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New Topical Medication to Prevent Dry Eye Symptoms After Epi-LASIK

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ABSTRACT

PURPOSE

The aim of this study was to compare the effects of two different commercially available artificial tear products for standard treatment after Epi-LASIK, a carbomer-based eye gel (Vidisic; Dr. Gerhard Mann Chem-pharm Fabrik GmbH, Berlin, Germany) and a spray based on phospholipid-liposomes (Tears Again; Optima Pharmazeutische GmbH, Moosburg, Germany).

METHODS

Twenty patients undergoing Epi-LASIK on both eyes were included in this controlled and randomized clinical study. The Epi-LASIK procedure was carried out with the Gebauer EpiLift microkeratome and a Zeiss MEL 80 excimer laser under standardized conditions. After their surgery, all patients were instructed to apply the carbomer eye gel six times per day for 12 weeks into the conjunctival sac of one eye and the liposomal spray onto the closed lid of the other eye. Follow-up examinations were done after 1 day, 4 weeks, and 12 weeks and included lid-parallel conjunctival folds (LIPCOF), break-up time (BUT), Schirmer testing, lid-margin examinations, and uncorrected visual acuity. The subjective evaluation of post-refractive pain was documented by using a special dry eye questionnaire.

RESULTS

The Epi-LASIK procedure was uneventful in all surgeries. There were no complications during the entire follow-up period. The contact lens was removed on day 3 from 15 eyes in the carbomer group and from 16 eyes

in the Tears Again group. In five eyes in the carbomer group and in four eyes in the Tears Again group, there was a contact lens exchange and a final removal of the lenses at day 5.

All patients reported a relief of symptoms after applying either the carbomer or the liposomal eye spray. The average maximal pain score appeared in both groups between day 1 and day 2. The patients reported greater relief, efficacy, and tolerability for the liposomal eye spray, and they showed better results in BUT and uncorrected visual acuity.

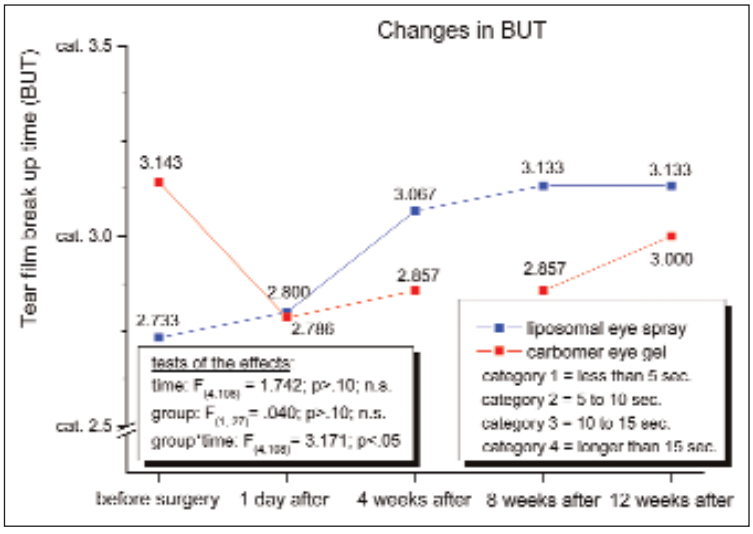

Figure 1. Changes in BUT during the course of the study.

CONCLUSIONS

Both artificial tear products have proved their applicability for the treatment of dry eye symptoms after refractive surgery. Because the liposomal eye spray is applied over closed eye lids, it is easier to apply and has less risk of hurting the eye, which gives it greater patient satisfaction over the carbomer.

INTRODUCTION

Since the introduction of Epi-LASIK, this technique is getting more and more popular. However, the first refractive procedure was photorefractive keratectomy (PRK), followed by laser in situ keratomileusis (LASIK), which is still the most common refractive surgery procedure.

Alternative techniques, such as laser subepithelial keratomileusis (LASEK) and epithelial laser in situ keratomileusis (Epi-LASIK), have been developed to reduce common complications.[1]

While LASIK is currently the predominant and the most popular procedure in refractive surgery,[2] LASEK may prove to be superior in some ways.[3]

Surface-based procedures like LASEK and Epi-LASIK have a preserved and fully intact epithelial flap, which could be repositioned on the laser-treated area. This epithelial sheet acts like a natural contact lens, as it is required to hold the flap position and to reduce the foreign body sensations. This flap also positively affects postoperative pain and haze formation. Whereas in the standard LASEK procedure, alcohol is needed for the separation of the epithelial flap, Epi-LASIK is an alternative surface method that uses a specially designed device that features a blunt oscillating blade for epithelial separating and does not require the use of alcohol.[4] Thus, this approach ought to have a positive effect on postoperative wound healing.

Clinical results show that Epi-LASIK is a safe and efficient method for the correction of myopia[5] up to higher grades as well as myopic astigmatism,[6] with a low incidence of pain postoperatively.[7]

A comparative histological evaluation of mechanical and alcohol-assisted epithelial separation has shown that the epithelial discs were excised by mechanical separation, the lamina densa and lamina lucida were preserved, and the hemidesmosomes had normal morphology along almost the entire length of the basement membrane. The basal epithelial cells of the separated epithelial discs showed minimal trauma and edema.[8]

Another histological evaluation showed that 24 hours after mechanical separation, the epithelial cell morphology was already close to normal.[9]

Dry eye is the most common subjective complaint after refractive surgery, even in patients with no history of dry eyes. The symptoms occur particularly in females and are associated with refractive regression.[10,11] An effective treatment of dry eyes is required in all patients,[12] because of evidence-based management strategies.[13]

After the surgery, a soft bandage contact lens has to be applied to fixate the epithelium. To minimize the foreign body sensation from the contact lens and cell debris and also to manage the dry eye during the first postoperative weeks, a proper lubricant has to be provided.

In this study, we compared the efficacy of two different and commercially available artificial tear products as a standard postoperative therapy after Epi-LASIK to prevent or to improve the possible symptoms of dry eye.

SYNOPSIS

By comparing the efficacy of the two tear products, it could be determined that both products are, in principle, convenient. However, the liposomal eye spray proved to be superior in many respects.

MATERIALS AND METHODS

Twenty patients undergoing Epi-LASIK on both eyes were included in the controlled and randomized clinical study. After 12 weeks, 19 patients completed the study.

One patient was excluded from the study after the first follow-up examination because he was not comfortable with either tear product.

Eleven patients (55%) were female and nine (45%) were male. Seventeen patients were between 25 and 45 years old, whereas three patients were younger than 25 years. Seventeen patients (85%) had contact lenses to adjust their refractive error before surgery. At least 2 weeks before undergoing the procedure, the patients had to stop wearing their contact lenses.

All the patients were examined by the same observer. The participants were instructed to apply the carbomer eye gel into the conjunctival sac of one eye and to apply the liposomal spray onto the closed lid of the other eye six times per day.

The eyes of each patient were randomized to the groups; the eyes treated with the carbomer eye gel were identified as group A, while the eyes treated with the liposomal eye spray were labeled group B.

The Epi-LASIK procedure was carried out with the Gebauer EpiLift microkeratome and a Zeiss MEL 80 excimer laser. After the laser treatment, the epithelial sheet was repositioned, and a therapeutic contact lens was applied to the eye for 3 to 5 days.

The patients were enrolled after the normal preoperative examination. Follow-up examinations were done after days 1 and 4 and at 12 weeks and included the following parameters: lid-parallel conjunctival folds (LIPCOF), tear film BUT, Schirmer I value, examination of the lid margin, and the uncorrected visual acuity. The results were documented by grading into categories as far as practical.

The postoperative level of pain in each eye was assessed after days 1 and 3 and at 1 week after surgery using a visual analogue scale. In addition, the subjective evaluation of patients was determined by a special dry eye questionnaire, which was filled out after days 1 and 3 and weeks 1, 2, 4, 8, and 12.

The statistical analysis was performed with the statistical program SPSS v.12.0 (SPSS Inc., SPSS version 12.0 [available at www.spss.com]).

RESULTS

The Epi-LASIK procedure was uneventful in all cases. The therapeutic contact lens was removed 3 days after surgery in 15 eyes of the carbomer treatment group and in 16 eyes of the phospholipid-liposomes treatment group. There was a contact lens exchange and a final removal of the lenses 5 days after surgery in five eyes of the carbomer treatment group and in four eyes of the phospholipid-liposomes treatment group.

No complications occurred during the entire 12-week duration of the study, as ensured by several follow-up examinations.

OBJECTIVE PARAMETERS

TEAR FILM BUT

Only descriptive statistical differences of the values of tear film BUT between both groups could be observed at the study's commencement. The average BUT of tears observed in group A was up to 13.2 seconds, while in group B, it was up to 11.2 seconds. This difference was not significant with respect to inference (Mann-Whitney U test: $z = -1.671$; $P>.05$; n.s.).

Figure 1 illustrates the varying developments of the BUT values during the study (GLM ANOVA with repeated measures; interaction [moderating effect] of time and group).

Observed was a constant increase of the average BUT in group B, beginning from the preoperative examination to the final follow-up examination. The average BUT in group A decreased considerably on day 1 after surgery and did not return to the preoperative baseline within the study.

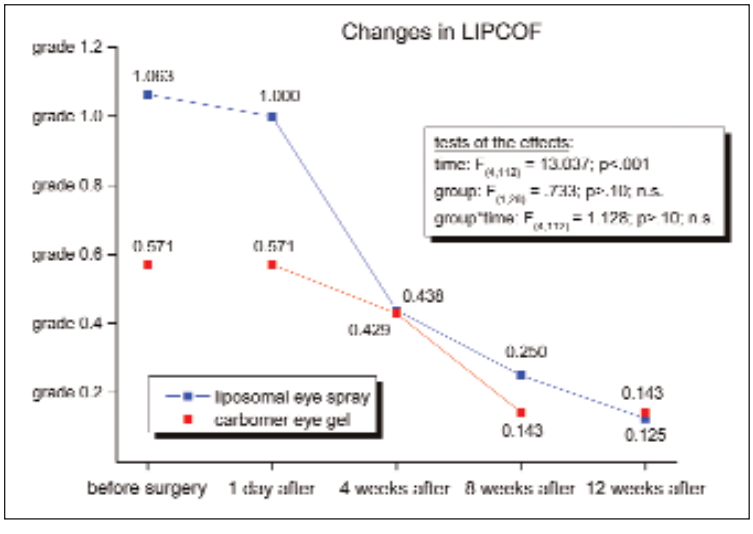

Figure 2. Changes in LIPCOF grades during the course of the study.

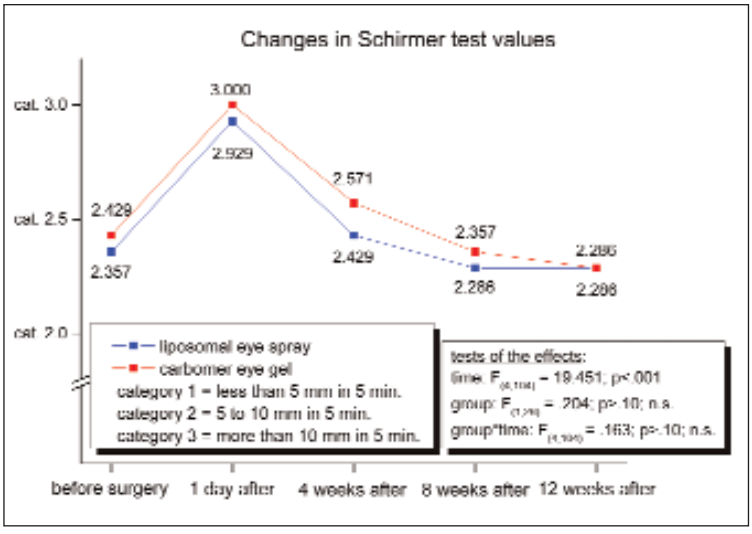

Figure 3. Changes in Schirmer test values during the course of the study.

LID-PARALLEL CONJUNCTIVAL FOLDS (LIPCOF)

The groups did not differ considerably in the grade of LIPCOF at the beginning of the study (Mann-Whitney U test: z = -1.215; P>.05; n.s.). The grade in group A amounted to 0.57 on average, while it was 1.06 in group B.

Both groups displayed a significant improvement of the grade during the time of the study (GLM ANOVA with a repeated measured time factor: $F_{(4,112)}$ = 13.037; P<.001). Therefore, the average grade in group B decreased to .938 grades, while it declined only .571 grades in group A.

The average grade showed a similar level in both groups after 12 weeks. Even though the improvement in group B turned out to be greater descriptively, it could not be found inferentially that both groups did differ significantly in the study (GLM ANOVA with repeated measures; interaction of time and group: $F_{(4,112)}$ = 1.128; P>.10; n.s.).

By 4 weeks after treating with the liposomal eye spray, no eye from group B still had a grade of 2 or worse. Also, after 8 weeks, the eyes of group A showed a lower level of LIPCOF than grade 2.

Figure 2 illustrates the improvement of the LIPCOF of both groups.

SCHIRMER I VALUE

Both groups showed the same mean values of about 9.5 mm within 5 minutes before surgery (Mann-Whitney U test: z = -.788; P>.100; n.s.) and did not vary in the values of priori.

One day after the surgery, a considerable increase of the values was ascertainable in both groups to an equal extent (GLM ANOVA with repeated measured time factor: F [4,104] = 19.451; P<.001; significance of all higher-order contrasts for the factor time), namely an increase of the mean value of 2.86 mm. In the course of the study, the values of the Schirmer test results returned to the base level, approximately.

Figure 3 depicts the changes of the values of the Schirmer test results in both groups.

VISUAL ACUITY

Neither group showed a change in uncorrected visual acuity 1 day after surgery. The eyes had an uncorrected visual acuity of approximately 20/50, on average.

However, improvements in the average uncorrected visual acuity varied widely between the groups during the course of the study, as illustrated in Figure 4.

Four weeks after surgery, group B, treated with the liposomal eye spray, showed an uncorrected visual acuity of about 20/160 on average, while group A still had an average uncorrected visual acuity of almost 20/100.

In week 8, the average uncorrected visual acuity of group A increasingly conformed to the value of group B. Nevertheless, a difference of 0.052 existed between

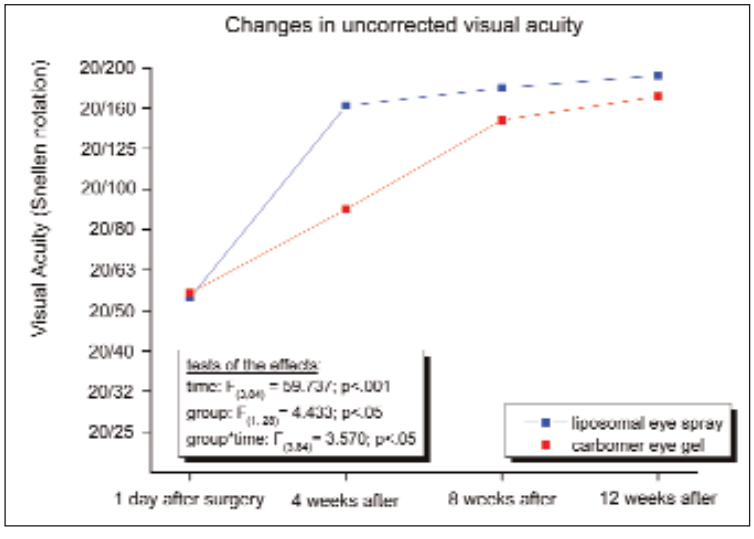

Figure 4. Changes in uncorrected visual acuity during the course of the study.

both groups as expressed in the LogMAR stabilized scale. Thus, a significant main effect of condition, or rather group membership, could be ascertained for the entire duration of the study; i.e., the eyes of group B treated with the liposomal eye spray had a better average uncorrected visual acuity (group effect: F (1,28) = 4.433; P<.05).

EXAMINATION OF THE LID MARGIN

The groups did not differ in their number of noticeable problems of the lid margins before surgery (Mann-Whitney U test: z = -.301; P>.100; n.s.), all patients displayed the the same number of symptoms.

There was a considerable increase in the number of symptoms 1 day after surgery in both groups (significant time factor: F (4,108) = 22.424; P<.001; significance of all higher-order contrasts of the time factor).

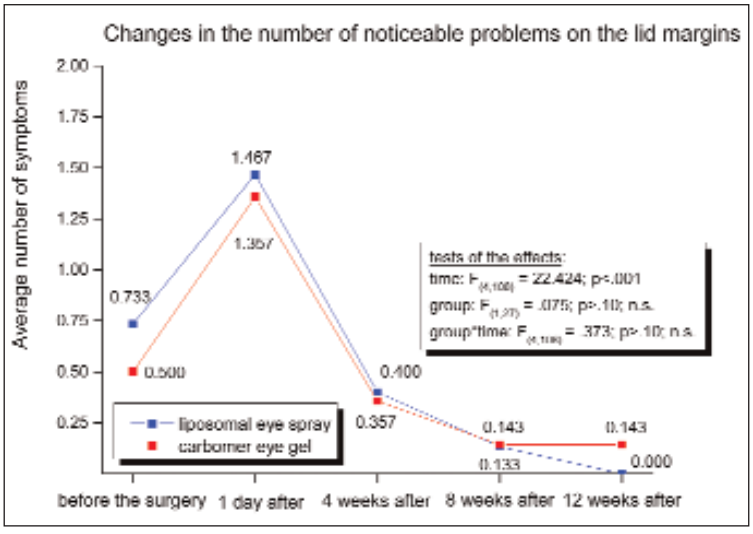

Figure 5. Changes in the number of noticeable problems on the lid margins in course of the study.

Four weeks after surgery, the average number of symptoms decreased again in both groups: 45.4% in group B and 28.6% in group A.

The number of symptoms decreased to a minimum during the following weeks. Group B, treated with the liposomal eye spray, achieved a reduction of 100%, which means that the lid margins were free of symptoms. Group A, treated with the carbomer eye gel, had a decrease in the average number of symptoms by 72.4%.

While both groups did differ descriptively, a significant inferential difference could not be found (interaction of time and group: F (4,108) = .373; P>.10; n.s.).

Figure 5 shows the improvements in the average number of symptoms of both groups.

REMOVAL OF THE THERAPEUTIC CONTACT LENS

The therapeutic contact lens was removed after 3 days in 15 eyes of group A and in 16 eyes of group B.

In the remaining eyes, there was a replacement of the therapeutic contact lens and a final removal after 5 days in five eyes of group A treated with the carbomer eye gel and in four eyes in group B treated with the liposomal eye spray.

SUBJECTIVE PARAMETERS

DRY EYE SYMPTOMS

There were no significant differences between the groups observed in the number of dry eye symptoms suffered (t test for independent/unpaired samples: T = 1.082; df = 31: P>.100). The most common symptoms described by the patients were tenderness (59%), dryness (48.7%), and fatigue (43.6%).

Also, 67.6% of all the patients reported that they suffered from the dry eye symptoms for a period of 1 to 5 years.

RELIEF OF SYMPTOMS

During the study, typical discomfort was relieved after application of either the carbomer eye gel or the liposomal eye spray. However, it was reported that the liposomal eye spray produced more relief than the carbomer eye gel. Figure 6 illustrates the progression of the reported relief.

RATING OF THE EFFICACY

The answer to the question, "How do you judge the effect of the preparation?" turned out to be different within 1 day after surgery. The patients were asked to grade the efficacy of the respective product according to German school grades, with "1" being "very good" and a "6" being "unsatisfactory."

One day after surgery, the average grade in group A was 3.57, and in group B, it was 2.67.

Illustrated in Figure 7, the initial difference of the average grade between both groups stabilized (GLM ANOVA with repeated measures: group effect: F (1,27) = 14.106; P<.001), although the grading of the efficacy improved in both groups in the course of the study (time factor: F (6,162) = 19.212; P<.001; interaction of time and group: F (6,162) = .579; P>.100; n.s.).

The grading of the efficacy highly correlated with the

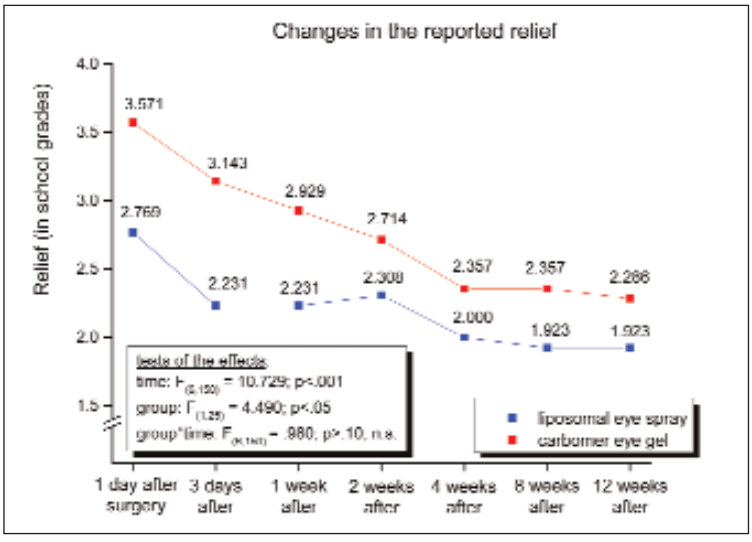

Figure 6. Changes in the reported relief during the course of the study (in school grades).

reported relief of symptoms (significant correlation between the measured comprising values greater than .50).

RATING THE TOLERABILITY

Also, the grading of the tolerability tended to result in superior grades in group B just 1 day after surgery. The average grade in group A was 3.07, whereas it was 2.29 in group B.

Though the difference between both groups decreased over the course of the study, it remained stable within 12 weeks of treatment (GLM ANOVA with repeated measures: (group effect: F (1,26) = 7.649; P<.01), regardless of the considerable improvement in grades (time factor: F (6,156) = 9.966; P<.001; interaction of time and group: F (6,156) = .166; P>.100; n.s.).

Figure 8 illustrates the changes in the average grading of the tolerability.

PREOPERATIVE PAIN SCORE

The maximal average pain score was 4.7 in the carbomer treatment group and 4.4 in the phospholipid-liposomes treatment group. The average maximal pain score in both groups was between day 1 and day 3 after surgery.

DISCUSSION

While the reported appearance of dry eye symptoms before surgery may have been due to the wearing of contact lenses,[14] the discomfort in the early postoperative phase may have been caused by the refractive surgery.

In this study, we used the fellow eye to compare the efficacy of the treatment with both artificial tear products, as it has proved valuable in other trials,[15,16] especially in comparing different treatments of dry eyes.[17-20] However, this study design may make it difficult for the patients to differentiate accurately between both eyes, for example, to grade the discomfort or rather the efficacy and tolerability of the two used tear products. It is probably only such a design that allows us to compare the objective changes during the treatment period in the specific individuals.

Even though there is a low incidence of pain after Epi-LASEK, all patients complain about initial postoperative pain to a greater or lesser extent. Thus, it is interesting that the use of the liposomal eye spray seems to reduce the postoperative pain compared to the use of the carbomer eye gel.

We suggest that this effect may be due to a persistent stabilization of the tear film, as evidenced most notably in the increased tear film BUT, the faster recovery of LIPCOF grades, and the faster improvement of uncorrected visual acuity. Although dry eye after refractive surgery cannot be equated with the usual dry eye syndrome one-to-one, the results are in line with the results of previous studies, such as when Lee et al[21] reported on the supremacy of the treatment with phospholipid-liposomes, especially in evaporative dry eye associated with chronic blepharitis.

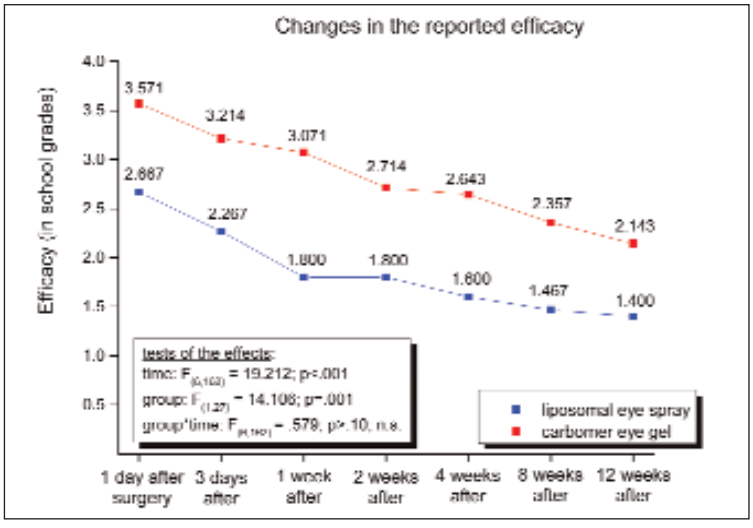

Figure 7. Changes in grading of efficacy during the course of the study (in school grades).

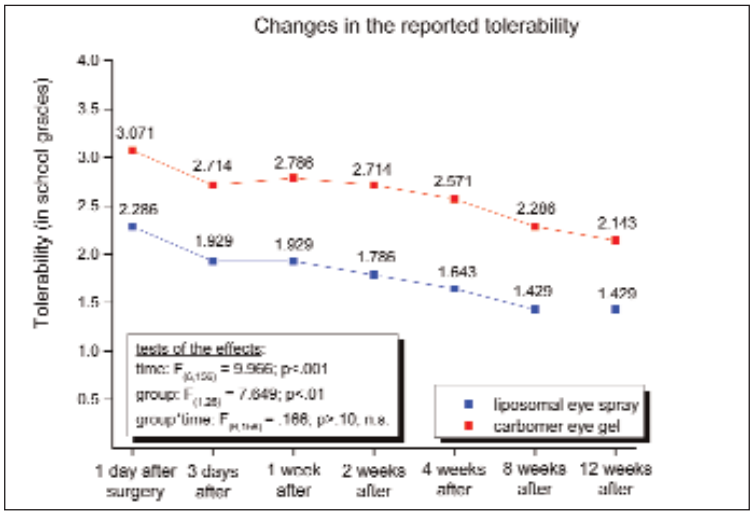

Figure 8. Changes in grading of tolerability during the course of the study (in school grades).

The current physical-chemical model of the tear film lipid layer suggests that it consists of two phases: a thin polar layer, predominantly consisting of phospholipids, adjacent to the aqueous-mucin phase and a relatively thick outer layer, containing nonpolar lipids (eg, wax esters, sterol esters, triglycerides) associated with both the polar phase and the air interface.[22]

The barrier function to evaporation that the lipid layer provides is ultimately determined by its outer nonpolar lipid phase, but the functional integrity of this phase is in turn dependent on the stability of the underlying polar lipids that act as a surfactant to allow interface with aqueous, explaining why the evaporation rate does not explicitly correlate with lipid layer thickness. The polar phase of the lipid layer owes its surfactant properties to its amphipathic phospholipids, which facilitate making contact with both aqueous and nonpolar lipids.[23]

While the carbomer eye gel simply provides lubrication on the ocular surface, the liposomal eye spray is thought to have quite a different mode of action. Liposomes are vesicles and consist of one or more concentric phospholipid bilayers separated by aqueous compartments. The phospholipid-liposomes are sprayed onto the closed eyelids, wherefrom a certain part of them will reach the lid margin and mix with the reservoir of meibomian lipid secretions. The supplemented phospholipids will stabilize the lipid layer when spreading over the tear film together with the meibomian secretions.[24]

Patel et al[25] suggested that the poorer-quality lipid layer may predispose the cornea to symptoms of dry eye after refractive surgery, because the quality of the lipid layer within postoperative LASIK patients was significantly different from the control group. A low-quality lipid layer is generally associated with lessened stability and an increased tear-evaporation rate.

It is well accepted that reduced corneal sensitivity may suppress the efficiency and ability of the natural blink response to reconstruct the tear film. Therefore, a surgically induced decrease in corneal sensitivity may disrupt the balance of the tear film by causing inadequate blinking.

Because meibomian gland secretion is controlled by eyelid blinking, meibomian gland dysfunction can be caused by a reduced blink rate after refractive surgery. Corneal denervation by refractive surgery not only disrupts the reflex controlling of the lacrimal gland but also disrupts the reflex controlling the meibomian gland and eyelid blinking, the latter of which indirectly controls meibomian secretions.[26]

The tear-film deposition is thought to be a two-step process: in the first step, as the upper lid rises, it pulls a layer of tear film over the cornea by capillary action. In the second step, it is proposed that the tear film is considerably thickened by an upward drift of the superficial lipid layer, which drags up aqueous tears with it.[27]

The changes of the surface tension during the spreading of the lipid layer caused a flow of tear fluid from the tear menisci into the tear film on the ocular surface (Marangoni effect).[28]

The surface tension of aqueous tears is highly important for normal tear function, because it determines the wetting power of the tears on the corneal surface and is involved in determining the balance of forces between the tear film and the meniscal strips. Consequently, the surface tension helps to control the thickness of the tear film immediately after a blink. The stability and lifetime before break-up of the tear film are related to the total surface free energy of the system. Dry eye tears are less surface-active (ie, their surface tension is increased). The greatest effect in lowering the surface tension is shown by phosphatidylcholine,[29] which is the main component of the phospholipid-liposomes in the liposomal eye spray.

If the blinking frequency is reduced, the quality of the lipid layer may be affected, which results in a reduced flow of tear fluid from the tear menisci into the tear film.

It has been estimated that the superior and inferior tear menisci hold 75% to 90% of the total volume of tear fluid,[30] so that supporting the natural lipid layer by supplementation of phospholipids should be sufficient to

provide for adequate moistening of the ocular surface with the natural tear fluid.

Since LASEK alters ocular surface hemostasis and reduces corneal sensation in the early postoperative period, subjective symptoms of dry eye are reported primarily during the first 2 months after surgery.[31] The corneal nerves are disrupted during LASEK surgery, and the procedure results in a significant reduction of corneal sensation. During the first month after surgery, the depressed corneal sensation improves and subsequently goes back to preoperative values.[32]

It has been reported that recovery of corneal sensitivity is completed 3 to 6 months after LASEK surgery.[33] The recovery time needed after Epi-LASIK will be comparable or even shorter, according to our experience at present.

Apart from that, it has been reported that liposomes support wound healing,[34,35] so that there may also be a positive effect on wound healing in the cornea after refractive surgery. This hypothesis seems to be confirmed by the slightly differing lengths of removal of the therapeutic contact lenses, which tended to be earlier in the eyes treated with the phospholipid-liposomes, as well as the faster recovery of the LIPCOF grades. However, further studies are required to establish the assumed effect of the phospholipid-liposomes on wound healing in the cornea, in which higher falling numbers have to be evaluated.

A persistent dry eye after refractive surgery may often be attributed to a nonrecognized lipid tear deficiency,[36] since lipid deficiencies are determined most frequently in about 78% of the patients in general.[37]

CONCLUSION

An initial treatment with a suitable tear product for at least 12 weeks after refractive surgery and—if required—an additional period depending on each individual case is useful.

While both tested tear products proved their applicability for the treatment of dry eye after a refractive surgery procedure in general, the treatment with phospholipid-liposomes proved to be superior in many respects, especially with regard to patient satisfaction. ■

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