Topical Ketorolac Tromethamine in the Reduction of Adverse Effects of Laser *in Situ* Keratomileusis†

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Abstract

Purpose : To evaluate whether topical ketorolac tromethamine can reduce the adverse effect of laser in situ keratomileusis (LASIK).

Design : A prospective randomized controlled clinical study.

Participants : Nineteen patients who underwent bilateral simultaneous LASIK performed at Siriraj Hospital.

Intervention : Patients received two drops of ketorolac tromethamine in one eye immediately after surgery.

Main Outcome Measures : Symptoms of tearing, photophobia, foreign body sensation and pain were evaluated at 30 minutes, 6 hours and 24 hours.

Results : There was no statistically significant difference in symptoms at 30 minutes. At 6 and 24 hours, ketorolac-treated eyes had significantly fewer symptoms compared to non-treated eyes.

Conclusions : Ketorolac tromethamine reduces some unfavorable symptoms within the first 24 hours after LASIK.

Key word : Laser *in Situ* Keratomileusis, Topical Ketorolac Tromethamine

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Laser *in situ* keratomileusis (LASIK) is a popular procedure of choice for the correction of myopia, astigmatism and hyperopia at present (1,2). This procedure consists of lifting a corneal flap with microkeratome and photoablation on the stromal bed by 193 nm. argon fluoride excimer laser. One study on monkey eyes has shown that the cornea undergoes several biomedical transitions after photoablation including deposition of laminin, fibrinogen and fibronectin at the ablated surface within 24 hours(3). Initial biochemical inflammatory responses include the release of lymphokines, kinins, amines and arachidonic acid metabolites, prostaglandin E_2 (PGE_2) and others. The wound healing response to tissue disruption by excimer laser is similar to that occurring in a mechanical wound(4-7). Furthermore, it increases local keratocyte concentration and changes in collagen composition(8,9). Leukotriene B4 (LTB4), lipoxygenase products are highly chemotactic for leukocytes and may play a role in the inflammatory response(10). Prostaglandins play a role in chemotaxis and stimulating lymphokine secretion and pain(11). However, application of corticosteroid immediately after surgery to inhibit these responses can delay wound healing and increase the risk of infection(12). However, Vantesone et al reported that the administration of the topical nonsteroidal anti-inflammatory agent, diclofenac compared with prednisolone acetate led to stable wound healing, without regression and decreased postoperative inflammation in LASIK patients at one month(13). But no study has shown the adverse effects following LASIK such as pain, discomfort and foreign body sensation, although their severity is less than in photorefractive keratectomy(14). The nonsteroidal anti-inflammatory drug, topical ketorolac tromethamine, has a similar anti-inflammatory response to corticosteroid by inhibition of the cyclooxygenase and lipoxygenase pathway, but it is superior to diclofenac in lower levels of LTB_4(15). Therefore, topical ketorolac tromethamine may relieve pain and discomfort in the first day postoperatively in LASIK.

The purpose of the study was to evaluate the efficacy of ketorolac tromethamine in reducing adverse effects within the first day of LASIK.

MATERIAL AND METHOD

Nineteen patients with myopia and astigmatism from the consecutive cases from the Excimer Laser Clinic, Siriraj Hospital were enrolled from September through December 1999. Bilateral simultaneous LASIK was performed under topical anesthesia using automatic corneal shaper microkeratome (Chiron Vision, Irvine, CA, U.S.A.) and 193 nm. argon-fluoride excimer laser (Meditec, MEL 60, Germany) after obtaining informed consent. A nasally hinged corneal flap 160 microns thick and 8.5 mm in diameter, was performed. The ablation depth and zone diameter depended on the intended correction and the preoperative corneal thickness in order to have the residual stromal bed greater than 250 microns. The interface was irrigated with balanced salt solution to remove debris and epithelial cells. The corneal flap was replaced without suture. Topical antibiotic 0.3 per cent tobramycin, and topical anesthetic drug, 0.4 per cent benoxinate hydrochloride was instilled 10 minutes before the operation in each eye, and topical antibiotic was instilled immediately postoperatively.

Thirty-eight bilateral LASIK procedures for correcting myopia ranging from – 3.00 to – 10.50 dioptres (D.) and astigmatism – 0.25 to – 2.75 D. in 19 patients were performed at Siriraj Hospital. After the procedure, one eye of all patients by simple random assignment of 20 patients for this pilot study to generate the allocation schedule of code without concealment was instilled with topical ketorolac tromethamine immediately postoperatively and again after 10 minutes by an assistant nurse in the operating room. All the topical eye drops were similar in appearance, colorless and had a slight burning sensation. Inclusion criteria was uncomplicated LASIK, normal anterior segment, no pregnancy or allergy to used medication. One patient was excluded from complicated LASIK. The patients were interviewed with regard to their symptoms of tearing, photophobia, foreign body sensation, pain, and other complaints 30 minutes after instillation in each eye by an interviewer. The patients were asked to fill out the questionnaire of symptoms at 6 hours and 24 hours after the procedure. At 1 day postoperatively, patients underwent an eye examination by slit-lamp biomicroscope for evaluating injection (redness), keratitis and healing.

At each clinical observation, ocular symptoms and signs were graded on a 4 point scale : 0 = none, 1 = mild, 2 = moderate, and 3 = severe,

Table 1. Grading of symptoms and signs post LASIK.

	None (Grade 0)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Burning / stinging pain discomfort	Absent	Occasionally	Can tolerate	Not tolerated
Tearing	Absent	More tears in the eye	Occasionally wipe eye	Wipe eye several time
Photophobia	Absent	Hardly open eye	Occasionally close eye	Frequently close eye
Foreign body sensation	Absent	Occasionally feels sandy	Increase blinking	Frequent blinking all day
Injection	No redness	Minimal	Obvious	Diffuse redness
Keratitis	None	Superficial punctate keratitis	Stromal infiltration	Stromal infiltration and white opacity

Table 2. The severity of tearing in control and treated eyes.

Post-operation		Control		Treated eyes		P-value
		n	%	n	%	
At 30 mins	None	14	73.7	13	68.4	0.542
	Mild	4	21.1	5	26.3	
	Moderate	1	5.3	0	0	
	Severe	0	0	1	5.3	
At 6 h	None	6	33.3	14	77.8	0.034
	Mild	5	27.8	3	16.7	
	Moderate	4	22.2	0	0	
	Severe	3	16.7	1	5.6	
At 24 h	None	7	36.8	15	78.9	0.022
	Mild	10	52.6	3	15.8	
	Moderate	0	0	1	5.3	
	Severe	2	10.5	0	0	

as shown in Table 1. The allocation schedule of the test drug in each eye was revealed at the end of the study.

The overall outcomes at 24 hours of tearing, photophobia, foreigh body sensation, pain and discomfort were graded by the patient with these symptions as "worse", and "without these symptoms" were graded as better.

The comparative analysis of the data were analyzed according to the group in which they were originally assigned.

Each interval difference for mean rank of severity of symptoms was tested by Wilcoxon Signed Rank test for non-normally distributed data and all interval differences by Friedman test.

Group differences in mean rank of severity of symptoms at each time interval were tested by Mann-Whitney test for independent variables.

Group differences for ordered qualitative variables were tested using the Chi-Square or Fisher Exact test. Differences were considered statistically significant when p-values were less than 0.05.

RESULTS

Fourteen patients (74%) of the study were female. Mean age was 35.2 ± 9.1 years (mean ± standard deviation ; range, 22-56 years). There was a statistically significant difference in increase in the severity of each symptom at 6 hours in the eyes with tobramycin only between each interval and among all intervals (<0.05). In ketorolac treated eyes, the severity of all symptoms was not significantly different, except for pain (p=0.012).

The masking among participants and outcome assessors were successful because many medications were instilled intraoperatively and postoperatively. Only one patient forgot to fill in the questionnaire at 6 hours postoperatively.

As shown in Table 2-5, at 6 hours postoperatively, the severity of tearing, foreign body sensation and pain in the non-treated eyes had increased more than the ketorolac treated eyes (p< 0.01). At 24 hours postoperatively, there was a statistically significant increase in the severity of tearing and foreign body sensation of the eyes

Table 3. Comparison of the severity of photophobia between control and treated eyes.

Post-operation		Control		Treated eyes		P-value
		n	%	n	%	
At 30 mins	None	16	84.2	16	84.2	1.000
	Mild	3	15.8	3	15.8	
At 6 h	None	9	50.0	14	77.8	0.310
	Mild	5	27.8	3	16.7	
	Moderate	3	16.7	1	5.6	
	Severe	1	5.6	0	0	
At 24 h	None	11	57.9	17	89.5	0.055
	Mild	7	36.8	11	5.3	
	Moderate	0	0	0	0	
	Severe	1	5.3	1	5.3	

Table 4. Comparison of the severity of foreign body sensation between control and treated eyes.

Post-operation		Control		Treated eyes		P-value
		n	%	n	%	
At 30 mins	None	14	73.7	13	68.4	0.487
	Mild	4	21.1	6	31.6	
	Moderate	0	0	0	0	
	Severe	1	5.3	0	0	
At 6 h	None	5	27.8	15	83.3	0.003
	Mild	4	22.2	3	16.7	
	Moderate	6	33.3	0	0	
	Severe	3	16.7	0	0	
At 24 h	None	10	52.6	18	94.7	0.026
	Mild	5	26.3	0	0	
	Moderate	3	15.8	1	5.3	
	Severe	1	5.3	0	0	

instilled with tobramycin only, more than ketorolac treated eyes ($p<0.05$). Sixty-three per cent and 68 per cent of ketorolac treated eyes had no keratitis and a good overall result (Table 6, $p<0.05$). No injection and no discomfort were found in 100 per cent and 68.4 per cent of ketorolac treated eyes.

DISCUSSION

Many studies have found that topical ketorolac tromethamine 0.5 per cent was safe and effective as the corticosteroid in reducing postoperative inflammation after cataract surgery and ocular pain after radial keratotomy[16-20]. In our study, ketorolac tromethamine was shown to have an anti-inflammatory effect immediately after LASIK. Our observations and records of less tearing, photophobia and foreign body sensation in treated eyes showed no statistically significant differences among each interval, except for pain decreasing significantly between 30 minutes and 24 hours. Although the mean rank of each symptom in the treated eyes at 6 hours and 24 hours decreased compared with responses at 30 minutes, photophobia at 6 hours in treated eyes increased more than at 30 minutes but without statistical significance. Unlike the control eyes, all symptoms at 6 hours and 24 hours increased significantly, compared with responses at 30 minutes, in spite of slightly decreased symptoms at 24 hours. When comparing the control and the treated eyes at each interval significantly less tearing, less foreign body sensation and less pain in the treated eyes at 6 hours and 24 hours were found, but less photophobia was found only at 24 hours. These data suggested that instillation of

Table 5. The severity of pain in control and treated eyes.

Post-operation		Control		Treated eyes		P-value
		n	%	n	%	
At 30 mins	None	16	84.2	13	68.4	0.447
	Mild	3	15.8	6	31.6	
At 6 h	None	9	50.0	17	94.4	0.026
	Mild	4	22.2	1	5.6	
	Moderate	3	16.7	0	0	
	Severe	2	11.1	0	0	
At 24 h	None	14	73.7	19	100.0	0.056
	Mild	4	21.1	0	0	
	Moderate	1	5.3	0	0	

Table 6. Comparison of the symptoms and signs at 24 hours between control and treated eyes.

Post-operation		Control		Treated eyes		P-value
		n	%	n	%	
Discomfort	No	7	36.8	13	68.4	0.091
	Mild	10	52.6	5	26.3	
	Moderate	0	0	1	5.3	
	Severe	2	10.5	0	0	
Keratitis	No	4	21.1	12	63.2	0.008
	Mild	11	57.9	6	31.6	
	Moderate	3	15.8	1	5.3	
	Severe	1	5.3	0	0	
Injection	No	16	84.2	19	100	0.075
	Mild	2	10.5	0	0	
	Moderate	1	5.3	0	0	
Overall	Worse	13	68.4	6	31.6	0.025
	Better	6	31.6	13	68.4	

two drops of a nonsteroidal anti-inflammatory drug immediately after surgery might relieve the adverse effects of LASIK during the first day after the end of the action of the topical anesthetic drug, (around 45 minutes).

In general, the anti-inflammatory drug was usually given the following day for 1 week because of less inflammation in LASIK surgery, but could persist for 2 weeks without this medication(21). The authors found less keratitis and a high percentage of good overall result in the treated eyes compared to the control eyes with statistical significance in the first postoperative day. It was, thus, confirmed that this could help the patient quickly return to normal rather than with antibiotics alone. In addition, the adverse reaction of ketorolac tromethamine was burning and stinging. Only mild burning in some eyes was found in both the treated eyes and control eyes because of the action of the topical anesthetic at that time. Therefore, the use of ketorolac tromethamine did not disturb the patient and was tolerated well.

The ketorolac tromethamine was effective against ocular inflammation within the first day of LASIK and could relieve the adverse effects of LASIK without any adverse events. Further study on this anti-inflammatory action of ketorolac tromethamine should be investigated and compared to corticosteroid.

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ผลการใช้ยาหยอดตาคีโตรอแลค ทรอมเมธามีนลดอาการหลังผ่าตัดสายตาผิดปกติด้วยแสงเลเซอร์†

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อาการตาแดง ปวดและเคืองตาพบได้บ้าง หลังการผ่าตัดสายตาสั้นและเอียงด้วยแสงเลเซอร์วิธีเลสิค ผู้วิจัยได้ทำการศึกษาเพื่อประเมินผลยาหยอดตาคีโตรอแลค ทรอมเมธามีน ซึ่งเป็นยาลดการอักเสบกลุ่มไม่ใช่สตีรอยด์ เพื่อลดอาการดังกล่าวหลังผ่าตัดทันที โดยหยอดยาเพียงสองครั้งในหนึ่งตา ตาอีกข้างไม่ได้หยอด วิธีแบบสุ่มตัวอย่าง ทั้งสองตาได้รับยา–หยอดตาปฏิชีวนะเหมือนกันในผู้ป่วยที่ได้รับการผ่าตัดสายตาสั้นและเอียงด้วยแสงเลเซอร์วิธีเลสิคพร้อมกัน 2 ตา จำนวน 19 รายที่โรงพยาบาลศิริราชโดยผู้ป่วยตอบแบบสอบถามอาการน้ำตาไหล สู้แสงไม่ได้ เคืองตา ปวดตา เมื่อครบ 30 นาที 6 ชั่วโมง และ 24 ชั่วโมงหลังผ่าตัด พบว่าไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติที่เวลา 30 นาที แต่ที่ 6 ชั่วโมงและ 24 ชั่วโมงหลังผ่าตัด ตาข้างที่หยอดยาคีโตรอแลค ทรอมเมธามีน มีอาการปวดเคืองตาน้ำตาไหลน้อยกว่าข้างที่ไม่ได้ยา ดังนั้น คีโตรอแลค ทรอมเมธามีนช่วยลดอาการไม่พึงประสงค์หลังผ่าตัดเลสิคภายใน 24 ชั่วโมงแรก

คำสำคัญ : ผ่าตัดสายตาสั้นและเอียงด้วยแสงเลเซอร์วิธีเลสิค, ยาหยอดตาคีโตรอแลค ทรอมเมธามีน

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