Nepafenac Ophthalmic Suspension 0.3% for the Management of Ocular Pain After Photorefractive Keratectomy

George A. Kontadakis, MD, PhD; Konstantina G. Chronopoulou, MD; Rodoula Tsopouridou, MSc; David Tabibian, MD; George D. Kymionis, MD, PhD

ABSTRACT

PURPOSE: To investigate the effect of nepafenac 0.3% in a once daily dosage regarding pain and healing after photorefractive keratectomy (PRK).

METHODS: This was a prospective, comparative, contralateral randomized study of 35 patients undergoing PRK for the correction of low to moderate myopia and myopic astigmatism. After randomization, patients received nepafenac 0.3% ophthalmic suspension once daily in one eye (nepafenac 0.3% group) and nepafenac 0.1% ophthalmic suspension three times a day in the other eye (nepafenac 0.1% group) until the second postoperative day. Pain was evaluated every 2 hours on the day of the operation and then once daily using a scale ranging from 0 to 4. Patients were then examined at 2 weeks and 1, 3, 6, and 12 postoperative months. Visual acuity and subepithelial haze were also assessed.

RESULTS: No differences were detected between groups in pain scores, subepithelial haze scores, or visual acuity. Refractive predictability was also similar.

CONCLUSIONS: Nepafenac 0.3% ophthalmic suspension in a daily regimen after PRK seems to be an effective treatment for pain and ocular discomfort with effects similar to the 0.1% suspension.

PATIENTS AND METHODS

This was a prospective, comparative, contralateral randomized study of patients undergoing PRK for the correction of low to moderate myopia and myopic astigmatism. Patients were recruited from a continuous cohort of patients seeking laser surgery for the correction of their refractive error. All patients underwent a full preoperative examination and those eligible were scheduled to undergo PRK. Criteria for inclusion in the study were age of at least 19 years, central corneal thickness of more than 500 µm suitable for simultaneous bilateral PRK, myopia up to -5.00 diopters (D), astigmatism up to -3.00 D, and no other corneal pathology evident on clinical evaluation or topography. Exclusion criteria were history of previous ocular surgery or trauma, previous corneal infection, greater than 2.00 D difference in spherical equivalent between eyes, recent (within 6 months) use of ocular medication, and dry eye or any other ocular pathology apart from refractive error. Additionally, patients with previous allergic reaction to aspirin or topical NSAIDs, collagen vascular disease, diabetes mellitus, and pregnancy or lactation were excluded from the study. Patients with intraoperative complications or poor compliance with postoperative instructions were also excluded from the study.

The protocol was approved by the Institutional Review Board of Athens University. Patients considered eligible were thoroughly informed about the context of the study and gave an informed consent according to the tenets of the Declaration of Helsinki.

CLINICAL EVALUATION

The preoperative evaluation of our patients consisted of corneal topography and tomography (Pentacam; Oculus Optikgeräte GmbH, Wetzlar, Germany), uncorrected (UDVA) and corrected (CDVA) distance visual acuity assessment with manifest refraction, slit-lamp biomicroscopy, assessment of tear film break-up time, Schirmer’s I test with anesthesia and corneal staining with fluorescein, application tonometry, and ultrasound pachymetry. All examinations were conducted with the reported order. Patients were instructed to discontinue use of contact lenses at least 2 weeks before the preoperative visit to avoid possible effects on the corneal surface.

SURGICAL TECHNIQUE

All patients underwent PRK with the Allegretto WaveLight excimer laser (WaveLight AG, Erlangen, Germany). After instillation of topical preoperative hydrochloride 0.5% (Alcaine; Alcon Laboratories, Inc., Fort Worth, TX), 20% alcohol was applied to an 8-mm diameter well for 20 seconds and then rinsed from the eye using balanced salt solution (BSS; Alcon Laboratories, Inc.). Epithelium was then removed with a Merocel sponge (Beaver-Visitec International, Inc., Waltham, MA) within the 8-mm diameter. Subsequently, excimer laser ablation was performed and mitomycin C (MMC) was applied to the corneal surface with a soaked corneal sponge for 12 seconds in all cases. At the end of each procedure, a combination steroid and antibiotic drop (Tobradex; Alcon Laboratories, Inc.) was administered in all patients and a silicon-hydrogel bandage contact lens (Lotrafilcon B, Air Optix, Ciba Vision, Duluth, GA; 14-mm diameter, 8.6 base curvature, Dk = 140 barrers) was applied and kept in place until full corneal reepithelialization occurred.

POSTOPERATIVE MEDICATION AND EVALUATION

Patients were assigned to receive nepafenac 0.3% ophthalmic suspension once daily in one eye (nepafenac 0.3% group) and nepafenac 0.1% ophthalmic suspension three times a day in the other eye (nepafenac 0.1% group) until the second postoperative day. Eyes were randomly allocated to the study or control group. Postoperative treatment in nepafenac 0.3% and nepafenac 0.1% group eyes started immediately postoperatively and included (apart from the respective nepafenac suspension) a drop of Tobradex four times a day and preservative-free artificial tears (Thealoz-Duo; Thea Laboratories, Clermont-Ferrand, France) every 2 hours until reepithelialization. No oral analgesics was prescribed with the consent of the patients once the purpose of the study had been explained. If patients were experiencing intolerable pain, oral analgesics were provided and the patient was excluded from the study.

After reepithelialization, a course of fluorometholone 0.1% eye drops (FML; Allergan, Inc., Irvine, CA) with weekly tapering was applied for 1 month, and patients were advised to use preservative-free artificial tears for the first 6 postoperative months or at the patient’s discretion.

All procedures were performed in our center by the same surgeon (GDK).

Patients were examined twice daily (morning and afternoon) until the removal of the therapeutic lens. Early follow-up included recording of UDVA, subjective pain score, and biomicroscopy. Pain scores were evaluated according to a predetermined scale ranging from 0 to 4 (0 = no discomfort or pain; 1 = mild discomfort; 2 = moderate burning pain; 3 = burning pain requiring oral medication [Mesulid; Boehringer Ingelheim GmbH, Ingelheim, Germany]; 4 = severe constant or sharp pain). On the day of the operation, patients were asked to record pain scores every 2 hours for a total of five consecutive times. The same scale was used in the following daily visits and a single pain and discomfort score was obtained from each enrolled patient.
All enrolled patients were further examined at 2 weeks and 1, 3, 6, and 12 months postoperatively. The assessment included UDVA and CDVA, manifest refraction, biomicroscopy, topography, and applanation tonometry. Subepithelial haze was graded according to a predetermined scale (0 = clear cornea; 1 = trace haze that could be seen only with broad beam illumination; 2 = mild haze visible by slit-beam illumination; 3 = moderate haze somewhat obscuring iris details; and 4 = marked haze obscuring iris detail).

**Statistical Analysis**

Pain scores, line gain or loss, and haze scores were evaluated with the use of the Pearson chi-square test with contingency tables. Whenever the sample did not meet the requirement that 80% of the cells have expected values of 5 or more, the likelihood ratio chi-square test was used. The paired samples t test was used to compare UDVA and CDVA between the two groups. A P value of less than .05 was considered statistically significant. Statistical analysis was performed using SPSS software (version 20.0; SPSS, Inc., Chicago, IL).

**RESULTS**

Thirty-five patients (18 men, 17 women) were included in our study. Average age was 28 ± 5.07 years (range: 19 to 36 years). Average spherical equivalent in all eyes was -4.08 ± 1.02 D (range: -2.00 to -6.00 D). Patient demographics, spherical equivalent refraction, and CDVA for each group are presented in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total</th>
<th>Nepafenac 0.3% Group</th>
<th>Nepafenac 0.1% Group</th>
<th>Pb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>28 ± 5.07 (19 to 36)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myopia (D)</td>
<td>3.50 ± 1.05 (1.50 to 5.00)</td>
<td>3.52 ± 1.08 (1.50 to 5.00)</td>
<td>3.48 ± 1.05 (1.50 to 5.00)</td>
<td>.49</td>
</tr>
<tr>
<td>Myopic astigmatism (D)</td>
<td>1.15 ± 0.55 (0.00 to 2.50)</td>
<td>1.14 ± 0.57 (0.00 to 2.25)</td>
<td>1.16 ± 0.54 (0.00 to 2.50)</td>
<td>.65</td>
</tr>
<tr>
<td>Spherical equivalent (D)</td>
<td>4.08 ± 1.02 (2.00 to 6.00)</td>
<td>4.09 ± 1.05 (2.00 to 5.88)</td>
<td>4.07 ± 0.99 (2.50 to 6.00)</td>
<td>.65</td>
</tr>
<tr>
<td>CDVA (logMAR)</td>
<td>-0.003 ± 0.027 (-0.079 to 0.055)</td>
<td>-0.006 ± 0.03 (-0.079 to 0.055)</td>
<td>0.000 ± 0.024 (-0.057 to 0.046)</td>
<td>.46</td>
</tr>
</tbody>
</table>

D = diopeters; CDVA = corrected distance visual acuity. Values are presented as mean ± standard deviation (range). *Paired samples t test.

**Epithelial Healing Time**

Time to complete reepithelialization showed no difference between the two groups. In both groups, most eyes had completely healed postoperatively at day 3, apart from 9 eyes that healed at day 4. The nepafenac 0.3% group eye healed on the third day and the nepafenac 0.1% group eye on the fourth day in 5 patients (14.3%). The nepafenac 0.1% group eye healed on the third day and the nepafenac 0.3% group eye on the fourth day in 4 patients (11.4%).

**Pain Scores**

Pain scores of both groups are presented in Table 2. No statistically significant differences were found in pain scores of both groups at all time points.

**Haze Scores**

There was no significant difference in corneal haze between the two groups at any postoperative interval (P > .05, chi-square test). At 3 months, 1 patient (3%) had moderate haze (stage 3) in both eyes, which improved to trace haze at 6 months. At 1 month, 5 patients (14.28%) had more haze in the nepafenac 0.3% group eye and 6 patients (17.14%) had more haze in the nepafenac 0.1% group eye.

**Visual Acuity and Refractive Results**

No statistically significant difference was found in UDVA and CDVA at any time point between our groups. At the last follow-up visit, UDVA was 0.002 ± 0.048 logMAR in the nepafenac 0.3% group and 0.008 ± 0.059 logMAR in the nepafenac 0.1% group (P = .66, paired samples t test). CDVA at 12 months was 0.013 ± 0.033 logMAR in the nepafenac 0.3% group and 0.008 ± 0.033 logMAR in the nepafenac 0.1% group (P = .54, paired samples t test). No eye lost any line of CDVA in both groups, whereas 3 eyes in the nepafenac 0.3% group (8.6%) and 4 eyes in the nepafenac 0.1% group (11.4%) gained one line of CDVA at 1 year postoperatively (P > .05, chi-square test).

Refractive predictability was similar in both groups. At 1 year postoperatively, 88.5% (31 eyes) of each group was within ±0.50 D of target refraction, whereas all (100%) eyes were within ±1.00 D of target refraction.

**DISCUSSION**

Postoperative discomfort or pain is still considered a bothersome side effect of PRK and a deterrent...
for performing the procedure to numerous patients. Some patients who are not ideal candidates for LASIK postpone PRK due to the fear of postoperative pain. Methods to relieve postoperative pain include different techniques of epithelium removal, such as LASEK, epi-LASIK, phototherapeutic keratectomy, use of chilled balance salt solution postoperatively, bandage contact lenses and topical medication, and NSAIDs. The latter are the main methods to overcome this issue.

The mechanism of action of NSAIDs in the treatment of pain after refractive surgery involves a specific molecular pathway of pain. PRK causes injury to the corneal sensory afferent nerves with the release of pain-inducing inflammatory factors such as prostaglandins and neuropeptides. NSAIDs target COX, the enzyme that catalyzes the synthesis of prostaglandins from arachidonic acid. By inhibiting prostaglandin biosynthesis, NSAIDs exhibit potent analgesic, anti-inflammatory, and antipyretic effects. Although the link between prostaglandins and hyperalgesia is not fully understood, it is believed that prostaglandins cause hyperalgesia by sensitizing pain nerve endings. Other NSAIDs that have been tried for pain control after PRK include ketorolac tromethamine, diclofenac sodium, flurbiprofen sodium, and indomethacin. In contrast to other ocular NSAIDs, nepafenac is a prodrug that rapidly penetrates the cornea and is deamminated by intraocular hydrolases within ocular tissues to form the active metabolite amfenac. Nepafenac and amfenac are potent inhibitors of the COX enzymes COX-1 and COX-2.

This study demonstrated that the new nepafenac 0.3% suspension in a once daily dosage is non-inferior in reducing pain in comparison to nepafenac 0.1% three times a day. Pain scores were similar in both groups at all time points postoperatively. The efficacy of nepafenac 0.1% for the treatment of pain after refractive surgery has been already established in previous studies and also has been compared to that of other NSAIDs in studies, which mostly demonstrated similar values. In a randomized, double-masked study of 132 eyes undergoing PRK, Caldwell and Reilly concluded that nepafenac 0.1% in comparison to placebo significantly reduced postoperative pain immediately following surgery without having a significant adverse effect on epithelial healing time, despite a larger defect in the nepafenac group on the second postoperative day. Donnenfeld et al. compared nepafenac 0.1% with ketorolac 0.4% in a randomized, double-masked, contralateral eye study of 40 patients undergoing bilateral PRK and concluded that both had similar results in terms of pain, although the nepafenac group demonstrated an overall superior comfort score on the third postoperative day. Epithelium healing time in this study was similar in both groups. Durrie et al. compared nepafenac, ketorolac, and brofenac, and showed a slight superiority of nepafenac.

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Group</th>
<th>Pain Score [n (%)]</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Nepafenac 0.3%</td>
<td>14 (40%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nepafenac 0.1%</td>
<td>15 (43%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Nepafenac 0.3%</td>
<td>13 (37%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nepafenac 0.1%</td>
<td>17 (49%)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Nepafenac 0.3%</td>
<td>16 (51%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nepafenac 0.1%</td>
<td>17 (49%)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Nepafenac 0.3%</td>
<td>18 (51%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nepafenac 0.1%</td>
<td>17 (49%)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Nepafenac 0.3%</td>
<td>18 (51%)</td>
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<tr>
<td></td>
<td>Nepafenac 0.1%</td>
<td>17 (49%)</td>
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</tr>
<tr>
<td>24</td>
<td>Nepafenac 0.3%</td>
<td>23 (66%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nepafenac 0.1%</td>
<td>24 (68%)</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>Nepafenac 0.3%</td>
<td>28 (78%)</td>
<td></td>
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<tr>
<td></td>
<td>Nepafenac 0.1%</td>
<td>24 (68%)</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>Nepafenac 0.3%</td>
<td>30 (66%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nepafenac 0.1%</td>
<td>32 (68%)</td>
<td></td>
</tr>
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</table>

<sup>a</sup>Likelihood ratio chi-square test.
on postoperative days 1 and 2, Colin and Paquette\textsuperscript{12} compared nepafenac 0.03%, nepafenac 0.1%, and diclofenac, and showed superiority of the 0.1% suspension to the 0.03%, but a non-significant difference with diclofenac. In terms of reepithelialization time, nepafenac had a faster healing time in comparison to diclofenac, without the difference being statistically significant.

In our study, epithelial healing time in both groups was similar. The reepithelialization rate after careful removal of central epithelium and the use of bandage contact lenses in healthy eyes in our study was rapid and not differently affected by NSAIDs. As previously described, most of the studies failed to demonstrate a significant difference in epithelium healing time between nepafenac and other NSAIDs or placebo.\textsuperscript{3,9-12} The exception to this is a study by Trattler and McDonald\textsuperscript{13} that demonstrated a delayed reepithelialization in eyes treated with nepafenac versus those treated with ketorolac, although the difference was not statistically significant. Additionally, in that study the eyes treated with nepafenac seemed to have more haze than the eyes treated with ketorolac, a finding that was not confirmed in other studies. In our study, we did not observe such a complication, although a control group treated with placebo or an agent other than nepafenac is necessary to perform a comparison. A possible reason for this may be the use of MMC, which was cathartic in our study according to our practice, in contrast to the study by Trattler and McDonald,\textsuperscript{13} where MMC was used only in one patient with ablation of more than 75 µm.

Apart from haze, other significant complications have also been reported with the use of NSAIDs. Common ocular side effects of topical NSAIDs include transient burning, stinging, and conjunctival hyperemia.\textsuperscript{1,3} Additional significant side effects are superficial punctate keratitis, corneal infiltrates that might reduce visual acuity, and epithelial defects.\textsuperscript{14,15} Even corneal melting has been reported with the use of NSAIDs after refractive and corneal surgery.\textsuperscript{16-18} Delayed reepithelialization, epithelial defect, burning sensation, and subepithelial infiltrates are side effects that have been reported with the use of nepafenac. Corneal melting has been reported in a single case of a patient treated with nepafenac after PRK but was associated with a frequent dosing of one drop every 2 hours.\textsuperscript{19} Because nepafenac is the only topical NSAID delivered in a suspension form, this may increase the amount of time the drug remains in contact with the epithelium and thus may increase toxicity. On the other hand, comparative studies with other agents and with placebo do not prove a superiority against nepafenac in terms of safety.\textsuperscript{3,9-12,20,21}

The new nepafenac 0.3% suspension has a higher concentration of the active molecule (nepafenac 0.3%) and can be used in a once daily dosage regimen. Additionally, it has a reduced particle size compared with nepafenac 0.1%, which increases the surface area for dissolution, and added guar, a retention agent that enhances the bioavailability of nepafenac in the eye compared to nepafenac 0.1%. In a randomized double-masked vehicle- and active-controlled phase 3 study, Modi et al.\textsuperscript{22} demonstrated the efficacy of the 0.3% suspension in reducing pain and inflammation after cataract surgery in comparison to vehicle-treated eyes, and the non-inferiority in comparison to the 0.1% suspension. According to that study, the reduced dosage regimen offers the advantage of better patient compliance without reducing the clinical benefits of the agent. In our study, we also observed a similar effect of nepafenac 0.3% to nepafenac 0.1% suspension in pain and epithelial healing after PRK, thus confirming the non-inferior clinical efficacy of the 0.3% suspension.

Nepafenac 0.3% ophthalmic suspension in a once daily regimen after PRK seems to be an effective treatment for pain and ocular discomfort. Treated eyes had a similar response in terms of pain score when compared with the 0.1% suspension and no difference in healing time. A possible advantage of the lower dosage regimen in comparison to the 0.1% suspension in terms of patient compliance favors the use of the 0.3% suspension, especially in patients after PRK.

**AUTHOR CONTRIBUTIONS**

Study concept and design (GDK); data collection (GAK, KGC, RT); analysis and interpretation of data (GAK, DT, GDK); writing the manuscript (GAK, KGC, RT, GDK); critical revision of the manuscript (DT, GDK); statistical expertise (GAK); administrative, technical, or material support (RT); supervision (GDK)

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