Review Article

Mitomycin C application after photorefractive keratectomy in high, moderate, or low myopia: Systematic review and meta-analysis

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Photorefractive keratectomy (PRK) is considered a safe approach laser procedure with a clinical significance in correcting myopia results. PRK requires removing the whole superficial epithelium. The integrity of the epithelial basement membrane and the deposition of abnormal extracellular matrix can put the cornea in a probable situation for corneal haze formation. Mitomycin C (MMC) is applied after excimer laser ablation as a primary modulator for wound healing, limiting corneal haze formation. We aim to summarize the outcomes of MMC application after laser ablation. We searched Scopus, PubMed, Cochrane CENTRAL, and Web of Science till December 2020 using relevant keywords. The data were extracted and pooled as mean difference (MD) or risk ratio (RR) with a 95% confidence interval (CI), using Review Manager software (version 5.4). Our analysis demonstrated a statistically significant result for MMC application over the control group in terms of corneal haze formation postoperatively (RR = 0.29, 95% CI: [0.19, 0.45], $P < 0.00001$). Regarding corrected distance visual acuity (CDVA), no significant difference was observed between the MMC group and the control group (MD = 0.02; 95% CI: [-0.04, 0.07]; $P = 0.56$). Regarding the uncorrected distance visual acuity (UDVA), the analysis favored the MMC application with (MD -0.03, 95% CI: [-0.06, -0.00]; $P = 0.05$). There was no statistically significant increase in complications with MMC. In conclusion, MMC application after PRK is associated with a lower incidence of corneal haze formation with no statistically significant side effects. The long term effect can show improvement regarding UDVA favoring MMC. However, there is no significant effect of MMCs application regarding CDVA, and SE.

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Myopia is a common disorder of refraction in which near objects are seen clearly, but distant objects are blurred due to focusing images in front of the retina instead of on the retina.[1] Mild myopia is 0 to − 1.5 D, moderate − 1.5 to − 6.0 D, and high myopia − 6.0 D or more. Pathological myopia occurs with more than − 8.0 D.[2]

Photorefractive keratectomy (PRK) is a laser approach with safe results in correcting myopia.[1] Many approaches are used for correcting myopia, such as LASIK, Femto-LASIK, and PRK, to correct myopia.[3,4] Steven Trokel and his group developed PRK in 1983; then, it was first implemented by Theo Seiler in 1987.[1] The FDA-approved PRK in 1996, and it became the chosen surgical procedure in treating ametropias for its significant results.

PRK is done on the corneal surface and requires removing the whole superficial epithelium under Bowman's layer, then remodeling the corneal surface through ablation of the stroma by the excimer laser.[5] With the recent advances in technology, a new PRK procedure has emerged, less invasive than conventional PRK. Trans-epithelial PRK is a hand-free operation in which both the epithelium and stroma are removed in a single step, unlike conventional PRK, which requires a manual or alcohol-assisted removal of the cornea.[6] There are two techniques for PRK: wavefront-guided (WFG) or wavefront-optimized (WFO), and there is no significant difference between the two techniques.[7,8] PRK may be complicated with mild pain, delayed visual recovery, and corneal haze.[9] Corneal haze is one of the late complications of the PRK procedure caused by the migration of keratocytes and deposition of glycosaminoglycans and collagen in the anterior stroma during the healing period.[9] Kim *et al*. 2004[10] developed a grading scale for corneal haze after photoablation: Scale 0 means clear cornea, scale 0.5 means faint haze, scale 1 means mild haze seen only with tangential illumination, scale 2

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means faint opacity seen with direct illumination, scale 3 means opacity obscuring iris details, while scale 4 means opacity seen without slit lamp.[10] Mitomycin C (MMC) is applied after the ablation as prophylaxis against the recurrent corneal haze or primary as a modulator for healing.[11,12] The first use of MMC was a chemotherapeutic agent for its antimitotic action. It blocks DNA synthesis by producing cross-linking between guanine and adenine in the DNA molecule.[13–15] Hence, it became widely used in refractive surgeries for its effect as a wound healing modulator and its effect as a healing modulator compared to PRK alone. PRK with MMC did not show any significant side effects on corneal keratocytes.[12,16] Strikingly, several studies reported that the topical use of 0.02% MMC with PRK is safe and decreases haze formation, produces better results regarding uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), and better refractive outcomes.[11,17–19] The application of MMC intraoperatively during PRK did not produce significant changes in endothelial cell density (ECD) or tear deficiency.[20,21] In a recent study on 130 myopic patients,[22] MMC 0.002% prevented haze formation after PRK and recommended using low MMC concentrations to avoid the unclear long-term effects.[22] However, other clinical trials concluded that the use of MMC might result in corneal endothelial cell loss and the rate of loss depends upon the duration of exposure to MMC.[23,24]

Therefore, this systematic review and meta-analysis aim to summarize MMC application outcomes during the PRK procedure, either WFG or WFO, and conclude whether MMC use is a safe application.

Methods

We carried out this systematic review and meta-analysis according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA checklist) guidelines and the Cochrane handbook for interventional studies.[25,26]

Inclusion and exclusion criteria

We included all randomized clinical trials (RCTs) that met the following criteria: (1) patient undergoing PRK, (2) intervention is MMC application during surgery, (3) data on humans only, and (4) outcome was the efficacy and safety of MMC application after PRK surgeries.

We excluded the following: (1) thesis and conference papers, (2) non-English studies, (3) editorials and letters, (4) animal and *in vitro* studies, (4) book chapters, (5) duplicates and overlapping data sets, and (6) study designs other than clinical trials.

Literature search and studies selection

We conducted a systematic search in the four electronic databases: PubMed,

Scopus, Web of Science, and Cochrane Central Register of Controlled Trials

(CENTRAL) using the following search strategy: ("Mitomycin C" OR "Mitomycin-C" OR "Mitocin-C" OR "Mitocin C" OR "MitocinC" OR "NSC-26980" OR "NSC 26980" OR "NSC26980" OR Ametycine OR Mutamycin) AND ("Photorefractive Keratectomy" OR "Photorefractive Keratectomies"). The retrieved records' titles and abstracts were screened by four independent reviewers, followed by full-text screening for eligibility. Any disagreements were solved through debate and consensus.

Data Extraction

All authors extracted the data in the form of the following domains: (1) Baseline characteristics including the number of participants in each group, age, and the ablation depth; (2) summary of the included studies including the study design, country, length of follow-up, inclusion criteria, and the characteristics of each group's treatment dose, 3) risk of bias domains including selection bias, performance bias, detection bias, reporting bias, attrition bias, and other types of bias, and (4) study outcomes. All reviewers extracted the data from the included articles independently, and there was a discussion to solve any discrepancies.

Quality assessment

We used the Cochrane quality assessment tool (version 1) reported in the Cochrane Handbook of Systematic Review Interventions 5.1.0 (updated March 2011).[26] Risk of bias the assessment

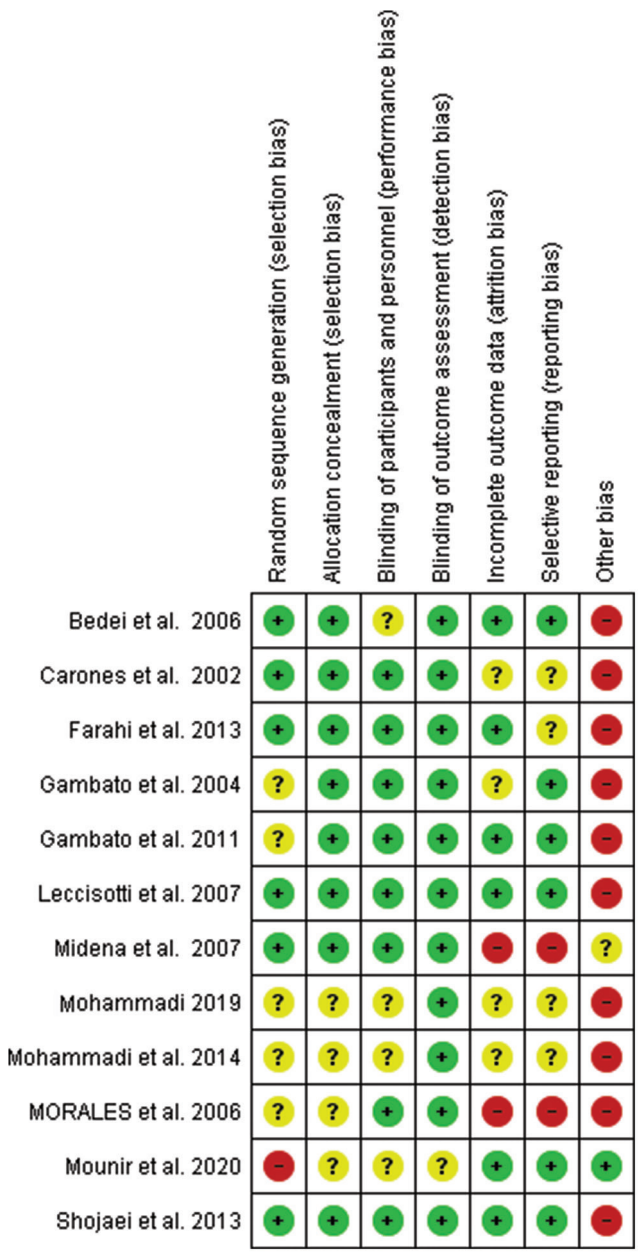

Figure 1: Risk of bias summary of the included studies.

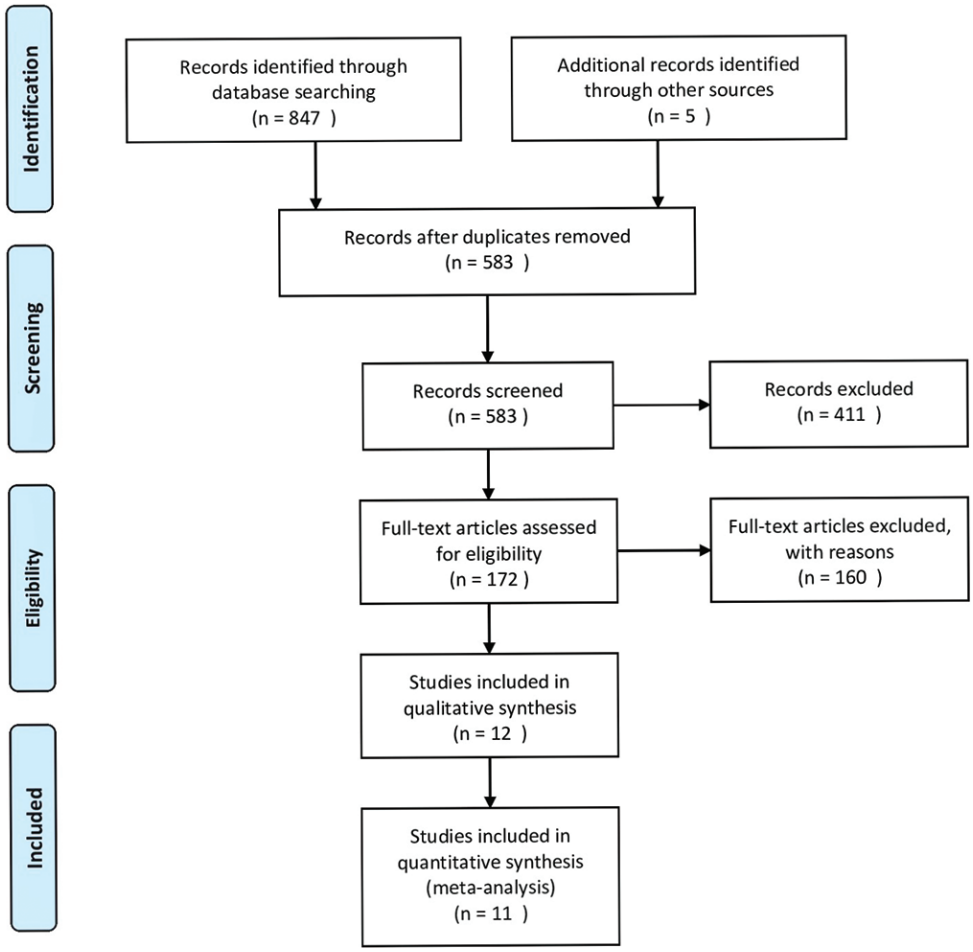

Figure 2: PRISMA flow chart

included the following domains: sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias. The authors' judgments are categorized as "Low risk," "High risk," or "Unclear risk" of bias. We used the quality assessment table (part 2, Chapter 8.5) in the same book.[26] According to Egger and colleagues, publication bias assessment was not reliable due to the limited number of the included studies.[27] Hence, in this review, we were unable to assess the presence of publication bias by Egger's test for funnel plot asymmetry. (Fig. 1)

Data synthesis

We used the mean difference (MD) to analyze continuous outcomes and used the risk ratio (RR) to analyze dichotomous outcomes. The analysis was performed using (Review Manager software, version 5.4) under a fixed-effect model in case of homogenous outcomes and a random effect model in case of heterogeneous outcomes. In the case of missing standard deviation of mean change from baseline, it was calculated from standard error or 95% confidence interval (CI) according to Altman.[28] We used Review Manager software 5.4 to conduct the meta-analysis.

Heterogeneity assessment and measurement were done by visual inspection of the I-Square and Chi-square test on the forest plot. We test the existence of significant heterogeneity by Chi-square test, while I-square quantifies the variability in effect estimates due to heterogeneity.

The I-Square test was defined according to the guidelines of the Cochrane Handbook of Systematic Reviews and meta-analysis (0– 40%: might not be important; 30–60%: may represent moderate heterogeneity; 50– 90%: may represent substantial heterogeneity; and 75– 100%: considerable heterogeneity). Significant heterogeneity was considered at Chi-square $P < 0.1$.

Subgroup analysis

We conducted a subgroup analysis to assess whether the effect estimates differ significantly according to the period of administration of MMC.

Results

Results of the literature search

The literature search yielded 579 unique citations. Following title and abstract screening, 172 full-text articles were screened for eligibility regarding our inclusion criteria. Of these 172 articles, 12 were included in our study (see PRISMA flow diagram) [Fig. 2].

Table 1: Summary of the included studies

Study ID	Study design	Country	Length of follow-up	Inclusion criteria	Exposure group	Control group	Treatment dose	Disease
Shojaei *et al.* 2013[29]	Prospective randomized sham-controlled double-masked clinical trial	Iran	6 months	"The inclusion criteria were an ablation depth less than 65 mm, a stable refractive error for at least 1 year, and a corrected distance visual acuity (CDVA) of 0.1 logMAR or better"	93 received intraoperative topical MMC 0.02% for 5 s chloramphenicol + dexamethasone	91 control received balanced salt solution (BSS) + chloramphenicol + dexamethasone	0.02% MMC for 5 s	low myopia
Morales *et al.* 2006[24]	Prospective, randomized, double-blind, placebo-controlled crossover trial	Israel	3 months	"Nine subjects (18 eyes) with bilateral myopia who needed 75 mm or more of corneal ablation"	9 eyes was randomly assigned to intraoperative topical MMC treatment + gentamycin	9 eyes (the control eye) was treated in a standard fashion with topical balanced salt solution (BSS) + gentamycin	0.02% MMC for 30 s	bilateral myopia
Leccisotti *et al.* 2007[30]	Prospective, randomized, double-masked, same-day, paired eye study	Italy	12 months	"Inclusion criteria: bilateral spherical equivalent (SE) between 26.5 and 210 D, difference of SE between the 2 eyes of 0.75 D, central pachymetry 0.520 mm, with a difference between the 2 eyes of 0.20 mm, follow-up 12 months"	52 eyes Underwent PRK with MMC + levofloxacin + diclofenac	the other eye of the 52 patients underwent PRK + levofloxacin + diclofenac	0.02% MMC for 45 s	-
Gambato *et al.* 2011[31]	prospective, double-blind, randomized study	Italy	5 years	(1) persistent postconcussion symptoms for more than 3 months following mTBI; (2) no contraindications to lumbar puncture (LP); (3) no structural damage on conventional magnetic included 28 subjects (56 eyes) with bilateral myopia	28 eyes highly myopic eyes underwent PRK with MMC	the other 28 eyes underwent PRK + steroid application	0.02% MMC 2 min	high myopia
Gambato *et al.* 2004[12]	Prospective, double-masked, randomized clinical trial	Italy	18 months	"36 subjects (72 eyes) with bilateral high myopia (7 diopters [D]). The difference between one eye and the fellow eye of the same subject was 0.75 D, to avoid any relevant influence of stromal ablation on clinical results"	36 eyes underwent PRK with MMC+ofloxacin	36 eyes underwent PRK with steroid application + ofloxacin	0.02% MMC 2 min	high myopia
Farahi *et al.* 2013[21]	prospective, randomized, double-blind study	Iran	12 months	"Ages between 16 and 75 with a severe TBI based on an admission GCS ≤8 with positive findings on head CT and had at least two CSF samples available for analysis of cortisol and inflammatory markers"	PRK with MMC + ATB	PRK with MMC + BSS	0.02% MMC for 20 s	myopia

Contd...

Table 1: Contd...

Study ID	Study design	Country	Length of follow-up	Inclusion criteria	Exposure group	Control group	Treatment dose	Disease
Carones *et al.* 2002[11]	The prospective randomized	Italy	6 months	"The inclusion criteria were corneal pachymetry greater than 480 m but not thick enough to allow an ablation with an optical diameter of 6.0 mm with an additional 3.0 mm transition zone diameter. In these eyes, the estimated residual stromal thickness beneath the flap after the ablation would have been <250 m. In planning for PRK, the residual corneal thickness postablation was calculated to be >400 m"	30 eyes the study group eyes were treated with a single intraoperative dose of mitomycin-C (0.2 mg/mL), applied topically with a soaked micro sponge placed over the ablated area and maintained for 2 min + steroid	30 eyes underwent PRK with BSS + steroid	0.02% MMC for 2 min	-
Mohammadi *et al.* 2014[32]	Double-masked randomized clinical trial	Iran	6 months	"8- to 45-year-old patients with spherical equivalent (SE) myopia of 0.75-3.87 D, astigmatism up to 1.75 D, and refractive stability for more than 1 year. Excimer laser PRK was performed at the Refractive Surgery Unit, Farabi Eye Hospital, Tehran. Patients received a full explanation of the study; those who signed a written informed consent form were included"	60 underwent PRK with MMC + steroid	60 with balanced solution + steroid	0.02% MMC for 15 s	-
Midena *et al.* 2007[16]	prospective, randomized, double-masked study	Italy	-	"preoperative myopia 7.00 D, best spectacle-corrected visual acuity (BSCVA) of 20/25 or better in both eyes, normal corneal topography, and stable manifest refraction as documented by a 0.50-D change in manifest refractive spherical equivalent shift within the 12 months prior to surgery"	28 eyes underwent PRK + MMC + placebo	28 eyes underwent PRK and receive steroid + fluoroquinolone	0.02% MMC for 2 min	high myopia
Bedei *et al.* 2006[18]	Prospective, consecutive, observational study	Italy	1 year	"Inclusion criteria were age between 22 and 60 years, at least 1 year of refractive stability before surgery, and an attempted spherical equivalent (SE) correction greater than -5.0 diopters (D)"	31 eyes underwent PRK with MMC application + steroid + hyaluronic acid	31 eyes underwent PRK + BSS + steroid + hyaluronic acid	0.02% MMC for 2 min	-
Mohammadi *et al.* 2019[33]	5-year follow-up of a prospective randomized controlled trial	Iran	5 years	-	MMC-treated eyes	BSS-treated eyes	MMC 0.02% for 15 s	low to moderate myopia
Mounir *et al.* 2020[34]	Randomized clinical trial	Egypt	-	-	T-PRK + MMC treated Eyes	Femoto-LASIK-treated eyes	MMC 0.02% for 40 s	-

Table 2: Baseline characteristics

Study ID	Age (years)				Number of patients				Gender (Male/Female)		Ablation depth					
	Intervention		Control		Intervention		Control		Intervention group	Control group	Exposure			Control		
	Mean	SD	Mean	SD	Number of patients	Number of eyes	Number of patients	Number of eyes			Mean	SD	Total	Mean	SD	Total
Shojaei *et al.* 2013[29]	28.58	4.3	29.21	8.56	78	78	74	74	21/57	19/55	48.01	11.22	78	46.76	10.97	74
Morales *et al.* 2006[24]	-	-	-	-	9	9	9	9	-	-	89.9	24.6	9	86.1	25.5	9
Leccisotti *et al.* 2007[30]	33	-	33	-	52	52	52	52	23/29	23/29	-	-	-	-	-	-
Gambato *et al.* 2011[31]	39.9	7	39.9	7	28	28	28	28	12/16	12/16	95.4	19.9	28	93.1	20	28
Gambato *et al.* 2004[12]	34.2	7.07	34.2	7.07	36	36	36	36	16/20	16/20	-	-	-	-	-	-
Farahi *et al.* 2013[21]	25	3.27	25	3.27	27	27	27	27	-	-	-	-	-	-	-	-
Carones *et al.* 2002[11]	31.8	-	31	-	30	30	30	30	-	-	-	-	-	-	-	-
Mohammadi *et al.* 2014[32]	26.76	4.9	26.76	4.9	60	60	60	60	18/42	18/42	-	-	-	-	-	-
Midena *et al.* 2007[16]	39.7	7	39.7	7	28	28	28	28	12/16	12/16	96	18	-	96	18	-
Bedei *et al.* 2006[18]	36	-	35.6	-	31	62	31	62	11/20	13/18	-	-	-	-	-	-
Mohammadi *et al.* 2019[33]	32	5	32	5	54	54	54	54	41/19	41/19	-	-	-	-	-	-
Mounir *et al.* 2020[34]	-	-	-	-	72	72	84	84	32/40	28/56	50	-	72	90	-	84

The total number of patients was 1118 (505 assigned to the MMC group and 513 to the control group). A summary of the finally included 12 articles is presented in Table 1, and the baseline characteristics of their patients are shown in Table 2.

Risk of bias assessment

All studies were low risk in random sequence generation except[23] with high risk and[6,18,24–26] with insufficient data to permit judgment regarding selection bias. All articles were low risk in allocation concealment except four articles,[24,32–34] which have insufficient data making it unlikely to judge. It was unclear to judge the four studies[18,32–34] regarding blinding participants and personnel. All studies were at low risk of bias in the blinding of outcome assessment except one study,[34] which had insufficient data to permit judgment. All studies were at low risk of bias regarding incomplete outcome data except two studies[16,24] with high risk and four studies[11,12,32,33] with insufficient data to permit judgment. Two studies[16,24] were at high risk of bias in selective reporting, and four studies[11,21,32,33] were unclear.

Outcomes

(1) Corrected distance visual acuity:

The pooled studies showed no significant difference in CDVA between the MMC group and the control group (MD = 0.02; 95% CI: [-0.04, 0.07]; $P = 0.56$). Pooled results were homogeneous ($I^2 = 0\%$, $P = 0.70$). Follow-up ranged from 6 to 36 months after surgery.[12,18,34,35] (Fig. 3)

(2) Postoperative uncorrected visual acuity (logMAR):

After 6 and 12 months follow-up, the pooled analysis revealed no significant difference between the MMC group and the placebo group (MD = -0.00, 95% CI: [-0.01, 0.01], $P = 0.91$), (MD 0.00, 95% CI: [-0.04, 0.04], $P = 0.68$), respectively. Pooled results were homogeneous ($I^2 = 0\%$, $P = 0.50$), ($I^2 = 0\%$, $P = 0.65$).

However, after 5 years follow-up, the pooled analysis favored the MMC treatment with a significant difference between the two groups (MD -0.03, 95% CI: [-0.06, -0.00]; $P = 0.05$); pooled studies were homogeneous ($P = 0.42$; $I^2 = 0\%$).[12,21,31,33–35] (Fig. 4)

(3) Spherical equivalent (SE):

After 3 and 6 months follow-up, pooled results showed no significant difference between the two groups (MD = -0.21; 95% CI: [0.53, 0.11]; $P = 0.19$), (MD = -0.03; 95% CI: [-0.11, 0.05]; $P = 0.49$) respectively. Pooled studies were heterogeneous ($I^2 = 85\%$, $P = 0.001$), ($I^2 = 54\%$, $P = 0.05$). The analysis was done under the random effect model and was solved by excluding Farahi *et al*. (2013)[21], and the analysis became significant.

After 12 months follow up, pooled results also showed no significant difference between the MMC group and the control group (MD = 0.12; 95% CI: [0.04,0.29]; $P = 0.15$). Pooled studies were heterogeneous ($I^2 = 72\%$, $P = 0.15$). The analysis was done under a random effect model, and the heterogeneity was best solved by excluding Farahi *et al*. (2013).[21] (Fig. 5)

(4) Corneal haze:

Corneal haze levels are graded from 0 to 4. Visually, significant corneal haze (≥1) is sight-threatening. The proportion of corneal haze grade 1 or higher after PRK was reported from nine studies.[11,12,18,21,29,32,31,34,35]

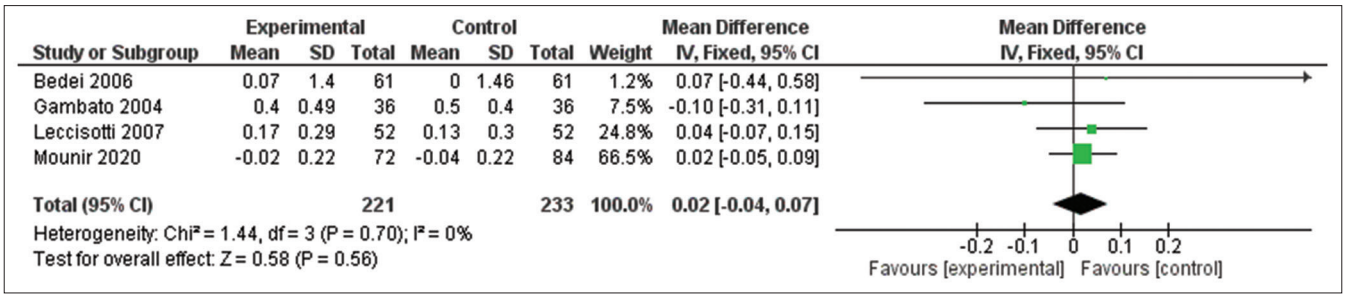

Figure 3. CDVA from 6 to 36 months follow-up

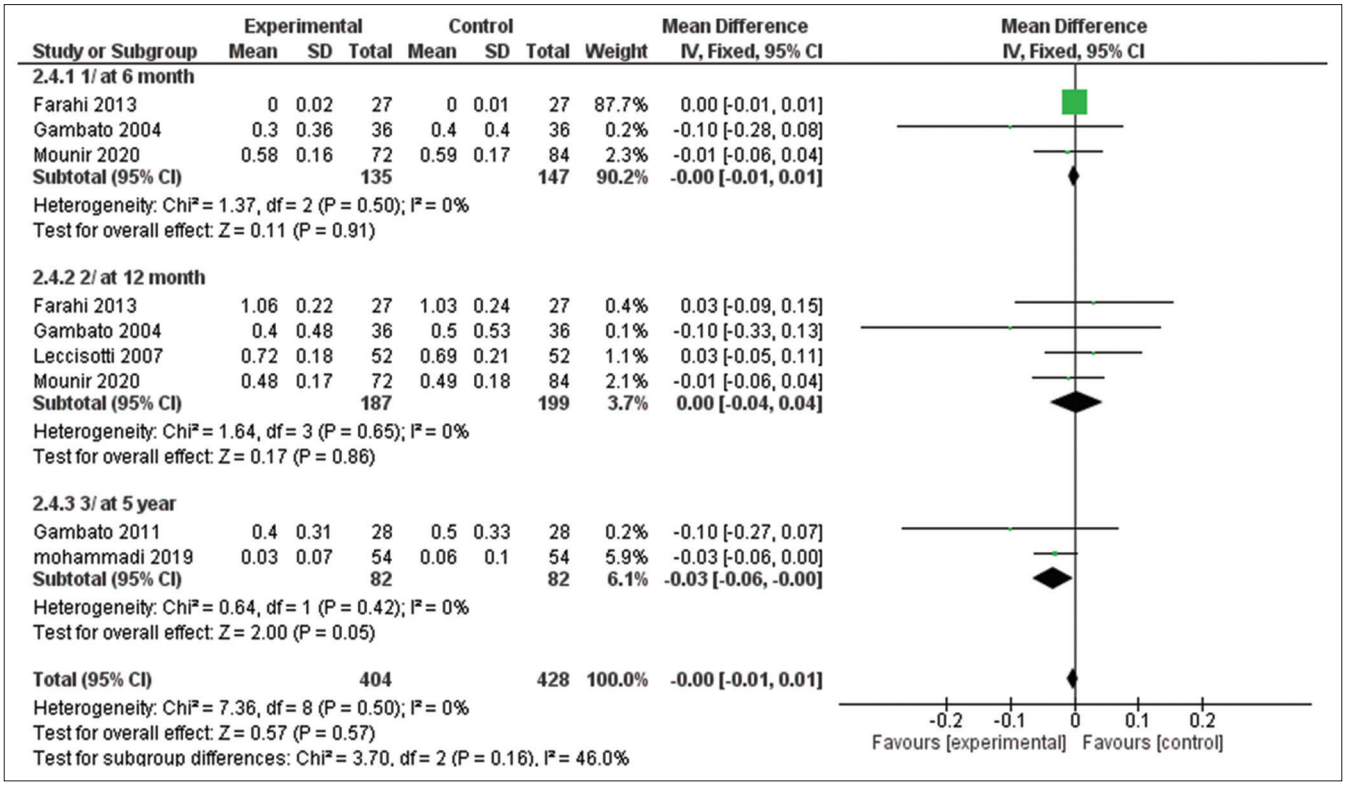

Figure 4. Postoperative Uncorrected Visual Acuity(logMAR) from 6 months to 5 years follow up.

After 3 months follow-up, pooled results showed no significant difference between the two groups in the incidence of corneal haze grade 1 or higher (RR = 0.55; 95% CI: [0.10, 2.90]; *P* = 0.48). Pooled studies were homogeneous (I^2=51%, *P* = 0.15).

However, after 6 months follow-up, the pooled analysis showed that MMC application significantly reduces the incidence of corneal haze grade 1 or higher (RR = 0.12; 95% CI: [0.03, 0.50], *P* = 0.004). Pooled studies were homogeneous (I^2=0%, *P* = 0.75).

After 12 months follow-up. Pooled results showed a significant decrease in the incidence of haze grade 1 or higher after MMC application (RR = 0.33; 95% CI: [0.21, 0.52], *P* = 0.00001). Pooled studies were homogeneous (I^2 =38%, *P* = 0.18).

The overall effect estimate of the follow-up durations favored the MMC group over the control group regarding the corneal haze modulation (RR = 0.29, 95% CI: [0.19, 0.45], *P* < 0.00001). The pooled studies were homogenous (I^2 = 25%, *P* = 0.22). (Fig. 6)

(5) Side effects:

A- Endothelial cell loss:

Pooled results showed no significant differences in endothelial cell loss between the MMC group and the control group (MD = 0.53; 95% CI: [3.05, 4.11], *P* = 0.58). Results were heterogeneous (I^2=71%, *P* = 0.02)[12,24,29,35] The analysis was done under a random effect model, and the heterogeneity was best solved by excluding Morales *et al*. (2006).[24] (Fig. 7)

B- Other side effects:

Delayed epithelial healing was observed in two eyes from a total of 72 eyes in the study group in Mounir *et al*. (2020),[34] and one eye suffered from toxic epitheliopathy and was controlled by switching to a preservative-free eye.[34] In Mohammadi *et al*.,[32], exaggerated epithelial healing was observed in three eyes (two in the MMC group and one in the control group). No eyes showed signs of delayed epithelialization or any other adverse side effects during follow up in the other included studies.[12,16,18,21,24,31,35 37]

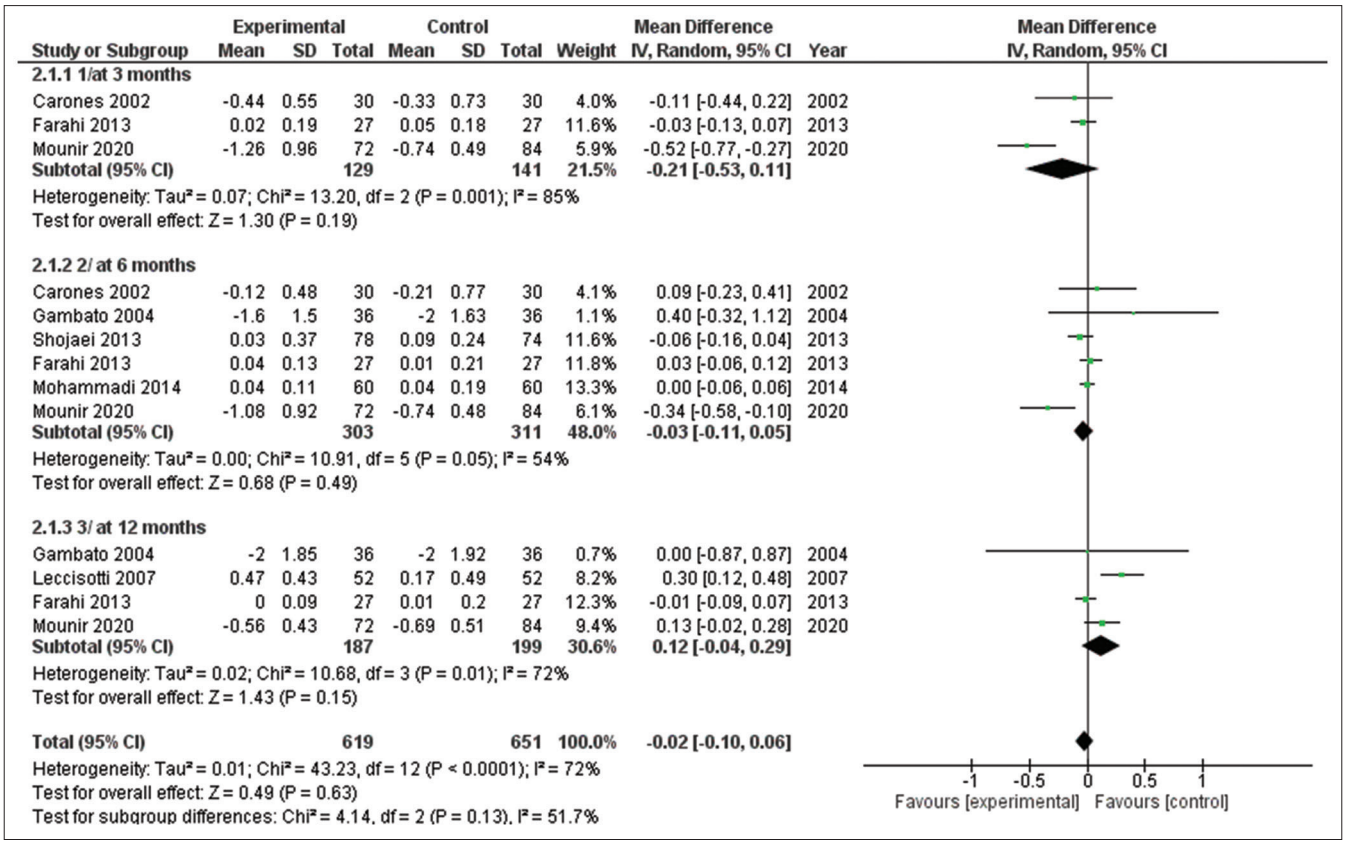

Figure 5. postoperative SE) Up to at 3, 6, 12 months follow-up.

Discussion

Our analysis revealed that MMC application has no significant outcome in CDVA and postoperative UDVA at 6 and 12 months. On the other hand, there was a significant difference of 5 years postoperatively in terms of UDVA. MMC application showed no significant outcome after 3 months of follow up. It has a significant lowering effect on the corneal haze incidence after 6 and 12 months follow-up. Also, no significant differences regarding side effects after MMC application were found.

PRK has a reliable effect in treating myopia and astigmatism;[38] however, several adverse effects might occur intra or postoperatively mainly due to the abnormal healing process, such as the unleashed wound healing response caused by ablation of the central Bowman layer and anterior stroma, which may lead to subepithelial haze formation or to regress the initial correction. In particular, the higher the ametropia that has to be corrected, the higher the possibility of haze development.[39] Other conditions such as the greater ablation depth, the integrity of the epithelial basement membrane, and the deposition of abnormal extracellular matrix as part of the corneal wound-healing process[40] correlate with post PRK complications.

Our results showed a significant reduction in Corneal Haze graded greater than 1 in the MMC-treated eyes. The question that needs to be addressed is the healing properties of MMC provides in the prevention of haze formation. MMC is an antibiotic with alkylating properties derived from Streptomyces caespitosus.[41] The activated metabolite of MMC "mitosene" blocks DNA synthesis after nonspecific DNA cross-links in a cell-dependent manner.[41] This is accomplished via the N-alkylation of two DNA bases. Both alkylations are sequence-specific for a guanine nucleotide in the sequence 5′-CpG-3′. It has antitumoral activities and can inhibit mitosis, RNA replication, and protein synthesis.[41] MMC application reduces or completely inhibits myofibroblast regeneration, lower keratocyte, abnormal collagen, and extracellular matrix deposition,[42-44] thus preventing the loss of corneal transparency and haze formation.

Our meta-analysis shows a long-term effect on UDVA in the MMC-treated eyes compared to the control group. The efficacy and predictability of PRK with the intraoperative application of MMC have already been reported in several studies. Carones *et al.*[11] noted better UDVA and CDVA and more accurate refractive outcomes with prophylactic use of a single dose of MMC 0.02% at the end of PRK compared to controls. Our findings are comparable to those reported by Lee *et al.*[45] who observed UDVA of 20/20 or better in 86% and UDVA of 20/40 or better in 98% of eyes after PRK with MMC, and that 86 and 93% of eyes were within ± 0.50 and ± 1.00 D of target refraction postoperatively.[46] The long-term effect of MMC on UDVA shown in our analysis provides great significance since, in most of the included studies, the patients are living under a hot or sunny desert climate.[47-50] This is particularly important because living under a high UV environment may worsen the outcomes of PRK.[51] Concerning the exposure time, Hofmeister *et al.*[52] used 0.01% of MMC, which was applied at different durations (60, 30, 15 s), and found no difference in UDVA in the other different groups.

In terms of endothelial cell loss, there were no significant differences between the groups in our analysis. From the

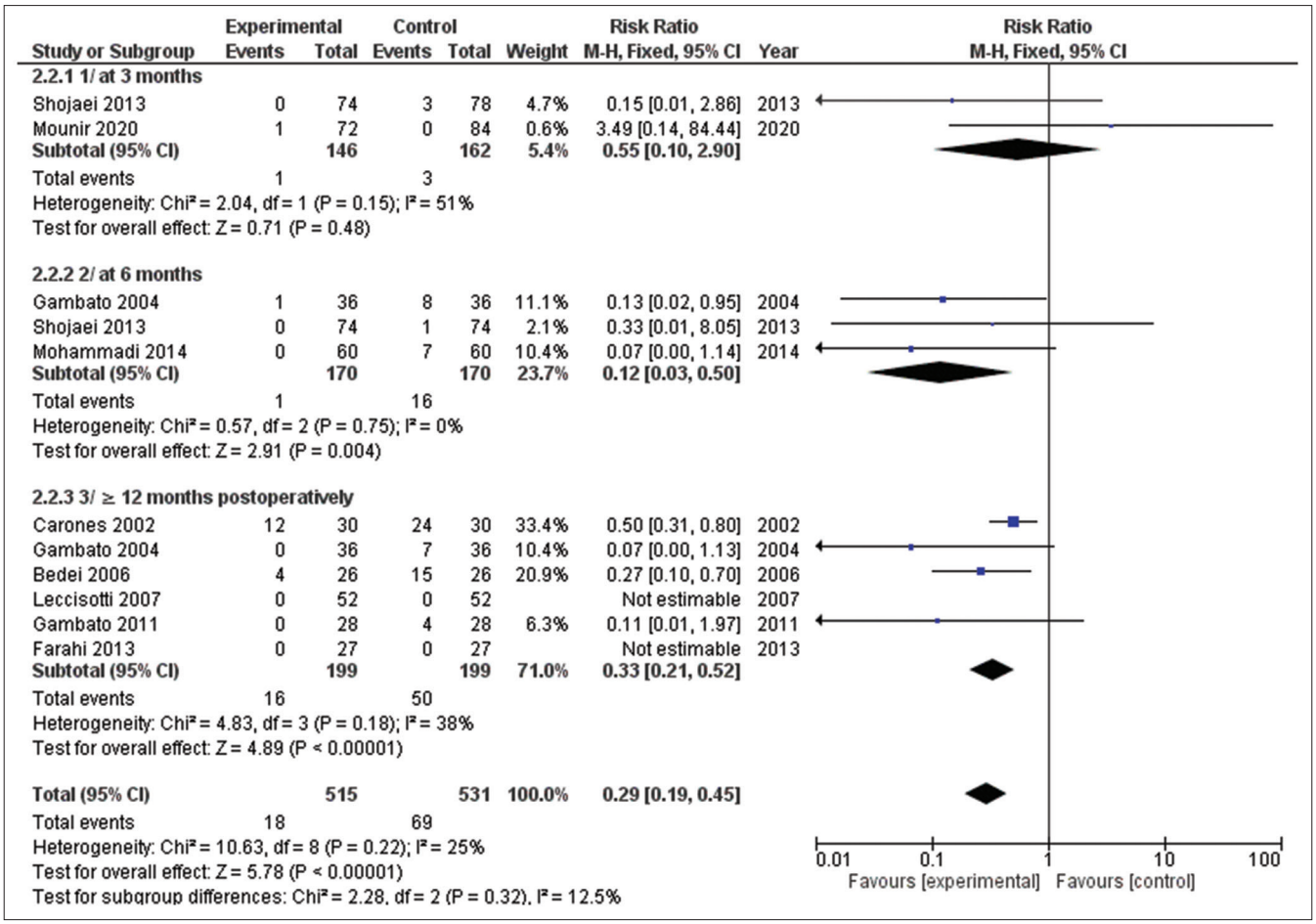

Figure 6. Corneal Haze formation postoperatively up to 5 years follow-up

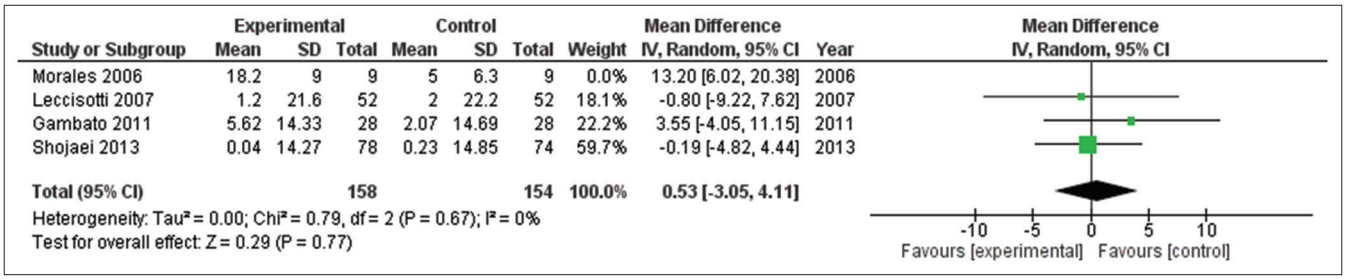

Figure 7. Endothelial cell loss

included RCTs, Morales *et al*. l[24] found a statistically significant decrease in endothelial cell count after MMC application. Other studies did not show any significant decrease.[31,35,36] In Gambato *et al*.,[31] the loss of endothelial cells 5 years after surgery was not statistically significant and is suggested to be related to the physiologic decrease in corneal endothelial cells.[53]

The decrease in keratocyte density is correlated with MMC concentration, and the exposure time[54] similar assumption can be applied to the endothelial cell. Moreover, ablation depth is one of the main theoretical reasons for explaining endothelial loss after MMC, deeper ablation leaves a thinner residual stroma, allowing the drug to penetrate deeper in the anterior chamber, and with its apoptotic properties, the loss in endothelial cells might be greater.[55] In our meta-analysis, the ablation depth ranged from 46, 76 to 96 µm, and in depths exceeding 75 µm, MMC's use shows a considerable reduction in ECD after the PRK procedure.[23] In Morales *et al*.,[24] the mean ablation depth was 86.1, which may in part explain the loss in endothelial cells. However, the study has some limitations; they reported a high standard deviation of endothelial cell counts, but the group had fewer patients.[24]

In a case series, MMC was safe on endothelial cells and did not adversely affect ECD and morphology up to 6 months.[56] Other studies support the results of our meta-analysis with no measurable effect on ECD or morphology after a single intraoperative application of 0.02% MMC as Lee *et al*.[45] described in their retrospective study that there were no measurable changes in ECD after 1 month of PRK with 0.02%

of MMC application.[11] Moreover, Zhao *et al*.[44] followed-up endothelial cell changes to 6 months after PRK with 0.02% MMC application for 15 s, and no quantitative or qualitative changes were observed. Another study compared LASEK with or without MMC application for 30 seconds showed no significant difference in endothelial cell damage between both groups.[57] The same results in other prospective studies were observed with follow-up durations ranged from 3 to 18 months.[12,20,44,57,58]

In terms of epithelial healing, Kremer *et al*.[48] showed that topical MMC 0.02% for 20 s delay the epithelial healing process compared with the control group. In our analysis, the concentration of MMC used in the included trials was 0.02%, and the duration of application ranged from 30 s to 2 min. Also, there were no noticeable differences in terms of epithelial healing with the period of less than 1 min or the one exceeding 1 min. Epithelial healing defects were observed only in two trials[32,48,59] in which the duration of application was 15 and 40 s, and all the other studies had a complete and correct healing process.[12,16,18,21,24,31,35-37] Hofmeister *et al*.[52] used 0.01% of MMC in different durations and found that the density of endothelial cells was not influenced by the exposure time of MMC.

Leccisotti *et al*.[30] observed in nine MMC-treated eyes small epithelial dots in the central cornea; they were prominent and not associated with any stromal modification, which may be due to areas of epithelial hyperplasia. They caused a temporarily irregular surface with a short delay of full visual recovery. However, they were all disappeared after 1 month. Further studies are needed to clarify this result.

Evaluating corneal layers by Corneal confocal microscopy was used in three studies and showed unchanged Keratocyte density in the posterior stromal area comparing with preoperative evaluation.[16] As for the anterior chamber, the results were varied; Midena *et al*.[16] showed a statistically significant reduction in keratocyte density after PRK. However, it was not significant between the treatment and control group. Also, Gambato *et al*.[12] showed a progressive increase in keratocyte density and increased cellular reflectivity, which was decreased by 6–12 months postoperatively in the MMC-treated group and remained higher in the control group;[12] as for the number and density of fibers detected by the confoscan, it was significantly higher in the MMC-treated eyes compared with the corticoid-treated eyes 5 years after PRK, which might be referred to a toxic effect of topical corticosteroids.[31] These results suggest that MMC does not by itself have long-term effects on mitochondrial DNA during the regeneration of nerve fibers.[31]

We included 12 RCTs in the quantitative analysis constituting a strong evidence level. The included studies are ranged from moderate to high quality.

We tried to search comprehensively for obtaining a trusted and considerable level of evidence by reporting outcomes following MMC application after PRK covering up to 5 years of postoperative changes. We conducted subgroup analyses regarding the follow-up durations. However, our study had some limitations, SE and endothelial cell loss were heterogeneous, and heterogeneity was best solved by excluding one study for each outcome. Also, we could not assess the publication bias due to the limited number of the included studies, and there is a lack of data along with the long-term effect.

Conclusion

We conclude that MMC application after PRK is associated with a lower incidence of corneal haze formation with no statistically significant side effects. No significant effect of MMC application regarding UDVA and CDVA in the short term effect, but the long term effect can show improvement regarding UDVA favoring MMC application. Future studies are required to show the difference between "epithelium off" versus trans epithelial PRK in terms of corneal haze.

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Conflicts of interest

There are no conflicts of interest.

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