Results of treatment with topical mitomycin C 0.02% following excision of primary pterygium

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Abstract

Aims—The effectiveness of instillation of mitomycin C eyedrops on the recurrence rate of pterygium was assessed in patients undergoing primary pterygium surgery. Any side effects were also noted.

Methods—Primary pterygia in 38 consecutive patients were surgically excised during July to December 1992. After surgery, mitomycin C 0.02% eyedrops twice daily for 5 days as well as dexamethasone 0.1% four times tapered for the next 6 weeks were instilled. Postoperative follow up ranged from 6 to 11 months.

Results—In one patient the pterygium recurred after 3 months (recurrence rate 2.6%). The side effects encountered were: avascularised sclera in 13 cases between 1–10 months postoperatively; ocular discomfort and lacrimation in five cases; superficial punctate keratitis during the first month in three cases; pyogenic granuloma in two cases. In one patient steroid induced increased intraocular pressure was found 4 weeks after surgery. The adverse side effects were all mild, self limiting, and easily treated.

Conclusion—This study suggests that postoperative instillation of mitomycin C 0.02% eyedrops twice daily for 5 days following excision of primary pterygium is an effective and safe treatment to obviate pterygium recurrence.

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The recurrence rates of pterygia following surgical removal is significantly high. In a recent review it was stated to be between 25–45%.¹ In recent years there have been several reports showing that following excision the recurrence rate of the pterygium could be decreased by using topical treatment with mitomycin C eyedrops after surgery.^{1–7} Mitomycin C is an alkylating agent. It inhibits the synthesis of DNA and cellular RNA. It is a potent inhibitor of fibroblast proliferation.^{8–10}

The length of therapy and the concentration of the mitomycin C eyedrops varies among those studies. Serious sight threatening complications associated with the use of the drug have been reported recently.^{11–13} In the study published by Rubinfeld *et al*¹¹ the severe eye complications reported with this treatment included scleral melting, severe secondary glaucoma, iritis, corneal perforation, and sudden onset of mature cataract. The authors urged caution in the further application of mitomycin C for this purpose.

The aim of this prospective study was to

evaluate the effectiveness and complications encountered with the use of the lower content of topical mitomycin C eyedrops (0.02%) instilled twice daily for 5 days following excision of the primary pterygium.

Materials and methods

Between July to December 1992, 42 consecutive patients with primary pterygia were treated surgically in our department and were included in the study.

Patients were excluded from the study if they had previous ocular disease or ocular surgery, as well as any predisposing condition to ulceration or poor wound healing such as Sjogren's syndrome, atopic keratoconjunctivitis, acne rosacea, or herpes keratitis. We also did not include in the study patients with one eye only or pregnant women. The study was approved by the Helsinki Committee of our hospital and written informed consent was obtained from each of the patients.

A complete ocular examination, refraction, and photographic documentation of the pterygia were performed for each patient before surgery.

All the surgical procedures were performed on an outpatient basis by two surgeons (SL, HL). Each pterygium was excised using the bare sclera technique. The bare sclera was then minimally cauterised leaving an area of bare sclera measuring on average 3×5 mm.

The mitomycin C eyedrops were freshly prepared on the day of surgery under sterile conditions from the commercially available injectable form of the medication. Sterile distilled water was used as diluent to achieve a concentration of 0.02%.

Postoperative topical treatment which was started on the first day after surgery included mitomycin C 0.02% twice daily for 5 days only. In addition, dexamethasone 0.1% eyedrops were instilled four times daily and tapered gradually over the following 6 weeks. All patients were examined on postoperative days 1, 7, 21, 42, and monthly thereafter.

Results

Of the 42 operated patients, four patients who did not comply with the protocol were excluded from the study. Three of them failed to instil the mitomycin C eyedrops and the fourth patient who did instil the drops was lost to follow up after the first week.

Of the 38 remaining patients, 23 (60%) were male and 15 (40%) were female. The mean patient age was 49.9 (SD 11.83) years which ranged between 28 to 71 years. All of the

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Table 1 Complications following treatment with topical mitomycin C 0.02%

Complications	No of eyes (%) (n=38)
Avascularised sclera	13 (34.2)
Ocular discomfort and lacrimation	5 (13.1)
Superficial punctate keratitis	3 (7.9)
Pyogenic granuloma	2 (5.2)
High intraocular pressure	1 (2.63)
Recurrence of the pterygium	1 (2.63)

Figure 1 Avascularised area associated with superficial melting of sclera appeared immediately following surgery and persisted 4 months.

Figure 2 Avascularised sclera with diffuse superficial melting. Note the foci of ulceration with marked fluorescein stain.

Figure 3 Recurrence of pterygium 3 months postoperatively.

pterygia were located nasally, their mean size was 3.51 (1.25) mm (range 2.0–6.8 mm). The mean postoperative follow up period was 8.43 (1.98) months (range 6–11 months).

Complications following surgery are summarised in Table 1. In 13 cases (34.2%), avascularised areas were found in the nasal sclera during the follow up period. In 11 patients (28.9%), the avascularised area appeared at the middle of the bare sclera zone during the first month postoperatively, and gradually revascularised by the end of the follow up period. There was no positive fluorescein stain at any time during the follow up; the patients were asymptomatic.

In two other patients (5.2%) the avascularised area was associated with superficial melting of sclera and a positive fluorescein stain. Both were treated with patching, lubricants, and antibiotic ointment. Both patients were symptomatic and complained of ocular discomfort.

In the first patient (Fig 1) the lesion persisted for 4 months after surgery and healed in the fifth month.

In the second patient (Fig 2), the lesion appeared 7 months after surgery, persisted for 3 months, then resolved. Mild superficial punctate keratitis appeared in three patients (7.9%). The corneal stain resolved during the first month postoperatively in two of them (5.2%). In the third (2.6%) superficial punctate keratitis persisted to a lesser degree after 9 months.

Pyogenic granuloma occurred in two cases (5.2%). The lesions resolved spontaneously after 7 weeks. There was recurrence of pterygium in one patient (2.6%) 3 months postoperatively (Fig 3). In one patient (2.6%) there was elevation of intraocular pressure 4 weeks after operation to values between 20 and 25 mm Hg which resolved upon discontinuation of the steroids.

Five patients (13.1%) complained of ocular discomfort and lacrimation at the end of the follow up period. Pterygium recurred in one; two patients had scleral blanching; the two other patients had no remarkable cause of discomfort or lacrimation.

Discussion

Mitomycin C is an antineoplastic antibiotic alkylating agent isolated from the fermentation filtrate of *Streptomyces caespitosus*. The anti-tumour effect of mitomycin C is attributed to the inhibition of DNA replication by forming covalent linkages with guanosine residues in DNA. Therefore, by preventing mitosis, mitomycin C leads to cell death. The effects of these compounds to some extent mimic those of α radiation and for this reason they are described as radiomimetic, having the same long term complications.^{11 14} In tissue culture, it is a potent inhibitor of fibroblast proliferation.^{9 10}

There are several studies^{2–5} concerning the use of mitomycin C eyedrops following excision of pterygium in order to prevent recurrence of the pterygium postoperatively.

Mitomycin C proved to be very effective in preventing the recurrence following surgery. The concentration of the mitomycin C eye-drops, the length of treatment as well as percentage of complications vary among the studies. In mitomycin C untreated patients pterygia recur during the first 6 months after surgery if they recur. As the follow up period in our study ranged between 6 to 11 months (mean 8.43 months), there was ample time for recurrence in those patients in whom there was recurrence.

According to our study, postoperative instillation of mitomycin C 0.02% twice daily for 5 days is an effective and safe treatment for all cases of primary pterygium. In only one patient (2.61%) was recurrence of the pterygium noted (3 months postoperatively). This recurrence rate is lower than the 7% reported by Hayasaka *et al*³ who followed the same protocol of mitomycin C in 29 eyes of 26 patients with primary pterygium.

Singh *et al*² reported 2.3% recurrence rate with higher concentration of mitomycin C (0.04% and 0.1%) in 44 eyes with primary and recurrent pterygium after 6 months of follow up. With an extended follow up time of 18 months, no additional recurrences of pterygia formation were noted, and no additional complications occurred except in an eye treated with 1.0 mg/ml of mitomycin C, which had lower lacrimal punctum occlusion occurring 4 months postoperatively.⁷ However, it is important to emphasise from Singh's articles that mitomycin C induced conjunctival irritation, ocular pain, photophobia, tearing, and foreign body sensation to varying degrees of severity – common symptoms experienced by all the patients.^{2,7} They felt that mitomycin C 0.02% used twice a day for 5 days was not the optimal dosage to treat pterygia and thus recommended 0.04% four times a day for 10–14 days to achieve this goal.^{2,15}

It is stated in the latest reports^{11,14} that toxic effects of the drug increase dramatically with increasing cumulative dose. Rubinfeld and his colleagues¹¹ described 10 patients who underwent excision of pterygium in several medical centres and showed severe ocular complications – that is, severe secondary glaucoma, scleral melting, iritis, corneal perforation, and sudden onset of mature cataract. These complications occurred between 3 weeks and 7 months (mean 2.8 months) after therapy with mitomycin eye-drops. In eight out of their 10 patients, the concentration of mitomycin C eye-drops was higher than 0.04% and was applied for longer periods of time than in our study, averaging 2 weeks. Therefore, a large cumulative dose of mitomycin C was probably the reason for the severe complication. In the other two patients, a concentration of 0.02% was used four times daily for 3 days in one patient, and beyond 2 weeks by the other one. In our patients, complications, when they occurred, began to appear on average 2.8 months after therapy with mitomycin C eye-drops. The most prevalent ocular complication was avascularised sclera in 13 patients (34.2%);

most of them were mild without further sequelae – that is, ulceration or necrosis (Table 1). Two out of 13 patients with avascularised sclera had symptomatic complaints and a positive fluorescein stain. Both needed additional therapy such as prolonged patching and lubricants until their clinical finding resolved.

Superficial punctate keratitis appeared in three patients (7.9%); resolved completely in two patients after 1 month and remained to a lesser degree, asymptomatic, in the third patient after 9 months of follow up.

Rubinfeld hypothesised that the toxic effect of mitomycin C on stem cells, particularly vascular endothelial cells and limbal pleuripotent stem cells, might explain some of the long term effects of mitomycin.¹¹ We agree with this hypothesis and we think that the avascularised scleral bed and the superficial punctate keratitis that appeared in our patients, although in a mild form, is a symptom of the toxic and antimetabolic effect of the drug.

Pyogenic granuloma appeared in two of our patients (5.2%) and resolved spontaneously. Symptomatic complaints of mild ocular discomfort and lacrimation were found in a rate of 13.1%. These complications were also encountered by other investigators.^{2,3}

In one patient steroid induced increased intraocular pressure was found. Two weeks after discontinuation of the topical steroids the intraocular pressure returned to normal values. The lowest efficient dosage of topical mitomycin C needed to obviate the recurrence of pterygium still has not been determined. Frucht-Pery and Ilisar have recently suggested the use of mitomycin C 0.01% twice daily for 5 days, but reported a recurrence rate of 8% with mild complications.⁶

Our prospective study suggests that treatment with mitomycin C 0.02% eyedrops twice a day for 5 days following excision of pterygium is quite safe and is a very effective therapy in order to prevent recurrence of pterygium.

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History of ophthalmology

The short history of heat cauterisation of the cornea

In 1873, two ophthalmologists independently had the idea of heating a metal instrument to red heat and applying it to the diseased cornea. Samelsohn, in 1874, described heating the instrument with electric current, and termed this 'galvanocautery'. Martinache, in 1873, was content with an ordinary flame. In general, the idea was not attractive to their readers. Neiden felt that this was due to the apparent crudity of the method. However, one or two were inspired to try it, and Sattler presented a report on cautery at the meeting of the German Ophthalmological Society in 1879.

This inspired Fuchs and Arlt in Vienna, who endorsed the method in the *BMJ* in 1880. Fuchs's instrument was a pea-sized metal ball on a probe, which he heated in a gas flame. Having applied it to numerous smallpox ulcers, Fuchs stated that it was a powerful caustic, destroying suppuration and infectious germs to bring about cure. Fuchs's report inspired Gruening to use cautery in a larger series, partly because the advent of cocaine meant that it 'no longer filled the patient's heart with terror'. However, he still heated his platinum probe in a spirit lamp hidden behind the patient's chair. Seven of this series had good results after one application, and the resultant eschar always separated within 24 hours. However, three needed repeated cautery, and in one case the cornea perforated and the iris prolapsed. Gruening, undaunted, states that even this recalcitrant ulcer finally healed. To underline its efficacy in advanced cases, he describes a 'derelict and destitute old woman' who had a deep corneal defect and pus filled anterior chamber. Given three applications of cautery as an outdoor patient, satisfactory corneal healing was achieved.

The most comprehensive trial was done by Neiden, who preferred galvanocautery, while realising its pitfalls. These included using too many elements to arm the loop (which simply melted it) and using white heat (which dazzled the operator's eye). Goodness knows what it did to the patients' eyes! Neiden reported that sometimes, when the loop glowed, the patient noticed the heated point before the ulcer could be touched, and made unforeseen movements. (Undoubtedly straight through the door on some occasions!) Often this caused the loop to graze the adjacent cornea, producing an opaque stripe which fortunately disappeared after 24 hours.

In extensive hyopyon, cautery was used to perforate the ulcer and evacuate the pus. Neiden admits that this sounds rather dangerous on first consideration. Happily, experience showed him that the rapid outrush of aqueous humour cooled the loop, and the danger of heat injury to lens or iris was thus removed. In deliberate corneal perforation, however, the loop had to be balanced carefully on its fulcrum for prompt withdrawal when the stream of aqueous appeared. 'This demands certain steadiness of hand and immobility of eyeball,' stated Neiden.

Initially, he agreed with others that repeated attempts were necessary to remove the detritus from the ulcer base, but learned with experience to cauterise more thoroughly at the first sitting. Cautery was also used in traumatic injury, both to remove rust rings after foreign bodies, and to treat the infective corneal ulcers which sometimes resulted. Neiden was intrigued by the fact that these infections usually occurred in boilermen, whose lesions were also the most resistant to cure. This was put down to the fact that, when injured, they had to continue their shift in conditions of extreme heat, the inevitable profuse sweating being conducive to infection. (Requests to leave work to see the doctor in 1880 would have been met with incredulity, if not physical violence.) Neiden then extended the use of cautery to trachoma and tumours of the lids. His patients appeared to tolerate it well, in spite of the 'considerable hissing' which occurred when probe met cornea. He admits that he cauterised under the pretence of being obliged to remove a foreign body clinging to the eye. (So much for informed consent in the 1880s.)

Although Neiden, Sattler, Fuchs, and Arlt agreed that cautery had much to recommend it, these were mere small islands in the general sea of dissent. With 'chemical' treatments of ulcer such as antiseptic and iodoform just around the corner, reports on cautery rapidly disappeared from the literature, never to be seen again.

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