Effect of preemptive topical diclofenac on postoperative pain relief after photorefractive keratectomy

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PURPOSE: To assess the prophylactic effect of preoperative application of topical diclofenac on postoperative pain control in patients having photorefractive keratectomy (PRK).

SETTING: Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran.

DESIGN: Randomized masked clinical trial.

METHODS: In this paired-eye study, patients having bilateral PRK received 1 drop of diclofenac 0.1% in 1 eye and 1 drop of placebo in the fellow eye 2 hours before PRK. Postoperatively, both arms of the trial (both eyes of each patient) received topical diclofenac every 6 hours for 2 days. One day and 2 days postoperatively, patients were asked to rate the perceived pain in each eye using an 11-point verbal numerical rating scale. A trained examiner noted the eye-specific responses.

RESULTS: All 70 patients (140 eyes) completed the study and were included in the statistical analysis. Twenty-four hours after PRK, patients reported pain scores that were clinically and statistically significantly lower in the eyes pretreated with diclofenac than in the fellow eyes (0.97 versus 2.09) ($P=.018$). Pain scores at 2 days did not differ significantly ($P=.877$).

CONCLUSION: Administration of a single drop of topical diclofenac 0.1% 2 hours before PRK seemed to increase the efficacy of postoperative pain management in a clinically and statistically significant manner.

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Laser vision correction performed with an excimer laser is among the most common procedures in ophthalmology. An increasing number of surgeons favor surface ablation techniques, including photorefractive keratectomy (PRK), laser-assisted subepithelial keratectomy, and epithelial laser in situ keratomileusis, for vision correction.[1] Reasons for this preference include, but are not limited to, a lower risk for postoperative keratectasia and the possibility of greater ablations in thin corneas, especially in cases with higher refractive errors. Although PRK has many benefits, it also has drawbacks, the most notable of which is pain. After surface ablation, patients often report moderate to severe ocular pain, especially in the first 24 hours. Pain usually begins within 1 hour after PRK, increases during the next 3 to 4 hours, and subsides once corneal reepithelialization is complete.[2]

Over the past years, different methods to promote pain relief after PRK have been studied. Interest has risen in the use of topically applied nonsteroidal

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antiinflammatory drugs (NSAIDs) for ocular discomfort after refractive surgery. At present, the U.S. Food and Drug Administration (FDA) has approved only diclofenac 0.1% and ketorolac 0.4% and 0.5% for this use.[3] Two recent prospective randomized double-masked trials[4,5] found nepafenac 0.1% has similar analgesic properties. However, thus far, neither nepafenac nor bromfenac has been approved by the FDA for post-PRK discomfort.[3]

Corneal surface ablation leaves numerous highly sensitive nerve endings exposed, leading to severe pain and neurogenic inflammation.[6] This response is mediated by prostaglandins synthesized from arachidonic acid by cyclooxygenase (COX). Findings have shown COX activity to be associated with 2 distinct isoenzymes: COX-1 and COX-2. It is hypothesized that COX-1 is involved in the maintenance of physiologic functions, such as gastric protection and hemostasis, whereas COX-2 is thought to be involved in pathophysiologic processes, such as inflammation, pain, and fever.[7] Nonsteroidal antiinflammatory drugs suppress the activity of COX, prevent inflammation, and decrease free-nerve stimulations, which produces an analgesic effect.[8,9] To optimally reduce postoperative inflammation or pain, the drug should theoretically be administered before exposure to the inflammatory stimuli. Cyclooxygenase inhibitors work best when they are given before the onset of inflammation.[10–12] This study was designed to determine the effect of preoperative administration of diclofenac on pain control compared with that of a placebo in patients having PRK.

PATIENTS AND METHODS

Study Design

This randomized double-blind placebo-controlled paired-eye efficacy study evaluated the effect of 2-hour preoperative diclofenac application on pain relief after PRK. It enrolled patients who had bilateral PRK at Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran, from May 2009 to August 2009. The university's institutional review board approved the study protocol. After receiving an explanation of the details of the study, including the possible risks, all patients signed a consent form.

Patients were eligible for enrollment if they were aged 19 years or older and were scheduled to have myopic excimer laser PRK after documented refraction stability of at least 1 year. Corneal thickness had to be at least 480 μm and the corrected distance visual acuity (CDVA) better than 20/20. Patients were excluded if they had any of the following: a history of refractive or cataract surgery, keratoconus, a history of allergic reaction to aspirin or other NSAIDs, bleeding disorders, a history of glaucoma, a CDVA worse than 10/10, irregular astigmatism, collagen vascular disease, or diabetic retinopathy. Recruited patients were excluded from the final statistical analysis if they missed 2 or more drops of study medication a day, dislocated or replaced a contact lens, or had significant postoperative trauma to the eye.

The 2 eyes of each patient were randomly assigned to 1 of the 2 arms of the study. All eyes were treated the same except that in 1 arm of the study, 1 drop (almost equal to 25 μL) of diclofenac 0.1% (Voltaren) was applied to the eyes 2 hours before PRK. In the other arm of the study (ie, untreated eyes), a placebo (artificial tears) was given as a counterpart 2 hours preoperatively. Right after surgery, 1 drop of diclofenac was applied to both eyes of each patient, after which patients were instructed to self-administer the same medication every 6 hours for 2 days postoperatively.

Surgical Technique

The same surgeon (M.M.) performed all PRK procedures. Before excimer laser application, topical tetracaine 0.5% was applied 2 times in 10 minutes. A standardized epithelial defect was created using an 8.5 mm well into which 20% alcohol was instilled and left for 20 seconds. The alcohol was rinsed from the eye using 50 cc of a balanced salt solution and the epithelial layer removed with a hockey spatula. Stromal ablation was performed with a Technolas 217-Z excimer laser (Bausch & Lomb). After surgery, a bandage contact lens (Acuvue, Johnson & Johnson Vision Care) was placed over both eyes.

Postoperative Protocol

Other than diclofenac, perioperative medications included chloramphenicol and betamethasone drops 4 times daily. The bandage contact lens was not removed until complete corneal reepithelialization was confirmed. Chloramphenicol was discontinued after contact lens removal 5 days postoperatively. Betamethasone was administered 4 times daily for 3 weeks and then tapered over the next 2 months.

Patients were examined as close to every 24 hours as possible for 2 days postoperatively. Each examination included uncorrected distance visual acuity and a review of medication use. Slitlamp biomicroscopy was also performed to determine whether conjunctival injection was present and to evaluate corneal clarity, anterior chamber inflammation, and the longest and shortest dimensions of the remaining epithelial defects.

The primary study outcome was subjectively reported pain. One day and 2 days postoperatively, patients were asked to assess the level of pain in each eye using an 11-point verbal numerical rating scale of 0 to 10 (0 = no pain; 10 = the most excruciating pain imaginable). A trained examiner recorded the subjective pain scores. Neither the examiner nor the patient knew which eye had received the diclofenac eyedrop preoperatively.

Statistical Analysis

To calculate the target size of each arm of the trial, the minimum size of the difference between mean pain scores that the analysis would be able to detect had to be established. For this, the concept of a minimum clinically significant difference in pain scores was briefly reviewed. The mean minimum clinically significant difference derived from Holdgate et al.'s[13] observations, in which patients rescored their pain every 30 minutes, was 1.4 units (95% confidence interval, 1.2-1.6) for a visual analog scale and a verbal numerical rating scale. Yamamoto et al.[14] showed that within the same subject, smaller visual analog scale differences are clinically significant when intervals between pain assessments are shorter. For simultaneous paired pain assessments, the difference in the minimum visual analog scale description was approximated

to be 0.5 cm. In the literature, there was no similar study describing the minimum clinically significant difference in verbal numerical rating scale for paired comparisons. However, on the basis of the aforementioned findings, it intuitively and logically follows that the minimum clinically significant difference in verbal numerical rating scale pain scores is probably smaller than 1.4 and possibly about 0.5. In the present study, it was agreed that it was appropriate to detect a difference between mean scores of 1 unit or more.

For the standard deviation (SD) of the distributions of pain scores in each group, the results of a study by Blake et al.[15] were used; in that study, the SD of the verbal numerical rating scale pain scores of patients receiving diclofenac after PRK was 1.9. The agreed-on power and significance level required in the present study was 80% and 5%, respectively. Applying the formula for sample-size determination in a comparison of 2 means[16] with these values gave 66 as the target size of each arm of the study, to which 3 more were added to compensate for probable loss to follow-up.

Statistical analyses were performed using SPSS for Windows software (version 13.0, SPSS, Inc.). Data are expressed as the mean ± SD. A paired *t* test was used for between-intervention comparison, with eyes as the primary analytical unit. Results are based on an intention-to-treat analysis.

RESULTS

All 70 patients (140 eyes) who fulfilled the criteria completed the study and were included in statistical analysis. The mean age of the 24 men (34.3%) and 46 women (65.7%) was 26.14 years (range 19 to 46 years).

The preoperative diagnosis in all patients was bilateral myopia with or without astigmatism. There was no significant difference in spherical equivalent (SE) between the eyes in the 2 arms of the trial. The preoperative mean was −3.23 diopters (D) in eyes treated preoperatively with diclofenac and −3.43 D in the eyes receiving the placebo ($P = .371$).

Table 1 shows the pain scores. The patient-reported pain was statistically significantly less in the pretreated group than in the placebo group ($P = .018$). There was, however, no difference between the 2 groups at 2 days ($P = .877$).

During the postoperative follow-up, there were no serious diclofenac-related complications, such as epithelial healing delays or corneal haze, in the pretreated eyes or in the eyes receiving placebo.

Table 1. Postoperative assessment using a verbal numerical rating scale.

Time	Group: Diclofenac (n = 70)*	Group: Placebo (n = 70)*	*P* Value
1 day postop			.018
Mean ± SD	0.97 ± 1.97	2.09 ± 3.36	
Range	0–10	0–10	
2 days postop			.887
Mean ± SD	0.89 ± 1.77	0.84 ±1.48	
Range	0–10	0–10	

*Preoperative data available for all 70 patients

DISCUSSION

There are many techniques and methods for the management of postoperative pain; of these, preemptive analgesia is of great interest. The effects of a preoperative analgesic regimen remain controversial, and developing effective treatments for postoperative pain is a goal of widespread clinical study. Surgeons beyond the boundary of ophthalmology have described preemptive or preoperative analgesia with NSAIDs to reduce the total amount of analgesic agents administered postoperatively.[17–19]

In the field of ophthalmic surgery, studies have assessed the antiinflammatory effect of NSAIDs administered before cataract surgery. El-Harazi et al.[20] evaluated the efficacy of ketorolac administered 30 minutes preoperatively in controlling inflammation after phacoemulsification. Significant differences in antiinflammatory effects (manifested by returning flare and cells to preoperative baseline levels) were not observed when ketorolac was administered 30 minutes before surgery versus 1 day postoperatively. The authors concluded this might be the result of inappropriate timing of the preoperative dose because other studies of NSAIDs[10,21,22] found additional antiinflammatory benefits when the NSAID was given 1 day and 3 days before surgery. Even with these data, additional studies of preemptive analgesia in ophthalmic surgical procedures are needed.

It is well established that administering topical diclofenac postoperatively significantly reduces the ocular pain and discomfort after PRK over the pain with a placebo. However, we are not aware of a trial that specifically addressed the efficacy of preoperative NSAIDs in post-PRK pain relief. It has been proposed that rapid and sustained production of prostaglandin E_2 makes a major contribution to post-PRK pain.[23] As do other NSAIDs, diclofenac prevents the release of prostaglandins by inhibiting COX, an enzyme that catalyzes the initial step of arachidonic acid metabolism and prostaglandin production. To optimally reduce postoperative inflammation or pain, the drug should theoretically be administered before exposure to the inflammatory stimuli. Sawa and Masuda[24] state that COX inhibitors prevent synthesis of prostaglandins but do little to antagonize their effect once present.

We aimed to contribute to the current literature by assessing the prophylactic effect of topical diclofenac on preventing post-PRK pain. The prospective paired comparative randomized nature of our study contributes to it strength. By allocating both interventions

(treating preoperatively with diclofenac versus placebo) to a single patient whose eyes have the same operative setting, we avoided confounding factors, such as oral postoperative analgesic regimens. Meanwhile, the effect of excimer laser treatment time on pain was negated because the amount of myopia targeted for correction was not statistically different between the eyes of the same patient. Furthermore, an independent unbiased observer masked to preoperative interventions performed the postoperative follow-up and administered the pain evaluations.

In our study, eyes that were pretreated with diclofenac had a statistically significantly lower mean pain score in the early phase of the study (1 day postoperatively) than eyes that received the placebo (0.97 versus 2.09, $P = .018$). Yamamoto et al.[14] state that a minimum limit must exist for a difference in subjectively stated pain scores to be clinically significant (as opposed to merely statistically significant). In fact, differences of small magnitude in pain scores, although statistically significant, may not be clinically noticeable by most patients. Under the design of our study (intrapatient simultaneous paired comparison), the minimum clinically significant difference seemed to be about 0.5 unit, on the basis of Yamamoto et al.'s[14] observations. Thus, one could infer that the difference in pain scores between the 2 treatment arms reflects a perceivable pain reduction in the pretreated eyes.

We acknowledge that the magnitude of possible adverse effects must be weighed against the benefits of achieving improvement in pain control. Nevertheless, despite the published concerns about probable toxicity of topical diclofenac, its application for a reasonable length of time in appropriate patients with proper monitoring appears to be safe.[3] During the postoperative follow-up in the present study, no serious diclofenac-related complications occurred in the 70 pretreated eyes. We believe it is unlikely that administering a single drop of diclofenac 2 hours before PRK would lead to a significant increase in diclofenac-attributable complications.

In conclusion, 2-hour preoperative administration of a single drop of topical diclofenac 0.1% in patients having PRK seemed to increase the efficacy of postoperative pain management in a clinically and statistically significant manner. The best preoperative interval for preemptive analgesia in patients having PRK remains an emerging challenge that should be addressed in future studies.

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