Short Note

Photorefractive Keratectomy with Adjuvant Application of Mitomycin C

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Abstract

Photorefractive Keratectomy (PRK) changes the refraction or especially the shape of the cornea by surface ablation using an excimer laser with a wavelength of 193nm and a relative power of 60mW. The excimer laser (ArF) was firstly applied in organic tissue in 1981 [1]. Physically it performs a photoablation and the ultraviolet light is absorbed by organic material. A lot of studies proofed the procedure as predictable and effective with a good safety profile [2,3].

INTRODUCTION

Refractive surgery comprises all surgical procedures to correct common vision problems such as myopia, astigmatism, hyperopia or combinations of those. The photorefractive keratectomy (PRK) changes the refraction or especially the shape of the cornea by surface ablation using an excimer laser with a wavelength of 193nm and a relative power of 60mW. The excimer laser (ArF) was firstly applied in organic tissue in 1981 [1]. Physically it performs a photoablation and the ultraviolet light is absorbed by organic material. A lot of studies proofed the procedure as predictable and effective with a good safety profile [2,3].

Indications

The corneal refractive procedure being most frequently performed is LASIK [4] (laser-assisted in situ keratomileusis), although the PRK is a good option especially when LASIK is not possible. Typical indications for PRK include small palpebral fissures, thin cornea (< 500µm), mild suspicious topography or higher risk of trauma (i.e. martial arts or boxing).

The PRK procedure inherently avoids flap-associated complications such as free flaps or buttonholes. Today there is a spectrum of surface ablation (SA) procedures including alcohol assisted PRK (aPRK), transepithelial PRK (tPRK) and Epi-LASIK. The procedure of the aPRK is explained below. An alternative is the tPRK that comprises an ablation of the epithelium via excimer laser. Epi-LASIK combines the procedures of PRK and LASIK. A thin flap (50µm) is prepared and afterwards the visual correction with excimer takes place and the flap is positioned. Within the last years there has been a revival of the tPRK with i.e. the smart Surf laser system by Schwind. It allows the removal of the epithelium and the refractive correction without touching the eye in just one laser system.

Laser treatment

The procedure is performed under aseptic precautions and topical anesthesia. Skin disinfection is performed with betaisodonna. After removing the epithelium with 20% alcohol for 30 seconds the auto eye tracking system is positioned. The ablation is centered on the visual axis (first purkinje image). The patient is asked to focus on a target light offered by the laser. The laser treatment is performed and afterwards a therapeutic contact lens is applied and the wire speculum removed. Postoperatively topical lubricants, antibiotics and non-steroidal anti-inflammatory drugs are applied. After epithelial closure the therapeutic contact lens will be removed and the topical antibiotics are not more necessary.

Transepithelial photorefractive keratectomy is a possible option to reduce the incidence of haze. In this case the epithelium is also removed with the excimer laser [5]. We have analyzed the incidence of haze of 3924 patients that underwent SA between 04/2006 and 09/2010. In myopic eyes 3% of the eyes treated with aPRK had haze and being treated with tPRK haze incidence was 12% and being treated with Epi-LASIK 4%.
Adjuvant intraoperative mitomycin C application is used to modulate the wound healing of the cornea and reduce postoperative occurrence of haze (reversible reduction of transparency). MMC can be applied in a metal cylinder well or sponge. The authors prefer the MMC sponge application because it implies less stress to the patient’s cornea. Postoperative application of MMC after refractive surgery is not advisable.

Complications of PRK

Usually there is a postoperative pain for 24 to 48 hours and the time to full functional vision recovery takes 3 to 7 months. A refractive stability is reached after 3 weeks to a couple of weeks [6]. Compared to LASIK there is a higher potential of keratocytes activation, which results in a higher risk for postoperative haze and visual regression [4]. The risk of scarring postoperatively amounts 1-2 % [6]. Other evaluations resulted in 2-4% or more haze formation postoperatively [7]. In the studies of Netto et al., depends on the level of the haze depends of the aspirated correction [7].

In our analysis the preoperative sphere had no significant influence on the incidence of haze. Those patients who had no haze postoperatively had a mean sphere of -4,14 dpt and the patients with haze had a mean sphere of -4,50 dpt (p = 0,072). In our analysis the myopic patients with haze had a mean cylinder of -1,27 dpt and the myopic patients without haze had a cylinder of -0,95 and the difference was statistically significant (p = 0,018). For the hyperopic patients there was in our analysis no influence of the aspirated correction neither sphere nor cylinder on the incidence of haze.

Modulation of the wound healing

Postoperatively there is an activation of the keratocytes and increased collagen deposition leading to haze and regression [5]. The possible reduction of postoperative epithelial opacity because of performing a transepithelial PRK is controversially discussed. The most common prophylaxis is the application of topical steroids, but there has never been a proof of significant therapeutic effects [8]. Another option is the intra-operative application of mitomycin C [4,5,7]. There are also new substances such as heparan sulfate mimicking regenerating agent (RGTA) i.e. Calcicol. The application of RGTA suppresses the antioxidant imbalance and also reduces the production of prooxidant metabolites. Playing the role of heparin sulfate RGTA supports the epithelial healing. In the study of Aslanides et al., a full epithelial healing post keratoplasty was achieved in a mean of 2,7 days with RGTA and in 4,6 days without RGTA [9]. Further studies are necessary to analyse the epithelial healing and its possible advantages of MMC.

Mitomycin C

Mitomycin C (MMC) is a derivate of Streptomyces caesipitosus and has antibiotic and antineoplastic qualities [10]. The mode of action is alkylating cross links between adenine and guanine to suppress DNA synthesis during the GI and S phases [10,11]. Thus MMC is able to reduce fibroblast proliferation and differentiation and inhibits the synthesis of proteins of the extracellular matrix (for example collagens). Consequently myofibroblast formation is blocked. Myofibroblasts are primarily responsible for corneal haze [12]. In ophthalmology MMC is used in Pterygium surgery or to prevent scarring after glaucoma surgery or as a follow-up adjuvant therapy of neoplasia [10]. In refractive surgery surface ablation it is used to prevent subepithelial fibrosis [10] (= haze).

The ophthalmological standard concentration is 0,02% and based on pterygium surgery or glaucoma surgery. Haze formation is one of the most frequently side effects of corneal surface ablations [8]. Gambato et al., compared two experimental groups (PRK for high myopia > 7 dpt). The first group obtained 0,02% MMC for two minutes post PRK and the second group applied topical steroids postoperatively [8]. Both groups obtained tear substitutes for three months. The incidence of haze ≥ 1 according to Fantes haze grading system in the reference group (using topical steroids) was 20% compared to no haze ≥ 1 in the MMC group. Usually MMC is applied in a concentration of 0,02% but there also have been experiment comparing a low dose MMC with 0,01% [13].

They analyzed two study arms comparing the application of 45 sec of low dose MMC (0,01%) to the application of MMC 0,02% [13]. According to the study of Razmjoo et al., there has been no significant difference between a group of patients being treated with 0,01% (low dose MMC application) and the group being treated with 0,02% MMC. First descriptions of Majmudar et al., suggested an application time of 2 minutes [14]. They analyzed 8 eyes being treated with MMC post operationem (radial keratotomy (50%) or photorefractive keratectomy) and neither of them showed postoperative epithelial opacity within the 6 - 25 months follow up period.

Adverse side effects of MMC are for example a prolonged time for epithelial closure [15]. But this is also controversially discussed. Diakonis et al., proved out in their study that epithelial closure post PRK took 3,9 days and was not significantly prolonged [4]. Kim et al., analyzed the stromal side effects especially the number of keratocytes post PRK (1 month and six months post operationem) using different concentrations of MMC (0,002% or 0,02%). Postoperatively there were significantly more keratocytes using 0,002% [5].

Midena et al., also pointed out that a treatment with MMC reduced the number of keratocytes, but not significantly [16]. Over the last years there have been many efforts to reduce the application time of MMC without reducing the preventive effect [4]. Diakonis et al., proved a safe haze inhibition with a 15 sec exposure [17]. They also demonstrated that MMC has no significant effect on the endothelial cells [17]. Goldsberry et al., verified also that the application of MMC has no significant effect on the endothelium: neither quantitative nor qualitative [18].

But even today the possible side effects on other ocular tissues such as the sclera are controversial discussed. We therefore advise to only apply MMC to the cornea and meticulously protect the limbus intraoperatively. Adverse side effects of MMC are associated with its concentration, time of application and application strategy (intra - versus postoperatively). Due to this a responsible and well - dosed application is necessary [19]. Especially patients suffering from blepharitis, sicca or limbal stem cell deficiency should not be treated with MMC [19]. Furthermore a detailed elucidation of the off-label use is necessary.
CONCLUSION

Mitomycin C plays an important role in ophthalmology especially in refractive surgery. The intra-operative application of MMC is a safe and predictable option to prevent haze. Possibly the combination out of larger optical zones, modern flying spot systems and MMC reduces the risk of refractive regression. Especially for difficult treatments, re-treatments or scarred tissue the application of MMC is advisable. In our protocol we apply MMC between 15-30 seconds (myopia SE > 4 dpt MMC for 30 seconds). In therapeutic excimer treatment for scarred corneae or dystrophies the intra-operative application of MMC is highly recommended [19].

REFERENCES