



The Effect of Mitomycin-C Application Time on Pterygium Recurrence After Surgical Excision

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Abstract

Objective: The purpose of the study was to establish the safest and the most efficacious duration of application of MMC in patients undergoing primary pterygium excision to prevent recurrence.

Methods: An interventional study was carried out at Isra Postgraduate Institute of Ophthalmology/Al-Ibrahim Eye Hospital, Karachi, Pakistan from 2010 till 2017. Patients underwent surgical removal of pterygium using bare sclera method with MMC in concentration of 0.2 mg/ml (0.02%) with variable exposure time of 1 - 5 minutes. Classification of patients was done randomly with MMC application time ranging from 1 to 5 minutes. Patients were followed at 3, 6, 9 and 12 months postoperatively to record any recurrence.

Results: A total 273 eyes of male patients with mean age of 35.9 ± 1.23 years were included in the study. The overall pterygium recurrence rate at each follow-up was 5.66%, 6.92%, 7.90% and 9.3% at 3rd, 6th, 9th and 12th months respectively. There was a significant decline in recurrence in the number of patients with MMC application time of greater than 3 minutes at all follow-ups. Maximum of recurrence was seen in patients between 31 to 40 years at the final follow-up.

Conclusion: These results suggest that a MMC application time of less than 3 minutes increases the chances of pterygium recurrence after surgical excision. MMC application time of greater than 3 minutes is recommended to prevent recurrence of such high risk recurrent pathology.

Keywords: Pterygium; Recurrence; Mitomycin-C; Duration

Introduction

Pterygium is a common conjunctival surface degenerative disorder seen in countries with hot and dusty climate [1-3]. Apart from cosmetic blemish, pterygium can disturb the tear film resulting in chronic irritation and once it encroaches over the cornea

can cause irregular astigmatism with disturbed vision [4]. Over the years, there has been several surgical approaches advised for pterygium excision with and without the adjunctive use of Mitomycin C (MMC) and conjunctival and amniotic membrane grafts. The most common method has been the bare scleral excision technique, first

described by Ombrian [5]. However, the major limitation to simple excision is the high rate of postoperative recurrence [6,7]. The use of topical Mitomycin C (MMC) as an adjunct therapy to prevent pterygium recurrence has considerably increased since its first introduction by Kunitomo and Mori of Japan [8] and its subsequent usage by multiple workers [9-12].

MMC was first developed in 1955 from *Streptomyces Caespitosus* by Hata., *et al.* [13] and since its inception, it has been used successfully for treating various ocular disorders ranging from pterygium to glaucoma [14,15]. A number of research studies have been carried out to document the influence of age, gender, appropriate dosage of MMC in treating pterygium and preventing its recurrence and have documented the lesser recurrence seen in female gender and older age groups [16,17]. However relatively few studies have evaluated the role of different exposure time of MMC in pterygium recurrence, especially in the context of the local population of Asia where there is high recurrence of pterygium. Hence to prove the hypothesis that the increased duration of MMC application will lead to fewer cases of pterygium recurrence postoperatively, we undertook this study to evaluate the effect of variable MMC application time in cases of primary pterygium in local population.

Methods

An interventional study was carried out at Isra Postgraduate Institute of Ophthalmology/Al-Ibrahim Eye Hospital, Karachi, Pakistan from 2010 till 2017. A total of 273 male patients (273 eyes) with age duration 16 - 50 years were enrolled in the study. The study protocol was reviewed and approved by an ethics committee at the study center and the study was carried out in accordance with the declaration of Helsinki of 1975 as revised in 1983. Classification of subjects was done randomly with MMC application time ranging from 1 to 5 minutes.

The primary outcome measure was the comparison of Pterygium affected eye for any kind of recurrence after excision with variable intra-operative MMC application time of 1 - 5 minutes at 3, 6, 9 and 12 months follow-up.

Patients with established diagnosis of unilateral progressive primary pterygia encroaching on the cornea were included in the study. Recurrent pterygia or any conjunctival and corneal growth other than pterygia were excluded. All patients provided written informed consent for surgery with use of MMC.

All patients had their detailed medical history taken, with complete ocular examination including best corrected visual acuity (BCVA), bio-microscopic examination of anterior segment with Goldman applanation tonometry and fundus examination with +90DS lens.

Pterygium excisions were performed on an outpatient basis by the same surgeon using the same technique [9]. After excision with bare scleral technique under topical anesthetic (Proparacaine - Alcon Belgium), a sterile sponge (5x5mm) soaked in 8 - 10 drops of 0.2 mg/ml MMC (0.02%) (Mitomycin-C, Kyowa - Japan) was applied over cornea-sclera and the area from where pterygium was excised with a variable time duration of 1-5 minutes. The sponge was removed and eye irrigated with 20 ml of Normal saline 0.9%. This was followed by topical administration of Dexamethasone 0.1% + Tobramycin 0.3% (Tobradex-Alcon, Belgium) and Hydroxypropyl Methylcellulose (Tear Naturale II - Alcon, Belgium) four times a day for 4 weeks. The dosage of MMC was calculated in line with the international recommendations [18,19]. Patients were regularly followed up at 3, 6, 9 and 12 months after the procedure with complete ocular examination including BCVA and anterior segment slit lamp bio microscopy. Any adverse effect or physical findings were noted at each visit. Recurrence of pterygium was defined as an encroachment of fibrovascular connective tissue across the limbus and onto the cornea for any distance in the position of the previous lesion during the follow-up period. All these follow-ups and any recurrence was recorded by an ophthalmologist other than the primary surgeon (IAB).

Statistical analysis

Data were entered in Statistical Package for Social Sciences (SPSS) version 20.0. Mean \pm SD was computed for quantitative variables while frequencies and percentages were calculated for categorical variables. Chi-Square test was applied to check the association between two categorical variables. P-value \leq 0.05 will be considered as statistically significant.

Results

A total 273 eyes of male patients with mean age of 35.9 ± 1.23 years were included in the study. In 249 (91.2%) eyes, Pterygium was located on the nasal side, with 20 (7.3%) eyes had it on the temporal side and 4 (1.4%) eyes were affected on the either side. Baseline characteristic was shown in table 1.

| Characteristics of Patients | Frequency | Percent (%) |
|-----------------------------|-----------|-------------|
| Affected Eye | | |
| Right | 119 | 43.5 |
| Left | 154 | 56.4 |
| Site of Pterygium | | |
| Nasal | 249 | 91.2 |
| Temporal | 20 | 7.3 |
| Central | 4 | 1.46 |
| Age Groups | | |
| 16-30 | 52 | 19 |
| 31-40 | 128 | 46.9 |
| 41-50 | 93 | 34.1 |
| Total | 273 | 100 |

Table 1: Baseline characteristics of patients.

At 3 months, 265 patients attended follow-up, while 8 were lost to follow-up. Of 265 patients, 44 were given exposure of MMC for 1 min, among them 7 (15.9%) showed recurrence while remaining 37 (84.1%) didn't show any recurrence. Similarly, when we give 5 mins exposure of MMC to 30 patients, only 1 (3.3%) showed recurrence whereas 29 (96.7%) patients showed no recurrence (Table 2).

| MMC Application Time | Recurrence | | | P-value |
|----------------------|---------------|-----------------|---------------|---------|
| | Yes | No | Total | |
| 1 min | 7 | 37 | 44 | 0.026 |
| | 15.9% | 84.1% | 100% | |
| 2 min | 4 | 72 | 76 | |
| | 5.3% | 94.7% | 100% | |
| 3 min | 2 | 60 | 62 | |
| | 3.2% | 96.8% | 100% | |
| 4 min | 1 | 52 | 53 | |
| | 1.9% | 98.1% | 100% | |
| 5 min | 1 | 29 | 30 | |
| | 3.3% | 96.7% | 100% | |
| | 15 (5.66%) | 250 (94.33%) | 265 (100%) | |

Table 2: Pterygium recurrence with MMC application time at 3 month follow-up.

At 6 months, 260 patients attended follow-up, while 13 were lost to follow-up. Of 260 patients, 43 were given exposure of MMC for 1 min, among them 8 (18.6%) showed recurrence while remaining 35 (81.4%) didn't show any recurrence. Similarly, when we give 5 mins exposure of MMC to 34 patients, no patient showed any recurrence (Table 3).

| MMC Application Time | Recurrence | | | P-value |
|----------------------|---------------|-----------------|---------------|---------|
| | Yes | No | Total | |
| 1 min | 8 | 35 | 43 | 0.007 |
| | 18.6% | 81.4% | 100% | |
| 2 min | 6 | 68 | 74 | |
| | 8.1% | 91.9% | 100% | |
| 3 min | 3 | 57 | 60 | |
| | 5.0% | 95.0% | 100% | |
| 4 min | 1 | 48 | 49 | |
| | 2.0% | 98.0% | 100% | |
| 5 min | 0 | 34 | 34 | |
| | 0.0% | 100.0% | 100% | |
| | 18 (6.92%) | 242 (93.07%) | 260 (100%) | |

Table 3: Pterygium recurrence with MMC application time at 6 month follow-up.

At 9 months, 253 patients attended follow-up, while 20 were lost to follow-up. Of 253 patients, 42 were given exposure of MMC for 1 min, among them 9 (21.4%) showed recurrence while remaining 33 (78.6%) didn't show any recurrence. Similarly, when we give 5 mins exposure of MMC to 30 patients, no patient showed any recurrence (Table 4).

At last follow-up of 12 months, 248 patients attended follow-up, while 25 were lost to follow-up. Of 248 patients, 40 were given exposure of MMC for 1 min, among them 10 (25%) showed recurrence while remaining 30 (75%) didn't show any recurrence. Similarly, when we give 5 mins exposure of MMC to 34 patients, no patient showed any recurrence (Table 5).

The overall recurrence was seen in 15 (5.6%), 18 (6.9%), 20 (7.9%) and 23 (9.3%) patients at 3, 6, 9 and 12 months respectively.

| MMC Application Time | Recurrence | | | P-value |
|----------------------|---------------|-----------------|---------------|---------|
| | Yes | No | Total | |
| 1 min | 9 | 33 | 42 | 0.005 |
| | 21.4% | 78.6% | 100% | |
| 2 min | 6 | 66 | 72 | |
| | 8.3% | 91.7% | 100% | |
| 3 min | 3 | 56 | 59 | |
| | 5.1% | 94.9% | 100% | |
| 4 min | 2 | 48 | 50 | |
| | 4.0% | 96.0% | 100% | |
| 5 min | 0 | 30 | 30 | |
| | 0.0% | 100.0% | 100% | |
| | 20 (7.90%) | 233 (92.09%) | 253 (100%) | |

Table 4: Pterygium recurrence with MMC application time at 9 month follow-up.

| MMC Application Time | Recurrence | | | P-value |
|----------------------|---------------|-----------------|---------------|---------|
| | Yes | No | Total | |
| 1 min | 10 | 30 | 40 | 0.001 |
| | 25.0% | 75.0% | 100% | |
| 2 min | 7 | 64 | 71 | |
| | 9.9% | 90.1% | 100% | |
| 3 min | 5 | 50 | 55 | |
| | 9.1% | 90.9% | 100% | |
| 4 min | 1 | 47 | 48 | |
| | 2.1% | 97.9% | 100% | |
| 5 min | 0 | 34 | 34 | |
| | 0.0% | 100.0% | 100% | |
| | 23 (9.27%) | 225 (90.72%) | 248 (100%) | |

Table 5: Pterygium recurrence with MMC application time at 12 month follow-up.

At final follow-up of 12 months, overall 23 patients found with recurrence, in which 4 (17.3%) patients were between 16 to 30

years, 11 (47.8%) patients were between 31 - 40 years and 8 (34.7%) patients were above 40 years of age (Table 6).

| Age Groups (Years) | Frequency of recurred patients | Percentage |
|--------------------|--------------------------------|------------|
| 16 - 30 | 4 | 17.39% |
| 31 - 40 | 11 | 47.82% |
| 41 - 50 | 8 | 34.78% |
| Total | 23 | 100% |

Table 6: Age wise recurrence at final follow-up.

There was a definite trend of lesser rate of recurrence in patients with MMC application time of greater than 3 minutes was seen at each follow-up.

Corneal nebular opacity was the frequent finding seen in most patients postoperatively irrespective of MMC application time with one patient developing conjunctival cyst at the site of excision (MMC Application 3 minutes).

Discussion

Pterygium remains a common conjunctivo-corneal entity globally but more or so in Asian countries like Pakistan with plenty of sunshine and dusty climate [1]. The present study was motivated by the invariably high recurrence of pterygium not only in Pakistan but world over [4,20].

The recurrence rate of primary pterygium in the present study was 9.3%. In a clinical trial carried out in the Pakistani population, Rahman., *et al.* [21] estimated a recurrence of pterygia in 10% of the population. In another prospective study, Cheng., *et al.* [22] observed a recurrence of 7.9% in subjects with primary pterygia and a recurrence of 19.2% in subjects with recurrent pterygia. However comparison between our study and others is likely to be biased attributed to the different study population, setting and type of pterygium. Patients above 50 years of age and female gender were excluded from the study because of substantial evidence of lesser recurrence documented in various studies. This helped us to remove any confounding variable in the study and focus entirely on the role of application time of MMC on pterygium recurrence, the importance of which in recurrence studies has not been documented to date [23-25].

The possible difference in the effect on recurrence of pterygium by the application of intra-operative topical MMC can be attributed to the difference in concentration as well as its application time. In a dose response study related to MMC, Robin, *et al.* [26] have shown that duration of exposure appears to be more important than the concentration of MMC. In the present study, there was no recurrence seen in patients treated with topical MMC for 5 minutes, however a high recurrence rate of 25% was seen in patients treated for 1 minute at the final follow-up. Other patients had a recurrence rate in between these two extremities. Similar results were also documented in a randomized trial carried out by Lam, *et al.* [27]. In their work, at a mean follow-up time of 30 months, a recurrence rate of 8.3% was seen in the patients applied 0.02% MMC for 5 minutes as compared to 42.9% seen in the group applied 0.02% MMC for 3 minutes. Though there was no recurrence seen in the 5 minute MMC application group, most cases of complication of corneal nebular opacity were seen among these patients.

The reason we choose male patients was as in our country as part of our culture, females are mostly home bound while males are out and about for their living exposed to the harsh climate thus having increased prevalence of pterygium [28].

The results of our study hold important implications for further work on MMC, as probably, duration of administration of MMC, holds the key in its effect on pterygium recurrence. The clinical efficacy of MMC application time has been amply demonstrated and the methodology employed is in research usage therefore the results of this study are of definite relevance and merit a follow up with larger clinical trials.

The limitation of our study include its single-center nature and about 9% of patients dropping out in final follow-up.

Conclusion

Our study found significant associations of pterygium recurrence with lesser duration of MMC supplication time. The result of the study suggests using MMC application time of greater than 3 minutes for high risk recurrent pathology, since no major complication like scleral thinning, ulceration or necrosis was seen in our patients.

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Conflict of Interest

The Authors declare no conflict of interest or any funding support.

Authors Contribution

PSM: Manuscript writing.

ASM: Collection of Data.

IAB: Review of Patients and Data.

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