Original Article

Efficacy of preoperative injection versus intraoperative application of mitomycin in recurrent pterygium surgery

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Purpose: To determine the efficacy of preoperative subconjunctival injection of mitomycin C a day before surgery in the management of recurrent pterygium. **Materials and Methods:** Randomized comparative case series. Fifty eyes with recurrent pterygium were randomly divided into two groups; the mitomycin injection group (25 eyes) and the mitomycin application group (25 eyes). The mitomycin injection group underwent preoperative subconjunctival injection of mitomycin C in low dose (0.1 ml of 0.15 mg/ml) a day before bare sclera pterygium excision surgery. The mitomycin application group underwent bare sclera pterygium excision with topical application of mitomycin C (same concentration). **Results:** At one year of follow-up, 24 of 25 eyes (96%) in the mitomycin injection group and 23 of 25 (92%) eyes in the mitomycin application group were free of recurrence. The difference was statistically insignificant. As regards postoperative complications, delayed epithelization (more than two weeks) occurred in two eyes (8%) in the mitomycin injection group and in one eye (4%) in the mitomycin application group. Scleral thinning was reported in one eye (4%) in the mitomycin application group which resolved within three weeks after surgery, no other serious postoperative complications were reported. **Conclusion:** Preoperative subconjunctival injection of mitomycin C in low dose (0.1 ml of 0.15 mg/ml) a day before pterygium surgery is a simple and effective modality for management of recurrent pterygium. It has the advantage of low recurrence and complications' rate.

Key words: Intraoperative application of mitomycin C, mitomycin C, postoperative complications, preoperative subconjunctival injection, recurrence rate, recurrent pterygium

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Pterygium is a worldwide condition commonly seen in the Cameron belt located between 37° north and south of the equator. Pterygium is a triangular fibrovascular subepithelial ingrowth of degenerative bulbar conjunctival tissue encroaching onto the cornea. The exact cause of pterygium is not well understood. However, long-term exposure to sunlight, especially ultraviolet rays and chronic eye irritation from dry, dusty conditions seem to play an important role.[1,2]

Simple excision of the pterygium alone has a very high rate of recurrence, about 30-70%.[3] Various adjunctive strategies such as irradiation treatment, anti-metabolites, conjunctival autograft, limbal autograft and amniotic membrane graft have been employed over the years to reduce the high recurrence rate, with mixed success.[4,5]

In the last decade, mitomycin C had been used more commonly in pterygium surgery. The mechanism of action of mitomycin C seems to inhibit fibroblast proliferation at the level of the episclera. The use of intraoperative application of mitomycin C gives a high success rate, however, serious complications have been reported.[6] Subconjunctival injection of mitomycin C as adjunctive therapy before surgery allows exact titration of mitomycin C delivery to activated fibroblasts and minimizes epithelial toxicity.[7]

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Materials and Methods

A randomized comparative case series study was conducted between January 2009 and May 2010 in the Ophthalmology Department, Suez Canal University Hospital; where 50 eyes of Egyptian patients with recurrent pterygium encroaching onto the cornea following simple excision were recruited.

Patients with other ocular surface diseases, dry eye and progressive ocular disease unrelated to corneal condition were excluded from the study.

Patients underwent full preoperative evaluation (complete history and ophthalmological examination). Patients signed an informed consent after complete discussion of the procedure before participation in the study. Patients dropping-out from follow-up were excluded.

Patients were randomly divided into two groups (block randomization was used to assure equal sample size in each group). The mitomycin injection (MI) group: 25 eyes received 0.1 ml of 0.15 mg/ml mitomycin C injected subconjunctivally into the head of the pterygium one day before surgical excision using the bare sclera technique. The mitomycin application (MA) group: 25 eyes underwent surgical removal with the bare sclera technique and intraoperative topical application of 0.15 mg/ml of mitomycin C.

Preoperative subconjunctival injection of mitomycin C (MMC) was done at the outpatient clinic under aseptic conditions one day before surgery. With the patient in supine position and magnifying loupe, surface anesthesia was achieved by benoxinate 0.4% eye drops; then eye speculum was applied and MMC was injected into the head of the pterygium

at the limbus using 30G needle followed by pressure with micro-sponge to prevent drug leakage and irrigation with 50 mL balanced salt solution. Ofloxacin 0.3% and dexamethasone 0.1% eye drops (three times/day) were prescribed and the eye was patched for one day before scheduled surgery next morning.

Patients underwent pterygium excision by bare sclera technique in the operating room under surgical microscope. After preparing and draping the eye in normal sterile fashion, the lids were opened using eye speculum. Surface anesthesia was achieved with benoxinate 0.4% eye drops. Lignocaine 0.5 ml of 2% solution was injected into the pterygium. The head of the pterygium was grasped with St Martin's toothed forceps and excision was begun with No. 15 Bard-Parker blade about 0.5 mm ahead of the pterygium and carried down clearly to the limbus. The conjunctiva and subconjunctival tissue were then cleaned over the sclera towards the insertion of the medial rectus muscle and excision of the pterygium was carried out to 4 mm posterior to the limbus. Hemostasis was ensured. No conjunctival sutures were used.

In the MI group, intraoperative eye irrigation with 200 mL of balanced salt solution was done following pterygium excision to wash out residual subconjunctival MMC.

In the MA group, intraoperative application of mitomycin C was done using 5-mm surgical sponge soaked with 0.15 mg/ml mitomycin C solution and placed on the exposed scleral surface for 3 min. After the sponge was removed, the eye surface was irrigated with 200 mL of balanced salt solution.

Postoperative treatment included ofloxacin 0.3% and dexamethasone 0.1% eye drops (four times/day) and combined tobramycin and dexamethasone eye ointment at bedtime for four weeks in both groups. Postoperative follow-up visits were scheduled one day, one week, one month, two months, three months, six months and 12 months after surgery. In each visit, complete ophthalmological examination was done with special attention to pterygium recurrence and complications of mitomycin C such as corneal edema, glaucoma, corneal or scleral melting, keratitis and cataract.

Recurrence of pterygium was defined as a fibro-vascular growth beyond the limbus into the cornea with conjunctival drag.

Data was coded, entered and analyzed using Statistical Package for the Social Sciences (SPSS Version 10.0) software for analysis. According to the type of data, the following tests were used to test differences for significance: Chi square, paired t test, and one-way ANOVA with least significance difference.

Results

The study included 50 eyes divided into two groups. The MI group consisted of 13 (52%) women and 12 (48%) men with mean age 35.15±13.96 years. While the MA group consisted of 14 (56%) women and 11 (44%) men with mean age 36.11±13.23 years.

Both groups were Egyptian with recurrent pterygium encroaching onto the cornea (3 to 5 mm in size) that had been operated within one year prior to inclusion. The indications for pterygium surgery were visual loss from proximity to visual axis (nine eyes in the MI group and 11 eyes in the MA group), reported growth by patient (12 eyes in the MI group and 10 eyes in the MA group) and intractable symptoms of irritation (four eyes in the MI group and three eyes in the MA group).

There was no statistical difference ($P>0.05$) between the two groups as regarding the age and sex. So the two groups were statistically homogenous and comparable.

The mean preoperative best corrected visual acuity (BCVA) was 0.53 ± 0.15 in the MI and 0.58 ± 0.20 in the MA groups upon inclusion into the study. The mean postoperative BCVA was 0.8 + 0.11 in the MI and 0.83+ 0.16 in the MA groups. There was a highly statistically significant difference between the preoperative and postoperative results ($P<0.05$), while the difference between the two groups was statistically insignificant ($P>0.05$).

One year postoperatively, the recurrence rate was one (4%) eye in the MI group (a 5-mm pterygium that was removed after reported growth by the patient) and two (8%) eyes in the MA group (a 4-mm pterygium that was removed for proximity to visual axis and a 3-mm pterygium that was removed after reported growth by the patient). The difference in the recurrence rate between both groups was statistically insignificant ($P>0.05$). Recurrence of pterygium was noted three to five months postoperatively.

As regards postoperative complications, delayed epithelization (more than two weeks) occurred in two eyes (8%) in the MI group and in one eye (4%) in the MA group. Scleral thinning was reported in one eye (4%) in the MA group which occurred at one month and resolved within three weeks under conservative treatment with topical lubricant therapy; no other serious postoperative complications were reported.

Discussion

Recurrent pterygium is a challenging ocular surface disorder that is often resistant to conventional surgeries. Although various surgical approaches have been advocated, recurrence is still common, with an incidence ranging up to 55%.[8]

There are generally accepted reasons for removing pterygium; a few ophthalmologists have attempted to categorize pterygia with respect to surgical outcome like the indication for surgery and morphology (vascularity, the degree of fibrosis, elevation, epithelial characteristics and inflammation). However, pterygia, with these possible confounding variables, have all been concatenated into larger groups in which the variable being examined is the variety of different methods of removal and adjunctive therapy.[3]

Adjunctive mitomycin C (MMC) in pterygium surgery was first described in Japan by Kunitomo and Mori in 1963.[9] Since then several modalities of usage have been described including preoperative injection and intraoperative application.[7,10]

MMC is an effective intraoperative treatment for preventing recurrence of pterygium.[10-12] The effect of the drug depends on the dose and the length of application.[13] Unfortunately, complications from intraoperative MMC application in pterygium surgery have been reported including vision-threatening complications such as glaucoma, corneal edema, corneal perforation, scleral melting, and cataract formation.[6]

Subconjunctival application of MMC allows exact

dose delivery with minimal epithelial and scleral toxicity. Subconjunctival MMC was investigated in animal models, glaucoma, ocular cicatricial pemphigoid and pterygium surgery without serious complications.[14-17]

The concept of the study originated from a previous study by Donnenfeld and co-workers who reported a case series of subconjunctival MMC injection one month before surgery in recurrent pterygium. Their results showed that pterygia were less vascular and less inflamed at one month and all pterygia were quiescent at the time of surgical excision. However, the recurrence rate was comparable to previous studies with MMC application.[7]

The major endpoint of pterygium removal relates to recurrence. As long as there are no evidence-based guidelines to relate recurrence to the surgical indications or characteristics of the pterygium, judging on the effective duration between MMC injection and surgery on the basis of changes in pterygium characteristics will be unsupported, as recurrence rate will remain the final judge of any duration.

Good penetration of MMC following topical application was documented in animal models through either intact or non-intact corneal epithelium, where MMC was detected in the aqueous humor 10 min after topical application, with a statistically significant difference between intact or non-intact corneal epithelium. The aqueous humor concentration of MMC increased in a dose-dependent manner with increasing exposure time and application concentration.[17,18]

Based on these reports of ocular penetration of MMC, the drug could be detected in the aqueous humor 10 min after topical application, and could penetrate the eye more easily through non-intact epithelium like that following pterygium excision. A study of low-dose MMC through subconjunctival injection with shorter duration of exposure before pterygium excision seemed logic to maintain the efficacy of the drug and avoid long unnecessary exposure with subsequent penetration of MMC.

In our comparative case series the recurrence rate was 4% in the MI group and 8% in the MA group. These results are considered as effective as other modalities of preoperative and intraoperative adjuvant MMC in recurrent pterygium, and better than some reports like Luanratanakorn and co-workers who reported a recurrence rate 52.6% with amniotic membrane transplantation and 21.4% with conjunctival autograft for recurrent pterygium after a six-month follow-up period.[19]

Recurrence rates reported with intraoperative MMC application as adjuvant treatment in recurrent pterygium surgery ranged from 12.5–42.9% depending on the MMC concentration and duration of application.[20,21] Combining conjunctival advancement or graft with intraoperative MMC reduced recurrence rates and improved safety.[22]

In the clinical non-comparative case series of Donnenfeld and co-workers, 36 eyes with recurrent pterygium received 0.1 ml of 0.15 mg/ml MMC subconjunctivally one month before surgery; the reported recurrence rate was 6% over a mean follow-up of 24.4 months.[7]

In another trial preoperative injection of MMC into primary pterygium one month prior to combined pterygium and cataract surgery resulted in no recurrence and no serious complications up to 23 months of follow-up.[23]

As regards postoperative complications, only one eye (4%) had mild avascular scleral thinning in the MA group that resolved within three weeks after surgery and no other serious complications were reported.

Complications occurring after pterygium surgery with adjunctive MMC have been well reported with different modalities of application, concentrations and durations. Avascularized scleral thinning was reported in 13 out of 36 eyes (34.2%) following the use of topical MMC 0.02% eye drops after primary pterygium excision.[24]

Carrasco and co-workers reported local scleral necrosis in a patient who received subconjunctival 0.15 mg/ml MMC one month before pterygium excision. However, that patient had severe dry eye with history of punctal cauterization.[25]

These findings should be seen in consideration of the limitation of our work including the small number of patients in each group which probably limited the value of the statistical comparison. Further research to assess endothelial toxicity, intraocular pressure changes and long-term follow-up following subconjunctival MMC injection is required to judge its safety and efficacy.

Preoperative subconjunctival low-dose MMC injection one day before bare sclera excision showed encouraging clinical results in the management of recurrent pterygium in appropriate patient population with comparable success to topical application of mitomycin.

The subconjunctival injection negates the ability of tear film to dilute the medication, increasing exposure time to the subconjunctival tissue and decreasing the ocular penetration through the intraoperative keratectomy.

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