• Clinical Research •

Efficacy of 3% diquafosol sodium eye drops at different frequencies in the treatment of dry eye after FS-LASIK

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Abstract

● **AIM:** To compare the efficacy of 3% diquafosol sodium (DQS) eye drops at different frequencies in dry eye (DE) after femtosecond laser-assisted *in situ* keratomileusis (FS-LASIK).

● **METHODS:** In this prospective study, DE patients after FS-LASIK were randomly divided into two groups. All patients were administered routine anti-inflammatory and anti-infective drugs after FS-LASIK. Additionally, both groups were treated with DQS, at frequencies of 4 (DQS4 group) and 6 (DQS6 group) times daily. Corneal fluorescein staining (CFS) score, non-invasive tear breakup time (NIBUT), tear meniscus height (TMH), lipid layer thickness (LLT), and incomplete blink rate (IBR) were assessed in patients preoperatively and at 1wk, 1, and 3mo postoperatively. The Ocular Surface Disease Index (OSDI) questionnaire was also administered.

● **RESULTS:** Totally 119 patients (238 eyes) were randomly divided into the DQS4 group (60 individuals with 120 eyes) and DQS6 group (59 individuals with 118 eyes). From 1wk to 1mo after FS-LASIK, the CFS score in the DQS6 group decreased with statistical significance (P=0.014), while the DQS4 group showed an upward trend. Comparing with preoperative values, the NIBUT of both groups was significantly prolonged at various time points after FS-LASIK (P<0.05). Within 1mo post FS-LASIK, both groups had significantly higher OSDI scores compared with preoperative values (P<0.05). At postoperative 3mo, the DQS4 group recovered to a level similar to that before surgery (P>0.05), while the DQS6 group remained a little higher than preoperative values (P>0.05). The TMH levels in the DQS4 group increased significantly at 1wk postoperatively (P<0.05), while there was no statistically significant change in the TMH levels in the DQS6 group (P>0.05). There was no significant difference in IBR and LLT between the two groups within 1mo postoperatively. At postoperative 3mo, the LLT in the DQS4 group was significantly higher than that in the DQS6 group (P<0.05).

● **CONCLUSION:** Within 1mo post-FS-LASIK, applying DQS six times daily is superior to four daily applications in improving CFS score, and in increasing NIBUT meanwhile. After 1mo, applying DQS four times daily also effectively alleviate DE symptoms and improve DE signs. Therefore, we recommend DE patients using DQS eye drops 6 times daily within 1mo after FS-LASIK, and maintaining it 4 times daily until 3mo postoperatively.

● **KEYWORDS:** diquafosol; frequencies; dry eye; femtosecond laser-assisted *in situ* keratomileusis

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INTRODUCTION

In recent years, corneal refractive surgery has undergone rapid development. Among the new approaches, femtosecond laser-assisted *in situ* keratomileusis (FS-LASIK) is one of the mainstream surgical techniques for correcting refractive errors[1]. Multiple studies have demonstrated that FS-LASIK is effective, safe, and predictable in patients with low to high and even super-high myopia, with favorable patient satisfaction regarding postoperative visual acuity[2]. Dry eye (DE) is one of the most common complications of FS-LASIK, typically lasting 3-6mo[3-5]. Studies have reported incidence rates for DE at 1wk, 1, and 6mo postoperatively of approximately 50%, 40%, and 20%-40%, respectively[6-8]. Although postoperative DE symptoms are usually transient, some individuals experience severe discomfort, which often leads to negative comment of the surgery[9-10]. Therefore, post-

FS-LASIK DE requires attention from clinical physicians and timely treatment.

Diquafosol sodium (DQS) is a P2Y2 receptor agonist. P2Y2 receptors are found on ocular surface structures, *e.g.*, eyelids, conjunctival epithelium, goblet cells, adipocytes, and ductal epithelial cells of the meibomian glands, and are activated by adenosine triphosphate (ATP) or uridine triphosphate (UTP)[11]. DQS, a derivative of UTP, promotes the secretion of conjunctival water and mucin by activating P2Y2 receptors and may also induce lipid production in meibomian glands[12-13]. Animal experiments have demonstrated that DQS promotes Cl^- secretion from the serosal side to the mucosal side by activating P2Y2 receptors on rabbit conjunctiva, thus enhancing fluid transport[14]. Otherwise, DQS can also suppress the excitability of P2Y2 immune reactive neurons in the trigeminal nerve by reducing the overexpression of P2Y2 in the trigeminal ganglion, thereby reducing eye pain[15]. Clinical trials have demonstrated the safety and efficacy of DQS in DE treatment, with significantly improved corneal fluorescein staining (CFS) score and increased tear secretion, even lipid layer thickness (LLT) levels[16-18]. Therefore, DQS is widely used in the treatment of DE. Currently, DQS is commonly recommended at six daily applications in the treatment of DE. However, in clinical practice, a proportion of patients had difficulty complying with the prescribed dosage of six daily administrations. Most cases undergoing FS-LASIK surgery are young individuals, and their busy study and work schedules make it challenging to adhere to this requirement. No relevant study has examined the efficacy of DQS used less than six times daily for DE after FS-LASIK surgery. Therefore, the aim of this study was to assess the therapeutic effects of different frequencies of DQS on DE after FS-LASIK.

PARTICIPANTS AND METHODS

Ethical Approval This study was performed adhering to the Declaration of Helsinki, and has been approved by the Ethics Committee of Tianjin Medical University Eye Hospital, ethical approval number is 2021KY-18. All patients provided signed informed consent before participating in the study.

Participants Selection DE patients administered FS-LASIK surgery at Tianjin Medical University Eye Hospital from October 2022 to December 2022 were screened. Inclusion criteria were: 1) age between 18 and 45y; 2) preoperative spherical equivalent between -3.0 and -6.0 D, with cylinder diopter ≥-3.00 D; 3) eyes meeting the conditions for FS-LASIK; 4) bilateral FS-LASIK treatment; 5) diagnosis with DE according to the Chinese Dry Eye Expert Consensus diagnostic criteria one day after FS-LASIK surgery; 6) willingness to undergo spectacle removal, with awareness of potential issues and agreement to participate in the study. Exclusion criteria were: 1) history of allergy or adverse reactions to experimental drugs or their components; 2) history of primary diseases potentially leading to DE syndrome, including pinguecula and systemic connective tissue diseases; 3) active eye diseases, uncontrolled systemic diseases, a history of ocular allergic diseases, previous refractive surgery, ocular surgery, or prior utilization of immunomodulators; 4) use of DQS within 2wk before surgery; 5) participation in other clinical trials in the past 3mo prior to screening; 6) intolerance to the drugs during the trial; 7) pregnancy and lactation in women, or planning to become pregnant during the study; 8) unsuitable for the study as judged by the investigators. All patients underwent preoperative assessment including tear meniscus height (TMH), LLT, non-invasive tear breakup time (NIBUT), incomplete blink rate (IBR), and CFS score, and completed the Ocular Surface Disease Index (OSDI) questionnaire.

Random Allocation Patients were divided into two groups using a simple randomization method. Draw up 119 serial numbers and use the random number table method to generate random numbers. Then sort the generated random numbers by size to generate a rank, represented by 1-119. Subjects with ranks 1-60 were assigned to the DQS4 group (DQS four times daily), while those with ranks 61-119 were assigned to the DQS6 group (DQS six times daily).

Treatment The patients were instructed to use 0.3% gatifloxacin eye drops (China Otsuka Pharmaceutical Co., Ltd.) for three days preoperatively. All surgeries were carried out by the same experienced surgeon under topical anesthesia. The FS-LASIK procedure was performed as follows. A corneal flap was generated using the Intralase FS60 femtosecond laser instrument (Intralase Corporation, USA), with a flap diameter of 8.5 mm, a flap thickness of 95-110 μm, and a flap side cut angle of 70°. The generated flap was lifted, and laser ablation was performed with the Schwind Amaris Excimer Laser 1050RS. The effective ablation zone diameter was 6.0-7.0 mm. After washing away corneal debris with balanced salt solution, the flap was repositioned, and the surgical procedure was completed. Confirmation of proper flap alignment was followed by the instillation of 5 g/L levofloxacin eye drops for infection prevention.

Both patient groups underwent postoperative administration of 0.3% gatifloxacin eye drops every 2h on the surgery day until bedtime, followed by four daily administrations for three consecutive days, as well as 0.1% fluorometholone eye drops (Santen Pharmaceutical Co., Ltd., China), starting at four daily administrations and tapering by one dose per week for a total of four weeks. Additionally, the two groups were administered 3% diquafosol sodium eye drops (Santen Pharmaceutical Co., Ltd., China) from postoperative day 1 to postoperative 3mo, four and six times daily, respectively. TMH, LLT, NIBUT, IBR, CFS score, and OSDI were evaluated at 1wk, 1, and 3mo postoperatively.

Clinical Outcomes and Evaluations LLT was evaluated with an ocular surface interferometer (Lipiview, Johnson & Johnson, USA). The patient was instructed to fix their head on the chin rest of the instrument, blink normally, and maintain fixation on the red flashing light in front of the instrument. The operator adjusted the focus to ensure the clearest reflection of eyelashes on the cornea. After 20s of data collection, the instrument automatically determined the average LLT.

The IBR was evaluated with an ocular surface interferometer (Lipiview, Johnson & Johnson, USA), following the same procedure described above.

NIBUT was assessed with a non-invasive ocular surface analyzer (Keratograph 5M, Oculus, Germany). The patient was instructed to blink normally twice and then focus until the Placido ring projected onto the cornea broke. The device automatically captured images and determined tear break-up time. The study utilized the average NIBUT.

TMH was measured with a non-invasive ocular surface analyzer (Keratograph 5M, Oculus, Germany). The central lower eyelid of each patient was focused using infrared light not inducing reflex tearing. After gently blinking, white light was quickly switched on for image acquisition, and TMH was assessed with the instrument's built-in measurement tools. Each eye was examined three times, and average values were recorded.

CFS used fluorescein sodium test strips moistened with saline solution (Tianjin Jingming New Technology Development Co., Ltd., China). The test strip was gently applied to the lower conjunctiva. The patient was instructed to blink several times to evenly distribute the fluorescein sodium solution on the ocular surface. After opening both eyes and looking straight ahead, observation was carried out under cobalt blue light using a slit lamp microscope. CFS data were scored on a 12-point scale with the cornea divided into four quadrants (temporal upper, temporal lower, nasal upper and nasal lower): no staining, 0 point; pinpoint staining, 1 point; small spot staining, 2 points; patchy staining, 3 points. Each quadrant was scored, and the maximum score was 12 points.

The OSDI scale, developed by the DEWS, is an FDA-certified questionnaire used for objective evaluation of ocular surface symptoms in clinical trials. The scale encompasses three aspects, including visual function, subjective sensation, and environmental triggers with a total of 12 questions. The visual function aspect includes asking the patient to evaluate the impact of eye symptoms in the past week on reading, driving at night, computer use, and watching TV. The subjective sensation aspect includes asking the patient to rate the severity levels of light sensitivity, foreign body sensation, eye pain, blurred vision, and decreased vision within the past week. The environmental triggers aspect includes asking the patient to describe eye discomfort under windy conditions, in dry environments, and in air-conditioned rooms. Each question was scored from 0 to 4 based on symptom severity, and the total score was derived as (sum of all items ×25) divided by the number of questions answered.

Table 1 Preoperative conditions and ocular surface indicators in two groups means±SD

Items	DQS4 group	DQS6 group	*P*
Age (y)	27.25±6.83	26.32±6.43	0.45
Gender (male/female)	23/37	25/34	0.71
CFS (score)	1.542±1.270	1.093±0.996	0.003
NIBUT (s)	9.364±3.365	9.337±4.370	0.958
OSDI (score)	12.69±7.07	13.88±8.06	0.395
TMH (mm)	0.242±0.071	0.256±0.068	0.120
IBR (%)	84.52±27.95	71.87±33.52	0.002
LLT (nm)	73.73±22.46	73.68±17.77	0.986

SD: Standard deviation; CFS: Corneal fluorescein staining; NIBUT: Non-invasive tear breakup time; OSDI: Ocular surface disease index; TMH: Tear meniscus height; IBR: Incomplete blink rate; LLT: Lipid layer thickness; DQS4 group: DQS 4 times daily; DQS6 group: DQS 6 times daily.

Statistical Analysis Statistical analysis was performed using SPSS version 25.0. Continuous data were presented as mean±standard deviation (SD). The normality of continuous data was determined by the Kolmogorov-Smirnov test. Normally distributed data between groups were compared by *t*-test, while the Mann-Whitney test was utilized for non-normally distributed data. For comparisons at different time points within a group, paired *t*-test and Wilcoxon rank test were used for normally and non-normally distributed data, respectively. $P<0.05$ was considered statistically significant.

RESULTS

A total of 119 participants (238 eyes) were randomly divided into two groups and administered DQS four (DQS4 group; 60 individuals with 120 eyes) and six (DQS6 group; 59 individuals with 118 eyes) times daily. There were no statistically significant differences in age and gender between two groups (Table 1).

CFS Score Both groups showed increased CFS score at 1wk postoperatively compared with preoperative levels, with the DQS6 group exhibiting a significant increase ($P<0.001$). At 1mo postoperatively, the DQS4 group also demonstrated a significant increase in CFS score compared with preoperative levels ($P=0.039$), while the DQS6 group showed a slight increase with no statistical significance. From 1wk to 1mo postoperatively, the DQS6 group exhibited significantly decreased CFS score ($P=0.014$), while the DQS4 group showed an increase trend during the same period. There was a statistically significant difference in CFS score change between the two groups ($P=0.03$; Figure 1). Both groups showed a

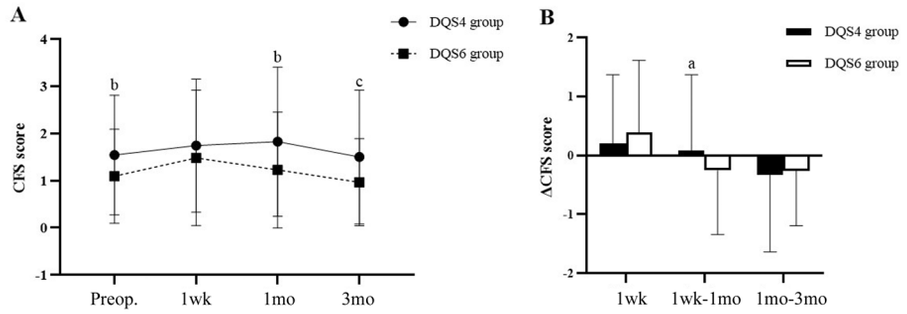

Figure 1 CFS scores of two groups (A) and changes in CFS scores at different time stages (B) after FS-LASIK surgery DQS4 group: DQS 4 times daily; DQS6 group: DQS 6 times daily; CFS: Corneal fluorescein staining. [a]*P*<0.05, [b]*P*<0.01, [c]*P*<0.001.

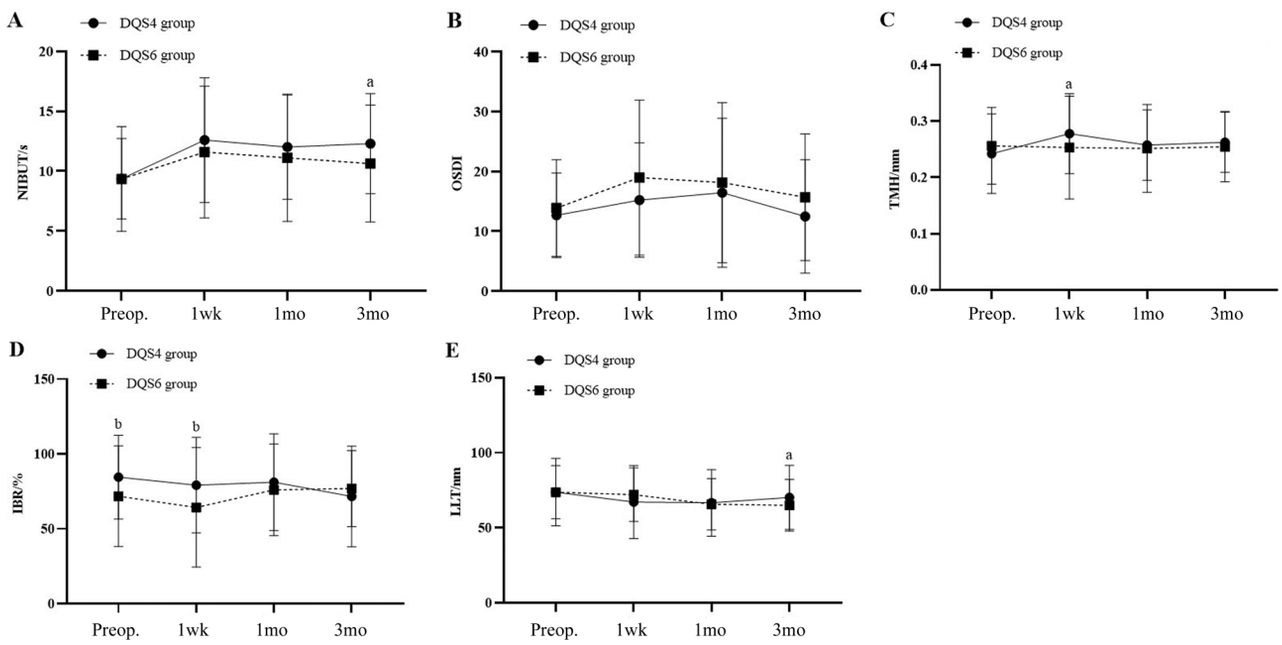

Figure 2 Changes in NIBUT (A), OSDI (B), TMH (C), IBR (D), and LLT (E) in patients of two groups DQS4 group: DQS 4 times daily; DQS6 group: DQS 6 times daily; NIBUT: Non-invasive tear breakup time; TMH: Tear meniscus height; LLT: Lipid layer thickness; IBR: Incomplete blink rate; OSDI: Ocular surface disease index. [a]*P*<0.05, [b]*P*<0.01.

slight decrease in CFS score at 3mo postoperatively compared with preoperative levels, but without statistical significance.

Non-Invasive Tear Breakup Time In the DQS4 group, NIBUT significantly increased at 1wk, 1, and 3mo postoperatively compared with preoperative levels (all *P*<0.001). Similarly, in the DQS6 group, NIBUT significantly increased at 1wk, 1, and 3mo postoperatively (*P*<0.001, *P*=0.001, and *P*=0.014, respectively). There were no significant differences between the DQS4 and DQS6 groups at baseline, 1wk and 1mo postoperatively. However, at 3mo postoperatively, NIBUT values were significantly higher in the DQS4 group compared with the DQS6 group (*P*=0.005; Figure 2A).

Ocular Surface Disease Index At 1wk and 1mo postoperatively, both groups exhibited significantly increased OSDI scores compared with preoperative levels (DQS4, *P*=0.002 and 0.003, respectively; DQS6, *P*<0.001 and *P*=0.001, respectively). At 3mo postoperatively, OSDI scores in the DQS6 group remained significantly higher than preoperative values (*P*=0.043), while decreasing to preoperative levels in the DQS4 group. Regarding trends, OSDI scores in the DQS4 group increased more gradually, peaking at postoperative 1mo, whereas the values in the DQS6 group peaked at 1wk postoperatively and gradually decreased thereafter (Figure 2B).

Tear Meniscus Height After FS-LASIK surgery, the DQS4 group exhibited a significant increase in TMH at 1wk, 1, and 3mo postoperatively (*P*<0.001, *P*=0.027 and *P*=0.003, respectively), with the most significant increase observed at postoperative 1mo (Figure 2C). In the DQS6 group, TMH slightly decreased at 1wk and 1mo postoperatively, but the differences were not statistically significant.

Incomplete Blink Rate At 1wk postoperatively, both groups showed decreased IBR compared with preoperative levels. At postoperative 1mo, the IBR in the DQS4 group remained slightly lower than the preoperative value, while it slightly increased in the DQS6 group. At postoperative 3mo, the IBR significantly decreased in the DQS4 group compared with the

preoperative level (P<0.001), while remaining slightly higher in the DQS6 group (Figure 2D).

Lipid Layer Thickness At 1wk postoperatively, both groups exhibited decreased LLT values compared with preoperative levels, with only the DQS4 group showing statistical significance (P=0.01). At postoperative 1mo, LLT values remained below preoperative levels (P=0.004 and P<0.001, respectively). In the DQS4 group, LLT values decreased at 3mo postoperatively compared with preoperative levels but showed slight uptrend compared with earlier postoperative values, while the DQS6 group still had significantly lower values than preoperative levels (P<0.001; Figure 2E).

DISCUSSION

In this study, the efficacy of DQS at different frequencies were compared for DE following FS-LASIK. The OSDI score reflects the subjective sensation and visual function postoperatively in patients, who often experience subjective symptoms of ocular discomfort after FS-LASIK surgery. Reports have shown that DE symptoms after LASIK surgery generally persist for more than one month and return to preoperative levels occurring by 6mo postoperatively[3]. In the present study, OSDI scores in both patient groups initially increased and then decreased. Both groups showed significantly increased scores at 1wk and 1mo postoperatively compared with preoperative scores. Similar results were reported in another study[4,19]. Among the examined patients, the DQS4 group had the highest OSDI scores at 1mo postoperatively, while the DQS6 group showed the highest scores at 1wk postoperatively, and the values gradually decreased thereafter. At postoperative 3mo, OSDI scores in the DQS4 group returned to preoperative levels, while those of the DQS6 group remained significantly higher versus preoperative levels. These data indicate that the mucus secretion and moisture induced by DQS within the first postoperative week is not sufficient to compensate for the surgery-related damage to the ocular surface and to relieve discomfort, hence both patient groups showed significantly increased OSDI scores within the first week. The application of DQS six times daily following FS-LASIK surgery could significantly improve DE symptoms 1wk postoperatively.

We found that six times daily application of DQS was superior to four daily applications in CFS score improvement. In the DQS6 group, CFS score elevation postoperatively was short-lived, with a decrease from 1wk postoperatively and significant decrease by postoperative 1mo, as well as a similar trend maintained until 3 postoperative months. In contrast, in the DQS4 group, the trend of CFS score elevation persisted until postoperative 1mo, with a significant increase detected at 1mo postoperatively versus preoperative levels. These findings suggest that six daily applications of DQS following FS-LASIK surgery could more rapidly improve corneal epithelial damage. In this study, due to randomness in patient selection and grouping, there was a significant difference in preoperative CFS score between the two groups (DQS4 group >DQS6 group). However, based on changes and trends in postoperative CFS score of both groups, six daily DQS administrations showed superiority over four daily treatments in improving CFS score.

Some studies have reported that the application of DQS significantly increases the BUT of patients with DE after ocular surgery[20-21]. This study found that following FS-LASIK surgery, DQS treatment significantly improved NIBUT. It has been reported that within 3mo post-FS-LASIK, tear BUT is shortened compared with preoperative levels, while DQS could significantly prolong BUT, aligning with the current study[4,6]. As shown above, preoperative NIBUT values were similar in both groups, which showed prolonged NIBUT at each postoperative time point compared with preoperative levels. This indicates that DQS induces the secretion of mucin and aqueous fluid in ocular surface tissues, better maintaining tear film stability in patients after FS-LASIK surgery. As NIBUT was extended in both groups compared with preoperative levels at 3 postoperative months, both four and six daily applications of DQS may achieve favorable results in stabilizing the tear film.

TMH, a commonly used tool for tear volume assessment, is widely applied for the diagnosis and treatment of DE syndrome[22]. This study found that in the DQS4 group, TMH increased at 1wk, 1mo, and 3mo postoperatively compared with preoperative values. In contrast, there were no significant changes in TMH at any time point in the DQS6 group, either preoperatively or postoperatively. A study by Wang *et al*[4] reported no significant differences in TMH changes with the combined use of hyaluronic acid and DQS for DE after FS-LASIK. Based on the results of both groups, we believe that DQS could maintain tear volume on the ocular surface postoperatively by inducing the secretion of aqueous fluid and mucin by the conjunctiva. The above data suggest that the four DQS daily treatment protocol is a more effective. Previous studies have rarely utilized TMH alone to reflect tear volume. Due to the large variability in TMH, further combination with the Schirmer test may better explain the results, which is absent in this study.

As shown above, the LLT of the tear film decreased postoperatively at all time points compared with preoperative levels. Within postoperative 1mo, the LLT decrease were similar in both groups. However, at 3mo postoperatively, the DQS6 group showed a more pronounced decrease in LLT compared with preoperative values. Recent findings have confirmed that DQS affects P2Y2 receptors on meibomian

gland cells in rabbits, promoting the release of lipids from the meibomian glands[23]. Fukuoka and Arita[24-25] reported that DQS increases LLT in both healthy individuals and DE cases with meibomian gland dysfunction in a short period. Previous studies by our research team have demonstrated that average LLT decreases within 1mo after FS-LASIK[26]. Wang *et al*[4] compared hyaluronic acid administered alone versus the combination with DQS in DE treatment after FS-LASIK and found that the addition of DQS significantly increases LLT after FS-LASIK, which is in disagreement with the current data. We speculate that changes in LLT after FS-LASIK may also involve other factors.

Furthermore, the current study also detected changes in incomplete blinking postoperatively. This study used machine-based automatic calculation to determine the ratio of incomplete blinks to total blinks (incomplete plus complete blinks), referred to as the IBR[27]. During blinking, the movement of eyelid muscles can extract the meibum stored in the meibomian gland ducts and evenly spread it across the ocular surface. Incomplete blinking may decrease LLT[28]. In this study, changes in LLT and IBR had opposite trends, suggesting an inverse correlation between the two factors. In the DQS6 group, at 1wk postoperatively, LLT decreased while IBR increased, whereas the opposite effects were observed in the DQS4 group. This may be due to enhanced relief in ocular discomfort with 6 daily DQS administrations. While in the DQS4 group, the discomfort induced complete blinking. Jie *et al*[27] found that the IBR is associated with BUT, with a higher proportion of incomplete blinking correlated with shorter BUT. This study demonstrated that at 3mo postoperatively, NIBUT was significantly higher in the DQS4 group compared with the DQS6 group, suggesting a potential association between NIBUT and incomplete blinking.

This study had limitations, including the lack of a blank control group, the absence of data collection for postoperative visual acuity in both groups, and the absence of the Schirmer test to evaluate tear secretion.

In conclusion, use of DQS after FS-LASIK surgery improves both the symptoms and signs of DE. Within postoperative 1mo, DQS administered six times daily is more effective than four daily applications for the alleviation of objective corneal damage. However, after 1mo postoperatively, four daily DQS administrations could still achieve good therapeutic effects. Therefore, we recommend DE patients using DQS eye drops 6 times daily within 1mo after FS-LASIK, and maintaining it 4 times daily until 3mo postoperatively.

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