Effect of nepafenac sodium 0.1% on delayed corneal epithelial healing and haze after photorefractive keratectomy

Retrospective comparative study

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PURPOSE: To assess delayed epithelialization and corneal haze related to nepafenac ophthalmic suspension 0.1% (Nevanac) use after photorefractive keratectomy (PRK).

SETTING: Private practice, Beverly Hills, California, USA.

METHODS: This retrospective comparative chart review comprised 69 eyes (44 patients) that were divided into 2 treatment groups that were not statistically significantly different in age or preoperative spherical equivalent. The nepafenac group consisted of 34 eyes (22 patients) that received nepafenac 0.1%, moxifloxacin, and fluorometholone postoperatively. The non-nepafenac group included 35 eyes (22 patients) that received moxifloxacin and fluorometholone only. Patients were seen between 1 day and 5 days postoperatively for evaluation of epithelial healing and haze formation. Delayed epithelialization was defined as healing after day 5. All patients were followed for haze formation for a minimum of 3 months.

RESULTS: Statistical analysis showed no difference between the nepafenac and non-nepafenac groups in delayed epithelialization ($P = .61$, chi-square test). Neither group had significant corneal haze.

CONCLUSION: Nepafenac did not appear to delay corneal epithelial healing or contribute to haze formation after PRK.

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Photorefractive keratectomy (PRK) treats myopia, hyperopia, astigmatism, or a combination by reshaping the deepithelialized cornea using an excimer laser. Compared with laser in situ keratomileusis, PRK results in prolonged wound healing and increased haze formation; however, the visual outcomes 6 months postoperatively are comparable.[1–5]

Nonsteroidal antiinflammatory drugs (NSAIDs) are commonly used for the management of postoperative pain and inflammation. Nevanac (nepafenac ophthalmic suspension 0.1%) is a prodrug used by some practitioners off-label for post-PRK relief. It penetrates the cornea and is converted by ocular tissue hydrolases into an NSAID, amfenac.[6] Amfenac inhibits the action of prostaglandin H synthase, reducing prostaglandin production, and therefore decreases inflammation.

A recent study[7] found that the use of nepafenac after PRK delays epithelial closure and increases the risk for haze formation. We performed this study to evaluate the effect of nepafenac on delayed reepithelialization, defined as epithelial defect healing after 5 days postoperatively, and on postoperative corneal haze.

PATIENTS AND METHODS

This retrospective chart review comprised 69 eyes (44 patients) that were divided into 2 treatment groups that were not statistically significantly different in age or preoperative spherical equivalent (SE). Controls (non-nepafenac group) were chosen to match the age and SE in the treatment group

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(nepafenac group). No patient had collagen, vascular, autoimmune, or immunodeficiency disease; a history of herpetic keratitis; or was pregnant or nursing.

The same surgeon (B.B.W.) performed all PRK procedures. A 7.0 mm optical zone marker was apposed to the corneal epithelium; 20% ethanol was carefully placed in the well of the optical zone marker for 20 seconds. The ethanol was removed with a surgical spear, and the cornea was copiously irrigated. An epitheliorhexis of the central epithelium was performed. The surface was dried with a surgical sponge. A LADAR4000 excimer laser (Alcon) was used for ablations. A circular sponge soaked with mitomycin-C (MMC) 0.02% was placed on the central cornea for 30 seconds and then removed, and the cornea was copiously irrigated with balanced salt solution (BSS). A bandage contact lens (SofLens 66, Bausch & Lomb) was placed on the eye. Extend absorbable synthetic punctal plugs (Odyssey Medical) were inserted in the inferior punctum.

The patients were transferred to the recovery room where 1 drop of moxifloxacin (Vigamox), fluorometholone (Flarex), and Nevanac were instilled in the nepafenac group, followed by Nevanac twice a day for 2 days, Vigamox 4 times a day for 1 week, and Flarex 4 times a day for the first week and twice a day for the second week. In the non-nepafenac group, only Vigamox and Flarex were instilled, followed by a regimen of Vigamox 4 times a day for 1 week and Flarex 4 times a day for the first week and twice a day for the second week. All patients were prescribed topical diluted proparacaine for discomfort for the first 2 days. In addition, patients used 3 flaxseed capsules (each 1000 mg) daily for 3 months.

Patients were seen by the surgeon who performed the PRK procedures between 1 day and 5 days postoperatively to assess for reepithelialization and corneal haze formation. Reepithelialization was graded from 0 (no epithelial defect) to 4 (complete epithelial defect). Haze was scored from 0 (totally clear), 0.5 (trace of opacity), and 1 (mild) to 4 (completely opaque cornea).[8] When the epithelium had completely healed, the bandage contact lens was removed. Delayed epithelialization was defined as epithelial healing at day 5. If an epithelial defect was present at day 5, as confirmed with fluorescein, the bandage lens was replaced and the patient was asked to return the next day for a repeat assessment and followed until epithelial healing was complete. All patients were followed for at least 3 months postoperatively for assessment of corneal haze as haze has been reported to occur by 2 weeks with nepafenac.[7]

The Student *t* test was used for between-group comparisons for numeric variables. The chi-square (χ^2) test with 1 degree of freedom and Fisher exact test (for cell count <5) were used for categorical variables. Subgroup analysis was also performed to assess whether myopic patients or hyperopic patients had haze or delayed epithelialization.

Statistical significance was set at 95% confidence levels for all tests. Statistical computing was performed using StatView SE (Abacus Concepts, Inc.) and Excel (Microsoft Corp.). Sample size power calculations showed that a sample size of 9 was required to detect a mean difference of 0.5 days ($\alpha = 0.05$, power = 0.8).

RESULTS

Patient Demographics

The nepafenac group consisted of 34 eyes (22 patients), 18 in men and 16 in women. The mean age of the patients was 39.27 years ± 12.59 (SD). The mean preoperative SE in hyperopic eyes was +1.53 ± 1.3 diopters (D) (range −0.75 to +2.75 D) and in myopic eyes, −3.75 ± 2.1 D (range −1.38 to −7.80 D).

The non-nepafenac group included 35 sequential eyes (22 patients), 14 in men and 21 in women. The mean age of the patients was 41.37 ± 11.94 years. The mean preoperative SE in hyperopic eyes was +1.58 ± 1.7 D (range +0.25 to +3.38 D) and in myopic eyes, −5.40 ± 3.9 D (range −1.50 to −13.25 D).

The myopic eyes in the nepafenac and non-nepafenac groups were not statistically significantly different in age ($P = .23$) or SE ($P = .08$). There was also no statistically significant between-group difference in hyperopic eyes in age ($P = .13$) or SE ($P = .99$).

Epithelial Healing

Complete epithelial healing occurred after a mean of 4.8 ± 1.1 days in the nepafenac group and 5.2 ± 0.8 days in the non-nepafenac group. Seven eyes (20.6%) in the nepafenac group and 9 eyes (25.7%) in the non-nepafenac group had epithelial healing after 5 days postoperatively. There was no statistically significant difference between the 2 groups (Table 1).

Subgroup analysis of myopic eyes and hyperopic eyes showed no difference in epithelial healing between the nepafenac group and the non-nepafenac group ($P = .49$ and $P = .99$, respectively). Table 2 shows the results of the Fisher exact test in myopic eyes and Table 3, in hyperopic eyes.

Corneal Haze

No significant haze occurred in either group. The mean haze score at the final follow-up was 0.13 in the nepafenac group and 0.10 in the non-nepafenac group. This was not statistically significant ($P = .68$). The between-group difference in haze scores at 7, 30, and 90 days was also not statistically significant ($P = .32$, $P = .67$, and $P = .73$, respectively (Figure 1). There was no significant difference between groups in the incidence of haze at 7, 30, or 90 days ($P = .49$, $P = .71$, and $P = .18$, respectively) (Table 4).

Table 1. Chi-square test with 1 degree of freedom for 2 × 2 contingency table for nepafenac and non-nepafenac groups and delayed reepithelialization.

	Observed	
Postop Time	Nepafenac	Non-Nepafenac
≤5 d	27 (26.12)	26 (26.88)
6+ d	7 (7.88)	9 (8.12)

$\chi^2 = 0.254 < 3.84$ ($\chi^2_{1,\ 0.95}$, $P = .614$)

Table 2. Subgroup analysis of delayed reepithelialization in myopic eyes.

	Number of Eyes	
Postop Time	Nepafenac	Non-Nepafenac
≤5 d	19	19
6+ d	3	6

P = .47, Fisher exact test

DISCUSSION

Published animal studies and clinical observations document delayed corneal wound healing and haze formation with topical NSAID use. Hersh et al.[9] found a negative effect on early epithelial healing with steroidal and nonsteroidal antiinflammatory drugs. In their masked controlled study, topical diclofenac sodium 0.1%, flurbiprofen sodium 0.03%, and prednisolone sodium 1% were compared in rabbits with epithelial scrape wounds that showed delayed healing time; however, there was no effect on the corneal stroma. Vetrugno et al.[10] compared 4 treatment arms (diclofenac, flurbiprofen, ketorolac, and indomethacin) in a randomized double-masked placebo-controlled clinical study that found all NSAIDs except flurbiprofen slightly prolonged the epithelialization rates ($P < .001$).

In a prospective randomized double-masked paired-eye comparison study by Trattler and McDonald,[7] nepafenac was compared with ketorolac tromethamine 0.4% (Acular LS) to assess the rate of epithelial healing and degree of postoperative pain. The NSAIDs were instilled directly on the cornea after PRK, but before the bandage contact lens was inserted. Patients continued to instill the masked drops 3 times daily for 5 days. Follow-up visits were 1 day and 5 days postoperatively. The study was halted due to safety concerns after 7 patients (14 eyes) developed significant haze. Haze formation was significantly higher in the nepafenac-treated eyes, with greater mean haze scores at week 2 ($P = .024$), and delayed epithelial healing was seen (mean 5.7 ± 1.1 days, ketorolac group; 7.9 ± 2.1 days, nepafenac group).

Table 3. Subgroup analysis of delayed reepithelialization in hyperopic eyes.

	Number of Eyes	
Postop Time	Nepafenac	Non-Nepafenac
≤5 d	8	7
6+ d	4	3

P = .99, Fisher exact test

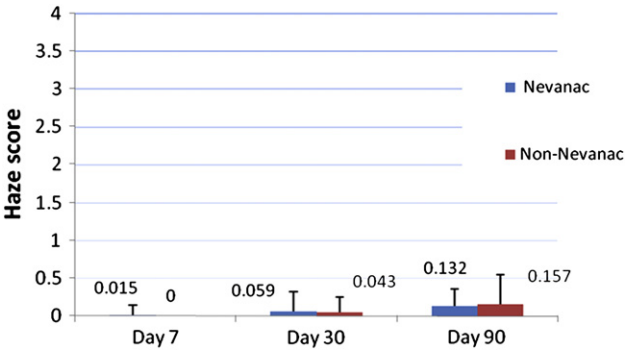

Figure 1. Mean haze scores for nepafenac and non-nepafenac groups 7 days, 30 days, and 90 days postoperatively. None of the comparisons at these time points were statistically significant.

One hypothesis is that delayed epithelialization with nepafenac occurs when it is placed directly on the stromal surface before the bandage contact lens is placed. The available formulation as a suspension may increase the duration the active ingredient remains in contact with the stromal bed and thus amplify the toxicity of nepafenac on the stromal surface. In our study, we instilled a drop of nepafenac on the operated eye after the bandage contact lens was placed. The contact lens on the stroma may have resulted in the absence of delayed epithelialization and haze formation. Larger studies of nepafenac application before and after a bandage contact lens is placed may help shed light on this theory.

Our regimen of nepafenac twice a day for 2 days (4 drops) compared with 3 times a day for 5 days (15 drops) may account for the faster recovery time we observed. Gabison et al.[11] hypothesize that prolonged NSAID (diclofenac) use after PRK was a factor in a case of corneal perforation after PRK. Immunohistochemical studies of the corneal button showed accumulation of metalloproteinases (MMPs) 3 and 9 in the

Table 4. Incidence of haze at each follow-up visit.

	Number of Eyes		
Visit/Haze Grade	Nepafenac	Non-Nepafenac	*P* Value*
7 days			.49
0	33	35	
0.5	1	0	
30 days			.71
0	30	32	
0.5	4	3	
90 days			.18
0	26	28	
0.5	7	3	
1.0	1	4	

*Fisher exact test

anterior wound corneal stroma. Animal laboratory studies support this theory, suggesting that MMPs play a role in the corneal toxicity of some NSAIDs.[12] The less aggressive and shortened duration of administration of NSAIDs after PRK in our study may account for the faster wound recovery time.

Other recent publications suggest that nepafenac may not delay epithelialization. Colin and Paquette[13] performed a clinical study to investigate the safety and efficacy of nepafenac. Sixty patients who had PRK were randomly assigned to 1 or 3 groups of 20 patients each to receive nepafenac 0.03%, nepafenac 0.1%, or diclofenac sodium 0.1%. The dose regimen was the same in all 3 groups. The authors found no significant differences between the groups in postoperative pain and no statistically significant difference in corneal reepithelialization rates. One possible explanation for the absence of delayed epithelium is the similarly short duration of medication application of 2 days, even though the regimen consisted of more drops—4 drops each day (8 drops total).

In our study, no patient developed significant haze (all scored no more than grade 1 out of 4), and there was no statistical difference between the nepafenac and non-nepafenac groups throughout the follow-up period. In vivo studies show that corneal haze after PRK increases to a peak level between 1 month and 3 months and declines slowly thereafter.[14] Our results concur. The application of MMC intraoperatively may be responsible for the reduced overall amount of corneal haze. Another reason for the reduced postoperative haze may be the normal rate of epithelial healing in both groups. All our patients fell within the definition of "normal healers" who have trace to 1+ haze and a refraction of 0.0 to +1.0 D at 1 month.[15]

The published literature offers opposing theories of the effect of NSAIDs on corneal healing from the molecular level to the clinical level. Our in vivo study suggests that nepafenac is a safe drug that does not cause delayed reepithelialization and has minimal side effects when applied twice a day for 2 days after PRK. Based on the results in this study, we recommend that nepafenac be instilled after the bandage contact lens has been placed and that MMC be used intraoperatively to reduce postoperative haze.

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