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Title

Dry-eye and inflammation of the ocular surface after cataract surgery: study on the effectiveness of a tear substitute based on trehalose/hyaluronic acid versus hyaluronic acid in the resolution of signs and symptoms

Running Head

The role of trehalose in the management of inflammation after cataract surgery

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Keywords

Cataract surgery, dry eye, trehalose/sodium hyaluronate/carbomer eye drops, post-operative

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ABSTRACT**Purpose**

To compare the effect of trehalose 3%/hyaluronic-acid 0.15% versus hyaluronic-acid 0.15% eye-drops in reducing ocular surface inflammation after cataract surgery.

Setting

Perugia, Italy

Design

Randomised, prospective study

Methods

Patients with healthy ocular surface were enrolled. Tear break-up-time (TBUT), Schirmer test, corneal fluorescein staining (CFS), Ocular Surface Disease Index (OSDI) and confocal microscopy (IVCM) were performed preoperatively and at 1, 4 and 8 months after surgery. Patients were randomly assigned to receive either trehalose 3%/hyaluronic-acid 0.15% eye-drops (Group A), hyaluronic-acid 0.15% eye-drops (Group B) or no treatment (Group C).

Results

Ninety-eight patients were randomised, 33 in Group A, 33 in Group B, 32 in Group C.

Schirmer test increased at 1-month follow-up in Group A and unchanged in Group B and C. TBUT and CFS increased at 1-month follow-up in Group A and after 8 months in Group B and C. OSDI score decreased at 1-month follow-up in Group A and at in Group B and C.

IVCM showed a reduction in the number of nerve fibres of the subbasal nerve plexus at 1 month in all groups and progressively increased to preoperative levels at 4 months in GroupA, and at 8 months in GroupB and C.

Tortuosity and reflectivity of subbasal plexus progressively decreased to become significant at 4month-follow-up in GroupA while increased at 1month-follow-up becoming normal at 8month-follow-up in GroupB and C. Langerhans cells and activated stromal keratocytes were higher in GroupB and C throughout the follow-up with a significantly lower density of hyper-reflective stromal cells in GroupA.

Conclusions

Cataract surgery induces persistent inflammation of the ocular surface. Trehalose3%/hyaluronic-acid0.15% eye-drops are effective in reducing inflammation and signs and symptoms of dry eye.

INTRODUCTION

Cataract surgery is one of the most common procedures performed worldwide with excellent clinical results, a rapid functional recovery and a low risk of complications.¹ However, it is known that surgery can cause transient dry eye or induce a worsening of pre-existing dry eye, even in healthy patients.^{2,3} After surgery many patients complain of ocular discomfort, sometimes significant, whilst a qualitative and quantitative alteration of the tear film is frequently observed. The return to the normal tear secretion levels can be slow, and it may take up to several months to return to preoperative levels.² It is estimated that in about 10% of patients, this surgery can trigger a vicious cycle of chronic dry-eye disease (DED).⁴ Following cataract surgery, an inflammatory state is common and has been demonstrated by the presence of pro-inflammatory cytokines and chemokines in the tear film, corneal nerve alterations and an increase in subbasal dendritic cells.⁵ These alterations may be present for weeks following surgery and have been linked to the alteration of tear secretion.⁶

Due to these potential complications, patients are often advised to use tear substitutes following cataract surgery. There are a large number of products commercially available as tear substitutes

and some clinical studies have evaluated their effectiveness in preventing or treating DED after cataract surgery.^{7–13} However, at present there is no standardised strategy for the postoperative management of the ocular surface following cataract surgery.

A therapeutic of particular interest for postoperative dry eye is a fixed trehalose and hyaluronic acid (HA) tear substitutes.

Of particular interest for postoperative dry eye is a fixed trehalose and hyaluronic acid (HA) tear substitutes. HA has been shown to be useful in dry eye patients for its ability to form a viscoelastic solution in water, which lubricates the ocular surface, keeping it hydrated and protecting it from mechanical damage.¹⁴ Trehalose's known properties include stabilizing the bilipid membranes and labile proteins against desiccation, and it has a role in protecting cells and their components from oxidative damage.^{15,16} To our knowledge, a prospective study evaluating the efficacy of a combination of these two molecules for reducing signs and symptoms of dry eye and corneal inflammation after cataract surgery, has not been performed”

MATERIAL AND METHODS

Study design

This study is a prospective, randomised, open-label, comparative study in patients undergoing unilateral cataract surgery and intra-ocular lens implantation. The study was conducted in accordance with Good Clinical Practices, the Declaration of Helsinki and was approved by local Ethics Committees (CEAS Umbria, Prot. n. 3411/19). Cataract surgeries were performed at the ophthalmology section of the Department of Medicine and Surgery, University of Perugia. All patients gave their written informed consent to the surgery and to their participation in the study.

Aim of the study

The aim of this study was to compare the effect of trehalose 3%/HA 0.15% combination eye drops *versus* HA 0.15% eye drops in reducing signs and symptoms of corneo-conjunctival inflammation, ocular discomfort and in improving tear-film stability after cataract surgery.

Study population

Patients eligible for inclusion were aged ≥ 18 years, with a healthy ocular surface, subclinical or mild DED¹⁷ who only used artificial tears occasionally and were undergoing unilateral cataract surgery and intra-ocular lens implantation. The main exclusion criteria were as follows: previous ocular surgery; a history of trauma or ocular inflammation; severe DED; any corneal pathologies; the use of contact lenses; anatomical or functional eyelid abnormalities; ocular hypertension or glaucoma; the concurrent administration of topical eye drops other than those included in the study protocol and use of eye drops for DED within 1 week before the screening visit and before surgery; any systemic drug that may contribute to DED, such as antihistamines, decongestants, antidepressants and spasmolytics. The administration of systemic corticosteroids or non-steroidal anti-inflammatory drugs was not allowed during the study. Patients experiencing any surgery related complications such as posterior capsule rupture, vitreous loss or postoperative anterior uveitis were withdrawn from the study.

Assessments

Prior to inclusion in the study the following assessments were carried out: tear break-up time (TBUT); Schirmer test; corneal fluorescein staining (CFS) (based on Oxford 0-5 grading scale); Ocular Surface Disease Index (OSDI) and corneo-conjunctival confocal microscopy.¹⁸ These examinations were also performed at the follow-up visits: Month 1, Month 4 and Month 8 after surgery.

In vivo confocal microscopic (IVCM) image acquisition and analysis was performed in the 6 mm central cornea and in the upper temporal area of the bulbar conjunctiva, near the surgical access by an expert examiner (GDL). The method used has already been described by the authors.^{19,20}

Other preoperative clinical evaluations were performed as part of the standard cataract surgery procedure.

Surgical procedures

On the day of surgery, eligible patients were randomly assigned to receive either trehalose 3%/HA 0.15% eye drops (Group A [study group]), HA 0.15% eye drops (Group B [Lubricant]) or no treatment (Group C [control group]) using a computer-generated randomisation list. The surgery was performed by one experienced surgeon (C.C.) who was blinded to the group assignments. The patients' pupils were dilated with a phenylephrine and tropicamide insert (Mydriaser®[®], Laboratoires Théa, Clermont Ferrand, France) about 60 minutes before surgery. Each procedure was performed under topical anaesthesia (lidocaine 4%) and standard phacoemulsification was carried out through an incision created 1 mm behind the sclero-corneal limbus, with the technique already described by the authors.²¹ Once discharged, all patients were treated with ofloxacin eye drops (Oftaquix®, Santen Italy) four times a day for the first week, chloramphenicol 0.25% and dexamethasone 0.13% eye drops (Betabioptal®, Laboratoires Théa) four times a day for two weeks, and Bromfenac 0.9% eye drops (Yellox®, Bausch & Lomb IOM S.p.A.) twice a day for two weeks. The preservative (Benzalkonium chloride 0.05 mg in 1 ml) was in the ofloxacin and bromfenac eye drops.

Patients in Group A received a fixed combination of unpreserved trehalose 3%/HA 0.15% eye drops (Thealoz Duo®, Laboratoires Théa) twice a day for 60 days, and patients in Group B received unpreserved HA 0.15% eye drops (Hyabak®, Laboratoires Théa) twice a day for 60 days. Patients in Group C did not receive any tear substitute during the study.

Statistical analysis

Statistical analyses were performed using SAS software (version 9.2) (SAS Institute). Assuming that the ratio between Group A, Group B and Group C is 1:1:1, with a variability of 10% between groups, the power of the study is estimated to be around 90% with a total sample of 90 patients.

Quantitative variables were expressed as mean $\pm$ SD. The Shapiro–Wilk test was used to test whether data were distributed normally. Given the results of this test we used the Kruskal–Wallis Test for group comparison. The Friedman test was used for longitudinal analysis within the same group of patients. The statistical significance was set with $p < 0.05$.

RESULTS

Ninety-eight (98) patients were enrolled (98 eyes) in the study and were randomised into three groups (33 patients in Group A, 33 in Group B and 32 in Group C). Ten patients left the study before completing the follow-up due to intraoperative complications or systemic disease (2 patients in Group A, 5 in Group B and 3 in Group C). Similar demographic and baseline values were observed between groups (Table 1), with no statistically significant differences observed. The mean age of patients was 67.7 ± 6.9 , whilst the percentage of male patients was 51.0% of the total study population. In the groups we witnessed a marked improvement in visual acuity after the surgery which remained stable throughout the follow-up, with no statistically significant differences between the three groups (Table 2)

There was a statistically significant increase in the Schirmer test at Month 1 from baseline in Group A (7.13 ± 3.17 mm to 8.47 ± 2.37 mm [$p < 0.05$]) and Group C (6.76 ± 3.46 mm to 8.86 ± 3.48 mm [$p < 0.05$]), whilst there was no observed changes in Group B. Between group comparisons showed that from Month 4, significantly higher values were recorded for Group A *versus* groups B and C (Table 3). In all three groups there was a progressive increase in TBUT values, and in Group A this increase was statistically significant at Month 1 from baseline (4.90 ± 2.23 sec to 6.27 ± 1.96 sec [$p < 0.05$]). In groups B and C, the difference between pre and postoperative values became statistically significant at Month 8 (Group B: 5.07 ± 2.77 sec to 6.04 ± 2.15 sec [$p < 0.05$] and Group C: 5.46 ± 1.79 sec to 6.23 ± 1.50 sec [$p < 0.05$]). Between group comparisons showed a statistically significant difference in TBUT at Month 4 and Month 8 for Group A *versus* groups B and C (Table 4).

A progressive improvement of ocular surface epithelial damage was observed in all groups at each follow-up visit. In Group A, a statistically significant difference at Month 1 from baseline was observed, whilst a statistically significant difference was observed at Month 8 in Group B (1.05 ± 0.56 to 0.62 ± 0.50 [$p < 0.05$]) and in Group C (1.21 ± 0.83 to 0.86 ± 0.36 [$p < 0.05$]). Between

group comparisons showed a statistically significant difference in ocular surface epithelial damage from Month 4 for Group A *versus* groups B and C (Table 5). The OSDI score decreased in all three groups from baseline, with the difference being statistically significant at Month 1 in Group A (44.51 ± 27.42 to 23.60 ± 18.86 [$p < 0.05$]), and at Month 4 in Group B (38.72 ± 18.91 to 22.77 ± 14.63 [$p < 0.05$]) and Group C (35.67 ± 20.78 to 21.50 ± 14.44 [$p < 0.05$]). Between group comparisons showed a statistically significant difference in the OSDI score from Month 1 for Group A *versus* Groups B and C (Table 6).

A significant reduction in the density of the intermediate corneal epithelium was observed at Month 1 compared to the basal corneal epithelium in Group A and Group C. In Group A the corneal epithelial cell density reached baseline levels at Month 4 and was significantly higher than baseline levels at Month 8. In Group B there were no significant changes during the study and in Group C corneal epithelial cell density reached baseline levels at Month 4 (Table 7).

Analysis of the subbasal nerve plexus showed a significant reduction in the number of subbasal nerve fibres at Month 1 compared to basal nerve fibres in all groups. During the subsequent follow-ups, the subbasal nerve fibres progressively increased, returning to preoperative levels at Month 4 in Group A, and at Month 8 in groups B and C (Table 8). Regarding the tortuosity of these nerve fibres, in Group B there were no observed changes during the follow-up visits compared to basal and in Group C a significant increase was observed at Month 1, returning to basal values at Month 8. However, in Group A we recorded a progressive reduction in the tortuosity of the nerve fibres of the subbasal plexus, whose difference from basal was significant from Month 4. The comparison between the three groups showed that from Month 4 the tortuosity of nerve fibres in Group A was significantly lower than in groups B and C ($p < 0.05$) (Table 9). These results were similar for the reflectivity of subbasal nerve fibres in groups B and C, with a significant increase at Month 1 compared to the basal value, with return to preoperative values at Month 8. In Group A, we observed a progressive reduction of reflectivity during the study with the difference to baseline values becoming significant from Month 4. In addition, between group comparisons showed that

from Month 1, the reflectivity of nerve fibres in Group A patients was significantly lower than in groups B and C (Table 10).

The analysis of the number of Langerhans cells at subbasal nerve plexus level showed in all three groups a significant increase compared to the basal value at Month 1 after surgery. At Month 8, the number of Langerhans cells at subbasal nerve plexus level was higher in groups B and C compared to baseline levels and was statistically significant. In Group A, these values remained similar to baseline at Month 4, and were lower than baseline values at Month 8. Furthermore, the comparison between groups showed a significantly lower number of Langerhans cells in Group A compared to groups B and C at all postoperative follow-up visits (Table 11).

The analysis of the degree of activation of stromal keratocytes in Group A remained similar to baseline at follow-up visits, while in groups B and C, an increase in the degree of activation compared to the baseline value at Month 1 was observed. This value returned to baseline levels at Month 4 and Month 8. A comparison between groups showed that there were no differences between the Group B and Group C group throughout the study, while the patients in Group A showed a significantly lower density of hyper-reflective stromal cells compared to Groups B and C from Month 1 (Table 12).

The evaluation of leukocyte recruitment at the conjunctival site was qualitative. Specifically, we observed an increase of conjunctival leukocytes in intra- and extra-vascular leukocytes in all three groups at Month 1, which gradually decreased in the subsequent follow-up visits to the post-surgical inflammatory state of the ocular surface.

The postoperative treatment was well tolerated, with no patients reporting an adverse event.

DISCUSSION

In this prospective, randomised study, we observed that uncomplicated cataract surgery induces an alteration of tear secretion and changes to the cornea. In particular we observed the early appearance of signs and symptoms of dry eye and, at the corneal level, the appearance of cells

indicating an inflammatory state and an alteration of the subbasal nerve layer. These alterations were still present months after surgery. In our study, the administration of a HA-based tear substitute had a mild efficacy, whilst the use of a trehalose/HA tear substitute was associated with a significant improvement in symptoms related to dry eye and contributed to fast improvement of corneal parameters.

In recent years, a lot of attention has been paid to the postoperative symptoms of dry eye that a large number of patients develop after cataract surgery. In an attempt to correct tear film alteration and improve patient comfort, several topical strategies have been proposed including HA, diquafosol, rebamipid and cyclosporine that have a partial effect in reducing the incidence of postoperative dry eye.^{9,12,13,17,22}

Our study showed that administration of trehalose/HA tear substitute resulted in an increase in secretion and a better stability of the tear film, as demonstrated by results of the Schirmer test and TBUT, where a statistically significant increase from baseline was observed from Month 1, and between group comparison showed that from Month 4 increases were significantly higher with trehalose/HA compared to HA alone or with no eye drop substitutes. The improvement of the tear film using trehalose/HA was accompanied by an improvement in corneal epithelial trophism, as demonstrated by corneal staining values and confocal microscopy. These results confirm what has been observed in a similar study, where a trehalose/HA tear substitute following cataract surgery proved more effective than HA alone in treating ocular irritation and tear film alterations.¹⁰

In our study, the addition of trehalose provided a greater protective effect on the corneal epithelium as indicated by corneal fluorescein staining scores, and patients treated with trehalose/HA also showed a faster improvement in dry eye associated symptoms compared to HA alone or no treatment based on the OSDI score. This is highlighted by a statistically significant improvement from baseline being observed from Month 1 using trehalose/HA compared to Month 4 when patients used HA alone or no treatment. In addition, the recorded values in Group A were significantly lower than those in the other two groups throughout the study. This agrees with the

literature and could be due to trehalose ability to protect from the denaturation of cellular membrane phospholipids, to stabilize cellular proteins and protect these structures from desiccation and oxidative stress.^{15,23,24}

It has been documented that corneal and cataract surgery causes direct damage to the corneal nerve fibres due to the full thickness corneal incision at the site of the wound with nerve degeneration and subsequently reduced subbasal nerve density.^{25,26} However, as nerve changes are present in all sectors of the central area of the cornea, there are other contributing factors as topical medications containing epitheliotoxic substances, microscope light and phacoemulsification. In this study, the subepithelial nervous plexus in all three groups showed a significant reduction at Month 1, postoperatively. This potentially explains the alterations of the tear film and the consequent postoperative discomfort. Corneal innervation is critical for the correct secretion of the tear film because it provides neural feedback for regulation of the secretion of the tear film, and for corneal trophism because it has a trophic effect in the maintenance of corneal structure and function.²⁶

A postoperative significant increase in signs of inflammation is known from the literature, including the presence in the tear film of prostaglandins, leukotrienes and inflammatory cytokines, oxygen free radicals and proteolytic enzymes, and an increase in subbasal dendritic cells in all sectors of the central area of the cornea which can be considered a sign of inflammation due to the release of inflammatory mediators.^{5,6}

Uncomplicated cataract surgery induces a postoperative significant increase in signs of inflammation as the presence in the tear film of prostaglandins, leukotrienes and inflammatory cytokines, oxygen free radicals and proteolytic enzymes, and a significant increase in inflammatory cells in all sectors of the central area of the cornea, a reduction in nerve cells in the subbasal cornea with slow recovery to preoperative levels.^{5,6} The administration of a tear substitute containing trehalose/HA had a direct effect on all these parameters, in particular on the number of Langerhans cells and the state of activation of keratocytes. We also observed an effect on regrowth rate of the subepithelial nervous plexus, and on the number and morphology of the fibres. This was

accompanied by a similar improvement in signs and symptoms of dry eye. Therefore, the increased integrity of the lacrimal film and of the corneal epithelium can also be a consequence of a better condition of the subbasal nerve plexus fibres, whose damage causes a decrease in quality of tear secretion, corneal sensitivity, an alteration in the structure and function of epithelial cells, increased epithelial permeability, a decrease in migration and reduced cell mitosis.²⁷

Our study seems to indicate that postoperative treatment with a trehalose/HA based tear substitute promotes a faster recovery from the signs and symptoms of inflammation of corneal fibres: this would be of particular importance in patients with lower preoperative nerve fibre density and length, for example, in patients with dry eye or diabetes.²⁸

The main limitation of this study was that the phacoemulsification time, and the time of each single surgical procedure was not studied in order to quantify the damage induced by the single surgical procedure. It would be of interest to correlate the involvement of the subbasal nerve plexus to other parameters, in particular the amount of ultrasound used and the duration of surgery. Moreover, the corneal sensitivity was not evaluated and the damage induced to the corneal endothelium was not studied. Another limitation of the paper can be linked to the relative low number of cases studied: we therefore believe it is appropriate to verify these data with a larger number of patients and our findings need to be confirmed by prospective studies with larger case series. Overall, these results show that cataract surgery induces widespread and persistent inflammation of the corneal-conjunctival surface, leading to dry eye associated signs and symptoms. These study results suggest that 3% trehalose/0.15% HA could be regarded as a useful tool in postoperative therapeutic management following cataract surgery.

WHAT WAS KNOWN

- After cataract surgery patients frequently develop symptoms of dry eye, mainly due to inflammation. Several topical eye drops, including hyaluronic acid, have been used in order to improve these symptoms with limited and slow improvement.
- Trehalose/hyaluronic acid eye drops have been already shown to be more effective than hyaluronic acid only in the resolution of signs and symptoms of dry eye after the phacoemulsification procedure.

WHAT THIS PAPER ADDS

- Trehalose has been confirmed to play an important role in the management of postoperative inflammation after cataract surgery
- Our study also indicates that postoperative treatment with a trehalose/HA eye drops promotes a faster recovery from the signs of inflammation of corneal fibres, specifically trophism of the subepithelial nervous plexus, number of Langerhans cells and the state of activation of keratocytes

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Synopsis

The use of trehalose 3%/hyaluronic-acid 0.15% eye-drops in the management of signs and symptoms related to the inflammation after cataract surgery with positive results.

Table 1

Demographic results

	Group A (N=33)	Group B (N=33)	Group C (N=32)	Total (N=98)
Age (mean±SD) (years)	65.4 ± 7.2	63.9 ± 4.6	65.7 ± 7.0	67.7 ± 6.9
Gender number (%)				
Male	17 (51.5)	19 (57.6)	14 (43.8)	50 (51.0)
Female	16 (48.5)	14 (42.4)	18 (56.2)	48 (49.0)

Group A: Trehalose/HA Group

Group B: HA Group

Group C: Control Group

Table 10

Subbasal nerve fibres reflexivity preoperatively and Month 1, Month 4 and Month 8 postoperatively

	Baseline	Month 1	Month 4	Month 8
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Group A	2.33 $\pm$ 0.71 ^{c,d}	2.23 $\pm$ 0.82	1.47 $\pm$ 0.57 ^{c,e,f}	1.13 $\pm$ 0.43 ^{d,g,h}
Group B	2.42 $\pm$ 0.59 ^a	2.73 $\pm$ 0.45 ^a	2.54 $\pm$ 0.51 ^e	2.38 $\pm$ 0.50 ^g
Group C	2.43 $\pm$ 0.84 ^b	2.93 $\pm$ 0.66 ^b	2.68 $\pm$ 0.72 ^f	2.46 $\pm$ 0.74 ^h

Group A: Trehalose/HA Group

Group B: HA Group

Group C: Control Group

a: $p < 0.05$

b: $p < 0.05$

c: $p < 0.05$

d: $p < 0.05$

e: $p < 0.05$

f: $p < 0.05$

g: $p < 0.05$

h: $p < 0.05$

Table 11

Number of Langerhans cells at subbasal nerve plexus preoperatively and Month 1, Month 4 and Month 8 postoperatively

	Baseline	Month 1	Month 4	Month 8
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Group A	0.23 $\pm$ 0.83 ^a	1.03 $\pm$ 0.67 ^a	0.30 $\pm$ 0.47	0.07 $\pm$ 0.25
Group B	0.19 $\pm$ 0.41 ^b	2.27 $\pm$ 0.61 ^b	1.62 $\pm$ 0.49	1.27 $\pm$ 0.54
Group C	0.21 $\pm$ 0.42 ^c	2.50 $\pm$ 1.11 ^c	1.93 $\pm$ 0.94	1.54 $\pm$ 0.64

Group A: Trehalose/HA Group

Group B: HA Group

Group C: Control Group

a: $p < 0.05$

b: $p < 0.05$

c: $p < 0.05$

Table 12

Degree of activation of stromal keratocytes preoperatively and Month 1, Month 4 and Month 8 postoperatively

	Baseline	Month 1	Month 4	Month 8
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Group A	2.13 $\pm$ 0.57	2.10 $\pm$ 0.55 ^{a,b}	1.17 $\pm$ 0.46 ^{c,d}	1.00 $\pm$ 0.00 ^{e,f}
Group B	2.23 $\pm$ 0.45	2.77 $\pm$ 0.42 ^a	2.35 $\pm$ 0.50 ^c	1.96 $\pm$ 0.52 ^e
Group C	2.14 $\pm$ 0.71	2.79 $\pm$ 0.42 ^b	2.32 $\pm$ 0.48 ^d	2.04 $\pm$ 0.64 ^f

Group A: Trehalose/HA Group

Group B: HA Group

Group C: Control Group

a: $p < 0.05$

b: $p < 0.05$

c: $p < 0.05$

d: $p < 0.05$

e: $p < 0.05$

f: $p < 0.05$

Table 2

Best Corrected Visual Acuity of the groups studied

	BCVA Preoperative	BCVA Month 1	BCVA Month 4	BCVA Month 8
Groups	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Group A	0.51 $\pm$ 0.23	1.00 $\pm$ 0.18	1.20 $\pm$ 0.22	1.20 $\pm$ 0.24
Group B	0.57 $\pm$ 0.21	1.00 $\pm$ 0.20	1.20 $\pm$ 0.23	1.20 $\pm$ 0.24
Group C	0.53 $\pm$ 0.24	1.00 $\pm$ 0.19	1.20 $\pm$ 0.22	1.20 $\pm$ 0.23

Group A: Trehalose/HA Group

Group B: HA Group

Group C: Control Group

BCVA: Best Corrected Visual Acuity

SD: Standard Deviation

Table 3

Schirmer Test preoperatively and Month 1, Month 4 and Month 8 postoperatively

	Baseline	Month 1	Month 4	Month 8
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Group A	7.13 $\pm$ 3.17 ^a	8.47 $\pm$ 2.37 ^a	9.37 $\pm$ 1.07 ^{c,d}	9.53 $\pm$ 1.33 ^{e,f}
Group B	7.81 $\pm$ 2.80	8.44 $\pm$ 2.24	8.12 $\pm$ 1.90 ^c	8.38 $\pm$ 1.42 ^e
Group C	6.76 $\pm$ 3.46 ^b	8.86 $\pm$ 3.48 ^b	8.50 $\pm$ 1.67 ^d	8.46 $\pm$ 1.67 ^f

Group A: Trehalose/HA Group

Group B: HA Group

Group C: Control Group

a: $p < 0.05$

b: $p < 0.05$

c: $p < 0.05$

d: $p < 0.05$

e: $p < 0.05$

f: $p < 0.05$

Table 4

TBUT preoperatively and Month 1, Month 4 and Month 8 postoperatively

	Baseline	Month 1	Month 4	Month 8
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Group A	4.90 $\pm$ 2.23 ^a	6.27 $\pm$ 1.96 ^a	8.20 $\pm$ 0.96 ^{d,e}	9.13 $\pm$ 1.33 ^{f,g}
Group B	5.46 $\pm$ 1.79 ^c	5.23 $\pm$ 2.18	5.69 $\pm$ 1.95 ^d	6.23 $\pm$ 1.50 ^{c,f}
Group C	5.07 $\pm$ 2.77 ^b	5.07 $\pm$ 2.19	5.54 $\pm$ 2.67 ^e	6.04 $\pm$ 2.15 ^{b,g}

TBUT: Tear Break-Up Time

Group A: Trehalose/HA Group

Group B: HA Group

Group C: Control Group

a: $p < 0.05$

b: $p < 0.05$

c: $p < 0.05$

d: $p < 0.05$

e: $p < 0.05$

f: $p < 0.05$

g: $p < 0.05$

Table 5

Corneal fluorescein staining scores preoperatively and Month 1, Month 4 and Month 8 postoperatively

	Baseline	Month 1	Month 4	Month 8
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Group A	1.33 $\pm$ 0.84 ^a	0.87 $\pm$ 0.63 ^a	0.33 $\pm$ 0.48 ^{d,e}	0.13 $\pm$ 0.43 ^{f,g}
Group B	1.05 $\pm$ 0.56 ^b	1.15 $\pm$ 0.37	1.08 $\pm$ 0.27 ^d	0.62 $\pm$ 0.50 ^{b,f}
Group C	1.21 $\pm$ 0.83 ^c	1.11 $\pm$ 0.57	1.04 $\pm$ 0.51 ^e	0.86 $\pm$ 0.36 ^{c,g}

Group A: Trehalose/HA Group

Group B: HA Group

Group C: Control Group

a: $p < 0.05$

b: $p < 0.05$

c: $p < 0.05$

d: $p < 0.05$

e: $p < 0.05$

f: $p < 0.05$

g: $p < 0.05$

Table 6

OSDI scores preoperatively and Month 1, Month 4 and Month 8 postoperatively

	Baseline	Month 1	Month 4	Month 8
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Group A	44.51 ± 27.42 ^a	23.60 ± 18.86 ^{a,b,c}	11.88 ± 7.53	7.89 ± 4.54
Group B	38.72 ± 18.91 ^b	30.06 ± 18.99	22.77 ± 14.63 ^b	19.45 ± 11.73
Group C	35.67 ± 20.78 ^c	27.36 ± 17.52	21.50 ± 14.44 ^c	21.46 ± 14.57

OSDI: Ocular Surface Disease Index

Group A: Trehalose/HA Group

Group B: HA Group

Group C: Control Group

a: p<0.05

b: p<0.05

c: p<0.05

Table 7

Density of the intermediate corneal epithelium preoperatively and Month 1, Month 4 and Month 8 postoperatively

	Baseline	Month 1	Month 4	Month 8
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Group A	6523.15 $\pm$ 653.84 ^{a,c}	6359.31 $\pm$ 985.82 ^a	6477.85 $\pm$ 896.13	6667.08 $\pm$ 921.47 ^c
Group B	6308.42 $\pm$ 785.58	6183.29 $\pm$ 762.14	6258.71 $\pm$ 714.81	6295.33 $\pm$ 724.68
Group C	6294.96 $\pm$ 716.73 ^b	6037.42 $\pm$ 972.23 ^b	6111.65 $\pm$ 802.60	6130.19 $\pm$ 785.78

Group A: Trehalose/HA Group

Group B: HA Group

Group C: Control Group

a: $p < 0.05$

b: $p < 0.05$

c: $p < 0.05$

Table 8

Number of subbasal nerve fibres preoperatively and Month 1, Month 4 and Month 8 postoperatively

	Baseline	Month 1	Month 4	Month 8
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Group A	4.80 $\pm$ 1.63 ^a	3.30 $\pm$ 1.30 ^a	4.37 $\pm$ 1.10	4.60 $\pm$ 0.88
Group B	4.73 $\pm$ 1.40 ^b	3.73 $\pm$ 1.33 ^b	3.77 $\pm$ 0.95	4.19 $\pm$ 0.87
Group C	4.46 $\pm$ 1.10 ^c	3.86 $\pm$ 1.17 ^c	3.82 $\pm$ 0.98	4.25 $\pm$ 0.89

Group A: Trehalose/HA Group

Group B: HA Group

Group C: Control Group

a: $p < 0.05$

b: $p < 0.05$

c: $p < 0.05$

Table 9

Subbasal nerve fibres tortuosity preoperatively and Month 1, Month 4 and Month 8 postoperatively

	Baseline	Month 1	Month 4	Month 8
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Group A	2.43 $\pm$ 0.90 ^a	2.40 $\pm$ 0.77	1.53 $\pm$ 0.51 ^{a,c,d}	1.23 $\pm$ 0.43 ^{e,f}
Group B	2.65 $\pm$ 0.92	2.81 $\pm$ 0.78	2.69 $\pm$ 0.70 ^b	2.58 $\pm$ 0.59 ^e
Group C	2.89 $\pm$ 0.99 ^b	3.43 $\pm$ 0.79 ^b	3.14 $\pm$ 0.71 ^{c,d}	2.93 $\pm$ 0.60 ^f

Group A: Trehalose/HA Group

Group B: HA Group

Group C: Control Group

a: $p < 0.05$

b: $p < 0.05$

c: $p < 0.05$

d: $p < 0.05$

e: $p < 0.05$

f: $p < 0.05$