• Clinical Research •

Improving the post-oculoplastic tear film: trehalose as a critical adjunct

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Abstract

● **AIM:** To evaluate the comparative effects of a combined trehalose-sodium hyaluronate (TD) formulation versus sodium hyaluronate (SH) monotherapy on postoperative ocular surface recovery following eyelid surgery, with additional analysis across surgical subgroups.

● **METHODS:** This retrospective comparative study included patients who underwent eyelid surgery for ectropion, entropion, or eyelid reconstruction between August 2021 and July 2024. Patients were divided into two treatment groups based on the postoperative tear substitutes used: Group SH treated with 0.15% SH eye drops, and Group TD treated with a combination of 3% trehalose and 0.15% SH. Postoperatively, patients received either 0.15% SH alone or a combination of 3% trehalose and 0.15% SH four times daily for 3mo. Ocular surface parameters—including tear break-up time (TBUT), Ocular Surface Disease Index (OSDI), Oxford staining score, meibomian gland loss (MGL), and central corneal epithelial thickness (CCET)—were assessed at baseline and 3mo. Subgroup analyses were performed by surgical indication.

● **RESULTS:** A total of 114 patients were included in the study (mean age: 70.3±12.1y; 25 females). Group SH comprised 57 patients (15 females, mean age: 69.2±11.4y), while the Group TD also included 57 patients (10 females, mean age: 71.5±12.8y). Both groups showed significant improvement across all parameters; however, the TD group demonstrated superior outcomes in TBUT (mean difference: +0.77s, 95%CI: 0.12–1.42, *P*=0.036), Oxford score (mean difference: −0.39, 95%CI: −0.75 to −0.03, *P*=0.036), and MGL (mean difference: −2.02%, 95%CI: −3.78% to −0.26%, *P*=0.025). Subgroup analysis revealed that the TD formulation resulted in significantly better outcomes in patients undergoing reconstruction (*P*<0.05 for all parameters) and in most measures within ectropion and entropion subgroups. No significant differences were found in OSDI between groups, despite objective improvements favoring the TD group.

● **CONCLUSION:** This study is the first to comparatively assess trehalose-based tear supplementation across distinct oculoplastic surgery subgroups. The combination of TD significantly enhanced postoperative ocular surface parameters—especially in complex reconstructive settings—compared to SH alone. These findings highlight the potential of tailored, antioxidative tear film strategies in optimizing recovery after eyelid surgery.

● **KEYWORDS:** dry eye; trehalose; sodium hyaluronate; eyelid surgery; ocular surface; meibomian gland

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INTRODUCTION

The eyelids play a critical role in maintaining ocular surface integrity by providing physical protection against ultraviolet radiation, foreign bodies, and environmental irritants. Alongside the lacrimal gland and ocular surface, they form the lacrimal functional unit, which is essential for tear production, composition regulation, and the preservation of a stable and healthy tear film. This unit ensures optimal light transmission through the refractive media of the eye, ultimately enabling high-quality visual perception. Within this system, the meibomian glands—located in the eyelids—contribute to the lipid layer of the tear film, limiting evaporation and ensuring its even distribution across the ocular surface[1-2].

Disruption of eyelid anatomy and function due to age-related malpositions, trauma, malignancy, or involutional changes may impair this functional unit, leading to ocular surface disorders, most commonly dry eye disease (DED)[3]. Furthermore,

surgical correction of eyelid pathologies may exacerbate DED symptoms through the use of topical anesthetics, antiseptic agents (such as povidone-iodine or chlorhexidine), temporary lagophthalmos, and postoperative medication regimen[4]. These iatrogenic factors can delay wound healing, worsen patient-reported symptoms, and diminish postoperative quality of life.

Among the various topical therapies used for DED, sodium hyaluronate (SH) eye drops are widely recognized for their hydrating and viscoelastic properties. SH contributes to tear film stability, protects the corneal epithelium, and enhances overall ocular surface comfort[5-6]. A recent systematic review[7] has further highlighted the value of SH as a key component in artificial tear formulations, emphasizing its effectiveness in both alleviating symptoms and supporting long-term ocular surface integrity. Meta-analyses have confirmed these benefits, showing superiority of hyaluronate over saline in improving tear production and stability, although outcomes are often comparable to other artificial tears[8]. Similarly, higher concentrations of hyaluronate appear to improve corneal staining but not necessarily tear break-up time (TBUT) or Ocular Surface Disease Index (OSDI), suggesting that concentration alone may not address all aspects of ocular surface dysfunction[9].

In recent years, trehalose—a naturally occurring disaccharide-has attracted increasing attention for its multifaceted biological properties, including antioxidant, anti-inflammatory, and osmoprotective effects. Trehalose has been shown to maintain cellular morphology, prevent oxidative damage, stabilize lipid membranes, and activate autophagy-related signaling pathways, all of which contribute to epithelial preservation and tear film homeostasis[8-13]. Recent reviews have further highlighted its role in interrupting the inflammatory cycle of DED and enhancing epithelial resilience under hyperosmotic stress[14-15]. Clinical studies have also demonstrated that trehalose–hyaluronate combinations improve signs and symptoms of DED across different age groups, particularly in peri- and post-menopausal women[16]. Moreover, systematic evidence suggests that while hyaluronate remains the benchmark comparator in artificial tear research, osmoprotectants such as trehalose may provide incremental benefits[17].

The synergistic combination of trehalose and SH offers multifactorial benefits in the management of DED, including epithelial protection, anti-inflammatory effects, and tear film stabilization. While their efficacy has been explored in non-surgical settings, evidence regarding their role in oculoplastic patients remains limited-especially during the early postoperative period when the ocular surface is most susceptible to inflammation and disruption. Recent pharmacological reviews have emphasized a paradigm shift toward multimodal tear substitutes that combine humectants with osmoprotectants or antioxidants, further supporting the rationale for evaluating trehalose–hyaluronate formulations in this context[14,18].

In our study, we evaluated whether a formulation containing 3% trehalose and 0.15% sodium hyaluronate (TD) provides superior ocular surface recovery compared to SH monotherapy following eyelid surgery. To the best of our knowledge, this is the first study to evaluate the post-oculoplastic ocular surface recovery using a trehalose-based tear substitute, not only in a general cohort but also stratified by distinct surgical subgroups (ectropion, entropion, and reconstructive procedures). A key strength of our study lies in its stratified analysis by surgical indication (ectropion, entropion, and eyelid reconstruction), offering novel insight into how postoperative tear film dynamics and epithelial healing may differ across oculoplastic subtypes.

PARTICIPANTS AND METHODS

Ethical Approval This was a retrospective, comparative study conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Ankara Etlik City Hospital (approval number: AEŞH-EK1-2023-625). Informed consent was waived due to the retrospective nature of the study. Because of its retrospective nature, treatment allocation was not randomized but based on real-world clinical practice.

Study Design A total of 114 patients who underwent eyelid surgery (including entropion, ectropion, traumatic defects, or eyelid malignancies) between August 2021 and July 2024 were included. Patients were divided into two treatment groups based on the postoperative tear substitutes used: Group SH (n=57): treated with 0.15% SH eye drops; Group TD (n=57): treated with a combination of 3% trehalose and 0.15% SH.

SH was chosen as the comparator because it represents the most widely accepted baseline supportive therapy in ocular surface disease and is routinely prescribed in the postoperative management of oculoplastic patients, owing to its hydrating, viscoelastic, and epithelial-protective properties[5-7].

Patients received either 0.15% SH (Eyestil®, SIFI S.p.A., Catania, Italy) or TD (Thealoz Duo®, Théa Pharma, Clermont-Ferrand, France), administered four times daily for 3mo. Both formulations contained identical buffer and preservative composition. Lot numbers were recorded and are available upon request. All patients were instructed to use the prescribed drops four times daily for 3mo postoperatively. In Group SH, there were 25 patients with ectropion, 15 with entropion, and 17 who underwent eyelid reconstruction. In Group TD, there were 23 patients with ectropion, 17 with entropion, and 17 who underwent reconstruction. Treatment allocation was based on physician preference in routine practice; no systematic bias in availability or cost.

Surgical Procedures All procedures were performed by a single experienced oculoplastic surgeon. The lateral tarsal strip (LTS) technique was employed for ectropion correction, and the Wies procedure for entropion. Patients undergoing reconstruction received techniques such as full-thickness skin grafts, rotational flaps, or tarsorrhaphy, as appropriate.

Exclusion Criteria The exclusion criteria included: age under 18y; systemic medications affecting tear film (*e.g.*, antihistamines, antidepressants); incomplete clinical data; preexisting corneal ectatic or degenerative disorders; history of ocular surface surgery (*e.g.*, refractive surgery, corneal cross-linking); ocular surface evaluation.

The following clinical parameters were assessed both preoperatively and at 3-month follow-up: TBUT: measured with fluorescein; OSDI: a validated symptom questionnaire; Oxford staining score: evaluated using fluorescein staining; meibomian gland loss (MGL): determined by meibography using Sirius topography (CSO, Florence, Italy). Percent dropout was automatically calculated with the built-in software (default threshold/binarization settings), and values were expressed as a percentage of total tarsal area. All images were reviewed by a single experienced grader masked to treatment group; therefore, inter-grader repeatability could not be assessed; non-invasive TBUT (NITBUT): assessed *via* corneal topography; central corneal epithelial thickness (CCET): measured by anterior segment optical coherence tomography (OCT; RTVue-XR, Optovue Inc., USA). Representative images from meibography, NITBUT, and OCT measurements are presented in Figures 1-3.

Statistical Analysis Data were analyzed using SPSS software version 23.0 (IBM Corp., Armonk, NY, USA). Between-group comparisons were performed using independent-samples *t*-tests for normally distributed data or Mann-Whitney *U* tests for non-normally distributed data. Within-group pre/post comparisons were analyzed using paired *t*-tests or Wilcoxon signed-rank tests, as appropriate. Subgroup analyses followed the same approach. Categorical variables were evaluated with Chi-square or Fisher's exact tests. All *P*-values were two-tailed, and a value of <0.05 was considered statistically significant. As this was a retrospective study including all consecutive eligible cases during the study period, no a-priori sample size calculation was performed. To convey precision, between-group mean differences with 95% confidence intervals are reported for primary and key secondary outcomes. All patients had complete datasets for the evaluated parameters; therefore, analyses were performed on a complete-case basis without imputation.

RESULTS

A total of 114 patients were included in the study (mean age: 70.3±12.1y; 25 females, 89 males). Group SH comprised 57 patients (15 females, 42 males; mean age: 69.2±11.4y), while Group TD also included 57 patients (10 females, 47 males; mean age: 71.5±12.8y). There were no statistically significant differences between groups regarding age, gender, or surgical indication (Table 1).

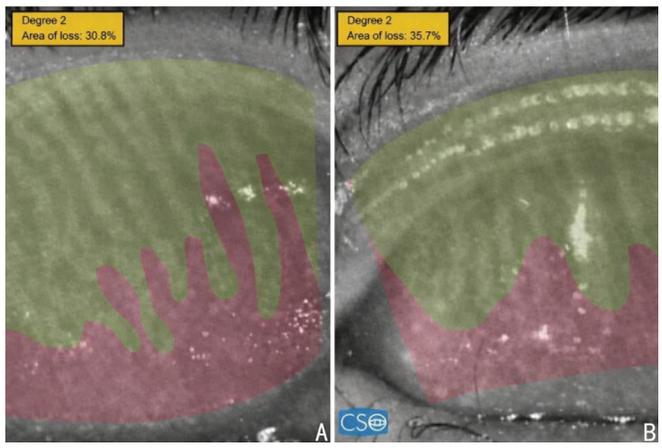

Figure 1 Representative pre- and post-operative infrared meibography images obtained with Sirius topography (CSO, Florence, Italy) from a patient in the ectropion subgroup A: Pre-operative image showing partial meibomian gland dropout (MGL=30.8%, Degree 2); B: Post-operative image of the same patient at 3mo showing a similar gland loss pattern (MGL=35.7%, Degree 2). The small difference in percentage is most likely related to illumination, lid eversion, or thresholding artefacts rather than true anatomical change. MGL: Meibomian gland loss.

Table 1 Demographic and surgical characteristics of the study groups

Variable	SH group (*n*=57)	TD group (*n*=57)	*P*
Age (mean±SD, y)	69.2±11.4	71.5±12.8	0.552
Gender (F/M)	15/42	10/47	0.204
Ectropion (*n*)	25	23	0.812
Entropion (*n*)	15	17	0.793
Reconstruction (*n*)	17	17	0.961

SH: Sodium hyaluronate; TD: Trehalose+sodium hyaluronate; SD: Standard deviation; F/M: Female/male.

Both treatment groups demonstrated postoperative improvements across all ocular surface parameters; however, the TD group showed more pronounced changes in most outcomes (Table 2).

Subgroup Analysis Ectropion (*n*=48): TD-treated patients (*n*=23) exhibited greater improvement in TBUT, Oxford score, MGL, and CCET compared to SH-treated patients (*n*=25). TBUT increased by 3.58s in the TD group versus 2.93s in the SH group (*P*=0.041). No significant difference was found in OSDI (*P*=0.461). Entropion (*n*=32): TD treatment resulted in significantly better outcomes for TBUT (*P*=0.038), Oxford score (*P*=0.030), and CCET (*P*=0.045). Improvements in OSDI were comparable between groups (*P*=0.552), while MGL showed a favorable but non-significant trend in the

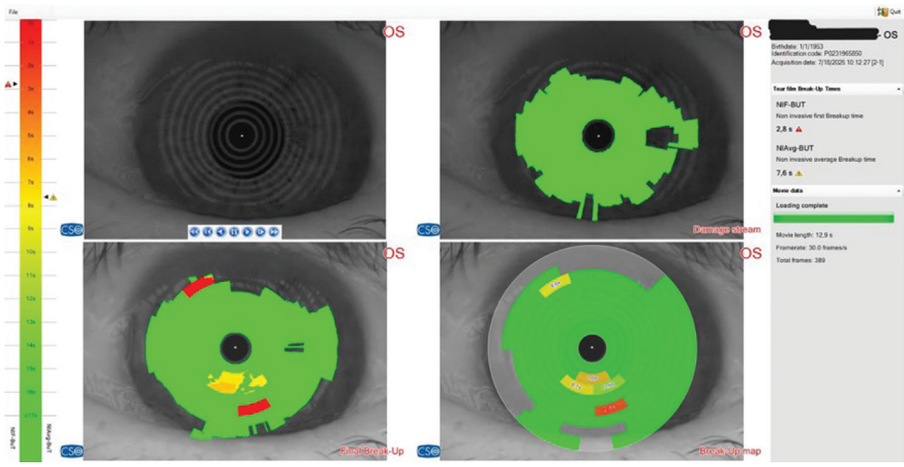

Figure 2 Representative non-invasive tear break-up time (NIBUT) assessment obtained with Scheimpflug-based corneal topography (Sirius, CSO, Florence, Italy) The color-coded scale bar indicates tear film stability, with shorter times (red zones) representing earlier break-up and increased tear film instability.

Table 2 Comparison of clinical parameters before and after treatment mean±SD

Parameter	SH group		TD group		*P*
	Before	After	Before	After	
TBUT (s)	4.48±1.84	7.62±1.42	4.92±1.71	8.39±1.28	0.036
OSDI	52.12±6.45	41.99±6.02	51.91±7.14	42.90±4.77	0.533
Oxford staining score	1.96±0.90	1.06±0.84	1.75±0.84	0.67±0.47	0.036
MGL (%)	49.79±8.67	50.55±6.56	46.96±9.61	45.60±9.45	0.025
CCET (μm)	52.60±3.90	53.30±3.50	52.80±4.10	54.70±3.20	0.048

Between-group comparisons were performed using independent-samples *t*-tests or Mann-Whitney *U* tests, as appropriate. Between-group mean differences with 95% confidence intervals (CI) are reported; all *P*-values are two-tailed. SH: Sodium hyaluronate; TD: Trehalose+sodium hyaluronate; TBUT: Tear break-up time; OSDI: Ocular Surface Disease Index; MGL: Meibomian gland loss; CCET: Central corneal epithelial thickness; SD: Standard deviation.

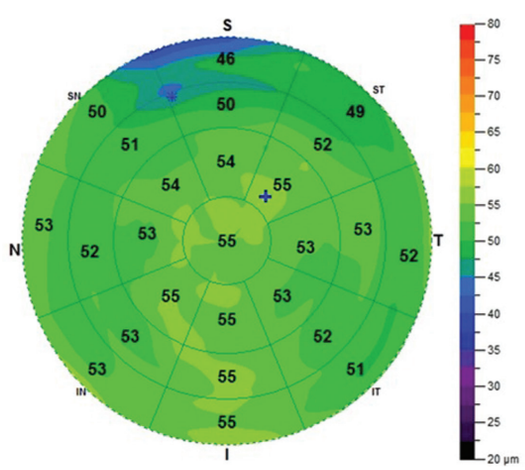

Figure 3 Representative epithelial thickness map obtained *via* anterior segment optical coherence tomography (AS-OCT) Color-coded distribution illustrates regional variability in corneal epithelial thickness (CCET). Central epithelial thickness measures 55 μm (blue cross), with relatively uniform paracentral values (range: 51–55 μm). The superior quadrant shows localized thinning (down to 46 μm), while the inferior zone remains thicker. The scale bar (right) indicates thickness in micrometers (μm).

TD group (*P*=0.184). Reconstruction (*n*=34): TD-treated patients demonstrated significantly superior outcomes across all measured parameters, including TBUT (*P*=0.018), OSDI (*P*=0.043), Oxford score (*P*=0.022), MGL (*P*=0.037), and CCET (*P*=0.041), suggesting a particular benefit in complex surgical settings. A complete breakdown of subgroup pre- and postoperative values, along with corresponding *P*-values, is presented in Table 3.

DISCUSSION

In our study, trehalose-based therapy led to superior improvements in TBUT, epithelial staining scores, and CCET, with notable protection against postoperative MGL—particularly in patients undergoing reconstructive procedures. This study is one of the first to evaluate these effects across surgical subgroups (ectropion, entropion, and reconstruction), revealing distinct advantages of trehalose-based therapy in both objective outcomes and complex surgical settings.

Dry eye symptoms are commonly observed following eyelid surgery and are often attributed to intraoperative and postoperative factors. The use of topical anesthetics, antiseptics such as povidone-iodine or chlorhexidine, prolonged exposure to surgical lights, and postoperative lagophthalmos can all contribute to iatrogenic ocular surface damage and tear

Table 3 Subgroup analysis of pre/post values mean±SD

Parameters	Ectropion (pre to post)		*P*	Entropion (pre to post)		*P*	Reconstruction (pre to post)		*P*
	SH	TD		SH	TD		SH	TD	
TBUT (s)	4.42±1.78 to 7.35±1.48	4.60±1.70 to 8.18±1.23	0.041	4.30±1.74 to 7.05±1.42	4.50±1.65 to 8.05±1.18	0.038	4.15±1.88 to 6.75±1.55	4.10±1.70 to 8.35±1.07	0.018
OSDI	51.6±6.3 to 42.1±5.7	51.2±7.0 to 42.6±4.4	0.461	52.1±6.6 to 41.6±6.1	52.6±6.7 to 42.4±4.5	0.552	53.0±6.3 to 42.3±6.2	52.7±6.2 to 42.1±4.3	0.043
Oxford score	1.92±0.87 to 1.08±0.82	1.75±0.84 to 0.66±0.46	0.032	2.00±0.91 to 1.18±0.83	1.82±0.87 to 0.64±0.43	0.030	2.05±0.92 to 1.20±0.86	1.84±0.89 to 0.59±0.39	0.022
MGL (%)	49.6±8.7 to 50.3±7.0	47.1±9.0 to 45.2±8.9	0.027	50.3±8.9 to 50.8±7.2	47.2±9.1 to 45.5±9.0	0.184	50.9±9.1 to 51.4±7.6	46.4±9.2 to 44.7±9.3	0.037
CCET (μm)	52.5±3.7 to 53.2±3.5	52.9±4.1 to 54.7±3.2	0.049	52.1±4.0 to 53.0±3.6	53.0±4.1 to 54.6±3.4	0.045	52.0±3.8 to 53.0±3.7	53.2±4.2 to 54.8±3.3	0.041

Subgroup comparisons were analyzed using independent-sample *t*-test or Mann-Whitney *U* tests, as appropriate. Between-group mean differences with 95% confidence intervals (CI) are reported; all *P*-value are two-tailed. SH: Sodium hyaluronate; TD: Trehalose+sodium hyaluronate; TBUT: Tear break-up time; OSDI: Ocular Surface Disease Index; MGL: Meibomian gland loss; CCET: Central corneal epithelial thickness; SD: Standard deviation.

film instability[3-4]. These factors may worsen pre-existing dry eye symptoms, delay epithelial healing, and negatively affect patient satisfaction. Therefore, identifying an effective treatment strategy that supports ocular surface recovery is of particular clinical importance.

SH is widely used in the management of DED due to its viscoelastic and water-retentive properties. It helps restore tear film stability, improve corneal hydration, and enhance patient comfort. Its high molecular weight allows for prolonged residence time on the ocular surface, which improves epithelial healing and reduces mechanical irritation[5-6]. Recent systematic reviews have supported its effectiveness, although growing evidence suggests that SH may be further enhanced when combined with trehalose-based agents for greater biological impact[7]. Recent Meta-analyses have further confirmed these benefits, showing that hyaluronate outperforms saline in improving tear stability and corneal staining, although its efficacy is sometimes comparable to other artificial tear formulations, and concentration alone may not fully address all aspects of ocular surface dysfunction[8-9].

Trehalose, a non-reducing disaccharide, has gained attention for its antioxidative and osmoprotective properties. It has been shown to reduce oxidative stress, maintain epithelial integrity, and prevent desiccation-induced apoptosis. Furthermore, trehalose activates cellular autophagy pathways, which help clear damaged proteins and organelles, thereby preserving ocular surface homeostasis[10,12,19]. In addition, trehalose has demonstrated anti-inflammatory effects by downregulating proinflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and matrix metalloproteinase-9 (MMP-9), all of which play a role in ocular surface inflammation[19-20]. This mechanistic role has been confirmed in human corneal epithelial models exposed to hyperosmotic stress, suggesting its particular relevance to post-surgical inflammation[19]. Beyond these cellular effects, recent reviews emphasize that trehalose not only mitigates oxidative and osmotic stress but also interrupts the self-perpetuating inflammatory cycle of DED, thereby positioning it as an attractive adjunct in multimodal tear substitutes[14-15]. Our observation is further supported by recent *in vitro* evidence showing that hyaluronate–trehalose formulations enhance epithelial resilience under oxidative and hyperosmotic stress while suppressing pro-inflammatory mediators, providing a mechanistic explanation for their clinical benefits[21].

In the present study, both treatment groups showed significant improvement in dry eye signs and symptoms after eyelid surgery. However, the combination of 3% trehalose and 0.15% SH (Group TD) led to greater improvements in TBUT, Oxford staining scores, and meibomian gland integrity compared to SH alone. These findings suggest that trehalose may provide additional protective benefits beyond symptomatic relief, potentially contributing to tissue-level healing and homeostasis.

Although OSDI scores improved similarly in both groups, objective clinical parameters-such as TBUT, staining scores, and gland loss—demonstrated the superiority of the trehalose-containing formulation. These results are consistent with previous studies reporting enhanced epithelial recovery and reduced inflammation with trehalose-based therapies[10,12,19]. Additionally, a randomized comparative trial reported superior OSDI improvement in patients using hyaluronate-trehalose solutions versus SH alone, reinforcing the advantage of this combination in moderate to severe dry eye[22]. Notably, recent short-term dry eye trials found that trehalose–hyaluronate combinations improved comfort but did not significantly differ from other artificial tears in NIBUT outcomes, suggesting that the stronger benefit observed in our surgical cohort may reflect the additive oxidative and inflammatory stress induced by surgery[23].

Our study also showed that trehalose was more effective in minimizing MGL postoperatively. Given that meibomian gland dysfunction is a major contributor to evaporative dry

eye, this finding highlights the potential long-term benefits of trehalose in preserving tear film quality and lipid layer stability. These findings are especially relevant in patients undergoing reconstructive eyelid procedures. Recent evidence indicates that such surgeries may permanently affect ocular surface health and meibomian gland structure, particularly in upper eyelid reconstruction cases[24-25].

Furthermore, the role of eyelid malpositions such as ectropion and entropion in exacerbating ocular surface inflammation has been demonstrated in large-scale studies, suggesting that patients with these conditions are already at a disadvantage in terms of tear film integrity[26-27]. In this context, protective agents such as trehalose may yield disproportionately greater benefit.

Although previous studies have reported gender-related variability in subjective symptom perception, particularly higher OSDI scores among female patients despite comparable clinical findings, our study showed no significant intergroup difference in OSDI scores, likely due to the balanced gender distribution between treatment arms[28]. Moreover, the discrepancy between objective improvements and subjective scores supports the notion that OSDI may not fully capture treatment-related ocular surface changes. In line with recent expert recommendations[29], comprehensive assessment combining both subjective and objective parameters is essential to guide multimodal treatment strategies in complex ocular surface settings.

A major strength of this study is the inclusion of stratified subgroup analyses, which enabled a refined understanding of how trehalose-based therapy performs across varying oculoplastic procedures. To our knowledge, this is the first clinical investigation to systematically assess the efficacy of trehalose in specific surgical subpopulations—namely ectropion, entropion, and reconstructive cases—revealing differential benefits, particularly in complex reconstructions. The combined use of both subjective and advanced objective metrics, such as CCET and infrared meibography, further strengthens the validity and clinical relevance of our findings.

However, several limitations should be acknowledged. The retrospective design limits the ability to infer causality, and the absence of randomization in treatment allocation may have introduced selection bias despite comparable baseline characteristics between groups. Although the 3-month follow-up provides meaningful short-term outcomes, it may not fully capture long-term ocular surface remodeling. While the sample size was adequate for statistical comparisons, future prospective studies with larger cohorts and extended follow-up are warranted to validate and expand upon these findings. Additionally, the study lacked an a-priori power calculation, and subgroup analyses were exploratory; therefore, some comparisons—particularly OSDI and smaller subgroups—may be under-powered. The small, non-physiologic increase in MGL observed in the SH group over the short follow-up is likely measurement-related, reflecting variability in illumination/contrast, eyelid eversion tension/angle, postoperative contour/edema, and the threshold sensitivity of the binarization algorithm. In addition, inter-grader repeatability (κ/ICC) could not be assessed for the full dataset because grading was performed by a single evaluator in routine practice; this is acknowledged as a methodological limitation. In addition, the distribution of patients across subgroups was not entirely balanced, particularly between reconstructive and non-reconstructive cases, which may limit the generalizability of subgroup comparisons. More advanced statistical methods (*e.g.*, propensity matching or regression adjustment) could not be applied due to dataset limitations, which represents another potential source of bias. Another limitation is that neither patients nor examiners were masked to treatment allocation, which may have introduced observer or reporting bias.

In conclusion, the addition of trehalose to SH therapy significantly enhances postoperative ocular surface recovery following eyelid surgery. This benefit was particularly evident in patients undergoing reconstructive procedures and was consistently supported by improvements in both epithelial and meibomian gland metrics. Trehalose may serve as a critical adjunct in postoperative care protocols, especially in high-risk oculoplastic patients. Future studies should further explore its role in long-term tear film stabilization and patient-reported quality of life.

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Data Avaliability: All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of Interest: Arslan N, None; **Kakil ŞB,** None; **Çoban A,** None.

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