Clinical Results and Complications of Adjunctive Subconjunctival Mitomycin C Injection before Pterygium Excision

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Abstract

Purpose: To evaluate whether adjunctive subconjunctival mitomycin C before pterygium excision was a safe and effective treatment.

Setting: Medical University of Mashhad; Khatam-Al-Anbia eye hospital.

Design: Interventional non-comparative case-series.

Patients & Methods: 42 eyes of 38 patients with pterygium received 0.1 ml of 0.2 mg/ml mitomycin C subconjunctivally injected into the body of the pterygium 1 month before bare sclera surgical excision.

Main outcome measure: Complication and rate of recurrence in adjunctive subconjunctival mitomycin C injection before pterygium excision.

Results: Mean follow up was 8 months. Pterygium recurred in two eyes (4.7%) of a patient with pterygium. The only complication after subconjunctival mitomycin C injection is mild chemosis and redness in the site of injection for few days that were seen in six patient. There were no intraoperative complications. In follow up visit no toxicity of mitomycin C were found.

Conclusion: Adjunctive subconjunctival mitomycin C before pterygium excision safe and effective treatment and reduce mitomycin C toxicity. It is also reduce rate of recurrence.

Key words: Pterygium Excision, Mitomycin C, Subconjunctival.
Introduction

A pterygium is a fibrovascular growth of actinically damaged conjunctiva that extends across the limbus and invades the cornea. Pterygium is a worldwide condition with a "pterygium belt" between the latitudes 30° north and south of the equator. Pterygium is prevalent in Iran.

There are a number of generally accepted reasons for removing pterygium. The primary surgical indication for pterygium removal is decreased visual acuity. Few people would argue that a pterygium that extends close to the visual axis and appears to be active should be removed. This is based on the understanding that whenever a pterygium is removed, there will be some scarring in the cornea as a result. If the scarring extends close to the visual axis, irregular astigmatism and reduced vision may occur.

There would also be little disagreement that pterygia that restrict eye movement should be removed. Conversely, there may be some argument about the usefulness of removing pterygia that result in significant degrees of astigmatism, as it is unclear from the scientific literature how much of the astigmatism will revert after successful removal. However, removal of the pterygium would appear to be the first sensible step in attempting to correct large degrees of "with the rule" astigmatism that may be due to the pterygium itself.

Discomfort and irritation, difficulty with contact lens wear, refractive surgery, and cosmetic deformity are other reasons for surgical intervention. Pterygia with unusual appearances should be removed in case they represent a masquerading disease such as dysplasia. Most of the other indications for removal of pterygium are less specific, less well-defined, and more controversial. A list of indications for the removal of the pterygium in ranked order of significance is provided in Table 1.

There are many different surgical approaches for the management of pterygia. The treatment of pterygium is still quite controversial, with various treatments being advocated in the scientific literature. Unfortunately, there are very few well-conducted controlled clinical trials of treatments. However, years of anecdotal and noncontrolled studies have confirmed that some methods, such as bare scleral closure, are no longer acceptable in the treatment of pterygium and that other methods are likely to be more useful.

Table 1. Indications for treatment of pterygium in ranked order of significance

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Visual loss from proximity to visual axis</td>
<td>10/10</td>
</tr>
<tr>
<td>2 Threatening the visual axis</td>
<td>10/10</td>
</tr>
<tr>
<td>3 Visual loss from astigmatism</td>
<td>8/10</td>
</tr>
<tr>
<td>4 Eye movement restriction</td>
<td>8/10</td>
</tr>
<tr>
<td>5 Atypical appearance such as possible dysplasia</td>
<td>8/10</td>
</tr>
<tr>
<td>6 Observed growth by ophthalmologist</td>
<td>6/10</td>
</tr>
<tr>
<td>7 Reported growth by patient</td>
<td>4/10</td>
</tr>
<tr>
<td>8 Symptoms of irritation etc</td>
<td>4/10</td>
</tr>
<tr>
<td>9 Cosmetic concerns</td>
<td>4/10</td>
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</table>

In the future it will be important to develop a grading system, and surgeons will need to be conservative in the treatment of pterygium until such time as a single treatment provides a lower recurrence rate and complication rate. The simplest technique, the bare sclera technique, is associated with a recurrence rate of 37% to 91%. In conjunctival autografting for the treatment of pterygia, which has become popular over the last 15 years, resected conjunctiva from the superior limbus (where it is protected from solar damage by the upper lid of the same eye) is transplanted to the area of the pterygium excision. This technique effectively prevents pterygium recurrence. However; conjunctival autografting is a more challenging surgical technique in which the placement of the graft generally requires more significant anesthesia, markedly increased operative time, and increased expense. In addition, patients who undergo this procedure may experience more postoperative discomfort compared with the bare sclera technique. Either suture removal or suture degradation is necessary, and there can be scarring at the donor-graft site that precludes future glaucoma filtering surgery. Kenyon et al reported a recurrence rate of 5.3% after pterygium excision with conjunctival autografting. Lewallen in a randomized trial of conjunctival autografting vs. bare sclera excision reported a 40% recurrence rate with bare sclera and a 7% recurrence rate with conjunctival autografting. The complications
associated with conjunctival autografting include conjunctival graft edema, dellen formation, and the development of pyogenic granuloma either at the surgical excision or the graft placement site. Mitomycin C is an alkylating, antineoplastic agent which prevents cellular division and replication by inhibiting DNA synthesis. The mechanism of action of mitomycin C during glaucoma filtering surgery and in the prevention of pterygium recurrence seems to be inhibition of fibroblast proliferation at the level of the episclera. This prevents the development of fibrosis and aggressive wound healing that are responsible for the closure of glaucoma filtering blebs and pterygia recurrence. The benefit of mitomycin C is that it has the prolonged, if not permanent, effect of suppressing human fibroblasts. The original treatment involved bare sclera surgical excision of the pterygium, followed by the administration of 0.4 to 1 mg/ml of mitomycin C four times daily for 1 week. Although multiple studies have reported recurrence rates of approximately 5% to 12% with the use of topical mitomycin C, this technique has been associated with rare but significant conjunctival and corneal toxicity.

In an attempt to decrease ocular morbidity, the intraoperative use of mitomycin C applied directly to the scleral bed has gained increasing acceptance. Recently, combined pterygium removal with intraoperative mitomycin C and conjunctival autografting was described.

Operative complications during pterygium removal are extremely rare and interestingly are virtually not reported in any of the scientific literature. The principal complications of the treatment of pterygium are recurrence and visual disturbance or loss (Table 2).

Complications associated with the use of topical mitomycin C have been well documented and include vision-threatening complications of glaucoma, corneal edema, corneal perforation, scleral melting, and cataract formation.

The purposes of this study were to decrease morbidity associated with mitomycin C and to increase its effectiveness by applying the medication in a low concentration and low volume.

### Table 2: Complications of pterygium surgery

<table>
<thead>
<tr>
<th>Operative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Thinning of the cornea or sclera by dissection</td>
<td>1. Recurrence</td>
</tr>
<tr>
<td>2. Excessive cautery</td>
<td>2. Corneo-scleral necrosis</td>
</tr>
<tr>
<td>3. Damage to the medial rectus muscle</td>
<td>3. Endophthalmitis</td>
</tr>
<tr>
<td>4. Perforation of the globe with needle</td>
<td>4. Scleritis</td>
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<tr>
<td>5. Intraoperative bleeding</td>
<td>5. Infective scleritis</td>
</tr>
<tr>
<td>6. Damage to canalicular system</td>
<td>6. Infective keratitis</td>
</tr>
<tr>
<td>7. Reversal of conjunctival autograft</td>
<td>7. Inclusion cyst</td>
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<tr>
<td></td>
<td>8. Pyogenic granuloma</td>
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<tr>
<td></td>
<td>9. Dellen</td>
</tr>
<tr>
<td></td>
<td>10. Persistent astigmatism</td>
</tr>
<tr>
<td></td>
<td>11. Persistent epithelial defects</td>
</tr>
</tbody>
</table>

### Materials and Methods

Consecutive patients from June 2003 to August 2004 presenting for pterygium excision (primary and recurrence) at tertiary referral Khatam-Al-Anbia eye hospital were recruited after full informed consent. Exclusion criteria were collagen vascular disease or other autoimmune disease, pregnancy, ocular surface pathology or infection, previous limbal surgery. After surgery, patients were followed up at 1 day, 1 week, 1 month after pterygia excision and every three months. Patients were examined at all visits for conjunctival erythema, epithelial defects, and pterygium recurrence. Recurrence was defined as fibrovascular growth of conjunctival tissue extending>1mm past the limbus. Corneal topography after and before mitomycin C injection from four patients were undertaken.

### Surgical Technique

All surgeries were done by the same surgeon (Dr. Khaksoor). Patients were first given a drop of Tetracaine 0.5% topical anesthetic in the involved eye. Under an examination lamp the patients were injected subconjunctivally with a 30-gauge needle on an insulin syringe containing 0.1 ml of 0.2 mg/ml of mitomycin C. The injection was done directly into the pterygium 1mm from limbus (Figure 1).
scissors was used to dissect the underlying conjunctiva and Tenon's capsule to bare sclera approximately 3-4 mm posterior to the limbus (Figure 5).

The patient received one drop of Chloramphenicol 0.5% and Betametasone 0.1% which was continued four times daily for 2 days. The patients were seen 1 day and 1 month after the subconjunctival injection of mitomycin. Refraction, keratometry, complete slit-lamp examination and intraocular pressure measuring were performed at each visit. One month after mitomycin C injection, the patients underwent bare sclera excision of the pterygium with subconjunctival 2% lidocaine anesthesia (Figure 2).

The hook inserted beneath pterygium then head of the pterygium was avulsed from the underlying cornea (Figure 3) and the cornea was polished with a #15 blade (Figure 4). The pterygium was then grasped, and a Wescott
If excess bleeding were seen light cautery was done. The scleral bed was then polished with a #15 blade. The eyes were patched until the next day. Next day, patients were treated with Betametasone 0.1% and Chloramphenicol 0.5% four times daily for 1 week and then with Betametasone 0.1% four time a day for 3 weeks.

Results
Forty nine patients (28 males and 21 females; mean age, 35.2 years) participated in this study. Because 38 patients (42 eyes) participated in follow up visit four at least 6 mounts they are included (although excluded patients, had no recurrence in their follow up period. Sixteen (30%) patients had recurrent pterygium (15% had more than two time pterygium surgery). The patients were followed up from 6 to 12 months after surgery (mean follow-up, 8 months. Among included patients, in two eyes, pterygium reoccurred and (recurrence rate of 4.7%) over this time period. The recurrences were noted at 6 months in follow up visit. In one case there was a 1.2mm and in the other 2mm recurrence of fibrovascular tissue.

One day after the subconjunctival injection of mitomycin C, 6 patients complained of irritation accompanied by mild conjunctival swelling. All swelling and irritation completely resolved by the 1-week evaluation with use of more frequent Betametasone 0.1%. The pterygia were less vascular and less inflamed at the 1-month visit after mitomycin C injection (immediately before bare sclera pterygium excision) than before the subconjunctival injection of mitomycin C (Figure 1 and Figure 2). We also detected reduce of size of pterygium (mean size before mitomycin C injection:

6.3mm (base) \times 2.4\text{mm} (apex) \times 4.4\text{mm} (length) vs. mean size after mitomycin C injection: 6.0mm \times 2.1mm \times 4.1mm). One month after injection we detect no complication and no significant change in visual acuity and intraocular pressure. At the time of excision, the surgery was easier than routine bare scleral excision, the pterygia was peeled from cornea comfortably with less bleeding.

The patients were all seen on the first postoperative day and had corneal epithelial and conjunctival defects. By the 1-week postoperative visit, all epithelial defects had closed completely, and there was no conjunctival staining with fluorescein. The pterygia healed uneventfully without recurrence in 40 (95%) of 42 eyes. No patient developed a persistent epithelial defect, dellen, scleral melting or other complication at any time during the postoperative follow-up.

Discussion
This study evaluated safety and efficacy of subconjunctival mitomycin C in the treatment of primary and recurrent pterygia. Intraoperative use of mitomycin C significantly retards epithelial healing in a dose-related manner in rabbit corneas. Mitomycin C was shown to be 125 times more potent than 5-fluorouracil in inhibiting corneal epithelial healing.12 For this reason, copious irrigation of the eye is recommended after mitomycin C is applied to the ocular surface. Salomao et al10 recently described conjunctival changes associated with topical mitomycin C. Significant damage to the epithelium occurred with topical application, including nuclear enlargement and cell necrosis with chronic inflammation. In fact, the potent effect of topical mitomycin C on the conjunctival epithelium was demonstrated by its ability to prevent the recurrence of conjunctival intraepithelial neoplasia.11 Chen et al9 showed that a concentration of 0.10 mg/ml inhibits fibroblast replication and that concentrations of \geq 0.3 mg/ml actually cause death of fibroblasts.

In the past, 0.5 ml of 0.2 mg/ml of subconjunctival mitomycin C was administered to rabbits and monkeys16 without side effects. Subconjunctival mitomycin C in the same dose was safe and effective in patients with glaucoma.7 Subconjunctival mitomycin C in the same dose of 0.5 ml of 0.2 mg/ml was used to effectively treat nine patients with ocular cicatricial pemphigoid without adverse effects (mean follow-up, 23.5 months).8 In all previous studies of subconjunctival mitomycin C, no wound healing or deleterious effects were observed. Recently, new study evaluated adjunctive subconjunctival mitomycin C (0.1 ml of 0.15 mg/ml) before pterygium excision. They reported recurrence rate of 6% with no sever complication.17 We chose their method but we
used mitomycin C in higher concentration (0.1 ml of 0.2 mg/ml) to reduce rate of recurrence of pterygium. The advantage of low-dose subconjunctival mitomycin C is that it is effective in preventing pterygium recurrence yet avoids the ocular surface toxicity associated with epithelial and bare sclera delivery of the medication. The medication is administered directly to the activated fibroblasts in the subconjunctival space, where it can work directly on the cells responsible for pterygium recurrence. It is to be hoped that this will avoid or diminish long-term epithelial healing difficulties associated with mitomycin C. Intraoperative mitomycin and postoperative mitomycin are two of the methods of adjunctive therapy that have been most commonly reported recently. Intraoperative mitomycin has been reported in at least 15 series since 1994 when it was first used in Japan. Generally there is bare scleral closure, although it has been used with conjunctival closure and the most commonly utilized dose is 0.2 mg/ml applied for 3 minutes during the surgery. The recurrence rate appears to be acceptably low at less than 10%. Of greater doubt is the variable description of complications, which include severe pain, scleral necrosis, and even scleral perforation. Most of the complications of mitomycin C are associated with persistent epithelial defects and ischemic scleral necrosis. Both of these complications are secondary to side effects produced by the direct action of mitomycin C on these tissues. Because the epithelium and sclera are not target tissues for the mitomycin C and because inadvertently treating these tissues does not contribute to the prevention of pterygium recurrence but is associated with significant side effects, the conjunctival epithelium and sclera should be avoided. With subconjunctival application of mitomycin C, the epithelial and scleral toxicity can be diminished. The other advantage of subconjunctival administration of mitomycin C is that it minimizes and exposure to mitomycin C and act as a depot. The subconjunctival route allows exact dose delivery, which is equivalent to approximately one drop of 0.2 mg/ml mitomycin C, rather than the inexact and substantially higher dosing with sponge delivery during ocular surgery. Low recurrence rate and safety profile with a mean follow-up of longer than 6 months without complications show the efficacy of this treatment and compare favorably with previous studies with mitomycin C in the treatment of pterygia. Other treatment modalities, such as beta irradiation and thiotepa, have low recurrence rates but have fallen into disfavor because of the significant risk of complications. 18 Our recurrence rate is comparable to that of pterygium excision combined with the use of amniotic membrane transplantation19 and compares favorably to pterygium excision followed by the use of human processed pericardium. 20 However, this treatment should be avoided in patients with wound-healing abnormalities or dry eye syndrome because of the increased risk of mitomycin C – associated complications. Furthermore, the subconjunctival application negates the ability of the tear film to dilute the medication, increasing exposure time to the subconjunctival tissue. It is imperative that the concentration and dosage of mitomycin C be carefully monitored, because we are concerned that errors will lead to significant side effects.

Conclusion

Low recurrence rate and safety profile with a mean follow-up of longer than 6 months without complications show the efficacy of this treatment.

References

برسی نتایج و عوارض تزریق زیر ملتحمه میتومایسین C
یک ماه قبل از اکسیژین ناخنک

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چکیده

هدف: بررسی نتایج و عوارض تزریق زیر ملتحمه میتومایسین C پک ماه قبل از اکسیژین ناخنک.

مکان: دانشگاه علوم پزشکی مشهد، بیمارستان خانم لانیی (ص).

طرح مطالعه: مداخله‌ای، آننده‌نگر و غیرمقایسه‌ای.

روش و پیمان: ۲۴ جسم از ۳۸ بیمار مبتلا به ناخنک تحت تزریق زیر ملتحمه ۱/۰ میلی‌لیتر از محلول ۱/۰ میلی‌گرم در میلی‌لیتر میتومایسین C پک ماه قبل از اکسیژین فرآور گرفتند.

پایان‌ها: میانگین پیگیری ۸ ماه بود. ناخنک در دو چشم (۷/۷) عود کرد. نهایتاً عارضه ادم و قرمزی گذازی در محل تزریق بوده و در ۴ بیمار مشاهده شد. هیچ عارضه‌ای جرم در حجم جراحی رخ نداد. در مدت پیگیری نشانه‌ای از تثبیت میتومایسین C به چشم نخورده.

نتیجه‌گیری: تزریق زیر ملتحمه میتومایسین C پک ماه قبل از اکسیژین، روش موثر و بی‌خطری در درمان ناخنک می‌باشد.

این روش احتمال وقوع را کاهش می‌دهد.

کلمات کلیدی: ناخنک، میتومایسین C، تزریق زیر ملتحمه، اکسیژین.

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