

# Trans-scleral Effect of Mitomycin-C on Ciliary Body Epithelium

P. S. Mahar

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See end of article for authors affiliations

Correspondence to:  
P. S. Mahar  
Department of Surgery, Section of Ophthalmology, Aga Khan University Hospital  
Stadium Road, Karachi 74800, Pakistan

**Purpose:** To determine the toxic effect of intraoperative adjunctive topical Mitomycin C (MMC) on ciliary body epithelium resulting in decrease in intraocular pressure (IOP).

**Material and Methods:** An interventional case series of 120 patients (120 eyes) with pterygium treated from 2005 to 2010. All patients underwent pterygium excision with intraoperative MMC, (0.2 mg/mL) administered for 3 minutes. The toxic effect of MMC on ciliary body was determined through changes in the IOP. Any change in IOP of greater than 5 mm Hg was considered significant. The IOP was recorded on day 1, day 7, at 1 month and at 3 months. The data were analyzed using proportion, group means, standard deviations and student t test.

**Results:** There was no significant decline in IOP throughout the follow-up period ( $p = 0.44$ ). At 3 months postoperatively, 105 eyes (87.5%) had no changes in IOP of  $>5$  mm Hg. The mean IOP changed from a preoperative level of 14.85 mm Hg to 14.44 mm Hg at 3 months follow up signifying no change statistically.

**Conclusions:** Our results showed that use of MMC as an adjunctive treatment in pterygium excision has no effect on intraocular pressure and do not support the trans-scleral toxic effect of MMC on the ciliary body epithelium as an intraocular pressure lowering mechanism.

Mitomycin C (MMC) has been used for treating various ocular disorders ranging from pterygium to glaucoma. Chen et al<sup>1</sup> were the first researchers to use MMC intraoperatively for refractory glaucoma. Since then it has become the drug of choice to augment trabeculectomy for effectively controlling intraocular pressure (IOP) in different types of glaucoma. The success of MMC has been attributed primarily to its antimetabolitic and antifibrotic effect shown in numerous clinical<sup>2,3</sup> and laboratory studies<sup>4,5</sup>. The most important postoperative complications of this procedure are early and late hypotony<sup>6-8</sup>. In the immediate postoperative state, increased flow of aqueous through the filtering site has been cited as the major contributing factor resulting in decreased IOP<sup>9</sup>. Conversely, this does not explain the late onset of hypotony ( $< 6$  mm Hg) in some patients undergoing trabeculectomy with MMC. There is growing evidence from experimental studies that MMC may be toxic to the ciliary body epithelium, resulting not only in

decreased IOP, but also affecting aqueous humor dynamics and causing a number of other complications<sup>10</sup>.

Xia et al observed swelling of the intracellular mitochondria along with the non-pigmented epithelium of the ciliary body in rabbit eyes exposed to MMC, signifying its toxic effect, with decreased aqueous production resulting in hypotony<sup>11</sup>. In a study by Levy and coworkers, microscopic examination of rat eyes treated with MMC showed pyknotic nuclei in conjunction with irregular flattened cells in the ciliary body<sup>12</sup>. The severity of changes correlated with the concentration and duration of exposure to MMC. The authors concluded that MMC and other antimetabolites have a direct toxic effect on the ciliary body epithelium, besides their known effect on the conjunctiva. The application of MMC, both topically in glaucoma filtering surgeries and by the subconjunctival method of Mahar et al in glaucoma patients,<sup>13</sup> has yielded significant decreases in IOP in

both experimental and human models. Since topical MMC is extensively used as an adjunct in pterygium excision to prevent recurrence, the purpose of this study was to determine the effect of MMC on ciliary body epithelium through the changes in IOP in eyes that were undergoing pterygium excision with topical MMC.

## MATERIAL AND METHODS

This non-randomized interventional case series was performed at the Section of Ophthalmology, Department of Surgery, Aga Khan University Hospital, Karachi, Pakistan, from 2005 to 2010. One hundred and fifty six patients with unilateral progressive pterygium who had undergone supervised surgical excision by the bare sclera technique with MMC were enrolled. The exclusion criteria were previous drainage surgery, suspicious growth other than pterygia or corneal scarring, antiglaucoma therapy in either eye, history of Sjogren's syndrome or any other ocular disease, and keratoconjunctivitis sicca. The study protocol was approved by the Hospital Ethics Committee and the study was performed in accordance with the Declaration of Helsinki. All patients provided informed consent. The primary outcome measure was to determine the toxic effect of MMC on the ciliary body epithelium through the comparison of mean baseline IOP with the IOP measured in the ipsilateral eye affected by pterygium at 3 months after intraoperative treatment with topical MMC.

The baseline IOP measurement was established by taking the mean of the two highest values measured at 9:00 am and 4:00 pm by Goldmann applanation tonometry (GAT) before pterygium excision.

All patients underwent complete ocular examination, including best-corrected visual acuity, biomicroscopic examination of the anterior segment with GAT, and fundus examination with a +90 diopter lens.

Pterygium excisions were performed on an outpatient basis by the same surgeon (PSM) using the same technique.<sup>14</sup> No premedication was given to any patient. After pterygium excision with the bare scleral technique under topical anesthesia (Proparacaine, Alcon - Belgium), a 5- x 5-mm sterile sponge soaked in 8 to 10 drops of MMC (Kyowa - Japan) 0.2 mg/mL<sup>19-21</sup> was applied over the corneosclera and the area from where pterygia was excised for 3 minutes. The sponge was removed and the eye was irrigated with 20 ml of 0.9% normal saline. This was followed by topical

administration of dexamethasone 0.1% plus tobramycin 0.3% (Tobradex, Alcon - Belgium) and hydroxypropyl methylcellulose (Tear Naturale II, Alcon - Belgium), which was instilled 4 times daily for 4 weeks to prevent postoperative inflammation. The patients' IOPs were measured on days 1, day 7 at 1 month and after 3 months. Any adverse effects or physical findings were also noted at each visit.

## Statistical Analysis

The data analysis was conducted into the statistical package for the social sciences version 16 (SPSS Inc. Chicago, USA). The entire continuous variable i.e. age, baseline IOP, post-op IOP and change in IOP presented as mean  $\pm$  standard deviation and categorical variables like gender, affected eye, IOP and pterygium site presented as frequency and percentage. To estimate the comparison between the IOP's, we applied paired sample t test using preoperative levels. The IOP was considered to be higher or lower than the preoperative level if the difference was more than 5 mm Hg. The IOP value measured preoperatively was taken as the baseline measurement to reduce any bias due to recruitment.

## RESULTS

One hundred and fifty six patients were enrolled; 120 eyes of 120 patients were followed for at least 3 months, 36 patients were lost to follow-up and hence their data has been excluded from this study. There were 76 male (63.3%) and 44 female (36.7%) with a mean age of 52.3 years (range, 26 to 83 years) and standard deviation 2.4. The pterygium was located on the nasal side in 99 eyes (82.5%) and on the temporal side in 21 eyes (17.5%). There were 55 right eyes and 65 left eyes. The baseline characteristics of the patients are shown in (Table 1).

There were no significant changes in IOP in 105 eyes (87.5%) at 3 months ( $p = 0.44$ , paired Student *t* test); Eight eyes (6.7%) had a decrease in IOP  $>5$  mm Hg and 7 eyes (5.8%) had an increase in IOP  $>5$  mm Hg, which were not statistically significant (Tables 2 and 3).

Fifty five affected eyes were on the right side, of which 49 eyes (89.1%) had no significant change in IOP throughout the follow-up period ( $p = 0.23$ ); 17 eyes (30.9%) had no change in IOP and 31 (56.4%) had minimal changes ( $\leq 5$  mm Hg). Three eyes (5.4%) had a decrease in IOP of  $> 5$  mm Hg and 4 (7.3%) had an increase in IOP of  $> 5$  mm Hg. There was a change in

IOP level from a mean of 14.90 mm Hg  $\pm$  1.5 SD at baseline to a mean of 14.35 mm Hg  $\pm$  1.8 SD after 3 months, which was statistically not significant.

**Table 1:** Pre-operative characteristics of patients (n = 120)

Variable	No. of Eyes (%)
Age (mean $\pm$ SD)	52.3 $\pm$ 2.4
Gender	
Male	76 (63.3)
Female	44 (36.7)
Affected Eye	
Right	55 (45.8)
Left	65 (54.2)
Pterygium Site	
Nasal	99 (82.5)
Temporal	21 (17.5)

SD = Standard Deviation

**Table 2:** Change in intraocular pressure from baseline at 3 months

Intraocular Pressure (mmHg)	No. of Eyes (%)
Decreased (> 5)	08 (6.7)
Unchanged ( $\leq$ 5)	105 (87.5)
Increased (> 5)	07 (5.8)

p = 0.44, paired Student *t* test

Sixty five affected eyes were on the left side, of which 56 eyes (86.1%) had no significant change in IOP throughout the follow-up period (p = 0.64); 21

eyes (32.3%) had no change in IOP and 36 eyes (55.4%) had minimal changes ( $\leq$  5 mm Hg). Five eyes (7.7%) had a decrease in IOP of > 5 mm Hg and 3 (4.6%) had an increase in IOP of > 5 mm Hg. There was a change in IOP level from a mean of 14.80 mm Hg  $\pm$  1.4 SD at baseline to a mean of 14.53 mm Hg  $\pm$  1.1 SD after 3 months, which was statistically not significant.

## DISCUSSION

This study investigated the toxic effect of MMC on ciliary body epithelium through the changes in IOP in eyes, undergoing pterygium excision with topical MMC. In a laboratory study by Letchinger et al<sup>15</sup>, subconjunctival injection of MMC was administered to rabbit eyes and a consequent drop in IOP was noted. In an experimental study in monkeys, Kee et al noted a decrease in IOP from baseline after administration of MMC, and a possible mechanism of aqueous suppression was suggested to be responsible for the IOP reduction<sup>16</sup>. In a clinical study by Gandolfi et al,<sup>17</sup> subconjunctival injection of MMC was administered to 12 eyes with no perception of light and a decrease of about 5 mm Hg (SD, 1.61 mm Hg) in IOP was observed at 60 days. These researchers also performed tonography on their patients to detect the possible effect of MMC on the aqueous outflow from the eye, and found no significant change in the 'C' coefficient throughout the follow-up period.

The results of this study differ from the results of the above mentioned studies,<sup>15-17</sup> in that the decrease in IOP was observed only in 4% to 5% of patients, which is statistically insignificant. In a prospective study, Raiskup et al described the long-term effect of intraoperative application of MMC 0.2 mg/mL for 5 minutes in patients undergoing pterygium excision and noted a normal IOP on follow-up.<sup>18</sup> Similarly in a study by Mahar et al. patients undergoing pterygium excision with MMC applied topically in 5 different group of patients with application time difference of 1

**Table 3:** Mean change in intraocular pressure at 3 months from baseline.

Affected Eyes	Baseline IOP (mmHg) Mean $\pm$ SD	Post-op IOP (mmHg) Mean $\pm$ SD	Change in IOP (mmHg) Mean $\pm$ SD	P-value*
Right	14.90 $\pm$ 1.50	14.35 $\pm$ 1.82	-0.55 $\pm$ 1.66	0.23
Left	14.80 $\pm$ 1.40	14.53 $\pm$ 1.17	-0.27 $\pm$ 1.28	0.64
Total	14.85 $\pm$ 1.45	14.44 $\pm$ 1.49	-0.41 $\pm$ 1.47	0.44

\*Pair - wise comparison, Student *t* test

\*P-value < 0.05 considered as statistically significant

to 5 minutes, no change in IOP greater than 5 mmHg was seen in either of the groups<sup>19</sup>.

The difference in the effect of application of intraoperative topical MMC on IOP can be attributed to the variation between the procedures carried out for pterygium excision and glaucoma filtering surgery. In trabeculectomy, a partial thickness flap is created at the corneoscleral junction, with a window opening under the flap made by removing a portion of the trabecular meshwork. This allows aqueous fluid to flow out of the eye, resulting in decreased IOP with the formation of a bleb. The scarring at the conjunctivoscleral interface is prevented by the application of MMC due to its anti-fibrotic property, which can sometimes lead to hypotony. The disparity in the results of this study with those carried out in glaucoma filtering surgery,<sup>20-22</sup> in which a significant drop in IOP was noted, suggests that scleral flap formation with internal sclerotomy may be responsible for the decline in IOP by either causing damage to the ciliary body by diffusion of MMC inside the eye or increasing the aqueous outflow by preventing scleral adhesions<sup>4</sup>. In pterygium excision where no such flap is formed, there is no trans-scleral effect of MMC on the ciliary body epithelium and hence there is no change in IOP. Other factors, not effecting IOP could be smaller dosage of MMC at 0.2 mg/ml, when MMC has been used in concentration of 0.1 mg/ml to 0.5 mg/ml in various studies. The smaller application time of 3 minutes of MMC can also be other contributory factor.

Our data showed no significant decrease in IOP after intraoperative topical application of MMC during pterygium surgery. The eye in this study had not undergone any previous surgery or medical treatment, so IOP changes by these methods seems unlikely. To decrease the effect of inflammation or prostaglandin release after surgery, corticosteroids that do not have any IOP - lowering effects were administered. Furthermore, to exclude the effect of steroid response among the study population, the prevalence was assumed to be that of the general population (18% to 36%)<sup>23</sup>. Although most people with primary open angle glaucoma (POAG) are classified as steroid responders, in this study none of the patients had POAG. However, while there are steroid responders who do not have POAG, most of the patients (96.6%) did not show an increase in IOP to such an extent as to be classified as steroid responders. Hence, any change in IOP attributed to steroid use is unlikely. This study found no significant effect on IOP by intraoperative

use of topical MMC in patients undergoing pterygium excision, confirming the safety of MMC with regards to any effect on the ciliary body for this type of surgical procedure.

## CONCLUSION

Our results showed that use of MMC as an adjunctive treatment in pterygium excision has no effect on intraocular pressure, at least for three months after the surgery. These results also do not support the trans-scleral toxic effect of MMC on the ciliary body epithelium as an IOP lowering mechanism.

## Author's Affiliation

Prof. Dr. P.S. Mahar  
Department of Surgery  
Section of Ophthalmology  
Aga Khan University Hospital  
Stadium Road, Karachi 74800

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