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Mitomycin C application in refractive surgery

Aplicação da mitomicina C na cirurgia refrativa

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ABSTRACT

Over the years, mitomycin C has been used by refractive surgeons to prophylactically decrease haze after surface ablation procedures and therapeutically in the treatment of preexisting haze. Development of mitomycin C treatments has had a significant role in the revival of surface ablation techniques. We reviewed the literature regarding mechanism of action of mitomycin C, its role in modulating wound healing after refractive surgery, and its safety and efficacy as adjuvant therapy applied after primary photorefractive keratectomy surgery or after photorefractive keratectomy re-treatment after laser in situ keratomileusis and other corneal surgeries and disorders. The drug is a potent mitotic inhibitor that effectively blocks keratocyte activation, proliferation, and myofibroblast differentiation. Many studies have suggested that mitomycin C is safe and effective in doses used by anterior surface surgeons, although there continue to be concerns regarding long-term safety. After initial depletion of anterior keratocytes, keratocyte density seems to return to normal 6 to12 months after the use of mitomycin C when corneas are examined with the confocal microscope. Most clinical studies found no difference between preoperative and postoperative corneal endothelial cell densities when mitomycin C 0.02% was applied during refractive surgery,with exposure time of 2 minutes or less. After approximately 14 years of use, mitomycin C has been found to be effective when used for prevention and treatment of corneal haze.

Keywords: *Mitomycin; Photorefractive keratectomy; Myofibroblasts; Wound healing*

RESUMO

A mitomicina C teve seu uso profilático e terapêutico estabelecido, ao longo dos anos, para diminuir o *haze* depois da ablação superficial. A mitomicina C é segura e eficaz como uma terapia adjuvante aplicada após um procedimento primário de ceratectomia fotorrefrativa ou após um retratamento com ceratectomia fotorrefrativa após o *laser in situ keratomileusis* LASIK. A mitomicina age modulando a cicatrização após a cirurgia. Constitui-se num potente inibidor de mitose, bloqueia a ativação e a profliferação dos fibroblastos e a diferenciação dos miofibroblastos. Embora existam muitos estudos apontando a segurança da mitomicina nas doses ultilizadas, ainda persistem dúvidas quanto à segurança, a longo prazo, do uso da mitomicina. Quando as córneas são examinadas com microscópios confocal, após depleção inicial dos ceratócitos, a densidade celular parece retornar ao normal seis a 12 meses após o uso de mitomicina C . A maioria dos estudos clínicos não encontrou diferença significativa entre a densidade endotelial celular pré-operatória e pós-operatória quando a mitomicina C 0.02% foi aplicada durante a cirurgia com um tempo de exposição de 2 minutos ou menos. Em aproximadamente 14 anos, a mitomicina C mostrou-se eficaz na prevenção e tratamento do *haze* corneano.

Descritores: Mitomicina; Ceratectomia fotorrefrativa; Miofibroblastos; Cicatrização

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Introduction

In 1956[1], mitomycin A and B were isolated from Streptomyces caespitosus. Shortly after mitomycin C (MMC) was discovered[1,2]. Mitomycin is an antibiotic that belongs to the family of anticancer quinolone. It acts as an alkylating agent after enzymatic activation, resulting in cross-linking of DNA. The powerful effect of MMC in cell replication has called the attention of eye researchers. Its potential benefits in preventing or inhibiting scar formation indicate a range of possible applications. The application of MMC has optimized the results of previous treatments of anterior segment disorders, such as glaucoma, pterygium, and corneal and conjutival intra-epithelial neoplasia. [3,4]

Corneal scarring after refractive procedures

The corneal scarring contributes to the effectiveness and safety of all refractive procedures. The variability in scarring is the main factor involved in cases of overcorrection, undercorrection, stromal opacity, and other possible complications of these surgeries. [5] Depending on the level of desired correction, corneal scarring and stimuli for the fibrotic response may be stronger after PRK. In fact, the main effect is the structural and functional defects of the base epithelial membrane occurring when there is great irregularity of the surface, after high corrections. [6.7] The conclusion is that keratocyte apoptosis, as well as the subsequent proliferation and generation of myofibroblasts, was qualitatively and quantitatively different in PRK for high myopia. This difference also occurred for PRK compared to low myopia or LASIK to high myopia.

MMC as adjuvant therapy after PRK

The original surface ablation technique, a.k.a. PRK, involves the mechanical removal of the epithelium, with the removal of the base membrane and subsequent laser photoablation of the Bowman's layer and the anterior stroma. [8] The subsequent corneal scarring response to PRK is usually more intense than after LASIK for similar levels of correction. Complications related to scarring such as *haze* and regression tend to be more significant after PRK surgery. There are several interrelated processes, and sometimes an unpredictable biological response involved in corneal scarring process after refractive procedures. Subsequent to PRK, the organization of the extracellular matrix can be changed in the anterior stroma. This may be associated to decreased transparency (called *haze*) in some corneas. In most patients, the level of stromal opacity formed after PRK is not clinically significant. However, in some cases, and particularly after high levels of correction, the opacity can be severe. The generation and persistence of myofibroblast seem to be a primary biological response responsible for the development of corneal *haze*.[9,10] Myofibroblasts are contractile cells with reduced transparency, supposedly by decreasing the intracellular production of *crystallin*.

Previous corneal opacity or *haze* occurs in 1% to 4% of eyes undergoing surface ablation procedures, such as PRK without prophylactic MMC. [11,12] The disappearance of *haze* is associated to the disappearance of myofibroblasts and the remodeling of the stromal collagen by keratocytes.

The possible formation of severe corneal subepithelial *haze* tended to limit the surface ablation procedures and the options to correct high refractive errors [13]. After a few years, the intraoperative use of topical MMC associated to PRK has been considered an effective adjuvant treatment to limit the formation of subepithelial corneal *haze*, especially after high myopia correction. [14] In 2000 arise the first reports on the efficacy of MMC 0.02% in preventing the recurrence of subepitleial corneal fibrosis [15]. It was also shown that the concentration of MMC0.02% was as effective as 0.002%). The short exposure times up to 12 seconds were as effective as long exposures (2 min and 1 min) in reducing subepithelial *haze* and depleting the myofibroblasts density in the anterior stroma after 1 month of PRK -9D. However, for moderate myopia and superfitial depth, the lowest dose seems to be equally effective. Changes in the exposure time impact less the absorption of MMC by the cornea and aqueous humor than the changes in concentration. [16, 17] Thus, the drug is generally applied from 12 seconds to 1 minute, depending on the depth of ablation. [18, 19] The standard approach starts with MMC 0.02% for 30 seconds in the primary cases of PRK and MMC 0.02% for 1 minute in more complicated cases, such as the *buttonhole flaps* after LASIK, PRK after radial keratotomy or penetrating keratoplasty, or retouches with PRK after LASIK. [20] The most important effects of the MMC after ablation surface are the inhibition of keratocytes proliferation (and hence, the repopulation of the anterior stroma) and the resulting inhibition of differentiation of the myofibroblasts of precursor cells. [21] Although the cell death of keratocytes via apoptosis or necrosis is also higher after the treatment with MMC after PRK [22], this effect does not seem to be responsible for the clinical effectiveness of the MMC.

There was a decrease in the cellularity of the anterior stroma when compared to the controls up to 1 month after treatment with PRK associated to MMC, persisting for up to 6 months after surgery. This raises the concern about the long term safety of the treatment with MMC.() Some comfort can be obtained in studies with confocal microscopy, whose results show that the keratocytes density has returned to normal after the initial depletion after 6 to 12 months post-MMC use. [23-24] However, longer follow-up and decades of histological studies after the treatment with MMC are necessary to disperse concerns about long-term complications. Another concern of the refractive surgeons is the potential effect of MMC on the corneal endothelium.[25,26]

Most clinical studies found no difference between pre- and postoperative endothelial cell density when MMC 0.02% was applied for refractive procedures. There are significant limitations in the studies on the safety of MMC in the endothelial layer.[27,28]

MMC after retreatment with PRK after LASIK

In some cases it is very difficult to conduct a flap lifting, especially if the flap of LASIK was performed with femtosecond laser. [29,30] A retreatment in the previously ablated surface area is more susceptible to formation of *haze* due to repeated injury to the base membrane and the presence of residual activated keratocytes at the site of ablation. Some authors have performed retouches to the surface ablation without MMC, and found no significant incidence of postoperative haze in the treatment of residual myopia.[31,32] However, the tendency to develop *haze* is directly proportional to the number of retreatments. Several studies have reported post-operative opacity in eyes that had PRK and subsequent LASIK without the use of MMC.[33,34] The use of PRK with MMC as an adjuvant therapy to correct refractive residual error after LASIK was proven to be safe and effective.[35,36] Although there is a consensus on the need to use

MMC in the post-PRK treatment for the correction of residual myopia, studies suggest that their use is safe for touches on surface ablations.[37,]ablações superficiais[37].

Conclusion

Over 10 years ago ophthalmologists have started using MMC prophylactically and therapeutically to control *haze*.

This potent inhibitor of cell proliferation and myofibroblasts generation proved to be effective in the modulation of scarring. Therefore, it is a potent adjuvant for the treatment and prevention of *haze* after ablative procedures.

MMC seems to be safe in the doses used routinely by surgeons of the anterior surface, with few reports of problems such as endothelial decompensation or necrosis greater than 1:25 D or tissue removal by laser ablation greater than 50 to 75ìm stromal. A common recommendation in the refractive surgery community is the prophylactic use of MMC with PRK for treatments greater than -4 and -6 D of myopia, astigmatism.

Despite the undoubted efficacy of MMC in the prevention and treatment of haze, some questions still remain about what the optimal treatment parameters for MMC and which is the safety profile of its long-term use.

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