Combination Therapy With Diquafosol Tetrasodium and Sodium Hyaluronate in Patients With Dry Eye After Laser In Situ Keratomileusis

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• PURPOSE: To evaluate the possible advantages of combination therapy with diquafosol tetrasodium and sodium hyaluronate for dry eye after laser in situ keratomileusis (LASIK).

• DESIGN: Prospective randomized comparative trial.

• METHODS: A total of 206 eyes of 105 patients who underwent LASIK were enrolled in this study. Patients were randomly assigned to 1 of 4 treatment groups according to the postoperative treatment: artificial tears, sodium hyaluronate, diquafosol tetrasodium, and a combination of hyaluronate and diquafosol. Questionnaire responses reflecting subjective dry eye symptoms, uncorrected and corrected visual acuity, functional visual acuity, manifest refraction, tear break-up time, fluorescein corneal staining, Schirmer test, and corneal sensitivity were examined before and 1 week and 1 month after LASIK.

• RESULTS: Distance uncorrected visual acuity was significantly better in the combination group than in the hyaluronate group 1 week and 1 month after LASIK. Near uncorrected visual acuity was significantly better in the combination group than in the artificial tear and diquafosol groups 1 week and 1 month after LASIK. Distance functional visual acuity improved significantly only in the combination group 1 month after LASIK. The Schirmer value in the combination group was significantly higher than that in the hyaluronate group at 1 month after LASIK. Subjective dry eye symptoms in the combination group improved significantly compared with those in the other groups 1 week after surgery.

• CONCLUSIONS: Our results suggest that hyaluronate and diquafosol combination therapy is beneficial for early stabilization of visual performance and improvement of subjective dry eye symptoms in patients after LASIK. (Am J Ophthalmol 2014;157:616–622. © 2014 by Elsevier Inc. All rights reserved.)

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LASER IN SITU KERATOMILEUSIS (LASIK) HAS BEEN established as the most popular corneal refractive surgery in the world. Patient satisfaction is usually very high because LASIK provides a high quality of vision. However, most patients experience temporary worsening of dry eye symptoms during the early postoperative period. It is well known that LASIK affects the ocular surface and tear dynamics, and dry eye is one of the most common complications after the procedure.[1]

Traditional therapies for post-LASIK dry eye are artificial tears and sodium hyaluronate eye drops, which are useful for temporary relief of symptoms but may be insufficient in severe and/or longstanding cases. Punctal plugs and autologous serum eye drops[2] are effective in such cases, because they preserve and supply tear components including growth factors, hormones, and vitamins that exist in normal tears[3,4] and work to maintain a healthy ocular surface. However, punctal plug occlusion results in several adverse events, including spontaneous extrusion,[5] migration,[6] pyogenic granuloma,[7] biofilm formation,[8] and corneal ulceration.[9] Autologous serum eye drops are also effective for treating post-LASIK dry eye,[10] but they are inconvenient because patients are required to visit the hospital every 3 months. Protective glasses with side panels have been used in combination therapy,[11] but glasses may not be desired by patients after LASIK.

A new eye drop, 3% diquafosol tetrasodium ophthalmic solution (DIQUAS ophthalmic solution 3%; Santen Pharmaceutical Co Ltd, Osaka, Japan), was launched in Japan for treating dry eye.[12] This eye drop is a purinergic $P2Y_2$ receptor agonist, which has a novel mechanism to stimulate water and mucin secretion from conjunctival epithelial cells and goblet cells.[13,14] Clinical trials in patients with dry eye show that topical application of 3% diquafosol ophthalmic solution significantly decreases ocular surface damage, as evaluated by fluorescein and rose bengal staining, and improves subjective dry eye symptoms.[15,16] In addition, combination therapy with diquafosol tetrasodium and hyaluronate is effective in improving objective and subjective symptoms in patients with dry eye.[17]

The purpose of this study was to evaluate the possible advantage of combination therapy with 3% diquafosol ophthalmic solution and 0.3% sodium hyaluronate ophthalmic solution, in comparison with monotherapy with either agent for dry eye symptoms, signs, and visual performance after LASIK.

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PATIENTS AND METHODS

THIS PARALLEL, PROSPECTIVE RANDOMIZED COMPARATIVE clinical study was carried out with approval by the Institutional Review Board and ethics committee of Minamiaoyama Eye Clinic and followed the tenets of the Declaration of Helsinki. Written informed consent to participate in this study was obtained from all patients. This study was registered at www.umin.ac.jp/ctr/(UMIN000012111).

• **SUBJECTS:** A total of 206 eyes in 105 patients (mean age, 33.4 ± 10.1 years) who underwent LASIK at Minamiaoyama Eye Clinic, Tokyo, Japan from April 1, 2011 to May 31, 2012 were enrolled in this study.

All patients were screened by dry eye tests preoperatively, including Schirmer test, fluorescein staining of ocular surface, tear break-up time, and symptoms. The patients without definite dry eye determined by Japanese Dry Eye Diagnostic Criteria[18] were included in this study.

A corneal flap was created with a femtosecond laser (Intralase; Abbott, Chicago, Illinois, USA), and laser ablation was performed using an excimer laser (EC-5000; NIDEK, Aichi, Japan). After surgery, low-dose corticosteroid and antibiotic eye drops were prescribed 5 times daily for 1 week. Patients were excluded from the study if they had any other ocular disease or were taking any medications causing dry eye.

• **PROTOCOL:** The study protocol was designed with a preoperative observation period, followed by a postoperative 4-week treatment period. The patients were randomly assigned to 1 of 4 treatment groups before LASIK: artificial tears (SoftSantear ophthalmic solution; Santen; artificial tear group), 0.3% sodium hyaluronate ophthalmic solution (Hyalein ophthalmic solution 0.3%; Santen; hyaluronate group), 3% diquafosol ophthalmic solution (DIQUAS ophthalmic solution 3%; Santen; diquafosol group), and a combination of hyaluronate and diquafosol (combination group). Patients applied 1 drop of the ophthalmic solution 6 times daily in both eyes. Follow-up visits were 1 week and 1 month after surgery. On each visit, patients were asked to complete a dry eye questionnaire and were examined for uncorrected and spectacle-corrected visual acuity, functional visual acuity, manifest refraction, tear break-up time, fluorescein corneal staining, Schirmer test, and corneal sensitivity.

• **FUNCTIONAL VISUAL ACUITY:** A functional visual acuity measurement system (Kowa, Tokyo, Japan) was used to examine changes in continuous visual acuity over time. The Landolt optotypes were presented on the equipment monitor, and their sizes changed depending on the correctness of the response. In brief, the optotypes are displayed automatically, starting with the small ones. Even the smaller optotypes are presented when the response is correct. If the response is incorrect, larger optotypes are presented automatically. Visual acuity is measured continuously from the baseline best-corrected Landolt visual acuity. Subjects were instructed to blink naturally during the measurement period. Patients delineated the orientation of the automatically presented Landolt rings by manipulating a joystick. Functional visual acuity was measured during a 60-second period without instillation of topical anesthesia. Functional visual acuity was defined as the mean value of the timewise change in visual acuity during the overall examination. Functional visual acuity was measured with spectacle best-corrected vision before LASIK and uncorrected vision after LASIK.

• **OCULAR SURFACE AND TEAR FUNCTION:** The ocular surface was stained with 2 μL of 1% preservative-free fluorescein solution instilled into the conjunctival sac. Tear break-up time was the interval between the last complete blink and the first disturbance of the stained corneal tear film. Fluorescein staining was graded from 0-3 for the upper, middle, and lower third of the cornea. The grading scale was defined according to the extent of staining: 0, negative; 1, scattered minute; 2, moderate spotty; 3, diffuse blotchy staining. The Schirmer test was performed without anesthesia to evaluate tear function, as described previously.[1] A Schirmer strip was placed for 5 minutes. The length of the wet portion was measured. Corneal sensitivity was measured with a Cochet-Bonnet esthesiometer consisting of a nylon filament 60 mm long and having 0.12 mm diameter. Patients were asked to look straight ahead and to indicate when the top of the nylon filament touched the cornea. Corneal sensitivity was defined as the length of the filament that produced the first positive response.

• **DRY EYE SYMPTOMS:** The presence of dry eye symptoms was evaluated by a questionnaire for symptoms of dryness and eye fatigue. Symptom severity was assessed on a 4-point scale from 0-3 as follows: 0, no symptoms; 1, mild symptoms; 2, moderate symptoms; 3, severe symptoms.

• **STATISTICAL ANALYSIS:** The data analysis was performed using the paired *t* test or Wilcoxon signed rank sum test before and after LASIK. The Steel-Dwass or Tukey-Kramer tests were used to compare data among the treatment groups. A P value of $<.05$ was considered significant. All statistical analyses were performed using JMP software, version 10.0 (SAS Institute, Cary, North Carolina, USA).

RESULTS

A TOTAL OF 206 EYES OF 105 PATIENTS WERE RANDOMLY assigned to the 4 treatment groups as follows: 50 eyes of 25 patients to the artificial tear group, 46 eyes of 23 patients to the hyaluronate group, 60 eyes of 30 patients to the diquafosol group, and 50 eyes of 27 patients to the combination