Topical Diclofenac in the Treatment of Ocular Pain After Excimer Photorefractive Keratectomy

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ABSTRACT

BACKGROUND: Following excimer laser photorefractive keratectomy, patients experience significant ocular pain until corneal reepithelialization. Despite the use of cold compresses, bandage soft contact lenses, cycloplegics, narcotics, and topical corticosteroids, the pain has not been adequately controlled in many patients.

METHODS: A randomized, double-masked, parallel-group study of diclofenac sodium 0.1% ophthalmic solution and its placebo vehicle was evaluated. Patients undergoing excimer myopic photorefractive keratectomy on their second eye were admitted overnight. Postoperative procedures included two drops of diclofenac or placebo immediately after surgery and then qid until reepithelialization, topical tobramycin (qid), 0.1% fluoromethalone (q2h), cycloplegics, and a disposable soft contact lens. Thirty-two patients (diclofenac = 16, placebo = 16) were evaluated from +30 minutes to +96 hours by several types of questionnaires.

RESULTS: Most patients who received placebo experienced pain, starting within 1 hour, peaking at 4 to 6 hours and lasting 36 to 48 hours. The diclofenac-treated patients rarely experienced the early peak in pain, had less pain overall until 72 hours postoperatively, and experienced significantly less photophobia and burning/stinging. Significantly fewer patients on diclofenac required oral narcotics. Three patients (diclofenac = 2, placebo = 1) developed corneal infiltrates, the etiology of which is not known. In a separate study we conducted, there was no difference in epithelial healing times between the diclofenac-treated eyes and those not receiving the drug.

CONCLUSIONS: Diclofenac appears to significantly reduce the ocular pain following excimer photorefractive keratectomy. (Refract Corneal Surg. 1993;9:425-436.)

RÉSUMÉ

INTRODUCTION: Les patients éprouvent une douleur oculaire significative après la kératectomie photorefractive au laser excimer jusqu'à la ré-épithelialisation cornéenne. Malgré l'emploi de compresses froides, le port de lentilles de
contact, la cyclopélie, l'utilisation de narcotiques, et de corticoïdes, la douleur ne fut pas contrôlée chez un grand nombre de patients.

MÉTHODES: Une étude randomisée, doublement masquée, de groupes en parallèle fut réalisée afin d'évaluer la solution de diclofénac sodium à 0,1% et son véhicule placebo. Les patients furent admis à l'hôpital la nuit suivant la kératectomie photoréfractive sur le deuxième œil. Les procédures en post-opératoire comprenaient deux gouttes de diclofénac sodium ou le véhicule immédiatement après chirurgie et quatre fois par jour jusqu'à la ré-épithélialisation complète, tobramycine quatre fois par jour, 0,1% fluromethalone toutes les deux heures, de la cyclopélie, et une lentille de contact à usage unique. Trente-deux patients (16 dans chaque groupe) furent évalués de 30 minutes jusqu'à 96 heures post-opérativement à l'aide de plusieurs questionnaires.

RÉSULTATS: La plupart des patients qui ont reçu le placebo ont éprouvé une douleur, ce qui commençait dans la première heure, atteignait son niveau maximum entre 4-6 heures et durait 36-48 heures. Ceux qui furent traité avec diclofénac ont rarement éprouvé le pic maximum de douleur, et ont éprouvé moins de douleur au total jusqu'à 72 heures après opération et ont éprouvé significativement moins de photophobie et de sensations de brûlure ou de piqûre. Les patients utilisant la diclofénac ont eu significativement moins besoin des narcotiques. Trois patients (diclofénac-2, placebo-1) ont développé des infiltrations cornéennes, l'étiologie desquelles n'étant pas connue. Dans une étude différente chez nous, il n'y avait pas de différence dans le temps de ré-épithélialisation entre les patients traités et non-traités avec le diclofénac.

CONCLUSION: Il semble que le diclofénac sodium réduise la douleur oculaire après la kératectomie photo-réfractive. (Translated by Robert Mack, MD, Iowa City, la.)

SOMMARIO
PREMESSA: In seguito alla chirurgia fotorefrattiva con laser ad eccimeri (PRK), i pazienti riportano un vivace dolore oculare fino alla ri-epiteliizzazione corneale. Nonostante l'uso di compresse fredde, lenti a contatto terapeutiche, ciclopelgici, narcotici e agenti corticosteroidi ophthalmici, il dolore in molti pazienti non viene adeguatamente controllato.

METODI: Abbiamo condotto uno studio randomizzato, a doppio cieco, a gruppi parallelli, sulla soluzione oftalmica di diclofénac sodico 0,1% ed il suo veicolo placebo. Pazienti sottoposti a PRK miopic sul loro secondo occhio sono stati ricoverati. La terapia postoperatoria ha incluso due gocce di diclofénac o placebo immediatamente dopo la chirurgia e quindi quattro volte al giorno (qid) fino alla ri-epiteliizzazione, tobramicina topica (qid), 0,1% fluromethalone (q2h), ciclopelgici, e una lente a contatto morbida monouso. Trentadue pazienti (diclofénac = 16, placebo = 16) sono stati indagati tra i 30 minuti e 96 ore con diversi questionari.

RISULTATI: La maggior parte dei pazienti che hanno ricevuto il placebo hanno riferito dolore, a partire dalla prima ora, con un picco tra le 4-6 ore e perdurante 36-48 ore. I pazienti trattati con diclofénac hanno riferito il picco di dolore solo saltuariamente, hanno avuto meno dolore in assoluto fino alle 72 ore postoperatorie e hanno riferito una significativa minore fotofobia e bruciore. I pazienti trattati con diclofénac hanno richeisto significativamente meno narcotici orali. Tre pazienti (diclofénac = 2, placebo = 1) hanno sviluppato un infiltrato corneale, la cui eziologia non è nota. In uno studio separato che abbiamo condotto, non c'è stata differenza nel tempo di cicatrizizzazione epiteliale tra gli occhi trattati con diclofénac e quelli che non hanno ricevuto il farmaco.

CONCLUSIONI: Il diclofénac sembra ridurre significativamente il dolore oculare dopo PRK con laser ad eccimeri. (Translated by Francesco Carrones, MD, S. Raffaele Hospital, University of Milano, Milano, Italy.)

The use of the 193-nanometer excimer laser has continued to generate wide interest for the treatment of myopia3–4 and corneal scar.5,6 Patients may experience moderate to severe eye pain after excimer photorefractive keratectomy. This pain usually begins within 30 to 60 minutes after the procedure and becomes severe within 4 to 6 hours despite preoperative counseling and treatment with oral narcotics, cyclopelgics, and ice packs.

Diclofenac sodium (Voltaren, Ciba-Geigy, Summit, NJ) is a potent nonsteroidal antiinflammatory drug (NSAID) used as an antiinflammatory and analgesic agent in relieving the signs and symptoms associated with rheumatoid arthritis, degenerative joint disease, and allied conditions. In 1991, an ophthalmic NSAID formulation, diclofenac sodium 0,1% ophthalmic (Voltaren Ophthalmic, Ciba Vision Ophthalmics, Atlanta, Ga) was introduced in the United States for the treatment of postoperative inflammation following cataract surgery. Sher et al4 suggested that topical diclofenac could reduce postoperative pain after excimer photorefractive keratectomy, especially when combined with a bandage soft contact lens. Anecdotal experience from other investigators has confirmed this impression (personal communication, McDonald MB, Eiferman RA, Arshinoff S, Robin J, Sedaravic O, 1992). Further
evidence has been derived from a retrospective review of charts of 20 patients which showed significant reduction in post-photorerefractive keratectomy pain after receiving topical diclofenac in addition to fluoromethalone 0.1% solution (FML, Allergan, Irvine, Calif), tobramycin ophthalmic solution (Tobrex, Alcon, Fort Worth, Tex), 0.25% scopolamine hydrobromide (Isopto Hyoscine, Alcon), and a disposable soft contact lens (Acuvue, Vistakon, Claremont, Calif). In a survey of postoperative pain conducted 24 hours after photorerefractive keratectomy, the diclofenac group rarely indicated more than mild pain. To determine the efficacy and safety of diclofenac sodium ophthalmic solution for the attenuation of postoperative ocular pain following excimer photorerefractive keratectomy, a prospective, two-center, randomized, double-masked, parallel group, placebo-controlled comparison trial was performed.

MATERIALS AND METHODS

Study Population

Thirty-two patients were enrolled who met the criteria for inclusion in the U.S. FDA defined protocol under an investigational device exemption for phase III trials for myopic photorerefractive keratectomy. All patients had undergone excimer photorerefractive keratectomy in the opposite eye approximately 6 months before and all had preoperative refractive errors (spherical equivalent) between −1.00 and −8.00 D. Patients were excluded who had concurrent therapy with any systemic or topical NSAID, analgesic, or topical eye medication within 2 weeks prior to surgery as well as pregnant patients and those having a hypersensitivity to any of the drugs used. After approval of this study by the appropriate institutional review boards, informed consent was obtained from each patient for this trial, as well the excimer laser study. A standardized statement describing postoperative pain was read to each patient before the surgery.

There were 21 females (66%) and 11 males (34%) included in this study, with 12 females (75%) and 4 males (25%) in the diclofenac-treated group, and 9 females (56%) and 7 males (44%) in the placebo group. All patients were white. The mean age of the diclofenac-treated group was 38.8 years (range, 22 to 52 years) and 32.8 (range, 18 to 53 years) in the placebo group. Twenty-eight patients were enrolled from the Phillips Eye Institute and four from the Eye Center of Florida. These differences between treatment groups were not statistically significant.

Refraction

Preoperative mean refraction (spherical equivalent, ± SD) in the diclofenac group was −4.32 ± 1.37 D and −4.80 ± 1.69 D in the placebo group. There were no statistically significant differences in the preoperative refractive errors or the attempted amount of correction between the two groups (p = 0.388 and 0.351 respectively, two-sided t-test).

Instrumentation and Surgical Procedure

The laser used at both sites was the VISX Model LV 2015. It used an argon fluoride gas mixture to produce a 193-nanometer wavelength at 10 Hz and was adjusted to deliver a fluence of 100 to 120 mJ/cm². A beam diameter of 6.5 to 6.8 mm was used. The preoperative evaluation and surgical procedure have been fully described elsewhere. In brief, the eye was anesthetized with three drops of 0.5% proparacaine topicaly over 5 minutes and the visual axis marked. A 7.0-millimeter corneal marker, premarked with gentian violet dye, was centered on the corneal epithelial impression, and the epithelium was gently removed. After alignment, laser energy was delivered in a series of predetermined pulses through a rotating series of 15 apertures of diminishing size.

Study Design

The study was a prospective, randomized, double-masked, parallel-group, comparison of diclofenac and placebo. The patients continued the study medication until the cornea was reepithelialized. To ensure masking of the groups, the patients, the investigators, the personnel at the two study sites, and the personnel of Ciba Vision Ophthalmics involved in conducting and monitoring the trial were masked as to the study drug codes, except in case of emergency. Patients were randomly assigned to one of the two treatment groups by receiving the next lowest available patient number on the prenumbered Case Report Forms. Each patient number was randomly reassigned to one of the two groups. A series of questionnaires, pain scales, and patient diaries were used to record patient responses.

Postoperative Medications

All patients received identical postoperative care except for diclofenac or its vehicle placebo solution which was administered in a randomized fashion. The vehicle placebo solution contained boric acid, edetate disodium (1 mg/mL), polyoxyxyl 35 castor oil, purified water, sorbic acid (2 mg/mL), and tromethamine. diclofenac contained the vehicle and diclofenac sodium 1 mg/mL. Both were supplied in identical sterile plastic dropper bottles for ocular administration. No preoperative sedation was used. Immediately after the laser procedure, the patients received two drops of diclofenac or placebo 5 minutes apart. In addition, immediately following the ablation, 0.1% fluoromethalone was administered every 2 hours, 0.3% tobramycin drops (Tobrex, Alcon) were given qid, and 5% homatropine hydrobromide (Alcon) was administered immediately postopera-
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A. CATEGORICAL PAIN SCALE—COMPLETED BY PATIENT

<table>
<thead>
<tr>
<th>The amount of pain in your eye at this moment is:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operated eye</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Opposite eye</td>
</tr>
</tbody>
</table>

B. VISUAL ANALOG PAIN SCALE—COMPLETED BY PATIENT

Please place an “X” on the dark, solid line below to indicate the amount of pain, if any, that you feel at this moment in your operated eye:

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Worst pain ever</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pain</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C. OCULAR DESCRIPTORS—COMPLETED BY PATIENT

In each category, circle one term which describes the type of sensation that you feel at this moment in your operated eye:

<table>
<thead>
<tr>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign body sensation</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Light sensitivity</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Deep headache-like pain within eye</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Stinging/burning</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Itching</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Figure 1: (A-C) Questionnaires filled out by patients.

A disposable soft contact lens (Vistakon Acuvue) + 0.50 D was placed. Diclofenac or placebo was applied to the operative eye every 6 hours. Patients were permitted to use acetaminophen or Mepergan Fortis (50 mg of meperidine and 25 mg of promethazine) (Wyeth-Ayerst, Philadelphia, Pa) every 4 to 6 hours. All Minnesota patients were admitted to the Phillips Eye Institute in-patient unit, and the Florida patients were admitted to a nearby hotel for the 24 hours following surgery and monitored by an ophthalmologist or specially-trained ancillary medical personnel.

Patient Questionnaires

During the first 24 hours, a subjective pain questionnaire was administered to each patient by the study personnel at 1 hour before surgery and then 30, 60, and 90 minutes and 2, 4, 6, 6.25, 6.5, 8, 10, 12, 12.25, 12.5, 18, 18.25, 18.5, and 24 hours postoperatively. A drop of the study medication was given immediately after the 6-, 12-, 18-, and 24-hour assessment. Thereafter, the patient completed the questionnaire at 12-hour intervals until reepithelialization. One questionnaire was categorical, allowing the patient to describe the eye pain as none, mild, moderate, or severe (Fig 1A). A second type of a questionnaire was a visual analog scale. The patient was asked to put an “X” on a horizontal line measuring 130 mm in length which showed a continuum of pain from “no pain” to “worst pain ever” (Fig 1B).

Other Subjective Descriptors

Patients were also asked at the same aforementioned times to describe as none, mild, moderate, or severe the following: foreign body sensation, light sensitivity, deep headache-like pain within the eye, stinging/burning, and itching. They were also asked to rate the temperature of the eye as normal, warm, hot, cool, or cold (Fig 1C).

Patient Global Assessments

At each 24-hour interval following surgery, patients were asked to make the following three assessments for the previous 24-hour period: 1) overall
satisfaction with the study medication, 2) overall amount of pain, and 3) overall relief from pain.

**STATISTICAL METHODS**

**Pain Scales**

Analyses were done at each time point, and for each rating scale, the following three derived efficacy variables were calculated:

1. Total pain intensity during the first 6 hours (Total 6);
2. Total pain intensity during the first 24 hours (Total 24); and
3. Maximum pain intensity during the first 24 hours (Max 24).

The total pain intensity during the first 6 hours was used to assess the effect of the first two drops of medication that were given immediately after surgery. Total 6 was obtained for each patient by taking a weighted sum of pain intensity scores during the first 6-hour postoperative period. All of these assessments were taken prior to the third drop given at 6 hours. A weight of 1/2 was used for the 30-minute, 1-hour, 1-hour-and-30-minute, and 2-hour scores, and a weight of 2 was used for the 4- and 6-hour scores. For a given assessment, the weight corresponds to the length of time in hours since the previous assessment. The formula used for calculating Total 6 is as follows:

\[
\frac{1}{2}(\text{score at hour } 0.5) + \frac{1}{2}(\text{score at hour } 1) + \frac{1}{2}(\text{score at hour } 1.5) + \frac{1}{2}(\text{score at hour } 2) + 2(\text{score at hour } 4) + 2(\text{score at hour } 6)
\]

The total pain intensity during the first 24 hours was used to assess the effect of the five drops of medication that were given during the first 24 hours after surgery. Total 24 was obtained for each patient by taking a weighted sum of pain intensity scores during the first 24-hour postoperative period. As with Total 6, these weights corresponded to the length of time in hours between two consecutive assessments. The maximum pain intensity during the first 24 hours was obtained for each patient by taking their highest pain intensity score over the first 24-hour period.

Differences between treatment groups, at each individual time point and for each of the three derived efficacy variables, were tested using the Wilcoxon rank sum test. Average ranks were used for all tied values. This is a nonparametric or "distribution free" test which makes minimal assumptions about the distribution of values within each group. This test was used because of the highly skewed distributions and apparent deviations from normality for many of the variables. The p-values were calculated using the normal approximation to the Wilcoxon test, with a continuity correction of 0.5 and a correction for tied values in the variance estimate. The Wilcoxon rank sum test was also used to analyze all other efficacy variables in this trial. All statistical tests performed were two-sided with a probability level of 0.050 used to declare statistical significance.

**Reepithelialization**

Some of the patients in the randomized trial were not seen daily for the study described above. As a result, epithelial healing rates could not be determined. To determine the daily rate of reepithelialization, a subsequent study was carried out using a separate group of 20 patients at the Phillips Eye Institute who were followed daily, and the epithelial defect measured using the micrometer on the slit-lamp microscope. These measurements were then converted into areas in square millimeters. A group of 10 consecutive myopic photorefractive keratectomy patients treated by one surgeon in our team was used as a control group. These patients had the same regimen as described above but did not receive a placebo vehicle or diclofenac. Another consecutive group of 10 myopic patients undergoing photorefractive keratectomy by another surgeon during that same period of time was treated as above but received diclofenac one drop immediately after surgery and three more times the day of surgery, and then four times a day until reepithelialization. All these patients underwent photorefractive keratectomy in an identical manner and received the bandage lens and other medications as described above.

**RESULTS**

All but one patient (Case 3) completed the study
as planned. No unmasking of patients during the trial occurred.

**Categorical Pain Scale**

The ocular pain assessment at 24 hours showed 62.5% of the diclofenac versus 25% of the placebo patients experiencing no pain. Close to one-third (31.3%) of the placebo group versus 6.3% of the diclofenac group experienced moderate pain (Fig 2). The time course of the development of pain is shown in Figure 3. The pain in the placebo group began within 1 hour and increased in intensity until 4 hours after the procedure. The pain experienced by the diclofenac group peaked at 1 hour and remained at an average "mild" level for the next 12 hours and then gradually declined until 24 hours. The more intense pain experienced by the placebo groups did not decline to the level of the diclofenac group until 72 hours. There was a statistically significant difference between the diclofenac and placebo groups beginning at 2 hours ($p = .050$) and continuing through 36 hours, except at hour 10 ($p = .066$) and hour 18 ($p = .061$). There were no statistically significant differences from 48 through 96 hours postoperatively.

**Visual Analog Pain Scale**

The results were similar to those of the categorical scale. Figure 4 shows the mean scores for both groups with significant differences appearing by 2 hours and continuing through 36 hours except at hour 10 ($p = .101$), hour 12 ($p = .057$), and hour 18 ($p = .266$).

**Total, Maximum Pain Intensity**

The derived variables which include the total pain
Table

Summary of Derived Efficacy Variables, Including Total Pain Intensity First 6 and 24 Hours and Maximum Pain Intensity First 24 Hours for Both the Categorical and Analog Scales

<table>
<thead>
<tr>
<th>Efficacy Variable</th>
<th>Median (Interquartile Range)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total pain intensity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>first 6 hours:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Categorical scale</td>
<td>5.5 (3.8 to 9.8)</td>
<td>10.8 (7.3 to 13.0)</td>
</tr>
<tr>
<td>Visual analog scale</td>
<td>89 (57 to 248)</td>
<td>347 (227-390)</td>
</tr>
<tr>
<td>Total pain intensity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>first 24 hours:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Categorical scale</td>
<td>20.5 (12.0 to 22.6)</td>
<td>34.0 (24.3 to 48.8)</td>
</tr>
<tr>
<td>Visual analog scale</td>
<td>565 (261 to 645)</td>
<td>1108 (772 to 1519)</td>
</tr>
<tr>
<td>Maximum pain intensity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>first 24 hours:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Categorical scale</td>
<td>2 (1 to 2)</td>
<td>3 (2 to 3)</td>
</tr>
<tr>
<td>Visual analog scale</td>
<td>61 (35 to 75)</td>
<td>90 (59 to 98)</td>
</tr>
</tbody>
</table>

*Statistically significant difference between DSO and PLA by the Wilcoxon rank sum test (2-sided). In all cases, the DSO group was favored.

Figure 5: Patient assessment of light sensitivity after photorefractive keratectomy. Represents time course to 96 hours after surgery. Points represent mean of 16 patients in each group through hour 48, after which the numbers decrease as patients heal. Extended bars represent SE.

intensity during the first 6 and 24 hours, and the maximum pain intensity during the first 24 hours, all statistically favored the diclofenac group (Table).

**Foreign Body Sensation**

Significant differences favoring the diclofenac group were observed at hours 6.25, 6.5, 12.5, 18.25, and 18.5 following dosing of the test medication.

**Light Sensitivity**

Significant differences favoring the diclofenac group were seen as early as 4 hours ($p < .001$) and continued through 48 hours (Fig 5).
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Figure 6: Patient assessment of stinging and burning after photorefractive keratectomy. Represents time course to 96 hours after photorefractive keratectomy. Points represent the mean of 16 patients in each group through hour 48, after which the numbers decrease as patients heal. Extended bars represent SE.

![Graph showing mean score over hours after surgery.]

Figure 7: Percent of patients taking 0, 1, 2, 3, or 4 oral narcotic pills during the first 24 hours after excimer photorefractive keratectomy.

![Bar chart showing percentage of patients by number of pills taken.]

Deep Headache-Like Pain Within Eye

Significant differences favoring the diclofenac group were observed at hours 1.5, 2, 4, 8, 10, 12.25, 12.5, 18.25, 18.5, and 48.

Stinging/Burning

Significant differences favoring the diclofenac group appeared at 2 hours (p = .050) and continued through 24 hours except at hour 12 (p = .055) and hour 18 (p = .068) (Fig 6).

Figure 8: Epithelial healing in a separate group of 20 patients undergoing myopic photorefractive keratectomy. Ten of the patients received diclofenac, fluorometholone, tobramycin, homatropine, and a bandage soft contact lens. The other 10 patients were treated in an identical manner but did not receive diclofenac. All points represent the mean of 10 patients. Extended bars represent SE.

![Graph showing remaining epithelial defect over hours after surgery.]

Oral Narcotics

The amount of pain medication was recorded for each patient and is shown in Figure 7. Seventy-five percent of the patients receiving diclofenac did not require any supplemental oral narcotic compared to 31.3% of placebo patients. The difference between the two groups was statistically significant (p = .015, rank sum).
Patient Global Assessments

All three patient global assessments were statistically significant favoring the diclofenac group at all four 24-hour intervals, except the overall amount of pain at 72 and 96 hours.

Itching, Temperature

There were no statistically significant differences between the two groups at any interval, except for itching at hour 24 ($p = 0.039$).

Refractive Results

There was no apparent difference in the postoperative refractive results at 1 month. The mean amount of correction in the diclofenac and placebo group was 5.35 and 5.71 D respectively, with no statistical difference between the two groups ($p$-value = .601, two-sample $t$-test).

Epithelial Healing

The mean residual epithelial defect for the diclofenac-treated eyes versus those which did not receive diclofenac are shown in Figure 8. All 20 patients were healed by day 3 in both groups. Although the diclofenac-treated group of patients had a smaller residual defect on day 1 ($p$-value = .014, two sample $t$-test), there were no significant differences on day 2 or 3 ($p$-values, .381 and .201, respectively).

Complications or Adverse Effects

There were no systemic complications or allergic reactions noted. Three patients in the study, one in the placebo group and two in the diclofenac group, experienced a delay in healing or corneal infiltrate. They are described in detail below:

Case 1. R.G., a 23-year-old male, underwent uneventful photorefractive keratectomy and was entered into the protocol. He was in the placebo group and was discharged from the Phillips Eye Institute 24 hours after surgery. The evening of discharge from the hospital, he noticed the treated eye was irritated and despite instructions to the contrary, removed the disposable soft lens. He did not call his surgeon but rinsed out his eye with a saline solution he kept at home and placed his own disposable contact lens in the eye. The eye became more irritated over the next 2 days, but the patient did not see his physician until day 3. At that time, the patient had a central epithelial defect with infiltrate. Corneal scrapings for culture showed no growth. The patient was started on ciprofloxacin 0.3% (Ciloxan, Alcon) hourly and the tobramycin was increased to q2h and then gradually tapered and discontinued over the next 10 days. Over the next week, the epithelium healed and the infiltrate gradually resolved. At 3 months after surgery, the patient had a subepithelial scar below the visual axis. The refraction was +0.50 sph and the best spectacle-corrected visual acuity was 20/25.

Case 2. M.C. is a 44-year-old woman who underwent photorefractive keratectomy in her left eye at the Phillips Eye Institute approximately 6 months prior to having her right eye treated. Diclofenac was used qid for 4 days with an uneventful postoperative course. The patient underwent uneventful photorefractive keratectomy in the right eye (preop -4.25 sph) as part of this protocol, and her epithelium was healed by the third day after surgery. At that time, the soft contact lens, diclofenac, and tobramycin were discontinued. On day 4, there was a 0.25-millimeter, circular, white epithelial and subepithelial infiltrate, concentric with the pupil which was 5.5 mm in diameter. It had the clinical appearance of an "immune ring."

The eye was not inflamed. Corneal scrapings for bacterial and fungal culture, as well as cultures of the test medication, were performed and showed no growth. The flurometholone was discontinued and 1% prednisolone acetate and ciprofloxacin drops q2h were begun. The infiltrate gradually resolved over the next 10 days with the epithelium remaining intact (Fig 9). A faint whitish subepithelial ring concentric to the pupil was still visible at 3 months. The central cornea had mild subepithelial haze typical of most postoperative photorefractive keratectomy patients at the same time interval. At 3 months, the refraction was -0.75 + 0.75 x 81. The uncorrected visual acuity was 20/30 and the best spectacle-corrected visual acuity was 20/25.

Case 3. G.E.R., a 52-year-old woman, underwent uncomplicated photorefractive keratectomy at the Eye Center of Florida on her other eye 6 months previously. Diclofenac was used and there were no adverse effects. She underwent photorefractive keratectomy as part of this protocol with a preoperative MR of -6.50 + 0.50 x 50 (best spectacle-corrected visual acuity 20/25) and received diclofenac. On the next day, visual acuity with soft contact lens was 20/30, and the patient tolerated the study medication well. That evening, the bandage lens came out.
The patient rinsed the lens with a saline solution she had at home and reinserted it. At that time she noted some increased pain but failed to notify any of the study personnel until day 4. At that time, there was a small central epithelial defect remaining. The bandage lens was replaced and she was continued on FML g2h, diclofenac qid and tobramycin qid. On day 6, there was still a small but persistent epithelial defect. The bandage soft contact lens and diclofenac were discontinued. The patient was patched with tobramycin ophthalmic ointment (Alcon), and she was seen again on day 8 with a pinpoint epithelial defect. The patch was reapplied with a 24-hour collagen shield. At day 11, confluent superficial punctate keratitis was noted without epithelial defect. A bandage soft contact lens was reinserted and topical ciprofloxacin was started. On day 14, a definite infiltrate was noted in the area of prior epithelial defect. Ciprofloxacin was increased to q1h and erythromycin ophthalmic ointment qid (Ilotycin, Eli Lilly, Indianapolis, Ind) was started. Corneal cultures were negative. This gradually resolved with subepithelial anterior stromal scarring. At 3 months, best spectacle-corrected visual acuity was 20/60 with \(-1.00 + 1.25 \times 009\).  

**DISCUSSION**

Diclofenac sodium solution has been approved for ophthalmic use in the U.S. for control of inflammation after cataract surgery since 1991. It belongs in a class of drugs which are cyclo-oxygenase inhibitors, which includes flurbiprofen (Ocufen, Allergan), Suprofen (Profenal, Alcon), and most recently ketorolac (Acular, Allergan). Flach reviewed the ophthalmic uses of cyclo-oxygenase inhibitors, which include the control of postoperative inflammation following cataract surgery, the treatment of cystoid macula edema, and the intraoperative inhibition of miosis. Cyclo-oxygenase inhibitors produce some of their effect by inhibiting the production of prostaglandins by blocking the transformation of arachidonic acid to prostaglandins. Arachidonic acid is the precursor for a number of inflammatory mediators, including prostaglandins, thromboxanes, and leukotrienes. Prostaglandins, including prostaglandin E₂ and leukotrienes are generally thought responsible for the classic signs of inflammation, such as erythema, increased vascular permeability, edema, and pain. Diclofenac is also thought to partially inhibit leukotrien production, not by inhibiting lipoxigenase but by decreasing arachidonic acid levels by shunting arachidonic acid to the triglyceride pool and reducing its bioavailability. Diclofenac significantly reduces prostaglandin E₂ levels in rabbit corneas undergoing photorefractive keratectomy. Topical corticosteroids also inhibit prostaglandin biosynthesis at a more preliminary location in the pathway due to inhibition of phospholipase A₂, which blocks arachidonic acid from the phospholipase pool. The combined use of a corticosteroid such as fluorometholone and a cyclo-oxygenase inhibitor such as diclofenac, which in combination block these pathways in several locations, may act in a synergistic manner to reduce the inflammatory response to excimer photorefractive keratectomy. It has recently been demonstrated that there may not be a need for postoperative corticosteroids after photorefractive keratectomy. These authors found no significant effect from corticosteroids on long-term corneal haze or refractive error, but did not comment on the effects of postoperative pain. These effects may be laser specific and caution should be used in eliminating corticosteroid usage with replacement by a topical cyclo-oxygenase inhibitors in the early postoperative period. The early infiltration of polymorphonuclear cells (PMNs) seen after epithelial removal and in ultraviolet radiation-induced keratitis may not be controlled by cyclo-oxygenase inhibitors alone. In an experimental *Pseudomonas* keratitis model, it has been demonstrated that cyclo-oxygenase inhibitor may increase leukotriene B₄ formation and result in increased PMN infiltration with resultant increase of corneal ulceration. Blocking cyclo-oxygenase alone may lead to an increased amount of arachidonic acid which then provides increased substrate into the lipoxygenase pathway and the formation of leukotrienes. These leukotrien compounds are chemotactic for PMNs which can cause inflammation and sensitization of pain receptors.

The pain after refractive keratotomy procedures such as radial keratotomy usually peaks at 4 to 6 hours and has been described as mild and a foreign body like sensation. It is rarely severe. The pain after photorefractive keratectomy is much more severe and is akin to the pain of a severe corneal abrasion, erosion, or UV keratitis. Patients usually describe the pain as severe, sometimes throbbing in nature. It is usually associated with a burning, stinging sensation, as well as tearing and nasal congestion. Some have characterized this pain as the worst they ever experienced. The use of bandage soft contact lenses immediately after surgery improves patient comfort; however, a significant number of patients experience moderate pain as demonstrated by our placebo-treated patients. The use of narcotics has significant drawbacks including gastrointestinal complaints, lethargy, and the inability to return to work or safely operate a motor vehicle.

Recently, Herschel et al found similar reductions in pain in postoperative photorefractive keratectomy patients. In their study, patients received either fluorometholone, diclofenac, or artificial tears. All patients received bandage soft contact lenses. The diclofenac treated group had significantly less pain. There may be a number of reasons for the intense...
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The primary cause may be the mechanical disruption of the epithelium and the complex of corneal nerve endings over a wide area (36 to 49 mm²) of ablated cornea. Other physical effects of the excimer include UV keratitis, thermal effects, and acoustic shock wave damage. Ultraviolet radiation exposure of the cornea reduces a UV keratitis with tearing, stipping, hyperemia, haze, discharge, photophobia, blepharospasm, and pain. Rabbit corneas exposed to subablative exposures of 193-nanometer excimer ultraviolet radiation demonstrated a UV keratitis. Some of these effects may also have been secondary to secondary fluorescence from longer UV wavelengths. It is thought that 193-nanometer excimer produces its precise removal of tissue by directly breaking molecular bonds (photoablation) and ejection of tissue with each pulse. Although the process is predominantly photochemical, thermal effects are present in adjacent tissues. Bende et al found a temperature rise in the cornea from 7.5° to 15° C in an experimental model. This temperature rise may injure nerve end receptors. The laser pulses can also produce acoustic shock waves which can damage tissues.

These physical stimuli, which disrupt cell membranes, may release a number of chemical factors such as prostaglandins, substance P, histamine, epithelial neurotropic factors, and other chemicals. Some of these chemical mediators have been shown to produce pain in a variety of tissues. It is likely that diclofenac produces its effect in part by blocking prostaglandin production after the physical trauma. In rabbit eyes, corneal sensitivity is depressed for 36 hours after topical diclofenac. Corneal nerve conduction was depressed after corneal stimulation in rabbits after topical diclofenac.

It was not possible to determine the reepithelialization rates in this study as some of the patients were not seen daily. In the study of epithelial healing performed subsequently, we found no difference after the first postoperative day in the healing rates when a soft bandage lens was used with diclofenac. It is not known if the use of bandage soft contact lenses promotes or inhibits healing. It should be noted that corticosteroids, fluribiphen, and diclofenac each inhibited epithelial healing after mechanical scrape injuries to the rabbit cornea.

Rapid reepithelialization after excimer photorefractive keratectomy is desirable for a number of reasons including the elimination of pain and discomfort, the reduced risk of infection, and the more rapid improvement of visual acuity. It is not known which postoperative regimen, ie, bandage lenses, collagen shields, or patching aid in achieving the quickest reepithelialization. The use of a bandage soft contact lens may predispose the eye to a higher risk of bacterial keratitis and delayed healing. This risk may be offset by the more frequent application of antibiotics which can be achieved with a non-patched eye. It is our clinical impression that the immediate use of a bandage soft contact lens improves patient comfort and promotes an earlier return of visual acuity. The main disadvantage of bandage soft contact lens is the difficulty in fitting the ablated cornea. The lenses are frequently tight when seen the next day and it is not unusual to see mild striate folds in the cornea. If the lens is too tight or has significant deposits, it should be replaced or discontinued. The patients should be strictly cautioned against replacing the lens themselves at home if it is displaced. This is the probable source of the infiltrates in patient R.G. In over 750 cases of photorefractive keratectomy and phototherapeutic keratectomy at the Phillips Eye Institute, there has been one other case of bacterial keratitis, possibly caused by the patient's use of a contaminated contact lens solution at home. The best way to reduce healing complications is to follow patients daily until the epithelium heals.

The etiology of the infiltrate in patient M.C. is not understood. She did not have excessive pain and denied using diclofenac more than qid. Two cases of similar circular "immune rings" were seen in patients who did not receive diclofenac but did have bandage soft contact lenses and fluorometholone (Eiferman R, personal communication, 1992). The etiology of the delayed healing and keratitis seen in patient G.E.R. is not known. The use of the diclofenac or the bandage soft contact lens must be considered.

The frequent application of fluorometholone, diclofenac, and tobramycin on a deepithelialized eye with a bandage soft contact lens may be a source of corneal toxicity and delayed healing. There has recently been an observation that topical diclofenac, when used hourly after surgery, produces delayed epithelial healing and corneal infiltrates in some patients. There have been scattered similar observations of toxicity from Europe using the thimersol-preserved preparation; however, the dosage and clinical details are not known (personal communication, Tennant J, Trokel S, 1993). The U.S. formulation of diclofenac contains sorbic acid as the preservative while the European formulation (Naclof) contains thimerosal. Caution must be used before extrapolating conclusions from these data to other formulations of diclofenac and other cyclo-oxygenase inhibitors.

The optimal dosage of both diclofenac and fluorometholone is not known but four times a day dosing for 3 to 4 days seems to work well and less frequent dosing should be investigated. Reduction of potential corneal toxicity from the multiplicity of drops used postoperatively may be possible with the use of nonpreserved formulations of these drugs. At present, these drugs are not available in a nonpreserved...
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sterile unit dose, except in the United Kingdom where a nonpreserved form of diclofenac was introduced in January 1993.

In summary, this study demonstrates that the immediate postoperative use of diclofenac, combined with topical fluoromethalone and a bandage contact lens, significantly reduces the pain, burning/stinging, and light sensitivity after excimer photorefractive keratectomy and reduces the need for narcotics. The long-term effects of diclofenac on wound healing and refractive change are not yet known, and the optimal dosage and timing of treatment remain to be determined. To avoid the potential for corneal toxicity, there is little apparent need to apply diclofenac more than qid or longer than 48 to 72 hours on a deep epithelialized cornea after surgery. These preliminary studies are encouraging and warrant further investigation.

REFERENCES