Long term results of intraoperative mitomycin C in the treatment of recurrent pterygium

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Abstract

Aim—The study was designed to evaluate the long term results of intraoperative mitomycin C in patients with one recurrence of pterygium.

Methods—In 45 white patients with one recurrence of pterygium the 'bare sclera technique' was performed and a sterile sponge soaked in a 0.2 mg/ml (0.02%) mitomycin C solution was placed intraoperatively on the sclera for 3 minutes. The control group underwent surgical excision only. Recurrences were analysed by the χ^2 test and the method of Kaplan-Meier (life table analysis); the difference between survival curves was tested by the log rank test. The χ^2 test with Yates's correction or Fisher's exact test were used to analyse the difference in complications and side effects between the two groups.

Results—After a mean postoperative follow up of 34.55 (SD 13.70) months, 6 recurrences (12.5%) were observed in the mitomycin C treated patients and 16 (35.6%) in the control patients ($p=0.027$). The 24 and 48 month life table success rates were 89% and 83% in the mitomycin C treated group and 66% and 63% in the control group, respectively ($p=0.022$). No severe side effects appeared during follow up. Superficial punctate keratitis appeared in the early postoperative period in only seven mitomycin C treated eyes (15.5%) ($p=0.018$).

Conclusion—This study confirms the efficacy of intraoperative mitomycin C in improving the success rate after recurrent pterygium surgical excision.

(*Br J Ophthalmol* 1996; 80: 288-291)

Mitomycin C is an antibiotic antineoplastic agent inhibiting RNA, DNA, and protein synthesis. Results and complications of the postoperative use of mitomycin C eyedrops for prevention of recurrent pterygium were widely reported.¹⁻¹⁴

Ophthalmologists have recently considered the effectiveness of the intraoperative use of mitomycin C in pterygium surgery.¹⁵⁻¹⁷ Our previous study showed short term results to be encouraging in the treatment of recurrent pterygium.¹⁶

The aim of our study was to show the long term results of intraoperative administration of mitomycin C in the surgical treatment of recurrent pterygium and to evaluate long term complications.

Materials and methods

From January 1991 to December 1994, 90 white patients (90 eyes) undergoing surgical treatment for recurrent pterygium were selected for a prospective, randomised, masked study.

Inclusion criteria were first recurrence of pterygium and pterygium growth on the cornea for a minimum of 2 mm from the limbus. Pterygium growth on the cornea was measured with Castroviejo compasses.

The patients were divided at random in two age and sex matched groups: group 1 consisted of 45 patients (28 males, 17 females; mean age 40.8; range 21-59 years) with group 2 also of 45 patients (27 males, 18 females; mean age 40.7, range 21-61 years) (Table 1).

All of the surgeries were performed by the same surgeon (LM) under local anaesthesia. Approximately 0.4 ml of mepivacaine (Carbocaine) 1% were injected under the pterygium to elevate it into its attachment to the cornea.

The head of the pterygium was grasped with toothed forceps. Dissection of the pterygium was started using a Beaver 64 surgical blade about 0.5 mm ahead of the pterygium apex and carried down clearly to the limbus.

In group 1 we added intraoperative administration of mitomycin C (Kyowa Hakko Kogyo Co Ltd, Tokyo) to the pterygium surgery.

A sterile sponge (5×5 mm) was soaked in a sterile container containing 2 ml of a 0.02% mitomycin C solution (50 mg of 4% mitomycin C powder mixed with 10 ml of balanced salt solution). By measuring the amount of solution remaining in the container it was possible to state that after soaking in the sponge there were 0.2 ml of solution.

After the pterygium head was detached from the cornea, the soaked sponge was placed under the conjunctival flap containing the pterygium, on the sclera. After 3 minutes the sponge was removed and the site was rinsed thoroughly with 10 ml of balanced salt solution.

Surgery was completed with pterygium excision ('bare sclera technique'). The subconjunctival tissue superficial to the sclera was cleaned towards the insertion of the medial rectus muscle and triangular excision of the pterygium and conjunctiva, including the

Table 1 Demographic and preoperative data

Preoperative	Mitomycin C treated group	Control group
No	45	45
Age (years)		
Mean (SD)	40.8 (12.1)	40.7 (11.4)
Sex (% male)	62.2	60
Follow up (months)		
Mean (SD)	34.05 (13.60)	29.11 (14.31)

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Accepted for publication 30 November 1995

Figure 1 Survival curve for the mitomycin C treated group and the control group. Success rate (SE) versus postoperative follow up time (log rank test = 5.31, $p=0.022$) (n =no of patients).

adjacent Tenon's capsule, was performed. The corneal surface was smoothed using a scalpel blade. Two sutures (8-0 silk) were placed along the horizontal meridian closing the conjunctival wound and leaving a bare scleral area of approximately 4×3 mm.

In group 2 only pterygium excision was performed using the same surgical technique ('bare sclera technique').

In all cases the diagnosis of pterygium was histopathologically confirmed. During the post-operative period all patients were examined weekly for the first month and then monthly, by a clinician who was masked to the patient treatment.

Recurrence was diagnosed when a fibrovascular growth, in the position of the previously excised pterygium, crossing the limbus and extending onto the cornea for any distance, occurred. In case of recurrence, follow up was stopped at the time of the diagnosis.

All patients were examined with a Zeiss SL30 slit-lamp to evaluate the recurrence of pterygium and the appearance of complications (conjunctival, corneal and scleral changes, anterior chamber reaction, intraocular pressure changes).

Complications were graded as absent, light, and severe (–, +, ++) according to the severity of the clinical findings.

The patients were questioned specifically about side effects (pain, photophobia, and foreign body sensation). Side effects were also graded (–, +, ++) according to patients' discomfort.

Statistical analysis was performed using Student's t test to compare the follow up of the two groups and the ages of patients experiencing recurrence between the two groups. Success rates were calculated employing the χ^2 test and the life table analysis to calculate survival curve by the Kaplan-Meier method; the difference between survival curves was tested by the log rank test. The success rates calculated by the Kaplan-Meier method differ from those of cross sectional analysis because they represent the cumulative probability of success based only on patients who have not yet failed or dropped out and they exclude a patient from further analysis once that patient has failed.¹⁸

The χ^2 test with Yates's correction or Fisher's exact test was used to analyse the difference in adverse reactions between the two groups.

Informed consent for participation in the study was obtained from all patients before their enrolment.

Results

The follow up period was 6–54 months (mean 34.55 (SD 13.70) months) in group 1 and 7–50 months (mean 29.64 (14.42) months) in group 2.

Six recurrences (12.5%) were observed in group 1 (mitomycin C treated patients) and 16 (35.6%) in group 2 (control patients). The

Table 2 Life table analysis

Follow up (months)	No of patients		Recurrences		End of follow up (no of patients)		Cumulative probability of success		SE	
	MM-C	Control	MM-C	Control	MM-C	Control	MM-C	Control	MM-C	Control
0–6	45	45	2	6	1	1	0.96	0.87	0.029	0.051
7–12	42	38	3	6	3	0	0.89	0.73	0.046	0.067
13–18	36	32	0	2	5	2	0.89	0.69	0.046	0.069
19–24	31	28	0	1	3	2	0.89	0.66	0.046	0.072
25–30	28	25	0	0	5	3	0.89	0.66	0.046	0.072
31–36	23	22	0	1	5	6	0.89	0.63	0.046	0.077
37–42	18	15	1	0	6	11	0.83	0.63	0.074	0.077
43–48	11	4	0	0	9	4	0.83	0.63	0.074	0.077

MM-C=mitomycin C.

Table 3 Complications and side effects (–=absent, +=light, ++=severe)

	Mitomycin C treated group			Control group		
	–	+	++	–	+	++
Complications						
Superficial punctate keratitis*	38 (84.4%)	7 (15.6%)	0	45 (100%)	0	0
Side effects						
Ocular pain	18 (40%)	27 (60%)	0	21 (46.7%)	24 (53.3%)	0
Photophobia	28 (62.2%)	17 (37.8%)	0	31 (68.9%)	14 (31.1%)	0

*Fisher's exact test, $p=0.018$.

difference between the groups was statistically significant ($p=0.027$).

The data of life table analysis of both groups are shown in Table 2. Survival curves are shown in Figure 1.

In group 1 all recurrences except one occurred during the first 10 months. One recurrence was seen after 40 months of follow up.

In group 2 the highest incidence of recurrence was seen within the first 18 months. In group 1 the mean age of patients experiencing recurrence of pterygium was 30.83 (7.73) years (range 21–42 years) and in the control group it was 39.94 (9.36) years (range 21–53 years). The difference was statistically significant ($p=0.047$).

Complications and side effects were observed only during the first 2 weeks of follow up. In the mitomycin C treated group, the only complication was light superficial punctate keratitis. Side effects were ocular pain and photophobia in both groups (Table 3). After 4 weeks of follow up in one mitomycin C treated eye an area of avascularity in the site of the previous excised pterygium was detected; nevertheless no corneal changes or subjective symptoms were reported.

Discussion

Mitomycin C is an antibiotic antineoplastic agent, activated to an alkylating agent in tissues: it inhibits RNA DNA dependent synthesis, preventing cellular division and duplication; it has therefore been used to prevent fibroblast proliferation and scarring after filtration surgery. Since 1962 mitomycin C eye-drops have been used to prevent recurrence of pterygium after surgery, on the basis that the fibrovascular reaction in the pathogenesis of pterygium is the result of a chronic irritation.¹⁹ Recently, the possibility of mast cells contributing to the pathogenesis of pterygia has been supposed.²⁰

The use of mitomycin C eyedrops after pterygium surgery seemed to be an effective and safe method to prevent recurrence of pterygium, in fact recurrence rates of between 1.4% and 13% have been published.^{3 5 6 21 22} Unfortunately, topical mitomycin has been reported to cause a variety of complications. Sometimes complications are very severe, such as symblepharon,⁶ scleral ulceration¹⁰ and necrosis,¹¹ secondary glaucoma, and corneal perforation.¹³ It is not acceptable that the surgical excision of a generally benign pathology such as pterygium should cause such serious complications.

Some authors have proposed the use of low dose mitomycin C (0.01%) after pterygium excision.²³ A prospective, multicentre, randomised comparison has begun of recurrence rates after pterygium excision and intraoperative 0.04% mitomycin C for 3 minutes versus other techniques.¹⁵

Since 1991 we have used intraoperative mitomycin C in patients with one recurrence of pterygium undergoing surgical excision. Encouraging results were shown in our preliminary study.¹⁶ The long term results

confirm the efficacy of this kind of therapy to prevent recurrence of pterygium: only six recurrences were detected in the mitomycin C treated group as against 16 recurrences in the control group ($p=0.027$). Life table analysis showed a success rate of 89% and 83% in the mitomycin C treated group and of 66% and 63% in the control group after 24 and 48 months of follow up, respectively (Fig 1).

The recurrence rate in the control group is similar to those found in previous studies on bare scleral closure (24–68%).^{24–29}

Five out of six (83.3%) and 12 out of 16 (75%) recurrences occurred within the first year in the mitomycin C treated group and control group, respectively. Our data confirm those of Hirst *et al*³⁰ who affirm that a 12 month follow up is able to identify more than 97% of recurrences. In the mitomycin C treated group no patient who has not yet experienced pterygium recurrence has a follow up shorter than 1 year.

The mean age of the patients experiencing recurrence of pterygium differs significantly between the two groups ($p=0.047$). In the mitomycin C treated group failures were seen only in young people (mean age 30.83 (7.73); range 21–42 years). In controls recurrences were seen mostly, but not exclusively, in young people (mean age 39.94 (9.36); range 21–53 years). These data seem to show that in younger people the inhibiting effect of mitomycin C on fibroblast proliferation may be less effective in preventing fibrovascular reaction.

Although a relatively small number of patients was treated to detect complications with a very low rate, a very encouraging fact emerging from our study was the absence of the unpleasant complications and side effects reported for prolonged mitomycin C eyedrop therapy.

The exposure of the sclera for no more than 3 minutes, the accuracy of cut of the sterile sponge, and the diluted mitomycin C solution (0.2 mg/ml of mitomycin C powder in balanced salt solution) all contributed to the standardisation of the method.

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