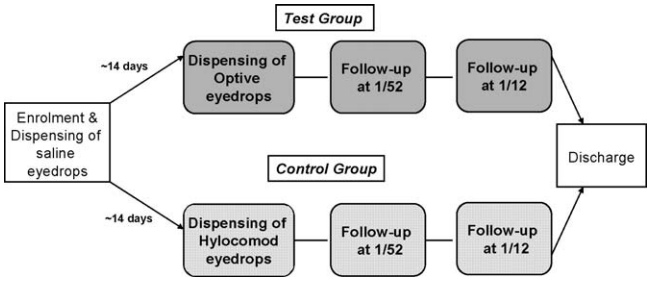

Fig. 1. Study design example.

system and a Kodak Wratten #12 contrast enhancing filter in the observation system. Staining was rated by the investigator at ×25 magnification in four different conjunctival zones (nasal, temporal, superior and inferior); the findings were recorded for each zone on a 5 point scale (0 = None; 1 = Trace; 2 = Mild; 3 = Moderate; and 4 = Severe). The scale 0–4 and the descriptors were chosen to match the International Standards Organization (ISO) scale used for the rating of conjunctival hyperaemia in contact lens clinical trials (no scale exist for conjunctival staining) [16]. The response was summarised in terms of the worst (Maximum) response over the area and the average response over the area (Median) for the limbal and bulbar regions independently to match the ISO recommended methodology [16]; the limbal region corresponds to a 2 mm circular band around the cornea and the bulbar zone the remaining exposed conjunctiva visible during the examination.

The conjunctival was photographed under controlled lighting and recording conditions using the Topcon SL-D7 digital slit lamp biomicroscope (Fig. 2). The photographs were analysed post hoc in a masked fashion by a technician according to a proprietary routine developed for Sigma Scan Pro image analysis software. Two parameters were calculated to summarise the findings. The extent of true staining was measured in terms of the size of puncti (average size, minimum size and maximum size in mm^2). Secondly, from the individual puncti results, the total area of staining (in mm^2) was calculated and compared to the total conjunctival area, giving an objective measurement of the level of conjunctival lissamine green staining in percentage (coverage (%)). The analysis was carried out independently for the limbal and conjunctival regions to match the subjective classification; an example of the relevant zones is given (Fig. 3).

The study population included contact lens wearers and non-wearers to create a population typical of mild or greater dry eye sufferers. The contact lens wearers continued to use their habitual contact lenses with their habitual lens care and replacement schedules. The subjects were, therefore, randomly allocated to the test or control groups with separate randomisation scheme for contact lens wearers and non-wearers.

The data at the dispensing visit after two weeks of saline eyedrop usage was the reference baseline for each population subgroup and the one-month visit was the response data to quantify the effects of Optive and Hylocomod eyedrop usage. The comparative statistics between products were carried out, for parameters with data available for each eye, by univariate ANOVA test with product and eye as fixed factors.

A number of additional variables were recorded to monitor subjects' compliance, acceptance and ocular safety. Tissue toler-

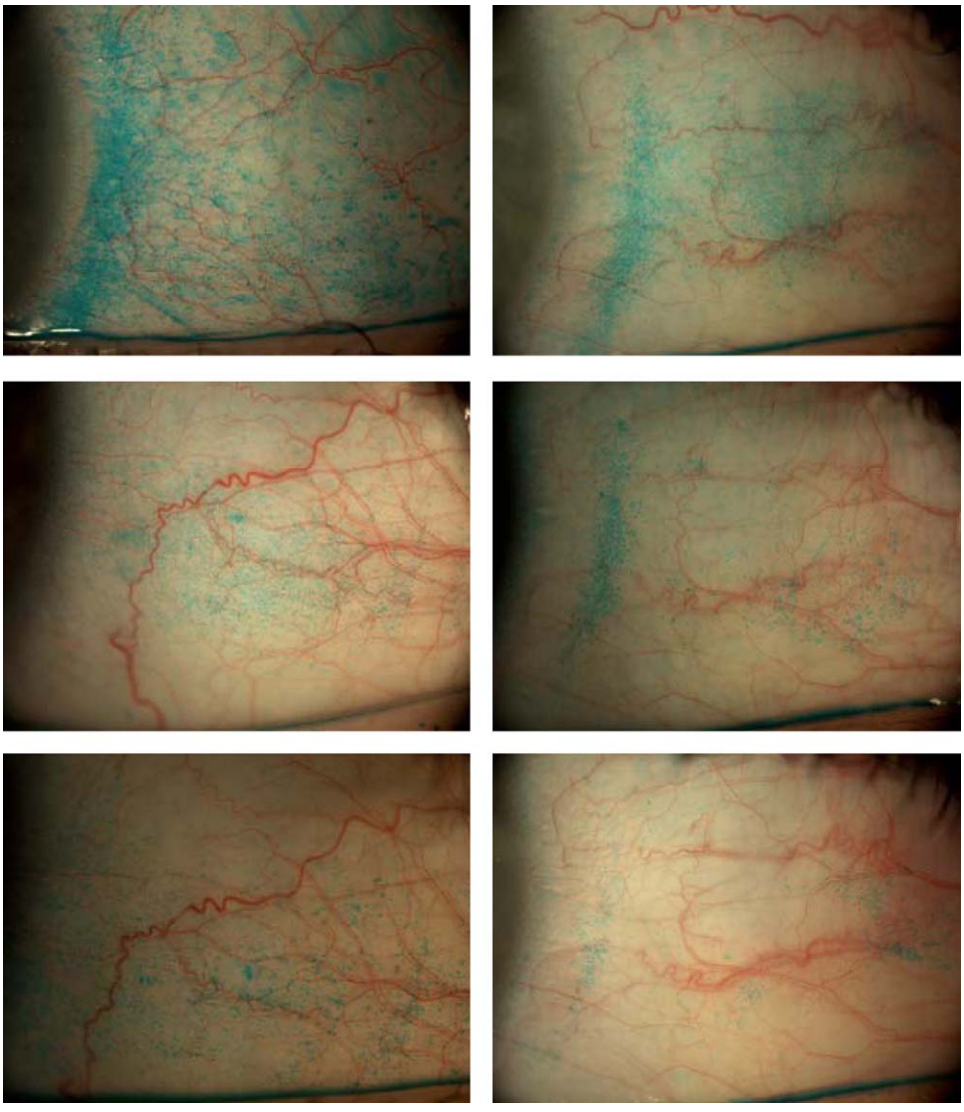

Fig. 2. Examples of conjunctival staining photography with lissamine green in white light.

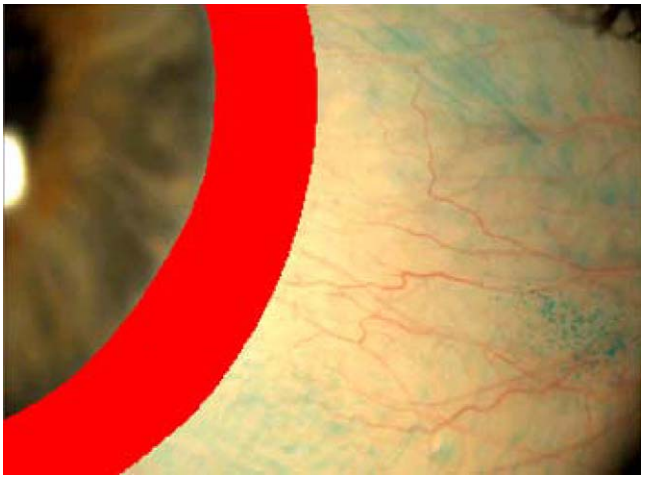

Fig. 3. Conjunctival staining—identification of zones used for analysis (red zone = limbal region).

ance was monitored by the measurement of corneal fluorescein staining and of conjunctival hyperaemia. Subjects' compliance was evaluated via the monitoring of eyedrops usage and the products' acceptance by the rating of comfort, vision and ocular symptoms on VAS scales. Finally, high contrast visual acuity was checked at each visit.

3. Results

A total of 73 subjects consented to take part in the investigation, out of which, 64 subjects were successfully enrolled and dispensed with the pre-study saline eyedrops; 9 subjects did not fulfil the entry criteria. Out of the 64 subjects, 50 proceeded to the study phase; the reasons for the 14 subjects not to progress to the study phase were: no longer fulfilling the entry criteria (9), failure to attend the dispensing visit (3) and discharge due to a change in contact lens type (2). From the 50 subjects in the study: 22 were randomised to use Optive test eyedrops and 28 to use Hylocomod control eyedrops; each eyedrop was used continuously for a period of one month as needed and at least three times a day. Forty-seven subjects completed the investigation and made up the cohort population (Optive: $n = 21$, Hylocomod: $n = 26$) which was well matched between the two studies product groups as indicated below. The three discontinuations were due to: loss to follow-up (1), one toxic reaction at the one month visit for each eye drop tested (2).

- The 21 subjects (5 male and 16 female) who formed the cohort population for the test eyedrop were aged 44.8 ± 16.4 years (range 19–72 years). The test study population was made up of 12 soft contact lens wearers (57%) and 9 non-wearers (43%). All subjects reported at least some mild dry eye symptoms, with an average OSDI score after two week usage of the pre-screening eyedrop of 29.6 ± 14.6 (range: 13.9–62.5).
- The 26 subjects (6 male and 20 female) who formed the cohort population for the control eyedrop were aged 39.9 ± 14.8 years (range 19–71 years). The control study population was made up of 14 soft contact lens wearers (54%) and 12 non-wearers (46%). All subjects reported at least some mild dry eye symptoms, with an average OSDI score after two week usage of the pre-screening eyedrop of 30.0 ± 13.5 (range: 13.6–72.9).

No ocular medication was used by the subjects at the onset of the study. A minority of subjects (Optive 33%; Hylocomod 42%) used eyedrops prior to enrolment in the study and the majority of the population (Optive 67%; Hylocomod 65%) was free from taking any systemic medication.

The subjects were questioned as to their eye drop usage at all scheduled visits in terms of days per week and total daily usage (number of instillations per day by number of drops per instillations). The results revealed good overall compliance. At the one-month follow-up visit, both eyedrops were used on average 7 days per week with on average 3.3 ± 1.0 Hylocomod eye drops and 3.7 ± 1.4 Optive eye drops used per day. When comparing the eyedrop usage of both groups, no statistically significant difference was recorded at the one-month visit ($p = 0.163$). At the final one-month follow-up visit, the volume of unused eyedrop was measured and the actual volume of eyedrop used calculated. The usage was statistically similar for both products ($p = 0.351$) with, average usage of 5.5 ± 2.6 ml of Optive eyedrop solution and of 4.9 ± 1.5 ml of Hylocomod eyedrop.

The maximum limbal conjunctival staining recorded using sodium fluorescein was similar ($p = 0.616$) for the two study products at the dispensing visit prior to study eyedrop usage. The staining at dispensing was most commonly rated as absent (Optive 41%; Hylocomod 46%), whereas, mild and moderate staining were the second most common ratings (Optive 36%; Hylocomod 33%). The same staining rating recorded at the one month follow-up visit was significantly different for the two study products ($p = 0.002$); the staining in the Optive group was significantly less than in the Hylocomod group. The difference was associated with a greater incidence of no staining with Optive (Optive 74%; Hylocomod 52%) and lesser incidence of mild and moderate staining (Optive 6%; Hylocomod 33%) (Table 3 and Fig. 4).

The maximum limbal conjunctival staining recorded using lissamine green produced similar findings to the sodium fluorescein vital stain. At the dispensing visit prior to study eyedrop usage the staining was similar ($p = 0.566$) for the two study products. The staining at dispensing was most commonly rated as absent (Optive 48%; Hylocomod 42%), whereas, mild and moderate staining were the second most common ratings (Optive 40%; Hylocomod 40%). The same staining rating recorded at the one month follow-up visit was significantly different for the two study products ($p = 0.002$), the staining in the Optive group was significantly less than in the Hylocomod group. The difference was associated with a greater incidence of no staining with Optive (Optive 79%; Hylocomod 50%) and lesser incidence of mild and moderate staining (Optive 10%; Hylocomod 33%) (Table 3 and Fig. 5).

The maximum staining in the bulbar region at the dispensing visit was similar for the two study products with both vital stains (sodium fluorescein $p = 0.404$; lissamine green $p = 0.318$). Most commonly, the staining was rated as mild for both eye drops (Mild or greater staining: sodium fluorescein; Optive 83%; Hylocomod 85%–lissamine green: Optive 95%; Hylocomod 98%). However, at the one-month visit, a statistically lower level of staining was recorded with Optive than with Hylocomod when assessed using lissamine green only ($p = 0.002$). The difference was associated with a higher prevalence of no staining (Optive 14%; Hylocomod 0%) and a lower prevalence of moderate staining (Optive 19%;

Table 3
Maximum conjunctival sodium fluorescein (FL) and lissamine green (LG) staining rating—mean and standard deviation (Scale 0–4).

		Optive		Hylocomod	
		Disp	1 Month	Disp	1 Month
Limbal	Fluo	1.10 ± 1.10	0.31 ± 0.56	0.98 ± 1.08	0.87 ± 1.01
	LG	1.14 ± 1.24	0.31 ± 0.64	1.00 ± 1.14	0.90 ± 1.03
Bulbar	Fluo	2.10 ± 0.85	1.95 ± 0.73	2.25 ± 0.90	2.21 ± 0.61
	LG	2.26 ± 0.63	1.79 ± 0.93	2.38 ± 0.57	2.29 ± 0.61

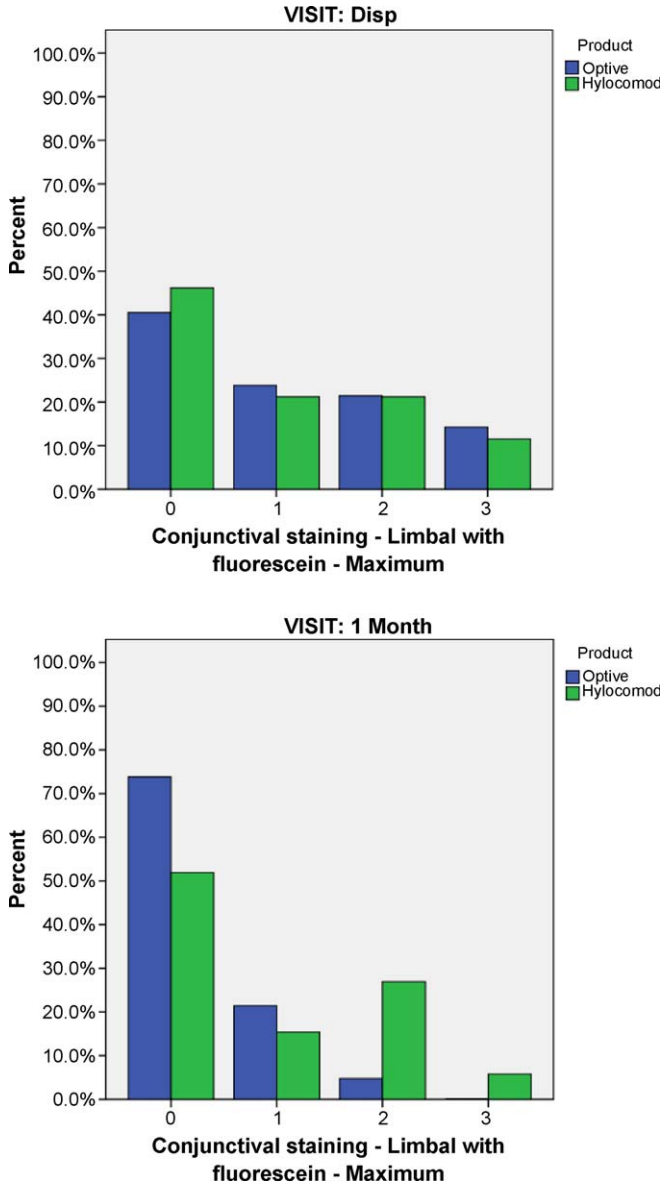

Fig. 4. Limbal staining (sodium fluorescein)—bar charts for each product at dispensing and one month follow-up visits.

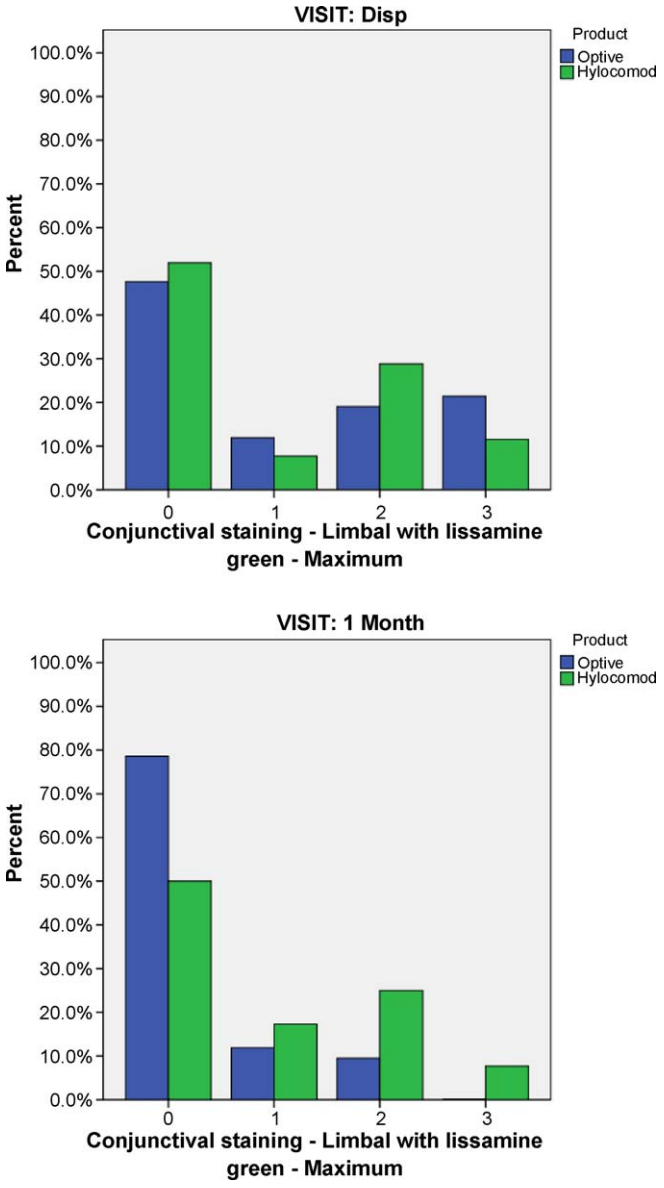

Fig. 5. Limbal staining (Lissamine green)—bar charts for each product at dispensing and one month follow-up visits.

Hylocomod 37%) with Optive than with Hylocomod (Table 3 and Fig. 6).

In the limbal region, no statistically significant difference was recorded in lissamine green staining between the two products at any visit for either coverage % ($p = 0.323$ and 0.473) or puncti size ($p = 0.344$ and 0.777). Prior to the dispensing of the study products, the percentage coverage was on average $1.8 \pm 3.1\%$ and $1.3 \pm 2.5\%$ respectively with Optive and Hylocomod and after one month of eyedrop usage, the average values were respectively $1.2 \pm 1.9\%$ for Optive and $0.9 \pm 1.9\%$ for Hylocomod.

In the bulbar region there was no difference in lissamine green staining between the two study products for either coverage % ($p = 0.461$) or puncti size ($p = 0.664$) at the dispensing visit. In contrast, after one month of usage of the study products, a statistically significantly lesser staining coverage % was recorded with Optive than with Hylocomod (Coverage: $0.5 \pm 0.6\%$ vs. $1.2 \pm 1.9\%$; $p = 0.028$). The average size of the puncti was also significantly smaller with Optive than with Hylocomod ($0.0010 \pm 0.0007\ mm^2$ vs. $0.0026 \pm 0.0040\ mm^2$; $p = 0.014$) at the one-month follow-up visit (Figs. 7 and 8).

4. Discussion

Dry eye encompasses a vast range of anomalies characterised by the presence of subjective complaints and/or ocular signs [1]. The range of symptoms of dry eye experienced by the patient is: dryness, grittiness, burning/stinging, foreign body sensation, pain, and photophobia. Symptoms severity varies from mild and transient irritation, through more persistent irritation, burning, itching, and ocular redness, to an intolerable feeling of sand and grit in the eyes with pain at every blink. The complications of the condition may be sight threatening, including corneal ulceration and ocular infections.

Signs of dry eye vary greatly, but conjunctival anomalies, most commonly staining with dyes and redness, are prominent features [2,6,9,10]. The presence of signs of ocular tissue changes indicates that the condition is creating changes that may become permanent and progressive. Hence, identifying a reversal in such signs is an important indication of the efficient management of the condition that goes beyond symptom relief but addresses the fundamental problem. In that context identifying improvement in the status of

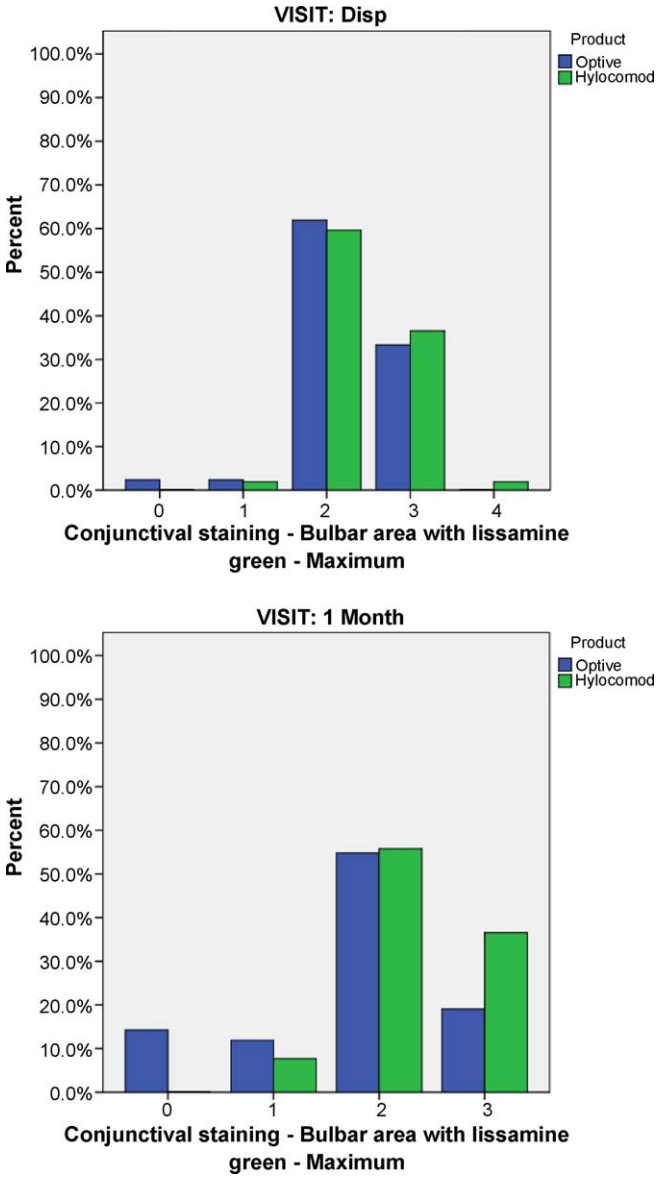

Fig. 6. Bulbar staining (Lissamine green)—bar charts for each product at dispensing and one month visits.

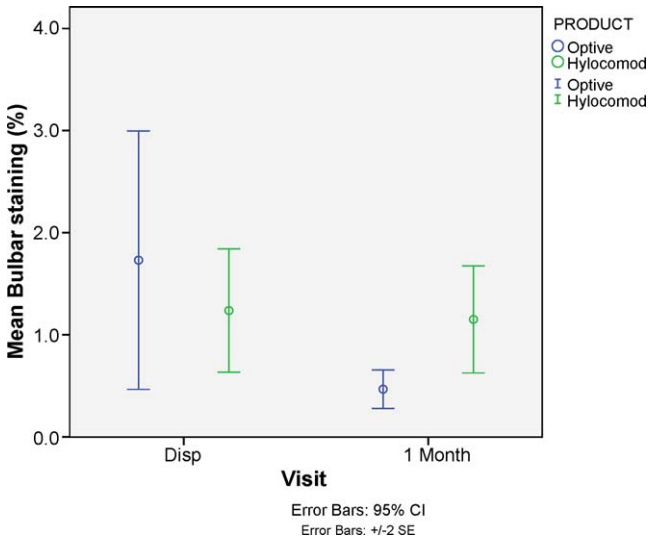

Fig. 7. Bulbar staining (Lissamine green)—average puncti size measured for each product at dispensing and one month visits.

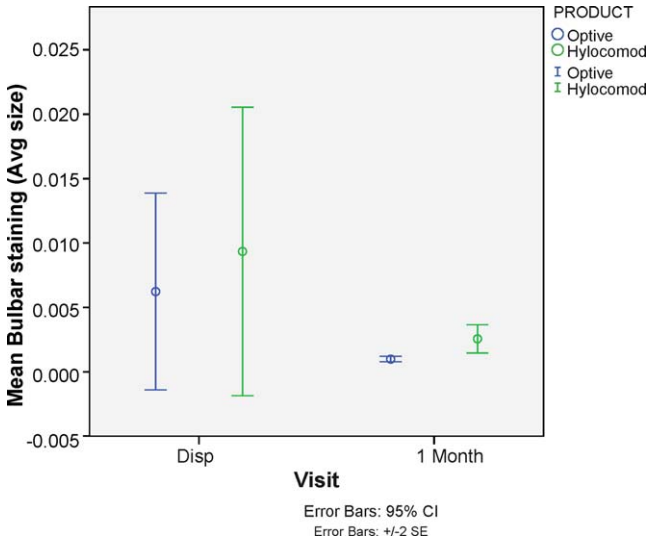

Fig. 8. Bulbar staining (Lissamine green)—percentage coverage measured for each product at dispensing and one month visits.

the ocular surface via a decrease in conjunctival staining is a key observation.

The challenge for the practitioner is to select a product that offers relief and recovery to a wide spectrum of sufferers. Due to the chronic nature of the conditions and associated induced tissue anomaly, as described in DEWS report [1], achieving short term relief does not suffice and tissue recovery is essential to achieve long term success. The current investigation was carried out in that context: can we achieve tissue recovery in a broad range of dry eye sufferers that included both contact lens wearers and non-wearers with a single eye drop?

In order to ensure that the subjects enrolled were representative of patients that would attend eye care practitioners for dry eye relief we used the validated UK version of the OSDI questionnaire; all subjects had to achieve a score that confirmed them as complaining at least of mild dry eye symptoms. The range was chosen as it represents the vast majority of subjects with the condition. The ocular parameter of interest in our case was conjunctival staining. The presence of such staining is indicative of ocular surface desiccation leading to symptoms [2,17]; the relief of staining in that area indicates that the ocular surface has returned to a normal status.

The results of the current investigation carried out on a representative sample of mild to moderate dry eye sufferers, demonstrated a superior performance for Optive than for Hylocomod in controlling conjunctival anomalies. Whereas, all the evaluations revealed similar conjunctival staining for the two eyedrops at baseline, after one month of use the conjunctival staining observed with Optive was either similar to or lower than the conjunctival staining observed with Hylocomod. In the limbal region, the maximal staining was judged by the investigators to be significantly lower with Optive than with Hylocomod for both dyes used. In the bulbar region, the maximal staining judged by the investigators and directly measured from digital photographs were shown to be lower with Optive than with Hylocomod.

Conjunctival staining indicates epithelial cell damage and therefore necessarily damage to the overlying gel-like mucin layer. In the exposed area the aetiology is incomplete coverage of the surface by an unbroken tear film at all times between blinks leading to incomplete surface lubrication. This incomplete

lubrication produces two aetiological causes for surface damage: desiccation during the inter-blink period and/or increase friction between the palpebral and bulbar conjunctivas during blink. The greater efficacy of Optive than Hylocomod can be hypothesised to be linked to the different active ingredients present in the two eyedrops. Hylocomod formulation includes a lubricant (sodium hyaluronate) that mimics the rheological properties of the aqueous layer, hence produces a beneficial effect to the ocular surface by stabilising that layer. Optive also includes a lubricant that has the same effect (Carboxymethylcellulose (CMC)). In addition Optive incorporates three osmoprotectants (glycerin, L-carnitine and erythritol) which are reported to act directly at the cellular surface providing a more hydrated and less hyperosmotic environment characteristics of dry eyes; the latter has been shown to enhance cell recovery.

The two dyes which were used during the study lead to similar conclusions. Because of the ease of use and greater reliability in judging conjunctival staining with lissamine green compared to sodium fluorescein, in agreement with Korb et al. [14] the former is recommended for routine use in practice.

5. Conclusion

Artificial tears featuring a polymeric lubricant (sodium carboxymethylcellulose or sodium hyaluronate) produced an improvement in ocular tissue status of dry sufferers, presenting with corneal or conjunctival staining, following one month of treatment. In this study, the improvement was in the conjunctival region. Optive (0.5% sodium carboxymethylcellulose and compatible solutes) was found to deliver a greater reduction in conjunctival staining than Hylocomod (0.1% sodium hyaluronate).

Acknowledgement

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