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Effectiveness of cyclosporine nanoemulsion eye drops in patients with mild-to-moderate dry eyes: objective and subjective evaluation

Su Young Moon[1†], Ho Seok Chung[1,2†], Jae Hyuck Lee[1], Hun Lee[1], Hungwon Tchah[1] and Jae Yong Kim[1,2*]

Abstract

Background To compare and evaluate objective and subjective clinical parameters between 0.05% cyclosporine nanoemulsion (CsN) and 0.15% hyaluronic acid (HA) administration in patients with mild-to-moderate dry eyes.

Methods In this prospective, randomized, double-masked, single-center, and placebo-controlled parallel study, patients with mild-to-moderate dry eyes were randomly allocated to be treated with 0.05% CsN or 0.15% HA twice daily. Patients were followed-up at 4, 8, and 12 weeks. Objective and subjective parameters were evaluated during each visit.

Results A total of 35 patients were enrolled in this study. Compared with baseline, tear film break-up time and fluorescein staining scores at 4, 8, and 12 weeks significantly improved in the CsN group. However, the Schirmer I test showed no statistically significant change until week 12. Using the Symptom Assessment in Dry Eye (SANDE) score, both groups gradually showed significant improvement compared with baseline values. However, the Dry Eye-Related Quality-of-life Score Questionnaire (DEQS) showed no statistically significant change during the treatment period.

Conclusions Both 0.05% CsN and 0.15% HA administration twice a day effectively improved the objective signs and subjective symptoms of patients with mild-to-moderate dry eyes. However, patients treated with 0.05% CsN experienced greater and faster improvement.

Keywords Cyclosporine, Dry eye, Symptom Assessment in Dry Eye (SANDE), Dry Eye-Related Quality of life score (DEQS)

†Su Young Moon and Ho Seok Chung contributed equally to this work.

*Correspondence:
Jae Yong Kim
jykim2311@amc.seoul.kr
[1]Department of Ophthalmology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, South Korea
[2]Department of Ophthalmology, Graduate School, University of Ulsan College of Medicine, Ulsan, South Korea

Background

Dry eye is a multifactorial disease of the ocular surface characterized by loss of tear film homeostasis accompanied by ocular symptoms. Tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities are important etiological factors [1]. Several treatments have been developed to manage inflammation in dry eye diseases, including administration of cyclosporine A, which acts as an anti-inflammatory factor by inhibiting calcineurin. This inhibition leads to improvement in tearing, protection of epithelial cells, and inhibition of goblet cell loss [2–5]. Moreover, cyclosporine A has a better long-term safety profile compared with corticosteroids. However, due to its large molecular weight and hydrophobic nature, administration of cyclosporine A with conventional topical ophthalmic delivery methods has proven challenging [6, 7]. Anionic oil-in-water emulsion has been widely used over decades, but is often associated with side effects, including visual disturbance and conjunctival hyperemia [8]. To maximize ocular bioavailability, various drug delivery methodologies have been developed [9].

The self-nanoemulsifying drug delivery system is a transparent anhydrous homogenous mixture diluted in water that provides better chemical and physical stability, as well as increased efficacy [6, 7, 10]. However, there is a lack of prospective studies evaluating the objective and subjective parameters that validate the safety and efficacy of 0.05% cyclosporine nanoemulsion (CsN) in patients with mild-to-moderate dry eyes.

Recently, hyaluronic acid (HA) has been widely used to treat dry eye disease. HA treatment has been reported to improve both signs and symptoms of dry eye disease in most cases [11–13]. Therefore, in this randomized, double-masked, single-center, and placebo-controlled parallel study, the improvement in symptoms of dry eyes were evaluated and compared between 0.05% CsN and 0.15% HA administration for 12 weeks. Considering individual differences in symptoms, various types of questionnaires with different questions have been developed to comprehensively evaluate dry eye disease [14]. Three questionnaires were implemented in the present study, and correlations between them were analyzed.

Methods

This study was conducted according to the ethical guidelines outlined in the Declaration of Helsinki and the Good Clinical Practice Guidelines. Written informed consent was obtained from all patients before the start of the study, and power analysis was performed to justify the number of enrolled patients. The study protocol and informed consents were reviewed and approved by the institutional review board of Asan Medical Center at the University of Ulsan in Seoul (Approval number: 2019−0884).

Study design

This was a prospective, randomized, double-masked, single-center, and placebo-controlled parallel study comparing 0.05% CsN (Cyporin N, Taejoon, Inc., Seoul, Korea) with 0.15% HA administration (New Hyaluni, Taejoon, Inc.) over a 12-week treatment period in patients with mild-to-moderate dry eyes. The study was conducted from November 2019 to July 2020. Participants were requested to discontinue administration of any topical eye drops, including artificial tears, and entered a 4-week washout period. Eligible patients were then randomized with an allocation ratio of 1:1 to receive either 0.05% CsN or 0.15% HA and instructed to apply one drop of the assigned medication twice daily for 12 weeks. Randomization for the enrollment order at the ophthalmology clinic was performed using computer-generated random allocation. Both the patients and caregivers were blinded to the intervention. Efficacy and safety were assessed at 4, 8, and 12 weeks. Sample size estimation was performed using the SAS software v.9.4 (SAS Institute Inc., Cary, NC, USA). Initially, a sample size of 42 patients was determined to achieve 80% power to detect a significant difference between two independent groups, with a type I error of 0.05. Despite the inclusion of 35 patients in this study, the calculated power was sufficiently high at 75%, indicating adequate sensitivity for detecting differences.

Study cohort

Inclusion criteria were as follows: (1) diagnosis according to the Korean Corneal Disease Study Group under level I or II and (2) corneal fluorescein staining score according to the National Eye Institute (NEI) scale≤6 points and (3) over 19 years old [15]. In the classification established by the Korean Corneal Disease Study Group, Level I or II includes patients with mild to moderate dry eye disease. Specifically, Level I dry eye comprises patients who experience symptoms sometimes, have an Oxford staining score below Grade I, and exhibit variable results for tear breakup time and the Schirmer-1 test. Level II dry eye includes patients who have symptoms often, an Oxford staining score Grade II, tear breakup time between 6 and 10 s, and Schirmer-1 test between 5 and 10 mm. Exclusion criteria included a history of refractive corneal surgery, contact lens use, Stevens–Johnson syndrome, ocular cicatricial pemphigoid, or chemical or thermal burns. Patients with a history of previous ocular surgery, proven or suspected glaucoma or ocular hypertension, those who were pregnant, and those taking systemic medications that might affect tear secretion were also excluded. When both eyes of the patient met the inclusion criteria, only the eye with more severe symptoms

was included. The right eye was included when patients had the same severity of dry eye symptoms in both eyes.

Ocular surface evaluation: objective parameters

The tear film break-up time (TBUT), NEI scale for grading fluorescein staining, and Schirmer I test without anesthesia were assessed at baseline and at weeks 4, 8, and 12. Matrix metalloproteinase 9 (MMP-9; InflammaDry®, Quidel Corp., San Diego, CA) tests were performed at baseline and at week 12 (final visit).

Patients were instructed to blink several times for a few seconds to ensure adequate mixing of the dye. TBUT was measured three times with a stopwatch, and the mean value was then calculated. The Schirmer I test without anesthesia was performed by placing a strip in each eye and recording the part of the strip (measured in mm) that became wet after 5 min. The ocular surface was initially stained with 2-μL 2% preservative-free fluorescein solution instilled into the conjunctival sac using a micropipette. Corneal fluorescein staining was assessed for each of the five regions of the cornea (central, superior, inferior, nasal, and temporal) using a 0-to-3 scale (0=no punctate staining; 3=severe diffuse or coalescent macropunctate staining) for each region. The score for each region was summed to acquire the total corneal staining score (range, 0–15).

Extracellular MMP-9 secretion is induced during the early stages of the inflammatory cascade, and it promotes migration of inflammatory cells to the ocular surface. Therefore, elevated MMP-9 indicates the presence of clinically significant ocular surface inflammation, leading to tear film instability and dry eye [16]. MMP-9 in the eye was evaluated by the same trained technicians after dabbing of a sampling fleece along the palpebral conjunctiva of the patient's lower eyelid until the device became saturated [17]. It was then placed into the sample transfer window of the test cassette body. Next, the technician immersed the absorbent tip in the buffer vial. Results were recorded and reviewed after 10 min. The existence of one blue line and one red line in the MMP-9 test result window indicated a positive test result (MMP-9≥40 ng/mL), while a single blue line indicated a negative test result (MMP-9<40 ng/mL) [18].

Evaluation of ocular symptoms: subjective parameters

Patients' ocular symptoms were evaluated using dry eye questionnaires including Symptom Assessment in Dry Eye (SANDE) [19], Dry Eye-Related Quality-of-Life Score (DEQS) Questionnaire [20], and Ocular Discomfort Analog Scale (ODAS) [21] at baseline and weeks 4, 8, and 12.

SANDE includes two questions using a 100 mm horizontal linear visual analog scale (VAS). The measurement of symptom frequency ranged from "rarely" to "all of the time," and symptom severity ranged from "very mild" to "very severe" [19].

The DEQS questionnaire was a 15-item instrument developed to assess six questions regarding subjective dry eye symptoms and nine on the effects on daily living activities within the previous week. Each question had columns A and B to denote the frequency and severity of symptoms, respectively. Responses to the frequency portion in column A were based on a five-point scale ranging from "none of the time" (no points) to "all of the time" (four points). A score between 1 and 4 points prompted the respondent to proceed to column B to answer questions regarding severity on a four-point scale. The Quality-of-Life Scale (QOLS), ranging from 0 to 100 points, was calculated by multiplying the total points in column B by 25 and dividing the result by the number of valid responses. QOLS was positively correlated with the severity of the subjective dry eye symptoms and their impact on daily life. The cut-off value for dry eye was 15 points [20].

The ODAS questionnaires included seven questions, including ocular discomfort during digital media use (sensitive to bright light, tightness, dry sensation, foreign body sensation, burning sensation, blurring, and fatigue) and ODAS8 for the time of eye discomfort onset during TV watching [7].

Correlation between symptomatic questionnaires

To validate the ODAS score, correlations between the data obtained from each questionnaire were analyzed [19].

Statistical methods

Data are shown as mean±standard error. Monocular data analyses of eligible eyes were performed for statistical comparisons. Efficacy analyses of the ocular surface included assessment of the statistical significance of the change in TBUT, corneal fluorescein staining score, and Schirmer I test at 4, 8, and 12 weeks. Symptomatic efficacy analyses assessed changes in symptomatic questionnaires. Correlations between questionnaires were also analyzed with the Pearson correlation coefficient. The Mann-Whitney test was used for comparison between groups, and the Wilcoxon signed rank test was used for comparison before and after treatment. Categorical variables were compared using the chi-square or Fisher's exact test. Statistical analyses were performed using the SPSS software (version 18.0 for Windows; SPSS, Inc., Chicago, IL), and $p<0.05$ was considered statistically significant.

Results

A total of 35 patients were enrolled in this study; however, three patients (one in the HA group and two in the CsN group) withdrew consent, and two patients in the CsN group discontinued treatment due to ocular discomfort. There were no statistically significant differences in the background characteristics and baseline parameters between the two groups (Table 1).

Ocular surface findings

TBUT at weeks 4, 8, and 12 increased in both groups compared with the baseline. This increase was statistically significant at weeks 4, 8, and 12 in the CsN group ($p=0.004$, 0.001 and <0.001, respectively); however, significance was only observed at week 12 in the HA group ($p=0.004$). In addition, there were no significant differences between the two groups until weeks 4 and 8 compared with baseline, but significance was evident between the two groups at week 12 ($p=0.004$).

Table 1 Characteristics and Baseline Data of the study cohort

	HA 0.15% (*n* = 15)	CsN 0.05% (*n* = 15)	*P* value
Disposition	16	19	
Completed the study (%)	15 (93.75%)	15 (78.95%)	1.000
Subjects' discontinuation (%)	1 (6.25%)	4 (21.05%)	0.523
Reason for discontinuation, n (%)			
Withdrawal of consent by the patient	1 (100%)	2 (50%)	0.899
Adverse events	0	2(50%)	0.655
Demographics			
Sex, female	13 (86.67%)	14 (93.33%)	1.000
Age, years	47.87 ± 16.92	41.13 ± 11.43	0.212
VDT use time, hours/day	8.10 ± 1.54	11.13 ± 4.72	0.134
Baseline Data			
Objective data (Surface evaluation)			
TBUT, seconds	4.68 ± 1.30	4.15 ± 1.62	0.328
Staining score (NEI scale)	3.33 ± 2.35	3.27 ± 2.19	0.936
Schirmer Test I, mm	6.00 ± 1.73	5.93 ± 1.03	0.899
MMP-9 (negative/positive), n (%)	13 (86.67%) / 2 (13.33%)	14 (93.33%) / 1 (6.67%)	1.000
Subjective data (Symptomatic evaluation)			
SANDE score	70.13 ± 24.96	72.70 ± 20.43	0.761
DEQS (Ocular symptom)	41.67 ± 23.68	47.12 ± 12.54	0.459
DEQS (Impact on Daily life)	39.68 ± 27.49	38.66 ± 10.89	0.899
DEQS (Summary score)	40.47 ± 24.64	40.26 ± 11.98	0.977
ODAS1-7	31.67 ± 16.17	25.46 ± 15.59	0.313
ODAS8 (minutes)	51.43 ± 44.83	41.08 ± 32.64	0.502

HA = Hyaluronic acid 0.15%; CsN = Cyclosporine Nanoemulsion 0.05%; VDT = Visual display terminal; TBUT = Tear Break-up Time; NEI = National Eye Institute; MMP-9 = Matrix Metalloproteinase-9; SANDE = Symptom Assessment in Dry Eye; DEQS = Dry Eye-Related Quality of life Score Questionnaire; ODAS = Ocular Discomfort Analog scale

NEI staining scores at weeks 4, 8, and 12 decreased in both groups compared with baseline. In the CsN group, statistically significant reductions over baseline were observed at weeks 4, 8, and 12 ($p=0.007$, 0.003, and <0.001, respectively). However, in the HA group, no statistically significant reduction was observed at any time point. In addition, there was no significant improvement in the staining score between the two groups.

The results of Schirmer I test at weeks 4, 8, and 12 compared with baseline increased in both groups. In the CsN group, a statistically significant increase compared with baseline was observed only at week 12 ($p=0.005$). Moreover, a significant increase was noted in the HA group at 8 weeks ($p=0.043$). Significance differences were also observed between the two groups at 12 weeks ($p=0.042$; Table 2; Fig. 1).

The MMP-9 tests showed no significant difference between baseline and any follow-up period (Table 1). Only two patients in the HA group (13.33%) and one in the CsN group (6.67%) showed positivity for MMP-9, and all remained negative after the fourth week.

Subjective parameters

Both groups showed significant improvement in SANDE score from baseline at all time-points except for the HA group at week 4 (4, 8, and 12 weeks: $p=0.354$, < 0.001 and 0.002, respectively, in the HA group; $p=0.040$, < 0.001 and <0.001, respectively, in the CsN group). However, no significant change was observed according to the DEQS at any time point (Table 3).

Furthermore, there was no significant difference in ODAS1-7 within the groups at weeks 4, 8, and 12 compared with baseline and no significant differences between the two groups were observed. Additionally, no significant difference in ODAS8 was found at any time point; however, the onset time of ocular discomfort significantly increased in the CsN group at 12 weeks ($p=0.036$; Table 4).

Correlation between symptomatic questionnaires

Pearson's correlation coefficient revealed a significant correlation between SANDE and DEQS scores ($R=0.672$; $p<0.001$; Fig. 2A), between SANDE and ODAS1-7 scores ($R=0.796$; $p<0.001$; Fig. 2B) and between DEQS and ODAS1-7 scores ($R=0.756$; $p<0.001$; Fig. 2C). However, there was no significant correlation between ODAS8 and SANDE or DEQS scores.

Discussion

In this prospective, randomized, double-masked, and placebo-controlled study including a cohort of patients with mild-to-moderate dry eyes, treatment with 0.05% CsN rapidly improved the associated signs and symptoms, as well as the objective and subjective parameters.

Table 2 Comparison of changes in TBUT, staining score (NEI scale), and unanesthetized Schirmer Test I between the hyaluronic acid and cyclosporine nanoemulsion groups

	HA 0.15% (*n* = 15)	CsN 0.05% (*n* = 15)	*P* value
TBUT (s)			
Base line	4.68 ± 1.30	4.15 ± 1.62	0.328
Week 4	5.44 ± 1.69	5.61 ± 1.91	0.793
Baseline vs. Week 4	0.76 ± 1.39 (*p* = 0.052)	1.47 ± 1.63 (*p* = 0.004)*	0.212
Week 8	5.57 ± 1.49	6.21 ± 1.97	0.321
Baseline vs. Week 8	0.89 ± 2.00 (*p* = 0.108)	2.07 ± 2.01 (*p* = 0.001)*	0.119
Week 12	5.72 ± 1.33	7.34 ± 1.94	0.012*
Baseline vs. Week 12	1.04 ± 1.18 (*p* = 0.004)*	3.20 ± 2.26 (*p* < 0.001)*	0.004*
Staining score (NEI scale)			
Base line	3.33 ± 2.35	3.27 ± 2.19	0.936
Week 4	2.80 ± 2.57	2.07 ± 1.62	0.358
Baseline vs. Week 4	-0.53 ± 2.47 (*p* = 0.418)	-1.20 ± 1.47 (*p* = 0.007)*	0.378
Week 8	2.33 ± 2.16	2.07 ± 2.12	0.735
Baseline vs. Week 8	-1.00 ± 2.51 (*p* = 0.145)	-1.20 ± 1.32 (*p* = 0.003)*	0.787
Week 12	2.13 ± 2.07	1.40 ± 1.88	0.318
Baseline vs. Week 12	-1.20 ± 2.34 (*p* = 0.067)	-1.87 ± 1.68 (*p* < 0.001)*	0.378
Schirmer Test I (mm)			
Base line	6.00 ± 1.73	5.93 ± 1.03	0.899
Week 4	7.07 ± 3.08	6.47 ± 1.55	0.508
Baseline vs. Week 4	1.07 ± 2.84 (*p* = 0.168)	0.53 ± 1.46 (*p* = 0.178)	0.525
Week 8	7.33 ± 2.85	7.33 ± 3.42	1.000
Baseline vs. Week 8	1.33 ± 2.32 (*p* = 0.043)*	1.40 ± 3.40 (*p* = 0.133)	0.950
Week 12	6.80 ± 2.08	9.07 ± 3.77	0.054
Baseline vs. Week 12	0.80 ± 1.97 (*p* = 0.138)	3.13 ± 3.68 (*p* = 0.005)*	0.042*

* Statistically significant ($p < 0.05$).

HA = Hyaluronic acid 0.15%; CsN = Cyclosporine Nanoemulsion 0.05%; TBUT = Tear Break-up Time; NEI = National Eye Institute.

The ocular surface findings were significantly better in the CsN group than in the HA group across all follow-up periods. These results demonstrate the superiority of 0.05% CsN over 0.15% HA treatment for dry eye, consistent with the findings from previous studies [7, 10, 22].

Dry eye is induced by the aqueous deficiency or hyperevaporative state of the tear film, resulting in hyperosmolarity [23]. Hyperosmolarity triggers mitogen-activated protein kinase or nuclear factor kappa beta that promote secretion of inflammatory cytokines, which damage epithelial cells and mucin-secreting goblet cells in the conjunctiva. The tear film then becomes unstable, increasing ocular surface damage and undesirable ocular symptoms [23]. The anti-inflammatory effects of cyclosporine A have been demonstrated through various mechanisms, including inhibition of T-cell activation and cytokine production, and reduction of the expression of epithelial cell apoptosis marker, thereby increasing conjunctival goblet cell density and decreasing squamous metaplasia [24–26]. Meanwhile, topical cyclosporine A used in the present study uses a self-nanoemulsifying drug delivery system, which has a larger surface area and improved homogeneity and stability compared to the conventional anionic oil-in-water emulsions. In an animal study using a murine model of dry eye, the anti-inflammatory effect was confirmed within 2 weeks when CsN was used, and corneal epithelium and conjunctival goblet cell protection were more efficiently achieved than conventional agent [6]. In a clinical study conducted on patients with Sjögren's syndrome, CsN also showed faster improvement compared to conventional agent, suggesting that the induction time of the agent could be reduced by enhancing the physicochemical properties [22].

HA is a form of artificial tears that has been extensively used to treat dry eye disease for a long time. HA's abundance of hydroxyl groups attracts water molecules, thickening and stabilizing the tear film, and its lubricating properties reduce mechanical trauma to the ocular surface [11, 13]. Additionally, HA contributes to re-epithelization of the corneal epithelium and prevents hyperosmolality of the tear film, thereby reducing ocular surface inflammation [11, 12]. Besides HA, mucin secretagogues such as diquafosol and rebamipide are increasingly used in South Korea to stabilize the tear film [27]. They stimulate mucin secretion from conjunctival goblet cells, increase the number of these cells, and improve mucosal epithelium [28]. However, achieving a sufficient anti-inflammatory effect using HA or mucin secretagogues alone is challenging. Topical cyclosporine is a single potent treatment tool targeting anti-inflammatory effects compared with other treatments for dry eye disease. Although comparisons between HA or mucin secretagogues and cyclosporine have been reported, data to prove a specific treatment's superiority are insufficient, and follow-up studies are required.

Compared with baseline, TBUT and fluorescein staining scores at weeks 4, 8, and 12 significantly improved in the CsN group. Previous studies have shown that the effects of cyclosporine A typically begin after approximately 1 month, and the CsN group in this study has showed significant improvements in TBUT and fluorescein staining score from week 4, unlike the HA group, which is consistent with previous results [25, 29]. In Schirmer I test without anesthesia, a significant increase from baseline was observed at week 12 in the CsN group, and there was a statistically significant difference in the amount of change between the two groups at week 12. The Schirmer I test reflects improvement in

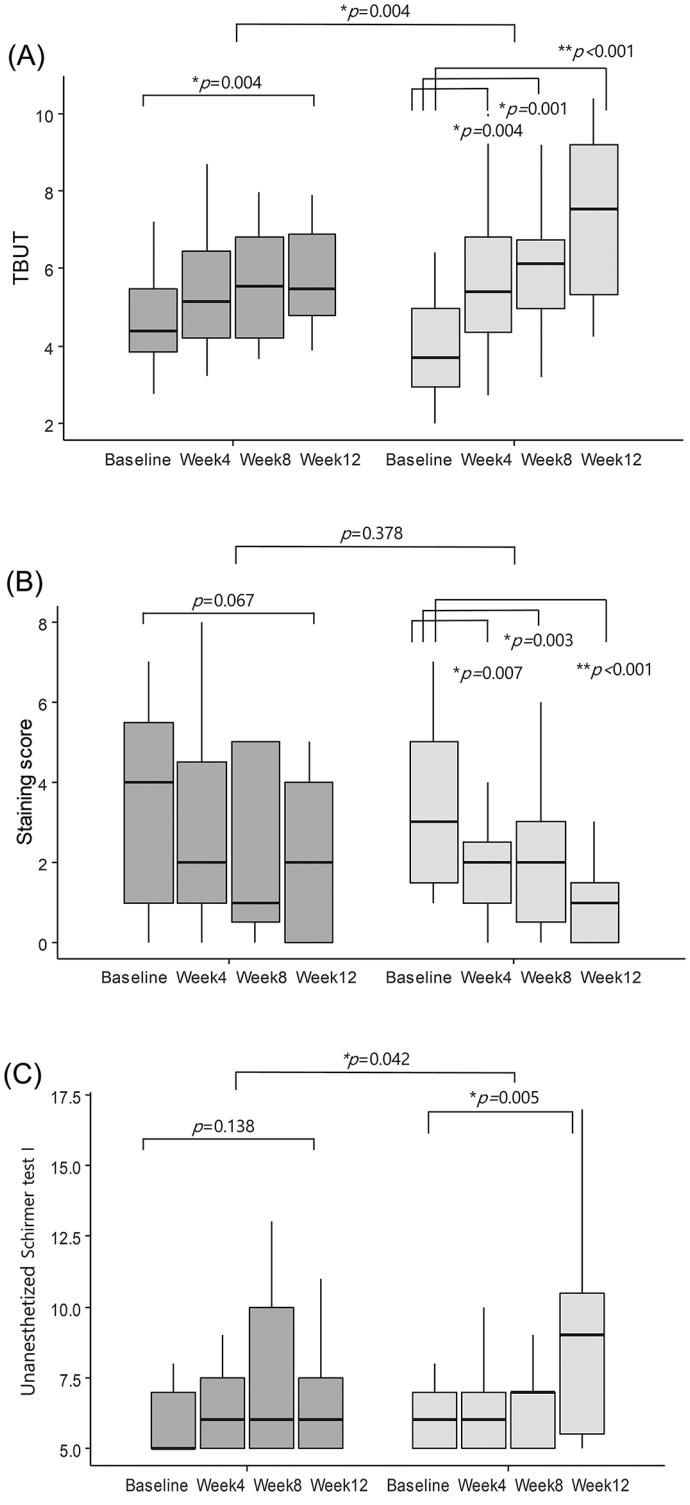

Fig. 1 Comparison between time points within groups and between the Hyaluronic acid group (dark gray) and the Cyclosporine A group (light gray) at 12 weeks. **(A)** tear break-up time (TBUT), **(B)** staining score by National Eye Institute (NEI) scale, and **(C)** Schirmer Test I without anesthesia. HA = Hyaluronic acid 0.15%; CsN = Cyclosporine Nanoemulsion 0.05%; *$p < 0.05$, **$p < 0.001$

Table 3 Comparison of changes in SANDE and DEQS (ocular symptom and impact on daily life) between the hyaluronic acid and cyclosporine nanoemulsion groups

	HA 0.15% (*n* = 15)	CsN 0.05% (*n* = 15)	*P* value
SANDE			
Base line	70.13 ± 24.96	72.70 ± 20.43	0.761
Week 4	63.67 ± 27.67	63.65 ± 17.81	0.999
Baseline vs. Week 4	-0.42 ± 15.09 (*p* = 0.354)	-8.95 ± 14.66 (*p* = 0.040)*	0.425
Week 8	56.75 ± 23.20	56.54 ± 18.99	0.979
Baseline vs. Week 8	-13.38 ± 12.45 (*p* < 0.001)*	-16.06 ± 11.17 (*p* < 0.001)*	0.548
Week 12	53.09 ± 28.09	47.13 ± 24.89	0.543
Baseline vs. Week 12	-17.04 ± 16.96 (*p* = 0.002)*	-25.57 ± 20.37 (*p* < 0.001)*	0.224
DEQS (Ocular symptom)			
Base line	41.67 ± 23.68	47.12 ± 12.54	0.459
Week 4	40.77 ± 27.45	48.72 ± 16.35	0.375
Baseline vs. Week 4	-0.89 ± 10.61 (*p* = 0.758)	-1.74 ± 15.84 (*p* = 0.711)	0.873
Week 8	42.31 ± 24.64	45.24 ± 17.28	0.722
Baseline vs. Week 8	-0.32 ± 18.28 (*p* = 0.951)	-3.53 ± 12.60 (*p* = 0.333)	0.607
Week 12	39.88 ± 24.05	39.88 ± 20.33	1.000
Baseline vs. Week 12	-1.79 ± 13.04 (*p* = 0.617)	-9.62 ± 20.08 (*p* = 0.110)	0.238
DEQS (Impact on Daily life)			
Base line	39.68 ± 27.49	38.66 ± 10.89	0.899
Week 4	38.09 ± 26.99	42.66 ± 21.53	0.625
Baseline vs. Week 4	-1.594.36 (*p* = 0.686)	4.17 ± 19.15 (*p* = 0.467)	0.390
Week 8	42.09 ± 25.96	33.73 ± 15.97	0.319
Baseline vs. Week 8	4.27 ± 18.13 (*p* = 0.412)	-4.40 ± 10.76 (*p* = 0.184)	0.164
Week 12	41.66 ± 27.64	38.10 ± 20.83	0.703
Baseline vs. Week 12	1.98 ± 20.25 (*p* = 0.720)	-1.16 ± 15.42 (*p* = 0.800)	0.665

* Statistically significant ($p < 0.05$).

HA = Hyaluronic acid 0.15%; CsN = Cyclosporine Nanoemulsion 0.05%; SANDE = Symptom Assessment in Dry Eye; DEQS = Dry Eye-related Quality of life Score Questionnaire.

Table 4 Comparison of changes in ODAS (1–7) and ODAS8 (time the symptom started) between the hyaluronic acid and cyclosporine nanoemulsion groups

	HA 0.15% (*n* = 15)	CsN 0.05% (*n* = 15)	*P* value
ODAS (1–7)			
Base line	31.67 ± 16.17	25.46 ± 15.59	0.313
Week 4	31.80 ± 19.08	28.15 ± 18.71	0.607
Baseline vs. Week 4	0.133 ± 8.87 (*p* = 0.954)	2.69 ± 14.69 (*p* = 0.521)	0.255
Week 8	31.47 ± 16.29	25.92 ± 15.46	0.451
Baseline vs. Week 8	-0.20 ± 9.19 (*p* = 0.934)	-0.50 ± 11.74 (*p* = 0.885)	0.524
Week 12	32.13 ± 16.44	25.50 ± 16.04	0.282
Baseline vs. Week 12	0.47 ± 9.26 (*p* = 0.848)	-2.58 ± 11.02 (*p* = 0.434)	0.442
ODAS8 (minutes)			
Base line	51.43 ± 44.83	41.08 ± 32.64	0.502
Week 4	43.08 ± 26.02	60.36 ± 81.54	0.513
Baseline vs. Week 4	-10.00 ± 35.65 (*p* = 0.332)	20.00 ± 59.81 (*p* = 0.318)	0.148
Week 8	52.69 ± 32.83	57.27 ± 55.69	0.805
Baseline vs. Week 8	0.38 ± 42.60 (*p* = 0.975)	13.00 ± 36.83 (*p* = 0.293)	0.464
Week 12	42.31 ± 20.06	82.08 ± 89.78	0.159
Baseline vs. Week 12	-8.46 ± 43.51 (*p* = 0.497)	44.50 ± 69.70 (*p* = 0.074)	0.036*

* Statistically significant ($p < 0.05$).

HA = Hyaluronic acid 0.15%; CsN = Cyclosporine Nanoemulsion 0.05%; ODAS = Ocular Discomfort Analog Scale.

sensory-stimulated reflex tearing associated with lacrimal gland tear production responses to ocular damage and is, therefore, appropriate for identifying long-term therapeutic effects [21]. A previous study demonstrated that eyes with detectable MMP-9 expression had significantly decreased tear production over time compared with those without detectable MMP-9 expression [30]. However, in the present study, all eyes remained negative for MMP-9 after 4 weeks of treatment. Tear production improved as shown in the Schirmer I test after 12 weeks.

Given the lack of association between the signs and symptoms of dry eye, various specific questionnaires have been developed. For example, some questionnaires evaluated the impact of dry eye on patient's quality of life, whereas others focused on diagnosis, severity assessment, or screening [31]. In our study, both groups showed gradual, significant improvement in the SANDE score compared with baseline. The CsN group showed significant improvement in the SANDE score at 4 weeks, and both groups significantly improved at weeks 8 and 12. Although the Ocular Surface Disease Index (OSDI) is the most widely used questionnaire in dry eye clinical trials, it measures only the frequency, but not the severity, of dry eye symptoms, and shows poor correlation with the objective parameters in previous studies [19, 29]. However, SANDE as a short questionnaire based on VAS quickly reflected an improvement in the objective parameters, although it is not well refined. As a short and easily understandable questionnaire, SANDE has shown good reproducibility, repeatability, sensitivity, and specificity in assessing patients with symptoms of dry eye [19]. However, DEQS and ODAS did not show significant changes throughout the treatment period, which might reflect the differences in the characteristics of the questionnaires. DEQS was developed to assess the relationship between dry eye and quality of life in Japan [20]. Although it was based on the evaluation of quality of life

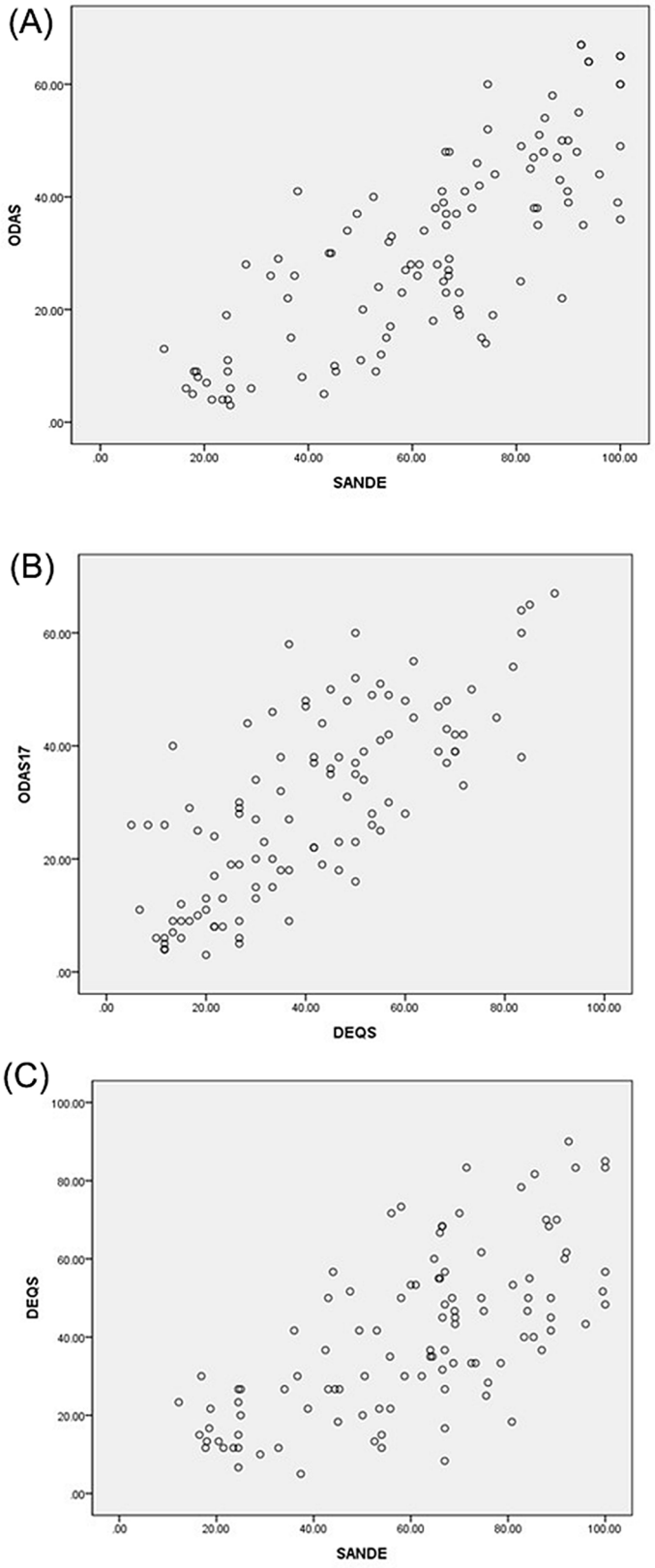

Fig. 2 Scatterplots showing the correlation between Symptom Assessment in Dry Eye (SANDE), Dry Eye-related Quality of life Score questionnaire (DEQS), and Ocular Discomfort Analog Scale (ODAS). **(A)** Pearson's correlation coefficient analysis revealed a significant correlation between SANDE and DEQS scores ($R = 0.672$; $p < 0.001$) **(B)** Correlation between SANDE and ODAS1-7 scores ($R = 0.796$; $p < 0.001$) **(C)** Correlation between DEQS and ODAS1-7 scores ($R = 0.756$; $p < 0.001$)

and the multifaceted impact on patient daily life, the correlations between clinical parameters and questionnaire scores were low in a previous study [20].

Among the various questionnaires used in this study, SANDE, DEQS, and ODAS1-7 scores all showed significant correlations with each other, except for ODAS8 related to the onset time of dry eye symptoms. Although not developed for evaluating dry eye disease, the ocular discomfort analog scale during digital media usage correlated with other dry eye questionnaires and was related to decreased blinking rate and tear film instability [32]. The discrepancy between subjective symptoms and objective parameters in diagnosis and treatment assessment of dry eye can be explained by the natural variability of disease pathophysiology, symptom subjectivity, and the variability of cornea sensation [33–35]. According to the increasing importance of subjective and objective factors for dry eye treatment, various symptomatic questionnaires have been developed, while the patient-reported outcome guidance of FDA questionnaires recommends that they include objective indicators, subjective symptoms, and psychological feasibility. However, increasing the number of items in questionnaires may lead to a reduced response rate or recall bias due to patient input requirements [14]. Appropriate questionnaires with proper evaluating items should therefore be used according to their proper assessment; the impact of dry eye on quality of life, screening or diagnosis for dry eye disease, and severity assessment of dry eye disease should be evaluated.

Treatment-related adverse events following the use of 0.05% cyclosporine included burning eye, foreign body sensation, conjunctival hyperemia, visual disturbance, and eye pain [36]. In the present study, two participants (10.5%) discontinued CsN due to ocular discomfort after administration. Although the discontinuing rate in the present study was relatively high compared to the 2.2% in previous reports, further investigation of adverse effects was necessary considering the small number of participants in this study [37].

Our study has several limitations. First, the duration may not be sufficient to prove the long-term effects of cyclosporine A. Cyclosporine A eye drops may affect conjunctival inflammation by preventing recruitment of T cells, which may require between 3 and 6 months. However, previous studies have already revealed the long-term safety and efficacy outcomes of cyclosporin A treatment [38]. Second, commonly used questionnaires such as OSDI and Standard Patient Evaluation of Eye Dryness Questionnaire (SPEED) were not utilized for symptomatic evaluation. However, OSDI is copyrighted by Allergan Inc., which can limit its use for other industry concerns in clinical trials. SANDE scores correlated with those of the OSDI in patients with mild-to-moderate dry eyes [19]. Third, this study comprised relatively young patients (47.9-years-old in the HA group, 41.1-years-old in the CsN group), who were predominantly female, and exclusively Korean. To generalize these findings, data should be collected from patients of diverse age groups, sexes, and races.

In conclusion, both 0.05% CsN and 0.15% HA administration effectively improved the objective signs and subjective symptoms of dry eye. However, patients treated with 0.05% CsN improved more rapidly and effectively than patients treated with HA.

Abbreviations

CsN	Cyclosporine nanoemulsion
TBUT	Tear film break-up time
MMP-9	Matrix metalloproteinase 9
SANDE	Symptom Assessment in Dry Eye
DEQS	Dry Eye-Related Quality-of-Life Score
ODAS	Ocular Discomfort Analog Scale
VAS	Visual analog scale
QOLS	Quality-of-Life Scale
OSDI	Ocular Surface Disease Index

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Author contributions

Conceptualization, H.L., H.T., and J.Y.K.; Data curation, S.Y.M., H.S.C., H.T., and J.Y.K.; Formal analysis, S.Y.M., H.S.C., J.H.L., H.L., H.T., and J.Y.K.; Funding acquisition, J.Y.K.; Investigation, S.Y.M., H.S.C., J.H.L., H.L., H.T., and J.Y.K.; Software, S.Y.M., H.S.C., and J.Y.K.; Supervision, H.L., H.T., and J.Y.K.; Visualization, S.Y.M.; Writing – original draft, S.Y.M., H.S.C., and J.Y.K.; Writing – review & editing, S.Y.M., H.S.C., J.H.L., H.L., H.T., and J.Y.K. All authors have read and approved the final manuscript.

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Data availability

The dataset used during current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted according to the ethical guidelines outlined in the Declaration of Helsinki and the Good Clinical Practice Guidelines. Written informed consent was obtained from all patients before the start of the study, and power analysis was performed to justify the number of enrolled patients. The study protocol and informed consents were reviewed and approved by the institutional review board of Asan Medical Center at the University of Ulsan in Seoul (Approval number: 2019 – 0884).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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