

Analgesic Efficacy and Safety of Ketorolac After Photorefractive Keratectomy

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ABSTRACT

PURPOSE: The analgesic efficacy and safety of topical ketorolac tromethamine 0.5% ophthalmic solution (Acular) in photorefractive keratectomy was compared to its vehicle.

METHODS: Double-masked, multicenter, study of 200 patients dosed with 1 drop of study medication (ketorolac or vehicle) in the operated eye immediately after surgery (eye patched), with four-times daily dosing for the next 3 days starting 3 hours after surgery. Mepergan Fortis was available as an escape pain medication.

RESULTS: Patients (102) in the ketorolac group reported significantly greater pain relief and less pain intensity than the vehicle group (98) at several time points ($P < .039$). Time to first use of escape medication was significantly longer in the ketorolac than the vehicle group (mean, 16.0 vs 5.5 hr; $P = .001$). Time to complete pain relief was significantly shorter in the ketorolac than the vehicle group (mean, 41.3 vs 50.3 hr; $P = .022$). Significantly fewer patients in the ketorolac group reported sleep difficulties, ocular discomfort, or other difficulties. Few adverse events were reported with ketorolac treatment (less than with vehicle), and there were no clinically significant changes in any of the safety variables monitored.

CONCLUSIONS: Ketorolac tromethamine 0.5% ophthalmic solution (Acular) is safe and signifi-

cantly more effective than vehicle in alleviating pain following photorefractive keratectomy. [*J Refract Surg* 1999;15:661-667]

There is general agreement that the pain following photorefractive keratectomy (PRK) can be severe¹⁻³, and surgeons often prescribe strong oral analgesics to help keep their patients comfortable. Inadequate control of pain after PRK pain can be a significant source of distress to patients, delay their return to normal activities, and interfere with their willingness to undergo a second PRK procedure or recommend such a procedure to a friend. Strong oral analgesics, such as meperidine or codeine, are very effective in controlling pain after PRK, but have a well-documented association with central nervous system and gastrointestinal adverse effects.

Topical non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to be effective in alleviating ocular pain associated with PRK¹⁻³, radial keratotomy^{4,5}, corneal abrasions⁶, and cataract surgery⁷ without causing any of the systemic adverse effects associated with oral analgesics. In addition, topical NSAIDs may provide additional benefits such as reducing or preventing myopic regression and stromal haze following PRK.¹

The NSAID ketorolac tromethamine 0.5% has been shown to be effective in reducing pain after PRK when applied before and after surgery in conjunction with homatropine 5% and a bandage soft contact lens¹, and to eliminate pain after PRK altogether when used before and after surgery in conjunction with dexamethasone 0.1% and a bandage soft contact lens.³ In both of these studies, patients in the active control groups (eg, homatropine alone, or dexamethasone alone) experienced minimal pain relief.

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We evaluated the analgesic efficacy and safety of topical ketorolac tromethamine 0.5% ophthalmic solution compared to its vehicle when used following PRK. The study design included a 3-day postoperative treatment period and a 30-day follow-up period. For compassionate reasons, patients were given a supply of oral analgesics (Mepergan Fortis) as an escape medication that they could take if they experienced intolerable pain. Use of escape medication was analyzed as a key efficacy variable along with patient perception of pain relief and pain intensity.

PATIENTS AND METHODS

Study Design

The analgesic efficacy and safety of ketorolac tromethamine 0.5% ophthalmic solution in pain after PRK was compared to its vehicle in a multicenter, double-masked, randomized, parallel-group, clinical study. The study was conducted between January 1994 and October 1994. The protocol was reviewed and approved by the Institutional Review Board at each investigational site and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all patients prior to enrollment in the study.

Study Population

Adult patients of either sex were enrolled in the study if they were scheduled to undergo first-eye PRK surgery for the correction of myopia, and were deemed likely to follow instructions and complete the entire course of treatment. Patients were only scheduled for surgery if they had myopia between -1.50 and 6.00 diopters (D), astigmatism of 1.00 D or less, and a stable history of myopia and astigmatism. Two-hundred patients were enrolled.

Patients were excluded if they had any uncontrolled ocular or systemic disease, a history of disorders that might interfere with the results of the study, a known hypersensitivity to any of the study or procedural medications, a known hypersensitivity to drugs pharmacologically related to the study medications, glaucoma or ocular hypertension, previous PRK or other corneal surgery, a history of adverse reactions to corticosteroids, required use of monoamine oxidase inhibitors in the 14 days before or the 8 days after surgery, or required use of any ocular medication not specified by the study protocol. Patients were also excluded if they were immunosuppressed, required systemic anti-inflammatory agents, were pregnant, lactating, or planning a pregnancy, or had been involved in another clinical trial within 30 days of entering the study.

Medications

Ketorolac tromethamine 0.5% ophthalmic solution (Acular, Allergan, Inc., Irvine, CA) and ketorolac ophthalmic solution vehicle (Allergan, Inc., Irvine, CA) were the two study medications. Procedural medications used during surgery included Celluvisc (Allergan, Inc.), Pilocar 1.0% (CIBA Vision Ophthalmics, location), and Tetracaine HCl 0.5% (Bausch & Lomb Pharmaceuticals, Tampa, FL). Ocuflax (Allergan, Inc.) was given postoperatively for antibiosis and Mepergan Fortis (Wyeth-Ayerst Laboratories, Philadelphia, PA) was made available to patients during the postoperative period as an escape medication for unacceptable pain.

Study Protocol

Qualified patients were randomly assigned to receive either ketorolac tromethamine 0.5% ophthalmic solution or ketorolac ophthalmic solution vehicle using a randomized block of eight design.

Baseline measurements of all efficacy and safety variables were taken on the day of surgery (day 0) immediately prior to surgery.

Immediately following surgery, the investigator or a qualified assistant instilled one drop of ofloxacin solution into the operated eye, followed 5 minutes later by one drop of study medication (ketorolac or vehicle). Patients were instructed to follow this same instillation procedure four times daily for 3 days starting 3 hours after the completion of surgery. The operated eye was patched following the initial dose of medication and patients were instructed to re-patch their eye, after instilling each dose, until the day 1 follow-up examination. At the day 1 follow-up examination, the eye-patch was removed and patients were instructed to discontinue the use of such patches. This is the protocol specified by the manufacturer of the PRK laser used (Summit Technologies, Inc., Waltham, MA).

Patients were given a supply of Mepergan Fortis as an escape pain medication. Patients were instructed not to use the escape medication unless they experienced intolerable pain. Patients were instructed not to use any other ocular medications, systemic or ophthalmic antiinflammatory agents, or any analgesics or narcotics other than the escape medication.

Patient Evaluations

All patients were evaluated at 4 hours and 1, 2, 3, and 30 days after surgery. In addition, patients were given a diary and instructed to rate their pain relief, pain intensity, and other variables at the time of each dose, just before they instilled their study

medication, and to make a note of the first time they used the escape medication (if applicable). The diary also included a written copy of patient instructions. At the 4-hour evaluation, a nurse or study coordinator conducted a phone interview with the patient, or adult relative if the patient was asleep, to collect information on efficacy and safety relative to the patient's last dose of study medication (administered 3 hours after surgery). Patients whose corneas had not re-epithelialized by day 3 were also examined on days 4 to 8, as needed, until re-epithelialization was observed. Such patients were continued on four-times-daily ofloxacin solution, but not study medication, until re-epithelialization was observed. The available pain medication for these patients was Mepergan Fortis.

Efficacy

The primary efficacy variables were pain relief and pain intensity. Just before instillation of each dose of study medication, patients rated the amount of pain relief that they received from the last dose of study medication on an 8-point scale: 0 = pain present and medication gave no relief; 1 = a little relief; 2 = some relief; 3 = moderate relief; 4 = a good deal of relief; 5 = a great deal of relief; 6 = complete relief; 7 = not having any pain when the eyedrops were last used. At the same time, patients rated their current pain intensity on a 7-point scale: 0 = no pain; 1 = very mild pain; 2 = mild pain; 3 = moderate pain; 4 = severe pain; 5 = very severe pain; 6 = extremely severe pain. Despite the availability of the descriptors for each of the values on these scales, the clinical experience indicates that the patients were thinking of expressing the degree of their pain (or pain relief) as a value between the two extremes that best expressed their pain or pain relief rather than choosing the descriptor that best matched their experience.

Another key efficacy variable was the time to first use of escape medication (if any). If escape medication was used, the patients were asked to note the time of their first dose and how many tablets they used on each study day.

Additional efficacy variables included quality of sleep, symptoms of ocular discomfort, and other general difficulties. Quality of sleep was assessed in terms of the number of hours of sleep, any difficulties in falling asleep, the need for escape medication in order to fall asleep, and if the patient was awakened by pain. Symptoms of ocular discomfort (foreign body sensation, photophobia, burning and stinging, tearing, itching) and general discomfort (headache and nausea) were recorded using a

5-point Likert scale: 0 = none; 1 = trace; 2 = mild; 3 = moderate; 4 = severe.

Safety Variables

Throughout the study, patients were monitored for signs and symptoms of adverse events. Any adverse event that occurred was graded for severity and assessed for its relationship to the study medication.

Visual function was assessed as spectacle-corrected, spectacle-corrected near (chart at 14 inches), spectacle-corrected with glare, and uncorrected visual acuity using the ETDRS visual acuity charts and the accompanying retroilluminated box and Alza near-vision chart. Visual acuity was recorded under both light and dark conditions.

In addition, complete ophthalmoscopic and slit-lamp microscope examinations were conducted at each study examination. Biomicroscopy was conducted without pupil dilation and included a detailed evaluation of the cornea for the presence of corneal haze. Corneal haze was recorded on a 5-point scale: 0 = clear; 1 = trace; 2 = mild; 3 = moderate; 4 = marked.

Data Analysis and Statistics

Unless indicated otherwise, diary entries for pain relief, pain intensity, and other variables were grouped into 6-hour time blocks starting immediately after surgery.

The Wilcoxon-Mann-Whitney rank-sum test was used to assess between-group differences in continuous or ordinal variables such as patient age, pain relief, pain intensity, quality of sleep, functional/activity assessments, corneal haze, and visual acuity. A generalized Wilcoxon rank-sum test from survival analysis was used to analyze the time to reach a pain relief response of complete, a pain intensity response of none, the time to first use of escape medication, and the time to re-epithelialization.

For ordinal and continuous variables, a two-way analysis of variance was used to analyze treatment-by-investigator interactions. For binomial variables, treatment-by-investigator interactions were analyzed using the Breslow-Day test.

Between-group differences in race, gender, iris status, and medical history variables were analyzed with two-sided chi square tests. In those cases where the expected value of any cell in a 2x2 table was less than 5, a two-tailed Fisher 2x2 exact test was used instead. These tests were also used to analyze incidence rates for use of escape medication, time to re-epithelialization, and biomicroscopic and

Table
Demographic Data for 200 Patients With
Ketorolac or Vehicle After PRK

	Ketorolac Group (n=102)	Vehicle Group (n=98)
Age (yr) ± SD	36 ± 10	36 ± 9
Sex (%)		
Male	60 (59)	63 (64)
Female	42 (41)	35 (36)
Race (%)		
Caucasian	95 (93)	86 (88)
Black	1 (1)	3 (3)
Asian	1 (1)	5 (5)
Hispanic	5 (5)	1 (1)
Other	0 (0)	3 (3)
Iris Color (%)		
Blue	39 (38)	35 (36)
Brown	29 (28)	38 (39)
Green	14 (14)	14 (14)
Black	0 (0)	1 (1)
Hazel	18 (18)	10 (10)
Gray	2 (2)	0 (0)

ophthalmoscopic findings.

The 102 patients in the ketorolac group and the 98 patients in the vehicle group, along with the observed variation, gave the study a power of 95% to detect as significant a difference of one or more units on a 7-point severity scale. A *P*-value of .05 or less was considered statistically significant.

RESULTS

Patient Disposition

Of the 200 PRK patients enrolled in the study, 102 were assigned to the ketorolac group and 98 to the vehicle group. Most of the patients in both the ketorolac (99%; 101/102) and vehicle (95.9%; 94/98) groups completed the 3-day treatment regimen and were followed for the full 30-day study period. Only one patient from the ketorolac group (1%; 1/102) was discontinued for improper entry and only three patients from the vehicle group (3.1%; 3/98) were discontinued for improper entry or missed visits. The only patient terminated due to an adverse event was from the vehicle group (1%; 1/98).

All 200 patients were included in all of the efficacy and safety analyses. However, for a given variable at a given time point, the number of evaluable subjects could vary due to patients that were asleep or otherwise failed to enter all required data in their diary.

Patient Population

The demographic characteristics of the patient population are listed in the Table. Patient age ranged from 21 to 65 years (mean, 36 yr). More than

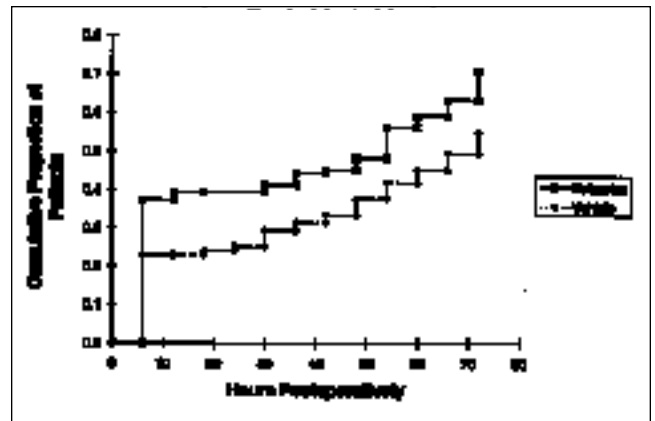


Figure 1. Cumulative number of patients with complete pain relief (from survival analysis); *P*=.022.

half of the patients were men (61.5%; 123/200), and the majority of patients were Caucasian (90.5%; 181/200). There were no statistically significant differences between the two treatment groups in age, sex, race, or iris color.

Efficacy

Pain Relief The pain relief scores were significantly higher (indicating greater pain relief) in the ketorolac group than the vehicle group at 4 hours (mean scores: 4.5 vs 2.9; *P*=.001), 7 to 12 hours (mean scores: 2.6 vs 0.9; *P*=.001), 31 to 36 hours (mean scores: 2.7 vs 2.0; *P*=.017), and 43 to 48 hours (mean scores: 2.9 vs 2.2; *P*=.039) after PRK. In addition, the time to complete relief was significantly less (*P*=.022) in the ketorolac (mean: 41.3 hours) than in the vehicle group (mean: 50.3 hours; Fig 1).

Pain Intensity Pain intensity scores were significantly lower (indicating less pain) in the ketorolac group than the vehicle group at 4 hours (mean scores: 2.9 vs 4.4) and 7 to 12 hours (mean scores: 3.5 vs 4.3) after PRK (*P*=.001). There was no statistically significant difference between the treatment groups in the mean time to reach a first response of no pain.

Use of Escape Medication The cumulative number of Mepergan Fortis (escape medication) capsules taken during the 3-day study period was comparable in the 2 study groups. However, the mean time to first use of escape medication was significantly longer (*P*=.001) in the ketorolac group (16.0 hr) than the vehicle group (5.5 hr). In addition, at 4 hours after PRK the incidence of escape medication use was significantly less in the ketorolac group (18.6%) than the vehicle group (55.2%; *P* = .001). However, after 3 days the incidence of escape medication use was greater in the ketorolac group (22.2%) than the vehicle group (10.5%; *P* = .034).

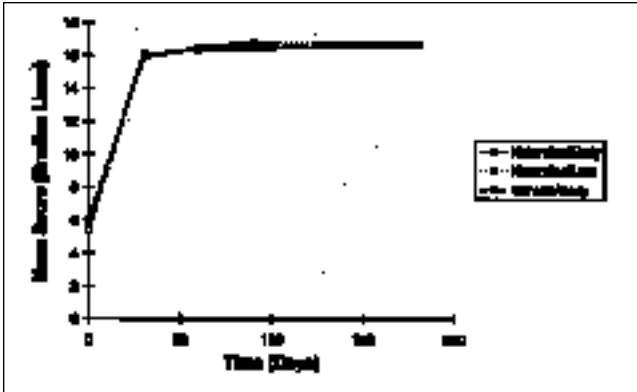


Figure 2. Visual acuity (uncorrected, distance) before and after PRK. Filled squares: ketorolac patients that re-epithelialized in < 3 days. Filled diamonds: ketorolac patients that re-epithelialized > 3 days. Open squares: vehicle patients that re-epithelialized early. Only two patients in the vehicle group re-epithelialized late, so their data are not shown.

Quality of Sleep Prior to surgery, there was no significant difference in the incidence of sleep disturbances in the two treatment groups. A smaller percentage of patients in the ketorolac than the vehicle group experienced sleep difficulties as a result of postoperative pain. At 4 hours postoperatively, significantly fewer patients in the ketorolac group were awakened by pain (ketorolac: 7.8%, 8/102; vehicle: 18.1%, 17/94; $P=.035$), had trouble falling asleep as a result of their pain (ketorolac: 13.7%, 14/102; vehicle: 47.4%, 45/95; $P=.001$), or required additional escape medication in order to fall asleep (ketorolac: 9.8%, 10/102; Vehicle: 34.4%, 33/96; $P=.001$). There was no significant difference in the incidence of sleep difficulties between the two groups at day 1. On day 2, significantly fewer patients in the ketorolac group were awakened by pain (ketorolac: 3.9%, 4/102; vehicle: 14.4%, 14/97; $P=.012$), or had trouble falling asleep as a result of their pain (ketorolac: 7.8%, 8/102; vehicle: 18.6%, 18/97; $P=.034$) than in the vehicle group.

Symptoms of Ocular Discomfort and Other Difficulties Prior to surgery, there was no significant difference in the incidence of moderate or greater ocular discomfort between the two treatment groups. At 4 hours postoperatively, the ketorolac group exhibited a significantly lower incidence than the vehicle group of moderate or greater foreign body sensation (ketorolac: 42.2%, 43/102; vehicle: 70.8%, 68/96; $P=.001$), photophobia (ketorolac: 30.7%, 31/101; vehicle: 69.8%, 67/96; $P=.001$), burning/stinging (ketorolac: 24.5%, 27/102; vehicle: 62.1%, 59/95; $P=.001$), and tearing (ketorolac: 52.9%, 54/102; vehicle: 78.9%, 75/95; $P=.001$). There was no significant difference in the incidence of moderate or

greater ocular discomfort between the treatment groups at day 1 or day 2.

The ketorolac group also had a lower incidence of other difficulties than the vehicle group. At 4 hours postoperatively, the ketorolac group had a significantly lower incidence of headache (ketorolac: 11/102; vehicle: 22/95; $P=.023$) and difficulty opening the surgical eye (ketorolac: 57/102; vehicle: 75/95; $P=.001$). There was also a significantly lower ($P=.003$) incidence of difficulty opening the surgical eye in the ketorolac (28.4%; 29/102) than the vehicle (49.5%; 48/97) group at day 2. There was no significant between-group difference in any of these variables at day 1, and no significant between-group difference in the incidence of headache at day 2.

Safety

Adverse Events Only 1% (1/102) of patients in the ketorolac group and 6.1% (3/98) of patients in the vehicle group experienced adverse events that were considered to be possibly or probably related to treatment. In the ketorolac group, the adverse event considered probably related to treatment was one case of burning after instillation. In the vehicle group, the adverse events considered possibly or probably related to treatment included one case each of conjunctivitis, irritation (stinging of the eye), and allergic conjunctivitis. The only patient terminated due to an adverse event was the one patient in the vehicle group with allergic conjunctivitis.

Time to Re-epithelialization The mean time to re-epithelialization was approximately one-half day longer ($P=.001$) in the ketorolac (3.2 days) than the vehicle group (2.7 days). This difference could also be seen in the cumulative proportion of patients in each group achieving re-epithelialization on each day.

Visual Acuity There was no statistically significant difference between the treatment groups in any visual acuity measurement (uncorrected, spectacle-corrected, spectacle-corrected with glare, spectacle-corrected near, and uncorrected near) either preoperatively or at any time-point postoperatively. There was also no difference in uncorrected visual acuity between those patients in the ketorolac group that re-epithelialized early and those that re-epithelialized late (Fig 2).

Intraocular Pressure, Corneal Haze, Biomicroscopy, and Ophthalmoscopy Through the last study examination (day 30), there were no statistically significant differences between the treatment groups in intraocular pressure or corneal haze. The only biomicroscopy findings that were significantly different between the two groups were in the

scores (on a scale of 0 to 4) for epithelial defects and corneal edema. The amount of epithelial defect in the ketorolac group was slightly larger in the ketorolac group than the vehicle group at day 2 (mean scores: 1.5 vs 1.1; $P=.001$) and day 3 (mean scores: 0.3 vs 0.0; $P=.001$). The amount of corneal edema was also slightly greater in the ketorolac group than the vehicle group at day 3 (mean scores: 0.1 vs 0.0; $P=.035$). The latter was due to the fact that 9% of patients in the ketorolac group and 2% of patients in the vehicle group exhibited trace edema. The between-group differences in epithelial defect and corneal edema were so small that it is unlikely that they were clinically significant.

DISCUSSION

Ketorolac tromethamine 0.5% ophthalmic solution has been shown to be effective in the treatment of seasonal allergic conjunctivitis⁸, cystoid macular edema⁹, ocular inflammation following cataract surgery^{10,11}, and ocular pain due to a variety of causes.^{1,3,4,6} In this study, ketorolac was more effective than the vehicle in alleviating pain following PRK without causing any of the systemic adverse events associated with oral analgesics. The greater analgesic efficacy of ketorolac was evident in the amount of patient pain relief and pain intensity, the use of escape medication, and the incidence of sleep difficulties, ocular discomfort and other problems.

In this study, the analgesic efficacy of ketorolac for pain after PRK appears to be lower than that in previous studies of the analgesic efficacy of ketorolac for pain after PRK.^{1,3} In a small study ($n=10$ in each treatment group) by Stein and colleagues³, pain after PRK was eliminated completely in all patients by administering 2 drops of ketorolac 0.5% preoperatively, followed postoperatively by applying a bandage soft contact lens and administration of 1 drop each of ketorolac 0.5% and dexamethasone 0.1% every 4 hours while awake. Patients treated with a bandage soft contact lens and ketorolac postoperatively, but not preoperatively, experienced minimal pain; patients treated with dexamethasone alone experienced severe to very severe pain during the first 24 hours.

In another small study ($n=15$ in the ketorolac treatment group) by Arshinoff and colleagues¹, ketorolac 0.5% was given preoperatively (1 drop every 15 minutes for 4 doses), intraoperatively (2 drops), and postoperatively (1 drop every 1 minute for 4 doses, then 1 drop every 3 hours) with postoperative homatropine 5% (4 drops), and a bandage soft contact lens. Nine of 15 patients reported no pain, 5 of 15 reported mild pain, 1 of 15 reported

moderate pain, and none reported severe pain.

The treatment regimen used in this study was designed to provide a rigorous test of the analgesic efficacy of ketorolac monotherapy and differed from the earlier studies in several respects. In the present study, no other antiinflammatory or mydriatic medications were used in combination with the study medication, study medication was not instilled until after surgery, and no bandage soft contact lens was used. In earlier studies, the other medications used could have had a synergistic interaction with ketorolac that enhanced its analgesic effect. The use of ketorolac preoperatively and intraoperatively could have enabled the drug to inhibit the production of trauma-induced chemical mediators of ocular pain before their synthetic pathways were stimulated. In addition, the use of a bandage soft contact lens in the earlier studies could have increased patient comfort by both providing a potential drug reservoir that continued to release ketorolac to the eye over a prolonged period of time, and by protecting the surface of the eye from contact with the eyelid. Despite the fact that the present study employed none of these techniques, ketorolac was still found to be significantly more effective in alleviating pain after PRK than was the vehicle, and this greater analgesic efficacy had a significant beneficial effect on patient overall comfort and quality of life.

The overall safety of ketorolac ophthalmic solution has been established in several studies^{8,10-12} and is supported by the present report. There was only one patient (1%) in the ketorolac group with a treatment-related adverse event (burning upon instillation); there were three such patients in the vehicle group (6%). The only other notable safety finding was that the mean time to re-epithelialization was approximately one-half day longer ($P=.001$) in the ketorolac than the vehicle treatment group. However, after 1 month there was no significant difference in visual acuity between the two treatment groups, or between patients within the ketorolac group who re-epithelialized early and those that re-epithelialized late (Fig 2). This suggests that the slightly delayed time to re-epithelialization in the ketorolac group was not clinically significant. In this study, visual acuity was not measured prior to 1 month after surgery, so it is not possible to determine if the difference in time to re-epithelialization resulted in any differences in visual acuity prior to this point. However, given the small difference in re-epithelialization time, it would be unlikely for this to result in a difference in visual acuity at any time point.

Our results demonstrate that ketorolac tromethamine 0.5% ophthalmic solution is safe and significantly more effective than the vehicle in alleviating the pain associated with PRK. Earlier results strongly suggested that more complete pain relief might be obtained by the use of ketorolac in a perioperative regimen combined with a bandage soft contact lens. The use of other medications (such as topical corticosteroids) in combination with ketorolac may further enhance the analgesic effect. Therefore, topical ketorolac may provide an attractive alternative to oral analgesics after PRK, particularly when incorporated into an optimized pain management strategy.

REFERENCES

1. Arshinoff S, D'Addario D, Sadler C, Bilotta R, Johnson TM. Use of topical nonsteroidal anti-inflammatory drugs in excimer laser photorefractive keratectomy. *J Cataract Refract Surg* 1994;20(suppl):216-222.
2. Binder PS. Excimer laser photoablation: Miracle or menace? *J Ophthalmic Nurs Technol* 1994;13:61-76.
3. Stein R, Stein HA, Cheskes A, Symons S. Photorefractive keratectomy and postoperative pain. *Am J Ophthalmol* 1994;117:403-405.
4. Epstein RL, Laurence EP. Relative effectiveness of topical ketorolac and topical diclofenac on discomfort after radial keratotomy. *J Cataract Refract Surg* 1995;21:156-159.
5. Gwon A, Vaughan ER, Cheetham JK, DeGryse R. Ocufen (flurbiprofen) in the treatment of ocular pain after radial keratotomy. *CLAO J* 1994 20:131-138.
6. Donnenfeld ED, Selkin BA, Perry HD, Moadel K, Selkin GT, Cohen AJ, Sperber LTB. Controlled evaluation of a bandage contact lens and a topical nonsteroidal anti-inflammatory drug in treating traumatic corneal abrasions. *Ophthalmology* 1995;102:979-984.
7. Fry LL. Efficacy of diclofenac sodium solution in reducing discomfort after cataract surgery. *J Cataract Refract Surg* 1995;21:187-190.
8. Tinkelman DG, Rupp G, Kaufman H, Pugely J, Schultz N. Double-masked paired-comparison clinical study of ketorolac tromethamine 0.5% ophthalmic solution compared with placebo eyedrops in the treatment of seasonal allergic conjunctivitis. *Surv Ophthalmol* 1993;38(suppl):133-140.
9. Flach AJ, Jampol LM, Weinberg D, Kraff MC, Yannuzzi LA, Campo RV, Neumann AC, Cupples HP, Lefler WH, Pulido JS, Lavelle C. Improvement in visual acuity in chronic aphakic and pseudophakic cystoid macular edema after treatment with topical 0.5% ketorolac tromethamine. *Am J Ophthalmol* 1991;112:514-519.
10. Flach AJ, Lavelle CJ, Olander KW, Retzlaff JA, Sorenson LW. The effect of ketorolac tromethamine solution 0.5% in reducing postoperative inflammation after cataract extraction and intraocular lens implantation. *Ophthalmology* 1988;95:1279-1284.
11. Flach AJ, Graham J, Krueger LP, Stegman RC, Tanenbaum L. Quantitative assessment of postsurgical breakdown of the blood aqueous barrier following administration of ketorolac tromethamine solution: a double-masked, paired comparison vehicle-placebo solutions study. *Arch Ophthalmol* 1988;106:344-347.
12. Ballas Z, Blumenthal M, Tinkelman DG, Kriz R, Rupp G. Clinical evaluation of ketorolac tromethamine 0.5% ophthalmic solution for the treatment of seasonal allergic conjunctivitis. *Surv Ophthalmol* 1993;38(suppl):141-148.