Topical Steroids for Prevention of Diffuse Lamellar Keratitis Following LASIK

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Purpose: To determine the role of prophylactic topical steroids in the prevention of diffuse lamellar keratitis (DLK) after laser in situ keratomileusis (LASIK).

Methods: This randomized double blind clinical trial included consecutive LASIK candidates aged 18 to 55 years with stable (≥1 year) myopia ranging from -2 to -12 diopters. The day before surgery, eyes were randomly allocated to topical betamethasone 0.1% or placebo every four hours. One hour preoperatively, the dosage was increased to every five minutes for at least six times. DLK was graded according to the Linebarger-Lindstorm classification. Patients were examined one week and one and three months after surgery. Best-corrected visual acuity (BCVA), manifest and cycloplegic refraction and severity of DLK were documented at each visit by a masked examiner.

Results: Overall, 198 eyes (100 in the treatment group and 98 in the control group) of 101 patients (97 bilateral and 4 unilateral cases) were operated. Pre- and post-LASIK refraction and BCVA were comparable in the study groups (P> 0.05). There were no significant complications in either group during or after LASIK except for DLK which developed in 55 eyes (55%) of the treatment group including 44 eyes with grade I and 11 eyes with grade II, versus 36 eyes (36.7%) of the control group including 29 eyes with grade I and 7 eyes with grade II DLK (P= 0.81).

Conclusion: Although steroids play a key role in the treatment of DLK, pretreatment with topical steroids 24 hours prior to LASIK does not seem prevent this complication.

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INTRODUCTION

Laser in situ keratomileusis (LASIK) has surpassed other types of refractive surgery over the past decade because of being easy to perform, rapid visual recovery and low incidence of pain and complications during and after the procedure.[1] LASIK is widely used for treatment of moderate to high myopia (up to -10 diopters), low to moderate hyperopia and moderate regular astigmatism.[2]

Although numerous intra- and post-operative complications have been attributed to LASIK, the actual rate is very low. Diffuse lamellar keratitis (DLK) can occur shortly after LASIK and lead to irreversible visual loss in severe cases. This complication was first reported by Smith and Maloney[3] in 1998. It is a non-infectious inflammatory reaction in the flap-corneal bed interface which usually occurs one week after LASIK. Other names given to this syndrome include Sands of Sahara, Shifting

Sands, non-specific diffuse lamellar keratitis, sterile interface diffuse lamellar keratitis, post-LASIK interface keratitis and lamellar keratitis.[4] But the term DLK which was used in the first report, appears more appropriate and is more commonly used.

DLK has been reported by excimer laser centers all over the world, however the exact etiology still remains unknown[5,6] but seems to be multifactorial.[7] Contributing factors include meibomian gland secretions, povidone-iodine, talc powder from surgical gloves, remnants of antiseptics used for cleaning surgical instruments, remnants of bacteria, endotoxins and exotoxins on surgical instruments, balanced salt solution (BSS), epithelial cells and red blood cells beneath the flap, polluted autoclave reservoirs and contaminations and deposits on the microkeratome.[8-12]

Preventive measures against DLK have not been successful. The role of topical and systemic steroids in the treatment of DLK and prevention of its progression have been studied.[13] In one study, topical steroids were used after lifting the flap and before laser application which seemed to decrease the risk of DLK.[14] The role of lid scrubbing and treatment of blepharitis prior to LASIK as well as use of systemic steroids and antihistamines in atopic individuals has already been established.[15] However, the role of topical steroids prior to LASIK for prevention of DLK has not been studied yet.

An episodic increase in the rate of DLK was seen in excimer centers in Tehran during the years 2002 to 2004 with no particular causative factor (unpublished data). This research was performed during the year 2004 at Negah Eye Center, Tehran, Iran during an outbreak of DLK to evaluate the role of preoperative topical steroids for prevention of DLK.

METHODS

This double blind randomized clinical trial was conducted on a consecutive series of patients 18 to 55 years of age undergoing LASIK. A complete ophthalmologic examination was performed in all patients including uncorrected visual acuity (UCVA), manifest and cycloplegic refraction, best spectacle-corrected visual acuity (BSCVA) using Nidek projection chart (Nidek, Kamagori, Japan), slitlamp examination, Goldmann applanation tonometry and funduscopy with a fully dilated pupil. Refraction and corneal topography (if available) were stable for at least one year. The patients had no other ocular condition other than refractive errors and no systemic disorders. Contact lenses were discontinued at least one and three weeks before videokeratography in soft and rigid gas permeable (RGP) lens wearers, respectively. All patients were instructed to scrub their eyelids with baby shampoo three days before surgery.

The study and its purpose were explained to all patients and informed consent was obtained. All subjects underwent computerized videokeratography (CSO, Italy), ultrasonic pachymetry (Somoned, USA) and Orbscan II topography (Bausch & Lomb, Germany) three days before LASIK. Topical betamethasone 0.1% eyedrops (Chauvin, France) were prescribed for eyes in the treatment group and placebo was administered to the control eyes every four hours one day prior to LASIK and every five minutes for at least six times one hour before the procedure. In bilateral LASIK candidates, one eye was randomized for treatment and the fellow eye received placebo.

All LASIK procedures were performed by one surgeon (FK) under topical anesthesia with 0.5% tetracaine. The Moria LSK Carriaso-Barraquer microkeratome (Moria, France) with a fixed plate was used to cut a flap of 160 micron thickness. Each microkeratome blade (Moria, France) was used once for each patient (i.e., for both eyes in bilateral cases) after cleaning by distilled water and wet spears and checking for any deposit or irregularities under the surgical microscope immediately before surgery. After creation of the flap and making sure of its normalcy and central position, laser ablation was performed using the Nidek EC-5000 CX-II (Nidek, Kamagori, Japan) excimer laser machine. The flap was then returned to its position and the undersurface was irrigated with a small amount of BSS until there was no

visible debris or foreign particles. After performing LASIK on the first eye, if there was no complication and the patient agreed, the procedure was performed in the fellow eye in bilateral cases. At the end of the operation, betamethasone and chloramphenicol eyedrops were instilled in the operated eye and continued every six hours. Chloramphenicol was discontinued after one week and betamethasone dosage was adjusted as described subsequently.

Postoperative examinations were performed by one masked observer, unaware of the treatment allocation of patients. Uncomplicated patients were visited every day during the first week and one and three months thereafter. Betamethasone dosage was adjusted according to degree of inflammation and grade of DLK based on Linstrom-Linebarger classification.[16] In the absence of DLK, betamethasone was gradually tapered and discontinued over two weeks. In the presence of DLK, treatment was continued based on DLK grading: in grade I, betamethasone frequency was increased to hourly. Grade II DLK was treated with betamethasone drops every one hour and betamethasone ointment at night together with oral prednisolone 1 to 1.5 mg/kg/day. The systemic steroid was discontinued over 7-10 days after control of DLK.

Severity of pain during the first six hours after LASIK was subjectively graded based on a 0 to 10-scale measure where zero and 10 indicated no and very severe pain, respectively. UCVA, BSCVA, refraction, slitlamp examination and tonometry were repeated one and three months postoperatively. Statistical analysis was done using paired and unpaired *t*-tests for mean values within and between the two groups, respectively and Chi-square test for frequency values with significance set at $P<0.05$.

RESULTS

From July to September 2004, 198 eyes (100 in the treatment group and 98 in the control group) of 101 patients (97 bilateral and 4 unilateral cases) with mean age of 30±12.7 (range 18–51) years were enrolled in this study. Seventy-five patients were female. Only one case was referred for enhancement surgery and others were new LASIK candidates. Each group included three hyperopic eyes which were excluded from data analysis due to the small number.

Pain score greater than four (mild) within the first six hours after LASIK was reported in four eyes of the treatment group and seven eyes of the control group ($P<0.05$). There was no case of severe pain in any group.

DLK occurred in 55 eyes (55%) including 44 (80%) grade I and 11 (20%) grade II in the treatment group and in 36 eyes (36.7%) including 29 (81%) grade I and 7 (19%) grade II in the control group (P=0.81). No case of grade III or higher DLK was observed in any group.

Mean spherical equivalent (SE) refraction in the treatment and control groups was -4.8±2.4 and -5.2±2.7 diopters (D) respectively (P=0.16). One week postoperatively, mean SE was -0.41±0.27 D and -0.42±0.39 D in the treatment and control groups, respectively (P=0.84). Mean UCVA was 0.09±0.6 and 0.07±0.05 LogMAR in the treatment and control groups, respectively (P=0.41) (Table 1).

Table 1 Uncorrected visual acuity one week after laser in situ keratomileusis

	Treatment group	Control group
20/15 to 20/25	89 (90.8%)	83 (86.3%)
20/25 to 20/50	9 (9.2%)	11 (11.6%)
<20/50	0	2 (2.1%)
Total	98 (100%)	96 (100%)

• Fisher exact test, P= 0.41

Three months postoperatively, 65 cases including 24 in the treatment group and 36 in the control group were available for final evaluation. Mean SE was -0.36±29 D and -0.49±31 D in the treatment and control groups respecttively (P=0.29). Mean UCVA was 0.09±0.04 LogMAR in the treatment group and 0.07±0.04 LogMAR in the control group (P=0.28). At final follow-up, no eye lost more than one line of BCVA; no irregular astigmatism was noted and

no patient complained of glare or ghost images. No case of corneal opacity, epithelial ingrowth, folds in the flap crossing the visual axis, flap displacement, infectious keratitis, cataract or IOP rise was seen.

DISCUSSION

LASIK is probably the most common keratorefractive procedure. The rate of post-LASIK complications has been reported from 3 to 12%.[4,5,7] DLK is usually a mild and transient condition but in severe cases may cause corneal scarring, irregular astigmatism and decreased vision. Multiple factors have been implicated in the development of DLK.[7-12,17] This condition seems to be an immunologic or inflammatory response of the cornea to antigens or debris introduced beneath the flap during the operation. Some authors believe that suppressing the immune response with steroids (topical and systemic) may control or prevent DLK.[13] Several prophylactic measures have been investigated, but due to the multifactorial nature of DLK, none has been definitely effective. In one study on atopic cases, with a postulated higher chance of DLK, prophylactic antihistamine (Loratadine) reduced the incidence of DLK.[15]

In the current study, topical steroids had no role in preventing DLK; there was no statistically significant difference between treatment and placebo groups regarding occurrence of DLK or final refraction. It is thought that frequent administration of topical steroids before LASIK may predispose the eye to infectious keratitis, one of the most severe and serious complications of LASIK, especially bacterial keratitis which is more common early after surgery. However, over three months of follow-up, we did not encounter any case of infectious keratitis in our series.

Overall, grade I and II DLK were seen in 36.5% and 9.1% of eyes in our study, respectively. The rate of grade I DLK has been reported less than 1% by Johnson et al[6], 2-4% by Linebarger et al[16], 4% by Stulting et al[18] and 9% by Wilson et al.[19] The incidence of grade II DLK has been reported from 0.18 to 0.5% in the above-mentioned studies. The difference in the incidence of DLK between our center in Tehran and other excimer centers around the world is unexplainable. Keratorefractive surgeons at different laser centers in Tehran have sought several remedies to control DLK outbreaks such as using different laser machines, different microkeratome blades, spears and irrigation solutions (Ringer vs BSS), avoiding ultrasound sterilization, chemical sterilization, use of powder-free gloves, regular cleaning and drying of the autoclave reservoir, stromal-flap bed irrigation with steroid containing solutions. The exact cause of the epidemic outbreaks of DLK in this city however remains unknown.

It has been postulated that prophylactic topical steroids can prevent DLK, but no definite study has been reported in this regard. Our study was not able to prove that topical steroids before LASIK can prevent this complication, however one may argue that initiation of topical steroids one day before LASIK may not be early enough to suppress the immunological response and prevent DLK. Cosar et al[20] have shown that early postoperative use of high frequency topical steroids can prevent DLK. They used prednisolone acetate or dexamethasone eye drops every hour after LASIK which was able to prevent epidemic DLK. Administration of non-steroidal anti-inflammatory drugs or corticosteroids in an animal model was also able to prevent or reduce DLK.[21]

In summary, topical administration of corticosteroids prior to LASIK did not prevent DLK. At the present time, the best way for prevention of DLK is to eliminate defined predisposing factors for DLK. Close follow-up during the early postoperative period for early diagnosis and treatment of this potentially sight-threatening complication may prevent permanent corneal damage.

REFERENCE

1. Salah T, Waring GO III, el-Maghraby A, Moadel K, Grimm SB. Excimer laser in situ keratomileusis (LASIK) under a corneal flap for myopia of -2 to -20 Diopters. *Am J Ophthalmol* 1996 121:143-153.

2. Salchow DJ, Zirm ME, Stieldorf CL. Laser in situ keratomileusis for myopia and myopic astigmatism. *J Cataract Refract Surg* 1998,24:175-182.
3. Smith RJ, Maloney R. Diffuse lamellar keratitis: a new syndrome in lamellar refractive surgery. *Ophthalmology* 1998;105:1721-1726.
4. Macaluso DC, MacRae S. Diffuse lamellar keratitis. In: Gimble HV, Anderson Penno EE, eds. LASIK complications prevention and management. Thorofare, NJ: Slack Inc; 2001: 103-115.
5. Buratto L, Brint S. Complications of LASIK. In: Buratto L, Brint S. LASIK: surgical techniques and complications. Thorofare NJ: Slack Inc.; 1999: 239-243.
6. Johnson JD, Harissi-Dagher M, Pineda R, Yoo S, Azar DT. Diffuse lamellar keratitis: incidence, associations, outcomes and a new classification system. *J Cataract Refract Surg* 2001;27:1560-1566.
7. Iskander NG, Peters NT, Anderson Penno EE, Gimbel HV. Postoperative complications in LASIK. *Curr Opin Ophthalmol* 2000;11:273-279.
8. Kaufman SC, Maitchouk DY, Chiou AGY, Beuerman RW. Interface inflammation after laser in situ keratomileusis: Sands of Sahara Syndrome. *J Cataract Refract Surg* 1998;24:1589-1593.
9. Webber SK, Lawless MA, Sutten GL, Rogers CM. Staphylococcal infection under a LASIK flap. *Cornea* 1999;18:361-365.
10. Sachder N, McGhee CN, Graig JP, Weed KH, McGhee JJ. Epithelial defect, diffuse lamellar keratitis and epithelial ingrowth following post-LASIK epithelial toxicity. J *Cataract Refract Surg* 2002;28:1463-1466.
11. Holland SP, Mathias RG, Morck DW, Chin J, Slade SG. Diffuse lamellar keratitis related to endotoxins released from sterilizer reservoir biofilms. *Ophthalmology* 2000;107:1227-1233, discussion: 1233-1234.
12. Kaufman SC, Maitchouk DY, Chiou AG, Bauerman RW. Post LASIK interface keratitis, Sands of Sahara Syndrome, and microkeratome blades. Letter to the editor. *J Cataract Rerfact Surg* 1999;25:603-604.
13. Macrae SM, Rich LF, Macaluso DC. Treatment of interface keratitis with oral corticosteroids. *J Cataract Refract Surg* 2002;28:454-461.
14. Peters NT, Lingua RW, Kim CH. Topical intrastromal steroid during laser in situ keratomileusis to retard interface inflammation. *J Cataract Refract Surg* 1999;25:1437-1440.
15. Boorstein SM, Henks HJ, Elner VM. Atopy: a patient–specific risk factor for diffuse lamellar keratitis. *Ophthalmology* 2003;110:131:137.
16. Linebarger EJ, Hardten DR, Lindstrom RL. Diffuse lamellar keratitis: diagnosis and treatment. *J Cataract Refract Surg* 2000;26:1072-1077.
17. Hirst LW, Vandeleur KW Jr. Laser in situ keratomileusis interface deposits. *J Refract Surg* 1998;14:653-654.
18. Stulting RD, Randleman JB, Couser JM, Thopson KP. The epidemiology of diffuse lamellar keratitis. *Cornea* 2004;23:680-688.
19. Wilson SE, Ambrosio JVR. Sporadic diffuse lamellar keratitis (DLK) after leaser in situ keratomileusis. *Cornea* 2002;21:560-653.
20. Cosar CB, Sener AB, Sen N, Coskunseven E. The efficacy of hourly prophylactic steroids in epidemic diffuse lamellar keratitis. *Ophthalmologica* 2004;218:318-222.
21. Holzer MP, Sandoval HP, Vargas LG, Kasper TJ, Vroman DT, Apple DJ, et al. Corneal flap complications in refractive surgery, Part 2: Postoperative treatment of diffuse lamellar keratitis in an experimental animal model. *J Cataract Refract Surg* 2003;29:803-807.