Does photorefractive keratectomy with mitomycin C application provide reasonable therapeutic and refractive solution for low to moderate myopic patients with type I granular corneal dystrophy and obviate the need for keratoplasty?

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To evaluate the use of photorefractive keratectomy (PRK) with mitomycin C (MMC) application as a therapeutic and refractive solution for low to moderate myopic patients with granular corneal dystrophy (GCD) type 1, to study the postoperative complications and the recurrence rate, and to answer this question: Can excimer laser ablation obviate the need for keratoplasty in those patients? Prospective non-randomized interventional study was employed. 7 eyes of 5 myopic patients with GCD type 1 were treated with WaveLight EX 500 excimer laser PRK with post ablation intra-operative MMC application. Preoperative and regular postoperative complete ophthalmologic examination, anterior segment colored photographing, and corneal investigations using WaveLight – Allegro Oculyzer pentacam and Optovu corneal ocular coherence tomography (OCT) were performed for all patients. The postoperative follow up period was 18 months. Manifest spherical equivalent (SEq) refraction, best corrected visual acuity (BCVA), and the central 7 mm corneal clarity. The results have shown; statistically significant improvement of mean (M) SEq refraction of the patients from -3.91±1.4737 preoperatively to -0.0714±0.4009 2 weeks postoperatively; (probability value (P)<0.0001), and statistically significant improvement of M BCVA of the patients from (0.314 ± 0.212) to (0.9 ± 0.115) 2 weeks postoperatively; (P<0.0001), and the central cornea became clear after PRK with MMC for all patients. Postoperative follow up revealed that, visually significant corneal haze has occurred in the first post operative few weeks in 2 eyes (28.6 %); and it was resolved by topical steroids, and recurrence of the granular deposits has occurred around 6 months postoperatively in 3 eyes (42.86%), this recurrence significantly caused alteration of the refraction and diminution of vision, with light sensitivity in one eye (14.29 %). PRK redoing was done to treat this eye after complete meticulous corneal examination and investigations. After redoing, all clinically significant opacities have been eliminated with returning of clear vision and stable refraction until the end of follow up period. In the light of suitable topographic and corneal OCT measures, PRK with MMC application can provide good therapeutic and refractive solution for clinically selected low to moderate myopic patients with GCD type 1, and can delay the need for keratoplasty in large numbers of patients in the short term. The recurrence of the GCD may occur but, fortunately; most recurrences don’t significantly affect the visual functions. Visually significant recurrences may be retreated by excimer laser when the clinical, topographic and corneal OCT measures permit.

Keywords: Granular corneal dystrophy, Corneal opacity, Corneal haze, Photorefractive keratectomy, Phototherapeutic keratectomy, Mitomycin C, Myopia, Ocular coherence tomography, Corneal topography, Scheimp flug.

INTRODUCTION

GCD is an autosomal dominant (AD), bilateral, non-inflammatory condition that results in deposition of discrete, irregularly shaped white granular opacities in the anterior stroma of the cornea with clear areas...
between these deposits (Klintworth, 2009). The granules are primarily located in the central cornea, with an absence of these deposits in the peripheral cornea. The deposits can resemble crushed breadcrumbs or snowflakes, and consist of hyaline eosinophilic granules that stain bright red with Masson trichrome stain. They react with antibodies to keratoepithelin. On electron microscope; the deposits appear trapezoidal or rod shaped (Mori et al., 2009).

GCD is a stromal dystrophy, but the epithelium and Bowman’s layer may be affected in late disease (Klintworth, 2009).

There are two clinically separate types: GCD type I (classic type) and GCD type II (Avellino CD); which tends to have fewer corneal deposits, potentially resembling a combination of lattice CD and GCD (Klintworth, 2009). GCD is uncommon worldwide. GCD type I is more common in Europe, while GCD type II is more prevalent in Japan, Korea, and the United States. No sexual predilection has been reported (Jester et al., 1999).

Risk of corneal haze increases with increased ultraviolet light exposure and related to the depth of the ablation, consequently, patients with high myopia (greater than six diopters (D)) will have a higher risk of a haze than those who are less near-sighted (Pietila et al., 2004). Haze tends to occur more in patients with brown irides (Tabbara et al., 1999).

The use of MMC has substantially reduced post PRK haze (Hashemi et al., 2015).

MMC was originally isolated from the organism Streptomyces caesipitosus and developed as a chemotherapeutic agent. MMC acts to stop cells from proliferating by cross-linking deoxyribonucleic acid (DNA). In laboratory studies, the anterior stroma of the corneas that underwent MMC treatment was found to have a decreased density of keratocytes when compared with eyes that underwent a similar laser procedure without MMC (Teus et al., 2003). Excimer laser ablation is safe and effective for the treatment of anterior corneal pathology. Recurrence of pathology; especially corneal dystrophies, do occur with time (Rapuano, 1997). Also, intraoperative application of MMC helps to prevent the recurrence (Ayers et al., 2006).

**MATERIALS AND METHODS**

Patients’ selection

This prospective non-randomized interventional study included 7 eyes of 5 myopic patients with GCD type 1 (2 patients: one males and one female; had bilateral significant opacities and the remaining 3 patients: two males and one female had the visually significant opacities affecting one eye), the M age was: 29.5 ± 5.36 years; range (R): 22-36 years). They were myopic of mild to moderate degree, the M myopic refractive error was -3.34 ± 1.46 S; R: (-1.5)- (-5.25 S)), with low myopic astigmatism (M: −1.15 ± 0.53 cylinder). The M corneal front diopteric power was: 42.7 ± 0.95 D; R: 42-
44 D; and M corneal back diopteric power was: -6 D. the M pachymetric thinnest location was: 527 ± 26.8 µm; R: 500-560 µm. the M distance between the Bowman’s membrane (BM) and the lower border of significant central corneal opacity was: 75 ± 31.09 µm; R: 45-120 µm.

Exclusion criteria

- General exclusion criteria: including factors affecting the wound healing:
  - Patients with chronic systemic diseases such as diabetes mellitus.
  - Patients with autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus.
  - Patients using systemic steroids.
- Ocular exclusion criteria: including other factors affecting the corneal epithelial healing, the contraindications of excimer laser refractive surgery, and other factors affecting the vision such as:
  - Eyes with marked surface irregularity.
  - Eyes with significant history of RCE.
  - Eyes with history of severe allergy, severe dryness, previous ocular infection such as viral keratitis or trauma.
  - Eyes with decreased corneal sensation.
  - Eyes with manifest refractive SEQ > -6 D.
  - Eyes with corneal pachymetry < 500 µm.
  - Eyes with cataract, glaucoma, or iridocyclitis.
  - Eyes with retinal diseases such as dystrophies and vascular disorders.

History taking

Detailed personal history, family history (which was positive in 100% of the cases), general medical history, and detailed ophthalmic history (including history of ocular diseases, medications, investigations, laser treatment or ocular surgeries, history of using glasses and at what time of life, and history of contact lenses (CL) use) were taken at base-line for all the patients, and all CL users are advised to stop one week before the PRK treatment.

Full ophthalmologic examination

Full ophthalmologic examination including the refraction, unaided visual acuity (UVA), BCVA; using Snellen’s decimal format, pupillary examination, slit lamp examination of the anterior segment, applanation tonometry, and dilated fundus examination of the macula, disc, retinal blood vessels and retinal periphery by slit lamp biomicroscopy were done at base line examination.

Corneal investigations

All patients had corneal investigations (at Oyoun Hospital, Cairo) including anterior segment photographing, corneal topography and pachymetry using Wavelight – Allegro Oculyzer pentacam (Alcon; a Novartis Company, US), and Optovue corneal OCT (Optovue, Inc, CA) prior to treatment, 2 weeks postoperatively, every 3 months, and at any time of new visual complaints until the end of follow up period.

Patients’ information

All patients were informed about the nature of the disease, the PRK with MMC operative details, the lesser predictable results of excimer laser treatment in the presence of that corneal pathology, the postoperative possible complications, and the possibility of recurrence of the primary pathology which may need further intervention. All patients provided informed consent prior to treatment.

Operative and post operative details

Operative steps summary

(PRK with MMC application at Oyoun Elneel Lasik Center, Cairo; using Wavelight EX 500 excimer laser (Alcon; a Novartis Company, US)).

Topical anesthetic drops were instilled starting about 15 minutes prior to surgery. After inserting the lid speculum, enough area of corneal epithelium was removed using the hockey-knife to allow central excimer laser ablation after drying. Then 0.002% MMC soaked sponge was applied onto the corneal surface for 12 seconds, finally about 30 cc of cold BSS was used for copious irrigation and soft bandage CL was applied to cover the epithelial defect.

Post operative Follow-up

Prophylactic topical antibiotics, topical steroids, as well as artificial tears to help lubrication were prescribed. Systemic analgesics and sometimes topical diclofenac sodium eye drops were also recommended to kill the post operative pain. Careful slit lamp and corneal examination were done at day one, and at day 5 to remove the CL after complete epithelial healing (which occurred in all patients between day 3-5). Weak steroids (with dose tapering) and artificial tears were continued about one and half months post-operatively.

Long term follow up

Full ophthalmologic examination and corneal investigations were done after 2 weeks from the operation, every 3 months for 18 months, and at any
time when patients had any complaints.

**Statistical analysis**

The changes of BCVA and the manifest SEq were statistically analyzed using the paired T-test. The data obtained including the R, the M, and the standard deviation (SD) were used to obtain P-value, and P value less than 0.05 was considered statistically significant (Franz et al., 2007).

**RESULTS**

The central corneal clarity, the BCVA and the manifest refraction improved in all patients after PRK with MMC application.

The changes of SEq from base-line examination to 2 weeks postoperatively are shown in table (1):

The changes of SEq from base-line examination to 2 weeks postoperatively are shown in table (2):

The M 2weeks postoperative corneal front diopteric power was: 39.15 ± 0.932 D; R: 37.7-40 D, The M postoperative pachymetric thinnest location was: 432 ± 14.39 µm; R: 415-450 µm.

**Post operative complications**

Visually significant corneal haze was noticed in the first post operative few weeks in 2 eyes (28.6 %) which were resolved by topical steroids. Visually insignificant recurrences of scattered few superficial granular deposits occur in 2 eyes (one eye of 22 years old male who had bilateral PRK (case 1), and the other eye of 36 years old female who had unilateral PRK) at the 6 months follow up period without any significant changes in their manifest refraction. On the other hand; visually significant recurrence was remarked in one eye (14.29%) which was the other eye of case 1 at the 6 months follow up period, and the patient had PRK redoing, and after redoing all significant opacities have been eliminated with returning of clear vision until the end of follow up period. So the total recurrences of the granular deposits have occurred in 3 eyes (42.86%).

**Case report**

The clinical course and investigations of case (1) are summarized in figures (1-12):

**DISCUSSION**

PTK is done regularly for anterior corneal diseases such as corneal dystrophies, corneal degenerations, scars, and band-shaped keratopathy, PTK should be limited to the anterior corneal lesions only, as deeper scars need deeper ablations and may result in a more haze formation (Rathi et al., 2012).

The visual and refractive outcome of excimer laser PTK for granular and lattice CD was studied by Das et al. (2005), and their results have shown improvement in the BCVA in 79% and 62% of eyes with granular and lattice CD, respectively. But spherical equivalent refraction increased by a M of 1.3 +/- 1.7 D for GCD and a M of 1.0 +/- 1.8 D for lattice CD.

Stark et al. (1996) have reported that Ablations above 85 – 100 microns show a hyperopic refractive shift, Starr et al. (1996) on studying the refractive changes after PTK have shown a refractive shift of more than or equal to 1 D in 63% of the patients.

Campos et al. (1993) have shown that BCVA improves and UVA may reduce after PTK treatment for different corneal opacities.

Dogru et al. (2001) have concluded that, a significant amount of PTK tissue removal will induce refractive error, the type and amount depends on the site and depth of ablation; central ablation will flatten the cornea and induce a hyperopic shift, similarly peripheral ablation will result in removal of tissue in the periphery and will induce myopia. They have also concluded that, with the better overall outcome of PTK procedures, the research should be directed toward preventing recurrences of primary disease pathology, and for better predictability of post-PTK refractive error and combining PTK with PRK for both good visual and symptomatic outcome.

Zaidman et al. (2006) have concluded that combined PTK/PRK have resulted in improvement of the visual and refractive results in patients with corneal surface disease and refractive errors.

In my study; as the refractive outcome is an important issue for the patients, in the light of topographic data, I have used PRK with MMC method which has not only cleared the corneal opacities and improved the visual acuity in all patients, but it has also corrected the patients’ refractive errors. The study of Das et al. (2005) have shown that Recurrences were observed in (20%) of eyes with GCD and 17% of eyes with lattice CD after excimer laser treatment during a mean follow up of 3.0 +/- 2.7 years.

Recurrence of corneal pathology after excimer laser PTK was studied by Dinh et al. (1999), including fifty PTK procedures performed in 43 eyes of 33 patients with corneal dystrophies. Preoperative diagnoses included Reis-Bücklers dystrophy (13 eyes), GCD (11 eyes), anterior basement membrane dystrophy (11 eyes), lattice CD (7 eyes), and Schnyder crystalline dystrophy (1 eye). Three (23%) of 13 eyes with GCD were found to have a significant recurrence after PTK. They concluded that, excimer laser treatment can restore and preserve useful visual function for a significant period of time in patients with anterior corneal
Table 1. Postoperative statistically significant improvement of SEq refraction

<table>
<thead>
<tr>
<th></th>
<th>preoperative</th>
<th>(2 weeks) postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEq (M±SD)</td>
<td>- (3.91 ± 1.4737)</td>
<td>- (0.0714 ± 0.4009)</td>
</tr>
<tr>
<td>M difference</td>
<td>-</td>
<td>3.8386</td>
</tr>
<tr>
<td>95% confidence interval of this difference</td>
<td>From - 5.0963 to - 2.5809</td>
<td></td>
</tr>
<tr>
<td>t</td>
<td>6.6499</td>
<td></td>
</tr>
<tr>
<td>Degree of freedom (df)</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Standard error of difference</td>
<td>0.577</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.0001</td>
<td>(extremely statistically significant)</td>
</tr>
</tbody>
</table>

Table 2. Postoperative statistically significant improvement of the VA

<table>
<thead>
<tr>
<th></th>
<th>Preoperative BCVA</th>
<th>2 weeks post PRK VA</th>
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<tr>
<td>VA (M±SD)</td>
<td>(0.314 ± 0.212)</td>
<td>(0.9 ± 0.115)</td>
</tr>
<tr>
<td>M difference</td>
<td>-</td>
<td>0.586</td>
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<tr>
<td>95% confidence interval of this difference</td>
<td>From - 0.784 to - 0.387</td>
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<tr>
<td>t</td>
<td>6.4293</td>
<td></td>
</tr>
<tr>
<td>df</td>
<td>12</td>
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<tr>
<td>Standard error of difference</td>
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<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.0001</td>
<td>(extremely statistically significant)</td>
</tr>
</tbody>
</table>

Figure 1. Preoperative slit lamp corneal images (BCVA: Rt. = 0.1, Lt. = 0.3, manifest refraction: Rt. = -5.25/-1@115, Lt. = -5.25/-1.25@60).

Figure 2. Preoperative corneal topography.
Figure 3. Preoperative corneal OCT (vertical and horizontal line scan images).

Figure 4. Day 1 postoperative slit lamp images (the PRK optical zone: 7mm, the ablation depth: Rt. = 106 µm, Lt. = 110 µm, the stromal bed: Rt. = 403 µm, Lt. = 401 µm).

Figure 5. 2 weeks postoperative corneal topography (VA: Rt. = 0.9, Lt. = 0.9).

Figure 6. 6 months postoperative scheimplug images showing clinical significant recurrence of the granular opacities in the Rt. cornea and mild recurrence in the Lt. cornea (BCVA: Rt. = 0.3 (with marked glare), Lt. = 0.8 (without patient’s complaint), manifest refraction: Rt. = -3.75/-1@120, Lt. = -0.50/-0.50@170).
Figure 7. 6 months postoperative 3D map images showing the dense clinical significant recurrent opacities (white color) in the Rt. cornea; (corneal front: red lines, corneal back: green line, Iris in Rt. C image: blue lines, Lens in Lt. C image: yellow lines, and the clear area below the mild recurrent superficial opacities in the Lt. C image: grey shadow).

Figure 8. Rt. C image at PRK redoing showing the recurrence of granular deposits with opacification of the intervening spaces.

Figure 9. Rt. C topography just before PRK redoing

Figure 10. Rt. C image at the end of PRK redoing (As regard the potential MMC toxicity on the endothelium in deeper ablation, application of MMC was not performed during PRK redoing)
dystrophies. Even though corneal dystrophies are likely to recur eventually after PTK, successful retreatment with PTK is possible.

In my study, visually insignificant recurrences have been remarked in 2 eyes (28.6%), while severe visually significant recurrence which affected the patient refraction and keratometric measures, and resulted in visual blurring and reduction of the BCVA has been remarked in 1 eye (14.3%). The M time of recurrences was the 6th postoperative month. The incidence of recurrences was directly related to the depth of the original preoperative corneal opacities in relation to the intact BM (> 85 microns in the 3 eyes).

Stewart et al. (2002) on studying the visual and symptomatic outcome of excimer PTK for corneal dystrophies have concluded that, residual deposits may remain in the cornea, but frequency of RCE is reduced in dystrophies and also the visual axis is relatively clear.

In my study, residual fine deposits mostly outside the central 7 mm of the cornea were noticed after the primary PRK treatment without any visual significance.

Vyas and Rathi (2008); on studying PTK for corneal dystrophies have concluded that, lattice, macular, and GCD are known to recur. The patient may have good vision even in the presence of a recurrence. Clinically significant recurrences may not need further intervention, unless it becomes a cause for visual disturbance.

In my study, PRK redoing was performed in 1 eye (case 1) who suffered from visual disturbance after marked recurrence of the granular deposits, after PRK redoing the visual axis was sufficiently cleared with regaining of the clear vision until the end of the follow up period.

Kim et al. (2006), and Ayres et al. (2006) have recommended the use of intra-operative MMC to prevent recurrent anterior corneal pathology after PTK.

Multiple studies by Morales et al. (2006), Epstien et al. (2007), and Roh et al. (2009) have evaluated the impact of MMC on the corneal endothelium during PRK, and these studies have shown conflicting evidence about whether MMC use results in a decrease in endothelial cells count in treated eyes, with some studies demonstrating a decline and others noting no statistically significant difference in cell counts.

Epstien et al. (2007) have published a study in which 16 eyes with a planned ablation depth greater than 75 µm underwent PRK followed by 0.02% MMC application for 12 seconds. Preoperative and one year postoperative specular microscopy was done, and they didn't find any significant differences in endothelial cell density or the percentage of hexagonal cells. They have concluded that reduction of MMC application time from 2 minutes to 12 seconds can effectively prevent keratocytes from turning into fibrocytes and starting a scarring reaction.

Thornton et al. (2008) have evaluated the efficacy of lower dose of MMC and shorter exposure time. And they have concluded that, reducing the dose of MMC to 0.002% seemed to produce similar results as the 0.02% for shallow ablations, it was not as efficacious in preventing haze in cases of high myopia that required greater ablation depths. Virasch et al. (2010) have also concluded that reducing the application time at surgery from two minutes to twelve seconds produces similar results in haze prevention and refractive results.

Since MMC does cause damage to cellular DNA and theoretically may delay healing of the epithelium after PRK, Leccisotti (2008) demonstrated that the epithelium

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**Figure 11.** Rt. C scheimpflug image 2 weeks after PRK redoing (VA= 0.9).

**Figure 12.** Anterior segment colored photo after pupillary dilation and Rt. C OCT image at the end of the follow up period showing clear red reflex and residual visually insignificant fine scattered deposits (VA= 0.9).
appears to heal over at the same rate with or without MMC.

To avoid the potential endothelial toxicity, and in the light of these valuable studies, I have used the least MMC dose (0.002%) and the least exposure time (12 seconds) in my study; especially in absence of high myopic patients who need greater ablation depths.

In my study, reversible visually significant corneal haze appeared in the first post operative few weeks in 2 eyes (28.6%). While this percentage is not statistically significant due to low number of the participants, but it may be related to the nature of the corneal pathology which may affect the corneal healing behavior, or it may be a result of using diluted dose of MMC. The role of MMC application to prevent the recurrence after excimer laser treatment for patients with GCD should be evaluated more specifically in larger studies.

I have used strict ocular exclusion criteria, and I gave special concern to represent and discuss the nature of GCD, the treatment details, the possibility of recurrence, and the importance of regular postoperative follow up with the patients to increase the safety measures of my study.

The low number of the study participants and the relatively short period of postoperative follow up are two shortage points of my study.

CONCLUSIONS

In the light of my study results, PRK with intra-operative low dose and short time MMC application can provide good therapeutic and refractive solution for low to moderate myopic patients with GCD type 1. The strict early and long-term postoperative follow up and patient compliance are very important to prevent postoperative visually significant haze. Because of the genetic nature of GCD, constant refractive and visual results can’t be guaranteed and the recurrence of GCD may occur. Most recurrences are mild and don’t affect the central corneal clarity and visual functions. In absence of corneal irregularity and RCE, and when the stromal bed thickness permits, PRK redoing can be performed to treat clinically significant recurrences which reduce and blur the vision. PRK with MMC application can delay the need for keratoplasty in large numbers of selected patients (who don’t have higher myopic refractive errors, don’t have any topography related contraindications to laser refractive surgery, and the depth of their central corneal opacities < 20 % of the corneal thickness) in the short term, but a lot of multi-centric studies with larger numbers of participants and longer follow up periods are needed to know if the excimer laser ablation can obviate completely the need for keratoplasty. Proper choice of the subjects, detailed ophthalmologic examination, detailed corneal investigations using high resolution corneal OCT in association with corneal pentacam, giving the patients detailed information about the nature of the disease and the treatment regimen, and the regular follow up increase the efficiency and safety of the procedure.

ACKNOWLEDGMENTS

My deep appreciation to my professors and colleagues in our Ophthalmology Department.

Abbreviations

AD ...............Autosomal dominant
BCVA ..............Best corrected visual acuity
BM ................Bowman’s membrane
CD ................Corneal dystrophy
CL ................Contact lenses
GCD ..............Granular corneal dystrophy
MMC ................Mitomycin C
OCT ................Ocular coherence tomography
PRK ..............Photorefractive keratectomy
PTK ..............Phototherapeutic keratectomy
RCE ...............Recurrent corneal erosions
SEq ................Spherical equivalent
TGFBI..............Transforming growth factor, beta induced
UVA ................. Unaided visual acuity

Source of support

None

Conflict of interest

None

REFERENCES

Thornton I, Xu M, Krueger RR (2008). “Comparison of standard (0.02%) and low dose (0.002%) mitomycin C in the prevention of corneal haze following surface ablation for myopia”, Journal of Refractive Surgery, Vol. 24, pp. 68-76.

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