The Effect of Topical Diclofenac Sodium 0.1% on the Corneal Epithelial Healing after Photorefractive Keratectomy

Mohammad Nasser Hashemian, MD¹ • Firoozeh Rahimi, MD² • Fatemeh Alipour, MD³
Ali Asghar Ahmadraji, MD⁴ • Hamid Reza Torabi, MD⁴
Niloofar Tavakoli, MD⁵ • Reza Soltani Moghadam, MD⁶

Abstract

Purpose: To evaluate the effect of topical diclofenac sodium 0.1% on the corneal epithelial healing after photorefractive keratectomy (PRK)

Methods: In this prospective randomized double blind clinical trial, PRK was performed on 82 patients. Thirty-three cases of them receiving topical diclofenac four times per day after surgical procedure and 45 patients did not receive this medication as a control group. Patients were compared for corneal epithelial healing after treatment.

Results: Statistically significant delayed epithelial healing has been found in the treatment group 24 hours after PRK but corneal reepithelialization has been completed in all patients four days after surgery.

Conclusion: Postoperative topical diclofenac used following PRK may delay the epithelial healing.

Keywords: Diclofenac Sodium, Photorefractive Keratectomy, Epithelial Healing

Introduction
Excimer laser photorefractive keratectomy (PRK) reprofiles the anterior corneal surface and modifies corneal power. One of the most significant short time adverse effects of PRK is sever postoperative pain that may be due to severe damage to corneal sensory nerve fibers. Pain usually initiates within one hour after PRK, rises during the next 3 to 4 hours, and wanes once corneal reepithelialization is complete, about 72 hours after surgery.

Surgeons routinely treat postoperative pain with analgesics including NSAIDs. These drugs show strong analgesic, anti-inflammatory, and antipyretic effects because they inhibit cyclooxygenase, the enzyme that catalyzes the synthesis of prostaglandins from arachidonic acid. However, it should be considered that these drugs may have some adverse effects such as retardation of epithelial healing.

Each NSAID has unique pharmacologic properties for example diclofenac sodium may decreases the intracellular availability of free arachidonic acid. We designed this study to assess the effects of topical diclofenac on the corneal epithelial healing in patients undergoing PRK surgery.

Methods
Between March and May 2009, 164 eyes (82 patients) enrolled to this prospective, randomized, double-masked clinical study. Preoperative evaluation consisted of a complete slit-lamp examination, uncorrected and best corrected visual acuities (UCVA, BCVA), cycloplegic refraction and altimetric corneal topography with pupilometry (Orbscan, Orbtex, Salt Lake City, Utah).

Inclusion criteria were myopia within -2 to -7 diopters (D) and lesser than 3 D of regular astigmatism. Patients were excluded if they had taken any topical or systemic NSAIDs or analgesic drugs during 1 month before surgery or if there were a history of ocular trauma, uveitis or other ocular diseases. No patient had autoimmune diseases or immunodeficiency or history of herpes simplex virus (HSV) keratitis and neither was pregnant or nursing.

All PRK procedures were performed by the same surgeon. An 8 mm ring as an optical zone marker was opposed to the corneal epithelium and 20% ethanol was carefully applied in it for 20 seconds. Then, irrigated using BSS and dried with a surgical sponge. A Technolas 217z100 excimer laser (Bausch and Lomb) was used for ablation. At the end of surgery a soft contact lens was applied and patients were discharged. The soft contact lens was removed after reepithelialization was complete.

Patients were randomly allocated to one of 2 groups: treatment group and control group. Topical betamethasone one drop each 6 hours and topical chloramphenicol one drop each 6 hours were prescribed for both treatment and control groups postoperatively and also, topical diclofenac sodium 0.1% (Sinadaru, Iran) was prescribed four times per day in the treatment group. All patients were allowed to take additional analgesic tablets (acetaminophen 325 mg) if pain was not controlled properly.

The patients were visited by the surgeon 24 hours postoperatively to assess the extension of reepithelialization. Other postoperative visits were planned for 8 AM on each following day until complete reepithelialization happened and the contact lens was removed. Reepithelialization was evaluated in the first visit by measuring the vertical and horizontal size of epithelial defect as the patient was examined using the slit-lamp. By subtracting these amounts from the size of ring used in the surgery, the healed epithelium was calculated.

Results
Totally 82 patients (164 eyes) consisted of 33 men and 49 women were included in this study. Treatment group composed of 37 patients (74 eyes) and control group composed of 45 patients (90 eyes).

The mean age was 29.1±4.7 and 26.9±5.2 years in the control and treatment groups respectively, and there was no statistically significant difference between them. Also, spherical equivalent had no significant difference between the two groups.

Table 1 presents the mean size of vertical and horizontal epithelial defects and also vertical and horizontal healed epithelium in the first postoperative day.

As seen in table 1, the mean size of epithelial defects is significantly larger and the
size of healed epithelium is significantly lesser in the patients that received topical diclofenac sodium 0.1%. In all eyes of both treatment and control groups epithelial defect was healed completely four days after surgery and bandage soft contact lens was removed in all of them.

| Table 1. The average size of vertical and horizontal epithelial defect and mean vertical and horizontal healed epithelium in both treatment and control groups |
|-------------------------------------------------|-----------|-----------|-----------|
| Treatment group | Control group | P |
| Mean vertical epithelial defect (mm) | 5.20 | 4.79 | 0.001 |
| Mean horizontal epithelial defect (mm) | 4.85 | 4.33 | 0.001 |
| Mean vertical healed epithelium (mm) | 3.24 | 3.73 | 0.001 |
| Mean horizontal healed epithelium (mm) | 3.64 | 4.16 | 0.001 |

Discussion

PRK is a popular procedure consisting of corneal epithelium removal and reshaping the corneal stroma with excimer laser. Epithelial removal is associated with pain; therefore different methods have been used to reduce it. Increasingly topical NSAIDs are used after PRK for prevention or reduction of postoperative pain.

Some published clinical studies have been reported that delayed corneal epithelial healing was happened with topical NSAIDs usage,7,8 while other studies supported the use of topical NSAIDs to reduce pain after PRK.9-11

Some studies reported that prolonged use of topical NSAIDs after PRK may be the cause of corneal melting that they observed in their patients.12-14 In addition Hersh and coworkers found a negative effect on early epithelial healing with topical NSAIDs.15

In contrast, some published studies confirmed the benefits of topical NSAIDs on the control of pain and inflammation after PRK. Cherry et al found that topical NSAIDs after PRK can effectively control the pain with no serious complications.16 Also, Assuelle et al have reported that indomethacin solution helps to control the pain induced by PRK without any adverse effects on the corneal epithelial wound healing.3 In another study Goes and coworkers observed that topical diclofenac and indomethacin solutions help to control the pain after PRK without epithelial wound healing retardation.17

Therefore the effect of topical NSAIDs in wound healing is controversial now. So, in this study we tried to find this effect. In our study, topical diclofenac sodium 0.1% each 6 hours after PRK delayed the epithelial wound healing in the first postoperative day; however, the cornea was reepithelialized completely four days after surgery in all patients in the treatment and control groups.

Expression of matrix metalloproteinase (MMP) by resident tissue cells is an important component of wound repair in the cornea and other tissues and excessive or inappropriate MMP activity is associated with corneal keratolysis.14 Topical instillation of diclofenac sodium 0.1% may be associated with abnormal MMP expression in the cornea and therefore result in delayed corneal epithelial healing after PRK.

The toxicity of diclofenac sodium 0.1% may be due to its preservatives.3,18 So future studies with preservative free diclofenac sodium 0.1% or other medications with a same preservative (e.g. artificial tears) as a control group may establish the role of preservatives on epithelial healing.

Conclusion

It is advisable to have in mind the side effects of topical diclofenac such as retarded epithelial healing in patients undergoing PRK when used to reduce the postoperative pain.
References

8. Sher NA, Golben MR, Bond W, et al. Topical bromfenac 0.09% vs. ketorolac 0.4% for the control of pain, photophobia and discomfort following PRK. J Refract Surg 2009;25(2),214-20.