

Mitomycin C 0.02 and 0.002% efficacy in preventing haze after photorefractive keratectomy

L. M. Coelho · R. O. Sieiro

Received: 10 May 2017 / Accepted: 15 December 2017 / Published online: 16 January 2018
© Springer Science+Business Media B.V., part of Springer Nature 2018

Abstract

Purpose To compare MMC 0.002% efficacy in preventing haze after PRK in relation to MMC 0.02%.

Patients and methods We conducted a prospective study with patients with myopia or myopic astigmatism undergoing PRK in the same conditions. After PRK, MMC was applied for 30 s in a concentration of 0.02% on the right eye (group 1) and 0.002% on the left eye (group 2). Age, gender, spherical equivalent and haze intensity (1, 3, 6 and 12 months postoperatively) were assessed. Haze was quantified at biomicroscopy (0–4 +). $P < 0.05$ was considered statistical significant.

Results We evaluated 130 patients, 77 women and 53 men, with a mean age of 30.2 ± 9 years. The

spherical equivalent was -3.66 D in the group 1 and -3.77 D in the group 2. In the 1st month after PRK, incidence of haze was 13.9% eyes in group 1 and 14.6% in group 2. In the 3rd month, incidence of haze was 50.0% eyes in group 1 and 48.5% in group 2 which presented with 3 +/4 + traces of haze. In the 12th month, incidence of haze was 7.7% eyes in group 1 and 5.4% in group 2. There was no correlation between haze and age ($p = 0.279/0.333$), gender ($p = 0.345/0.367$) or spherical equivalent ($p = 0.100/0.054$) in groups 1 and 2, respectively. There was no difference in haze between groups 1 and 2 ($p = 0.56$).

Conclusion MMC 0.002% was effective in preventing haze after PRK. As MMC long-term safety has not been proved, we suggest its use in a lower concentration, in order to prevent potential complications.

Keywords Refractive surgical procedures · Photorefractive keratectomy · PRK complications · Corneal haze · Mitomycin C

Setting: “Dr. Reinaldo Sieiro” and “Ocular Laser” Eye Clinics; Belo Horizonte; Minas Gerais; Brazil.

Project number and institution responsible for the approval of the Research Ethics Committee: 57213816.4.0000.5134/ Ethics Research Committee of “Faculdade de Ciências Médicas de Minas Gerais”.

L. M. Coelho (✉)
Instituto de Olhos de Belo Horizonte (IOBH),
Universidade Federal de Minas Gerais (UFMG), Padre
Rolim Street, 541, Belo Horizonte, MG, Brazil
e-mail: leticiamariacoelho@gmail.com

R. O. Sieiro
Faculdade de Ciências Médicas de Minas Gerais
(FCMMG), Belo Horizonte, MG, Brazil

Introduction

Mitomycin C (MMC) is a genotoxic antibiotic that blocks deoxyribonucleic acid (DNA) synthesis and inhibits cell mitosis. Its potential benefits in preventing or inhibiting scar formation have improved the results of treatments of anterior segment eye disorders, such

as glaucoma, pterygium, and conjunctival and corneal intraepithelial neoplasia [1].

The original surface ablation technique, photorefractive keratectomy (PRK), has proved to be a safe and an effective procedure to correct low to moderate levels of myopia, hyperopia and astigmatism. However, corneal wound healing response after PRK is usually more intense than that after laser in situ keratomileusis (LASIK) for similar levels of correction. Therefore, complications related to wound healing, such as haze and regression, tend to be more significant after PRK [1–4].

Several factors have been suggested to contribute to haze formation after PRK, including irregularity of the postoperative stromal surface, time required for epithelial defect healing, ablation depth, epithelial basement membrane removal, high astigmatism correction, exposure to ultraviolet (UV) light and genetic influences [1, 5].

Over the past few years, intraoperative use of topical MMC after PRK has been found to be an effective adjunct treatment to limit subepithelial corneal haze formation, especially after correction of high myopia. The most important effects of MMC after surface ablation are inhibition of keratocyte proliferation and of myofibroblasts differentiation [1, 2, 5–9].

However, studies with longer follow-up are necessary to prove MMC safety for anterior stroma and, specially, for endothelium.

The aim of this study was to compare the MMC 0.002% efficacy in preventing haze after PRK with MMC 0.02% usually employed.

Patients and methods

We conducted a prospective study with patients with myopia or myopic astigmatism undergoing PRK. All patients were informed about the nature of the study and provided informed consent in accordance with institutional guidelines and the Declaration of Helsinki.

Exclusion criteria were active anterior segment disease, previous intraocular or corneal surgery, a history of herpes keratitis, diagnosed autoimmune disease, systemic connective tissue disease or atopic syndrome, and corneal topographic findings suspicious for keratoconus.

Surface laser ablation procedure

All surgeries were performed by the same surgeon. After povidone–iodine scrub of the eyelid skin and topical anesthesia with proparacaine 0.5% drops, epithelium was mechanically removed. The excimer laser device (Technolas[®] 217z100 Bausch & Lomb[®] Germany) was employed for all of surgeries. After stromal ablation, MMC was applied to the stromal bed for 30 s at a concentration of 0.02% in the group 1 and 0.002% in the group 2. Surface was irrigated with balanced salt solution (BSS) and dried. Topical application of fluorometholone 0.1% and moxifloxacin eye drops was placed on the cornea together with a sterile soft contact lens.

Postoperative management and monitoring

Postoperatively, moxifloxacin and ketorolac tromethamine eye drops were instilled 4 times daily for the first week and fluorometholone 0.1% eye drops was instilled 4 times daily for 2 weeks.

Postoperative assessments and measurements were done at 1, 3, 6 and 12 months. Pre- and postoperative uncorrected visual acuity (UCVA) and manifest refraction were recorded using a standard Snellen projector system and phoropter for refraction.

Haze level was evaluated at biomicroscopy by the same observer and quantified in 0–4 + according to the Fantes scale.

Statistical analysis

Wilcoxon test was employed in order to evaluate spherical equivalent and haze level differences between eyes from group 1 and eyes from group. In order to test correlation between haze level and age and between haze level and spherical equivalent, Spearman's correlation coefficient was used. To seek difference in spherical equivalent and haze level in female and male gender, Mann–Whitney test was employed. An Generalized Estimating Equation Model was used to analyze change in haze over time, considering all patients. To assess whether there were differences in haze according spherical equivalent of each eye (< 3 D, 3–6 D and > 6 D), Kruskal–Wallis test was used. A *p* value < 0.05 was considered statistically significant.

Results

We evaluated 130 patients, of whom 77 (59.2%) were female and 53 (40.8%) were male. The average age of patients was 30.2 ± 9 years (18–69 years) and 75% of them were between 18 and 34 years. The average value of spherical equivalent in the group 1 was $- 3.66$ D, while in the group 2 was $- 3.77$ D ($p = 0.04$).

In the first month after surgery, 13.85% eyes from group 1 and 14.62% from group 2 presented haze. In the third month, haze occurred in 50.00% eyes from group 1 and in 51.54% from group 2. In the sixth month, 17.69% eyes from group 1 and 18.46% from group 2 presented haze. In 1 year, 7.69% eyes from group 1 and 5.38% eyes from group 2 presented haze. There was no significant difference in haze between eyes from groups 1 and 2 at any time (Table 1). None of the eyes presented severe haze (4 +) and haze value gradually decreased over time in both groups (Figs. 1, 2).

There was no correlation between haze value and patient age, neither between haze value and patient gender (Table 2). And when eyes were analyzed according spherical equivalent (< 3 D, 3–6 D and > 6 D), there was a weak positive linear correlation between haze value and spherical equivalent only in eyes from group 2 in the third month (Table 2).

Analyzing the role of different variables for haze, with an Generalized Estimating Equation Model, time was the only variable significant for haze ($p < 0.001$). MMC different concentrations were not statistical significant for haze after PRK ($p = 0.556$).

Discussion

Over the past few years, PRK has shown an increased preference among refractive surgeons [10]. As safe

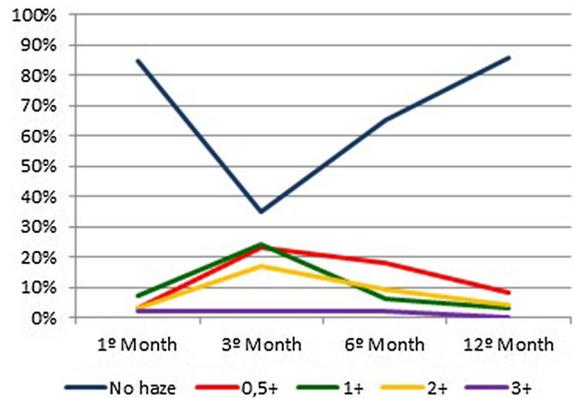


Fig. 1 Haze evolution in eyes from group 1 over 12 months after PRK

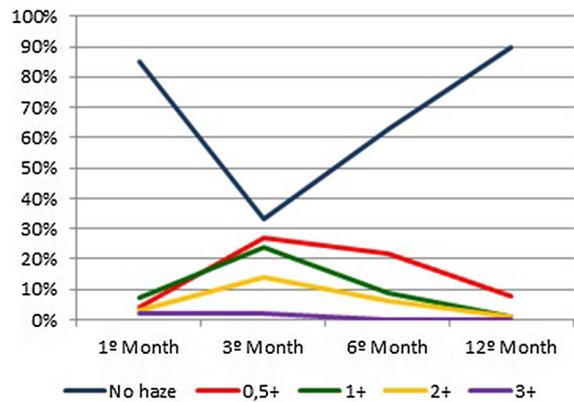


Fig. 2 Haze evolution in eyes from group 2 over 12 months after PRK

and effective as LASIK, PRK may prevents complications associated with flap construction and may reduce ectasia risk [1, 2, 11]. It is considered as the technique of choice in cases with low pachymetry, trauma susceptibility and changes in ocular surface [1, 11, 12]. And its limitations related to haze and

Table 1 Haze distribution in both groups over 12 months after PRK

	1st month		3rd month		6th month		12th month	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Haze (%)	13.85	14.62	50.00	51.54	17.69	18.46	7.69	5.38
Traces	3.08	3.85	16.92	20.77	9.23	10.77	3.08	3.08
+	6.15	6.15	18.46	18.46	3.08	4.62	–	–
++	3.08	3.08	13.08	10.77	4.62	3.08	–	–
+++	1.54	1.54	1.54	1.54	0.77	–	–	–
<i>p</i>	1.000		0.435		0.379		0.056	

Table 2 Statistical difference between eyes from groups 1 and 2, considering age, gender and spherical equivalent (SE)

<i>p</i> value	1st month		3rd month		6th month		12th month	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Age	0.601	0.579	0.634	0.728	0.279	0.333	0.424	0.916
Gender	0.230	0.385	0.729	0.385	0.345	0.367	0.080	0.018
SE	0.913	0.978	0.134	0.031	0.100	0.054	0.829	0.673

regression were significantly reduced with the use of MMC [1, 3, 4, 8–10].

Intraoperative use of topical MMC after PRK has been found to be an effective adjunct treatment to limit subepithelial corneal haze formation, especially after the correction of high myopia [1, 3, 4, 8–14]. But, even MMC use in refractive surgery has been shown to be safe until this moment, and long-term effects of MMC on cornea are not known.

Several studies were conducted to determine application time and optimal dose, able to prevent corneal haze, without local or systemic toxicity. Netto et al. [2] and Virasch et al. [11] found no significant difference in haze after MMC application for 12, 60 and 120s, in rabbits and humans, respectively. Song et al. [15] found greater number of keratocyte apoptosis by increasing the dose and exposure time of MMC. However, this correlation was higher with the dose applied than with the exposure time, showing that topical concentration of MMC seems to be the main determinant of MMC concentration in the aqueous humor and in keratocyte death and, therefore, should be further investigated. For this reason, in our study, we used the same MMC application time, changing only the concentration of this substance.

Evaluating different MMC concentrations, as well as in our study, several authors found no difference in the incidence of haze. Netto et al. [2] found no significant difference in haze after MMC application to 0.02 and 0.002% in rabbits. Naderi et al. [3] evaluated 105 PRK patients who received MMC 0.02% in RE and MMC 0.01% in LE, both for more than 40s, with no significant difference in haze in the sixth month of observation.

Thornton et al. [8], studying patients undergoing laser epithelial keratomileusis (LASEK), observed lower incidence of haze in the group treated with MMC 0.002% compared to the untreated group. However, when assessing patients undergoing PRK,

they found a lower incidence of haze in patients treated with MMC 0.02%, compared to those treated with MMC 0.002%, especially those with myopia greater than 6 diopters and with ablations larger than 75 μm . In patients with moderate myopia and lower ablations, MMC 0.002% proved to be as effective as MMC 0.02%. However, this study was a retrospective review, in which different patients received different concentrations of MMC.

Our study seems to be, so far, the only one that studied the contralateral eye as a control. This is critical, since both eyes were exposed to the same risk factors for haze, as genetic predisposition, individual response to excimer laser ablation, spherical equivalent and amount of ablation, surgical technique and postoperative exposure to ultraviolet light, an important risk factor in tropical countries [1, 5, 16]. And there was no significant difference in haze between eyes treated with MMC 0.02% and those treated with MMC 0.002%.

It is known that haze can be divided into two main types. The first one, more common, typically transient, is noticed between 1 and 3 months after PRK; it is rarely associated with clinical symptoms and tends to disappear within 1 year after surgery. The second one, slow, tends to appear between 2 and 5 months after PRK, or even years later, characterized by epithelial injury, and is more unpredictable, depending on the remodeling of cornea stroma [1, 16].

We observed that, in the first month after surgery, over 80% of patients had no haze. But in both groups, there was a higher incidence of haze from the third month of observation, which decreased over time, as expected, due to physiological response of cornea remodeling. We did not observe severe haze in any of our patients, showing MMC efficiency, even at a reduced concentration.

Hormonal differences between gender and a variable fibroblast activity with age could also influence

the haze [16]. However, there was no difference in haze between these groups with respect to these variables.

The follow-up time of 12 months in our study seemed to be enough to explore haze evolution, since at the end of the first year, stromal remodeling process already provides corneal transparency, stable refraction and results similar to those found in LASIK [1].

Although all results were statistically significant, sample reduced over time because of clinical follow-up discontinuation by patients. This is a limitation of this study, and studies with larger samples should be conducted in order to clarify the real role of some risk factors for haze such as age, spherical equivalent and gender, besides MMC concentration.

MMC efficiency in preventing haze after photoablation of corneal surface has been proved. However, its potential long-term toxicity has not yet been clarified and studies with longer follow-up in humans are still needed. The use of a lower concentration of MMC may be an alternative in reducing potential risks.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

- Santhiago MR, Netto MV, Wilson SE (2012) Mitomycin C: biological effects and use in refractive surgery. *Cornea* 31(3):311–321
- Netto MV et al (2006) Effect of prophylactic and therapeutic mitomycin C on corneal apoptosis, cellular proliferation, haze, and long-term keratocyte density in rabbits. *J Refract Surg* 22:562–574
- Naderi M, Ahmadi M, Jadidi K, Alishiri A, Rafizadeh P (2010) Comparison of standard and low dose mitomycin C in the prevention of corneal haze following photorefractive keratectomy. *Iran J Ophthalmol* 22(3):13–16
- Teus MA, Benito-Llopis L, Alió JL (2009) Mitomycin C in corneal refractive surgery. *Surv Ophthalmol* 54:487–502
- Netto MV, Mohan RR, Sinha S et al (2006) Stromal haze, myofibroblasts, and surface irregularity after PRK. *Exp Eye Res* 82:788–797
- Diakonis VF et al (2014) Contralateral-eye study of surface refractive treatments: clinical and confocal microscopy evaluation. *J Cataract Refract Surg* 40:224–231
- Lacayo GO III, Majmudar PA (2005) How and when to use mitomycin-C in refractive surgery. *Curr Opin Ophthalmol* 16:256–259
- Thornton I, Puri A, Xu M, Krueger RR (2007) Low-dose mitomycin C as a prophylaxis for corneal haze in myopic surface ablation. *Am J Ophthalmol* 144:673–681
- Majmudar PA et al (2000) Topical mitomycin-C for subepithelial fibrosis after refractive corneal surgery. *Ophthalmology* 107:89–94
- Sia RK, Ryan DS, Edwards JD, Stutzman RD, Bower KS (2014) The U.S. army surface ablation study: comparison of PRK, MMC-PRK, and LASEK in moderate to high myopia. *J Refract Surg* 30(4):256–264
- Virasch VV, Majmudar PA, Epstein RJ et al (2010) Reduced application time for prophylactic mitomycin C in photorefractive keratectomy. *Ophthalmology* 117:885–889
- Hofmeister EM, Bishop FM, Kaupp SE, Schallhorn SC (2013) Randomized dose-response analysis of mitomycin-C to prevent haze after photorefractive keratectomy for high myopia. *J Cataract Refract Surg* 39:1358–1365
- Gambato C, Ghirlando A, Moretto E, Busato F, Midena E (2005) Mitomycin C modulation of corneal wound healing after photorefractive keratectomy in highly myopic eyes. *Ophthalmology* 112:208–219
- Crawford C et al (2013) Systemic absorption of mitomycin-C when used in refractive surgery. *J Cataract Refract Surg* 39:193–196
- Song JS, Kim JH, Yang M, Sul D, Kim HM (2007) Mitomycin C concentration in cornea and aqueous humor and apoptosis in the stroma after topical mitomycin-C application. Effects of mitomycin-C application time and concentration. *Cornea* 26:461–467
- Stojanovic A, Nitter TA (2001) Correlation between ultraviolet radiation level and the incidence of late-onset corneal haze after photorefractive keratectomy. *J Cataract Refract Surg* 27:404–410