

Ascorbate Prophylaxis for Corneal Haze After Photorefractive Keratectomy

Aleksandar Stojanovic, MD; Amund Ringvold, MD, PhD; Tore Nitter, MD, PhD

ABSTRACT

PURPOSE: To evaluate whether prophylactic systemic ascorbic acid influences the average level of haze and the incidence of late onset corneal haze after photorefractive keratectomy (PRK).

METHODS: Two consecutive groups of eyes treated with PRK for myopia with or without astigmatism were retrospectively compared. The patients had been treated similarly, with the exception that systemic ascorbate had been supplied orally in one of the groups. Haze intensity was quantified on a scale from 0 (clear cornea) to 4 (anterior chamber not visible). The diagnostic criterion for late onset corneal haze was a haze grade 2 or higher, occurring 4 to 12 months after surgery.

RESULTS: One week, 1, 3, 6, and 12 months after surgery, the group without ascorbate (314 eyes) showed haze of average levels 0.61, 0.51, 0.50, 0.32, 0.10, respectively, and the group with ascorbate (201 eyes) showed haze of average levels 0.38, 0.18, 0.16, 0.09, 0.06, respectively. Comparison of the respective values showed a statistically significant difference between the two groups ($P < .01$) at 1 week, 1, 3, and 6 months. Late onset corneal haze was observed in 11 eyes in the group without ascorbate, and none was observed in the group with ascorbate ($P < .02$).

CONCLUSION: This retrospective nonrandomized clinical study suggests that oral ascorbic acid supplementation may have a prophylactic effect against haze development after PRK. However, routine prophylactic use of ascorbate can be recommended only after a randomized, prospective clinical trial substantiates its efficacy. [*J Refract Surg* 2003;19:338-343]

Loss of corneal transparency (haze) after excimer laser photoablation is due to stromal changes induced by the wound healing process and is more commonly seen following photorefractive keratectomy (PRK) than after laser in situ keratomileusis (LASIK). The frequency of this complication in a larger PRK series varies considerably—the higher the level of myopic treatments, the more severe the haze.^{1,2} Although exact figures are not comparable from one report to the next, it is safe to conclude that haze is a serious problem for a certain group of patients because it reduces visual outcome, promotes regression of the obtained refraction, and may create glare.

As customized ablation is becoming a realistic option in refractive surgery, PRK has been regaining popularity. Preliminary results with customized ablation treatments showed better outcomes with PRK than with LASIK³, presumably due to the lack of biomechanical effects of a keratectomy as well as the lack of flap alignment problems. Hence, the prevention of haze after PRK may become increasingly important in the future.

As can be seen in Figure 1, haze occurs in different variants, as judged from lag time after PRK. Opacity of the new epithelium generated by re-epithelialization after PRK represents the early-phase of regular haze. Anterior stromal opacity appears later, peaking in severity 1 to 3 months after surgery and gradually declining over the following weeks, and represents the late-phase of regular haze. In addition, late onset corneal haze may develop 4 to 12 months after PRK, after a haze-free interval or without any previous opacity.^{4,5} Late onset corneal haze may, if untreated, lead to permanent scarring and is considered the most dangerous variant of the three.

Stojanovic and Nitter⁶ first reported seasonal fluctuations in late onset corneal haze prevalence in patients after PRK, noting that these fluctuations co-varied with changes in environmental UV

From the Eye Department, University Hospital of North Norway, University of Tromsø, and SynsLaser Clinic, Tromsø, Trondheim, Norway (Stojanovic); Eye Department, Rikshospitalet, University of Oslo, Norway (Ringvold); and Øyelegesenteret, Tromsø, Norway (Nitter).

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Correspondence: Aleksandar Stojanovic, MD, Fløyvn. 32, 9020 Tromsdalen, Norway. Tel: 47.90.693319; Fax: 47.77.647929; E-mail: aleks@online.no

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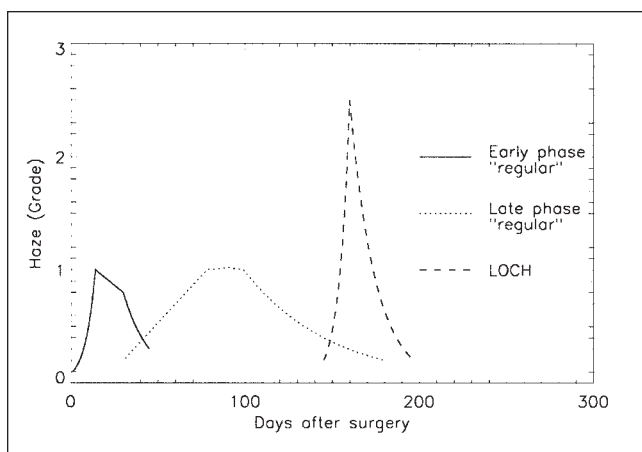


Figure 1. Haze grade for different types of haze vs. days after PRK. LOCH = late onset corneal haze.

radiation at a particular latitude. They concluded that environments with high UV-radiation levels might increase the risk for late onset corneal haze after PRK for moderate to high myopia.

Because of high molar absorptivity of ascorbic acid for UV-B and UV-C radiation, the heavy ascorbate loading of the anterior segment of diurnal mammals has been ascribed a protective role as UV filter for the eye.⁷⁻¹⁰ This was the rationale behind the recommendation to saturate the anterior eye with systemic ascorbate prior to excimer laser surgery in order to reduce postoperative haze, regression, and glare.¹¹ The therapeutic approach with ascorbate has now been tested in the setting previously used by Stojanovic and Nitter.⁶

PATIENTS AND METHODS

Two consecutive groups of patients treated with PRK for myopia with or without astigmatism were retrospectively compared. One group⁶ without ascorbate included 404 eyes of 212 patients, operated between February 1996 and July 1998, and the other group with ascorbate included 266 eyes of 152 patients, operated between August 1998 and January 2000. In both groups, the operation was performed throughout the indicated periods, irrespective of dark or light seasons. All patients were treated at the SynsLaser Clinic in Tromsø, Norway, according to the same protocol.

Evaluation before surgery included uncorrected visual acuity, best spectacle-corrected visual acuity, cycloplegic refraction, tonometry, corneal topography, slit-lamp and dilated fundus examinations, scotopic pupilometry, and tear-film function assessment. Exclusion criteria were age below 18 years, chronic eye disease such as cataract, glaucoma,

uveitis, keratoconus and dry-eye syndromes, and systemic disorders such as diabetes mellitus or autoimmune disease.

A flying spot excimer laser with a 1.0-mm beam diameter and a fluence of 89 mJ/cm² (Laser Sight Technologies, Orlando, FL) was used in all procedures. The ablation software changes that occurred during the study (from version 8.4 to version 9.0) concerned mainly the introduction of new treatment modalities (simple astigmatism and hyperopic astigmatism) and did not significantly affect the algorithms for treatment of myopia and myopic astigmatism that were used in this study. Unpreserved chloramphenicol and diclofenac eye drops were administered 30, 15, and 5 minutes before surgery. Unpreserved oxybuprocaine eye drops were administered prior to epithelial removal with the Amoils epithelial scrubber. The ablation zone varied from 5.5 to 7 mm, with a tapered transition zone of 1.0 to 1.5 mm, amounting to a total ablation diameter of 6.5 to 8.5 mm. After laser ablation, the cornea was hydrated with 2.5 mL of chilled salt solution, and a bandage lens was applied.

Unpreserved diclofenac was used four times on the first day after surgery, followed by a mixture of dexamethasone and chloramphenicol eye drops, four times daily during the first month. Dexamethasone eye drops alone were used from month 2 to month 3 after surgery and were tapered individually, depending on the amount of myopia corrected and the amount of regression, haze, or both (as a rule, two times daily during month 2 and once a day during month 3). The bandage contact lens was removed 3 to 5 days after re-epithelialization had been confirmed with biomicroscopy.

Regular follow-up examinations including haze grading were performed by the surgeon at 1 day, 1 week, and 1, 3, 6, and 12 months. All patients were urged to report any loss in quality of vision, and those who had loss of vision were examined within a few days.

Inclusion criteria for the study were: observation time minimum 12 months or longer, local corticosteroid treatment discontinued within 3 months of surgery (to avoid possible preventive effect on late onset haze)^{12,13}, and continuing local residence of the patient during the first 12 months after surgery (to standardize the environmental influence).

A scale from 0 to 4 was used for quantification of haze: 0 = clear cornea; 0.5 = trace opacity; 1 = mild, not affecting refraction; 2 = moderate, with difficult refraction; 3 = opacity that prevents refraction; grade 4 = unable to view anterior chamber.¹⁴ The

Table 1
Preoperative and Follow-up Parameters for Patients With and Without Ascorbate Supplementation Before and After PRK

	Without Ascorbate Supplementation (314 eyes)	With Ascorbate Supplementation (201 eyes)
Follow-up, months ± SD (range)	23.2 ± 8.3 (12 to 41)	22.5 ± 7.7 (12 to 41)
Age (yr) ± SD (range)	31.2 ± 9.3 (19 to 76)	30.6 ± 10.2 (18 to 68)
Sex	42% males; 58% females	40% males; 60% females
Preoperative manifest spherical equivalent refraction (D) ± SD (range)	-4.66 ± 2.11 (-1.25 to -11.50)	-4.38 ± 2.44 (-1.25 to -12.50)
Preoperative manifest spherical equivalent refraction (D); percent eyes ≥-6.00 D	23	21

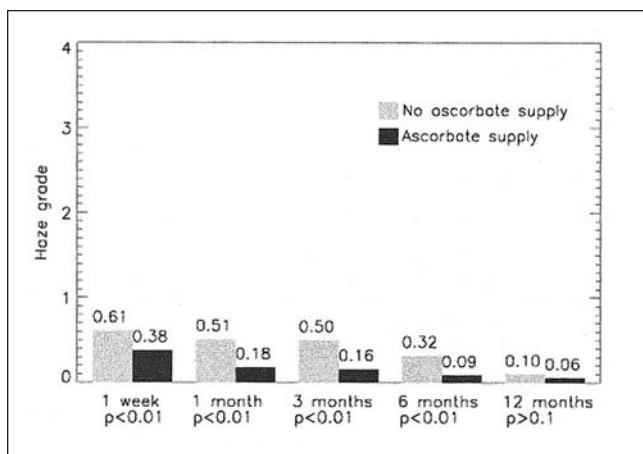


Figure 2. Average haze grade in groups with and without ascorbate supplementation at 1 week, and at 1, 3, 6, and 12 months after PRK.

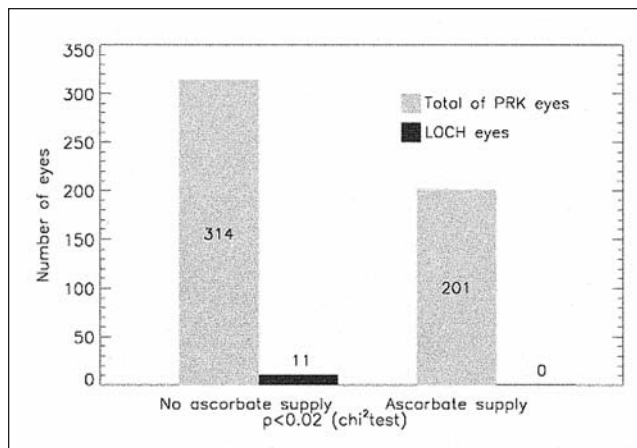


Figure 3. Number of eyes treated with PRK and number of eyes with late onset corneal haze (LOCH) in groups with and without ascorbate supplementation.

diagnostic criterion for late onset corneal haze was acute haze of grade 2 or higher, starting 4 months or later after PRK.

The introduction of systemic ascorbate supplementation was the only difference in treatment between the two groups. From August 1998, patients were given 1000 mg of ascorbic acid (Vitamin C) orally, at dose of 500 mg two times per day) from 1 week before surgery to 2 weeks after surgery.¹¹ The ascorbate treatment was reinitiated for 1 to 2 weeks in cases where patients were prone to activities involving high UV-exposure (eg, skiing). The patients did not receive any other vitamin treatment, or any other medication concurrently. The compliance was not monitored, except that patients were asked specifically about their ascorbate intake on follow-up examinations.

A Mann-Whitney two-tailed test and the chi-squared test were used to assess statistical significance.

RESULTS

The inclusion criteria were met in 314 of 404 eyes in the group without ascorbate and in 201 of 266 eyes in the group with ascorbate. Mean follow-up, age, sex distribution, and spherical equivalent refraction for the two groups were similar and the respective values are given in Table 1.

The average haze levels in groups with and without ascorbate at 1 week, and at 1, 3, 6, and 12 months are given in Figure 2. Hence, the haze reduction after ascorbate supplementation was statistically significant at all time intervals except at 12 months after surgery.

Five to 7 months after surgery, 11 eyes (3.5%) developed late onset corneal haze in the group without ascorbate versus none in the group with ascorbate, ie, statistically significantly less haze was observed in the ascorbate-treated patients (Fig 3). Table 2 shows age, sex, and amount of correction in patients that developed late onset corneal haze. Sex

Table 2
Age, Sex, and Spherical Equivalent Refraction in 11 Eyes With Late Onset Corneal Haze After PRK

Age (yr) \pm SD (range)	31.8 \pm 7.3 (23 to 45)
Sex distribution	45% males; 55% females
Preoperative manifest spherical equivalent refraction (D) \pm SD (range)	-7.50 \pm 2.25 (-2.25 to -10.50)
Preoperative manifest spherical equivalent refraction; percent \geq -6.00 D	91

and age distribution was similar to the rest of the group, while the amount of correction for myopia was significantly higher in patients who developed late onset corneal haze; 90.9% were corrected for -6.00 D or more (vs. 23.0% in the rest of the group).

Nine eyes (2.8%) from the group with no ascorbate and five eyes (2.4%) from the group with ascorbate developed an increase in intraocular pressure (IOP) with readings above 25 mmHg at 3 months after surgery. They reached their preoperative IOP levels after topical corticosteroid treatment was discontinued. Adverse effects of systemic application of ascorbate were not registered.

DISCUSSION

This was a retrospective, non-randomized, non-masked sequential study. It represents an extension of a previous work that indicated the significance of ambient UV-radiation for late onset corneal haze prevalence⁶ where during the follow-up time of 12 to 41 months, a late onset corneal haze prevalence rate of 3.5% was found.

The same clinical protocol was used in two sequential PRK groups with one exception: all patients in the last group were given ascorbic acid systemically in an attempt to minimize corneal haze. It is noteworthy that late onset corneal haze did not develop in any of the 201 eyes from the ascorbate-treated group versus 11 of 314 eyes in the untreated group (Fig 3). Although it occurs after a long latency, we can assume that late onset corneal haze has its origin in a tissue reaction initiated by PRK. We can further speculate that ascorbate administered close to the time of surgery may modify the mentioned tissue reaction and reduce the incidence of late onset corneal haze.

The amount of myopia correction was significantly higher in the patients that developed late onset

corneal haze compared to the rest of the group (90.9% of late onset corneal haze eyes were corrected for -6.00 D or more vs. 23.0% in the rest of the group). Nevertheless, the percentage of eyes corrected for -6.00 D or more was similar for the groups with and without ascorbate (21.3% vs. 23.0%) (Tables 1, 2).

The prevalence of early haze was also lower in eyes from the ascorbate-treated group compared to the controls (Fig 2).

Normal corneal wound healing is dependent on several processes in both the stroma and the epithelium^{15,16} hence various chemical agents have been introduced to minimize haze after PRK.^{1,17-19} The reason why some people are more prone to haze after PRK than others is poorly understood. To some extent the answer may be found in environmental factors, eg, regression increases in eyes exposed to solar radiation²⁰ and haze after PRK has been found to be unfavorably influenced by UV-radiation in an experimental setting.²¹

The extremely high ascorbate content in the human aqueous humour has long been established²² and, by raising the plasma level, saturation kinetics have been demonstrated in rabbits²³ and humans.²⁴ The concentration mechanisms are based on specific ascorbic acid transporters in the ciliary and corneal epithelium.²⁵ Ascorbate content of the corneal epithelium is dependent on the level in the corneal stroma, which equals that of the aqueous humor.^{26,27} Perhaps the stromal and aqueous reservoirs of ascorbate are linked through an intervening endothelial pump.²⁸ This all adds up to a chain of events in which the ascorbate reservoirs of the anterior eye are filled from serum provided through an adequate systemic supply.

Acute corneal changes following excimer laser surgery in rabbits are favorably modified by ascorbate treatment.²⁹ This observation refers to topical application only (one drop of a 10% ascorbate solution applied every 3 hours), confined to a time span of 24 hours after surgery, when the animals were killed and the eyes were processed for morphological studies. It was concluded that oxygen-radical tissue damage, quantified in terms of decreased number of lipid peroxidation compounds and polymorphonuclear cells, was reduced in the treated eyes. This 24-hour observation, along with our findings that not only late onset corneal haze but also regular haze development seems to be minimized after ascorbate supplementation, indicates that prophylactic ascorbate treatment may be useful in connection with excimer laser surgery.

The effect of ascorbate in the current setting can be questioned because of the interfering corticosteroid therapy. To minimize the significance of this interference on the incidence of late onset corneal haze and the amount of regular haze in the groups with and without ascorbate supplementation, identical criteria for dosage and duration of the local corticosteroid treatment were applied in both groups.

Prolonged topical corticosteroid treatment can induce serious complications, such as cataract, intraocular pressure increase, and infections, and the benefit of such treatment after PRK is controversial.^{1,30} Nevertheless, it seems that topical corticosteroid treatment has become an integral part of PRK at most refractive surgery centers—likely because of the unpredictability of the corneal healing response and the lack of agents able to modulate it. The reason why systemic ascorbate supplementation may reduce haze after PRK is still uncertain. Perhaps the ascorbate calms the connective tissue response to the point where the need for topical corticosteroid treatment is minimized. In addition, systemic ascorbate supplementation is known to reduce intraocular pressure.³¹

Excimer laser treatment of the cornea with a UV beam of 193 nm generates secondary radiation in the cataractogenic range 295 to 320 nm as well. These rays are transmitted by the cornea and reach the lens.³² The exposure of aqueous humor and lens to the secondary radiation generated after ArF 193-nm corneal excimer laser has been shown to induce biochemical components known to be markers of cataractogenesis.³³ We know that ascorbic acid has a high molar absorptivity just for this radiation⁷ and that the ascorbate in the aqueous humor has a protective effect against UV-induced DNA damage to the lens epithelium.⁸ Because development of UV-induced cataract is cumulative in nature, it is necessary to keep every dose at the lowest possible level. It is also suggested that exogenous maintenance of adequate aqueous humor levels of ascorbic acid after alkali burn prevents the development of corneal ulceration and perforation.³⁴ Williams and colleagues suggest that the very high concentration of ascorbic acid found in the aqueous humor of a number of species affords extracellular protection for the ocular tissues against oxygen radicals and metabolites released by infiltrating leukocytes during ocular inflammation.³⁵ These provide additional support for the beneficial effect of prophylactic ascorbate treatment in excimer laser surgery. However, only a prospective, randomized, masked clinical trial can clarify the efficacy of

ascorbate in preventing haze after PRK; routine prophylactic treatment with ascorbate in all PRK cases can be recommended only after such a study is available.

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