

Can pterygium excision with mitomycin C leaving bare sclera be salvaged?

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Abstract

Purpose: The aim of this study was to analyze the recurrence rate of pterygium following excision with intra-operative mitomycin C (MMC) and post-operative scraping of the perilimbal conjunctival defect, and the patients' satisfaction with this technique.

Methods: This is a retrospective analysis of a cohort of 33 eyes of 28 patients with primary or recurrent pterygium who underwent simple excision with MMC. They were followed up after a mean of 27.8 months. The main outcomes considered were the recurrence rate and patient satisfaction. A recurrence was defined as any regrowth of conjunctiva over the limbus and any complications were considered significant. The patients were interviewed with a standard questionnaire and examined.

Results: An objective recurrence was noted in 55% (18 out of 33 eyes). The recurrence rate after excision of primary pterygia was 46% (13 out of 28 eyes), and for recurrent pterygia it was 80% (four out of five eyes). In this study the complications included: six eyes that developed a granuloma, one case of bleeding which persisted for three days post-op, and one eye in which there was a suspected scleral melt at five weeks. 79% of the procedures resulted in a good patient satisfaction (26 out of 33 eyes), and only in 15% (five eyes) was there a subjective recurrence.

Conclusions: This technique in our study resulted in an unacceptably high recurrence rate, especially in the case of recurrent pterygia. However, patients still tended to be satisfied with the outcome.

Keywords

mitomycin C; MMC; pterygium; recurrence.

Introduction

A pterygium is a superficial, usually elevated, wing-shaped fold of conjunctiva that grows over the limbus and extends onto the corneal surface. Pterygia can vary from small, atrophic, quiescent lesions to large, aggressive, rapidly-growing fibrovascular lesions that can distort the corneal topography, and in advanced cases, obscure the optical centre of the cornea.

Pterygia are described as a proliferative disorder resembling an aberrant wound healing response.¹ It is a disease of limbal stem cells which are damaged primarily by chronic UV light exposure causing up-regulation of the p53 tumour suppressor gene. This leads to decreased apoptosis, increased activity of matrix metalloproteinases resulting in Bowman's layer dissolution, activation of cytokines and growth factors resulting in leukocytic infiltration, and activation of fibroblasts causing increased elastin deposition. The limbal predilection may be explained by the phenomenon

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of peripheral light focusing, in which incident light passes through the anterior chamber and is focused at the distal (nasal) limbus where limbal stem cells reside.

Typically, a pterygium consists of three distinct parts: cap, head, and body/tail. The cap or leading edge is a flat zone on the cornea that consists mainly of fibroblasts that invade and destroy Bowman's layer. The head is a vascular area that lies behind the cap and is firmly attached to the cornea. The body/tail is the mobile area of the bulbar conjunctiva, which can be easily dissected from the underlying tissue. Lesions larger than 3.5mm on the cornea are likely to be associated with more than one dioptre of astigmatism.

The main indications for surgical removal are: discomfort despite lubricants, decreased vision, diplopia, and cosmetic intolerance. Several surgical techniques exist and the best method would ideally have the least rate of recurrence and a short operating time. Techniques used are:

- Bare sclera technique – this has the highest rate of recurrence but relatively short operating time.²
- Conjunctival autograft technique – using sutures, fibrin glue, or autologous blood to fix the graft onto the scleral bed³; associated with less recurrence rate but longer operating time.
- Amniotic membrane graft (AMG) – fixed using sutures or fibrin glue; it is a useful alternative to conjunctival autografting especially in patients who have limited amount of conjunctiva. However, there is the issue of availability of such materials and most studies report a significantly higher rate of recurrence with AMG.⁴

Adjunctive therapies include the use of intraoperative mitomycin C (MMC) due to its anti-fibrotic and anti-angiogenic properties, or β -radiation; the latter is no longer in use due to its adverse effects on the eye.

MMC alkylates and cross-links DNA, and inhibits DNA, RNA, and protein synthesis. It probably has a long-term influence on cellular proliferation.⁵ It is thus used as a fibroblast inhibitor. The use of topical MMC as an adjunct to pterygium surgery was first introduced by Kunitomo and Mori in Japan and subsequently by Singh *et al.*⁶ Recurrence rates are reported to be 5.4–21% when MMC is used alone in treating

primary pterygium and 12.5–19.2% when treating recurrent pterygium.⁷ Various studies have shown that using MMC in patients with more severe pterygia as an adjunct to conjunctival autografting, lowers the recurrence rate.

In this study we are investigating the outcome with the bare sclera technique augmented with intra-operative MMC, followed by post-operative scraping of the scleral bed until corneal re-epithelialization.

Methods

This is a retrospective analysis of a cohort of 33 eyes of 28 patients who underwent primary or recurrent pterygium excision with intra-operative MMC in the same institution between November 2011 and December 2013. The procedures were carried out by six different surgeons – one consultant and five different trainees of varying experience (Table 1).

Table 1: Breakdown of the surgeons involved according to surgical experience

Level of experience	Number of procedures
Consultant	4
Young trainee 1	1
Young trainee 2	1
Senior trainee 1	9
Senior trainee 2	9
Senior trainee 3	9

The patient list was obtained from the database supplied by the surgical performance unit of the hospital. Formal ethics and data access approvals were granted. The patients were selected sequentially from the list in chronological order. The inclusion criterion was pterygium excision with intra-operative MMC and post-operative scraping as explained in this section. Exclusion criteria were: incomplete information including poor documentation, patients lost to follow-up and those who could not be contacted or come for the examination, and patients in whom the method of excision was different from the one described below.

Table 2: Data entry form devised for this study

ID
Name & Surname
Age now
Procedure details
Side
Date of procedure
Surgeon performing procedure
Months since procedure
Duration of pterygium prior to excision
Is indication for surgery clearly documented?
Pre-op VA
Pre-op size documented
Pre-op size /mm
Primary / recurrent pterygium
Biopsy submitted Y/N
Indication for surgery: Objective Subjective
Pain / foreign body sensation during surgery 0-10
Pain / discomfort post-op (during recovery) 0-10
Pain / foreign body sensation during post-op scrapings 0 - 10
No. of scrapings
Timing of scraping (days post-op)
Duration of post-op antibiotic & steroid regimen
Antibiotic & steroid regimen
Post-op lubricants Y/N
Peri-op complications
Post-op complications
Is the patient happy with the result?
Would the patient do this procedure again for a pterygium in the other eye?
Would the patient do this procedure again for a pterygium in the same eye?
Sunglasses being used regularly in the sun Y/N
Lubricants being used Y/N
Subjective recurrence Y/N
VA post-op (from file) and/or today
Objective recurrence Y/N
Size of recurrent pterygium, if present
Examination findings
Other remarks

The notes of the patients included in the study were reviewed, and the patients were called for questioning throughout the year 2015. A questionnaire devised by the study group was used (Table 2), and the patients were examined to assess for recurrent growth. As shown in Table 2, patients were also asked about use of lubricating drops and UV protection with sunglasses. A recurrence was defined as any growth of conjunctiva beyond the limbus. Patients were asked to recall the discomfort felt on scraping of the scleral bed carried out during the early post-operative reviews under topical anaesthesia with 0.4% oxybuprocaine.

The procedures were all done under local anaesthesia using topical 0.4% oxybuprocaine and subconjunctival 2% lignocaine with 1:200,000 adrenaline. The pterygium was excised from the cornea under an operating microscope, with attention to remove as much fibrovascular tags as possible. The excision included the adjacent thickened bulbar conjunctiva and underlying Tenon's capsule. This was followed by the application of 0.04% mitomycin C for two minutes on the scleral bed using soaked spear swabs avoiding contact with the limbus and cornea, followed by immediate copious irrigation of the conjunctival sac.

The typical post-operative regimen was a 1% chloramphenicol ointment patch till the following day. The patients were closely monitored early on and scraped as needed in an attempt to achieve healing of the cornea before the perilimbal conjunctival defect. The patients were mostly reviewed the first time on day 1-2 and the slough developing on the scleral bed was scraped away from the limbus with a cotton tip or the side of a wide-bore needle/blade. Further scraping was repeated until the corneal epithelium healed completely. The typical treatment prescribed was a combination of 0.3% tobramycin and 0.1% dexamethasone as ointment bd and as drops qds for 3-4 weeks.

Results

The male-to-female ratio was 3:1 and the mean age was 59.4 years (range: 31-86 years). There were four temporal pterygia, and five recurrent nasal pterygia. The patients were followed up after a mean of 27.8 months (SD: 8.9 months; maximum follow-up: 44 months).

The mean time that the patient spent in theatre

was 25 minutes (SD: 8.6 minutes; range: 15-45 minutes).

In this study the complications included: six eyes that developed a granuloma, one case of bleeding which persisted for three days post-op, and one eye in which there was a suspected scleral melt at five weeks. The granulomas were treated first-line with intensive application of topical steroids, and the case of possible melting was managed with a conjunctival advancement.

An objective recurrence was noted in 55% (18 out of 33 eyes). This included minimal overgrowth on the cornea. The recurrence rate after excision of primary pterygia was 46% (13 out of 28 eyes) and for recurrent pterygia it was 80% (four out of five eyes). The earliest recurrence was documented at four months.

Data on patient satisfaction showed that 79% were happy with the result (26 out of 33 eyes), and only 15% had noted a recurrence (five eyes). 88% said that they would be happy to do same procedure again on the same eye if a recurrent pterygium were to be removed. During the post-operative scrapings the mode pain score was 0/10, with a mean of 1/10.

Figure 1 shows the breakdown of subjective and objective indications for excision in our group of patients.

In the group of patients studied, only one excision specimen was submitted for histology. This was a case of a bilobed pterygium and it was submitted to exclude possible carcinoma due to the temporal component. Features characteristic of a pterygium were confirmed by the pathologist.

Only 24% said that they used lubricating drops post-op (eight out of 33 eyes).

Discussion

Over the past couple of decades, there has been a significant advancement in pterygium surgery techniques that has led to an increased variety of options available for the ophthalmic surgeon. In this study, MMC was used intra-operatively and patients were monitored closely post-operatively with conjunctival scraping if needed, in an attempt to achieve healing of the corneal epithelium before that of the perilimbal conjunctiva.

Data collected in this study reports an objective recurrence in 55% (18 out of 33 eyes). While the recurrence rate after excision of primary pterygia was 46% (13 out of 28 eyes), that for

recurrent pterygia was reported to be 80%. The fact that 79% of patients were satisfied with the result indicates that the patients were asymptomatic.

The use of high cumulative doses of MMC post-operatively, as well as poor selection of patients, can lead to the development of severe complications. To limit these complications, it is of utmost importance to set strict exclusion criteria, to use MMC only intra-operatively under controlled conditions, and to follow the patients closely until ocular surface re-epithelialization is complete.⁸

Patients suffering from conditions that predispose to poor wound healing should not be treated with MMC. These include patients with atopic keratoconjunctivitis, severe dry eye, acne rosacea, and herpes keratitis. Possible complications that can arise from the uncontrolled use of MMC or its use in high-risk patients include: corneal oedema or perforation, corectopia, iritis, scleral calcification, pain, secondary glaucoma, and cataract.⁹

Varying concentrations of MMC have been used intra-operatively, usually in the range of 0.02-0.04%. Also, the time of exposure of MMC to the subconjunctival space varies in different studies, usually from one to five minutes. In this study, the concentration of MMC used was 0.04% and the intra-operative exposure time was two minutes. This large variation makes it difficult to compare the results. The safest concentration and exposure time of intra-operative MMC that are effective in preventing pterygium recurrence without causing complications have still not been established. More large-scale prospective studies will need to be carried out to reach a conclusion.

Table 3 summarizes the findings of a meta-analysis carried out by Sanchez-Thorin *et al*,¹⁰ and studies by Manning and Young.¹¹⁻¹² In the latter two studies, the sclera was covered by conjunctiva at the end of the procedure.

Pterygium excision with conjunctival autograft is time-consuming and has a significant learning curve. Surgeons may also be reluctant to use a conjunctival autograft in patients who may need the conjunctiva for future surgical procedures. On the other hand, avoiding the use of MMC will not expose the patients to its possible side-effects, even though these are uncommon when MMC is used appropriately.

Figure 1: Indications for pterygium excision: Chart 1a - Subjective; Chart 1b – Objective

Chart 1 a – Subjective

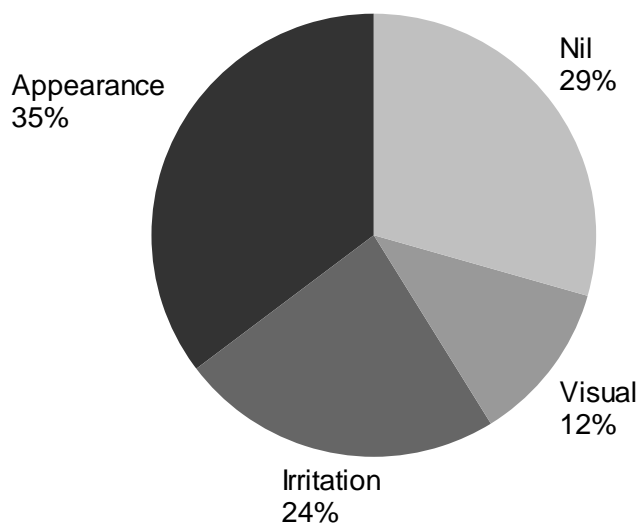
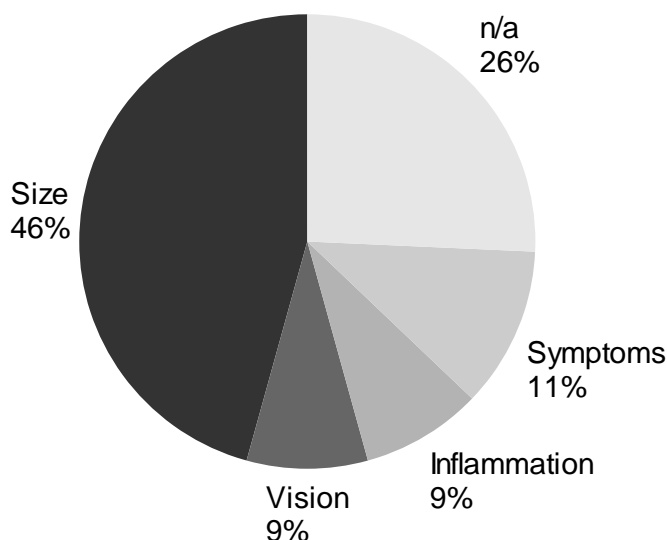


Chart 1 b – Objective



In our study, the rate of recurrence in primary pterygia was 46%. However, this percentage also included minimal overgrowth on the cornea (<1mm), therefore comparison to these studies is difficult since the definition of recurrence varied. For example, some defined recurrence as a regrowth of >1.5mm.¹¹ However, a recurrence actually starts when there is a reactivation of the inflammatory process (vascular congestion and thickening) in the treated area.¹³ It should be noted that our first recurrence was documented at four months, even though usually recurrences occur in the first three months after excision.¹⁴ Our method could thus have retarded the recurrence. Further studies would be needed to establish whether this effect is statistically significant.

Also, one has to take into consideration the

high UV index the Maltese population is exposed to throughout the year (Mediterranean climate), the ever-increasing environmental pollutants, and possible genetic factors that may influence recurrence rates.

As mentioned previously, pterygium excision with conjunctival autograft is time-consuming and has a steep learning curve. Variations to this procedure include the use of intra-operative MMC combined with closure of the conjunctiva to the limbus, thus avoiding bare sclera. This was reported to give good results and at the same time decrease the possible complications caused by MMC.¹⁵ In addition, this approach does not increase the procedure time significantly, therefore providing a good compromise.

Table 3: Summary of findings of a meta-analysis by Sanchez-Thorin et al 1998 (12)

Author	Year of publication	Technique	Number of Eyes	MMC concentration (%)	MMC contact time (minutes)	Recurrence rate (%)
Lewallen	1989	Bare sclera	16	n/a	n/a	40.0
Chen <i>et al</i>	1995	Bare sclera	17	n/a	n/a	88.2
Singh <i>et al</i>	1988	Bare sclera	18	n/a	n/a	88.9
Mahar, Nwokora	1993	Bare sclera	15	n/a	n/a	60.0
Manning <i>et al</i>	1997	Intra-operative MMC	19	0.04	3	10.5
Young <i>et al</i>	2004	Intra-operative MMC	53	0.02	5	15.9
Chen <i>et al</i>	1995	Conjunctival autograft	23	n/a	n/a	39.1
Lewallen	1989	Conjunctival autograft	17	n/a	n/a	17.6
Manning <i>et al</i>	1997	Conjunctival autograft	18	n/a	n/a	22.2
Young <i>et al</i>	2004	Conjunctival autograft	52	n/a	n/a	1.9
Manning <i>et al</i>	1997	Post-operative MMC	19	0.02	qds x1 wk	21.1
Chen <i>et al</i>	1995	Post-operative MMC	24	0.02	bd x5 days	37.5
Mahar, Nwokora	1993	Post-operative MMC	17	0.04	qds x2 wks	0

The main strength of this study is the long follow-up period. However, there were several limitations in this study. The sample size was small, and having different surgeons produces operator bias. With multiple surgeons there is variation in technique, and procedures carried out by trainee surgeons at different stages in their training were included. It is difficult to standardize quality of excision, even by the same surgeon. In addition, since this was a retrospective study, there is a likelihood of recall bias by the patients when they were questioned regarding their experience; a prospective approach would have been better to decrease recall and selection bias, and improve the

quality of the data. A visual analogue pain scale could have been better suited for patients to grade pain. Also, it is difficult to ensure patient compliance with the post-operative treatment and precautions. This is important since limited use of post-operative topical steroid is associated with a higher risk of recurrence.¹⁶ There are other confounding factors which influence the risk of recurrence, such as sun exposure and dry eye disease, but these are very difficult to control.

In our study the recurrence rate after recurrent pterygium excision was very high and this indicates that MMC alone is not sufficient for recurrent pterygia; even the overall recurrence rate was

unacceptably high. However, for patients who are unlikely to tolerate a long operation time for various reasons, this method remains an option, provided that the patient is aware of the higher recurrence rate.

Possible improvements on the intra-operative MMC method may be: increasing the MMC exposure time, and meticulous clearance of the limbus to remove all the vascular bridges.

The use of lubricants and sunglasses should be encouraged, especially in early pterygia and following excision, as this can decrease symptoms and possibly slow progression or recurrence.

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