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EFFECT OF POSTOPERATIVE ADMINISTRATION OF HYALURONIC ACID/TREHALOSE DROP ON CORNEAL HEALING AFTER PHACOEMULSIFICATION SURGERY

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Abstract: This study aimed to evaluate the efficacy of hyaluronic acid/trehalose drop for corneal epithelial and stromal healing after phacoemulsification surgery. It is a retrospective randomized comparative study. The patients had phacoemulsification surgery divided into two groups. These patients received either a mixture of sodium hyaluronate and Trehalose (Group 1) or sodium hyaluronate 0.15% (Group 2) postoperatively. The effect on corneal epithelial and stromal healing was evaluated using Oxford staining and the vertical scar length measured by optical coherence tomography. Preoperative and post-operative findings for Oxford staining, Schirmer's test, tear film break-uptime, and ocular surface disease index scores were also evaluated. The correlation between scar length and tear film parameters was examined. The effect of Trehalose on the epithelial healing and stromal scar formation was assessed. Group 1 and 2 each had 30 eyes. The two groups were similar according to age and sex distribution. In terms of epithelial healing, it was faster in the trehalose group, although there was no statistical difference between the two groups. The length of the stromal scar was not significantly different between groups. However, a smaller scar formation was observed in group 1 compared to those in group 2 at both one week and one month postoperatively. There was also no significant difference between the groups in tear film parameters. The stromal scar length was correlated with the Schirmer test on the 15th day. Although it was not statistically significant, the hyaluronic acid/trehalose may affect epithelial healing and stromal scar formation positively after phacoemulsification surgery. Larger and longer studies are needed.

Keywords: Hyaluronic acid/trehalose, Phacoemulsification surgery, Dry eye, Wound healing, Clear corneal incision

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1. Introduction

With the help of the advancing technology, phacoemulsification surgery became one of the most comfortable ophthalmologic operations; however, complaints such as burning sensation, blurred vision, pain inside and around the eye, and foreign body sensation are still frequent in the post-operative period (Sutu et al., 2016). Since the prevalence of dry eye disease (DED) increases with aging, it is common in patients undergoing phacoemulsification surgery. Post-operative DED can be due to reasons such as topical anesthetics, cutting of corneal nerve, inflammation, and loss of goblet cells. Because of these abovementioned reasons, patient satisfaction can be lower than expected even though the operation was problem free (Cho et al., 2009; Pinto-Bonilla et al., 2015; Trattler et al., 2015). Since DED has both inflammatory and physicochemical components, it can be assumed that the mechanism behind dry eye following phacoemulsification surgery may be inflammation. Topical anti-inflammatory drops such as steroids are usually administered to manage post-operative inflammation and facilitate healing after phacoemulsification surgery. Increased ocular surface inflammation also has a role in increased tear osmolality (Aragona et al., 2014), and this may affect the corneal healing, as well it may lead to denaturation of the cell membrane and proteins. (Chen et al., 2009; Hill-Bator et al., 2014; Chiambaretta, et al., 2017).

Trehalose is a naturally occurring disaccharide that preserves cellular vitality and acts as a free radical scavenger. It can protect the cells that are in the same environment with it against dryness, high temperatures, dehydration, and oxidation (Mateo Orobia et al., 2017). It is a bio-protective (Hovakimyan et al., 2012) and osmoprotectant agent. It stabilizes the cell membrane and proteins by inducing proinflammatory cytokine secretion and prevents apoptosis (Aragona et al., 2014; Hovakimyan et al., 2012; Mateo Orobia et al., 2017). Thealoz Duo® is an artificial tear preparation which contains Trehalose and hyaluronic acid. Topical corticosteroids and/or nonsteroidal anti-inflammatory drugs are considered as a standard treatment after phacoemulsification surgery; however, the additive effect of topical Trehalose on the stromal healing process has not been studied.

This study aims to investigate Trehalose's effect on the healing process, changes, and scar formation in epithelium and stroma following phacoemulsification surgery. Secondly, the difference in tear film parameters by post-operative administration of Trehalose was evaluated.

2. Material and Methods

This retrospective randomized comparative study was conducted between January 2016 and December 2018. Our institutional review approved the study protocol that adhered to the tenets of the Declaration of Helsinki.

Inclusion criteria to the study were; age between 60-75 years, no previous ocular surgery, no history of systemic diseases (Diabetes mellitus, hypertension, Sjögren syndrome, thyroid diseases, etc.), no record of DED, glaucoma, or any corneal pathology, and without a history of topical medication use for at least six months before cataract diagnosis.

All patients underwent phacoemulsification surgery and intraocular lens (IOL) implantation performed by the same surgeon (H.E) without intraoperative complications. Three-planed clear corneal incision (CCI) was done between 130 degrees and 140 degrees using a 2.2 mm metal blade (Alcon Laboratories, Inc.). A single-piece foldable acrylic IOL (Tecnis ZCBOO, Abbott Medical Optics, Inc.) was implanted. Minimal hydration was applied to the CCI using a balanced salt solution at the end of the surgery.

The patients were divided into two groups after surgery. The participants in group 1, trehalose 30 mg/mL, and sodium hyaluronate 1.5 mg/mL were applied four times a day on the eye had phacoemulsification surgery, and the participants in the second group only sodium hyaluronate 0.15% was used four times a day on the eye had phacoemulsification surgery. The standard post-operative anti-inflammatory treatment (prednisolone acetate 1.0%, Pred Forte) was administered to all patients every 2 hours on the day of surgery, one drop every 4 hours during the first post-operative week, and then drops stopped by reducing during the following three weeks. Findings for Oxford staining, Schirmer's test I, tear film break-up time (TBUT), and ocular surface disease index (OSDI) scores were examined preoperatively from the patients' field. Oxford staining was performed both post-operative 1st-day and 1st-month. Schirmer's test I, TBUT, OSDI tests were performed at post-operative 1st-month. Oxford staining was used both to evaluate epithelial healing and to evaluate DED findings (Bron et al., 2015).

The OSDI test is a 12-question questionnaire that evaluates the symptoms of ocular irritation and its visual-related functions to assess DED severity with scores ranging from 0 to 100 (Schiffman et al., 2000).

The Schirmer test measures the tear amounts on the eye surface by placing filter papers (SNO* Strips, Lab Chauvin, Aubenas, France) in the inferior fornix without topical anesthesia. The amount of wetting on the filter paper after 5 min is recorded as the test result. For our study, the results < 10 mm in the Schirmer test were accepted as positive for DED (McCarty et al., 1998).

In the TBUT test, the inferior fornix is touched using saline-soaked fluorescein sticks (Fluorescein, Haagen–Streit International, Koeniz, Switzerland). The patients are asked to blink and then abstain from blinking until told to do so. The time from the first blink to the detection of dry area formation on the cornea is recorded as the TBUT value. We used the TBUT values < 8 s to detect DED (McCarty et al., 1998).

The Oxford the scheme is a test to assess the state of the ocular surface using a fluorescein stick to stain the cornea, and the results are graded from 0 (no staining) to 5 (severe staining) (Bron et al., 2003).

The post-operative effect on corneal stromal healing was calculated using the vertical scar length measured with OCT, as previously described in the literature (Francoz et al., 2011). The OCT has a length measurement mode, and the device can automatically calculate the distance between two points. After the scar was detected, the upper and lower limit of the scar was manually marked, and the automatic measurement value was read. The measurement of the stromal scar formation at post-operative 15th day and 30th day was performed by determining the length from the shortest distance using the ruler mode, as shown in Figure 1.

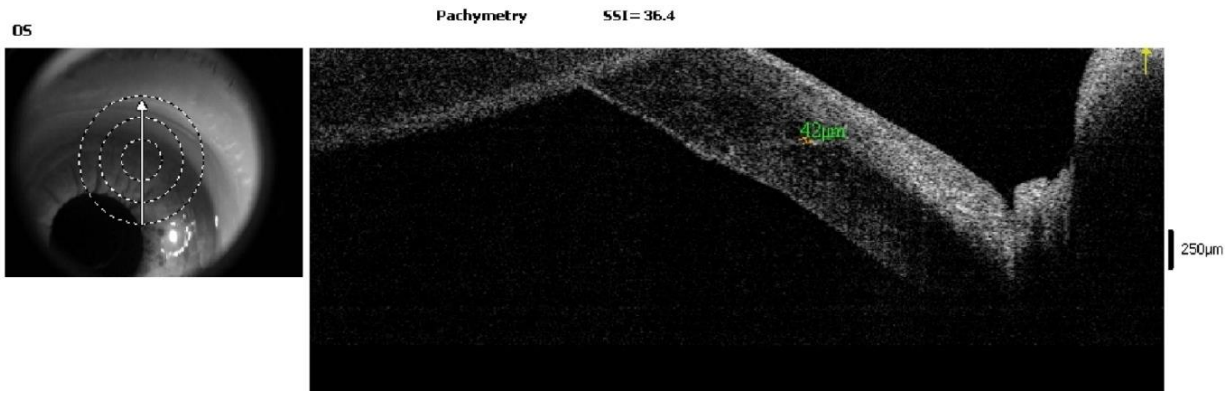

Figure1. Scar with the corneal OCT.

2.1. Statistical Analysis

Above mentioned parameters were compared between two groups using the Mann Whitney U test. The correlation between the length of scar incision and tear film parameters was evaluated with the Spearman correlation coefficient. A P-value of less than 0.05 was considered statistically significant.

2.2. Ethical Consideration

The study ethics committee approval was approved by the Maltepe University Ethics Committee with the number 2019/900/06.

3. Results

Sixty patients were included in the study. The gender and age distribution of patients are shown in Table 1.

Table 1. Gender and age distribution for two groups

	Group 1	Group 2	P*
Age (year)	55.08±6.11	55.66±6.58	P=0.645
Gender	Female 16 Male 14	Female 18 Male 12	P=0.786

Group 1= trehalose 30 mg/mL and sodium hyaluronate 1.5 mg/mL, Group 2= sodium hyaluronate 1.5 mg/mL
*Mann Whitney U test

There was no statistical difference between the gender and age distribution of study and control.

Preoperative and post-operative dry eye parameters, Oxford shame scores, and post-operative OCT scar length are shown in Table 2. As shown in Table 2, there was no statistical difference between the groups regarding preoperative and post-operative dry eye parameters. However, significant improvement was achieved in tear film function parameters in both groups during the post-operative period and was a better trehalose group. Oxford staining score, which is used for corneal epithelial cellular viability, was higher in the trehalose group but not statistically significant. There was no statistically significant difference between the groups for stromal scar length at the post-operative 15th and 1st month. Still, it was smaller in the trehalose group at both time points.

In correlation analysis, only a significant correlation was found between the Schirmer test and incision scar length on the 15th day in the Trehalose group (r=-0.275; P=0.034). Other tear film parameters, oxford shame, and incision scar length at 15th and 30th had no significant correlations for two groups.

Table 2. Dry eye parameters, OSDI scores and CCI scar length measured by oct for two groups

Parameter	Group 1 Mean ± SD (Range)	Group 2 Mean ± SD (Range)	P value*
Schirmer test (mm)			
preoperative	9.40±5.60 (3-25)	7.46±2.75 (2-13)	0.240
postoperative	13.76±8.06 (3-30)	13.36±6.92 (3-27)	0.947
BUT (second)			
preoperative	6.20±4.46 (2-25)	4.36±1.79 (2-7)	0.060
postoperative	7.16±3.14 (2-17)	6.06±2.36 (3-12)	0.166
Oxford score			
preoperative	1.36±0.96 (0-3)	1.56±0.62 (0-3)	0.318
postoperative	0.53±0.73 (0-2)	0.76±0.89 (0-3)	0.310
OSDI			
preoperative	22,84±10,92(11.36-36,36)	25.24±12.38 (11.36-68.18)	0.131
postoperative	10,39±5,44 (6.25-20.45)	12.92±6.57 (6,25-54,55)	0.394
Incision scar (μm)(OCT)			
15 th day	39.50±4.95 (25-46)	41.10±4.90 (31-47)	0.86
30 th day	25.80±6.93 (11-35)	29.30±5.05 (18-38)	0.75

OSDI= ocular surface disease index; CCI= clear corneal incision SD= standard deviation; BUT= tear film break up time; OCT= optical coherence tomography
Group 1= trehalose 30 mg/mL and sodium hyaluronate 1.5 mg/mL, Group 2= sodium hyaluronate 1.5 mg/mL
*Mann Whitney U test

4. Discussion

Trehalose is a naturally occurring substance found in other organisms, but it doesn't occur in humans. It is secreted during times of stress to protect the organism against external factors. Trehalose had been predominantly used to address dry eye symptoms. However, many studies in the literature had shown that Trehalose also protects cornea wound healing, as well as it suppresses corneal scar formation and inflammation (Cejka et al., 2019).

Many researchers thoroughly studied Trehalose's therapeutic effect in dry eye treatment, but there are a limited number of studies that investigate its role in post-operative treatment. These studies that have looked into Trehalose's post-operative effect after other surgical approaches in both rabbits who were exposed to UV and corneas in a hypoxic environment. It has been found that Trehalose helped with better epithelial wound healing and decreased both scar formation and neovascularization (Cejkova et al., 2012).

Additionally, there were reports on trehalose use in glaucoma surgery. It has been speculated that Trehalose decreases fibrosis via it is effective over fibroblasts and protects from infiltration (Takeuchi et al., 2010; Takeuchi et al., 2011). In these two studies, bare cell cultures that were not protected by any barrier were used, and cells are in direct contact with Trehalose.

When compared to conventional post-operative treatment after Lasik surgery in patients treated with 3% trehalose, the study in which dry eye parameters were examined, the trehalose group had better results in terms of oxford staining for epithelial integrity and healing. However, there was no difference between the groups in staining lissamine green (Mateo Orobia et al., 2017).

Similar results were obtained in a study performed in keratoconus patients. Epithelial healing was significantly faster in the patients who had received Trehalose for cross-link treatment when compared to sodium hyaluronate only. However, in this study, there was no information about the stromal effect of Trehalose (Ozek et al., 2018).

In the present study, it was investigated Trehalose's effect on corneal epithelial healing after phacoemulsification surgery. It has a similar impact on corneal epithelial healing to previous studies (Takeuchi et al., 2010; Takeuchi et al., 2011; Mateo Orobia et al., 2017; Ozek et al., 2018).

Oxford staining score, which is used for corneal cellular viability, was higher after surgery and epithelial healing was faster in the trehalose group but not statistically significant. Stromal scar formation after phacoemulsification surgery

Apart from the corneal incision, exposure to light by a microscope lamp, the phacoemulsification device's vibration, and temperature can be additional factors that can create additional wound stress. Therefore, both the surgical incision and the factors mentioned above may affect scarring and epithelial healing (Trattler et al., 2009; Cho et al., 2017; Situ et al., 2019; Zaleska-Żmijewska et al., 2019). MMP 9 is an important factor in the formation of fibrosis and scarring, and it is useful in remodeling, and scar formation increases. MMP increases with inflammation in the post-operative period (Sambursky et al. 2013; Nakamura et al., 2008). For the MMP effect, the drug should be in contact with the surface for more than 15 days (Gabison et al., 2005). There was no significant difference between the groups for stromal scar formation, but the scar area was smaller at both early and late stages for the Trehalose group. Also, the absence of stromal healing and epithelial healing was significant, maybe due to the low number of participants. Although the epithelial defect closed rapidly, and the epithelium creates a barrier for the Trehalose to contact the stromal surface, the scar area was smaller in the Trehalose group. These results may suggest that Trehalose may also act to the subepithelium. It may be necessary to conduct studies in which the contact of Trehalose with the bare stroma is longer and supporting this situation with histological studies will be more useful to evaluate the stromal effect of Trehalose.

Almost all previous studies reported that Trehalose is an effective agent that can be used for the management of dry eye safely (Matsuo, 2004; Wozniak et al., 2017) as the present study. Articles in the literature have almost similar OSDI scores and dry eye parameters for similar age groups (Kasetsuwan et al., 2013; Garg et al., 2020; Rico-Del-Viejo et al., 2018), this is similar for the current study. However, in groups with phacoemulsification surgery that did not use artificial tears after the operation, dry eye parameters worsened over time (Kasetsuwan et al., 2013; Garg et al., 2020), while dry eye parameters increased to a better level in the present study. This result may be due to the use of artificial teardrops in both groups for the current study. In this study for the Trehalose group, dry eye parameters, especially Schirmer test results on day 15th, were found to be better.

If the current study had a group without artificial tears, a more accurate assessment would be possible. As the study was designed retrospectively, this has been a limiting factor in the present study. And the other limitation of the present study was the small number of patients included. More significant results can be obtained with a bigger population. Also, we were not able to reach many participants to evaluate their long-term results, which restricted our assessment. These may affect the value of the drawn conclusions.

As a result, Trehalose seems to be effective in improving dry eye symptoms. Although not statistically significant, scar formation and corneal epithelial cell viability were higher in the trehalose group. However, the effect of Trehalose on stoma due to epithelial defect that has closed seems to be limited. Perhaps the stromal effect may be even more positive in patients where the epithelium is not closed for a long time. Trehalose may be an alternative option for managing CCI reconstruction after phacoemulsification surgery since it minimizes the corneal scar formation and accelerates corneal epithelization. Trehalose assists in improving dry eye parameters after phacoemulsification surgery. Further studies are required to prove its effectiveness in more significant patient populations with longer follow up.

Author Contributions

HE; data collection and writing, OM; statistical analysis and language editing.

Conflict of Interest

The authors declare that there is no conflict of interest.

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