IBAD Fen Bilimleri Dergisi
IBAD Journal of Science

ibadfen, 2020; (3):34-43 **Özgün Araştırma / Original Article**

Hyaluronat - Trehaloz Çözeltisinin Katarakt Cerrahisi Sonrası Oküler Konfor ve Gözyaşı Filmi İnstabilitesi Üzerine Etkisi

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Geliş tarihi: 20.08.2020
Kabul tarihi: 28.09.2020

Atıf bilgisi:
İBAD Fen Bilimleri Dergisi
Sayı: 3 **Sayfa:** 34-43
Yıl: 2020 **Dönem:** Bahar

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ÖZ

Giriş ve Amaç: Katarakt cerrahisi sonrası trehaloz ve sodyum hiyalüronat çözeltisinin oküler konfor ve gözyaşı filmi instabilitesi üzerine etkilerini değerlendirmek.**Gereç ve Yöntem:** Bu prospektif çalışma Mayıs 2017 ve Ocak 2018 tarihleri arasında gerçekleştirildi. Tek taraflı katarakt ameliyatı geçiren 18 yaş üstü hastalar çalışmaya alındı. Ameliyat öncesi tüm hastalara Schirmer testi ve gözyaşı filmi kırılma zamanı (TBUT) ölçümü yapıldı. Postoperatif 1. ayda oküler yüzey; Oküler Yüzey Hastalığı İndeksi (OSDI), Schirmer testi, TBUT ve kornea floresein boyaması kullanılarak değerlendirildi. Hastalardan kuru göz semptomlarının şiddetini (yabancı cisim hissi, yanma ve batma, gözlerini kapatma isteği, gözlerini kırpma sıklığı) görsel analog skalada (VAS) derecelendirmeleri istendi.**Bulgular:** Çalışma grubunda; Schirmer test sonuçlarında başlangıç ve postoperatif 1 ay arasında istatistiksel olarak anlamlı bir değişiklik görülmedi (p = 0.086), iki grupta da preoperatif TBUT değeri eşitti (her ikisi için 11 s, p> 0.05). Postoperatif 1. ayda TBUT değeri çalışma grubunda kontrol grubuna göre daha uzun saptandı (12 sn. 9 sn, p <0.001). Postoperatif 1. ayda OSDI skorları çalışma grubunda kontrol grubuna göre anlamlı olarak düşük bulundu (2.27'ye karşı 20, p <0.001). yabancı cisim hissi, yanma ve batma hissi çalışma grubunda kontrol grubuna göre anlamlı derecede düşük saptandı (sırasıyla p = 0.002 ve p = 0.004). Floresein kornea boyama skorları da çalışma grubunda kontrol grubuna göre anlamlı olarak düşük bulundu (p = 0.005).**Sonuç:** Bu çalışma katarakt cerrahisi sonrası% 3 trehaloz ve% 0.15 sodyum hiyalüronat çözeltisinin kullanımının kuru göz semptomlarını azalttığını, gözyaşı filmi tabakasını stabilize ettiği ve kornea hücresi canlılığını arttırdığını göstermektedir.

Anahtar Kelimeler: Hyaluronat çözeltisi, trehaloz çözeltisi, oküler konfor, gözyaşı filmi instabilitesi

Effect of a hyaluronate–trehalose solution on ocular comfort and tear-film instability after cataract surgery

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First received:20.08.2020
Accepted: 28.09.2020

Citation:
IBAD Journal of Science
Issue: 3 **Pages:** 34-43
Year: 2020 **Session:** Spring

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ABSTRACT

Background and Aim: To evaluate the effects of trehalose and sodium hyaluronate solution on ocular comfort and tear-film instability after cataract surgery**Materials and Methods:** This prospective study was conducted between May 2017 and January 2018. Patients over the age of 18 years who underwent unilateral cataract surgery were included in the study. Preoperatively, all patients underwent Schirmer test and tear film break-up time (TBUT) measurement. At postoperative month 1, the ocular surface was evaluated using the Ocular Surface Disease Index (OSDI), Schirmer test, TBUT, and corneal fluorescein staining. patients were asked to rate the severity of their dry eye symptoms (foreign body sensation, burning and stinging, desire to close the eyes, increased blinking frequency) on a visual analogue scale (VAS). **Results:** The study group showed no statistically significant change in Schirmer test results between baseline and postoperative 1 month in the study group ($p=0.086$), Preoperative TBUT was equivalent in the two groups (11 s for both, $p>0.05$). TBUT at postoperative 1 month was longer in the study group than the control group (12 s vs. 9 s, $p <0.001$). At postoperative 1 month, OSDI scores were significantly lower in the study group than the control group (2.27 vs. 20, $p<0.001$) .Foreign body sensation and burning and stinging sensation were significantly lower in the study group than in the control group ($p=0.002$ and $p=0.004$, respectively). Fluorescein corneal staining scores were also significantly lower in the study group than in the control group ($p=0.005$) .**Conclusion:** This study indicates that 3% trehalose and 0.15% sodium hyaluronate solution reduces dry eye symptoms, stabilized tear film layer, and increased corneal cell viability after cataract surgery.

Keywords: Hyaluronate solution , trehalose solution , ocular comfort, tear-film instability
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INTRODUCTION

Cataract is the leading cause of vision impairment worldwide.[1] Visual acuity can be restored with small-incision phacoemulsification surgery. However, a substantial proportion of patients report symptoms of dry eye syndrome (DES) such as pain, burning, photophobia, and foreign body sensation postoperatively.[2,3] Several factors have been implicated in the etiology of DES after cataract surgery, including topical anesthetic eye drops containing benzalkonium chloride, which is toxic to the cornea epithelium; excessive light exposure from the surgical microscope light source; and surgical incisions. Abnormalities in the components of the lacrimal functional unit (LFU) result in increased tear osmolarity, tear film instability, proinflammatory cytokine release, ocular surface inflammation, and apoptosis.[6]

DES negatively impacts quality of life and leads to patient dissatisfaction despite postoperative visual improvements. Artificial tears and topical steroids are used to alleviate symptoms and control inflammation. However, the transient effect of artificial tears and the side effects of steroids create the need for alternative therapies.[8-9]

A new ophthalmic solution combining 0.15% sodium hyaluronate and 3% trehalose (Thealoz Duo®, Thea Pharmaceuticals, France) has been developed to maintain ocular surface homeostasis and provide ocular comfort. The water-retentive properties of hyaluronic acid provide hydration and lubrication of the ocular surface. Being a bioadhesive molecule, it is retained on the corneal surface for an extended time and promotes corneal epithelial healing.[10] Trehalose is a natural bioprotectant against osmotic stress-induced apoptosis and inflammation. It is a powerful antioxidant that prevents the denaturation of lipids and proteins in cell membranes. Trehalose is known for its anhydrobiotic function of regulating osmotic balance, which in ocular applications helps end the vicious cycle of tear hyperosmolarity.[11] The combination of trehalose and sodium hyaluronate aims to promote restoration of the ocular surface through long-lasting lubrication as well as antioxidant and antiinflammatory activity.

In the present study we investigated the efficacy and safety of 0.15% sodium hyaluronate and 3% trehalose combination in the treatment of DES following cataract surgery.

PATIENTS AND METHODS

Study design

This prospective study was conducted between May 2017 and January 2018 at the Dr. Nafiz Körez Sincan State Hospital in Ankara, Turkey. The study protocol adhered to the Declaration of Helsinki and informed consent forms were obtained from all participants.

Study Population

Patients over the age of 18 years who underwent unilateral cataract surgery were included in the study. Exclusion criteria included preoperative DES (Schirmer test I <5.0 mm), history of rheumatologic disease (rheumatoid arthritis, systemic lupus erythematosus, scleroderma, etc.), the use of drugs that may lead to DES (antihistamines, antidepressants, isotretinoin), lid malformation (floppy eyelid syndrome, lagophthalmos), intraoperative complications during cataract surgery, and contact lens use.

Surgical Technique, Treatment, and Assessment

All surgeries were performed by the same experienced ophthalmologist (Ö.B.). A 2.2-mm clear corneal incision was made at 12 o'clock. An anterior capsule opening 5.5 mm in diameter was made by continuous curvilinear capsulorhexis. Following standard phacoemulsification (Whitestar Signature phacoemulsification system, Abbott Medical Optics, Inc.), an intraocular lens was implanted in the capsular bag. The patients were randomly divided into two groups. Postoperatively, both groups used 0.5% moxifloxacin (Vigamox; Alcon, Istanbul, Turkey) and 0.1% dexamethasone (Maxidex; Alcon, Istanbul, Turkey) starting at a dose of 5 times daily and reduced over the course of 1 month. The study group also received 3% trehalose and 0.15% sodium hyaluronate combination (Thealoz Duo®) 4 times daily for 1 month. Patients were evaluated preoperatively and at postoperative 1 month.

Outcome Measures

Preoperatively, all patients underwent Schirmer test and tear film break-up time (TBUT) measurement. At postoperative month 1, the ocular surface was evaluated using the Ocular Surface Disease Index (OSDI), Schirmer test, TBUT, and corneal fluorescein staining. Tear function tests were performed with an average interval of 10 minutes to avoid influencing the results. In addition, patients were asked to rate the severity of their dry eye symptoms (foreign body sensation, burning and stinging, desire to close the eyes, increased blinking frequency) on a visual analogue scale (VAS).

OSDI score was used to assess symptoms of ocular irritation (sensitivity to light, foreign body sensation, burning and stinging, blurred or reduced vision) that may occur in DES. The index consisting of three sections and 12 questions, with the ocular symptoms in each section scored from 0 to 4 (0=never, 4=always). The score is obtained by summing the total points from the questions answered, multiplying by 25, then dividing by the number of questions answered (total points x 25 / number of questions answered), yielding a final OSDI score ranging from 0 to 100.

Schirmer test was performed by instilling topical anesthetic, then placing one end of a standard Schirmer filter paper (TearFlo Sterile Strips, Rose Stone Enterprises, CA, USA) at the lower conjunctival fornix approximately one-third of the palpebral distance from the lateral canthus. After five minutes, the wetted portion of the strip was measured from the lid margin in millimeters.

TBUT was measured without topical anesthetic by wetting fluorescein-impregnated paper (BioGlo Sterile Strips, Rose Stone Enterprises, CA, USA) with saline, discarding the first drop, then applying the

remaining dye to the lower conjunctival fornix. The patient was asked to blink three to four times to distribute the fluorescein. The tear film was examined at the slit-lamp biomicroscope using broad illumination and a blue cobalt filter. The time from last blink to the first dry spot was determined in seconds. The measurement was repeated three times and the average was obtained.

The Oxford grading scheme was used to score fluorescein corneal staining as follows: 0=no staining, 1=minimal staining, 2=mild staining, 3=moderate staining, 4=marked staining, and 5=severe staining.[12]

In the VAS assessment of ocular surface discomfort, patients were asked to mark their level of pain on a 10-cm horizontal line labeled 'no pain' on end and 'most pain imaginable' on the other end. The distance from the 'no pain' end to the patient's mark was measured in centimeters.

Statistical analysis

Statistical analyses were done using IBM SPSS for Windows, version 24.0 (IBM Corporation, Armonk, NY, USA) and PAST 3 (Hammer, Ø., Harper, DAT, Ryan, PD. 2001. Paleontological statistics) software. Normality of the data was tested with Shapiro-Wilk test for univariate data and Mardia (Doornik and Hansen omnibus) test for multivariate data; Levene's test was used to test homogeneity of variance. Independent-samples t-test was used with Bootstrap results was used for between-group comparisons of quantitative data. The Mann-Whitney U test was used with Monte Carlo simulations. Paired-samples t-test (Bootstrap) and Wilcoxon signed ranks test (Monte Carlo) were used to compare repeated measures of dependent quantitative variables, and the general linear model-repeated measures ANOVA test was used to examine the interaction of repeated quantitative measures by group. Categorical variables were compared using Pearson chi-square tests with Monte Carlo simulation. Variables were analyzed at a confidence level of 95%, with p values below 0.05 accepted as significant.

RESULTS

The 79 patients included in the study were randomly divided into a study group and control group. The control group comprised 44 patients (22 [52.4%] females, 20 [47.6%] males) and the study group comprised 37 patients (20 [54.1%] females, 17 [45.9%] males). Mean age was 65.6±5.9 years in the study group and 64.6±5.3 years in the control group (p=0.446).

Preoperative mean Schirmer test score was 12.1±1.6 mm in the study group and 12.2±1.4 mm in the control group (p>0.05). The study group showed no statistically significant change in Schirmer test results between baseline and postoperative 1 month in the study group (p=0.086), while those of the control group were significantly lower at postoperative 1 month (p=0.001) (Figure 1).

Preoperative TBUT was equivalent in the two groups (11 s for both, p>0.05). TBUT at postoperative 1 month was longer in the study group than the control group (12 s vs. 9 s, p <0.001). Compared to preoperative values, TBUT at postoperative 1 month did not differ significantly in the study group (p=0.126) but decreased significantly in the control group (Figure 2).

At postoperative 1 month, OSDI scores were significantly lower in the study group than the control group (2.27 vs. 20, p<0.001) (Figure 3).

Foreign body sensation and burning and stinging sensation were significantly lower in the study group than in the control group (p=0.002 and p=0.004, respectively) (Figures 4).

Fluorescein corneal staining scores were also significantly lower in the study group than in the control group (p=0.005) (Figure 5).

None of the patients experienced drug-related adverse effects.

DISCUSSION

There are constant advances in cataract surgery. Large corneal surgeons have been replaced by small-incision phacoemulsification surgery to promote rapid healing postoperatively and reduce surgically induced astigmatism.[13]As in our study, small incisions of 2.2 mm result in reduced corneal sensitivity due to severing of corneal nerves, impaired wound healing, increased epithelial permeability, decreased epithelial metabolic activity, and cytoskeletal structural loss.[6]

In some patients, dry eye symptoms lead to serious dissatisfaction after successful cataract surgery despite improvements in vision. Gibbons et al.[15] reported a post-phacoemulsification dissatisfaction rate of 35% due to dry eye. Dry eye tests should be performed before cataract surgery in order to identify DES, and surgery should be scheduled after treatment; otherwise, treating the symptoms of dry eye is much more difficult postoperatively. Dry eye can also develop postoperatively in patients who did not have dry eye prior to cataract surgery. The prevalence of dry eye after cataract surgery was reported as 9.8% in one study[2] and 34% in another study.[14] These dry eye symptoms require postoperative therapy with agents that increase tear film stability and have an anti-inflammatory effect on the ocular surface. To our knowledge, our study is the first to investigate the efficacy of 3% trehalose and 0.15% sodium hyaluronic acid in the treatment of dry eye following cataract surgery.

In a study of 92 patients with 3 months of follow-up, Kasetsuvan et al.[2] reported that dry eye symptoms peaked in the first week and showed progressive decline at postoperative 1 and 3 months. Li et al.[4] reported that symptoms emerged in the first week and peaked in the first month. Therefore, in the present study we evaluated dry eye parameters at postoperative 1 month.

Mencucci et al.[8] reported significantly longer TBUT and significantly greater improvement in dry eye symptoms evaluated by VAS and fluorescein corneal staining in patients who used carboxymethylcellulose and hyaluronic acid compared to a control group at 5 weeks after cataract surgery. Park et al.[16] compared the efficacy of 3% diquafosol and 0.1% sodium hyaluronate in postoperative dry eye. TBUT, corneal fluorescein, and conjunctival staining scores were superior in the diquafosol group compared to the hyaluronate group, but significant differences were not observed in Schirmer test and OSDI scores. Mohammadpour et al.[9] reported significantly improved TBUT and OSDI scores in the omega-3 fatty acid supplementation group compared to the control group. In the present study, patients using 3% trehalose and 0.15% sodium hyaluronate artificial tears exhibited significantly longer TBUT, fewer dry eye symptoms, and lower OSDI and corneal fluorescein staining scores after cataract surgery compared to the control group. We attribute this finding to trehalose and sodium

hyaluronate rapidly improving homeostasis and tear stability on the ocular surface due to their lubricating, antioxidant, antiinflammatory, and antiapoptotic properties.

The protective effect of trehalose against desiccation and oxidative stress and its stabilizing effect on membrane lipids have been demonstrated in vitro and in clinical trials. One study compared seven different products containing trehalose, hydroxypropyl methylcellulose, polyvinyl alcohol, polyethylene glycol, and different concentrations of sodium hyaluronate and determined that trehalose was superior in preventing cell death.[17] Another study demonstrated that the combination of trehalose and sodium hyaluronate increased tear film thickness in moderate dry eye.[18] Furthermore, the study group exhibited less corneal fluorescein staining than the control group as a result of reduced corneal cell damage due to the antiapoptotic and cell membrane protective effects of trehalose. Our clinical results are consistent with cell culture studies suggesting that trehalose prevents desiccation-induced cell death.[19]

Limitations of the present study include the short duration of follow-up, small patient number, and not evaluating congestive impression cytology and tear osmolarity.

In summary, our study shows that 3% trehalose and 0.15% sodium hyaluronate solution reduces dry eye symptoms, stabilized tear film layer, and increased corneal cell viability after cataract surgery. Further studies comparing drugs that stabilize the tear film layer with longer follow-up and larger patient numbers are needed to clarify this topic.

Conflict of interest: No author has a financial or proprietary interest in any material or method mentioned.

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FIGURES

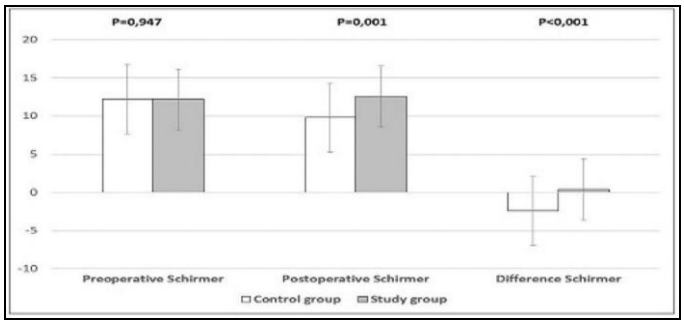

Figure 1. Mean Schirmer test scores preoperatively and 1 month postoperatively.

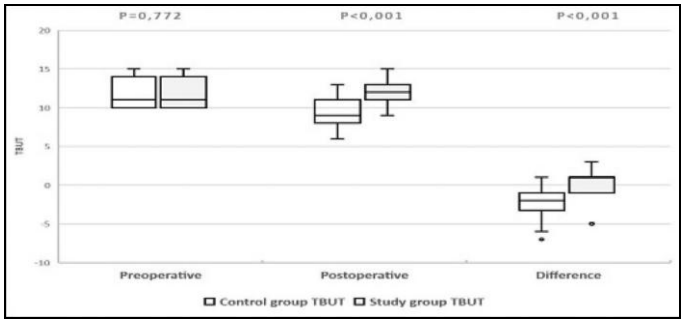

Figure 2. TBUT preoperatively and 1 month postoperatively.

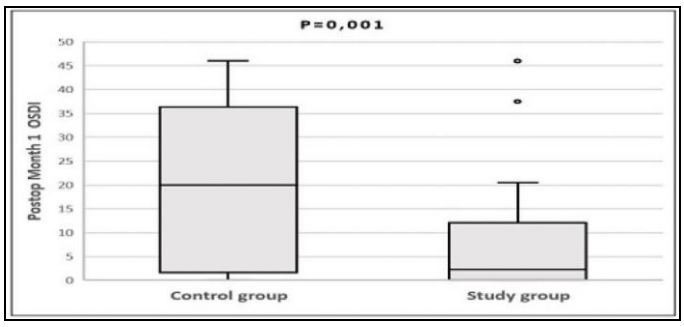

Figure 3. OSDI scores preoperatively and 1 month postoperatively.

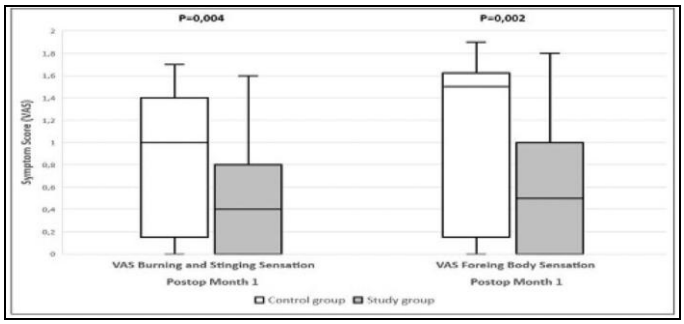

Figure 4. The symptom score as assessed by VAS at 1 month postoperatively.

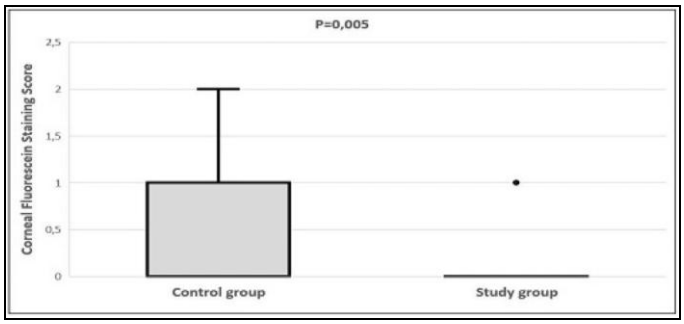

Figure 5. Corneal fluorescein staining scores at 1 month postoperatively.