Crosslinked hyaluronic acid with liposomes and crocin for management symptoms of dry eye disease caused by moderate meibomian gland dysfunction

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Abstract

Background: To study the effect of uncrosslinked and crosslinked hyaluronic acid combined with other artificial tear components in patients with dry eye caused by moderate meibomian gland dysfunction.

Method: Prospective, single-blind, contralateral eye study. Fifty eyes were analyzed (25 patients). Eye selection for each tear type was random, and the eye drop formulations Aquoral Forte® (artificial tear A) and Aquoral Lipo® (artificial tear B) were used. The determined dosing schedule was three times a day for six weeks, and the study participants underwent a clinical examination before and 45 days after lubricant treatment. The Schirmer test, tear breakup time (TBUT) test, and Ocular Surface Disease Index (OSDI) questionnaire were applied before and after instillation period with both types of artificial tears.

Results: On the Schirmer test, a significant improvement was obtained with both tear A ($p < 0.01$) and tear B ($p < 0.01$). On the TBUT test, a significant improvement was obtained with tear A ($p < 0.01$) and tear B ($p < 0.01$). The OSDI score significantly decreased after instillation period with both artificial tear types ($p < 0.01$).

Conclusion: Uncrosslinked hyaluronic acid combined with other components, such as tamarind seed polysaccharide, and crosslinked hyaluronic acid combined with liposomes and crocin are effective for management symptoms of dry eye disease.

Background

Dry eye has recently been defined as a multifactorial disease. [1–3] Loss of homeostasis of the tear film is a pathophysiological factor by which dry eye is classified according to its etiology as either aqueous-deficient or evaporative dry eye, with each being a continuation of the other. [2–4] Evaporative dry eye results from excessive loss of the aqueous layer, attributed to a deficient or unstable lipid layer, which controls evaporation of the tear film. The most common cause of evaporative dry eye is meibomian gland dysfunction (MGD). [5, 6] Abnormal lipid composition affects the physicochemical properties of the tear film and therefore its stability.

Dry eye is one of the causes of contact lens intolerance. One study [7] investigated the use of cyclosporine in patients with dry eye wearing contact lenses. Cyclosporine, as an immunomodulatory mediator, could have a helpful outcome on this inflammatory procedure and thereby improve patient symptoms. Questionnaires are also used to classify and diagnose dry eye in patients wearing contact lenses. [8] The Osaka study demonstrated that visual display terminals and electronic devices are a source of dry eye for workers exposed to these elements. [9]

The most common prescribed medication is preparation eye drops to modulate the inflammatory response of the ocular surface (cyclosporine or lifitegrast). Prescription device treatments for MGD, specifically, is an emerging market but there is a significant body of knowledge that already exists for

some prescription device treatments for MGD (vectored thermal pulsation indicated for MGD [10] and Intense Pulsed Light [11] in combination with manual expression for MGD patients).

Currently, the most common method to temporarily manage symptoms and temporarily supplement the tear layer is to use over-the-counter drops. These lubricants assume a deficiency in the lipid component of the tear film. In patients with evaporative dry eye, they cause a temporary renewal of the tear film but in some cases can increase tear evaporation. In these cases, lubricants are applied more frequently, involving discomfort and added cost for the patient.

In recent years, interest in using lipid-containing lubricants has increased, and thus, these products have been extensively commercialized. New formulations include Systane Balance (Alcon, Fort Worth, Texas), Neovis Total Multi (Horus Pharma, Saint-Laurent du Var, France), and Optive Advanced (Allergan, Irvine, California).

Since the discovery that hyaluronic acid can act as an ocular lubricant, it has been included in many artificial tear formulations. The viscoelasticity of this polysaccharide increases tear film stability, consequently reducing dry eye symptoms. [12–14] The high viscosity of the polysaccharide is largely due to the molecular weight of the hyaluronic acid chain. Crosslinked hyaluronic acid confers a higher molecular weight to the polysaccharide chain and has been investigated in recent studies, used alone and combined with other elements. [15, 16]

The purpose of this study was to evaluate the clinical efficacy of 0.4% uncrosslinked hyaluronic acid and 0.2% galactoxyloglucan (tear A) and 0.15% crosslinked (CXL) hyaluronic acid, crocin, and liposomes (tear B) in dry eye disease caused by meibomian gland dysfunction.

Methods

Design

This is a prospective, single-blind, contralateral eye study, conducted between December 1, 2017, and March 31, 2018. The study was carried out in the facilities of the School of Pharmacy (Optics and Optometry departments) at the University of Seville. The principles of the Declaration of Helsinki were followed

Subjects

Fifty eyes were analysed (25 patients). The subjects selected were over 18 years of age. No gender distinction was made in the selection of subjects. All subjects were silicone hydrogel contact lens wearers on a monthly replacement schedule. The subjects had no history of eye disease or previous eye surgery and were not taking systemic or ocular medications. All patients read, understood, and signed an informed consent form prior to participation in the study.

Materials

A slit lamp (TOPCON SL–6E, Japan) was used to study the tear film, and fluorescein strips (Bio Glo ContaCare Ophthalmics & Diagnostics, Gujarat, India) impregnated with saline solution were used for the tear breakup time (TBUT) test. Next, tears were examined with the cobalt blue filter of the slit lamp. TBUT strips and dry sterile applicators have been used. Subjects blinked naturally three times and then to stop blinking until instructed. Measurement was the break of time that elapses between a complete blink and the presence of the initial disruption in the tear film. The Schirmer test (Tear Flo, HUB Pharmaceutical, Michigan, USA) was used to measure tear volume. The Schirmer strip was placed between the outer and middle third of the lower eyelid. After 5 minutes, the wetted length was measured in millimetres. The location, time, and humidity conditions were the same for all patients examined.

The patients also completed the Ocular Surface Disease Index (OSDI) questionnaire during the first visit along with a questionnaire inquiring about their personal data, type of contact lenses used, and hours of wear time per day. To evaluate the meibomian glands, infrared meibography was performed with a COBRA® HD fundus camera (Construzione Strumenti Oftalmici, Firenze, Italy). MGD degree was measured by ImageJ method defined by Pult and Nichols. [17] MGD was classified as one of four grades according to the severity of the loss (Figure 1). MGD score of superior lids strong correlates with percent of superior lids meibomian loss ($r = 0.85$, $p < 0.01$) and MGD score of inferior lids strong correlates with percent of inferior lid meibomian loss ($r = 0.92$, $p < 0.01$).

Before the start of the study, the TBUT, Schirmer score, OSDI score, percentage of gland loss, and MGD grade were measured. After follow-up period, the TBUT, Schirmer score, and OSDI score were measured again. Meibomian gland loss was not re-measured because ocular lubricants do not alter the glandular pattern. A change in grade of Meiboscore was not expected and thus not gathered. In this sense, the function of the meibomian glands was not evaluated either. There was not any change in environmental conditions at the follow up appointment. Patients did not know the type of artificial tear instilled in each eye during the measurements.

Procedure

The contralateral eye was used to establish the two arms of the study to compare the two artificial tears. Eye selection for each artificial tear formulation was random, using a random number table, and the formulations were named artificial tear A and artificial tear B. Patients were not told the type of artificial tears they would use or their difference, and therefore, they were unaware of the possible benefits of such tears. The examiner knew the tears applied to each eye.

Regarding the lubricants, artificial tear A (Aquoral Forte®, ESTEVE®, Farmigea, Pisa, Italy) is a mixture of 0.4% uncrosslinked hyaluronic acid and 0.2% galactoxyloglucan. The galactoxyloglucan is extracted from the tamarind seed. The package contains 30 single 0.5-ml doses. The doses are packaged for daily

use, and thus, the lubricant cannot be used if 12 hours have passed since the dose dispenser was opened. It is a preservative-free lubricant.

Tear B (Aquoral Lipo® [in Spain]/Lumixa® [in Italy], ESTEVE®, Farmigea, Pisa, Italy) is a mixture of three components: 0.15% crosslinked (CXL) hyaluronic acid, crocin, and liposomes. It is an ophthalmic lubricant and antioxidant solution. The package is a 10-ml multidose container, and thus, the lubricant can be used for a prolonged period. The lubricant is composed of liposomes, 0.15% crosslinked hyaluronic acid sodium salt, ethylenediaminetetraacetic acid (EDTA) disodium salt, and crocin. Although this tear comes in a multidose container, it does not contain preservatives due to its dispenser, which impedes microorganisms from penetrating the solution inside. Contact lenses can be used while both lubricants are applied, and the study patients wore their monthly silicone hydrogel contact lenses throughout the study period.

All patients in the study spent one month using no artificial tears or eye drops. Once this ‘wash out’ period ended, patients were given instructions on the proper instillation technique for artificial tears. The artificial tears were administered three times a day for six weeks, and the study subjects underwent a clinical examination before and 45 days after lubricant period. Patients were instructed not to use any other lubricant or ocular therapy during the study period. Patient compliance was tracked with a weekly email reminder. The initial tests were repeated; however, meibography was not repeated because artificial tears were not expected to cause growth or modification of the meibomian glands.

Statistical analysis

The data were analysed using the SPSS 24 package for Windows (SPSS Science, Chicago, IL). The normality of the variables was verified using the Shapiro-Wilk test. A descriptive data analysis technique was developed, showing the count and proportion in each category of the qualitative variables and the mean and SD; failing this, the median and interquartile range of the quantitative variables is given. All statistical tests were performed with a 95% confidence level ($p < 0.05$).

Results

Fifty eyes were examined. Since this was a contralateral study, one of the eyes was treated with tear A (HA + GX, n = 25) and the other with tear B (CHA + L, n = 25). Table 1 shows the characteristics of the two study groups before treatment with artificial tears. For the variables sex, age, and OSDI score, the statistical significance is 1.00 when it is the same patient. The low significance of the results shows that both groups were homogeneous before treatment.

For the Schirmer test variable, a significant improvement was obtained for both tear A ($p < 0.01$) and tear B ($p < 0.01$), which corresponds to an improvement in aqueous tear volume. Likewise, for TBUT, a significant improvement was obtained with the tear composed of hyaluronic acid and galactoxyloglucan ($p < 0.01$) and the tear composed of crosslinked hyaluronic acid and liposomes ($p < 0.01$). This variable

evaluates the stability of the lipid component of the tear film. Lastly, the OSDI score decreased significantly ($p < 0.01$) after treatment with both artificial tears. Here, the results could not be measured monocularly because many respondents did not know how to differentiate between the two eyes for many of the questions asked in the OSDI questionnaire. The results are summarized in a box-and-whisker plot in Figure 2.

Both treatments were found to be safe and well tolerated by the patients during the three instillations per day and throughout the 45 days. No changes were found in intraocular pressure. All patients maintained their maximum corrected vision after the study. In a survey of the patients after using both ophthalmic lubricants, 12% of the respondents reported they had blurred vision with tear B. These symptoms of blurring disappeared quickly according to the recorded responses. Another issue addressed was the itching sensation. While only 8% of patients reported itching with tear A, this result increased to 32% of respondents with tear B. Finally, there were zero adverse events.

Discussion

This study evaluated the efficacy of two hyaluronic acid-based dry eye symptoms management in patients with moderate MGD. Our results showed significant improvement in the three variables analysed: Schirmer test values ($p < 0.01$), TBUT ($p < 0.01$), and OSDI score ($p < 0.01$) for both tears A and B.

Contact lenses and MGD

Meibomian gland obstruction and the extent of gland loss are related to contact lens wear. [18] The study patients were all contact lens wearers and suffered meibomian gland loss. The upper eyelid exhibited less loss in both the right eye and left eye (24.60 ± 9.55 [8.7—42.8] and 29.38 ± 10.77 [7.0—47.7], respectively). In the lower eyelid, gland loss was greater (49.88 ± 15.90 [20.8—84.7] and 46.04 ± 15.78 [22.0—84.8], right and left eye, respectively).

Ong & Larke [19] reported that damage to the meibomian glands was due to mechanical trauma caused by constant blink-induced contact lens movement. The contact lens material was not associated with a greater or lesser gland loss. Consistent with this study, Arita et al. [20] used infrared meibography to observe gland morphology with the eyelid everted. The results obtained support our findings; Arita et al. also described and classified gland loss using a 5-grade scale called the meiboscore. [21] This scale was based on the percentage of meibomian gland loss.

MGD is characterized by a thick secretion that can be observed when pressing the lower eyelid. Machalinska et al. [22] observed that contact lens wearers had a more viscous and poorer-quality secretion. Our study did not include meibum secretion among the study variables; however, when pressing the lower eyelid of the patients, we observed with the slit lamp that most of the eyes produced a thick, turbid secretion. In contrast, Pucker et al. [23] found no relationship between contact lens wear and

secretion. However, that study was conducted in several centres, and thus, differences in the protocol for measuring variables might have affected the results.

Wearing contact lenses has been proposed to have a significant impact on the meibomian glands during the first two years of use, because after two years, no further gland modifications appear to be produced. [24] In our case, the patients in the study had been wearing contact lenses for over four years, and thus, changes in meibomian gland morphology were reported in our study. Approximately 70% of contact lens wearers have dry eye symptoms. [3, 4] These symptoms cause patients to reduce the number of hours of wearing time per day. The OSDI questionnaire helped us obtain subjective information about the dry eye status of our patients. The OSDI questionnaire is the only test approved by the epidemiology subcommittee of Dry Eye Workshop (DEWS) 2017. [4]

Artificial tears in the symptom's management of MGD

This study analysed an artificial tear containing 0.4% uncrosslinked hyaluronic acid and 0.2% galactoxyloglucan, whereas the artificial tear used for the contralateral eye contained 0.15% crosslinked hyaluronic acid, liposomes, and crocin. This is the first time the latter artificial tear formulation has been the subject of a clinical study. Our results showed a significant improvement in the Schirmer test values, TBUT, and OSDI scores for both tear types. Previous studies have described the improvement achieved by hyaluronic acid combined with galactoxyloglucan. Barabino et al. [25] found that the galactoxyloglucan-based artificial tear was a good tear substitute. In addition, they concluded that the effect of galactoxyloglucan with hyaluronic acid on the tear is greater than that of HA alone and greater than carmellose. Their results, which are in line with ours, suggest that noncovalent interaction of galactoxyloglucan with other components improves treatment outcomes compared with use of the polymer alone.

Galactoxyloglucan is a natural polysaccharide derived from the tamarind seed mucin layer. The molecular structure of galactoxyloglucan confers its mucoadhesive properties, allowing xyloglucan formulations to act as a barrier that reduces bacterial adhesion and invasion and preserves tight junctions and paracellular flow, as observed in several in vitro and in vivo studies. [26] Thus, xyloglucan possesses protective properties enabling it to form a barrier film and is a nonpharmacological alternative for treatment of various diseases, such as dry eye. Tamarind seed polysaccharide has been used for the symptom's management of dry eye, and its efficacy and ocular surface tolerability have been verified. Rolando et al. [27] showed that 0.5% tamarind seed polysaccharide had an effect equivalent to that produced by 0.2% HA. In our case, the artificial tear formulation included both components, and thus, an added effect was observed in dry eye improvement. From a chemical point of view, excellent synergistic polysaccharide interactions have been found between tamarind seed polysaccharide and hyaluronic acid. [28] Tamarind seed polysaccharide can noncovalently stabilize hyaluronic acid; in this same study, Uccello-Barretta et al. determined a minimum concentration of 1.5 mg/ml of each polysaccharide to generate a stable union.

Use of the other artificial tear, containing crosslinked hyaluronic acid combined with liposomes and crocin, led to a significant improvement in the Schirmer test values, TBUT, and OSDI scores, along with an improvement in the initial symptoms. A wide variety of tears contain a lipid component, for example, homogenized oil eye drops, 1.25% castor oil emulsion, and carbomer-based lipid-containing gel. All these lubricants have been shown to improve the symptoms and signs of MGD under certain conditions. A summary of the studies conducted with these lubricants is included in a review by Sze Yee et al. [29]. A more recent review by Garrigue et al. [30] examines the currently marketed artificial tears. This review addresses aspects such as the addition of liposomes to ocular lubricants as a natural substitute for the lipid layer of the tear film.

Garrigue et al. also stated that lipid-based therapies are an attractive alternative to water-based artificial tears because they more closely resemble the tear film composition. Lipid-based therapies not only eliminate patient symptoms immediately after topical administration but also improve the lipid structure of the tear film, resulting in improved tear film stability. Another study also tested new lipid-based formulations for the effective symptoms management of dry eye [31] and for replacing the lipid layer of the tear film. More recently, lipid-containing gels have been described, producing results in accordance with ours. [32]

Studies examining the effect of crosslinked hyaluronic acid on dry eye are scarce. Moreover, these studies report combinations with components different from those of tear B in our study. In the first study conducted in vitro, [15] corneal epithelialization improved with two artificial tear formulations containing crosslinked hyaluronic acid combined with 0.02% and 0.4% urea; both compounds quantitatively improved the ocular surface. A recently published study examined the efficacy of an artificial tear containing crosslinked hyaluronic acid combined with coenzyme Q10 [16] and concluded that the resulting effect on the ocular surface is greater than that with hyaluronic acid alone. The hyaluronic acid/coenzyme Q10 combination led to a reduction in the OSDI score and in corneal and conjunctival staining.

Conclusion

In conclusion, uncrosslinked hyaluronic acid combined with other components, such as tamarind seed polysaccharide, and crosslinked hyaluronic acid combined with liposomes and crocin are effective for symptoms management of dry eye.

Abbreviations

TBUT: Tear break up time

OSDI: Ocular Surface Disease Index

MGD: Meibomian Gland Dysfunction

CXL: Cross Liking

EDTA: Ethylenediaminetetraacetic Acid

HA: Hyaluronic Acid

GX: Galacto-Xyloglucan

CHA: Crosslinking Hyaluronic Acid

DEWS: Dry Eye Workshop

Declarations

Ethics Approval and Consent to Participate

Ethics approval was obtained by Andalusian Ethics Committee by Junta de Andalucía with the number 0828-M1-18.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests

Availability of data and materials

The data that support the findings of this study are available from University of Seville but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of University of Seville.

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Authors' contributions

Study concept and design (J-MS-G, MCS-G, CD-H-C); data collection (J-MS-G); analysis and interpretation of data (J-MS-G, MCS-G, CD-H-C); writing the manuscript (J-MS-G, MCS-G, CD-H-C); critical revision of the manuscript (J-MS-G, MCS-G, CD-H-C); statistical expertise (J-MS-G); supervision (MCS-G, CD-H-C). All authors read and approved the final manuscript

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Table

Table 1. Descriptive characteristics of the patients in the study before treatment with artificial tears (baseline). A significance of 1.00 shows that because the contralateral eye was used, there was no difference between one group and another. *Mann–Whitney U Test. **Student's t-test. Statistical significance was established at $p < 0.05$.

	Tear A Group (n = 25)	Tear B Group (n = 25)	p value
Sex (M/F)	5 / 20	5 / 20	1.00*
Age (years) (mean ± SD [range])	21.76 ± 1.39 [19.00 – 25.00]	21.76 ± 1.39 [19.00 – 25.00]	1.00*
Intraocular pressure (mm Hg) (mean ± SD [range])	13.1 ± 1.8 [11.00 – 15.00]	13.9 ± 2.0 [10.00 – 16.00]	.32**
Upper meibomian gland loss (%)	24.60 ± 9.55 [8.7 – 42.8]	29.38 ± 10.77 [7.0 – 47.7]	.12*
MGD grade (meiboscore), upper eyelid	1.44 ± 0.58 [0 – 2]	1.60 ± 0.57 [0 – 2]	.28*
Lower meibomian gland loss (%)	49.88 ± 15.90 [20.8 – 84.7]	46.04 ± 15.78 [22.0 – 84.8]	.29*
MGD grade (meiboscore), lower eyelid	2.48 ± 0.71 [1 – 4]	2.40 ± 0.64 [1 – 4]	.56*
Schirmer test value (mm) (mean ± SD [range])	18.08 ± 8.99 [3 – 35]	16.76 ± 7.86 [2 – 30]	.55*
TBUT (s) (mean ± SD [range])	10.60 ± 3.40 [7 – 20]	11.24 ± 3.35 [5 – 20]	.27*
OSDI score (mean ± SD [range])	16.67 ± 8.47 [2.08 – 33.33]	16.67 ± 8.47 [2.08 – 33.33]	1.00*

Figures

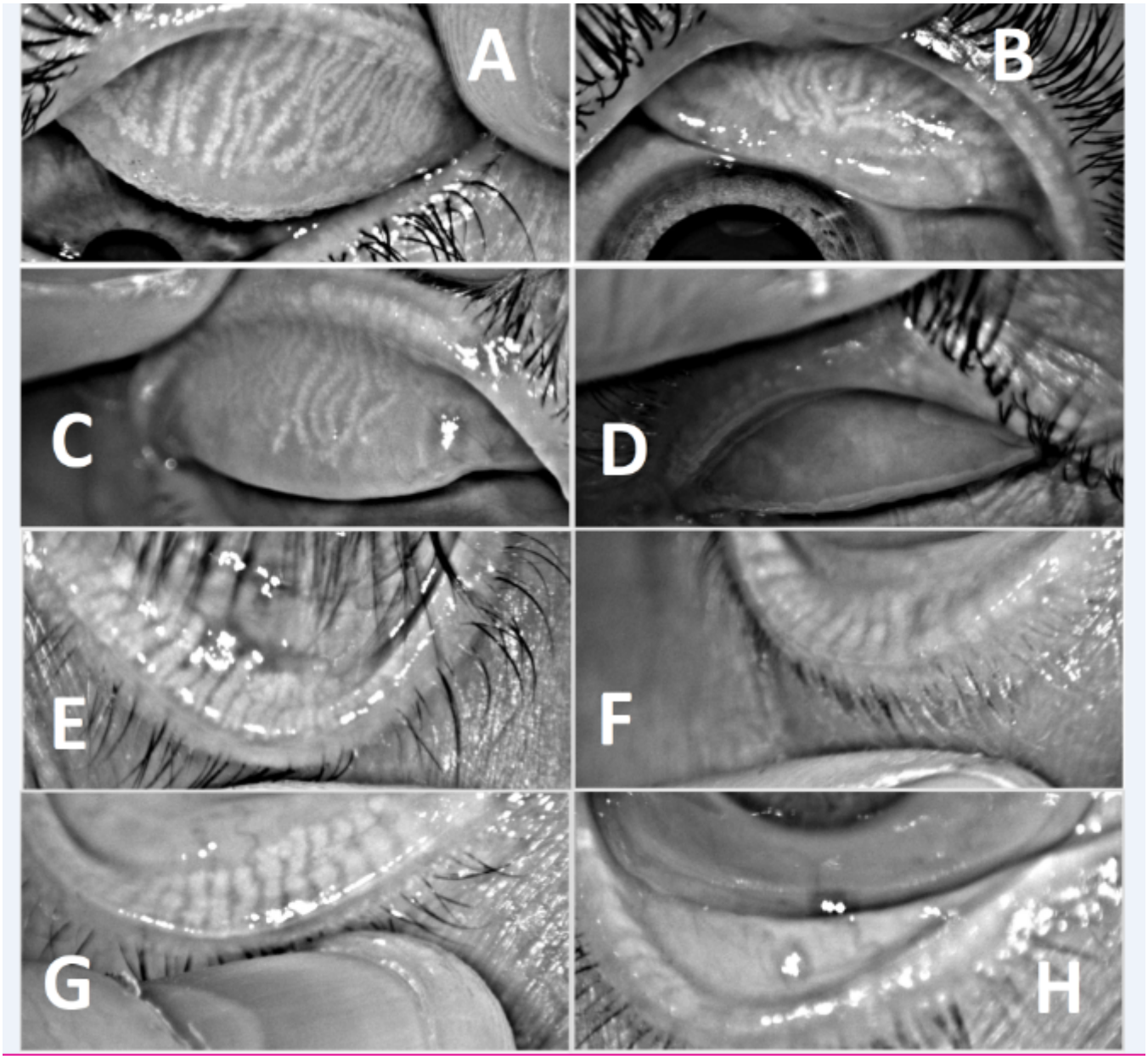

Figure 1

Meibomian gland dysfunction (MGD) patterns according to the meiboscore, which was based on the percentage of meibomian gland loss determined using image processing software. A. Grade 1 MGD of the upper eyelid. B. Grade 2 MGD of the upper eyelid. C. Grade 3 MGD of the upper eyelid. D. Grade 4 MGD of the upper eyelid. E. Grade 1 MGD of the lower eyelid. F. Grade 2 MGD of the lower eyelid. G. Grade 3 MGD of the lower eyelid. H. Grade 4 MGD of the lower eyelid. Images C and D do not correspond to patients included in the study but are incorporated here to show the reader all four MGD grades of the upper eyelid.

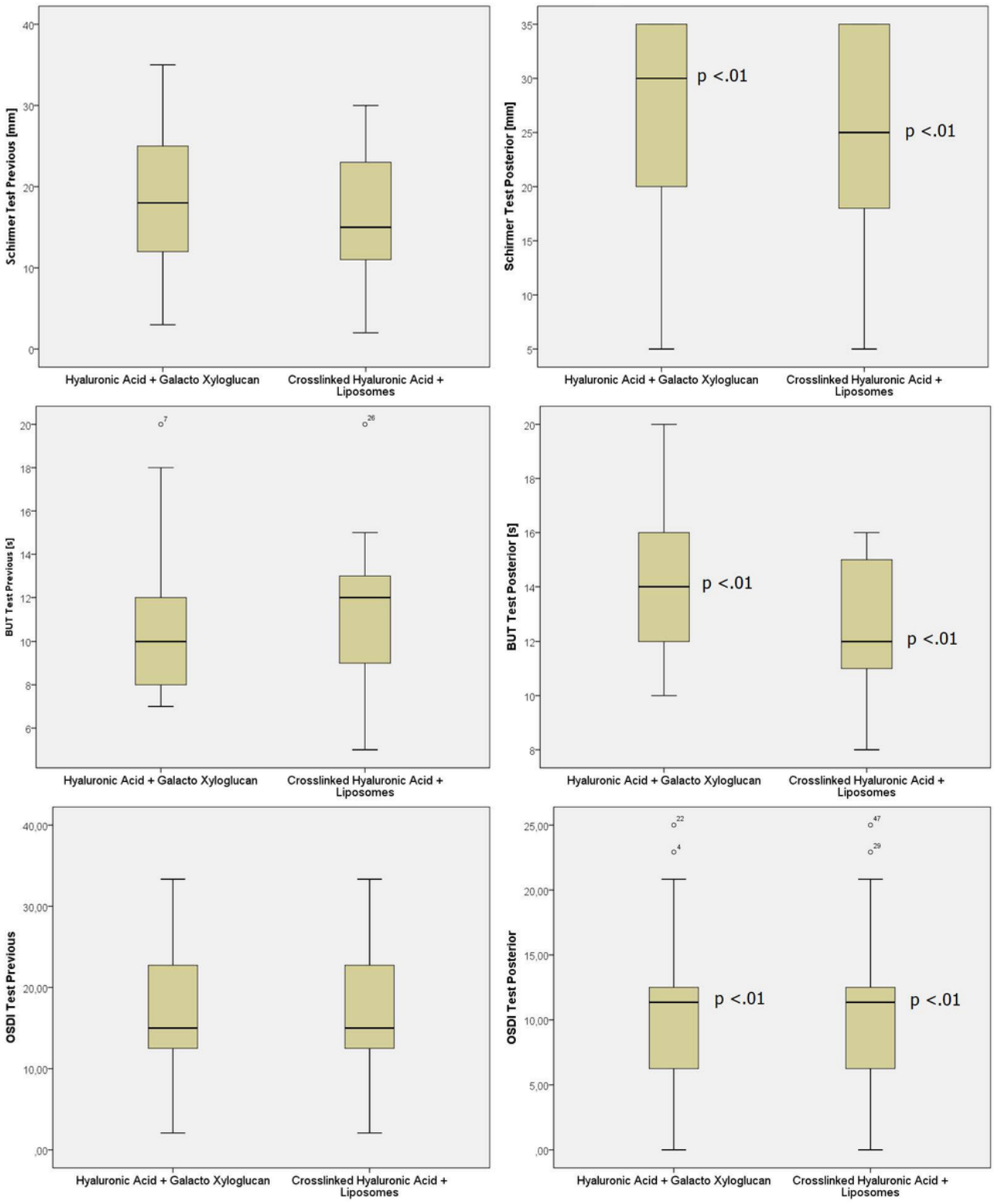

Figure 2

Comparative box-and-whisker plots between the Hyaluronic Acid + Galacto-Xyloglucan and Crosslinked Hyaluronic Acid + Liposomes groups. Top – On the left, the Schirmer test values before treatment; on the right, after treatment. Centre – On the left, the TBUT before treatment; on the right, after treatment. Bottom – On the left, the OSDI score before treatment; on the right, after treatment. To calculate statistical significance, a Wilcoxon test was used for related nonparametric variables.