MITOMYCIN C REDUCES SCAR FORMATION AFTER EXCIMER LASER (193 nm) PHOTOREFRACTIVE KERATECTOMY IN RABBITS

ISAAK SCHIPPER[1], CHRISTINE SUPPELT[1] and JAN-OLAF GEBBERS[2]
Lucerne, Switzerland

SUMMARY

Sixteen eyes of eight rabbits were randomised to either mitomycin C or Balanced Salt Solution (BSS) application after photorefractive keratectomy (PRK). Regular examinations of wound healing and haze were performed with the slit lamp. The animals were killed between 1 and 26 weeks after treatment, and the corneas examined by light and electron microscopy. While the grade of haze showed no relevant differences between the two groups, scar tissue was found histologically in the mitomycin group in only 1 of 8 corneas compared with 5 of 8 in the BSS group. A marked reduction in keratocytes in all mitomycin-treated corneas and a normal density of keratocytes in the BSS group was observed. Mitomycin reduced the number of keratocytes in the treated corneas, leading to less scar formation but not to a reduction in haze. Since no morphological correlate has been found, haze remains unexplained in the mitomycin-treated corneas.

Excimer laser photorefractive keratectomy (PRK) has become a common procedure in refractive disorders, but wound healing, responsible for possible scarring and regression, remains an unsolved problem.

Improvement in laser instruments and operative technique (including Lasik) have resulted in better wound geometry and seem to help in reducing (but not eliminating) scar formation and regression.[1,2] Following PRK, steroids are the most common prophylactic treatment against excessive haze formation and regression. However, the results of this treatment on haze and regression are contradictory.[3–12] Gartry *et al.*[3] found, after an initial statistically significant improvement in the induced refraction, a loss of this effect after 3 months when steroid application was discontinued. Additionally, these authors found no effect on haze development under steroid treatment. Considering the possible severe side-effects of long-term steroid treatment, it would be desirable to find an alternative to prevent haze and regression after PRK.

Mitomycin C, isolated from the fermentation filtrate of *Streptomyces caespitosus*, is a highly potent alkylating agent with antineoplastic and antibiotic activities.[13] By inhibiting DNA synthesis secondary to alkylation,[13] mitomycin C was found to suppress fibroblast proliferation.[14–16] This effect is already very successfully used and clinically well studied in filtrating glaucoma surgery,[17,18] where it prevents excessive scar formation of the filtration bleb. Mitomycin C is also effective in preventing recurrence of pterygium[19,20] and in treatment of corneal intraepithelial neoplasia.[21] However, corneal complications with these procedures have been described by several authors.[18,21–23]

Talamo *et al.*[24,25] described the effect of mitomycin C drops on excimer-laser-treated corneas in rabbits and cats. Analogous to the applied practice in glaucoma surgery, we tried a new approach to influence wound healing after PRK. Using a soaked sponge, we left the mitomycin on the laser-treated cornea for 5 minutes, rinsing well with BSS thereafter.

MATERIALS AND METHODS

All procedures on animals performed in this study were in accordance with NIH publication no. 86–23, revised 1985, and the current version of the Swiss Resolutions on the Use of Animals in Research. The study was also approved by the cantonal veterinarian.

Ten female Chinchilla bastard rabbits were used in this study, two of them for a prestudy. They weighed between 4 and 5 kg, which corresponds to the full-

From: [1]Eye Clinic and [2]Institute of Pathology, Cantonal Hospital, 6000 Lucerne 16, Switzerland.
Correspondence to: Isaak Schipper, MD, Eye Clinic, Cantonal Hospital, CH-6000 Lucerne, Switzerland. Tel: +41/412053301. Fax: +41/412053406.

grown weight at an age of approximately 6 months. Laser ablations were performed with the animal under general anaesthesia (intramuscular ketamine hydrochloride 60 mg/kg and xylazine 6 mg/kg) and after topical treatment with cocaine 2% drops and diclofenac 1 mg/ml drops. After mechanical removal of the epithelium, deep keratectomy of 9 D (81 μm at the deepest point, 5 mm in diameter) was performed while holding the eye with a fixating mask which incorporated a device for debris removal. The excimer laser (Aesculap Meditec MEL 60) was operated in the scanning mode at 22 Hz. Immediately after the ablation a sponge (6 mm diameter) soaked in mitomycin C solution (0.4 mg/ml = 0.04% solution) was placed on the laser-treated area for 5 minutes. After removal of the sponge, the eye was irrigated with 250 ml Balanced Salt Solution (BSS). The other eye was keratectomised in the same way, but a sponge soaked in BSS was placed on the eye for 5 minutes before irrigation with 250 ml BSS.

The eyes were randomised to each of the two treatments. Voltaren drops (diclofenac 1 mg/ml) and Neotracin ointment (neomycin 3.5 mg/g and bacitracin 250 iU/g) were instilled directly after the procedure. Eyes were examined daily using the slit lamp until epithelialisation was complete – usually within 1 week. Without knowledge of treatment, two examiners independently examined the eyes and graded the haze weekly (Table I). Slit lamp pictures (a survey, a broad slit and a fluorescein picture) were taken during each examination.

Eyes were enucleated at intervals of 1, 3, 5, 7, 9, 11, 13 and 26 weeks after PRK under general anaesthesia. The animals were then killed by intracardiac injection of 10 ml, 2.5% Pentotal (thiopental). The whole globes were instantly prefixed in Karnovsky solution, and after 2 hours the corneas were excised with a 9 mm trephine and refixed in the same solution. The trephined corneas were prepared for light and electron microscopy in the Institute of Pathology. For light microscopy, the material was fixed in 4% formalin and processed by routine methods for paraffin sections and haematoxylin–eosin stain. For electron microscopy, the material was fixed in Karnovsky solution and osmium tetroxide and processed for embedding. Ultrathin sections were contrast-stained with uranyl acetate and lead citrate and examined with a Zeiss 109 electron microscope.

We quantified the proportion of scar formation in relation to the total stroma and the number of keratocytes per square millimetre with an ocular grid in the light microscope.

We defined scar tissue as: disorderly, newly formed collagen fibrils with an accumulation of keratocytes, and haze as the change in corneal transparency seen by the observer as an opacity (caused by backward scatter of light).

In a prestudy, one rabbit underwent lasering and was treated (one eye mitomycin, one eye BSS as described above) but killed immediately after the procedure. In another rabbit, one eye was lasered and treated with mitomycin while the other eye served as a control and was left without any treatment. This rabbit was also killed immediately after the procedure. Corneas were prepared as described above.

Table I. Haze grading according to Lohmann *et al.*[34]

0	Absolutely clear, no haze visible
0.5	Trace haze, hardly visible with the slit lamp
1	Haze easily visible with slit lamp
2	Medium heavy haze
3	Pronounced haze
4	Scar; iris only visible with a pocket lamp

RESULTS

Prestudy

Immediately after PRK no histological difference was found between the BSS- and the mitomycin-treated corneas. With both treatment regimens preparations showed a lack of epithelium, irregular stromal surface, normal collagen bundles in the stroma, and a normal Descemet's membrane and endothelium. As expected, no immediate toxic effect of mitomycin could be observed. The number of keratocytes in the stroma ranged between 588 and 736/mm^2 (Table II).

Main Study

Clinical Observations

All corneas had epithelialised within 5–7 days after PRK, although we found some fluorescein staining during the whole experiment in both groups. While in the BSS group the mean haze score showed a peak between the third and fifth weeks after PRK and decreased thereafter, the haze score in the mitomycin group was high in the first week, decreased in the second week and then increased again slowly to higher levels than in the BSS group. Large variation was observed in both groups. One mitomcyin-treated

Table II. Number of keratocytes in the stroma (exclusively scar tissue)

	Time after PRK (weeks)	No. of keratocytes/mm^2	
Prestudy	0	588 (untreated)	
		Mitomycin C	*BSS*
	0	612	736
	0	659	
Main study	1	17	603
	3	53	489
	5	168	533
	7	21	679
	9	17	607
	11	38	543
	13	26	677
	26	226	657

Each row gives the median result of an examination of one cornea of one rabbit. Four serial sections were performed in each cornea

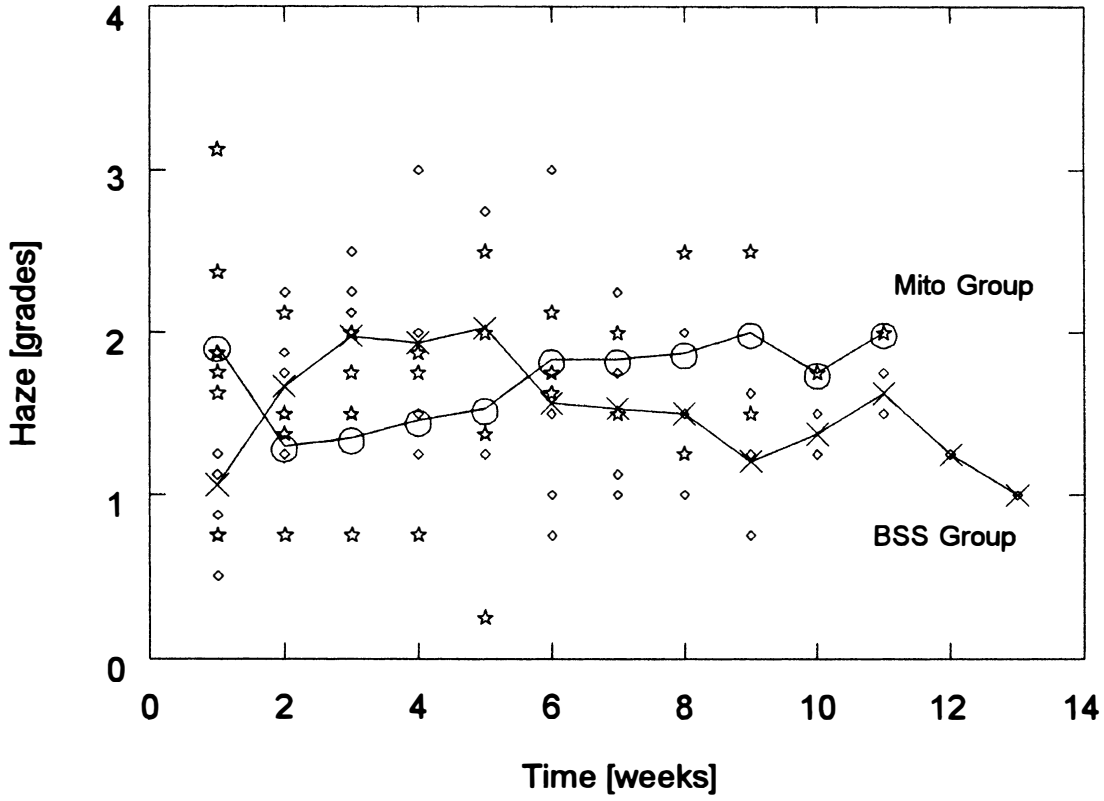

Fig. 1. *Haze development in the mitomycin C and BSS groups.*

eye was excluded from analysis (from a rabbit which was killed 13 weeks post-PRK) because it showed signs of acute infection on histological examination and was the only eye to develop scar formation after mitomycin treatment. No other ocular complications were seen in either group.

Histopathological Findings

Mitomycin Group. Under light and electron microscopy we found no scar formation (Fig. 2c, d). The one exception (excluded because of infection) showed severe scar formation (30% of the total stroma). Epithelial thinning was observed until the eleventh week; only after 26 weeks was the epithelium regular, with only a few vacuoles under the epithelium. Keratocytes were markedly reduced in all mitomycin-treated corneas; this was evident already in the first week, showing some recovery in the twenty-sixth week after treatment (Table II). Oedema developed in Descemet's membrane, and a few cells (probably fibroblasts) and interstitial vacuoles were seen in the endothelium.

BSS Group. Light microscopy showed newly synthesised collagen fibers in 5 of 8 corneas (in the third, fifth, seventh, eleventh and thirteenth weeks after treatment). The amount of scar formation (as a percentage of the full thickness stroma) had a peak at 5 weeks, decreasing thereafter from 22% to 3% (Table III). The number of keratocytes in the scar tissue reached a minimum at 5 weeks (1235 keratocytes/mm^2) and then increased up to 4938 keratocytes/mm^2 (Table III). The density of keratocytes in the stroma without scar tissue was comparable to the densities found in the untreated corneas and in those examined directly after PRK (Fig. 2a, b; Table II). As in the mitomycin group the epithelium was thin (with some areas of hyperplasia) in most of the corneas, independent of the time elapsed since PRK. Here also, intercellular vacuoles and fibroblasts were found in the endothelium.

Descemet's Membrane (Both Groups). In 2 of 8 corneas (weeks 9 and 13) in the BSS group and in 4 of 8 corneas (weeks 3, 9, 13 and 26) in the mitomycin group, Descemet's membrane presented a thin basophilic layer of electron-dense material posterior to the area of ablation. This line was found more anteriorly with the passage of time after PRK. In the mitomycin group, the part of Descemet's membrane posterior to this layer appeared less homogeneous than that in the BSS group.

Correlations

In the BSS group, a strong positive correlation (correlation coefficient 0.879) was found between the subjective grading of haze and the percentage of scar tissue (regression is $y = 0.737 + 0.089x$) (Fig. 3). In the mitomycin group the correlation coefficient between haze and scar formation was 0.091 (Fig. 3). Haze appeared in the absence of scar tissue and without morphological correlate. The difference

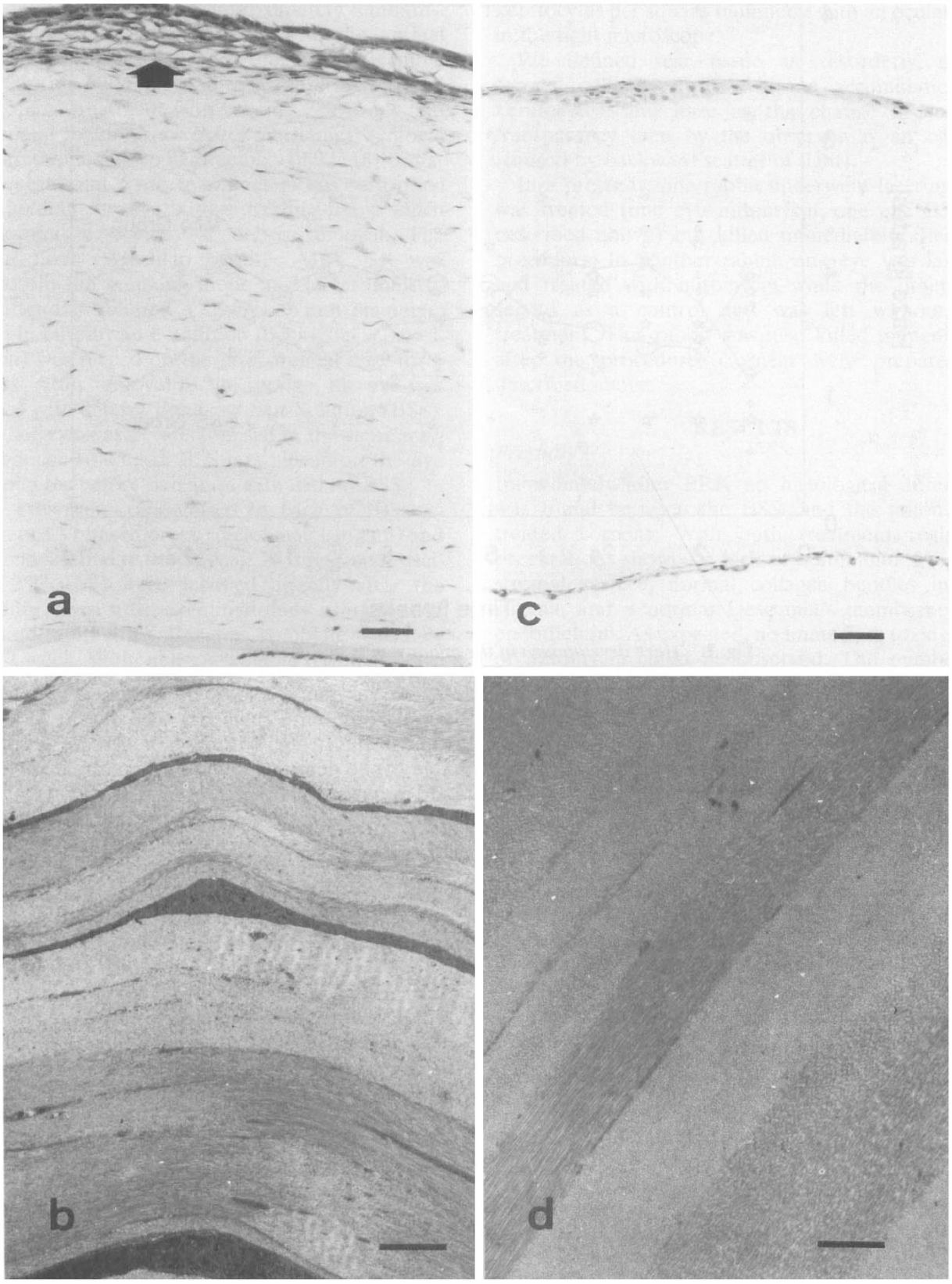

Fig. 2. *(a) Light micrograph of a BSS-treated cornea 11 weeks after PRK showing a normal (control) number of keratocytes and newly synthesised collagen directly beneath the epithelium (haematoxylin–eosin staining). Scale bar represents 36 μm. (b) Electron micrograph (transmission) of a BSS-treated cornea 1 week after PRK with normal number and appearance of keratocytes. Scale bar represents 1.8 μm. (c) Light micrograph showing a mitomycin-treated cornea 7 weeks after PRK almost without keratocytes or newly synthesised collagen (haematoxylin–eosin staining). Scale bar represents 36 μm. (d) Electron micrograph (transmission) of a mitomycin-treated cornea 1 week after PRK showing a marked reduction of keratocytes but an otherwise normal stroma. Scale bar represents 1.8 μm.*

Table III. Amount of scar tissue as a percentage of total stroma beneath the PRK lesion and number of keratocytes in the scar tissue

	Time after PRK (weeks)	Amount of scar tissue (% of total stroma)	No. of keratocytes/ mm^2 in the scar tissue
BSS group	3	20.0	1644
	5	22.2	1235
	7	5.0	3753
	11	7.1	3458
	13	3.3	4938
Mitomycin group	13	29.5	543

between mean haze in the mitomycin group and the BSS group was 0.82, which was not statistically significant ($p = 0.114$).

DISCUSSION

PRK causes a profound wound in the cornea which activates fibroblast proliferation.[16] The collagen tissue produced by these fibroblasts is much less organised than normal stromal tissue, showing matrix-free areas and fibres with irregular stereospatial relationship. Rawe *et al.*[27] found an increased number of keratocytes immediately below the epithelium, vacuoles, abnormally large proteoglycan filaments, amorphous material and newly synthesised collagen in rabbit corneas in the first weeks after laser keratectomy. The number of vacuoles and proteoglycan filaments decreased slowly with time. After approximately 3 months, a wider range of interfibrillar spacing, no well-defined lamellar structure, and normal proteoglycan staining, with occasionally larger filaments, were found compared with normal stroma. The proteoglycan filaments not associated with collagen persisted even after prolonged healing. In a steroid-treated group the authors discovered a similar morphology.

Corneal scar tissue is opaque because it is less organised.[28] Transparency improves as ultrastructural organisation improves.[29] A number of studies have focused on the correlation between haze and cellular as well as subcellular changes.[29–33] The reduced transparency is seen by the ophthalmologist as haze (backward scatter).[34] Regression of the refractive change is possibly also caused by the scar tissue. The deeper the ablation the higher is the risk of developing haze and/or regression.[35–39] Steroids are used by most surgeons in the post-operative treatment of PRK. Steroids inhibit immune reactions, collagen synthesis and neovascularisation.[40–42] Suppression of cellular activity is thought to minimise the number of newly formed collagen fibres after PRK.[40,42,43] Regression and scar formation can probably be minimised or even restored with steroids.[40,42] However, the effect might be of only short duration.[3,12]

The observed effects of PRK on the stroma beyond the first 3 months are probably not due to large-scale collagen remodelling but, rather, to changes in epithelial activity and water content of the stroma,[3] to disorganisation of collagen fibrils[44] and to new production of proteoglycans, including keratan sulphate and hyaluronic acid, which can cause accumulation of water and disruption in the lamellar arrangement. These might be the cause of regression and haze formation.[45]

The controversial effect of steroids on wound healing after PRK prompted the search for another substance to inhibit scar formation after excimer laser PRK. We chose mitomycin C because of its fast-acting and long-lasting suppression of fibroblast activity after only a single application.[14–16] Lack of compliance problems and minimal risk of side-effects with the one dose are advantageous. Mitomycin is thought to inhibit fibroblast proliferation, or to induce cell death due to inhibition of DNA synthesis.[5,14,15]

In our study a reduction in keratocytes to below-normal levels was already found after 1 week, suggesting death of keratocytes caused by mitomycin C in the concentration used (0.4 mg/ml). This

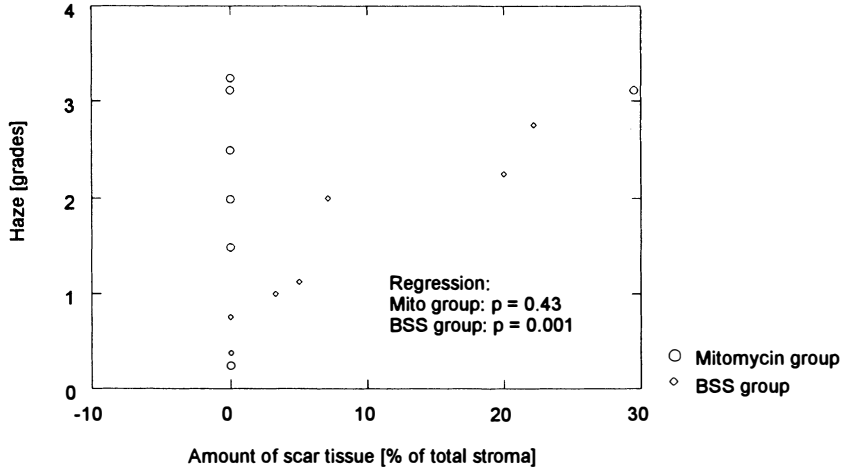

Fig. 3. *Haze score versus the amount of scar tissue in the mitomycin C and BSS groups.*

reduction in keratocytes possibly prevented scar formation. Since scar formation is commonly considered the morphological correlate for haze, some authors use scar formation and haze synonymously. However, in our mitomycin group haze (backward scattered light) occurred in moderate to severe degrees without any scar formation. In contrast, the extent of haze correlated strongly with the severity of scar tissue in the BSS group, while in the mitomycin group this correlation was not found. Our morphological examinations could not reveal the origin of haze in the mitomycin group. The accumulation of hyaluronic acid after excimer laser PRK is well known. Hyaluronic acid is capable of accumulating large amounts of water, which in turn can cause marked haze formation.

Our findings correlate very well with those of Talamo *et al.*[24] They treated three groups of rabbits: one received erythromycin eye drops only (2 rabbits), the second erythromycin combined with steroids (5 rabbits), and the third erythromycin combined with steroids and mitomycin C. They also found no difference in haze between the groups, but more scar formation (as seen with fluorescence microscopy) in the groups not receiving steroids and mitomycin, less scar formation in the group receiving steroids, and little or no scar formation in the group receiving steroids and mitomycin. Also, the corneas treated with mitomycin were thinner (statistically significant) than the corneas in the other groups. Our study differs from that of Talamo *et al.* in some points: mitomycin was shown to prevent scar formation without steroids; it was shown that a single application at the end of the operation is sufficient to markedly suppress keratocyte activity and scar formation; and the number of keratocytes (not measured by Talamo *et al.*) was significantly reduced in the mitomycin group. Also a single application of mitomycin has the advantage regarding compliance.

The additional layer that we found in some Descemet's membranes has been described by others also.[24,46] They considered it to be material shed directly from the cell membrane or cytoplasm of the endothelial cell. As it is also found after chemical insults, the authors consider it to be a non-specific response of the rabbit corneal endothelium. Attempts to identify the nature of the material histochemically were unrevealing. Talamo *et al.*[24] also described this layer, considering it to be probably unique to the rabbit eye, the pluripotent endothelium of which can regenerate and is quite sensitive to mechanical and chemical stimuli.

One rabbit was excluded from the study because of a severe inflammatory reaction, found in none of the other specimens. Toxic effects of mitomycin are well known and have been described before.[47,48] However, the mode of application was different. Severe corneal complications have been described after long-term topical application of mitomycin following pterygium surgery.[48] We rinsed the cornea with Balanced Salt Solution at the end of the mitomycin application, as is the rule when using mitomycin as an adjunct for glaucoma surgery.

Although mitomycin C application seems to be an interesting and promising approach in post-PRK treatment because of its suppressant effect on scar formation, further investigations into the appropriate dose (lower concentrations that affect fibroblast proliferation without killing the keratocytes) as well as the origin of the haze are necessary before its clinical application can be recommended.

Key words: Excimer laser, Mitomycin C, Cornea, Keratocytes, Haze, Wound healing.

REFERENCES

1. O'Brart BS, Corbett MC, Lohmann CP, Kerr Muir MG, Marshall J. The effects of ablation diameter on the outcome of excimer laser PRK: a prospective, randomised, double-blind study. Arch Ophthalmol 1995;113:438–42.
2. Snibson GR, Carson CA, Aldred GF, Taylor HR. One year evaluation of excimer laser photorefractive keratectomy for myopia and myopic astigmatism. Arch Ophthalmol 1995;113:994–1000.
3. Gartry DS, Kerr Muir MG, Lohmann GP, Marshall J. The effect of topical corticosteroids on refractive outcome and corneal haze after photorefractive keratectomy. Arch Ophthalmol 1992;110:944–52.
4. Goggin M, Foley-Nolan A, Algawi, K, O'Keefe M. Regression after photorefractive keratectomy for myopia. J Cataract Refract Surg 1996;22:194–6.
5. Tengroth B, Epstein D, Fagerholm P, Hamberg H, Fitzsimmons TD. Excimer laser photorefractive keratectomy for myopia: clinical results in sighted eyes. Ophthalmology 1993;100:739–45.
6. Fagerholm P, Hamberg-Nyström H, Tengroth B, Epstein D. Effect of postoperative steroids on the refractive outcome of photorefractive keratectomy for myopia with the Summit excimer laser. J Cataract Refract Surg 1994;(Suppl 20):212–5.
7. Campos M, Abed HM, McDonnell PJ. Topical fluorometholone reduces stromal inflammation after photorefractive keratectomy. Ophthalmic Surg 1993; 24:654–7.
8. Tuft SJ, Zabel RW, Marshall J. Corneal repair following keratectomy: a comparison between conventional surgery and laser photoablation. Invest Ophthalmol Vis Sci 1989;30:1769–77.
9. Seiler T, Kahle G, Kriegerowski M. Excimer laser (193 nm) myopic keratomileusis in sighted and blind human eyes. Refract Corneal Surg 1990;6:165–73.
10. O'Brart DPS, Lohmann CP, Klonos G, Corbett MC, Pollock WST, Kerr-Muir MG, Marshall J. The effects of topical corticosteroids and plasmin inhibitors on refractive outcome, haze and visual performance after photorefractive keratectomy: a prospective, randomised, observer-masked study. Ophthalmology 1994; 101:1565–74.
11. Tengroth B, Fagerholm P, Söderberg P, Hamberg-Nyström H, Epstein D. Effect of corticosteroids in postoperative care following photorefractive keratectomies. Refract Corneal Surg 1993;9 (Suppl):61–4.

12. Gartry DS, Kerr Muir MG, Marshall J. Excimer laser superficial keratectomy: a laboratory and clinical study. Br J Ophthalmol 1991;75:258–69.
13. Crooke ST, Bradner WT. Mitomycin C: a review. Cancer Treat Rev 1976;3:121–39.
14. Jampel HD. Effect of brief exposure to mitomycin C on viability and proliferation of cultured human Tenon's capsule fibroblasts. Ophthalmology 1992;99: 1471–6.
15. Khaw PT, Doyle JW, Sherwood MB, Grierson I, Schultz G, McGorray S. Prolonged localised tissue effects from 5-minute exposures to fluorouracil and mitomycin C. Arch Ophthalmol 1993;111:263–7.
16. Khaw PT, Sherwood MB, MacKay SLD, Rossi MJ, Schultz G. Five-minute treatments with fluorouracil, floxuridine and mitomycin have long-term effects on human Tenon's capsule fibroblasts. Arch Ophthalmol 1992;110:1150–4.
17. Bergstrom TJ, Wilkinson WS, Skuta G, Watnick RL, Elner VM. The effects of subconjunctival mitomycin C on glaucoma filtration surgery in rabbits. Arch Ophthalmol 1991;109:1725–30.
18. Charles JB, Ganthier R, Wilson MR, Lee DA, Baker RS, Leong KW, Glasgow BJ. Use of bioerodible polymers impregnated with mitomycin in glaucoma filtration surgery in rabbits. Ophthalmology 1991; 98:503–8.
19. Rosenthal G, Shoman A, Lifshitz T, Biedner B, Yassur Y. The use of mitomycin in pterygium surgery. Ann Ophthalmol 1993;25:427–8.
20. Singh G, Wilson MR, Foster S. Mitomycin eye drops as treatment for pterygium. Ophthalmology 1988;95: 813–21.
21. Frucht-Pery J, Rozenman Y. Mitomycin C therapy of corneal intraepithelial neoplasia. Am J Ophthalmol 1994;117:164-8.
22. Ando H, Ido T, Kawai Y, Yamamoto T, Kitazawa Y. Inhibition of corneal wound healing. Ophthalmology 1992;99:1809–14.
23. Kitazawa Y, Kawase K, Matsushita H, Minobe M. Trabeculectomy with mitomycin. Arch Ophthalmol 1991;109:1693–8.
24. Talamo JH, Gollamudi S, Green R, de la Cruz Z, Filatov V, Stark WJ. Modulation of corneal wound healing after excimer laser keratomileusis using topical mitomycin C and steroids. Arch Ophthalmol 1991; 109:1141–6.
25. Talamo JH, Lee K, Puliafito CA, Steinert RF. Corneal wound healing after excimer laser photorefractive keratectomy in cats: the role of mitomycin C and steroids. Invest Ophthalmol Vis Sci 1991;(Suppl 32):1247.
26. Kitano S, Goldmann JN. Cytology and histochemical changes in corneal wound repair. Arch Ophthalmol 1966;76:345–54.
27. Rawe IM, Zabel RW, Tuft SJ, Chen V, Meek KM. A morphological study of rabbit corneas after laser keratectomy. Eye 1992;6:637–42.
28. Cintron C, Schneider H, Kublin CL. Corneal scar formation. Exp Eye Res 1973;17:251–9.
29. Jain S, Khoury JM, Chamon W, Azar DT. Corneal light scattering after laser *in situ* keratomileusis and photorefractive keratectomy. Am J Ophthalmol 1995; 120:532–3.
30. Goodman GL, Trokel SL, Stark WJ, Munnerlyn CR, Green R. Corneal healing following laser refractive keratectomy. Arch Ophthalmol 1989;107: 1799–803.
31. Breuermann RW, McDonald MB, Shofner AS, Munnerlyn CR, Clapham TN, Salmeron B, Kaufmann HE. Quantitative histological studies of primate corneas after excimer laser photorefractive keratectomy. Arch Ophthalmol 1994;112:1103–10.
32. Fantes FE, Hanna KD, Waring GO III, *et al.* Wound healing after excimer laser keratomileusis (photorefractive keratectomy) in monkeys. Arch Ophthalmol 1990;108:665–75.
33. Del Pero RA, Gigstad JE, Roberts AD, *et al.* A refractive and histopathologic study of excimer laser keratectomy in primates. Am J Ophthalmol 1990;109: 419–29.
34. Lohmann C, Gartry D, Kerr Muir M, Timberlake G, Fitzke F, Marshall J. Haze in photorefractive keratectomy: its origins and consequences. Laser Light Ophthalmol 1991;4:15–34.
35. Gartry DS, Kerr Muir MG, Marshall J. Excimer laser keratectomy: an 18-month follow-up. Ophthalmology 1992;99:1209–19.
36. Heitzmann J, Binder PS, Kassar BS, Nordan LT. The correction of high myopia using the excimer laser. Arch Ophthalmol 1993;111:1627–34.
37. Lohmann C, Gartry D, Kerr Muir M, Timberlake G, Fitzke F, Marshall J. Haze in photorefractive keratectomy: its origins and consequences. Laser Light Ophthalmol 1991;4:15–34.
38. Ditzen K, Anschütz T, Schröder E. Photorefractive keratectomy to treat low, medium and high myopia: a multicenter study. J Cat Refract Surg 1994;(Suppl 20):234–8.
39. Caubet E. Cause of subepithelial corneal haze over 18 months after photorefractive keratectomy for myopia. J Refract Corneal Surg 1993;(Suppl 9):65–70.
40. Gassett PR, Lorenzetti DWC, Ellison EM, Kaufman HE. Quantitative corticosteroid effect on corneal wound healing. Arch Ophthalmol 1969;81:589–91.
41. Phillips K, Arffa R, Cintron C, Rose J, Miller D, Cublin CL. Effects of prednisolone and medroxy-progesterone on corneal wound healing, ulceration and neovascularisation. Arch Ophthalmol 1983;101:640–3.
42. Polack FM, Rosen PN. Topical steroids and tritiated thymidine uptake: effect on corneal healing. Arch Ophthalmol 1967;77:400.
43. McDonald TO, Borgmann AR, Roberts MD, Fox LG. Corneal wound healing. I. Inhibition of stromal healing by three dexamethasone derivatives. Invest Ophthalmol 1970;9:703–11.
44. Kahle G, Daqun X, Seiler T, Schröder-Kermani C, Wollensack J. Wundheilung der Cornea von Neuweltaffen nach flächiger Keratektomie: ER:YAG-Excimerlaser. Fortschr Ophthalmol 1991;8:380–5.
45. Fitzsimmons TD, Fagerholm P, Härfstrand A, Schenholm M. Hyaluronic acid in the rabbit cornea after excimer laser superficial keratectomy. Invest Ophthalmol Vis Sci 1992;33:3011–6.
46. Hanna KD. Corneal stromal wound healing in rabbits after 193 nm excimer laser surface ablation. Arch Ophthalmol 1989;107:895–901.
47. Rubinfeld RS, Pfister RR, Stein RM, Foster CS, Martin NF, Stolern S, Talley AR, Speaker MG. Serious complications of topical Mitomycin-C after pterygium surgery. Ophthalmology 1992;99:1647–54.
48. Derrick RJ, Pasquale L, Quigley HA, Jampel H. Potential toxicity of Mitomycin C [letter]. Arch Ophthalmol 1991;109:1635.