

# Topical Bromfenac 0.09% vs Ketorolac 0.4% for the Control of Pain, Photophobia, and Discomfort Following PRK

Neal A. Sher, MD, FACS; Mikhail P. Golben, BS; William Bond, MD; William B. Trattler, MD; Shachar Tauber, MD; Terry G. Voirin, DO

## ABSTRACT

**PURPOSE:** To compare the efficacy of two topical non-steroidal anti-inflammatory drugs with regards to the control of pain, burning, photophobia, foreign body sensation, and epithelial healing rates in patients who underwent photorefractive keratectomy (PRK).

**METHODS:** Two hundred twelve eyes were randomized to receive topical postoperative ketorolac 0.4% four times daily (Acular LS, Allergan) or bromfenac 0.09% twice daily (Xibrom, ISTA Pharmaceuticals) in an open label trial. Patients having both eyes treated received ketorolac in one eye and bromfenac in the other. The epithelium was removed using the 8.4-mm Amoils brush (Innovative Excimer Solutions), and various laser beam platforms were permitted for the surgery. Investigated drugs were applied after a bandage contact lens (Acuvue Oasys, Johnson & Johnson Vision Care) was fitted. All patients received postoperative cold saline (balanced saline solution [BSS]), prednisolone acetate 1.0% (Pred Forte, Allergan), gatifloxacin ophthalmic solution 0.3% (Zymar, Allergan), and in some cases, mitomycin C 0.02% (MMC). Patients recorded postoperative results for pain, photophobia, burning, and foreign-body sensation on a visual linear analog scale. During postoperative follow-up, the corneal epithelial defect was measured.

**RESULTS:** Two hundred twelve eyes from 149 patients were enrolled in the study. Of these eyes, 105 received bromfenac and 107 received ketorolac. No significant differences were noted in postoperative pain, burning, foreign-body sensation, and photophobia between the two drug populations at any time during the study or overall. There were no drug-related adverse events or differences in epithelial healing rates for either drug.

**CONCLUSIONS:** No significant differences were observed between the use of bromfenac (twice daily) and ketorolac (four times daily) with regard to postoperative PRK discomfort and safety when combined with postoperative measures such as cold BSS and a bandage contact lens. [*J Refract Surg.* 2009;25:214-220.]

Laser vision correction is one of the most commonly performed elective surgical procedures in the United States. A growing number of surgeons favor surface ablation techniques for laser vision correction, including photorefractive keratectomy (PRK), laser epithelial keratomileusis (LASEK), and epi-LASIK as an alternative to LASIK.<sup>1</sup>

With surface laser procedures, the corneal epithelium is removed by a variety of techniques (laser, manual debridement, diluted alcohol, epi-keratome)<sup>2-4</sup> prior to laser reshaping of the corneal stroma. Following the procedure, a soft contact lens is placed on the eye to promote epithelial regeneration. During this healing process, patients often complain of varying degrees of ocular pain and discomfort.<sup>4-6</sup>

Over the past 15 years, a variety of methods have been used to assist with reducing pain following surface laser procedures. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown in a number of studies to help reduce the degree of pain following PRK.<sup>7-14</sup> Topical dilute and full strength anesthetic solution have also been shown to assist with the reduction of pain following PRK.<sup>15,16</sup> Oral pain medications including opiates, NSAIDs, and gabapentin have also been advocated but these medicines have side effects.

The intraoperative practice of chilling the cornea directly following surface ablation has also been shown to reduce immediate and overall pain experienced by the patient. The application of cold balanced saline solution (BSS) directly on the corneal bed

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*From Eye Care Associates (Sher, Golben) and the Department of Ophthalmology, University of Minnesota Medical School (Sher), Minneapolis, Minn; Bond Eye Associates, Pekin, Ill (Bond, Voirin); The Center for Excellence in Eye Care, Miami, Fla (Trattler); and St John's Clinic-Eye Specialists, Springfield, Mo (Tauber).*

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*Correspondence:* Neal A. Sher, MD, FACS, 20th Fl Medical Arts Bldg, 825 Nicollet Mall, Minneapolis, MN 55402. Tel: 612.436.2117; Fax: 612.333.8306; E-mail: nsherm@comcast.net

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is believed to alleviate the pain caused by over-heated, exposed nerve endings and reduce corneal haze.<sup>17</sup>

In 1993, our investigative group at the Phillips Eye Institute showed the efficacy of a topical NSAID, diclofenac, in a randomized, double-masked controlled study in reducing postoperative PRK pain and discomfort with favorable results.<sup>7</sup> Since then, topical NSAIDs have been shown to possess considerable pain-reducing capabilities in addition to reducing postoperative photophobia and inflammation and have been widely used in postoperative PRK surgery treatment regimens.<sup>7-14</sup>

Surface ablation and the subsequent corneal epithelial defect leave numerous highly sensitive nerve endings exposed. The stimulation of these nerve endings results in intense pain and neurogenic inflammation.<sup>8,12,13</sup> This inflammation response is mediated by prostaglandins, synthesized from arachidonic acid by cyclooxygenase 1 (COX-1) or cyclooxygenase 2 (COX-2). Nonsteroidal anti-inflammatory drugs achieve their anti-inflammatory and analgesic properties by inhibiting the activity of these COXs, preventing inflammation and reducing free-nerve stimulation.<sup>8,9,11</sup> However, each NSAID has its own unique pharmacologic properties and effectiveness as an analgesic agent making it essential to investigate the differences between each NSAID.<sup>8</sup>

Ketorolac tromethamine ophthalmic solution 0.4% (Acular LS; Allergan, Irvine, Calif) is an NSAID whose anti-inflammatory and analgesic effectiveness have been well documented.<sup>10,14</sup> Originally, ketorolac 0.5% (Acular, Allergan) was approved by the United States Food and Drug Administration (FDA) for postoperative cataract surgery pain and burning control.<sup>10</sup> Clinical research on the off-label use of ketorolac in postoperative PRK pain control demonstrated favorable results.<sup>8,9,14</sup> In 2003, ketorolac 0.4% was approved by the US FDA for control of postoperative surface ablation pain.

In March 2005, the FDA approved another topical NSAID, bromfenac ophthalmic solution 0.09% (Xibrom; ISTA Pharmaceuticals, Irvine, Calif), for treatment of postoperative cataract inflammation and pain. Bromfenac was originally approved in Japan (May 2000) under the name Bronuck (Senju Pharmaceutical, Osaka, Japan). Bromfenac 0.09% is similar in structure to amfenac (Nevanac; Alcon Laboratories Inc, Ft Worth, Tex) except with the addition of bromine atoms in the 4-position of the benzyl ring; the addition of bromine to the bromfenac molecule imparts more pronounced effects on its *in vitro* and *in vivo* potency, absorption across the cornea, and penetration into ocular tissues.<sup>11</sup> Bromfenac 0.09% is FDA-approved for twice-daily dosage.

This randomized, open-label study investigates the efficacy and safety of the off-label use of bromfenac

0.09% in controlling postoperative PRK pain compared to ketorolac 0.4% ophthalmic solution.

## PATIENTS AND METHODS

### STUDY DESIGN

In this open-label, non-masked study, patients were randomized to receive either postoperative ketorolac 0.4% or bromfenac 0.09%. Patients who had surgery on both eyes (174 eyes) received ketorolac in one eye and bromfenac in the other. Patients recorded values for pain, burning, photophobia, and foreign-body sensations in a provided patient diary. Randomization was achieved by associating a patient number with a study drug on a spreadsheet that had been randomized in blocks of 10 using the Random Allocation Software developed by M. Saghaei, MD.<sup>18</sup> The second eye of a patient was automatically assigned a patient number that corresponded to the second study drug. The protocol was approved and monitored by Schulman Associates Investigational Review Board.

### STUDY POPULATION

From June 2006 to November 2006, 212 eyes of 149 patients (63 bilateral, 86 unilateral) were enrolled in the study. One hundred five eyes received bromfenac and 107 eyes received ketorolac. Thirteen eyes were removed from the statistical analysis of the study due to deviations in procedure. Data regarding the included population is presented in the Table. Data analysis was performed on the patient diaries and postoperative follow-up of the remaining 199 eyes.

Full informed consent was obtained for each patient. Patients were enrolled with myopia or hyperopia and varying degrees of astigmatism. There were no constraints on the degree of refractive error. Patients with medical or ocular conditions that could predispose delayed epithelial healing were excluded. Other causes for exclusion were prior LASIK within 12 months of the scheduled surgery; a history of allergic reactions to sulfites, aspirins, or NSAIDs; and bleeding disorders. Postoperatively, patients were excluded if they did not follow the protocol or used postoperative oral NSAIDs, aspirin, or narcotics.

### INSTRUMENTATION AND SURGICAL PROCEDURE

Prior to treatment with an excimer laser, all patients received a drop of a topical anesthetic, 0.5% proparacaine. Some patients received preoperative diazepam, 5 mg orally within 1 hour before the procedure at the discretion of the surgeon. In all cases, the epithelium was removed with the 8.4-mm head of an Amoils brush (Innovative Excimer Solutions, Toronto, Canada),

TABLE

**Preoperative Variables Between Populations of Eyes Receiving Bromfenac 0.09% (Xibrom) and Ketorolac 0.4% (Acular LS) After Photorefractive Keratectomy\***

|  | Population |           |        |
|--|------------|-----------|--------|
|  | Xibrom     | Acular LS | Study  |
| Eyes   | 97         | 102       | 199    |
| Average age (y)                              | 40.05      | 39.34     | 40.01  |
| Sex (M/F)                                    | 38/59      | 42/60     | 80/119 |
| Maximum spherical equivalent (D)             | -12.50     | -12.50    | -12.50 |
| Minimum spherical equivalent (D)             | -0.50      | -0.50     | -0.50  |
| Manifest refraction spherical equivalent (D) | -4.47      | -4.64     | -4.51  |
| Standard deviation                           | 3.42       | 3.42      | 3.42   |
| Mitomycin C 0.02% (%)                        | 88         | 82        | 85     |
| Laser (%)                                    |            |           |        |
| Alcon  | 6          | 4         | 5      |
| WaveLight                                    | 19         | 15        | 17     |
| VISX S4                                      | 75         | 81        | 78     |

\*Patients were randomly assigned a study drug. Patients having both eyes treated received the opposite drug for the second eye. Patients were treated with mitomycin C at their physician's discretion. The laser platform that was used for the surgery was dependent on the specific study site.

although the use of a Tooke knife (Accutome Inc, Malvern, Pa) for removal of residual tissue was permitted. In all cases, 30 cc of chilled BSS were applied to the cornea directly following the surface ablation treatment, and in some cases, following the optional application of 0.02% mitomycin C (MMC). At this point, a bandage contact lens (Acuvue Oasys; Johnson & Johnson Vision Care, Jacksonville, Fla) was placed on the operated eye. After the contact lens was in place, patients received drops of their postoperative medication regimen, including their assigned NSAID, 1% prednisolone acetate drops (Pred Forte, Allergan), and gatifloxacin ophthalmic solution 0.3% (Zymar, Allergan).

#### POSTOPERATIVE PROCEDURES

The postoperative regimen was strictly followed. Patients used the gatifloxacin ophthalmic solution 0.3% and 1% prednisolone acetate drops four times daily, and were encouraged to use Refresh (Allergan) artificial tears as often as required. Ketorolac, when assigned, was applied four times daily, 15 minutes after the other drops had been administered. Bromfenac, when assigned, was applied twice daily, 15 minutes after the other drops had been administered. Oral narcotics, aspirin, other NSAIDs, topical diluted anesthetics, and other analgesics were not permitted and the use of these drugs was grounds for exclusion from the study.

As part of their postoperative regimen, patients recorded their perception of pain, burning, photophobia,

and foreign-body sensations on analog scales provided in a patient diary. These scales utilized a 0 to 10 linear visual analog scale, and patients were asked to circle the number corresponding to the severity of the symptom. The recording of this data was to occur four times a day; once after every series of drops. Missed entries were treated using the Last Observation Carried Forward method. Failure to correctly maintain the diary was used as grounds for exclusion from the study.

Patients were observed by the investigator in postoperative visits on the day following surgery (day 2) and again two or three days later (day 4 or 5) until the epithelial defect had healed. Using maximum vertical and horizontal dimensions of defect as measured by the slit-lamp examination, the epithelial defect was taken at each follow-up to determine the rate of healing. Once the epithelial tissue had healed, the study was declared as completed and the use of the NSAID was discontinued.

#### STATISTICAL METHODS

Data analysis was performed by independent consultants Chuck Davis, PhD, and Sonia L. Minassian, PhD (CSD Biostatistics, San Diego, Calif). Each diary allowed for four records per day for each of the observed variables: pain, burning, photophobia, and foreign-body sensation. For analysis purposes, each day per patient was averaged prior to collective analysis. Due to the asymmetric nature of the data distribution, the

non-parametric Wilcoxon Mann-Whitney test was used to evaluate the null hypothesis that there is no difference between the ketorolac and bromfenac with regard to any ailment and over any day. Tests were performed on the whole study population (except those excluded for procedure deviations) and on the bilateral patients. Due to the fact that both eyes of the bilateral patient were treated at the same time, the bilateral regimen represents a better-controlled population. Thus, repeat tests were performed solely on the bilateral population. Additional data analysis examined the effects of MMC, variation in laser platform, and the use of preoperative diazepam. These additional tests were performed on each drug population separately as well as the whole study population. A  $P$  value  $\leq .05$  was used to determine a significant value, resulting in the rejection of the null hypothesis.

For analysis purposes the epithelial defect was calculated as though the defect were a rectangle: multiplying the maximum vertical length by the maximum horizontal length to determine the total defect. The defect was determined to be completely healed once the defect equaled zero. Patients who did not meet this requirement by postoperative day 5 were recorded as requiring greater than 5 days to recover. Due to scheduling conflicts, some patients were unable to make a postoperative visit until after they had completely healed, leaving doubt as to when they healed. Thus, patients who did not attend postoperative follow-up at least 2 days before their final follow-up were not included in epithelial healing data analysis. Epithelial healing rates were analyzed using Fisher's exact test. Again, the test was performed on the whole study population and separately on the bilateral population alone. A  $P$  value ( $P < .05$ ) signifies a significant difference in the healing rates between drugs.

## RESULTS

The average pain, burn, photophobia, and foreign-body sensation for bromfenac and ketorolac are displayed in Figure 1. No significant differences were noted in the scores for these parameters over any of the days. There was no significant change for any of these same parameters when analyzing the results on bilateral same-session surgery patients.

Figure 2 shows the average epithelial healing rates of bromfenac and ketorolac. No significant difference was observed in the rate of healing between the study medications ( $P_{\text{total}} = 0.73$ ,  $P_{\text{bilateral}} = 1.0$ ). There is no significant difference between ketorolac and bromfenac for pain, burning, photophobia, foreign-body sensation, or epithelial healing rate. The only instance of a serious adverse event (infectious keratitis) was deemed, by the

investigator and medical monitor, to be unrelated to the study drugs.

The additional analysis on both drug populations and the study population as a whole found no relevant differences in the use of MMC or preoperative diazepam. There was a significant difference ( $P = .0026$  and  $.0005$ , respectively) when comparing the VISX S4 (VISX USA Inc, Santa Clara, Calif) laser platform to the ALLEGRETTO (WaveLight Inc, Sterling, Va) laser platform for photophobia on days 1 and 2, favoring the VISX laser. There was also a significant difference in epithelial healing between the VISX S4 laser platform and the other laser platforms ( $P \leq .0001$  versus the ALLEGRETTO and  $P = .0014$  versus the LADARVision4000 [Alcon Laboratories Inc]) favoring the VISX S4.

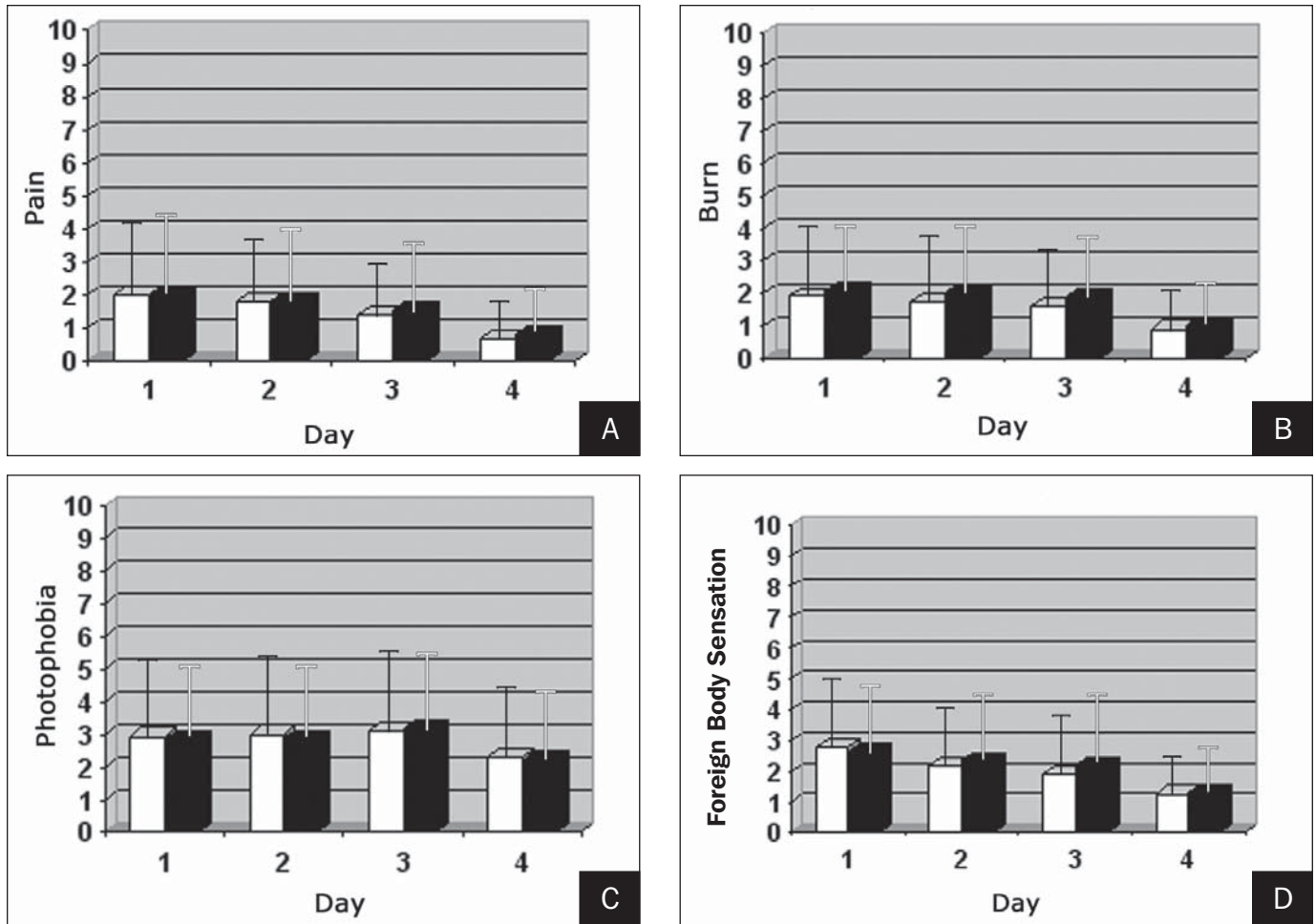
## DISCUSSION

This study was an open-label, randomized investigation into the efficacy and safety of topical bromfenac 0.09% as compared to ketorolac 0.4%. Due to the large amounts of existing literature demonstrating the effectiveness of NSAIDs, including ketorolac, as compared to placebo, it was determined that a placebo control was not necessary. The efficacy of NSAIDs in treating postoperative PRK pain was initially shown in the 1993 investigation of diclofenac versus a placebo.<sup>7</sup> Similar results have been exhibited when comparing ketorolac to placebo.<sup>8,10</sup> As these studies illustrated the ineffectiveness of the placebo, it was deemed unnecessary to subject patients to additional pain when results could be obtained by comparing one NSAID to another proven NSAID.

While designing the protocol of the study it was determined that despite its desirability, a masked study would not be advisable given the varying regimens for each drug. One of the most distinguishing aspects of bromfenac is its potency, penetration, and duration of effect using a twice-daily dose. Ketorolac, along with other NSAIDs, is designed to be administered four times daily. Altering either drug's administration frequency from its intended dosing might alter its efficacy. Furthermore, as it was critical to ensure that the patient diaries were filled out correctly, patients were repeatedly instructed on how many drops of NSAID they should be taking based on what drug they were using at the time. This task would have proven confusing during a masked study.

An analog scale, ranging from 0 to 10, was used as the patient's primary method of reporting pain and other symptoms. Other investigations have used this analog scale in the past, finding it quantitative and easy to use (N. Sher and W.B. Trattler, personal communication 2007). Patients were instructed to circle





**Figure 1.** Bromfenac (white bars) versus ketorolac (black bars). **A)** Pain, **B)** burning sensation, **C)** photophobia, and **D)** foreign-body sensation were recorded on an arbitrary analog scale ranging from 0 to 10. Values were recorded four times a day until the epithelium was declared healed and the bandage contact lens removed. Indicated values represent the mean of the four daily recordings averaged across each drug population for each corresponding day. Error bars represent +1 standard deviation from the mean.

the number corresponding with the amount of pain they were experiencing after taking their drops. This allows the patient to transform his/her perception of a qualitative pain to a quantitative value. Because every patient perceives pain differently, the individual analog scale seems appropriate for collecting subjective data. A large scale, such as 0 to 10, allows the patient to more precisely describe his/her pain compared to a smaller scale, such as 0 to 5. Similar analog scales were used to identify burning, photophobia, and foreign-body sensations. No significant difference was noted in any of the observed categories, over any period of the study, between either of the drugs.

Despite only being administered twice a day as compared to four times a day, there was no difference between the use of bromfenac and ketorolac in postoperative pain, burning, photophobia, and foreign-body sensations. As several studies have illustrated, ketoro-

lac possesses an ability to reduce postoperative PRK discomfort.<sup>8,9,14</sup>

Due to instances of corneal melting, delayed healing, and other severe complications that have been associated with topical NSAIDs in the past, the safety of a drug has become one of the crucial elements to be considered when assessing a new NSAID. In this study, epithelial defects and healing rates were closely followed. No significant difference was determined between the two drugs with regards to epithelial healing. It was not the intent of this study to prepare a placebo control with bromfenac or ketorolac. Accordingly, we cannot postulate the effect of either drug on the rate of reepithelialization versus a control. Adverse events were also recorded; however, the only instance of an adverse event, an infectious keratitis, was deemed unrelated to the NSAID used.

The complete closure of the epithelial defect is di-

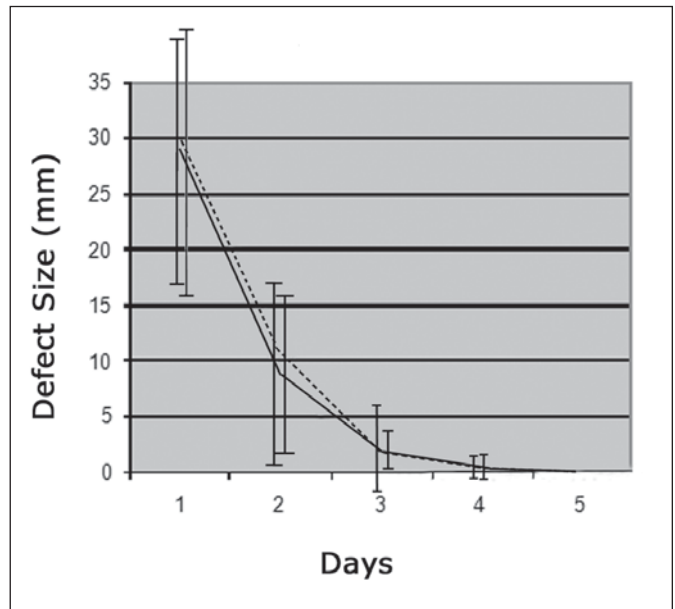
rectly correlated to the alleviation of postoperative pain. The exposed nerve endings are the primary stimulus of pain in the eye and delayed healing could lead to an increased risk of infection or corneal haze until the epithelium is healed.<sup>7,8,12,13</sup> Thus, it is vital that the duration of epithelial healing time is minimized. This will lead to greater patient satisfaction due to a shorter and more comfortable healing time and less chance for complications.<sup>4-6</sup>

In 2006, Trattler et al<sup>19</sup> reported a significant delay in the epithelial healing rates of postoperative PRK patients when an NSAID, nepafenac ophthalmic solution 0.1% (Nevanac, Alcon Laboratories Inc), was applied directly to the corneal bed before the bandage contact lens was in place. There may be some unique properties of nepafenac that, when applied directly to the corneal ablation bed, retard epithelial healing. This experience emphasizes the importance of observing the epithelial defect as a measure of an NSAID's safety and encourages us to critically observe the methods employed by other NSAID pain studies. Thus, it is worth noting again, that in this study, the NSAIDs were not applied directly to the bare corneal stroma, but rather were applied on top of the bandage contact lens to avoid potential complications. Using this method, neither ketorolac nor bromfenac exhibited any difference in epithelial defect healing rates.

A statistically significant difference was observed in photophobia experienced and epithelial defect healing rates between laser platforms. Due to the smaller size of the ALLEGRETTO and LADARVision4000 populations as compared to the VISX S4 population, it is possible that these results were highly influenced by a few outlying patients. Each of the three laser platforms used has a different ablation pattern and energy distribution, spot size, and transition zone. It would be speculation to make conclusions about epithelial healing in relation to the laser platform without additional studies.

The importance of following the postoperative regimen must be carefully instructed and stressed to the patient. Several studies, such as the Ikeda et al<sup>20</sup> 2001 investigation, have demonstrated that a decrease in the amount of required daily drops significantly increases the patient's willingness to adhere to the postoperative regimens, making the administration of a twice-daily agent an advantage. However, due to the four times daily nature of the other prescribed postoperative medications that a patient must administer, the advantage of a twice-daily dose is presently diminished.

The same mechanism of COX-2 inhibition that allows an NSAID to function as an anti-inflammatory agent, also grants the NSAID mild anesthetic properties; some of which are capable enough to reduce or



**Figure 2.** The 8.4-mm Amoils brush was used to create the initial epithelial defect in all cases. Using the length and width to estimate the defect size, the epithelial defect was recorded during each office visit. A value of 0 mm was used to indicate a fully healed epithelium. Indicated values represent the mean daily values for each drug population (bromfenac = dotted line, ketorolac = solid line). Error bars represent plus or minus one standard deviation from the mean.

eliminate the need for additional, stronger anesthetic drugs that may retard epithelial healing.<sup>9,11,13</sup> The mild nature of this secondary effect may have given an advantage to the four times a day agent, although one was not observed.

In conclusion, no significant differences were noted between the use of bromfenac and ketorolac with regard to postoperative PRK discomfort and safety when combined with postoperative measures such as cold BSS and a bandage contact lens.

#### AUTHOR CONTRIBUTIONS

*Study concept and design (N.A.S., M.P.G., W.B., S.T.); data collection (N.A.S., M.P.G., W.B., W.B.T., S.T., T.G.V.); analysis and interpretation of data (N.A.S., M.P.G., W.B.); drafting of the manuscript (N.A.S., M.P.G.); critical revision of the manuscript (N.A.S., M.P.G., W.B., W.B.T.); obtained funding (N.A.S.); administrative, technical, or material support (N.A.S.)*

#### REFERENCES

1. Albietz JM, McLennan SG, Lenton LM. Ocular surface management of photorefractive keratectomy and laser in situ keratomileusis. *J Refract Surg.* 2003;19:636-644.
2. Abad JC, An B, Power WJ, Foster CS, Azar DT, Talamo JH. A prospective evaluation of alcohol-assisted versus mechanical epithelial removal before photorefractive keratectomy. *Ophthalmology.* 1997;104:1566-1574.

3. Abad JC, Talamo JH, Vidaurri-Leal J, Cantu-Charles C, Helena MC. Dilute ethanol versus mechanical debridement before photorefractive keratectomy. *J Cataract Refract Surg*. 1996;22:1427-1433.
4. O'Doherty M, Kirwan C, O'Keeffe M, O'Doherty J. Postoperative pain following epi-LASIK, LASEK, and PRK for myopia. *J Refract Surg*. 2007;23:133-138.
5. Lui MM, Silas MA, Fugishima H. Complications of photorefractive keratectomy and laser in situ keratomileusis. *J Refract Surg*. 2003;19:S247-S249.
6. Tervo T, Moilanen J. In vivo confocal microscopy for evaluation of wound healing following corneal refractive surgery. *Prog Retin Eye Res*. 2003;22:339-358.
7. Sher NA, Frantz JM, Talley A, Parker P, Lane SS, Ostrov C, Cappel E, Doughman D, DeMarchi J, Lindstrong R. Topical diclofenac in the treatment of ocular pain after excimer photorefractive keratectomy. *Refract Corneal Surg*. 1993;9:425-436.
8. Vetrugno M, Maino A, Quaranta GM, Cardia L. A randomized, double-masked, clinical study of the efficacy of four nonsteroidal anti-inflammatory drugs in pain control after excimer laser photorefractive keratectomy. *Clin Ther*. 2000;22:719-731.
9. Weinstock V.M, Weinstock DJ, Weinstock S.J. Diclofenac and ketorolac in the treatment of pain after photorefractive keratectomy. *J Refract Surg*. 1996;12:792-794.
10. Solomon K, Donnenfeld ED, Raizman M, Sandoval HP, Stern K, VanDenburgh A, Cheetham JK, Schiffman R; Ketorolac Reformulation Study Groups 1 and 2. Safety and efficacy of ketorolac tromethamine 0.4% ophthalmic solution in post-photorefractive keratectomy patients. *J Cataract Refract Surg*. 2004;30:1653-1660.
11. Donnenfeld E, Donnenfeld A. Global experience with Xibrom (bromfenac ophthalmic solution) 0.09%: the first twice-daily ophthalmic nonsteroidal anti-inflammatory drug. *Int Ophthalmol Clin*. 2006;46:21-40.
12. Tutton M, Cherry P, Raj PS, Fsadni MG. Efficacy and safety of topical diclofenac in reducing ocular pain after excimer photorefractive keratectomy. *J Cataract Refract Surg*. 1996;22:536-541.
13. Assouline M, Renard G, Arne JL, David T, Lasmolles C, Malecaze F, Pouliquen YJ. A prospective randomized trial of topical soluble 0.1% indomethacin versus 0.1% diclofenac versus placebo for the control of pain following excimer laser photorefractive keratectomy. *Ophthalmic Surg Lasers*. 1998;29:365-374.
14. Frangouli A, Shah S, Chatterjee A, Morgan PB, Kinsey J. Efficacy of topical nonsteroidal drops as pain relief after excimer laser photorefractive keratectomy. *J Refract Surg*. 1998;14:S207-S208.
15. Verma S, Corbett MC, Marshall J. A prospective, randomized, double-masked trial to evaluate the role of topical anesthetics in controlling pain after photorefractive keratectomy. *Ophthalmology*. 1995;102:1918-1924.
16. Shahinian L Jr, Jain S, Jager RD, Lin DT, Sanislo SS, Miller JF. Dilute topical proparacaine for pain relief after photorefractive keratectomy. *Ophthalmology*. 1997;104:1327-1332.
17. Kitazawa Y, Tokoro T, Ito S, Ishii Y. The efficacy of cooling on excimer laser photorefractive keratectomy in the rabbit eye. *Surv Ophthalmol*. 1997;42:S82-S88.
18. Saghai M. Randomization. Available at: <http://mahmoodsaghaei.tripod.com/Softwares/ranalloc.html>. Accessed March 2007.
19. Trattler W, McDonald M. Double-masked comparison of ketorolac tromethamine 0.4% versus nepafenac sodium 0.1% for postoperative healing rates and pain control in eyes undergoing surface ablation. *Cornea*. 2007;26: 665-669.
20. Ikeda H, Sato M, Tsukamoto H, Sato E, Unei H, Kimura Y, Mishima H, Kihira K. Evaluation and multivariate statistical analysis of factors influencing patient adherence to ophthalmic solutions [Japanese]. *Yakugaku Zasshi*. 2001;121:799-806.