ejpmr, 2023, 10(5), 17-23

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

HOW DOES MITOMYCIN C AFFECT THE POSTERIOR STROMAL KERATOCYTE DENSITY AFTER PHOTOREFRACTIVE KERATECTOMY? SCIENCE HELPING TO FACILITATE PUBLIC HEALTH COSTS IN OPHTHALMOLOGY

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Article Received on 24/02/2023 **Article Revised on 17/03/2023** **Article Accepted on 06/04/2023**

ABSTRACT

Background: Mitomycin C is used to prevent corneal opacity. The present study seeks to investigate the influence of Mitomycin C on the number of Keratocyst in the posterior layer of corneal stroma after photorefractive keratectomy (PRK). **Materials and Methodology:** The cohort method was utilized to conduct this study. 26 eyes among those resorting to the eye hospital of Al-Zahra in Zahedan were selected and convenient sampling was carried out among those patients who had undergone photorefractive keratectomy (PRK). The number of Keratocyst layers in the posterior corneal layer of the patients was counted before the operation and three months after that. Student T-test was utilized to analyze the data. **Results:** Before the operation, the average spherical equivalent of refractive errors was -3.6 $\pm$ 15.6μ and the average corneal thickness of the patient was 538$\pm$41.2μ with the average depth of corneal removal being 74.7 $\pm$ 15.6μ. The average number of the Keratocysts in the posterior layer of corneal stroma before and three months after the operation were 714.6 $\pm$ 12.1 and 714.7 $\pm$ 12.9 repectively. No significant difference was observed between the number of Keratocysts before and after the operation (p=0.838). **Conclusion:** Using Mitomycin 0.02 C for 20 seconds during RPK in patients suffering from low myopia does not result in statistically significant changes in the number of Keratocysts in the posterior corneal layer in the 3-month follow up. Thus it doesn't seem necessary to impose Mitomycine C to patient's costs of surgery.

KEYWORDS: Photorefractive Keratectomy, Mitomycin C, Confoscan III.

INTRODUCTION

Photorefractive Keratectomy is a popular refractive surgery that is highly recommended and confirmed for its safety and for correcting the refractive errors in eyes.[1] Argon fluoride excimer laser which has a 193 nm wavelength reduces the refractive errors by carving through the anterior corneal stroma and changing the curvature of the anterior surface of the cornea. The absorption rate of the Argon fluoride excimer is considerably high in the cornea. A large portion of collagen peptides consists of carbon-carbon and carbon-nitrogen bonds. A photon with a wavelength of 193 nm is considerably capable of breaking the above-mentioned bonds. Radiation of the excimer laser breaks the corneal collagen peptides into small pieces and every pulse of the laser removes a specific amount of the cornea. After removing epithelium in photorefractive keratectomy, tissues are carved in order to change the refractive power of the cornea. The natural structure of the extra-cellular matrix changes after PRK. As the number and shape of the cells change, a variable level of disorganized extra-cellular matrix and Myofibroblasts are formed which will result in less transparency of the tissue by forming sub-Epithelial opacity that might be clinically significant in some patients.[2] Various studies have shown that reduction of cornea opacity after photorefractive

keratectomy through the prescription of Mitomycin C is possible.[3] Mitomycin C (MMC) is an alkylating anti-tumor medicine first separated from streptomyces caespitosus in 19564. MMC exerts its effect by interfering with DNA replication, thereby preventing protein synthesis and inhibiting mitosis. Regardless of the cell division phase, this substance influences all cells; however, its greatest anti-proliferation effect is recorded on cells with a high rate of mitosis. This substance has various applications in ophthalmology.[4,5]

Since the early 1960s, MMC has been used after Pterygium surgery in order to prevent recurrence and also to increase the chance of success in filtering surgery and as an alternative treatment in treating conjunctival epithelial neoplasia. MMC is also used as a useful pharmacokinetic method to adjust the restorative responses, reduce fibrosis, and improve the results of applying PRK.[6-13] Prophylactic application of 0.02% MMC solution results in less corneal opacity, uncorrected visual acuity (UCVA) and, as a result, better visual results after corneal refractive operations.[14] Despite these results, scientists have pointed to the toxic effects of MMC and there are some worries about the side effects of this medicine.[15] MMC is capable of causing damage to all three types of corneal cells namely epithelial (the distinguished cells of Epithelium and limbal area), stromal (Keratocyst), and endothelial cells.[16]

The study conducted by Fister has reported a case of corneal edema following phototherapeutic keratectomy using standard 0.02% MMC.[17] It is proved that topical prescription of MMC blocks fibroblast proliferation in the Conjunctivitis tissue.[18] Since Al-Zahra eye hospital of Zahedan uses PRK as one of the commonest types of corneal refractive surgery and many people resort to this hospital for it and topical MMC is used to prevent corneal opacity for every applicant[20-23] while it costs extra fees for patients, we decided to study its effect on the number of Keratocysts in the anterior layer of the corneal stroma to investigate weather could we reduce this cost imposition for patients or not.

METHODOLOGY

The study protocol was approved by Zahedan University of Medical Sciences Institutional Review Board and adheres to the tenets of the Declaration of Helsinki (thesis number:ت/533). Written informed consent was obtained from all subjects. Inclusion criteria for the study were age over 18 years, spherical myopia between −2.00 and −5.00 diopters (D), corrected distance visual acuity (CDVA) of 20/25 or better (≥0.1 logMAR), stable refraction for at least 1 year, central corneal thickness more than 500 µm and no use of any kind of contact lenses within the previous 2 weeks. After filling the consent form, all those patients qualified for the research with myopia levels ranging from 2 to 5 diopters were first diagnosed and checked by confocal microscopy (ConfoScan 3, Nidek Co. Ltd, Osaka, Japan) and the Keratocyst cells in the anterior layer of corneal stroma were counted. The information was then recorded on a CD. The following exclusion criteria were also defined: cases in which refractive surgery was contraindicated for them like dry eye, Blepharitis, corneal ulcer and scar, a history of herpetic keratitis, Keratoconus or unstable keratometry readings with irregularly shaped mires, corneal dystrophy or degeneration, Cataracts, glaucoma and retinal disease, those predicted to be left with less than 400 microns of residual stromal thickness of cornea, vascular or ocular collagen disease affecting tear performance or wound healing such as Sjogren's syndrome and using contact lens or any other ocular or systemic medications, immunodeficiency, previous intraocular or corneal surgery. Eyes with keratoconus and subclinical keratoconus were excluded by using the Pentacam Ambrosio-Belin module.

Clinical information of the patients including uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) measurement using Snellen chart, manifest and cycloplegic refractive abnormalities, objective auto refraction measurement using Topcon KR 8900 (Topcon Corp., Tokyo, Japan), anterior segment examination using Slit lamp (Haag Streit, Mason, OH, USA), dilated pupil retinal examination, intraocular pressure measurement (Goldmann applanation tonometry) and Scheimpflug topography (PentacamHR, Oculus Optikgeräte, Wetzlar, Germany) were registered in specific forms. All slit-lamp eye examinations were performed by the same surgeon (Dr. Koroush Shahraki MD.) before and after the procedure and a specially trained optometrist performed all confocal scan tests. At the end of the three-month follow-up period of the patients, the Keratocyst cells in the anterior layer were counted again using (ConfoScan 3, Nidek Co. Ltd, Osaka, Japan) and the results were recorded. Keratocyst cells were manually taken from the central section of the cornea in order to count them. So that a complete layer from endothelium to epithelium was obtained each time and it was shown as a curve by Z scan, and the distance of 50 microns behind the Desme membrane was considered as the posterior layer of the stroma. Using the Navis application which was running on the device, the cells were counted manually in an area of $0.4 mm^2$. The operation was conducted by an expert surgeon who experienced operating using Linear Nide excimer laser devices with a wavelength of 193 nm and a fixed pulse rate of 40 Hz and a ray contact of 96 mJ. The following medicines were used: topical 0.5% Tetracaine (Anestocaine®, Sina daru, Iran) for corneal anesthesia, 10% Betadine as the antiseptics for the skin around the eye and eyelid for 3 minutes, and 20 cc of Saline solution for the purpose of rinsing. The ablation zone was matched with mesopic pupil diameter before the procedure. All surgeries were non-monovision treatments to achieve emmetropia. Using alcohol, 8 mm epithelium from the center of cornea was removed for 20 seconds and photo-ablation was conducted by special software. Then, MMC was prepared. 2 mg vial was

diluted using 10 ccs of distilled water. Then the cornea removed by laser is dried and a sponge dipped in the 0.02% MMC is robbed against the corneal stroma for 25 seconds. The cornea is then rinsed by BSS and a therapeutic disposable contact lens (PureVision, Bausch & Lomb, Rochester, NY, USA) replaces it. After the operation, patients would use 0.5% Chloramphenicol (Chlobiotic®, Sina daru, Iran) drop every 6 hours and 0.1% Betamethasone (Betasonate®, Sina daru, Iran) drop every 6 hours and preservative-free artificial tears, (Sinalone®, Sina Daru, Tehran, Iran) every 3 hours until the full Epithelialization of the cornea for one week. After the full recovery of corneal epithelium (between the 3rd and the 5th day), the contact lens is removed and follow up examinations will be conducted on the 1st, 3rd, and 7th days and on the 1th, 3rd and 6th month after the operation. As mentioned previously, the Keratocyst cells in the posterior layer of corneal stroma will be counted by Confoscan III. Finally, Statistical analysis was performed using SPSS for Windows (version 22, SPSS, Inc.). The Kolmogorov– Smirnov test was used to verify normal distributions. Paired t-test and the non-parametric Wilcoxon signed ranks test (data with no normal distribution) were used to compare any significant changes of mean differences pre and post-operatively. P-value <0.05 was considered statistically significant in this study.

RESULTS

13 patients (26 eyes) refering to Al-Zahra eye hospital participated for photorefractive keratectomy of whom 8 were male (61.5%) and 5 were female (38.5%). The average pre-operation refraction of the patients was -3.6 ± 0.8 Diopters while the lowest and the highest values were -5 and -2.25 respectively. The average corneal thickness of patients was 538.1 ± 41.2 micron with the least and the most values for thickness being 485 and 579 microns respectively. The average ablation levels recorded among the patients was 74.7 ± 15.6 with the least and the most values being 46.4 and 103.8 respectively. (Table 1)

In the present study, the average number of Keratocysts in the posterior layer of corneal stroma was 714.6 ± 12.1 before operation with the least and the most values being 698.5 and 726 respectively.

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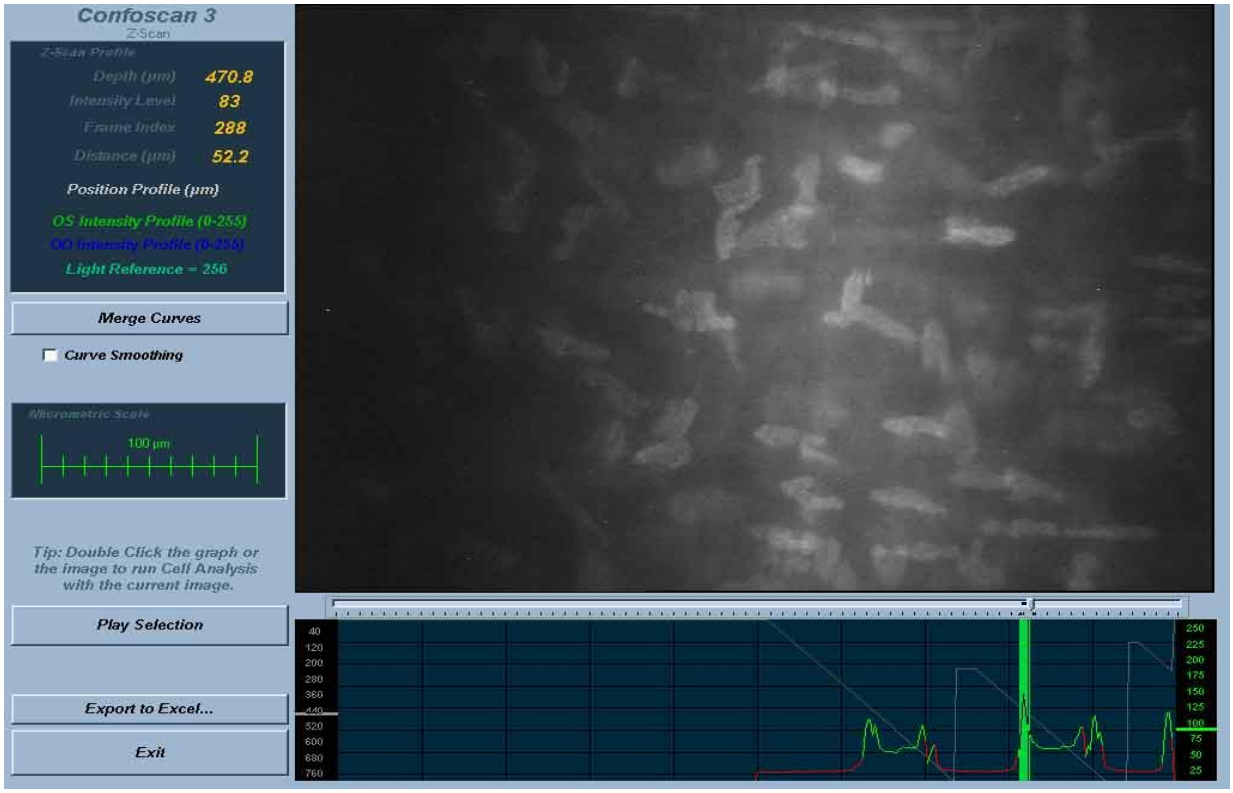

Figure 1: General Confoscan of the patient.

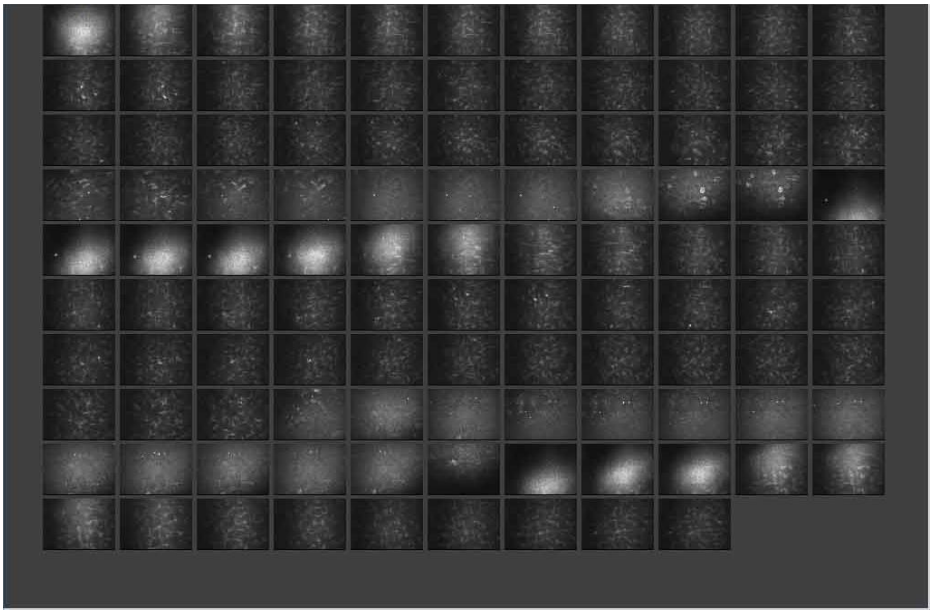

Figure 2: Z-scan curve and 50μ picture of the area behind membrane desme.

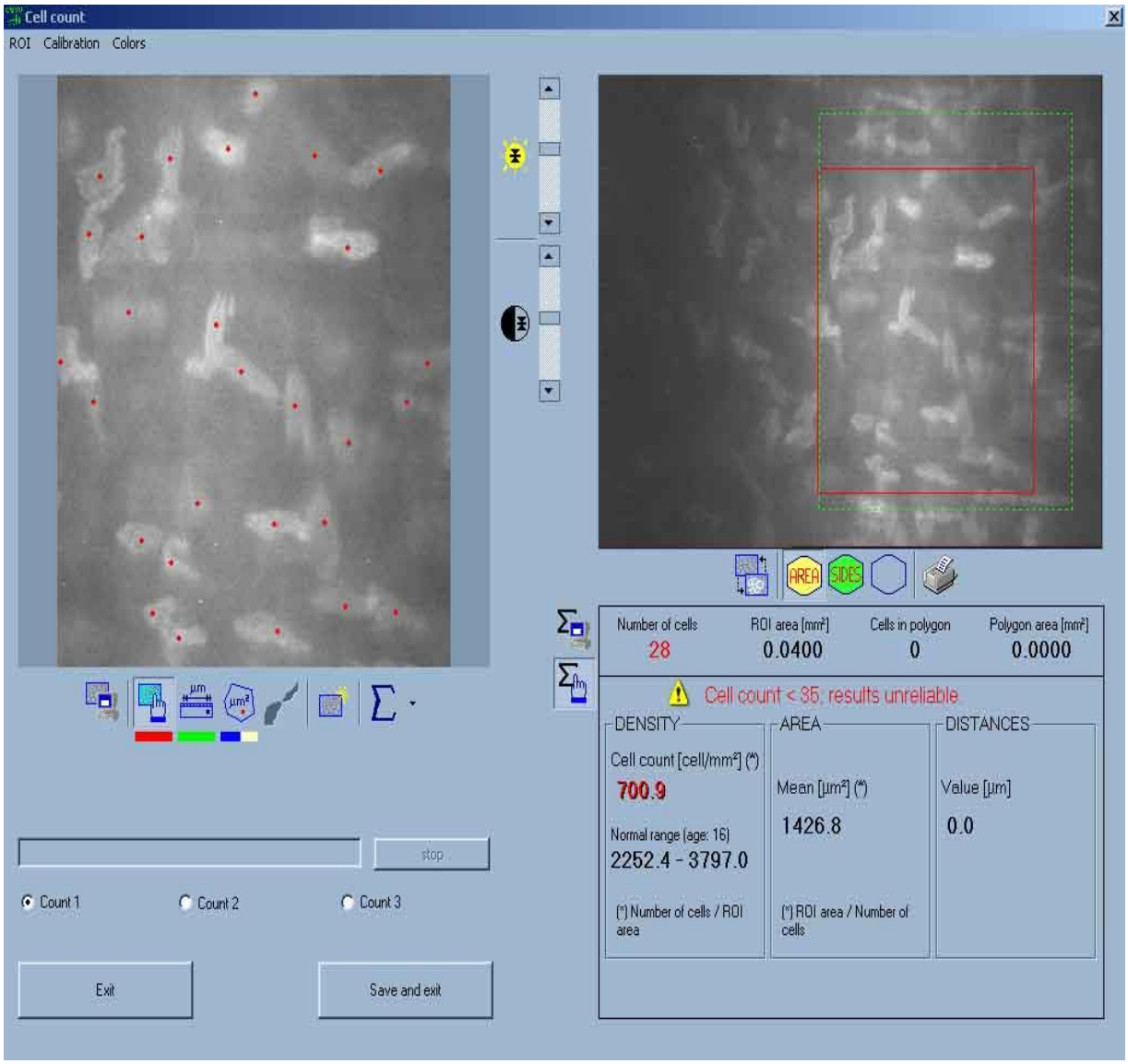

Figure 3: Number of Keratocysts in posterior stroma before operation.

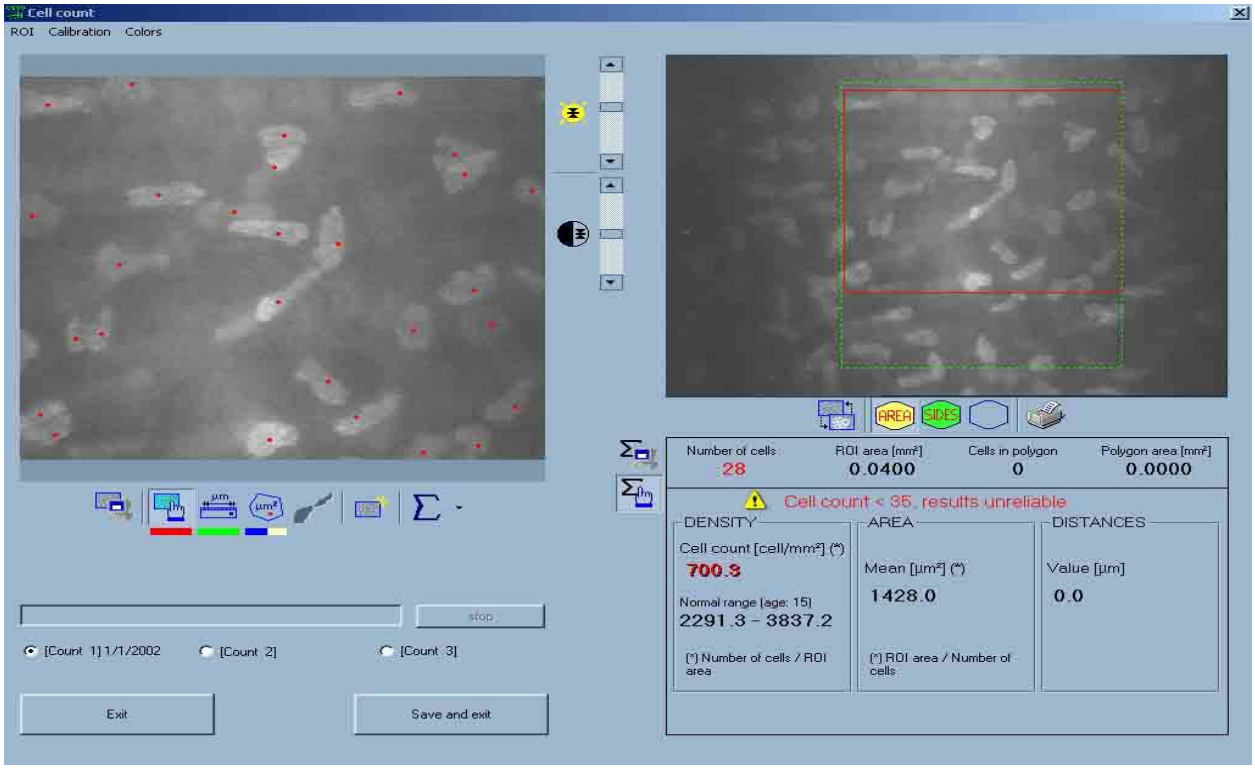

Figure 4: Number of Keratocysts in posterior stroma after operation in the same patient.

Table 1: Other measured variables.

Variable	n = 13 patients, 26 eyes
Sex, Male/female, n (%)	8 (61.5)/5 (38.5)
Age (y), Mean ± SD	25.66±5.22
Eye, Right/Left, n (%)	13/13
Pre-operative UCDVA in LogMAR, Mean ± SD	1.34 ± 0.22
Pre-operative BCDVA in LogMAR, Mean ± SD	0.00 ± 0.12
Post-operative BCDVA in LogMAR, Mean ± SD	0.00±0.012
Mesopic pupil diameter (mm), Mean ± SD	6.22±1.02
Pre-operative CCT(µm), Mean ± SD (Range)	538.1 ± 41.2 (485 to 579)
Post-operative CCT(µm), Mean ± SD (Range)	495.3±25.3(470 to 526)
Pre-operative SE (D), Mean ± SD (Range)	-3.60 ± 0.80 (-2.25 to -5.00)
Post-operative SE (D), Mean ± SD (Range)	0.025±0.25(-0.5 to 0.75)
Depth of ablation (µm), Mean ± SD	74.7 ± 15.6 (46.4 to 103.8)

Table 2: Number of Keratocysts before and after the operation.

	before operation Mean ± SD	after operation Mean ± SD	difference Mean ± SD	P-value
number of Keratocysts in the posterior layer of the corneal stroma	714.6±12.1	714.7±12.9	-0.08±1.72	0.838

DISCUSSION

Using prophylactic MMC might act as a good auxiliary treatment, especially in highly dangerous cases. However, the potential toxicity of MMC is one of the worrying factors. Thus, the advantages and disadvantages of MMC need to be further analyzed.[24-28]

Previous studies have indicated the capability of MMC 0.02% to reduce opacity after PRK.[4]

Causing damage to Epithelium cells during LASEK or PRK operations is the source of releasing cytokines such as IL-1 which results in activating the apoptosis process of Keratocysts through Fas-Fas ligand.[4] MMC can elongate the process of Keratocysts apoptosis after PRK.[29-31]

Generally after the local apoptosis of Keratocysts, their proliferation and transformation into myo-fibroblasts results in scar. The process of Keratocysts transformation into Myo-fibroblasts is restrained by MMC and Corticosteroid which results in less scars.[32]

This research also studied the influence of MMC on the number of Keratocysts in the posterior layer of corneal stroma and no significant change was observed before and after operation.

Most of the research conducted in this field was in line with our research. In a research conducted by Midena et al (2007), it was proved that PRK using MMC 0.02% had no negative effects on the number of corneal Keratocysts.[26] Goldsberry et al (2007) showed that prescribing MMC to prevent opacity after PRK has no qualitatively and quantitatively significant influence on the density of endothelial cells and morphometric parameters.[27] Ketbab et al (2007) concluded that applying MMC in the place of surgery in Keratorefractive operations has no negative effects on recovering the epithelium and flap place or endothelium health and recommended more human studies.[27]

Some researchers achieved different results. Lee et al (2001) showed that topical application of MMC will cause apoptosis in Keratocysts and might result in Myo-fibroblast death through apoptosis and necrosis induction.[24]

Netto et al (2006) also reported the reduction of cellularity of corneal anterior stroma one month after application of MMC.[25]

Kim et al (2003) have also reported the consistency of low cellularity more than 6 months after PRK through MMC.[4]

A 3-month follow-up period in this research showed no reduction in the number of Keratocysts. Thus, local application of MMC with the density and length mentioned previously poses no danger and has no negative effects on epithelium recovery or endothelium health during Keratorefractive operations. This is indicative of the efficacy of this method. However, longer follow-up periods are necessary to investigate the long-term side effects of MMC and vigilance is necessary while taking this medicine.

CONCLUSION

Locally applying MMC 0.02% during Keratorefractive operations has no influence on the number of Keratocysts in the posterior layer of corneal stroma. Therefore it makes sense to eliminate this drug from these procedures and reduce the cost of and time of surgery.

Funding, Acknowledgement, conflict of interest

No Funding, no Conflict of interest.

This paper is dedicated to the memory of our dear co-worker Dr. Mohammad Naeim Aminifard, who sacrifices his life for his country and people.

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