Efficacy of 0.28% Sodium Hyaluronate Eye Drops in Patients with Moderate to Severe Dry Eye: A Randomized Double-blind Controlled Trial.

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Abstract

Background: Dry eye disease (DED) is a prevalent ocular condition, particularly in Asian populations, that adversely affects quality of life and visual function. While sodium hyaluronate (SH) artificial tears are commonly used, the optimal concentration remains unclear. This study compared the efficacy and safety of 0.28% versus 0.18% SH eye drops in patients with moderate to severe DED.

Methods: In this prospective, multicenter, randomized, double-blind controlled trial, patients with moderate to severe DED (OSDI ≥ 23, Oxford grading scale ≥ 2, FTBUT < 7 seconds) were randomized to receive either 0.28% or 0.18% SH eye drops in both eyes, six times daily for 30 days. The primary outcome was change in Oxford grading scale. Secondary outcomes included tear osmolarity, best corrected visual acuity (BCVA), fluorescein tear break-up time (FTBUT), ocular surface disease index (OSDI), quality of life (DEQS-Th), and adverse events, assessed at baseline and after 30 days.

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Results: Forty-six patients (92 eyes) were enrolled. The 0.28% SH group showed a significantly greater reduction in Oxford grading scale scores at 30 days compared to the 0.18% group (p = 0.024), with improvement in 91.3% versus 73.9% of patients, respectively (p = 0.021). The 0.28% SH group also achieved a clinically significant reduction in tear osmolarity post-instillation. BCVA improved significantly only in the 0.28% SH group, whereas FTBUT increased in both groups. In addition, both groups improved in OSDI and DEQS-Th scores, with no significant difference between groups. Adverse events were mild and similar between groups.
Conclusions: The 0.28% SH eye drops are safe and effective for treating moderate to severe DED, significantly reducing corneal staining and dry eye symptoms, and improving visual acuity and quality of life.
Conflict of Interest: The authors declare no competing interest.
Keywords: Artificial tears, Dry eye, Oxford grading scale, Tear osmolarity, Sodium hyaluronate
Trial Registration: ClinicalTrials.gov. (registration number: NCT06860659).
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Introduction

Dry eye disease is a common condition often associated with various other illnesses, and reports on its prevalence vary; however, it has been estimated to range from 5% to 50% globally.[1]

A systematic review and meta-analysis of Asian populations estimated the pooled prevalence of dry eye disease (DED) at 20.1%.[2] In Thailand, a study conducted by the Department of Ophthalmology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok found a prevalence rate of 34% among patients aged 40 years and older.[3] Another study, conducted by the Department of Ophthalmology, Faculty of Medicine, Chulalongkorn University, Bangkok, examined 625 individuals aged 50 to 90 years old and reported a 14.2% prevalence.[4] A recent study of 449 Thai medical students with a mean age of 21.8 years found a prevalence of dry eye disease symptoms of 60.4%.[5] The condition is more commonly observed in women than in men and shows an increased incidence with advancing age.[2,6] It manifests with diverse clinical characteristics and varying degrees of severity. In patients with mild forms, symptoms may cause only minor discomfort without significantly affecting ocular health or daily activities. However, in more severe cases, the disease has been reported to impact physical health, psychological well-being, independence, environmental interactions, social relationships, and even spiritual well-being.[7,8] Diagnosis and management of dry eye disease worldwide are based on the recommendations of the Tear Film and Ocular Surface Society (TFOS) International Dry Eye Workshop (DEWS) II.[9] Treatment strategies include behavioral and environmental modifications, the use of artificial tears, pharmacological interventions, and surgical procedures. Artificial tears play a principal role in the management of dry eye disease and are available in a variety of formulations that differ in active ingredients, electrolyte composition, osmolarity, and viscosity.[10] Several systematic reviews and meta-analyses have compared sodium hyaluronate (SH) eye drops with other active ingredients, including carbomer, polyvinyl alcohol (PVA), hydroxypropylmethylcellulose (HPMC or hypromellose), dextran-70, and carboxymethylcellulose (CMC). However, differences in the concentration of active ingredients, osmolarity, pH, the presence or absence of preservatives, and other formulation factors between SH eye drops and comparator agents make direct efficacy comparisons challenging.[11-14]

If we specifically consider SH-based artificial tears, SH is naturally present in the tear film, outer cornea, and vitreous humor.[15] Its mechanisms of action include tear film stabilization, binding to the corneal epithelium, cytoprotective effects, and anti-inflammatory properties.[11] SH-based artificial tears which are available worldwide typically contain concentrations ranging from 0.1% to 0.4%,[15] raising questions regarding the optimal SH concentration. However, artificial tears formulated for the treatment of dry eye disease should exhibit hypo-osmolar properties, as tear hyperosmolarity is recognized as a key initiating factor in the development and progression of

the disease.[16-18] Meanwhile, the ideal SH-based eye drops should enhance viscosity and prolong retention time without exceeding the threshold for visual blurring.[19]

In Thailand, a research and development team has formulated a new 0.28% SH eye drop treatment containing high molecular weight SH,[20] hypo-osmolar properties, and no preservatives, packaged in a unit-dose format. This formulation is anticipated to provide prolonged adhesion to the ocular surface and extended therapeutic effects. This study compares the widely used 0.18% SH eye drops in Thailand, which are characterized by high molecular weight SH, hypo-osmolar properties, and preservative-free unit-dose packaging. We hypothesized that 0.28% SH eye drops are at least equal in efficacy to 0.18% SH eye drops in treatment of patients with dry eye.

Methods

Study Design

This prospective, multicenter, randomized, double-blind, controlled non-inferiority trial was conducted in accordance with the tenets of the Declaration of Helsinki. Patients with moderate to severe dry eye were enrolled between September 2024 and March 2025. The study was conducted at the Departments of Ophthalmology in seven hospitals across Thailand: Rajavithi Hospital, Nakhonpathom Hospital, Mettapracharak (Wat Rai Khing) Hospital, Naresuan University Hospital, Panyananthaphikkhu Chonprathan Medical Center, Sisaket Hospital, and Prachuap Khiri Khan Provincial Hospital. The study followed the protocol and diagnostic criteria established by TFOS DEWS II.[21]

Sample size

The difference between 0.28% HA and 0.18% HA was defined as 1 point on the Oxford score. Based on a standard deviation of 1.68 reported in a previous study, a total of 90 eyes (45 eyes per group) was required to provide 80% power at a two-sided significance level of 5%. Allowing for an anticipated drop-out rate of 10%, a total of 50 patients (100 eyes) was planned for randomization to ensure sufficient statistical power for the primary endpoint analysis.

Participants

All participants who met the inclusion criteria were randomly allocated to one of two treatment groups. The first group were given 0.28% sodium hyaluronate (SH) eye drops in both eyes, while the second group received 0.18% SH eye drops in both eyes, as outlined in the protocol flowchart (Figure 1).

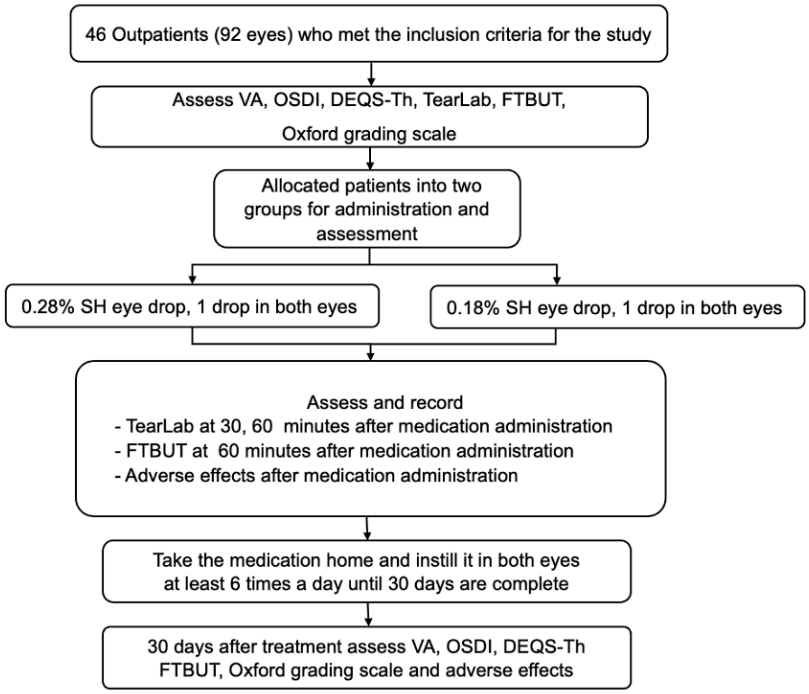


Figure 1: Protocol flow chart

The inclusion criteria required participants to fulfill the following conditions: (1) be at least 18 years of age; (2) have an Ocular Surface Disease Index (OSDI) score of 23 or higher; (3) exhibit an Oxford grading scale of at least 2 in both eyes; and (4) have a fluorescein tear break-up time (FTBUT) of less than 7 seconds in both eyes.

Patients were excluded if they met any of the following conditions: (1) presence of ocular diseases requiring treatment with medications not indicated for dry eye (e.g. steroid, glaucoma medications); (2) history of ocular surgery within the past 3 months, refractive surgery within the past 6 months, or prior history of punctal occlusion; (3) history of ocular trauma, infection, or ocular inflammation within the past 3 months; (4) current use of contact lenses; (5) documented allergy to sodium hyaluronate; (6) pregnancy or lactation; (7) systemic diseases adversely affecting ocular health that were not well controlled, such as uncontrolled diabetes mellitus, active autoimmune disease, or neurotrophic keratopathy induced by systemic neuropathy; or (8) use of medications known to cause persistent dry eye, such as retinoic acid derivatives, antihistamines, cholinergic agents, or antipsychotic treatments.

Ethical Approval

This study was approved by the Research Ethics Committees of Rajavithi Hospital, Nakhonpathom Hospital, Mettapracharak (Wat Rai Khing) Hospital, Naresuan University Hospital, Panyananthaphikkhu Chonprathan Medical Center, Sisaket Hospital, and Prachuap Khiri Khan Provincial Hospital (reference number: 67046). Written informed consent was obtained from all participants prior to their enrollment, and the study was conducted in accordance with the tenets of the Declaration of Helsinki.

Randomization

Participants were randomly assigned, using a computerized randomization method, to receive either 0.28% sodium hyaluronate eye drops (Vismax®, Pathumthani, Thailand; Lot No. A24029; expiry date: April 20, 2026) or 0.18% sodium hyaluronate eye drops (Vislube®, Abtsgmünd-Untergröningen, Germany; Lot No. SA0044; expiry date: April 20, 2026), with both interventions provided in masked-label packaging.

The randomization envelopes were opened exclusively by a research assistant, who was responsible for administering the assigned intervention to participants and was not involved in any outcome assessments.

Ophthalmologists evaluated VA, OSDI, DEQS-Th, FTBUT, and Oxford grading scale before instillation for 5 minutes and assessed adverse events up to 60 minutes after instillation. TearLab specialists measured and recorded tear osmolarity before the ophthalmologist performed the FTBUT and Oxford grading scale. These tests were timed before the instillation of the eye drops at 10 minutes, and then the measurements were repeated at 30- and 60-minutes post-instillation. Before discharge, participants were instructed about the administration technique, how to record in the daily medication log, and advised to discontinue eye drop use for at least three hours prior to the second visit.

Subjects continued treatment at least six times daily for 30 days and recorded each administration. A research assistant conducted weekly telephone inquiries to assess compliance with eye drop administration, the accuracy of the administration technique, and any adverse events.

Participants were reassessed during the second visit for VA, OSDI, DEQS-Th, FTBUT, the Oxford grading scale, adverse events, and the remaining medication count.

This study evaluated both short-term and long-term adverse events to assess the safety of the treatment. Short-term adverse events-including stinging, itching, irritation, redness, and other abnormalities-were assessed up to 60 minutes post-instillation. Long-term adverse events were monitored over a 30-day period following treatment.

Outcome measures

The primary outcome measure was the Oxford grading scale,[22] with a reduction in grade from baseline to post-treatment indicating the effectiveness of artificial tears in promoting corneal epithelial healing. The secondary outcome was tear osmolarity, as hyperosmolarity is a core mechanism in the pathogenesis of dry eye disease and leads to tissue damage.[23] Tear osmolarity is one of the three homeostasis marker tests recommended by TFOS DEWS II

for the diagnosis of dry eye;[21] this is based on the hypothesis that effective artificial tears would reduce tear osmolarity and maintain it within normal limits. In this study, tear osmolarity was measured with the Tear Lab Osmolarity system (TearLab, San Diego, CA, USA).

Abnormal tear osmolarity is defined as a tear osmolarity of ≥ 308 mOsm/L in either eye.[24-26] Other clinical outcomes of interest included visual acuity (VA), assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart; fluorescein tear break-up time (FTBUT); ocular symptoms, evaluated using the Ocular Surface Disease Index (OSDI); and quality of life, assessed using the Thai version of the Dry Eye-Related Quality-of-Life Score (DEQS-Th).[27-28] Adverse events were also recorded.

Statistical analysis

Descriptive statistics were used to summarize the data. Categorical demographic variables were expressed as frequencies and percentages, whereas continuous variables were presented as means with standard deviations for normally distributed data. For inferential statistics, comparisons of quantitative data between the treatment and control groups were performed using Student's *t*-test for patient-level data and generalized estimating equations (GEE) for eye-level data. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Differences in the number of eyes and patients demonstrating improvements in clinical outcomes and quality of life following treatment between groups were assessed using GEE and the Chi-square test. Linear mixed-effects models were employed to evaluate longitudinal changes over time and between-group differences. A two-sided P value < 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS software, version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Among the 62 screened patients (124 eyes) who provided informed consent, 46 patients (92 eyes) met the study's inclusion criteria. No participants dropped out of the study. A total of 92 eyes were included, with 44 participants (95.7%) being female and 2 (4.3%) being male. The mean age of participants in the 0.28% SH group was 51.52 ± 16.05 years, while the mean age in the 0.18% SH group was 52.48 ± 14.62 years (Table 1).

Table 1. Demographic and baseline characteristics

	0.28% SH eye drops	**0.18% SH eye drops**	**P value**
Number of patients	**23**	**23**	
Age, years (mean ± SD)	51.52 ± 16.05	52.48 ± 14.62	0.834[a]
Female, n (%)	22 (95.7)	22 (95.7)	1.000[b]
OSDI (mean ± SD)	49.71 ± 19.96	56.40 ± 20.65	0.270[a]
DEQS-Th (mean ± SD)	45.22 ± 20.87	45.72 ± 26.66	0.943[a]
Number of eyes	**46**	**46**	
Oxford grading scale (mean ± SD)	2.26 ± 0.44	2.39 ± 0.65	0.341[c]
BCVA LogMAR (mean ± SD)	0.15 ± 0.20	0.12 ± 0.20	0.637[c]
Tear osmolarity (mOsmol/L) (mean ± SD)	308.17 ± 26.63	308.24 ± 28.10	0.992[c]
FTBUT, seconds (mean ± SD)	3.78 ± 1.18	4.06 ± 2.11	0.549[c]

a = independent t-test / b = Fisher's exact test / c = Generalized estimating equation (GEE)

The Oxford grading scale results for each group, comparing scores pre-treatment and at 30 days post-treatment, are summarized in Figure 2. Both groups showed a statistically significant reduction in the Oxford grading scale ($P < 0.001$). In the 0.28% SH group, the mean reduction in the Oxford scale was significantly greater than that observed in the 0.18% SH group (1.37 ± 0.68 vs. 1.02 ± 0.86, $P = 0.024$).

In clinical practice, improvement in corneal epithelial damage is determined by a reduction in the Oxford grading scale, as recorded at each visit for comparison. Cases in which the Oxford grading scale decreased by ≥1 grade at 30 days post-treatment were classified as the "improved" group. As shown in Table 2, 91.3% of patients in the 0.28% SH eye drops group demonstrated a reduction in their Oxford grading scale after 30 days of treatment, compared to 73.9% in the 0.18% SH eye drops group. This difference is considered clinically significant ($P = 0.021$).

Best corrected visual acuity (BCVA) demonstrated improvement in the group treated with 0.28% SH eye drops ($P = 0.033$). In contrast, the 0.18% group exhibited no statistically significant change in BCVA ($P = 0.971$) (Figure 2).

Changes in tear osmolarity were observed at 30- and 60-minutes following instillation. In the group treated with 0.28% SH eye drops, the mean tear osmolarity decreased by 5.00 and 5.24 mOsm/L at 30 and 60 minutes respectively compared to baseline. In contrast, the group treated with 0.18% SH eye drops exhibited an increase of 4.48 mOsm/L at 30 minutes, followed by a decrease of 2.30 mOsm/L at 60 minutes, relative to baseline (Table 3).

The mean FTBUT in both groups was significantly longer after 30 days of treatment compared to baseline, with $P < 0.001$ for the 0.28% SH group and $P = 0.031$ for the 0.18% SH group. There was no significant difference between FTBUT in the two groups at 30 days after treatment ($P = 0.754$) (Figure 2).

The clinical cut-off for short FTBUT is typically considered to be < 5 seconds.[29] When considering whether both treatments were able to shift patients from the short FTBUT group at baseline to the prolonged FTBUT group (> 5 seconds) at 30 days after treatment, it was found that in the 0.28% SH and 0.18% SH groups, 34.8% and 19.6% of patients respectively demonstrated an increase in FTBUT to greater than 5 seconds, with no statistically significant difference between the groups ($P = 0.105$) (Table 2).

Both treatments resulted in a significant decrease in OSDI scores at day 30 compared to baseline (0.28% SH: $P < 0.001$; 0.18% SH: $P < 0.001$). However, no statistically significant difference was observed between the mean OSDI scores of the two groups at day 30 post-treatment ($P = 0.810$) (Figure 2).

Clinical improvement was further assessed based on changes in OSDI severity categories, defined as follows: severe (score > 33), moderate (23-32), mild (13-22), and normal (<13).[21] A reduction in severity category after 30 days of treatment was classified as improved. At day 30 post-treatment, 82.6% of patients in the 0.28% SH group demonstrated clinical improvement, compared to 78.3% in the 0.18% SH group, with no statistically significant difference between the groups ($P = 1.000$) (Table 2).

Both treatments significantly improved quality of life (as indicated by decreased DEQS-Th scores) at 30 days when compared to baseline (0.28% SH: $P < 0.001$; 0.18% SH: $P < 0.001$) (Figure 2). However, no statistically significant difference was observed between the groups ($P = 0.776$).

A clinical cut-off point for DEQS-Th, indicating whether ocular symptoms affect daily life, is a decrease of less than 18.33.[28]

When comparing the two groups at 30 days, 34.8% of patients in the 0.28% SH group and 30.4% in the 0.18% SH group had a DEQS-Th score below 18.33. No statistically significant difference was observed ($P = 0.753$) (Table 2).

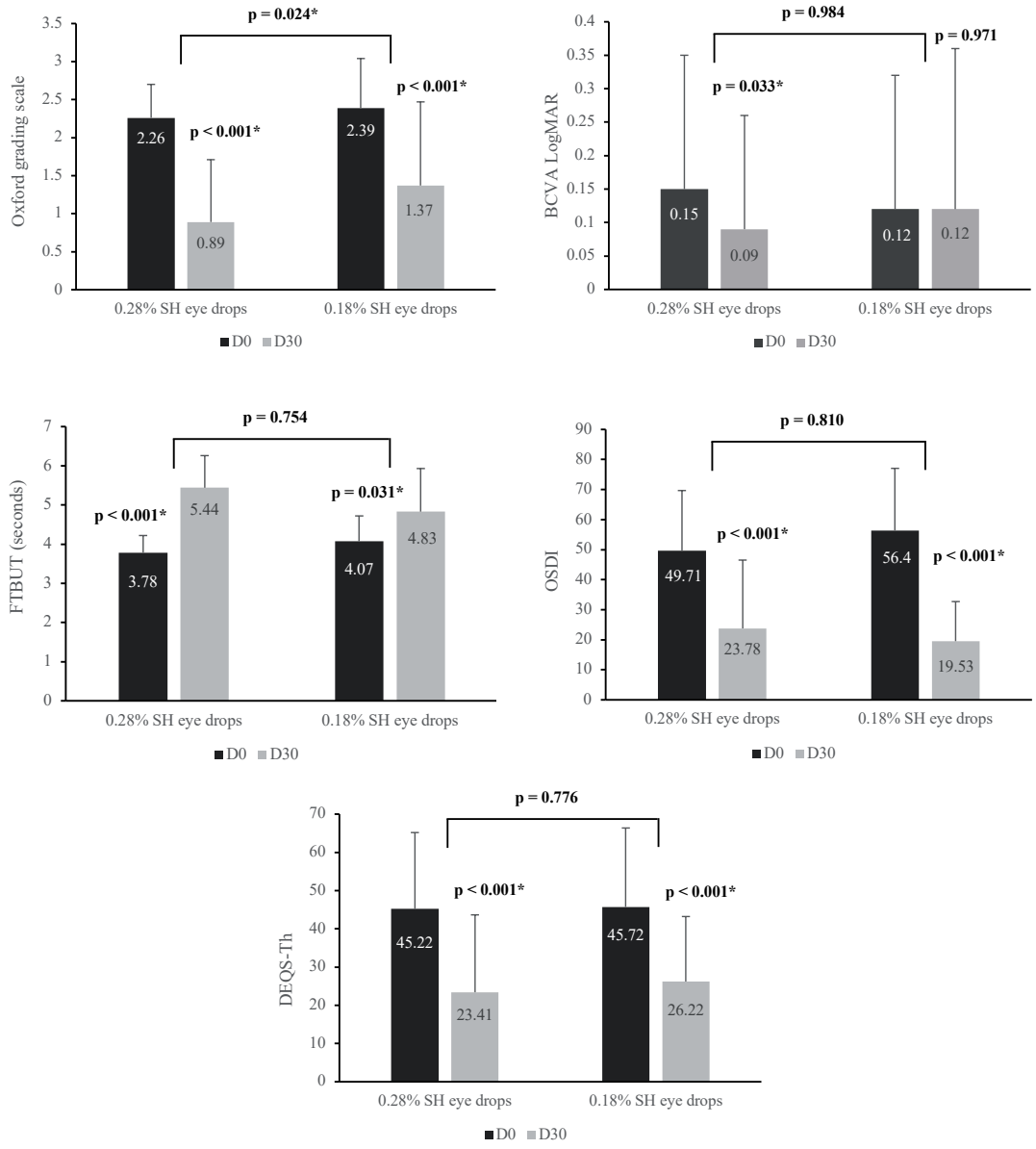


Figure 2: Changes in Oxford grading scale, BCVA LogMAR, FTBUT, OSDI, and DEQS-Th in patients with moderate to severe dry eye treated with either 0.28% or 0.18% sodium hyaluronate (SH) eye drops over 30 days of follow-up

Linear mixed-effect model
Statistically significant at $P < 0.05$
BCVA = best corrected visual acuity, FTBUT = fluorescein tear breakup time, OSDI = Ocular Surface Disease Index, DEQS-Th = Thai version of the Dry Eye–Related Quality-of-Life Score questionnaire

Table 2: Number of eyes and number of patients with improved clinical outcomes and quality of life following treatment

	0.28% SH eye drops n (%)	0.18% SH eye drops n (%)	P value
Number of eyes[a]	**46**	**46**	
Oxford grading scale			0.021*
Improved (≥1 grade reduction)	42 (91.3)	34 (73.9)	
FTBUT			0.105
Improved (FTBUT increased to ≥5 seconds)	16 (34.8)	9 (19.6)	
Number of patients[b]	**23**	**23**	
OSDI			1.000
Improved (reduction in OSDI severity level)	19 (82.6)	18 (78.3)	
DEQS-Th			0.753
Improved (reduction in DEQS-Th to <18.33)	8 (34.8)	7 (30.4)	

a = Generalized estimating equation (GEE) / b = Chi-square test
Statistically significant at $P < 0.05$

Table 3: Changes in tear osmolarity over time following treatment

	0.28% SH eye drops (n = 46) Mean ± SD (mOsmol/L)	Mean difference to baseline	0.18% SH eye drops (n = 46) Mean ± SD (mOsmol/L)	Mean difference to baseline	P value[a]
Pre-treatment	308.17 ± 26.63		308.24 ± 28.10		0.991
Post instillation 30 minutes	303.17 ± 18.62	-5.00	312.72 ± 28.30	+4.48	0.095
P value[b]	0.728		0.886		
Post instillation 60 minutes	302.93 ± 17.72	-5.24	305.94 ± 22.28	-2.30	0.598
P value[b]	0.663		1.000		

a = compare between groups by using Linear mixed-effect model
b = compare with pre-treatment by using Linear mixed-effect model

Adverse effects

Short-term side effects were assessed by observing participants for up to 60 minutes. One participant in the 0.28% SH group experienced bilateral eye fatigue, while two participants in the 0.18% SH group reported stinging sensations in one eye each. Statistical analysis indicated no significant differences in the occurrence of short-term adverse effects.

Long-term side effects were evaluated after participants applied the assigned eye drops at least six times daily for 30 days. In the 0.28% SH group, one participant experienced a sensation similar to dust in the eyes, one reported a sticky feeling, and one reported stinging. In the 0.18% SH group, two participants reported stinging, and one reported irritation. No statistically significant differences between adverse effects were observed in the two treatment groups.

Discussion

In the past, there was much debate regarding the optimal concentration of SH in artificial tears for achievement of the best therapeutic effects. Currently available artificial tears contain sodium hyaluronate concentrations ranging from 0.1% to 0.4%. However, variations in the previous populations studied, along with inconsistencies in the specification of disease severity, have limited the ability to make direct comparisons.

This study aimed to evaluate the efficacy of 0.28% sodium hyaluronate (SH) eye drops in patients with moderate to severe dry eye disease. The majority of participants were female, which is consistent with the higher prevalence of dry eye disease reported among women.[2,6]

The primary treatment goal for ophthalmologists is to promote the healing or improvement of corneal lesions in patients with dry eye disease. In our study, ocular surface staining, evaluated using the Oxford grading scale, revealed statistically significant differences between the two groups at baseline. Participants treated with 0.28% SH showed a significant decrease in corneal epithelial lesions compared to those treated with 0.18% SH after 30 days of treatment ($P = 0.024$) (Figure 2).

Furthermore, based on the reduction in Oxford grading (Table 2), it was observed that the group treated with 0.28% SH showed a clinically significant improvement in corneal healing after 30 days of treatment, compared to their 0.18% counterparts ($P = 0.021$). Corneal wound healing is a critical factor which ophthalmologists prioritize, as it plays a key role in guiding management decisions.

The findings of this study are consistent with those of the systematic review and meta-analysis by Ouyang XW et al., which indicated that higher concentrations of SH eye drops were more effective than lower concentrations in improving corneal fluorescein staining. The authors concluded that for dry eye with positive corneal staining, high-concentration SH eye drops are superior.[30]

The clinically significant corneal healing observed in patients treated with 0.28% SH may have contributed to the significant improvement in visual acuity (VA) observed in this group after 30 days of treatment compared to baseline, with P values of 0.033, in contrast to the group treated with the lower dose (Figure 2).

The evaluation of tear osmolarity provides an objective measure and serves as an important biomarker as well as a diagnostic criterion for assessing dry eye disease, as outlined by the TFOS DEWS II report.[9] In this study, tear osmolarity was measured using the TearLab Osmolarity System (TearLab, San Diego, CA, USA), and the reference cut-off values employed were those established specifically for the TearLab device. Due to the technical nature of the procedure and its implementation in a multicenter design, the measurements were conducted by specialists from TearLab who were proficient in operating the equipment. It was anticipated that the administration of eye drops would result in a reduction in tear osmolarity to within the normal range, thereby contributing to the restoration of tear film homeostasis.

Both intervention arms utilized formulations with hypo-osmolar properties. The objective was to investigate the short-term effects on tear osmolarity, with measurements scheduled at 30 and 60 minutes after eye drop instillation; these time points were selected based on calculations of human tear turnover rate. According to previous research, the basal tear turnover rate is approximately $24.0 \pm 14.2\%$ per minute, and the volume of the conjunctival sac is estimated to be $12.4 \pm 6.2\ \mu L$.[31] Based on these parameters, a single eye drop is expected to remain in the eye for approximately 4.2 minutes,

with a potential range of 2.6 to 10.2 minutes depending on individual tear volume and drainage rate. Therefore, measuring tear osmolarity at a time point earlier than 10 minutes may primarily reflect the osmolarity of the instilled solution itself. In contrast, measuring after 30 minutes provides greater confidence that the observed effect reflects the sustained action of the eye drops. The 60-minute time point was included because, in clinical practice in Thailand, ophthalmologists commonly prescribe 0.18% SH eye drops for severe dry eye to be administered every hour. Thus, the 60-minute measurement was intended to reflect real-world application and dosing frequency in clinical settings.

In our study, as illustrated in Table 3, the 0.28% SH group demonstrated a sustained reduction in tear osmolarity for up to 60 minutes. In contrast, the 0.18% SH cohort exhibited an increase in tear osmolarity at 30 minutes; however, the difference between these findings in the two groups at this time point did not reach statistical significance at 30 minutes after treatment (P = 0.095). By 60 minutes, a decrease in tear osmolarity was observed in the 0.18% SH group as well, and the difference between the two groups at this time point was also not statistically significant (P = 0.598).

The mean tear osmolarity in the 0.28% SH hypotonic eye drop group decreased by 5.00 and 5.24 mOsmol/L at 30 and 60 minutes post-instillation, respectively (Table 3). These reductions exceed the clinically significant threshold -defined as 5 mOsmol/L-[21] suggesting a clinically significant improvement in tear osmolarity that may have contributed to the restoration of ocular surface homeostasis. In contrast, the 0.18% SH hypotonic eye drop group demonstrated a mean increase in tear osmolarity of 4.48 mOsmol/L at 30 minutes, followed by a reduction of 2.30 mOsmol/L below baseline at 60 minutes.

A recent study by Kim W. investigated tear osmolarity using the TearLab system in patients with dry eye disease who had baseline tear osmolarity greater than 300 mOsmol/L. The results showed that patients receiving 0.18% hypotonic SH eye drops experienced a greater reduction in tear osmolarity at 1 and 5 minutes; however, this difference was no longer significant after 10 minutes. These findings suggest that the immediate effect of 0.18% hypotonic SH eye drops in lowering tear osmolarity may be transient, and sustained improvement may require more frequent administration.[32] It may reasonably be assumed that no effect persists at 30 minutes, which could explain why TearLab measurements at 30 and 60 minutes in our study reflected fluctuation rather than a true therapeutic effect.

A study by Muñoz EC investigated the immediate effects of instilling eye drops containing various polymer compositions, including SH-based formulations, on tear osmolarity in patients with moderate dry eye. The study found that the artificial tear most capable of sustaining osmolarity balance for the longest duration was a commercially available 2.5 mg/g carbomer 974P gel in preservative-free single-dose vials, which demonstrated the most substantial reduction in osmolarity at 15 minutes, with an average decrease of 11.54 mOsmol/L.[33]

The results of tear osmolarity measurements indicated that 0.28% SH eye drops were able to combat tear hyperosmolarity and sustain this effect for at least 60 minutes. This is in contrast with the findings of previous studies [32,33] which demonstrated a reduction in tear osmolarity lasting no longer than 15 minutes. It is possible that the populations in those studies had a lower baseline mean osmolarity (below 308 mOsmol/L), which may explain the lack of a clear effect in reducing tear osmolarity compared to those of our study. Nevertheless, the ability of 0.28% SH eye drops to maintain tear osmolarity within normal levels is crucial in breaking the vicious cycle in the mechanism of dry eye.[9]

In the assessment of tear film stability at 30 days post-treatment, although patients receiving 0.28% SH eye drops showed a statistically significant prolongation in FTBUT after 30 days of treatment (P < 0.001), with a mean post-treatment FTBUT of 5.44 seconds - exceeding the clinical threshold for short TBUT (defined as less than 5 seconds) - the difference between the two groups was no statistical significance (P = 0.754) (Figure 2).

These findings are consistent with the results of a systematic review and meta-analysis which reported no statistically significant difference in FTBUT outcomes between high- and low-concentration SH-based eye drop groups.[30]

In the evaluation of symptoms in patients with dry eye disease, both types of medication significantly reduced symptoms, as indicated by the OSDI after 30 days of treatment compared to baseline, with statistical significance ($P < 0.001$). No statistically significant difference, however, was observed between the two groups ($P = 0.810$) (Figure 2).

These findings are consistent with the results of a systematic review and meta-analysis which investigated the differences between high- and low-concentration SH-based eye drops.[30]

The adverse event findings in this study are consistent with previous research, indicating no severe side effects from SH-based eye drops.[15] Additionally, no concerns were identified regarding blurred vision after proper use of high-concentration SH eye drops, which aligns with the research by Calonge et al. Their study, which compared an intervention similar to that of each group in this study, found that 0.30% SH eye drops provided prolonged comfort without causing visual disturbances when compared to 0.18% SH eye drops.[34]

In contrast to the findings reported by Karaca EE, who observed that 4 out of 66 patients (6.1%) with mild to moderate dry eye experienced a blurring effect after receiving 0.3% SH eye drops,[35] our study did not report any such complaints. The absence of any blurring effect in our study may be attributable to differences in the study population, as participants had moderate to severe dry eye with corneal punctate epithelial erosions (PEE) and, consequently, suboptimal baseline VA; this may have made the blurring effect more difficult to detect.

Additionally, a proper instillation technique-administering one drop followed by keeping the eyes closed for 2-3 minutes-may have minimized immediate post-instillation blur. Some patients even reported subjective improvement in vision after using 0.28% SH eye drops. At the 30-day follow-up, when corneal PEE had improved significantly, this may have further contributed to the lack of blurred vision. Moreover, our results demonstrated that VA significantly improved in the 0.28% SH group after 30 days of treatment.

A strength of our study is its inclusion criteria, which specifically targeted patients with moderate to severe dry eye, defined by abnormalities in symptoms, tear break-up time, and corneal staining. This comprehensive approach ensured the enrollment of patients with clearly defined moderate to severe dry eye conditions. In contrast, some previous studies,[33] despite focusing on moderate to severe dry eye, selected specific diagnostic criteria as inclusion criteria, such as symptoms and abnormal tear osmolarity. However, when reporting their findings, the mean tear osmolarity prior to treatment was observed to be below 308 mOsmol/L. This raises the question of whether such an approach effectively included patients with moderate to severe dry eye, consistent with the study objective.

Another strength of our study is the utilization of TearLab specialists to perform tear osmolarity assessments across all centers, thereby minimizing potential variability in testing techniques. In contrast, some studies engaged physicians to conduct assessments for participants, which may result in variability in techniques.

A limitation of this study was that tear osmolarity could not be reassessed 30 days after treatment due to the limited availability of measurement devices in the multicenter study conducted across Thailand.

In our study, tear osmolarity data were collected for up to 1 hour following eye drop instillation. It is recommended that future research extend the observation period to 2 hours or longer. This extension may provide deeper insights into the dynamic changes following eye drop administration and help determine the optimal dosing frequency for each formulation, thereby minimizing unnecessary drug use.

Conclusion

This study evaluated the efficacy of 0.28% SH eye drops in patients with moderate to severe dry eye disease. The formulation maintains tear osmolarity balance for a longer duration than the comparator, thereby disrupting the vicious cycle of the disease. The beneficial properties of SH-its anti-inflammatory, cytoprotective, and water-retentive effects-support ocular surface homeostasis, reduce friction-induced damage, and promote epithelial healing. These mechanisms contribute to symptom relief, improved visual acuity, and enhanced quality of life.

Author Contributions

All authors contributed to the study conception, design, and data collection. Material preparation, data analysis, and drafting of the initial manuscript were performed by Pornlada Sunlakaviset. All authors commented on previous versions of the manuscript and read and approved the final manuscript.

Conflict of interest

The authors declare no competing interest.

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Data availability

Data in this study were anonymized and securely stored at Rajavithi Hospital, Bangkok, Thailand. The datasets generated during the study are available from the corresponding author upon reasonable request.

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