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Double-Masked Study of the Effects of Nepafenac 0.1% and Ketorolac 0.4% on Corneal Epithelial Wound Healing and Pain After Photorefractive Keratectomy

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ABSTRACT

Two NSAIDs—nepafenac 0.1% and ketorolac tromethamine 0.4%—were compared in terms of their effects on corneal reepithelialization and pain after photorefractive keratectomy (PRK) in a randomized, double-masked, contralateral eye, multicenter study. A total of 40 healthy adult patients who were undergoing sequential bilateral PRK received nepafenac 0.1% and ketorolac 0.4% in contralateral eyes, 1 drop 3 times daily for 3 d after bandage contact lens insertion. Patients were assessed on postoperative days 1, 3, 4, 5, and 7. At each visit, patients provided a general rating of pain. Each patient also assessed the sensation of each eyedrop following instillation (after-drop pain, irritation, burning/stinging, and overall comfort). Starting on day 3, epithelial defect size was assessed. Mean epithelial defect size was similar between treatments at each postoperative visit ($P>.05$). The average time-to-healing was 4.18 d for nepafenac 0.1% and 4.00 d for ketorolac 0.4% ($P=.3134$). No statistical difference was observed between nepafenac 0.1% and ketorolac 0.4% in mean postoperative pain scores ($P>.05$).

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On day 3, the nepafenac 0.1% group had significantly lower mean sensation scores than did the ketorolac 0.4% group for after-drop pain (P=.0090), irritation (P=.0007), and burning/stinging (P=.0003). Mean overall comfort score was also significantly better for nepafenac 0.1% on day 3 (7.43 vs 6.41; P<.0001). Nepafenac 0.1% and ketorolac 0.4% provide postoperative pain relief after PRK surgery without associated adverse effects on corneal epithelial healing. Nepafenac 0.1% treatment may offer greater comfort upon instillation in patients who have undergone PRK.

Keywords: photorefractive keratectomy; PRK; pain; epithelial healing; nepafenac; ketorolac

INTRODUCTION

Although laser in situ keratomileusis (LASIK) has become the predominant refractive surgery, photorefractive keratectomy (PRK) is commonly employed to treat refractive errors in patients with thin corneas, large pupils, topographic irregularities, or epithelial basement membrane disease, or who are otherwise not candidates for LASIK.[1,2] Although the selection of PRK for refractive errors appears to be increasing, it does have certain drawbacks. During the healing process, patients often complain of moderate to severe pain, which usually starts on the day of surgery and continues until corneal reepithelialization.[3,4] Systemic analgesics are frequently prescribed, but they may be associated with significant adverse effects, such as sedation and nausea.

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce pain following PRK.[5-10] Variability in the efficacy of different NSAIDs in controlling ocular inflammation and pain has been observed across studies, possibly related to differences in pharmaceutical properties among agents.[11] Some data suggest that topical NSAIDs may delay corneal healing.[3,9,11] Nepafenac 0.1% is a newer topical NSAID prodrug that has been approved for postoperative inflammation following cataract surgery. The prodrug nepafenac is absorbed by the cornea and is then converted to amfenac, which is a potent inhibitor of cyclooxygenase-1 and -2.[12] The current study was designed to compare the effects of nepafenac 0.1% (Nevanac®; Alcon, Fort Worth, Tex) versus those of ketorolac tromethamine 0.4% (Acular LS®; Allergan, Irvine, Calif) on corneal epithelial healing and pain control following PRK.

MATERIALS AND METHODS

Overall Study Design

This randomized, double-masked, multicenter, contralateral eye study examined adult patients who were undergoing sequential bilateral PRK surgery between February 17, 2006, and June 2, 2006. Patients received nepafenac 0.1% or ketorolac 0.4% in contralateral eyes, 1 drop 3 times daily for 3 d. Evaluation of corneal healing started on the third postoperative day. General postoperative pain for each eye was assessed beginning on day 1 with a 10-point visual analog scale (VAS). The protocol was approved by IntegReview Ethics Review Board, and signed informed consent was obtained from all patients.

Study Population

Forty healthy male and female patients older than 18 y of age with healthy ocular status, undergoing sequential bilateral PRK surgery were enrolled at 4 private practice ophthalmology centers in the United States. All patients had preoperative refractive anisometropia of less than 2.00 diopters between both eyes, a best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity score equivalent to 20/30 or better in each eye, and stable refraction over a period of 1 y.

Patients were excluded from the study for the following reasons: a desire for PRK in only 1 eye, a history of refractive or other surgery in either eye, any condition that could delay wound healing, intolerance to any component of study medications, required use of systemic NSAIDs during the study period, need for continued use of additional presurgical topical eyedrops (eg, glaucoma or allergy eyedrops), corneal staining with fluorescein of 1+ or worse on preoperative examination, previous treatment with Restasis® (Allergan, Irvine, Calif), dry eyes (defined as a decrease in tear production or tear quality), pregnancy, or breastfeeding.

Study Methods

Before entering the study, all patients underwent a complete eye examination with cycloplegic refraction, topography, and pachymetry. All eyes were evaluated for dry eye syndrome with the use of supravital staining with fluorescein of the cornea and lissamine green staining of the conjunctiva. In addition, all patients underwent Schirmer testing with anesthesia. Contact lenses were removed for a minimum of 1 wk prior to PRK. Patients underwent PRK surgery in both eyes on the same day.

On the day of surgery, all patients were administered 2 drops of proparacaine 1% in both eyes 5 min prior to the procedure. The lids of both eyes were prepped with 10% povidone-iodine solution. No povidone-iodine was placed in the patient's cul-de-sac. Epithelial debridement was performed by marking the central cornea with an 8.5-mm ring and manually debriding the epithelium with a spatula. The use of mitomycin C or alcohol debridement of the epithelium was not allowed during surgery, nor was the use of prepunctal or postpunctal plugs. The stromal bed was moistened with balanced salt solution and was dried with a Weck-Cel (Medtronic Inc., Minneapolis, Minn). The ablation zone was no greater than 9.0 mm in any dimension, and the largest ablation zone dimension was equal in both eyes. All procedures were performed with the physician's choice of laser.

Following the laser procedure, 2 drops of moxifloxacin 0.5% were instilled onto the cornea, followed in 5 sec by 2 drops of prednisolone acetate 1%. A bandage contact lens (BCL; Focus Night and Day™; CibaVision, Duluth, Ga) was applied to each eye. According to a random treatment assignment list specific to this contralateral eye study, masked study medication was instilled into the appropriate eye by a technician. Patients, surgeons, and independent postoperative examiners remained masked at all times to treatment assignment. Postoperative medications consisted of moxifloxacin 0.5% given 3 times daily for 1 wk, prednisolone acetate 1% 3 times daily tapered off over 1 mo, and Systane® Free drops (Alcon Laboratories, Fort Worth, Tex) as needed. To decrease the risk of cross-placement, study medication labels were marked with a large "R" or "L" that corresponded to the right or left eye, respectively. Patients were instructed to shake the bottle well and to place

1 drop into the designated eye 3 times daily after moxifloxacin and prednisolone drops, and on top of the BCL for 3 d. Hydrocodone 5 mg/acetaminophen 500 mg was also prescribed as needed for pain. All patients were given sunglasses with 100% ultraviolet (UV) ray protection and were instructed to wear the glasses outdoors for 1 wk.

Patients were seen on postoperative days 1, 3, 4, 5, and 7, or until epithelial defects closed in both eyes. The eyes were not expected to heal prior to day 3; therefore, corneal reepithelialization was evaluated beginning on day 3, and continuing on days 4, 5, and 7 after surgery. Epithelial defect size was measured with a slit lamp micrometer or high-density fluorescein, if necessary. Maximum vertical and horizontal dimensions of the epithelial defect were recorded at each visit. Once the epithelial defect had closed in 1 or both eyes, both BCLs were removed and digital photography was performed on both eyes. A new BCL was then placed on the nonhealed eye, if needed.

On postoperative days 1, 3, 4, 5, and 7, general pain scores were assessed before instillation of study drops. Each patient was asked to rate the pain in each eye separately according to the following question: On a scale of 1 to 10, where 1 stands for "Absolutely No Pain" and 10 stands for "Worst Pain Possible," regardless of the drop, how much pain are you experiencing IN GENERAL? This assessment was done separately for the left eye and then the right eye.

In addition to the general pain assessment, patients rated the subjective sensations of pain, irritation, and burning/stinging in each eye following study medication instillation (after-drop). The following question was asked of each patient: On a scale of 1 to 10, where 1 stands for "No Pain" and 10 stands for "Worst Pain Possible," IMMEDIATELY UPON PUTTING THE DROP IN YOUR EYE, how much pain are you experiencing after using the NSAID drop? Again, each eye was rated separately. Similar questions were asked to assess after-drop irritation and after-drop burning/stinging. In addition, an overall rating of study medication comfort was assessed by asking patients to rate from 1 to 10, ranging from greatest discomfort possible to very comfortable, respectively, the after-drop comfort of study medication following instillation.

Statistical Methods

A power calculation indicated that a study with 34 pairs of eyes was required to detect a difference of 0.5 d or longer in epithelial healing time between treatments, with 80% statistical power at a 95% confidence level under the assumptions that the correlation coefficient between the contralateral eyes would be 0.5 (d) or greater and the standard deviation would be 2.0 (d) or fewer. Therefore, 40 subjects would have been sufficient for study purposes with consideration of study withdrawals and losses to follow-up of up to 15%. The sample size (N=40) chosen for this study was also based on a recent study in the *American Journal of Ophthalmology* that examined the time to epithelial healing between 2 fourth-generation fluoroquinolones (N=35).[13] Patients were excluded from the final statistical analysis if they had missed 2 or more drops of study medication a day, had dislocated or replaced a BCL, or had experienced significant postoperative trauma to the eye.

Statistical analyses were performed by an independent biostatistician with the use of SAS (SAS-PC, version 9.1.2; SAS Institute, Cary, NC). The primary study outcome

was epithelial defect size in the contralateral eye on the day the epithelial defect had closed in the faster healing eye. Secondary endpoints included comparison between treatments in time to reepithelialization and in general postoperative pain. In each patient, a paired *t* test was used to analyze general postoperative pain scores for the eye treated with nepafenac 0.1% compared with the eye treated with ketorolac 0.4%. A comparison between eyes for after-drop pain, irritation, burning/stinging, and comfort was also evaluated.

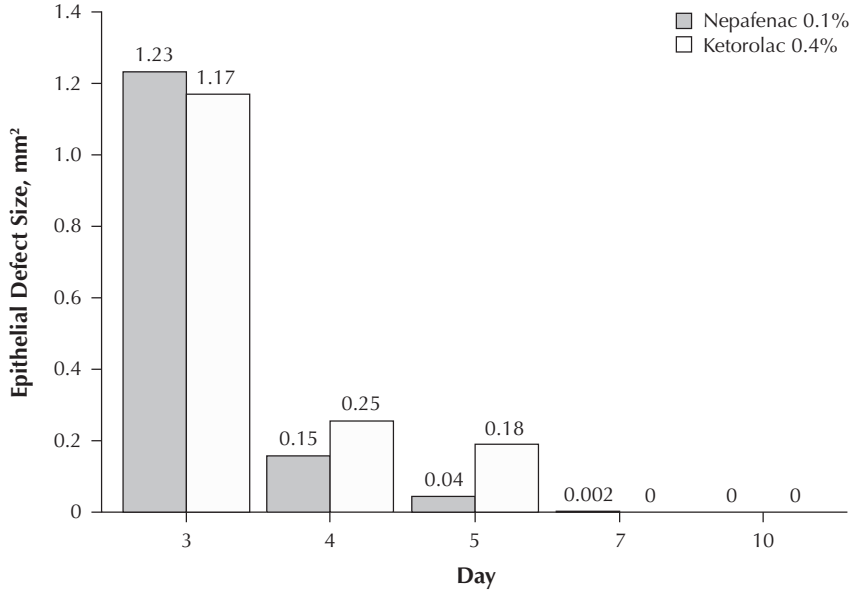
RESULTS

A total of 40 patients (80 eyes), including 21 men (52.5%) and 19 women (47.5%), underwent sequential bilateral PRK. The mean age of patients was 38 y (range, 23–62 y). Thirty-six patients (90%) were Caucasian, 2 (5%) were African American, 1 was Asian, and 1 was Hispanic. All patients completed the study except for 1 who experienced infectious keratitis and withdrew.

Corneal Healing

Mean epithelial defect size at each visit is summarized in Figure 1. At each postoperative visit, the mean epithelial defect size (mm^2) was similar between treatments with no statistical difference between groups ($P>.05$). Initial epithelial defect size was 8.5 mm for each patient. Average time to healing was 4.18 d for nepafenac 0.1% and 4.00 d for ketorolac 0.4% ($P=.3134$). In the nepafenac 0.1% group, complete

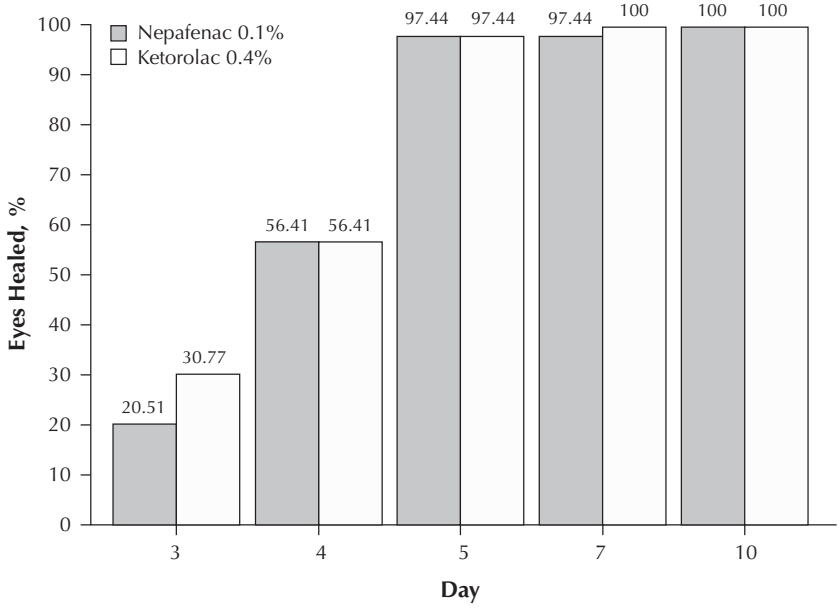
Fig 1. Mean epithelial defect size by postoperative visit.



No statistical difference in mean epithelial defect size was observed between groups at any postoperative visit.

closure was reported in 8 eyes (20.51%) at day 3, 14 eyes (35.90%) at day 4, 16 eyes (41.03%) at day 5, and 1 eye (2.56%) at day 10, compared with 12 eyes (30.77%) at day 3, 10 eyes (25.64%) at day 4, 16 eyes (41.03%) at day 5, and 1 eye (2.56%) at day 7 in the ketorolac 0.4% group. No statistical difference was reported between groups in the cumulative rate of eyes with reepithelialization at any postoperative visit (Fig 2).

Fig 2. Percent of eyes (cumulative) with complete corneal reepithelialization by visit.



No statistical difference in the cumulative rate of eyes with reepithelialization was observed between groups at any postoperative visit.

Pain Assessment

General pain scores for each eye by postoperative visit are presented in Table 1. No statistical difference was observed between nepafenac 0.1% and ketorolac 0.4% in mean general postoperative pain scores ($P>.05$). Mean pain scores at day 1 were 3.45 and 3.08 for nepafenac 0.1% and ketorolac 0.4%, respectively. At day 3, mean pain scores were 3.10 and 3.17, respectively, and they decreased progressively in both groups over days 4 to 7.

In all, 31 patients (77.5%) at day 1 and 28 patients (70.0%) at day 2 reported using hydrocodone/acetaminophen for pain control. Doses of hydrocodone/acetaminophen ranged from 1 to 15 tablets/d.

Table 1. Mean General Pain Scores by Postoperative Visit

Postoperative Visit	N	Nepafenac 0.1%	Ketorolac 0.4%
Day 1	38	3.45±2.55	3.08±2.12
Day 3	39	3.10±1.93	3.17±2.03
Day 4	31	2.32±1.89	1.97±1.36
Day 5	20	2.03±2.27	1.38±0.93
Day 7	11	1.27±0.79	1.18±0.60

Values are expressed as means±standard deviation. N=number of patients with data available.

After-Drop Comfort Assessment

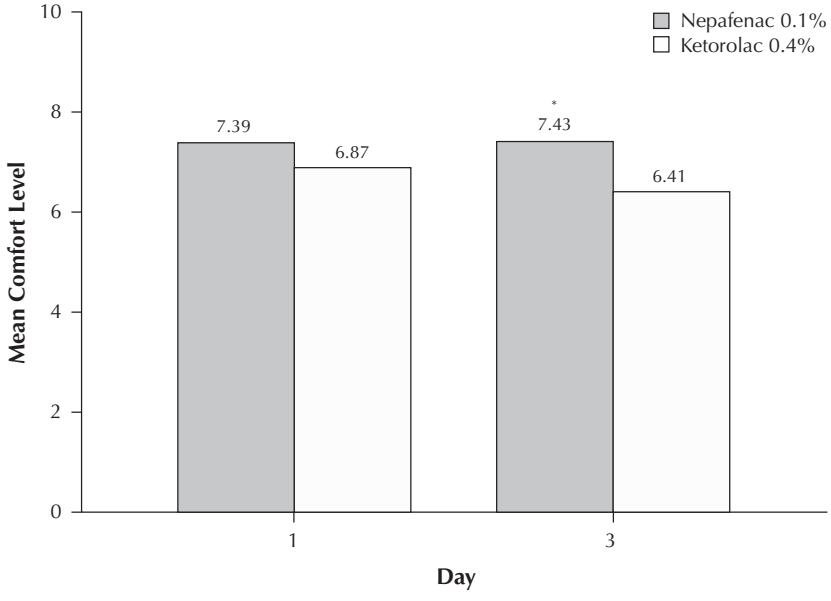
Mean sensation scores after study medication administration revealed no differences between treatments in after-drop pain, irritation, or burning/stinging sensation on day 1, although mean scores for each variable were slightly lower (indicating less pain, irritation, or burning/stinging following instillation) in the nepafenac 0.1% group (Table 2). On day 3, the nepafenac 0.1% group had significantly lower mean sensation scores than the ketorolac 0.4% group for after-drop pain (P=.0090), irritation (P=.0007), and burning/stinging sensation (P=.0003). Mean after-drop comfort scores on day 3 were also significantly greater in the nepafenac 0.1% group, indicating greater overall comfort (7.43 vs 6.41, P<.0001; Fig 3).

Table 2. Mean Sensation Scores Following Instillation by Postoperative Visit

Variables	Day 1 N	Day 1 Mean (SD)	Day 3 N	Day 3 Mean (SD)	*P* Value
Pain after drop					
Nepafenac 0.1%	38	2.32 (1.96)	38	1.70 (1.31)	.0090
Ketorolac 0.4%	38	2.61 (2.04)	38	2.29 (1.87)	
Irritation after drop					
Nepafenac 0.1%	38	2.68 (2.29)	38	2.11 (1.82)	.0007
Ketorolac 0.4%	38	2.97 (2.16)	38	3.11 (2.07)	
Burning/stinging after drop					
Nepafenac 0.1%	38	2.55 (2.15)	38	2.00 (1.77)	.0003
Ketorolac 0.4%	38	2.88 (1.98)	38	3.21 (2.32)	

Analysis based on all available data at each time point. N=number of patients with data available.

Fig 3. Mean after-drop comfort level by postoperative visit.



*P<.0001.

The nepafenac 0.1% group had a significantly greater mean comfort score at day 3 than the ketorolac 0.4% group.

Safety

Two adverse events were reported during the study. One patient was given a diagnosis of keratitis 2 d postoperatively in the eye that was treated with ketorolac 0.4%. This patient responded to treatment and did well postoperatively, with vision correcting to 20/25 bilaterally. A second patient was observed to have a small epithelial defect superiorly, away from the central defect in the eye treated with 0.1% nepafenac. This defect was located peripherally on the cornea, and the investigator believed it was most likely related to BCL removal. A new BCL was placed over the anterior segment phallus, and the patient continued in the study. The epithelial defect healed in 1 d. The investigators believed that both events were unrelated to study drug. No stromal or subepithelial infiltrates were reported.

DISCUSSION

Topical NSAIDs have been shown to reduce pain following PRK in several studies[11]; however, some studies have demonstrated a delay in wound healing with the use of NSAIDs following PRK.[3,9,11] These delays in wound healing may be related to the analgesic properties of the NSAID or to the presence of the preservative thimerosal in the formulations. The current study was designed to compare the effects of 2 currently marketed NSAIDs—nepafenac 0.1% and ketorolac 0.4%—on epithelial

healing following PRK, and to evaluate treatment differences in the control of postoperative pain.

No difference between agents was observed in epithelial defect size following surgery or in time to reepithelialization. Both agents produced epithelial healing in most patients within 5 d after surgery. These results add to the evidence reported from previous studies, which also demonstrated no adverse effect of nepafenac 0.1% on corneal reepithelialization.[14,15] Within the present study, however, neither agent was administered for longer than 3 d postoperatively. It is known that some patients have a greater risk of corneal epithelial breakdown with continued use; therefore, the present investigators do not recommend the use of any topical NSAID for longer than 3 d following PRK, and it is suggested that NSAID drops should be placed on top of the BCL instead of on the stromal bed, to minimize toxicity.

Nepafenac 0.1% and ketorolac 0.4% also demonstrated comparable efficacy in controlling postoperative pain following PRK surgery. As expected, mean general pain scores in both groups were highest on days 1 and 3 after surgery. Consistent with this was the use of as-needed narcotic analgesics during the early postoperative period. The investigators considered the possibility that as-needed hydrocodone/acetaminophen could confound the results of a study undertaken to evaluate general pain. The postoperative use of narcotic pain relievers following PRK is a standard of care, however, and the investigators believed that it would not be ethical to withhold breakthrough pain treatment. Therefore, this study was designed to analyze pain scores between fellow eyes (paired eyes) at each postoperative visit. This method of comparison should have minimized the influence of as-needed oral narcotics on pain results because the findings were comparative between eyes of the same patient. A standard regimen of postoperative steroid drops was administered identically in both eyes after surgery. Similarly, any influence of steroid therapy on reduction of inflammation and pain after PRK would be minimized by the paired analysis.

Patient-rated after-drop pain, irritation, and burning/stinging scores (sensation scores) were evaluated to assess the comfort of each study drop. Although no statistical differences in subjective comfort and sensation scores were observed between nepafenac 0.1% and ketorolac 0.4% on postoperative day 1, a trend for lower scores was noted in the nepafenac group (indicating less pain, burning/stinging, and irritation). On postoperative day 3, all 3 scores for after-drop pain, irritation, and burning/stinging were statistically lower in the nepafenac treatment group. Patients' overall assessment of after-drop comfort was also statistically higher (indicating greater comfort) with nepafenac 0.1% at the day 3 visit. These results suggest that nepafenac 0.1% may offer a slight comfort advantage over ketorolac 0.4% during the early postoperative period. The investigators recognize, however, that assessment of sensation scores and comfort within this study may have been confounded by the refractive procedure; a true comfort study would be needed to confirm these results.

During the study, no patients reported adverse effects with nepafenac 0.1%, nor was any evidence found of corneal toxicity with nepafenac 0.1%. Overall, nepafenac 0.1% appears to be well tolerated without significant adverse effects. Nepafenac 0.1% and ketorolac 0.4% provide postoperative pain relief following PRK surgery without associated adverse effects on corneal epithelial healing. Nepafenac 0.1% treatment may offer greater comfort upon instillation in patients undergoing PRK.

FINANCIAL DISCLOSURE

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