Effect of Intraoperative Use of Topical Mitomycin C on Intraocular Pressure in Patients with Pterygium Excision

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Aim: *To determine the effect of intraoperative adjunctive topical mitomycin C on intraocular pressure in patients undergoing pterygium excision.*
Methods: *This was a descriptive interventional case series of 102 patients (118 eyes) with different grades of pterygium treated from 1995 to 2008. All patients underwent pterygium excision with intraoperative mitomycin C 0.2 mg/mL administered for 1 to 5 minutes. Changes in intraocular pressure were recorded on days 1 and 7, and at 3 months. Data were analysed using proportion, group means, standard deviations, analysis of variance, and paired Student* t *test.*
Results: *There was no significant decline in intraocular pressure throughout the follow-up period (p = 0.435, Student* t *test). At 3 months postoperatively, 109 eyes (92.4%) had no changes in intraocular pressure >5 mm Hg, of whom 78 (72%) experienced minimal changes that were not statistically significant.*
Conclusions: *Intraoperative topical administration of mitomycin C has a minimal effect on lowering intraocular pressure in patients with pterygium. These results do not support the trans-scleral effect of mitomycin C on the ciliary body as an intraocular pressure–lowering mechanism in glaucoma filtering surgery.*

Key words: *Intraocular pressure, Mitomycin, Pterygium*

Asian J Ophthalmol. 2011;12:144-8.

Introduction

Pterygium is one of the most common conjunctival surface disorders treated by surgical excision. However, one of the major limitations to simple excision is the high rate of postoperative recurrence.[1] Therefore, a number of adjunctive therapies have been advocated during the past 3 decades with varying levels of success. The use of topical mitomycin C (MMC) as an adjunctive therapy to prevent pterygium recurrence has increased considerably since its introduction for pterygium by Kunitomo and Mori[2] of Japan and subsequent use in the USA by Singh et al.[3]

MMC was first developed in 1955 by Hata et al from *Streptomyces caespitosus*[4] and, since its inception, it has been used for treating various ocular disorders ranging from pterygium to glaucoma. Chen et al were the first researchers to use MMC intraoperatively for refractory glaucoma,[5] 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[6-9] and laboratory studies.[10,11] The most important postoperative complications of this procedure are early and late hypotony.[12-14] 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.[15] 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 humour dynamics and causing a number of other complications.[16]

In one such animal model, 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.[17] In another study by Levy et al, microscopic examination of rat eyes treated with MMC showed pyknotic nuclei in conjunction with irregular flattened cells in the ciliary body.[18] The severity of changes correlated with the concentration and duration of exposure to MMC.

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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,[19] 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, especially in developing countries, the purpose of this study was to determine the effect on IOP in eyes affected by different grades of pterygium that were undergoing pterygium excision.

Methods

Patients

This descriptive non-randomised interventional case series was performed at the Department of Surgery, Section of Ophthalmology, Aga Khan University Hospital, Karachi, Pakistan, from 1995 to 2008. One hundred and twenty eight patients with unilateral or bilateral progressive pterygium of any grade who had undergone supervised surgical excision by the bare scleral technique with MMC were enrolled. Exclusion criteria were previous drainage surgery, suspicious growth other than pterygia or corneal scarring, antiglaucoma therapy in either eye, history of Sjögren'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.

Design

The primary outcome measures were comparison of mean baseline IOP with the IOP measured in the ipsilateral eye at 3 months after intraoperative treatment with MMC and the effect of increasing MMC application time on IOP at 3 months.

Baseline IOP measurement was established by taking the mean of the 2 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 D lens.

Pterygium was graded according to the extent of corneal involvement, as follows:

- Grade 1 — between the limbus and a point midway between the limbus and the pupillary margin
- Grade 2 — the head of the pterygium reaching the pupillary margin (nasal pupillary margin in the case of nasal pterygium and temporal margin in the case of temporal pterygium)
- Grade 3 — crossing the pupillary margin.

Pterygium excisions were performed on an outpatient basis by the same surgeon using the same technique.[20] No premedication was given to any patient. After pterygium excision with the bare scleral technique under topical anaesthesia (proparacaine), a 5- x 5-mm sterile sponge soaked in 8 to 10 drops of MMC 0.2 mg/mL[21-23] was applied over the corneosclera and the area from where pterygia was excised for 1 to 5 minutes. The sponge was removed and the eye was irrigated with 0.9% normal saline 20 mL. This was followed by topical administration of dexamethasone 0.1% plus tobramycin 0.3% and hydroxypropyl methylcellulose, which was instilled 4 times daily for 4 weeks to prevent postoperative inflammation. The patients' IOPs were measured on days 1 and 7, and after 3 months. Any adverse effects or physical findings were also noted at each visit.

Statistical Analysis

Data were entered into the Statistical Package for the Social Sciences version 16 (SPSS Inc, Chicago, USA) and the results were evaluated using proportions, group means, and standard deviations. Comparison of change in IOP between different time points was done with pair-wise Student *t* test using preoperative levels. IOP was considered to be higher or lower than the preoperative level if the difference was more than 5 mm Hg. Alpha level of 0.05, confidence interval of 95%, and power of 0.8 were selected. Analysis of variance (ANOVA) of the mean IOP before and after topical intraoperative application of MMC in each eligible eye was done with regards to the duration of application of MMC. The IOP value measured preoperatively was taken as the baseline measurement to reduce any bias due to recruitment (regression to the mean).

Results

One hundred and twenty eight patients were enrolled; 118 eyes of 102 patients were followed for at least 3 months and 26 patients were lost to follow-up. There were 67 men and 35 women with a mean age of 48.2 years (range, 16 to 90 years). Seventy eight eyes (66.1%) had grade 1 pterygium, 21 eyes (17.8%) had grade 2, and 19 (16.1%) had grade 3. The pterygium was located on the nasal side in 102 eyes (86.4%), on the temporal side in 14 (11.9%) and on both sides in 2 (1.7%). There were 51 right eyes and 67 left eyes. The baseline characteristics of the patients are shown in Table 1.

There were no significant changes in IOP in 109 eyes (92.4%) at 3 months ($p = 0.435$, paired Student *t* test); 78 eyes (71.6%)

Table 1. Baseline characteristics of patients undergoing pterygium excision (n = 118).

Characteristic	Number of eyes* (%)
Sex	
Male	75 (63.6)
Female	43 (36.4)
Affected eye	
Right	51 (43.2)
Left	67 (56.8)
Pterygium grade	
1	78 (66.1)
2	21 (17.8)
3	19 (16.1)
Pterygium site	
Nasal	102 (86.4)
Temporal	14 (11.9)
Central	2 (1.7)

* 16 patients were affected bilaterally.

Table 2. Change in intraocular pressure from baseline 3 months after pterygium excision (n = 118).

Intraocular pressure (mm Hg)	Number of eyes (%)
Decreased (>5)	5 (4.2)
Unchanged (±5)	109 (92.4)
Increased (>5)	4 (3.4)

had minimal changes (≤5 mm Hg) in IOP and 31 eyes (28.4%) had no change in IOP. Five eyes (4.2%) had a decrease in IOP >5 mm Hg and 4 eyes had an increase in IOP >5 mm Hg, which were not statistically significant (Tables 2 and 3).

Fifty one affected eyes were on the right side, of which 47 eyes (92.2%) had no significant change in IOP throughout the follow-up period (p = 0.227); 15 eyes (29.4%) had no change in IOP and 32 (62.7%) had minimal changes (≤5 mm Hg). Two eyes (3.9%) had a decrease in IOP >5 mm Hg and 2 (3.9%) had an increase in IOP >5 mm Hg. There was a progressive decrease in IOP level from a mean of 13.90 mm Hg (SD, 2.5 mm Hg) at baseline to a mean of 13.45 mm Hg (SD, 2.1 mm Hg) after 3 months.

Sixty seven affected eyes were on the left side, of which 62 eyes (92.5%) had no significant change in IOP throughout the follow-up period (p = 0.644); 16 eyes (23.9%) had no change in IOP and 46 eyes (68.7%) had minimal changes (≤5 mm Hg). Three eyes (4.5%) had a decrease in IOP >5 mm Hg and 2 (3.0%) had an increase in IOP >5 mm Hg. There was a progressive decrease in IOP level from a mean of 13.88 mm Hg (SD, 2.4 mm Hg) at baseline to a mean of 13.73 mm Hg (SD, 2.01 mm Hg) after 3 months.

The application time for MMC was 1 minute for 2 eyes (1.7%), 2 minutes for 33 eyes (28.0%), 3 minutes for 59 eyes (50.0%), 4 minutes for 20 eyes (16.9%), and 5 minutes for 4 eyes (3.4%). However, there were no significant differences in IOP between the groups according to MMC application time (p = 0.841, ANOVA; Table 4) and there were no significant differences between mean baseline IOP and that measured at 3 months (p = 0.803 for right eyes and p = 0.880 for left eyes).

Corneal nebular opacity was the most frequent postoperative finding seen (n = 12) and 1 patient developed conjunctival cyst at the site of pterygium excision. No other complications were seen during the follow-up period.

DISCUSSION

This study investigated the IOP-reducing effect of intraoperative topical MMC in an Asian population with various grades of pterygia. The outcome of this study differs from those of other studies on the effect of MMC on IOP reduction.[24-26]

In a laboratory study by Letchinger et al, subconjunctival injection of MMC was administered to rabbit eyes and a consequent drop in IOP was noted.[24] 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.[25]

In a clinical study by Gandolfi et al,[26] 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,[24-26] 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

Table 3. Change in intraocular pressure from baseline 3 months after pterygium excision according to laterality (n = 118).

Affected eyes	Preoperative intraocular pressure (mm Hg) Mean (SD)	Postoperative intraocular pressure (mm Hg) Mean (SD)	Change in intraocular pressure (mm Hg) Mean (SD)	p Value*
Right	13.90 (2.55)	13.45 (2.07)	-0.45 (2.31)	0.227
Left	13.88 (2.41)	13.73 (2.01)	-0.15 (2.21)	0.644
Total	13.89 (2.46)	13.61 (2.03)	-0.28 (2.24)	0.435

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

Table 4. Change in intraocular pressure from baseline 3 months after pterygium excision according to mitomycin C application time (n = 118).

Time (minutes)	Number of eyes (%)	Intraocular pressure (mm Hg) Mean (SD)		p Value*
		Preoperative	Postoperative	
1	2 (1.7)	12.00 (0.00)	13.00 (1.41)	
2	59 (50.0)	13.98 (2.29)	13.94 (1.93)	
3	33 (28.0)	13.79 (2.87)	13.39 (2.10)	0.841
4	20 (17.0)	13.75 (2.55)	12.90 (2.34)	
5	4 (3.4)	15.00 (1.15)	14.25 (0.50)	

* Pair-wise comparison, analysis of variance.

patients undergoing pterygium excision and noted a normal IOP on follow-up.[27]

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. Scarring at the conjunctivoscleral interface is prevented by the application of MMC, which can sometimes lead to hypotony. The disparity in the results of this study with those carried out in glaucoma filtering surgery,[6,28-30] in which a significant drop in IOP was noted, suggests that scleral flap formation 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 scarring. In pterygium excision where no such flap is formed, there is no trans-scleral effect of MMC on IOP. The results of this study have important implications for further research into MMC, as the route of administration may hold the key to its different effect in pterygium and glaucoma drainage procedures.

These data showed no significant decrease in IOP after intraoperative topical application of MMC during surgery for pterygium of various grades. 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%).[31] 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 change in IOP for this type of surgical procedure. While this study fulfils the objective set by the study protocol of determining the effect of intraoperative topical MMC on IOP in patients undergoing pterygium excision, there are some limitations due to the small sample size. A large-scale prospective study with an appropriate power is recommended for further evaluation of the micro-structural changes in the eye to understand the dynamics of the different effects of MMC on IOP in different types of surgical procedures and whether the route of administration has a potential role.

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