Comparison of Clinical Outcomes of Dry Eye Treatment between Two Severity Assessment Techniques: Measurement of Corneal Epithelial Thickness by Spectral Domain Optical Coherence Tomography and Clinical Eye Examination

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Abstract

This randomized controlled study was performed to compare the outcome of dry eye treatment between two severity assessment techniques: corneal epithelial thickness (CET) measurement by spectral domain optical coherence tomography (OCT) and clinical eye examination.

The study involved > 18-year-old patients who had been diagnosed with dry eye by the Tear Film & Ocular Surface Society's Dry Eye Workshop II criteria. Ninety-two patients were randomized in a 1:1 ratio to the OCT group, in which the severity of dry eye was evaluated with spectral domain OCT, and the control group, in which the severity was evaluated by clinical eye examination. The severity of dry eye was categorized as either mild to moderate or severe. Both groups received 3 months of treatment according to their severity.

The primary outcome was the mean change in the tear breakup time (TBUT) at 1 and 3 months compared with baseline. The secondary outcomes were the mean change in the 5-Item Dry Eye Questionnaire (DEQ-5) score and the fluorescein stain grade at 1 and 3 months compared with baseline.

In the OCT group, 28 patients had mild to moderate dry eye and 18 had severe dry eye. In the control group, 31 patients had mild to moderate dry eye and 15 had severe dry eye. Seven patients were lost to follow-up. At 3 months, the mean TBUT was 0.21 seconds higher in the OCT than the control group, but without statistical significance (P = .487). The mean DEQ-5 score was 0.10 points higher in the OCT than control group, but also without statistical significance (P = .669). The mean fluorescein stain grade was 0.09 points lower in the OCT than the control group, again without statistical significance (P = .245). The agreement between OCT and clinical assessment for diagnosis of severe dry eye was 88.04% (Kappa coefficient, 0.7384), showing good agreement; however, there was no correlation between the TBUT and CET variance at baseline (Pearson's correlation, 0.0344).

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In conclusion, OCT measurement of CET can be used to quantitatively grade the severity of dry eye and has some advantages over clinical eye examination. However, this study showed no superiority of the treatment outcome of dry eye in the OCT group compared with the control group.

Keywords: Dry eye disease, corneal epithelial thickness, optical coherence tomography
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Introduction

Dry eye is a very common disease that generally affects patients' quality of life.[1,2] At present, the diagnosis and treatment of dry eye are based on the TFOS DEWS II in 2017.[3] The causes of dry eye are multifactorial and include both intrinsic and extrinsic factors.[4,5] Dry eye is classified into two types: aqueous tear-deficient dry eye (ADDE) and evaporative dry eye (EDE).[6] Dry eye causes symptoms of pain, discomfort, and watery discharge. Moreover, the inflammation from dry eye.[7]

The diagnosis of dry eye is based on the TFOS DEWS II criteria. First, screening questions are administered to rule out other ocular diseases. Next, a dry eye questionnaire (5-Item Dry Eye Questionnaire (DEQ-5)[8] or Ocular Surface Disease Index[9]) is administered. A complete clinical eye examination using a slit lamp biomicroscope is also performed, focusing on the tear breakup time (TBUT), tear film osmolarity, and ocular surface staining.[10] In addition to slit lamp examination, other techniques that help to evaluate the cause and severity of dry eye disease include lipid tear film interferometry, meibography, measurement of specific tear film biomarkers that increase in patients with dry eye,[11] and spectral domain optical coherence tomography (OCT). A lipid tear film interferometer is used to measure the thickness of the lipid layer of tears, which is particularly helpful in identification of EDE. Meibography is used to assess the quality and quantity of meibomian glands by taking a picture of the eyelid with infrared light. These tests are used for subtype classification of dry eye (EDE, ADDE, or mixed type).[12] Severity classification of dry eye is based on clinical grading of the frequency of discomfort, conjunctival injection and staining, corneal staining, lid and meibomian gland obstruction, TBUT, and the Schirmer score.[13] Management of dry eye is individualized to the patient according to the subtype classification and severity of dry eye. When performing spectral domain OCT, laser interferometry is used to capture a picture of the cross-section of the eye. The advantages of this method are its noninvasive nature, quantitative assessment, and widespread use throughout the field of ophthalmology.[14,15] Various studies have been performed to evaluate the corneal epithelial thickness (CET) in patients with dry eye using OCT, and the results were demonstrated in a CET map.[16] Variation of the CET was revealed in both increasing and decreasing, and more irregularities of the thickness throughout the cornea were found in patients with dry eye and was correlated with the severity of dry eye.[17-22] More severe dry eye has been shown to be associated with more irregularities of the CET as shown by OCT. In a study by Abou Shousha et al.[23] in 2020, 21 DED eyes were treated with autologous serum eye drops, and the CET was examined with ultrahigh-resolution OCT both before and after treatment. A highly irregular corneal epithelial surface was found in the dry eye group compared with the control group as measured by the CET profile variance. Furthermore, the CET range was higher in the dry eye group than in the control group and was correlated with the severity of dry eye. After the treatment of dry eye, the CET profile variance decreased. In addition, the epithelial irregularity factor, which is the measurement of the CET variance in the central 3-mm zone, was set at ≥ 3.949 as the cutoff point for diagnosis of severe dry eye with a sensitivity of 81.8% and specificity of 77.7%.

Based on this information, we performed the present study to compare the outcome of dry eye treatment between two severity assessment techniques: CET measurement using spectral domain OCT and clinical eye examination.

Methods

This randomized controlled study was conducted at the outpatient clinic of the ophthalmology department of Chulabhorn Hospital. The study was approved by the ethics committee and performed in accordance with the Declaration of Helsinki, and written informed consent was obtained from all patients. In addition, this study has been registered in the Thai Clinical Trials Registry at www.thaiclinicaltrials.org (TCTR ID: TCTR20210706006).

Participants

This study recruited patients who had been diagnosed with dry eye disease at the ophthalmology outpatient clinic of Chulabhorn Hospital. The inclusion criteria were an age of > 18 years; diagnosis of dry eye according to the TFOS DEWS II criteria; and a DEQ-5 score of ≥ 6 along with one of the following signs: noninvasive TBUT of < 10 seconds and ocular surface staining with either > 5 corneal spots, > 9 conjunctival spots, or a lid margin of ≥ 2-mm length and ≥ 25% width. The exclusion criteria were other corneal disorders such as epithelial basement membrane dystrophy, corneal scars, herpes infection, or recurrent corneal erosion; concurrent eyelid disorders with lagophthalmos and blinking problems; use of other topical medications such as anti-glaucoma drugs; contact lens use; treatment with medications that can increase the risk of dry eye, such as antihistamines, estrogen replacement therapy, antidepressants, or isotretinoin; a history of ocular surgery or eye trauma; and pregnancy and breastfeeding.

Study Protocol

Written informed consent was obtained from all patients before the start of the study. Demographic data (age, sex, duration of computer use per day, and current ophthalmic medications) were obtained, and the DEQ-5 was administered to the patients. A complete eye examination was performed with a slit lamp biomicroscope and fluorescein staining of the corneal surface to evaluate the baseline TBUT and fluorescein stain grade (modified Oxford scale),[12] and the data of the eye with more severe signs were used for analysis. The patients also underwent spectral domain OCT (Cirrus 500; Carl Zeiss Meditec, Dublin, CA, USA), and the findings were displayed on a CET map.[24]

The patients were separated into two groups in a 1:1 ratio using a four-block randomization method. The OCT group underwent dry eye severity assessment using the CET map obtained by OCT. The variance of the central 5-mm zone of the CET map was calculated, and a cutoff point of ≥ 4 was used as the criterion for the diagnosis of severe dry eye (the study by Abou Shousha et al.[23] was used as a reference; these authors reported that an abnormal CET is an early sign of corneal epithelium damage and can be evaluated by the central 5-mm zone of the CET variance map) (Figure 1). The control group underwent dry eye severity assessment by clinical grading; the criteria for the diagnosis of severe dry eye were moderate to marked conjunctival/corneal staining and a TBUT of ≤ 5 seconds (the data from the more severely affected eye were used).

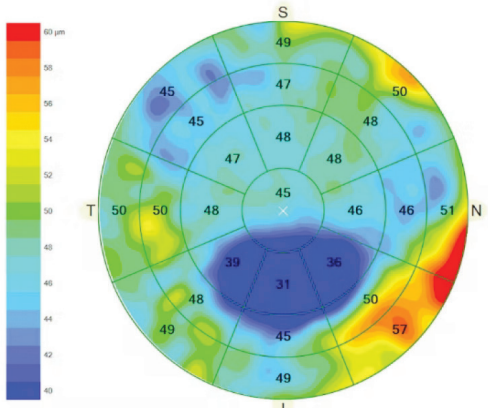

Figure 1: Data were collected in the central 5-mm zone (red bracket) to calculate the epithelial thickness variance.

In both groups, the treatment of dry eye disease was based on the severity of dry eye. Patients with mild to moderate dry eye received treatment with 0.3% hydroxypropyl methylcellulose preservative-free artificial tears four times per day in both eyes for 3 months. Patients with severe dry eye received treatment with 0.18% hyaluronic acid preservative-free artificial tears four times per day in both eyes for 3 months with temporary punctal occlusion at both inferior puncta at every visit.

Follow-up was performed at 1 and 3 months and involved assessment of the DEQ-5 score, TBUT, and fluorescein stain grade. Eye drop treatment adherence was also determined using the eight-item Morisky Medication Adherence Scale[25] in both groups.

Outcome Measures

The outcome measures were assessed at baseline and at 1 and 3 months after beginning treatment. The primary outcome was the TBUT, and the secondary outcomes were the DEQ-5 score and fluorescein stain grade.

The recruitment assessor and the outcome assessor were separated to reduce selection bias. This study involved only one outcome assessor to reduce inter-assessor variation. To decrease intra-assessor variation, we used a standardized quality picture to compare the fluorescein stain grades. To ensure accuracy of TBUT measurement, a digital clock was used to measure the time. Additionally, to ensure understanding of the DEQ-5, a Thai-translated version was provided to the participants.

The primary efficacy endpoint was the increase in the TBUT after 3 months of dry eye treatment compared with baseline. The secondary efficacy endpoints were the improvements in the DEQ-5 score and fluorescein stain grade after 3 months of dry eye treatment; these outcomes were compared between the OCT group and control group.

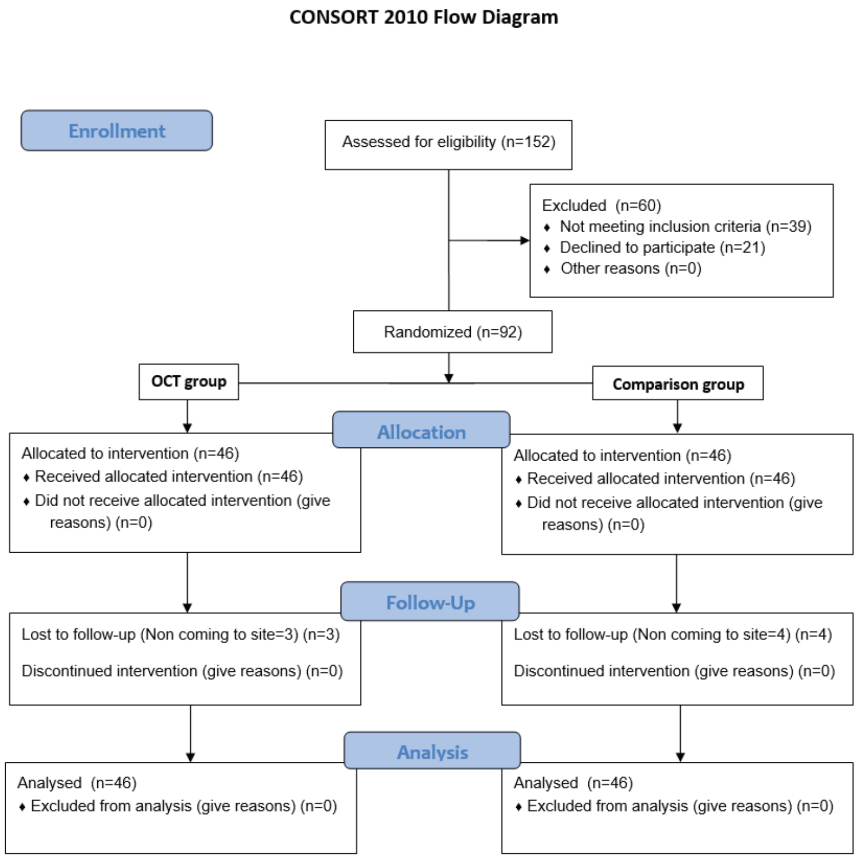

Figure 2: Consolidated Standards of Reporting Trials (CONSORT) 2010 flow diagram. OCT, optical coherence tomography

Statistical Analysis

STATA version 15.1 was used for the sample size calculation and data analysis. For the sample size calculation, the participants were separated into two groups. The OCT and control groups are divided in a one to one ratio. The primary outcome is TBUT and the secondary outcome is the DEQ-5 score and fluorescein stain grading. The hypothesized TBUT for the OCT group is 4 seconds while the TBUT in the control group is equal to 3.5 seconds based on the study from Shimazaki.[26] The standard deviation is 0.8 second, the alpha is 0.05 and the power is 80%. The sample size calculation reveals 42 participants for each group. However, with the setting of 10% loss follow up, the final participants equal 46 people for each group.

For the data analysis, the baseline characteristics are presented in a table using the descriptive statistics of percentage, mean, and standard deviation for comparisons between the OCT and control groups. The unpaired t test was used for continuous data, and the chi-square test was used for categorical data. All the possible variables that could be analyzed are shown in the same table. Multi-level mixed-effects linear models (random intercept, random slope) were used to assess differences between the OCT and control groups. The models were used to determine the treatment effects (adjusted mean change in the OCT group compared with the control group at each time point) and interaction effects (overall effects in the OCT group compared with the control group for all three time points: baseline, 1 month, and 3 months). The intention-to-treat (ITT) analysis included all randomized participants who attended at least one data collection visit (baseline visit included). All efficacy analyses were performed in the ITT population using the last observation carried forward method. Finally, the agreement of the two test methods was analyzed with the Kappa coefficient, and the correlation between the baseline TBUT and baseline CET variance was analyzed with Pearson's correlation coefficient.

Results

Participants

This study was conducted from August 2021 to January 2022, and 152 patients were initially screened. Of these, 92 patients were included in the study and randomized to either the OCT group (n = 46) or control group (n = 46). Seven patients were lost to follow-up; thus, the final number of participants was 85. Among the seven patients who were lost to follow-up, five were lost at both the first- and third-month visits (one patient in the OCT group and four in the control group). The two remaining patients were lost to follow-up at the third-month visit (both in the OCT group). The missing data were calculated using the principal of last observation carried forward, which is the method of ITT analysis.

The baseline characteristics were not significantly different between the two groups, as shown in Table 1. The patients' ages ranged from 24 to 87 years, with a mean ± standard deviation of 57.40 ± 13.44 years. Most of the patients were female (78.26%). Most spent 4 to 6 hours per day using a computer (66.30%). Most patients also had a history of using artificial tears before participating in the study (66.30%), whereas 33.70% had not previously used artificial tears.

The mean DEQ-5 score at baseline was 7.23 ± 1.36 in the OCT group and 7.15 ± 1.29 in the control group. The mean TBUT at baseline was 6.01 ± 1.60 seconds in the OCT group and 6.00 ± 1.49 seconds in the control group.

The baseline corneal fluorescein grade in the OCT group was grade 0 in 12 patients (26.09%), grade 1 in 33 patients (71.74%), and grade 2 in 1 patient (2.17%). The baseline corneal fluorescein grade in the control group was grade 0 in 7 patients (15.22%) and grade 1 in 39 patients (84.78%).

The treatment adherence in terms of the patients' regularity of using eye drops was evaluated with the Morisky adherence score. Treatment adherence was not significantly different between the two groups. Most patients had medium adherence of 56.52%, followed by high adherence (39.13%) and low adherence (4.35%).

Table 1: Baseline characteristics

	OCT group (n = 46)	Control group (n = 46)	Total (n = 92)
Age, years	58.3 ± 13.25	56.5 ± 13.72	57.4 ± 13.44
Sex			
Female	35 (76.09)	37 (80.43)	72 (78.26)
Male	11 (23.91)	9 (19.57)	20 (21.74)
Daily computer use			
4-6 hours/day	31 (67.39)	30 (65.22)	61 (66.30)
6-8 hours/day	13 (28.26)	11 (23.91)	24 (26.09)
> 8 hours/day	2 (4.35)	5 (10.87)	7 (7.61)
Eye drops use			
None	19 (41.30)	12 (26.09)	31 (33.70)
Artificial tears	27 (58.70)	34 (73.91)	61 (66.30)
Other eye drops	-	-	-
Baseline DEQ-5 score	7.23 ± 1.36	7.15 ± 1.29	7.19 ± 1.32
Baseline TBUT, seconds	6.01 ± 1.60	6.00 ± 1.49	6.00 ± 1.53
Baseline corneal fluorescein grade, 0-3			
0	12 (26.09)	7 (15.22)	19 (20.65)
1	33 (71.74)	39 (84.78)	72 (78.26)
2	1 (2.17)	0 (0.00)	1 (1.09)
3	-	-	-
Morisky adherence score[a]			
High	17 (36.96)	19 (41.30)	36 (39.13)
Medium	28 (60.87)	24 (52.17)	52 (56.52)
Low	1 (2.17)	3 (6.52)	4 (4.35)
Dry eye severity			
Mild to moderate	28 (60.86)	31 (67.39)	59 (64.13)
Severe	18 (39.13)	15 (32.60)	33 (35.86)

Data are presented as mean ± standard deviation or n (%).
OCT, optical coherence tomography; DEQ-5, 5-Item Dry Eye Questionnaire; TBUT, tear breakup time
[a]Morisky adherence score: 0 = high, 1-2 = medium, > 2 = low

Efficacy Findings

Among the 46 participants in the OCT group, 28 received treatment for mild to moderate dry eye and 18 received treatment for severe dry eye. Among the 46 participants in the control group, 31 received treatment for mild to moderate dry eye and 15 received treatment for severe dry eye. The outcome was evaluated 3 months after beginning treatment.

The result at 3 months showed statistically significant improvement in both groups compared with the baseline. The mean TBUT at 1 month was 7.20 ± 1.57 seconds in the OCT group and 6.79 ± 1.60 seconds in the control group. The mean TBUT at 3 months was 8.19 ± 1.57 seconds in the OCT group and 7.68 ± 1.72 seconds in the control group (Figure 3).

The mean TBUT in the control group increased by 0.52 seconds per month ($P < .001$). Although the mean TBUT in the OCT group improved to a greater degree than that in the control group (0.21 seconds at each visit), these improvements were not statistically significant ($P = .487$) (Table 2).

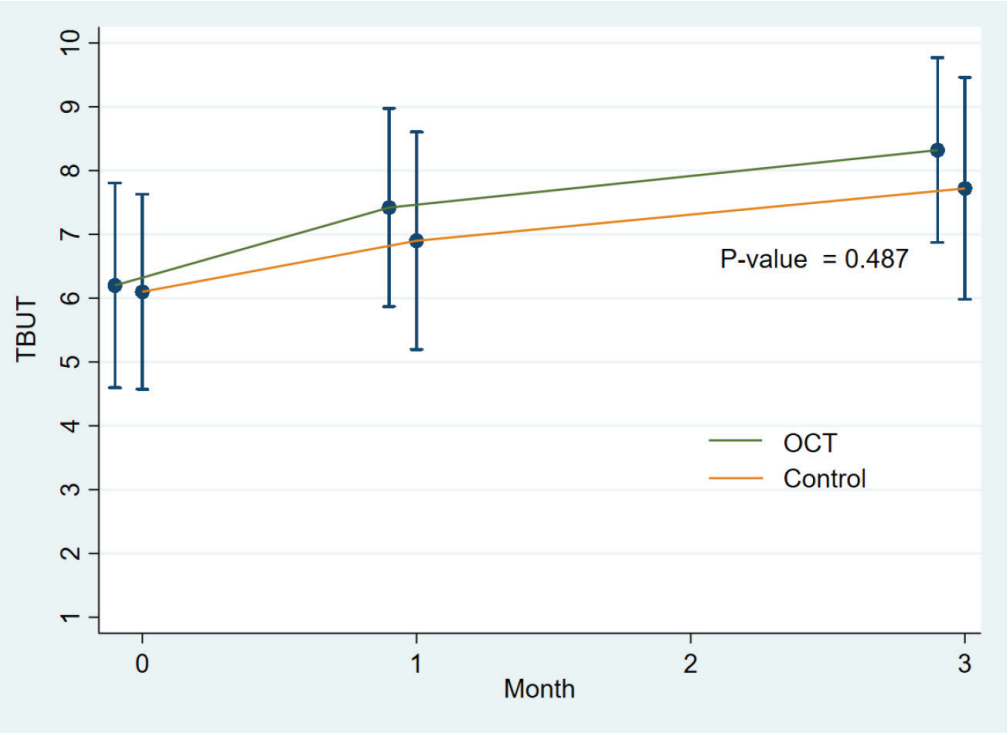

Figure 3: Mean TBUT (seconds) after treatment in OCT and control groups. TBUT, tear breakup time; OCT, optical coherence tomography

Table 2: Mean TBUT change (seconds) after treatment

Variable	Coef.	95% CI	*P*-value
Group	0.21	-0.38-0.80	.487
Month	0.52	0.40-0.65	< .001
Interaction (group, month)	0.15	-0.03-0.33	.100
Constant	6.21	5.80-6.63	< .001

TBUT, tear breakup time; Coef., coefficient; CI, confidence interval

The overall DEQ-5 score significantly decreased in both groups compared with baseline. The mean DEQ-5 score at 1 month was 6.08 ± 0.89 in the OCT group and 6.13 ± 0.93 in the control group. The mean DEQ-5 score at 3 months was 5.15 ± 1.01 in the OCT group and 5.54 ± 1.08 in the control group (Figure 4).

The mean DEQ-5 score in the control group decreased by 0.82 points each month ($P < .001$). The DEQ-5 score in the OCT group decreased to a greater degree than that in the control group (0.10 points at each visit), but the difference was not statistically significant ($P = .669$) (Table 3).

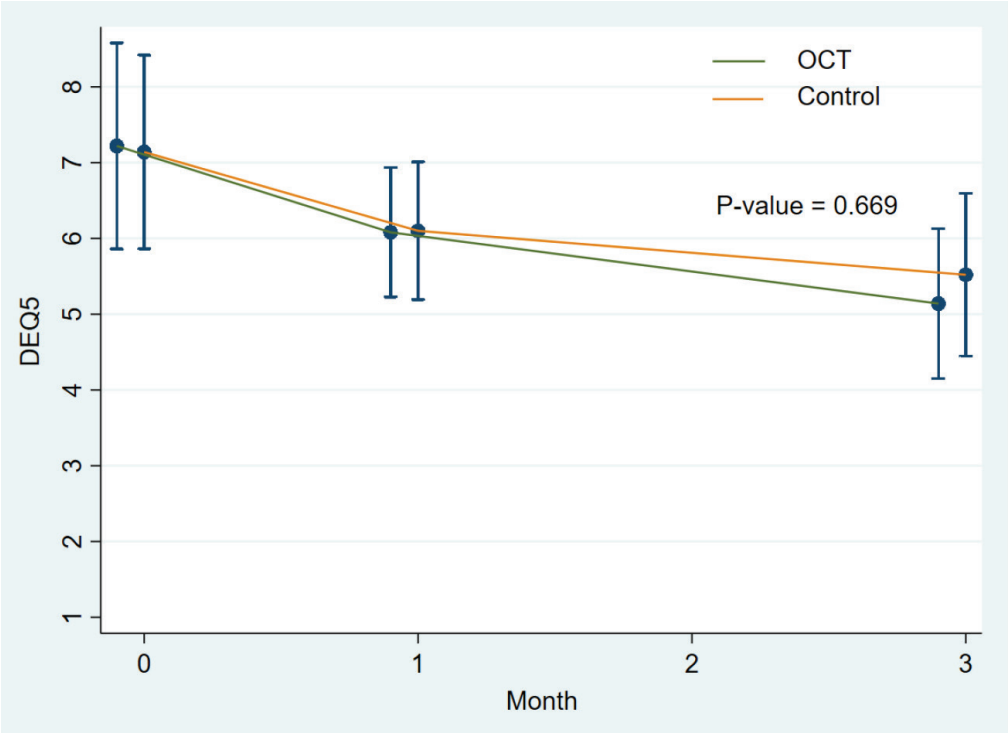

Figure 4: Mean DEQ-5 score after treatment in OCT and control groups DEQ-5, 5-Item Dry Eye Questionnaire; OCT, optical coherence tomography

Table 3: Mean DEQ-5 score change after treatment

Variable	Coef.	95% CI	*P*-value
Group	-0.10	-0.29 - 0.50	.669
Month	-0.82	-1.08 to - 0.56	< .001
Interaction (group, month)	0.16	-0.01 - 0.32	.058
Constant	6.93	6.65 - 7.20	< .001

DEQ-5, 5-Item Dry Eye Questionnaire; Coef., coefficient; CI, confidence interval

The overall fluorescein stain grade significantly improved in both groups compared with baseline. The fluorescein stain grade at 1 month in the OCT group was grade 0 in 30 patients (65.22%) and grade 1 in 16 patients (34.78%), and that in the control group was grade 0 in 28 patients (60.87%) and grade 1 in 18 patients (39.13%). The fluorescein stain grade at 3 months in the OCT group was grade 0 in 39 patients (84.78%) and grade 1 in 7 patients (15.22%), and that in the control group was grade 0 in 37 patients (80.43%) and grade 1 in 9 patients (19.57%).

The mean fluorescein stain grade in the control group decreased by 0.19 points per month ($P < .001$), whereas that in the OCT group decreased to a greater degree (0.09 at each visit); however, there was no statistically significant difference between the two groups ($P = .245$) (Figure 5).

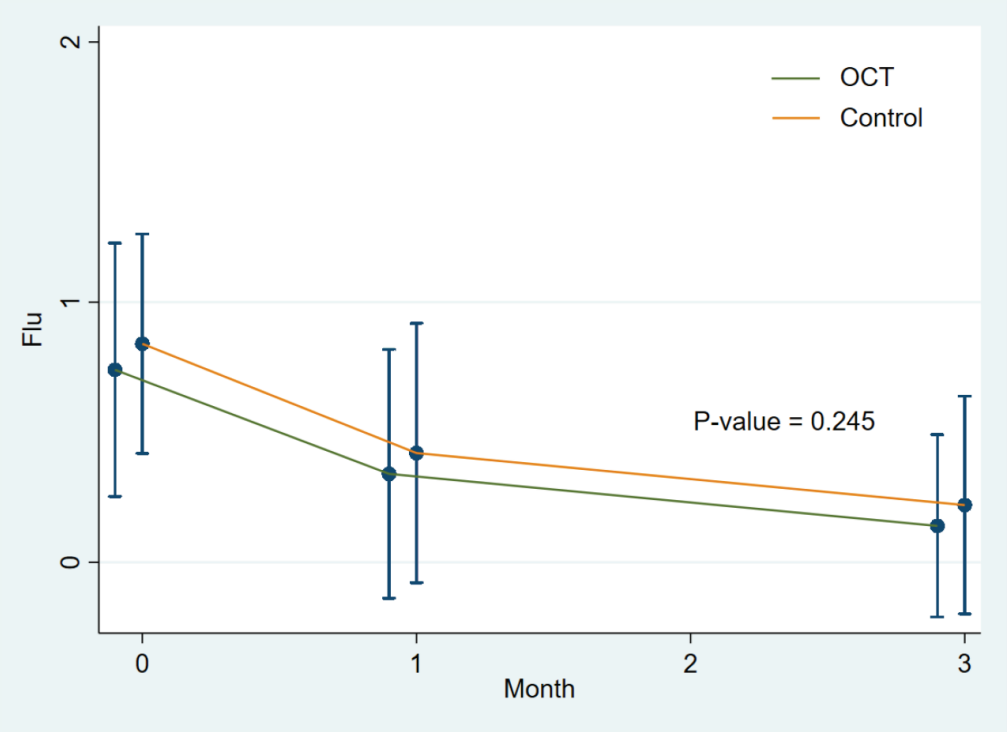

Figure 5 : Mean change in fluorescein stain grade after treatment in OCT and control groups
Flu, fluorescein stain grade; OCT, optical coherence tomography

The agreement between OCT measurement and clinical examination for diagnosis of severe dry eye was 88.04% (Kappa coefficient, 0.7384), indicating good agreement. However, there was no correlation between the TBUT and CET variance at baseline (Pearson's correlation, 0.0344).

Discussion

Dry eye disease reduces both the quality and quantity of the tear film. The diagnosis of dry eye is based on the TFOS DEWS II criteria, which mainly uses history-taking to measure the symptom score and clinical examination to identify abnormalities of the tear film (TBUT) and ocular surface (fluorescein staining). However, these techniques have limitations in some circumstances. Some studies have shown no correlation between clinical signs of TBUT and fluorescein staining compared with the symptoms of patients with dry eye.[27,28] This problem may be caused by operator-dependent factors in the clinical examination as well as the fact that some dry eye tests, such as Schirmer's test, are uncomfortable for patients. With the recent advancements in technology, dry eye testing has become less invasive, and standard measurable outcomes in the diagnosis and severity grading have been established. OCT-based measurement of the CET is one such technological advancement.

Evidence has revealed that OCT-based measurement of the CET has high repeatability in both normal corneas and in patients with corneal diseases and is effective for evaluation of the corneal surface of patients with dry eye.[29-31] The study by Abou Shousha et al.[23] in 2020 showed that patients with dry eye had a highly irregular corneal epithelial surface compared with the control group when the corneal epithelial surface was measured with ultrahigh-resolution OCT. Measurement of the CET profile variance could be used to grade the severity of dry eye. The epithelial irregularity factor is the amount of variance of the CET measured in the central 3-mm zone, with a cut-off point of > 3.949 being diagnostic for severe dry eye. The sensitivity of

this test is 81.8%, and its specificity is 77.7%. Moreover, after the treatment of dry eye, the CET profile variance decreases, supporting the hypothesis that an increased CET variance is correlated with the injurious effect of the ocular surface in patients with dry eye.

In the present study, spectral domain OCT was used to measure the CET for grading of the severity of dry eye. The cut-off point of CET variance of ≥ 4 for the diagnosis of severe dry eye was found in 18 of 46 patients (39.13%) in the OCT group, which was a higher proportion than in the control group. In the control group, severe dry eye was diagnosed by clinical examination using a TBUT cut-off of ≤ 5 seconds, which was found in 15 of 46 (32.6%) patients. The treatment of severe dry eye and non-severe dry eye differed. Patients with non-severe dry received treatment with artificial tears containing hydroxypropyl methylcellulose. In contrast, patients with severe dry eye underwent lacrimal punctum occlusion and received artificial tears containing hyaluronic acid, which is usually used in more severe cases of dry eye.[32-34] After dry eye treatment, the patients in both groups showed significantly better clinical outcomes (TBUT, DEQ-5 score, and fluorescein staining) at every visit compared with the pretreatment baseline. The improvement was noted at 1 month after beginning treatment and continued until 3 months after beginning treatment. The results showed that the OCT group had better clinical outcomes than the control group at every visit, but the difference was not statistically significant.

The agreement between OCT and clinical examination for the diagnosis of severe dry eye was 88.04% (Kappa coefficient, 0.7384), indicating good agreement; however, there was no correlation between the TBUT and variance CET at baseline (Pearson's correlation, 0.0344).

Notably, both OCT measurement and clinical examination had good agreement in this study, resulting in a similar proportion of patients diagnosed with severe dry eye in both groups. This may have caused the lack of significantly different clinical outcomes between the groups.

Limitations

This study had several limitations. First, discrepancies were noted between the patients' symptoms of dry eye and the physician's clinical findings, causing problems in the diagnosis of severe dry eye in patients with few or mild clinical signs. This discrepancy causes misdiagnosis of the severity of dry eye by a clinical eye examination.[35] Second, one patient was lost to follow-up, which may have caused a data dilution effect that impacted the statistical analysis. Finally, the patients were followed up for only a short period of time that may not have been long enough to demonstrate the statistically significant results of the treatment outcome. A further study with a longer follow-up period may improve this statistical result.

Conclusion

Evaluation of the CET by OCT measurement in patients with dry eye is an effective method that can be used to grade the severity of dry eye compared with clinical eye examination. It has advantages over clinical severity grading such as its high repeatability, noninvasive nature, standardization, and objective measurement. Disadvantages include the high cost of examination and the fact that it may not be widely used in all hospitals. However, severity grading by OCT-based measurement of the CET does not improve the treatment outcome of dry eye compared with severity grading by the normal clinical eye examination.

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