

# Stimulating Re-epithelialization After Photorefractive Keratectomy

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## ABSTRACT

**BACKGROUND:** Re-epithelialization is usually complete in eyes 3 to 4 days following photorefractive keratectomy (PRK). However, this process is delayed in 0.5% of these eyes, leading to early development of haze. The authors investigated a method to stimulate re-epithelialization following PRK.

**METHODS:** PRK was performed with the Nidek EC-5000 excimer laser. Following surgery, express-cytokinothrapy was applied. This method consisted of a single subconjunctival injection of 2.5 to 3.0 ml of ex juvanticus mixture of autoblood and immunomodulator Poludan. This mixture was then applied topically 4 times a day until re-epithelialization was complete. Poludan is an interferon inducer (complex polyA: polyU), stimulates expressed production of interferon and interleukin-2, and increases natural cytotoxicity.

**RESULTS:** Thirty eyes of 30 patients with delayed re-epithelialization were treated with the described method. The average time to re-epithelialization was  $7.00 \pm 0.64$  days. Total epithelialization was complete on day  $3 \pm 0.38$  after beginning the cytokinothrapy ( $P < .05$ ). Early haze developed in only 2 patients from this group. Occurrence of early haze in the control group of patients who had persistent epithelial defects 8 to 16 days postoperatively and were given traditional therapy including corticosteroid and non-steroidal drugs was reliably higher: 8 to 10 days ( $P < .01$ ).

**CONCLUSION:** Local express-cytokinothrapy appears to be an effective method to promote quick and complete epithelialization in eyes following PRK that experience delayed re-epithelialization.

This treatment may be an important part of the prevention of early haze development and achievement of better visual acuity. [*J Refract Surg* 1999;15(suppl):S234-S237]

Re-epithelialization following photorefractive keratectomy (PRK) is usually complete on the third or fourth postoperative day. Approximately 1.5% of eyes experience a delay in re-epithelialization, and subepithelial opacities occur in 0.5% of eyes experiencing this delay.<sup>1-3</sup> The corneal wound healing process (epithelial and stromal) appears to determine both the resulting optical clarity and the stability of the intended refractive change.<sup>3,4</sup> The major postoperative drawbacks of PRK are early formation corneal haze and regression of the desired refractive result.

The initial wound-healing milestone after PRK is a closure of the epithelial defect; re-epithelialization begins with an initial latent phase during which there is no significant migration of cells, followed by a linear healing phase.<sup>5-7</sup>

Experimental investigations show moderate reactive hyperplasia of epithelium as well as structural changes in the subepithelial layer in the early postoperative period (up to 14 days) after PRK. Pseudomembrane formation occurs first as a result of the reaction of corneal tissues to excimer irradiation; second, a friable edematous fibrillar matrix appears in the superficial stromal layers of cornea. These structural abnormalities uncharacteristic to normal cornea could be the origins of early haze. Delay of re-epithelialization and development of haze at this point could be related to apoptosis of cells (epithelial cells, keratocytes, lymphocytes) and the decrease of cell function and immune activity under the aseptic inflammation that results from the laser treatment. Some pharmacological agents can also affect the process of re-epithelialization.<sup>5-14</sup>

The purpose of our study was to evaluate

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**Table 1**  
**Re-epithelialization, Haze, and Uncorrected Visual Acuity**  
**in 3 Groups of Eyes After PRK**

	Uncorrected Visual Acuity at 1 mo	Haze at 1 mo (grade)	Uncorrected Visual Acuity at 3 mo	Haze at 3 mo (grade)	Uncorrected Visual Acuity at 6 to 12 mo	Haze at 6 to 12 mo (grade)
<b>Group 1 (Myopia)</b>						
17 eyes (94.5%) healed in 4 to 5 days	0.5 to 0.6	1 to 1.5	0.8 to 0.9	1	0.8 to 0.9	0 to 1
1 eye (5.5%) healed in 6 days	0.3 to 0.4	2	0.7	1.5	0.2 sphere 1.50 D = 1.0	1
<b>Group 2 (Hyperopia)</b>						
9 eyes (75%) healed in 4 to 5 days	0.5	1.5	0.6	0.5 to 1	0.6	0 to 1
3 eyes (25%) healed in 6 days	0.35	1.5	0.45 sphere 1.50 D = 0.85	1.0	0.45	1.0
<b>Group 3 (Control)</b>						
2 eyes (20%) healed in 4 to 5 days	0.35	1.5 to 2.0	0.35 sphere 1.50 D = 0.75	1.5	0.35 sphere 1.75 D = 1.0	1.0 to 1.5
8 eyes (80%) healed in 6 days	0.65	1.5	0.55 sphere 1.50 D = 0.75	1.0 to 1.5	0.45 sphere 1.50 D = 0.95	1.0

postoperative treatment to stimulate re-epithelialization following PRK in cases of delayed corneal healing.

#### PATIENTS AND METHODS

Forty patients from 21 to 48 years old (mean, 30.5 yr) were included. These patients had corneal epithelial defects ranging in size from 1.0 to 3.0 mm following PRK with the Nidek EC-5000 excimer laser. Patients were separated into three groups: 18 patients with myopia, 12 patients with hyperopia, and 10 patients who served as a control group.

Epithelial defects and haze in both the epithelial and subepithelial layers of the cornea have been noted during the PRK postoperative period. The intensity of the defect can be rated by the following scale developed by the authors: a score of 0 indicates a completely clean cornea as viewed with biomicroscopy, and a score of 1 to 3 indicates different levels of opacity in the superficial layers of the ablation zone.

An eye ointment consisting of a combination of corticosteroids and antibiotics was administered after PRK. The eyes were evaluated on the fourth postoperative day. If re-epithelialization was incomplete in the treated myopic and hyperopic eyes, they were treated by express autocytotherapy. A mixture of autoblood (6 ml) and immunomodulator Poludan 0.5 ml, 100 U (Russia) was injected subcon-

junctivally and then instilled 4 to 6 times a day until complete re-epithelialization occurred.

Antibiotic instillation and solcoseryl gel were administered to the control group after the fourth or fifth day.

#### RESULTS

Patient examinations were performed regularly until corneal re-epithelialization was complete, and then at 1, 3, and 6 months and 1 year postoperatively. Uncorrected visual acuity and spectacle-corrected visual acuity were measured and slit-lamp examination was performed at these intervals. After express autocytotherapy application, complete re-epithelialization of the cornea occurred in an average of  $3.00 \pm 0.38$  days; the average duration of defects before treatment was  $6.50 \pm 0.83$  days for the myopic patients. Corneal haze in the myopic group was graded 1.0 to 1.5, and uncorrected visual acuity was 0.5 to 0.6 in 94.5% of cases 1 month postoperatively. The haze intensity decreased to grade 1.0 at 3 months and the average uncorrected visual acuity was 0.85. From 6 months to 1 year postoperatively, haze decreased in these eyes to grades of 0.0 to 1.0, and average uncorrected visual acuity stayed at 0.85. Early haze, as a rule, was more intense within the optical zone when an epithelial defect was present.

One patient (5.5%) experienced complete

**Table 2**  
**Persistence of Corneal Epithelial Defect Before and After Treatment**

	Number of Patients	Persistence of Defect Before Treatment (days)	Persistence of Defect After Treatment (days)	Statistical Significance (P)
Group 1 (myopia)	18	6.5 ± 0.83	3.0 ± 0.38	≤.01
Group 2 (hyperopia)	12	7.0 ± 0.64	4.2 ± 1.2	≤.05
Group 3 (control)	10	7.5 ± 1.97	6.75 ± 1.3	>.05

re-epithelialization on the fifth day following express-autocytokinothrapy application. Grade 2 haze and uncorrected visual acuity of 0.3 to 0.4 was observed at 1 month postoperatively. At 3 months, the haze grade decreased to 1.5 and uncorrected visual acuity increased to 0.7. Six months following PRK and beyond, the haze level remained at grade 1 while uncorrected visual acuity decreased to 0.2 and residual myopia was 1.50 D.

For the hyperopic group, the duration of corneal epithelial defects before treatment was an average of 7.00 + 0.64 days. Following express autocytokinothrapy application, complete re-epithelialization occurred in an average of 4.20 – 1.20 days. A haze grade of less than 1.5 and uncorrected visual acuity of 0.5 and higher was observed in 75% of eyes at 1 month following PRK. At 3 months, the haze intensity reduced to grade 0.5 to 1.0 and remained stable through subsequent examinations. Average uncorrected visual acuity was 0.6 and higher. In 3 eyes (25%), re-epithelialization was complete by the sixth day. A haze grade of 1.5 and uncorrected visual acuity of 0.35 was observed at 1 month following PRK. At 3 months, the haze grade decreased to 1.0 and uncorrected visual acuity increased to 0.45. Haze intensity remained stable through subsequent examinations.

No allergic reactions occurred among the myopic or hyperopic patients as a result of express autocytokinothrapy.

Re-epithelialization occurred at 6.75 + 1.30 days in the control group following solcoseryl gel application. Haze graded 1.5 to 2.0 and uncorrected visual acuity of 0.35 was observed 1 month following PRK. At 3 months postoperatively, haze decreased to a grade of 1.5 and uncorrected visual acuity remained stable, but residual myopia was noted for 8 of 10 patients. From 6 months to 1 year postoperatively, haze graded 1.0 to 1.5 was observed, as well as residual myopia (Tables 1,2).

#### DISCUSSION

Express-autocytokinothrapy in the myopic and hyperopic patients studied resulted in complete re-

epithelialization in 3 to 4 days on average in 86.7% of subjects (n=26). Re-epithelialization occurred 5 to 6 days after the onset of treatment in 100% of these eyes. In the control group, re-epithelialization occurred in 4 to 5 days in 25% of patients, and in 7 to 9 days in 100%. Poludana biosynthetic polyribonucleid complex of polyadenil and polyuridin acids, which increase interferon production and strengthen natural cytokinotoxic activity of monocytes, T-lymphocytes, and interleukin I-II response, along with cytokines that possess immune-correcting properties and autofibronectin inherent in the bloodis effective in promoting re-epithelialization.<sup>15</sup>

This study demonstrates that express-autocytokinothrapy therapy promotes the healing process in the cornea and decreases the chance of early haze formation following PRK, leading to improved visual acuity without toxic reactions in the cornea.

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