



# Effectiveness of a New Active Tear Substitute Containing 0.2% Hyaluronic Acid and 0.001% Hydrocortisone on Signs and Symptoms of Dry Eye Disease by Means of Low- and High-Tech Assessments

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## ABSTRACT

**Introduction:** An innovative eye drops formulation containing 0.2% hyaluronic acid and a low concentration of hydrocortisone (0.001%; hereafter HALH) has been recently placed on the market (Idroflog<sup>®</sup>, Alfa Intes, Italy) to manage the dysregulated parainflammation in patients with dry eye disease (DED). In the present paper, the effectiveness of HALH on the signs and symptoms of DED was retrospectively evaluated and compared with that one obtained using standard tear substitutes (STS) by means of low- and high-tech (Keratograph<sup>®</sup>) assessments.

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**Methods:** This was a multicenter retrospective study carried out between February and April 2023, involving adult patients with DED diagnosis owing to post-cataract surgery, meibomian gland dysfunction, allergy, or glaucoma medications. The primary aim was to compare the changes induced by different therapies on Keratograph<sup>®</sup> parameters (noninvasive Keratograph tear breakup time [NIK BUT], tear meniscus height [TMH], eyelid meibography, conjunctival hyperemia, and conjunctivochalasis) or collected by traditional low-tech measures (tear breakup time [TBUT], Schirmer test, Efron score, and epithelial alterations) and the Ocular Surface Disease Index score.

**Results:** Data from 155 patients were analyzed. The effectiveness of HALH and STS was reported by both high- and low-tech measures. NIK BUT-

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first showed a significant improvement in the HALH group versus the STS one at 15 days ( $6.4 \pm 3.6$  vs  $5.4 \pm 3.7$  s,  $p = 0.02$ ), whereas this difference was latent with low-tech TBUT until 45 days ( $6.8 \pm 2.6$  vs  $5.6 \pm 2.3$  s,  $p = 0.03$ ). Patients with DED occurring after cataract surgery reported an enhanced activity of HALH versus STS, particularly for NIKBUT-first, TMH, Schirmer test, and hyperemia stage.

**Conclusion:** These findings highlighted the effectiveness of HALH in all DED subtypes, especially in patients with post-cataract surgery, as well as its superiority versus STS in terms of tear film stability improvement. We recommend longer observation (i.e., 3–6 months) to fully ascertain whether the early improvement detected by high-tech measures will be confirmed in subsequent time points even using low-tech tests.

**Keywords:** Dry eye disease; DED; Hydrocortisone; Inflammation; Tear film; Lubricating eye drops

### Key Summary Points

#### *Why carry out this study?*

Although traditional lubricating eye drops can relieve symptoms of dry eye disease (DED), they are poorly effective in counteracting specifically dysregulated parainflammation, one of the main underlying pathological mechanisms.

An innovative eye drops formulation containing 0.2% hyaluronic acid and a low concentration of hydrocortisone (0.001%; hereafter HALH) has been recently placed on the market to manage the dysregulated parainflammation in patients with DED.

In the present paper, the effectiveness of HALH on the signs and symptoms of DED was retrospectively evaluated and compared with that one obtained using standard tear substitutes (STS) by means of low- and high-tech (Keratograph®) assessments.

#### *What was learned from the study?*

The effectiveness of HALH and STS was documented by both high- and low-tech measures. However, the present results suggested the superiority of HALH treatment versus STS in terms of tear film stability improvement.

Early and additional significant differences between the two groups were reported with high-tech measures compared with low-tech assessments.

Longer observation (i.e., 3–6 months) are recommended to fully ascertain whether the early improvement detected by using high-tech measures will be confirmed at subsequent time points using low-tech tests.

## INTRODUCTION

Dry eye disease (DED) is a chronic, multifactorial disease of the ocular surface (OS), characterized by either decreased tear production or increased evaporation [1, 2]. DED alters OS homeostasis, causing reduced tear production, increased evaporation, OS inflammation, increased tear film osmolarity, and tissue damage [2]. This mechanism tends to perpetuate by creating the vicious circle of dry eye [3]. DED presents with a range of symptoms that vary in severity in each patient, and include eye irritation, stinging and foreign body sensations, ocular fatigue and vision impairment [1]. Although DED is one of the most common ocular disorders, with a prevalence range from 5 to 50% depending on the geographic region, it is still underdiagnosed and undertreated [4–8]. Some risk and predisposing factors for DED can be identified, such as ocular allergy, cataract surgery, preserved eye drops, and meibomian gland dysfunction (MGD) among others [9–12].

Traditionally, common clinical measures used for diagnosing DED and OS impairment are fluorescein tear breakup time (TBUT), OS fluorescein staining, Schirmer test and hyperemia assessment [13, 14]. However, both TBUT

and Schirmer test are limited by their invasiveness, which affects the OS response and may lead to increased tearing reflex. Moreover, different patterns of tear rupture can be seen in DED, making TBUT difficult to interpret, with consequent low repeatability and reproducibility [15, 16]. TBUT is also a subjective test whose cut-off values are not fully validated: generally, 10 s is an accepted cut-off [13], but it has been suggested that if the volume of fluorescein used is lower (a desirable strategy because it induces less OS modifications) 5 s would be a proper cut-off [17]. Likewise, the assessment of hyperemia can be influenced by the subjectivity of the operator. In addition, these parameters can be poorly related to symptoms and, sometimes, poorly responsive to adequate treatment [18, 19]. Otherwise, the ocular discomfort symptoms of DED are effectively measured with questionnaires, among which the OSDI (Ocular Surface Disease Index) score is the most validated [20].

Recently, new tools for the instrumental diagnosis and monitoring of DED have been introduced in the clinical practice [21]. Among these, Keratograph<sup>®</sup> is an all-in-one device increasingly used for the study of OS diseases, as it allows automated, non-eye contact evaluation of noninvasive Keratograph tear breakup time (NIKBT), tear meniscus height (TMH), eyelid meibography, conjunctival hyperemia, and conjunctival folds as a sign of conjunctivochalasis (hereafter conjunctivochalasis) [16, 22].

The use of tear substitutes to lubricate the OS is regularly prescribed in the case of DED, representing the mainstay of treatment [4]. Most products on the market contain hyaluronic acid (HA) as their main component, which has important lubricating and moisturizing properties able to improve the stability of the tear film thanks to the specific strong interactions with the mucus layer in the ocular surface [23–25]. HA also promotes wound healing thanks to its specific activity on CD44 receptors expressed by corneal epithelium [26]. Other products contain carboxymethylcellulose and polyethylene glycol [4]. However, traditional lubricating eye drops can relieve the symptoms of DED but are poorly effective in counteracting specifically the

main underlying pathological mechanism, namely dysregulated parainflammation, which has recently been recognized as an important pathogenetic step in the progression of tear dysfunction in DED [27, 28]. Therefore, to act on this pathological factor as well, an innovative HA-based eye drops formulation has recently been placed on the market (Idroflog<sup>®</sup>, Alfa Intes, Italy; class III medical device) [29]. In addition to the presence of 0.2% HA, this innovative product contains a low concentration of hydrocortisone (0.001%; hereafter termed hyaluronic acid and low-hydrocortisone eye drops, HALH), a synthetic analogue of cortisol, which is normally produced at the level of the OS to provide the first line of defense to potential exogenous, pro-inflammatory triggers and restore the homeostasis [30]. According to a recently published clinical study, the treatment with HALH proved to control macrophage infiltration, reducing the immune system involvement and leading to an easier recovery of OS homeostasis [31]. Therefore, the product has the advantage not only of lubricating and moisturizing the OS but also of controlling the sub-clinical inflammatory component [31].

In the present paper, the effectiveness of HALH was retrospectively evaluated and compared with standard lubrication to test the hypothesis that treating OS parainflammation might give a clinical advantage over standard lubrication on different subtypes of DED. A positive result of the study would allow a better customization of DED treatment. We also studied the impact of low- and high-tech measures on measuring OS changes over time after each therapy, thus proving further real-life data on the possible advantage of using high-tech imaging on DED management.

## METHODS

### Study Design and Setting

This was a retrospective analysis carried out at six Italian ophthalmologic referral centers (University Hospital “G. Martino”, Messina, coordinating center; San Paolo and San Giuseppe Hospitals, Milan; University Hospital

Careggi, Florence, University Policlinic “Mater Domini”, Catanzaro; Mediterranea Eye Clinic, Naples) between February and April 2023. The study involved adult ( $\geq 18$  years) patients with DED diagnosis (OSDI score  $> 13$ ; TBUT  $< 7$  s) related to one of the following conditions: (1) recent (at least 1 month and less than 12 months) cataract surgery-related dry eye; (2) MGD according to at least one sign among obstruction of the meibomian glands, alteration of the position of the glandular lumens relative to the mucocutaneous junction, and abnormal secretion (including foamy secretion); (3) allergic conjunctivitis based on both clinical signs (hyperemia, follicles and/or papillae) and symptoms (itching, lacrimation); (4) chronic use ( $> 1$  year) of hypotensive eye drops containing benzalkonium chloride or prostaglandin analogues following a diagnosis of ocular hypertension or glaucoma.

Patients using a tear substitute following the diagnosis of DED and receiving noninvasive examination using Keratograph<sup>®</sup> (K5M; Oculus Optikgeräte GmbH, Wetzlar, Germany) at the time of diagnosis and follow-up visits (after 15 and 45 days) were considered. Data from patients on topical anti-inflammatory therapy (corticosteroids, NSAIDs, cyclosporine), with Sjogren’s syndrome-related DED or other concomitant OS diseases, presenting moderate and severe corneal and/or conjunctival epitheliopathy (Oxford score  $> 3$ ), pregnant or lactating were not collected. Patients who used contact lenses or other concomitant topical eye drops, apart from hypotensive products containing benzalkonium chloride or prostaglandin in patients with glaucoma and antihistamine eye drops and membrane stabilizers in allergic patients, were not considered. Medical records from September 2021 to December 2022 were considered.

Patients were retrospectively divided into two groups according to the treatment prescribed at diagnosis:

1. Standard group: patients treated with a standard tear substitute (STS) (Systane<sup>®</sup> ultra, Alcon, hereafter termed STS treatment Su; Optive Fusion<sup>®</sup>, Allergan, hereafter

termed STS treatment OF; Thealoz<sup>®</sup> Duo, Thea, hereafter termed STS treatment TD);

2. HALH group: patients treated with the HA-based low-hydrocortisone eye drops containing 0.2% sodium hyaluronate and 0.001% hydrocortisone sodium phosphate (Idroflog<sup>®</sup>, Alfa Intes; Italy; medical device class III).

The study was conducted in accordance with the Declaration of Helsinki of 1964 and its later amendments. The inter-company Ethics Committee of Messina approved this study (Protocol number: 38–23). All participants provided written informed consent for using clinical data for scientific purposes.

### Study Measures

The study’s primary aim was to retrospectively compare the changes induced by different therapies on the parameters measured by Keratograph<sup>®</sup> or collected by traditional low-tech measures and the OSDI score.

The following Keratograph<sup>®</sup> parameters were collected from the medical records: NIKBUT (first, average and class), TMH, conjunctival hyperemia, eyelid meibography and conjunctivochalasis. Low-tech measures were TBUT, Schirmer test, epithelial damage and slit-lamp grading of hyperemia according to Efron scale. The OSDI score was also considered. All measures were collected retrospectively at the diagnosis (T0) and 15- and 45-day follow-up visits. For each patient, the worst eye at baseline – intended as the one with lower TBUT at T0 or, if both eyes had the same TBUT, the eye with lower NIKBUT – was considered. Eventual relevant side effects (e.g., increased intraocular pressure) were collected from medical records.

### Statistical Analysis

Continuous variables were shown as mean and standard deviation or median and interquartile range, and categorical variables as number and percentage. For comparison of continuous variables within the same patients, the Wilcoxon signed-rank test was used. For the

comparison of continuous variables between patients, the Mann–Whitney test was used. McNemar’s test was used to compare categorical variables among patients. An analysis by subgroups was carried out to verify a possible interaction between the pathology triggering lacrimal dysfunction and the effect of the eye drops. Three subgroups were identified based on the cause of the lacrimal dysfunction: allergy, MGD and DED owing to cataract surgery. Patients using glaucoma medications were excluded because of the small sample size ( $n = 9$ ). Furthermore, the comparisons were repeated for each eye drop to verify the possible interaction between the drug effect and each specific drug.

## RESULTS

### Demography and Baseline Characteristics

A total of 155 patients were considered in the study; 92 (59%) were females (mean [SD] age was 63 [16] years). At the diagnosis of DED, 76 (49%) patients were prescribed HALH, 79 (51%) STS. The demography and baseline characteristics of patients were homogeneous (Table 1).

The study’s main findings are reported in Table 2 (high-tech data) and Table 3 (low-tech data). Subgroup analyses according to DED subtype and STS treatment are reported in Table 4 and in Supplementary Tables 1–4.

### Tear Film Stability

A significant improvement in the NIKBUT-first parameter was reported after 15 and 45 days in all patients treated with HALH, compared with baseline ( $5.3 \pm 3.3$  vs  $6.4 \pm 3.6$  vs  $7.2 \pm 3.4$  s;  $p < 0.001$  at both time points; Fig. 1; Table 2). In patients treated with other products, the improvement was significant only after 45 days of treatment compared with baseline ( $5.4 \pm 4.6$  vs  $6.1 \pm 3.7$  s;  $p = 0.020$ ; Fig. 1; Table 2). At both time points, the NIKBUT-first was significantly improved in the HALH group compared with the STS group (Fig. 1; Table 2;  $p < 0.05$  for both).

Patients with MGD receiving HALH had better NIKBUT first than those receiving STS after 15 days of treatment ( $8.6 \pm 6.6$  vs  $4.5 \pm 4.8$  s,  $p = 0.026$ ); HALH was also more effective than STS in patients undergone cataract surgery after 45 days of treatment ( $7.5 \pm 3.5$  vs  $5.4 \pm 3.0$  s;  $p = 0.006$ ; Table 4). Subgroup analyses according to treatment further support this result, reporting a significant difference in NIKBUT-first between HALH and STS treatment Su (most used in patients with MGD) after 15 days ( $p = 0.010$ ; Table 4) and between HALH and STS treatment TD (most used after cataract surgery) at both time points ( $p = 0.029$  and  $p = 0.009$ , respectively; Table 4).

The NIKBUT-average parameter showed a significant improvement after 15 days ( $8.3$  [6.4–10.4] s) and 45 days ( $9.5$  [7.4–12.2] s) in patients treated with HALH compared with baseline ( $7.4$  [4.8–9.6] s;  $p \leq 0.001$ ) at both time points. Patients treated with other products showed a clinical improvement only after 45 days ( $8.8$  [6.5–11.8] versus  $7.0$  [5.0–9.7] s;  $p = 0.005$ ).

Regarding NIKBUT class, after 15 days of HALH, there was no significant variation (Table 5; McNemar’s test,  $p = 0.146$ ); in contrast, after 45 days of treatment, 22 (29%) patients improved their NIKBUT class, reporting a significant variation of this parameter (Table 5; McNemar’s test,  $p = 0.004$ ). No significant variation of NIKBUT class was reported among STS patients during the study period.

The mean TBUT assessed with low technology reported a significant improvement after 15 and 45 days of treatment in both patients group, compared with baseline ( $p < 0.001$  for all comparisons; Table 3). A significant improvement in mean TBUT was reported in the HALH group compared with the STS group only after 45 days of treatment ( $6.8 \pm 2.6$  vs  $5.6 \pm 2.3$  s,  $p = 0.002$ ; Table 3).

### Tear Production Assessment

The mean TMH values assessed by Keratograph<sup>®</sup> were homogeneous at baseline between groups ( $p = 0.610$ ; Table 2). No significant differences were reported in the mean TMH after 15 and



**Table 1** Baseline characteristics

Characteristics	HALH group	STS group	<i>p</i> value
Overall population			
<i>n</i> = 155	<i>n</i> = 76	<i>n</i> = 79	–
Females ( <i>n</i> = 92)	41 (54%)	51 (65%)	0.194
Age (years)	63 ± 17	64 ± 15	0.948
OSDI score	29 ± 15	29 ± 14	0.955
NIKBUT first (s)	5.3 ± 3.3	5.4 ± 4.6	0.502
TBUT (s)	4.5 ± 1.5	4.2 ± 1.7	0.202
Patients with allergy			
<i>n</i> = 37	16 (21%)	21 (27%)	–
Females ( <i>n</i> = 26)	9 (56%)	17 (81%)	0.108
Age (years)	42 ± 18	52 ± 20	0.162
OSDI score	31 ± 12	31 ± 13	0.938
NIKBUT first (s)	5.2 ± 3.5	5.2 ± 3.0	0.987
TBUT (s)	3.9 ± 1.3	4.0 ± 1.5	0.897
Patients with MGD			
<i>n</i> = 29	12 (16%)	17 (22%)	–
Females ( <i>n</i> = 26)	6 (50%)	9 (53%)	0.878
Age (years)	58 ± 18	67 ± 10	0.081
OSDI score	45 ± 18	38 ± 15	0.308
NIKBUT-first (s)	7.3 ± 6.3	3.6 ± 6.9	0.711
TBUT (s)	3.3 ± 1.2	2.6 ± 1.3	0.211
Patients post-cataract surgery			
<i>n</i> = 74	37 (49%)	37 (47%)	–
Females ( <i>n</i> = 42)	20 (54%)	22 (60%)	0.641
Age (years)	73 ± 8	70 ± 8	0.057
OSDI score	20 ± 7	21 ± 8	0.349
NIKBUT first (s)	5.0 ± 1.7	5.0 ± 4.2	0.158
TBUT (s)	5.5 ± 1.1	5.1 ± 1.4	0.211

**Table 1** continued

Characteristics	HALH group	STS group	<i>p</i> value
Patients with glaucoma			
<i>n</i> = 9	6 (8%)	3 (4%)	–
Females ( <i>n</i> = 9)	6 (8%)	3 (4%)	0.490
Age (years)	73 ± 8	73 ± 11	0.957
OSDI score	37 ± 17	43 ± 18	0.545
NIKBUT first (s)	4.0 ± 1.9	3.9 ± 2.3	0.933
TBUT (s)	3.7 ± 1.0	4.0 ± 0.0	0.577

Data are presented as *n* (%) or mean ± SD

*NIKBUT* noninvasive Keratograph tear breakup time, *TBUT* tear breakup time, *OSDI* Ocular Surface Disease Index, *MGD* meibomian gland dysfunction, *SD* standard deviation, *STS* standard tear substitute, *HALH* hyaluronic acid and low-hydrocortisone eye drops

45 days of treatment compared with baseline in the overall population (Table 2). Comparable mean TMH values were reported between groups at 15 and 45 days (Table 2).

Otherwise, in the subgroup of patients with DED after cataract surgery, an improvement in mean TMH was reported after 45 days of treatment in the HALH group compared with baseline and the STS group ( $p = 0.002$  for both; Supplementary Table 1).

The assessment of tear production by the Schirmer test reported a significant improvement in the HALH group at both time points compared with baseline ( $p = 0.041$  at 15 days, and  $p < 0.001$  at 45 days; Table 3); otherwise, in the STS group, the improvement was reported only after 45 days of treatment ( $p = 0.001$ ; Table 3). Comparable Schirmer test values were reported between groups at 15 and 45 days (Table 3).

Improvement in the Schirmer test at both time points compared with baseline was reported in patients with DED after cataract surgery treated only with the HALH ( $p = 0.023$  and  $p < 0.001$ , respectively; Supplementary Table 1); however, this difference was not significant when compared with the STS group (Supplementary Table 1).

**Table 2** High-tech data in the overall study population

	NIK BUT first (s)			TMH (mm)			Automated assessment of hyperemia			Eyelid meibography <sup>§</sup>			Conjunctivochalasis <sup>°</sup>		
	HALH (n = 73)	STS (n = 75)	p value <sup>^^</sup>	HALH (n = 75)	STS (n = 79)	p value <sup>^^</sup>	HALH (n = 75)	STS (n = 79)	p value <sup>^^</sup>	HALH (n = 76)	STS (n = 79)	p value <sup>^^</sup>	HALH (n = 63)	STS (n = 67)	p value <sup>^^</sup>
T0	5.3 ± 3.3	5.4 ± 4.6	0.502	0.33 ± 0.27	0.30 ± 0.16	0.610	1.5 ± 0.6	1.8 ± 2.1	0.935	60 (79%)	70 (87%)	0.103	12 (19%)	15 (22%)	0.671
T15	6.4 ± 3.6	5.4 ± 3.7	<b>0.021</b>	0.33 ± 0.25	0.30 ± 0.15	0.636	1.3 ± 0.5	1.5 ± 0.7	0.321	60 (79%)	67 (85%)	0.345	12 (19%)	13 (19%)	1.000
p value <sup>^</sup>	< <b>0.001</b>	0.331	-	0.922	0.308	-	< <b>0.001</b>	<b>0.038</b>	-	1.000 <sup>^^^^</sup>	0.250 <sup>^^^^</sup>	-	1.000 <sup>^^^^</sup>	0.625 <sup>^^^^</sup>	-
T45	7.2 ± 3.4	6.1 ± 3.7	<b>0.030</b>	0.31 ± 0.13	0.31 ± 0.15	0.321	1.3 ± 0.4	1.4 ± 0.6	0.600	59 (79%)	66 (84%)	0.441	12 (19%)	14 (21%)	1.000
p value <sup>^</sup>	< <b>0.001</b>	<b>0.020</b>	-	0.147	0.507	-	< <b>0.001</b>	<b>0.003</b>	-	1.000 <sup>^^^^</sup>	0.125 <sup>^^^^</sup>	-	1.000 <sup>^^^^</sup>	1.000 <sup>^^^^</sup>	-

Statistically significant differences were reported in bold

TMH tear meniscus height, NIK BUT noninvasive Keratograph tear breakup time, T0 baseline, T15 15 days after treatment, T45 45 days after treatment, HALH hyaluronic acid and low-hydrocortisone eye drops, STS standard tear substitute, DED dry eye disease

<sup>^</sup>Wilcoxon signed-rank test

<sup>^^</sup>Mann–Whitney test

<sup>^^^</sup>Chi-square analysis

<sup>^^^^</sup>McNemar's test

<sup>°</sup>Percentage of patients with altered eyelid meibography (score 1, 2, 3)

<sup>§</sup>Percentage of patients with conjunctivochalasis

**Table 3** Low-tech data in the overall study population

	Schirmer test (mm)			Efron scale score <sup>§</sup>			Epithelial alterations <sup>§</sup>			OSDI score					
	HALH (n = 75)	STS (n = 79)	p value <sup>^^</sup>	HALH (n = 67)	STS (n = 64)	p value <sup>^^</sup>	HALH (n = 63)	STS (n = 67)	p value <sup>^^</sup>	HALH (n = 75)	STS (n = 79)	p value <sup>^^</sup>			
T0	4.6 ± 1.4	4.2 ± 1.7	0.230	11.5 ± 6.3	11.6 ± 8.0	0.615	49 (73%)	47 (73%)	0.969	17 (27%)	29 (43%)	0.053	28.5 ± 15.5	28.7 ± 13.8	0.913
T15	5.7 ± 2.1	5.1 ± 2.5	0.075	12.2 ± 5.4	11.5 ± 6.7	0.095	42 (63%)	47 (73%)	0.189	15 (24%)	21 (31%)	0.339	20.8 ± 9.6	21.9 ± 9.4	0.318
p value <sup>^</sup>	< 0.001	< 0.001	-	0.041	0.597	-	0.065 <sup>^^^</sup>	1.000 <sup>^^^</sup>	-	0.727 <sup>^^^</sup>	0.039 <sup>^^^</sup>	-	< 0.001	< 0.001	-
T45	6.8 ± 2.6	5.6 ± 2.3	0.002	14.0 ± 6.6	12.8 ± 7.4	0.053	34 (52%)	39 (62%)	0.236	12 (19%)	15 (22%)	0.640	17.4 ± 9.8	18.5 ± 8.3	0.066
p value <sup>^</sup>	< 0.001	< 0.001	-	< 0.001	0.001	-	< 0.001 <sup>^^^</sup>	0.057 <sup>^^^</sup>	-	0.063 <sup>^^^</sup>	0.003 <sup>^^^</sup>	-	< 0.001	< 0.001	-

Statistically significant differences were reported in bold

T0 baseline, T15 15 days after treatment, T45 45 days after treatment, HALH hyaluronic acid and low-hydrocortisone eye drops, STS standard tear substitute, OSDI Ocular Surface Disease Index, TBUT tear breakup time

<sup>^</sup>Wilcoxon signed-rank test

<sup>^^</sup>Mann-Whitney test

<sup>^^^</sup>Chi-square analysis

<sup>§</sup>McNemar's test

<sup>§</sup>Percentage of patients with hyperemia (score 1, 2, 3, 4)

<sup>§</sup>Percentage of patients with epithelial alterations

## Conjunctival Hyperemia

Automated assessment of hyperemia showed a significant improvement in both groups of patients during the follow-up period ( $p < 0.001$  in the HALH group at both time points;  $p = 0.038$  and  $p = 0.003$  in the STS group at 15- and 45-days post-treatment, respectively; Table 2), without significant differences between groups (Table 2).

In the subgroup of patients with post-cataract surgery DED, hyperemia was improved after 15 and 45 days of treatment compared with baseline values ( $p = 0.008$  and  $p < 0.001$ , respectively) only in the HALH group (Supplementary Table 2). However, no significant difference was reported between the two groups at different time points ( $p = 0.241$  and  $0.331$  after 15 and 45 days of treatment, respectively). Among STS treatments, only OF treatment after 45 days showed a significant improvement in hyperemia compared with baseline ( $p = 0.023$ ; Supplementary Table 3).

A significant improvement in the Efron scale score was reported in the HALH group after 45 days of treatment ( $p < 0.001$ ; Table 3), without significant differences between groups at both time points (Table 3). However, after 15 days of HALH treatment, there was a significant improvement in the hyperemia stage in the subgroup of patients with post-cataract surgery DED ( $n = 9$ , 36% of patients improved their stage; McNemar's test,  $p = 0.004$ ). This improvement was enhanced at 45 days when 48% of patients ( $n = 12$ ) improved their hyperemia stage (McNemar's test,  $p \leq 0.001$ ). In the STS group, the improvement in the hyperemia stage was reported only at the 45-day follow-up visit ( $n = 12$ , 48%; McNemar's test,  $p < 0.001$ ).

## Eyelid Meibography and Conjunctivochalasis

No differences were reported between groups in the follow-up period for eyelid meibography and conjunctivochalasis parameters at each time point (Table 2).



**Table 4** Subgroup analyses of NIKBUT-first (seconds) according to lacrimal dysfunction and treatment

	HALH group	STS group	<i>p</i> value*
Patients with MGD			
Baseline	7.3 ± 6.3	3.6 ± 6.9	0.711
15 days	8.6 ± 6.6	4.5 ± 4.8	<b>0.026</b>
45 days	7.6 ± 4.1	7.1 ± 5.4	0.677
Patients post-cataract surgery			
Baseline	5.0 ± 1.7	5.0 ± 4.2	0.158
15 days	6.1 ± 2.9	5.5 ± 3.7	0.121
45 days	7.5 ± 3.5	5.4 ± 3.0	<b>0.006</b>
Patients with allergy			
Baseline	5.2 ± 3.5	5.2 ± 3.0	0.987
15 days	6.5 ± 2.3	6.8 ± 3.9	0.950
45 days	6.9 ± 2.5	6.7 ± 3.2	0.539
<b>STS treatment Su</b>			
	HALH group	STS treatment Su	<i>p</i> -value*
Baseline	5.3 ± 3.3	5.4 ± 5.4	0.190
15 days	6.4 ± 3.6	5.1 ± 4.0	<b>0.010</b>
45 days	7.2 ± 3.4	6.4 ± 4.0	0.203
<b>STS treatment TD</b>			
	HALH group	STS treatment TD	<i>p</i> value*
Baseline	5.3 ± 3.3	5.4 ± 5.0	0.213
15 days	6.4 ± 3.6	5.2 ± 3.6	<b>0.029</b>
45 days	7.2 ± 3.4	5.5 ± 3.7	<b>0.009</b>

Mean ± SD were reported

NIK BUT noninvasive Keratograph tear breakup time, HALH hyaluronic acid and low-hydrocortisone eye drops, STS standard tear substitute, MGD meibomian gland dysfunction, Su Systane® ultra, TD Thealoz® Duo, SD standard deviation

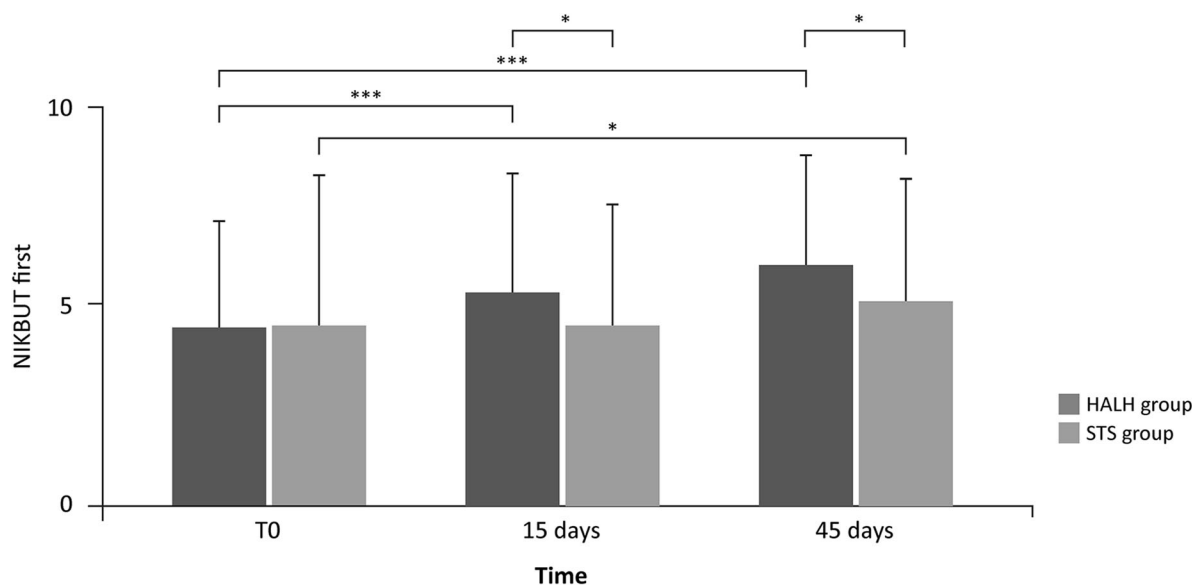
\*Statistically significant *p* values are reported in bold

### Epithelial Alterations

The proportion of patients with epithelial damage was reduced in both HALH and STS patients from baseline to the 45-day follow-up visit; the percentage reduction was significant only in the STS group ( $p = 0.035$  at 15 days and  $p = 0.003$  at 45 days). No significant differences were reported between the two groups (Table 3).

### OSDI Score

Both treatments reported significant improvement in symptoms during the follow-up as measured by the OSDI score ( $p < 0.001$  for all comparisons; Table 3). No differences were reported between groups at each time point (Table 3).



**Fig. 1** NIKBUT first. A significant improvement in the NIKBUT first was reported after 15 and 45 days in patients treated with the low-hydrocortisone eye drops and at 45 days in patients treated with standard tear substitutes, compared with baseline. The NIKBUT first was significantly improved in the HALH group compared with

the STS group at both time points.  $***p < 0.001$ ;  $*p < 0.05$ . NIKBUT noninvasive Keratograph tear breakup time, HALH hyaluronic acid and low-hydrocortisone eye drops, STS standard tear substitute

**Table 5** NIKBUT class analysis in the HALH group by follow-up visits

Class	Baseline, n (%)			
	0	1	2	3
15 days ( $n = 74$ )				
0	10 (14%)	1 (1%)	0	0
1	1 (1%)	27 (37%)	7 (10%)	0
2	0	3 (4%)	24 (32%)	1 (1%)
45 days ( $n = 75$ )				
0	9 (12%)	6 (8%)	1 (1%)	0
1	2 (3%)	21 (28%)	15 (20%)	0
2	0	4 (5%)	16 (21%)	1 (1%)

NIKBUT noninvasive Keratograph tear breakup time, HALH hyaluronic acid and low-hydrocortisone eye drops

In the subgroup of patients with post-cataract surgery DED treated with HALH, the OSDI score significantly decreased after 45 days

compared with the STS group ( $p = 0.048$ ; Supplementary Table 4). No relevant side effects (e.g., increased IOP) were reported in medical records.

## DISCUSSION

The noninvasive diagnostic workup of DED using high-tech, all-in-one devices, such as Keratograph<sup>®</sup>, have been recommended by experts and is gaining popularity in many settings thanks to several major advantages [32]. Indeed, the procedure is operator-independent, contactless, and no dyes are required. Aside from the request not to blink during the video recording of NIKBUT analysis, which may lead to increased tearing reflex, OS homeostasis is by far less altered than with low-tech measures, thus providing a more objective assessment of DED parameters than low-tech measures [16].

Keratograph<sup>®</sup> has been successfully used for the diagnosis and monitoring of various OS diseases in recent studies [21, 33–37], the most commonly studied parameter being NIKBUT. A

recent randomized trial showed that the discriminative ability of NIKBUT in detecting dry eye is significantly higher than TBUT (area under the receiver operating characteristic curve of 0.68 and 0.57, respectively) [38]. At the same time, the reproducibility of this measure is still debated: it has been reported that it may be high in some patients (even higher than TBUT) [39], although other reports suggested that TBUT is more reproducible than NIKBUT [16, 40, 41].

In this study, we retrospectively evaluated the activity of HALH versus standard lubricating eye drops in the most common types of DED (post-cataract surgery, MGD, allergy and glaucoma medications). Overall, the efficacy of HALH and STS in treating DED was confirmed by both high- and low-tech measures. Yet, HALH treatment achieved higher significance than STS when changes were inspected by Keratograph<sup>®</sup> NIKBUT-first ( $p < 0.001$  and  $p < 0.05$ , respectively; Table 2). NIKBUT-first showed a significant improvement in the HALH group versus STS at 15 days, whereas such a difference was latent with TBUT until 45 days.

The superiority of high-tech measures in detecting changes at follow-up was previously supported [34] while refuted elsewhere [35, 42]. Using Keratograph<sup>®</sup>, we were able to report early and additional significant differences among treatments compared with the use of low-tech assessments and to report the enhanced activity of the HALH treatment even in specific DED subgroups: NIKBUT-first in the HALH group was enhanced in patients with MGD after 15 days of treatment and in patients who had undergone cataract surgery after 45 days of treatment. Moreover, only patients in the HALH group reported a statistically significant improvement in the NIKBUT class after 45 days of treatment.

Such a feature was also reported by comparing other parameters. TMH and Schirmer are noninvasive and invasive tests for quantitatively evaluating tears amount, respectively [43]. In this study, both parameters significantly improved at follow-up; however, only TMH was able to identify earlier and more frequent changes than the Schirmer test, which were all in favor of HALH. Nevertheless, results on TMH

and Schirmer test should be interpreted with caution because the tearing reflex may have been stimulated during the study examination, particularly in the context of a retrospective, clinical-based study.

Conjunctival hyperemia is an important sign of OS irritation and inflammation [44]. Both STS and HALH treatments improved conjunctival hyperemia and reduced the percentage of patients reporting epithelial alterations. When considering hyperemia in patients with DED after cataract surgery treated with HALH, the improvement was significant compared with baseline at both time points ( $p = 0.008$  and  $p < 0.001$ , respectively), although without differences between groups. Low-tech measures supported this result, reporting a significant improvement in the hyperemia stage at both 15 days (36% of patients improved their stage) and 45 days (48% of patients improved their stage) of treatment in the HALH group. Regarding epithelial damage, a significant improvement was reported only in the STS group, although the difference at 45 days was not statistically significant between treatments. Moreover, it must be considered that the severity of epithelial damage at baseline was different in the two groups (27% for HALH versus 43% for STS), making recovery more likely in the STS group.

Both treatments reported significant improvement in symptoms during the follow-up period, as measured by the OSDI score in the overall population ( $p < 0.001$  for all comparisons). Again, considering the subgroup of patients with post-cataract surgery DED treated with HALH, the OSDI score significantly decreased after 45 days compared with the STS group.

Taken together, our results support the effectiveness of the new tear substitute containing HA and a low hydrocortisone concentration compared with STS in the qualitative and quantitative improvement in the tear film in patients with different types of DED. Yet, it is essential to highlight that statistically significant differences may not always be clinically relevant and, thus, caution in data interpretation is mandatory. In fact, in the literature there is paucity of studies that evaluate if the changes

in OS parameters are clinically meaningful. To the best of our knowledge, only one study measured the minimal clinically important difference for OSDI [45]. Assuming as clinically relevant a change of OSDI score in mild DED ranging from 4.5 to 7.3 units, both HALH and STS were clinically effective in the whole study population and in all subgroups.

Recent literature suggests that several degenerative changes in the OS occur with age, within a process called inflammaging [46, 47]. It is a chronic, subclinical form of dysregulated parainflammation that arises with aging and includes tear instability, decreased tear production, increased OSDI score, and inflammatory markers [48]. With aging, parainflammatory compensatory mechanisms fail to adequately restore OS homeostasis. This leads to a persistent asymptomatic inflammatory state, particularly evident following an insult, such as cataract surgery [48]. Low-concentration use of hydrocortisone can help the system to recover more effectively than STS [31]. From a speculative point of view, this may explain the observed enhanced activity of the HALH treatment, particularly in patients with surgically-related DED, who were older than other subgroups, and thus may be mainly involved in inflammaging processes.

Our findings related to the use of STS agree with previous studies evaluating the effectiveness of these treatments by assessing the OSDI score and TBUT value [49–52]. At the same time, high-tech parameters, such as NIKBUT, were previously used on DED subjects to assess the activity of STS [33, 42, 53–55].

Our data are consistent with previous findings that highlighted the possible advantages of high technology to better diagnose and monitor patients with DED. Nonetheless, the clinical advantage of high-tech still needs to be fully verified and more extensive research with head-to-head studies as well as meta-analyses are needed to draw firmer conclusions. In particular, the best NIKBUT parameter (first, average, or class) to use has not yet been defined, nor is the agreement between high- and low-tech measures. For instance, in our cohort, patients ameliorating one NIKBUT class ( $n = 43$ ) or more had a decrease in the OSDI score from  $29 \pm 16$

at baseline to  $17 \pm 7$  at day 45 ( $p < 0.001$ ). The OSDI score for patients with stable NIKBUT class ( $n = 94$ ) was  $27 \pm 13$  at baseline and  $18 \pm 9$  at day 45 ( $p < 0.001$ ). The OSDI score for patients who worsened NIKBUT class ( $n = 16$ ) was  $35 \pm 17$  at baseline and  $21 \pm 12$  at day 45 ( $p = 0.007$ ). The lack of significant correlation between low- and high-tech measures and the OSDI score, as well as the poor correlation between low- and high-tech measures, has already been reported using a cross-sectional dataset [35]. These aspects will be addressed in a subsequent paper, exploring the correlation occurring in DED measures during follow-up.

This study has some limitations, mainly related to the retrospective design and the lack of patient randomization. The sample size was large enough to provide robust statistics, but the glaucoma group was poorly represented and therefore not analyzed separately. In addition, the study duration was limited; despite the progressive amelioration of parameters in both groups at 45 days, it is reasonable to hypothesize that further improvement could have been achieved with a longer follow-up. However, our dataset reflects the multicenter, real-life clinical practice use of HALH and STS, which can be considered a study's strength potentially improving the generalizability of the results.

## CONCLUSION

Our study combines, for the first time, low- and high-tech measures to retrospectively compare the activity of HALH treatment versus STS. Obtained results suggest its effectiveness in all DED subtypes, especially in patients who had undergone cataract surgery, and its superiority in terms of tear film stability improvement.

Moreover, our data showed that the beneficial effects of HALH treatment are progressive over the observation period. Considering the concept of inflammaging, prolonged use is needed to fully recover system homeostasis. From this viewpoint, it is also possible that longer treatment will highlight further differences in terms of activity between HALH and STS.

Based on the variation in latency shown by low-tech versus high-tech measures, we recommend longer observation (i.e., 3–6 months) to fully ascertain whether the early improvement documented by means of high-tech measures will be confirmed at subsequent time points using low-tech tests.

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**Authors Contributions.** Study design: Paolo Fogagnolo; data collection and interpretation: Paolo Fogagnolo, Giuseppe Giannaccare, Rita Mencucci, Edoardo Villani, Vincenzo Orfeo, Pasquale Aragona; manuscript writing: Paolo Fogagnolo; manuscript editing: Paolo Fogagnolo, Giuseppe Giannaccare, Rita Mencucci,

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**Data Availability.** The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

### Declarations

**Conflicts of Interest.** Paolo Fogagnolo, Giuseppe Giannaccare, Rita Mencucci, Edoardo Villani, Vincenzo Orfeo and Pasquale Aragona have nothing to disclose.

**Ethical Approval.** The study was conducted in accordance with the Declaration of Helsinki of 1964 and its later amendments. The study was conducted with the protocol approved by the inter-company Ethics Committee of Messina (protocol number 38-23). All the participants signed an informed consent form.

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## REFERENCES

1. Tsubota K, Pflugfelder SC, Liu Z, et al. Defining dry eye from a clinical perspective. *Int J Mol Sci.* 2020;21:9271.
2. Willcox MDP, Argüeso P, Georgiev GA, et al. TFOS DEWS II tear film report. *Ocul Surf.* 2017;15:366–403.
3. Baudouin C, Messmer EM, Aragona P, et al. Revisiting the vicious circle of dry eye disease: a focus on the pathophysiology of meibomian gland dysfunction. *Br J Ophthalmol.* 2016;100:300–6.
4. Mohamed HB, Abd El-Hamid BN, Fathalla D, Fouad EA. Current trends in pharmaceutical treatment of dry eye disease: a review. *Eur J Pharm Sci.* 2022;175:106206.
5. Craig JP, Nelson JD, Azar DT, et al. TFOS DEWS II report executive summary. *Ocul Surf.* 2017;15:802–12.
6. Wróbel-Dudzińska D, Osial N, Stepień PW, Gorecka A, Żarnowski T. Prevalence of dry eye symptoms and associated risk factors among university students in Poland. *Int J Environ Res Public Health.* 2023;20(2):1313.
7. Papas EB. The global prevalence of dry eye disease: a Bayesian view. *Ophthalmic Physiol Opt.* 2021;41:1254–66.
8. Akowuah PK, Kobia-Acquah E. Prevalence of dry eye disease in Africa: a systematic review and meta-analysis. *Optom Vis Sci.* 2020;97:1089–98.
9. Villani E, Rabbio G, Nucci P. Ocular allergy as a risk factor for dry eye in adults and children. *Curr Opin Allergy Clin Immunol.* 2018;18:398–403.
10. Villani E, Catania AG, Luccarelli SV, et al. Dry eye and cataract surgery: narrative review and recommendations for management. *Eur J Ophthalmol.* 2023. <https://doi.org/10.1177/11206721231174060>. (online ahead of print).
11. Fogagnolo P, Torregrossa G, Tranchina L, et al. Tear film osmolarity, ocular surface disease and glaucoma: a review. *Curr Med Chem.* 2019;26:4241–52.
12. Villani E, Marelli L, Dellavalle A, Serafino M, Nucci P. Latest evidences on meibomian gland dysfunction diagnosis and management. *Ocul Surf.* 2020;18:871–92. <https://doi.org/10.1016/j.jtos.2020.09.001>.
13. Wolffsohn JS, Arita R, Chalmers R, et al. TFOS DEWS II diagnostic methodology report. *Ocul Surf.* 2017;15:539–74. <https://doi.org/10.1016/j.jtos.2017.05.001>.
14. Phadatare SP, Momin M, Nighojkar P, Askarkar S, Singh KK. Comprehensive review on dry eye disease: diagnosis, medical management, recent developments, and future challenges. *Adv Pharmaceutics.* 2015;2015:704946.
15. Nichols KK, Mitchell GL, Zadnik K. The repeatability of clinical measurements of dry eye. *Cornea.* 2004;23:272–85. <https://doi.org/10.1097/00003226-200404000-00010>.
16. Tian L, Qu JH, Zhang XY, Sun XG. Repeatability and reproducibility of noninvasive Keratograph 5m measurements in patients with dry eye disease. *J Ophthalmol.* 2016;2016:8013621.
17. Abelson MBO, Nally LA, Welch D, Krenzer K. Alternative reference values for tear film break up time in normal and dry eye populations. *Adv Exp Med Biol.* 2002;506:1121e5.
18. Bartlett JD, Keith MS, Sudharshan L, Snedecor SJ. Associations between signs and symptoms of dry eye disease: a systematic review. *Clin Ophthalmol.* 2015;9:1719–30. <https://doi.org/10.2147/OPHT.S89700>.
19. Kyei S, Dzasimatu SK, Asiedu K, Ayerakwah PA. Association between dry eye symptoms and signs. *J Curr Ophthalmol.* 2018;30:321–5. <https://doi.org/10.1016/j.joco.2018.05.002>.
20. Schiffman RM. Reliability and validity of the ocular surface disease index. *Arch Ophthalmol.* 2000;118(5):615.
21. Inferrera L, Aragona E, Wylęgała A, et al. The role of hi-tech devices in assessment of corneal healing in patients with neurotrophic keratopathy. *J Clin Med.* 2022;11:1602. <https://doi.org/10.3390/jcm11061602>.
22. Abdelfattah NS, Dastiridou A, Satta SR, Lee OL. Noninvasive imaging of tear film dynamics in eyes with ocular surface disease. *Cornea.* 2015;34:S48–52.
23. Huynh A, Priefer R. Hyaluronic acid applications in ophthalmology, rheumatology, and dermatology. *Carbohydr Res.* 2020;489:107950.
24. You IC, Li Y, Jin R, Ahn M, Choi W, Yoon KC. Comparison of 0.1%, 0.18%, and 0.3% hyaluronic acid eye drops in the treatment of experimental dry eye. *J Ocul Pharmacol Ther.* 2018;34:557–64.
25. Černohlávek M, Brandejsová M, Štěpán P, et al. Insight into the lubrication and adhesion properties of hyaluronan for ocular drug delivery.

- Biomolecules. 2021;11:1431. <https://doi.org/10.3390/biom11101431>.
26. Lardner E, van Setten GB. Detection of TSG-6-like protein in human corneal epithelium. Simultaneous presence with CD44 and hyaluronic acid. *J Fr Ophthalmol*. 2020;43(9):879–83.
  27. Reyes JL, Vannan DT, Eksteen B, et al. Innate and adaptive cell populations driving inflammation in dry eye disease. *Mediat Inflamm*. 2018;2018:1–12.
  28. Rolando M, Barabino S. The subtle role of para-inflammation in modulating the progression of dry eye disease. *Ocul Immunol Inflamm*. 2021;29:811–6.
  29. Idroflog®. SmPC. <https://www.alfaintes.it/storage/attachments/0220139001648132342.pdf>.
  30. Susarla R, Liu L, Walker EA, et al. Cortisol biosynthesis in the human ocular surface innate immune response. *PLoS ONE*. 2014;9: e94913.
  31. Rolando M, Vilella E, Loreggian L, et al. Long-term activity and safety of a low-dose hydrocortisone tear substitute in patients with dry eye disease. *Curr Eye Res*. 2023. <https://doi.org/10.1080/02713683.2023.2214948>. (Epub ahead of print).
  32. NEW 13.
  33. Mencucci R, Mercuri S, Cennamo M, Morelli A, Favuzza E. Efficacy of vector thermal pulsation treatment in reducing postcataract surgery dry eye disease in patients affected by meibomian gland dysfunction. *J Cataract Refract Surg*. 2023;49:423–9. <https://doi.org/10.1097/j.jcrs.0000000000001124>.
  34. Zarei-Ghanavati S, Hassanzadeh S, Azimi Khorasani A, Ehsaei A, Bakhtiari E. Efficacy of five-flash intense pulsed light therapy technique in patients with meibomian gland dysfunction. *Clin Exp Optom*. 2022;105:687–93. <https://doi.org/10.1080/08164622.2021.1976595>.
  35. Sutphin JE, Ying GS, Bunya VY, et al. Correlation of measures from the OCULUS Keratograph and clinical assessments of dry eye disease in the dry eye assessment and management study. *Cornea*. 2022;41:845–51. <https://doi.org/10.1097/ICO.0000000000002804>.
  36. Seo KY, Kang SM, Ha DY, Chin HS, Jung JW. Long-term effects of intense pulsed light treatment on the ocular surface in patients with rosacea-associated meibomian gland dysfunction. *Cont Lens Anterior Eye*. 2018;41(5):430–5. <https://doi.org/10.1016/j.clae.2018.06.002>.
  37. Vicente García-Marqués J, Talens-Estarellles C, García-Lázaro S, Cerviño A. Assessment of condition-induced changes on the ocular surface using novel methods to assess the tear film dynamics and the lipid layer. *Cont Lens Anterior Eye*. 2023;46:101799.
  38. Wang MTM, Craig JP. Comparative evaluation of clinical methods of tear film stability assessment: a randomized crossover trial. *JAMA Ophthalmol*. 2018;136:291–4.
  39. de Ruvo V, Strianese A, Roszkowska AM, et al. Variability of NIBUT and TBUT in healthy and dry-eye subjects. In: XXVII CONGRESSO NAZIONALE S. I.TRA.C, 16–18 February 2023.
  40. Cox SM, Nichols KK, Nichols JJ. Agreement between automated and traditional measures of tear film breakup. *Optom Vis Sci*. 2015;92:e257–63.
  41. Dutta D, Kim J, Sarkes M, Nath S, Markoulli M. The repeatability of subjective and objective tear ferning assessment and its association with lipid layer thickness, non-invasive tear break-up time and comfort. *Cont Lens Anterior Eye*. 2019;42:420–7.
  42. Kim YH, Kang YS, Lee HS, Choi W, You IC, Yoon KC. Effectiveness of combined tear film therapy in patients with evaporative dry eye with short tear film breakup time. *J Ocul Pharmacol Ther*. 2017;33:635–43. <https://doi.org/10.1089/jop.2017.0019>.
  43. Koh S, Ikeda C, Watanabe S, et al. Effect of non-invasive tear stability assessment on tear meniscus height. *Acta Ophthalmol*. 2015;93:e135–9. <https://doi.org/10.1111/aos.12516>.
  44. Aragona E, Arrigo A, Modorati G, Berchicci L, Banello F, Miserocchi E. Conjunctival vessel density analysis as a marker of inflammation in dry eye disease. *Ocul Surf*. 2023;29:398–400. <https://doi.org/10.1016/j.jtos.2023.06.011>.
  45. Miller KL, Walt JG, Mink DR, et al. Minimal clinically important difference for the ocular surface disease index. *Arch Ophthalmol*. 2010;128:94–101.
  46. Mashaghi A, Hong J, Chauhan SK, et al. Aging and ocular surface immunity. *Br J Ophthalmol*. 2017;101:1–5.
  47. Sharma A, Hindman HB. Aging: a predisposition to dry eyes. *Ophthalmology*. 2014;2014: 781683.
  48. Di Zazzo A, Micera A, Coassin M, et al. Inflammation at ocular surface: clinical and biomolecular analyses in healthy volunteers. *Investig Ophthalmol Vis Sci*. 2019;60:1769–75. <https://doi.org/10.1167/iov.18-25822>.
  49. Fogagnolo P, Romano D, De Ruvo V, Sabella P, Rossetti L. Clinical efficacy of an eyedrop containing hyaluronic acid and ginkgo biloba in the

- 
- management of dry eye disease induced by cataract surgery. *J Ocul Pharmacol Ther.* 2022;38:305–10. <https://doi.org/10.1089/jop.2021.0123>.
50. Fogagnolo P, Favuzza E, Marchina D, et al. New therapeutic strategy and innovative lubricating ophthalmic solution in minimizing dry eye disease associated with cataract surgery: a randomized, prospective study. *Adv Ther.* 2020;37:1664–74. <https://doi.org/10.1007/s12325-020-01288-z>.
51. Hynnekleiv L, Magno M, Vernhardsdottir RR, et al. Hyaluronic acid in the treatment of dry eye disease. *Acta Ophthalmol.* 2022;100:844–60. <https://doi.org/10.1111/aos.15159>.
52. Chiambaretta F, Doan S, Labetoulle M, et al. A randomized, controlled study of the efficacy and safety of a new eyedrop formulation for moderate to severe dry eye syndrome. *Eur J Ophthalmol.* 2017;27:1–9. <https://doi.org/10.5301/ejo.5000836>.
53. Roszkowska AM, Inferrera L, Spinella R, et al. Clinical efficacy, tolerability and safety of a new multiple-action eyedrop in subjects with moderate to severe dry eye. *J Clin Med.* 2022;11:6975. <https://doi.org/10.3390/jcm11236975>.
54. Vigo L, Senni C, Pellegrini M, et al. Effects of a new formulation of multiple-action tear substitute on objective ocular surface parameters and ocular discomfort symptoms in patients with dry eye disease. *Ophthalmol Ther.* 2022;11:1441–7. <https://doi.org/10.1007/s40123-022-00518-7>.
55. Molina-Solana P, Domínguez-Serrano FB, Garrido-Hermosilla AM, et al. improved tear film stability in patients with dry eye after hyaluronic acid and galactoxyloglucan use. *Clin Ophthalmol.* 2020;14:1153–9. <https://doi.org/10.2147/OPTH.S248949>.