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Intraoperative application of 5-fluorouracil and mitomycin C as chemoadjuvants in primary pterygium surgery

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Background/aim: To compare the effectiveness of intraoperative 5 fluorouracil (5-FU) and mitomycin C (MMC) application in preventing recurrence following primary pterygium excision.

Materials and methods: This was a prospective clinical trial that included 93 patients with primary pterygia assigned to three treatment groups in which 29 patients received an intraoperative application of 25 mg/mL 5-FU for 5 min, 32 patients received an intraoperative application of 0.02% MMC for 5 min, and 32 patients underwent only surgical excision (the control group). Follow-up visits were done on postoperative days 1, 3, 7, 15, and 30, and then every month.

Results: After a mean follow-up of 14 months, the surgical excision recurrence rates in the 5-FU, MMC, and control groups were 27.6%, 12.5%, and 43.75%, respectively. There was a statistically significant difference in the 5-FU and MMC groups when compared with the control group (chi-square; P = 0.04); however, the difference between the 5-FU and MMC groups was not significant. No serious complications were seen in the 5-FU and MMC groups.

Conclusion: Intraoperative application of MMC and 5-FU is effective and safe for the prevention of recurrence. Our findings suggest that MMC is more potent for the prevention of recurrence and it causes less complaints than 5-FU.

Key words: Adjunct therapies, antimetabolites, complications, recurrence, pterygium excision

1. Introduction

Pterygium is defined as an extension of fibrovascular growth from the conjunctiva onto the cornea. It can cause chronic irritative symptoms, cosmetic problems, and vision impairment (1,2).

Many surgical techniques have been developed for the treatment of pterygium. However, the recurrence rates are between 24% and 89% following simple pterygium excision (1–6). Because of these high recurrence rates, the use of adjunct therapies such as beta radiation, antimetabolites like mitomycin C (MMC) and 5-fluorouracil (5-FU), and conjunctival autograft has been advocated.

Direct comparisons between studies is difficult for various reasons, including a wide range of sample sizes, whether primary or recurrent pterygia were studied, and differences in the definition of pterygium recurrence and follow-up periods. These reasons contribute to the conflicting results that are sometimes observed in different studies (7).

The main objective of this study was to compare concurrent intraoperative 5-FU or MMC application with simple excision in the treatment of primary pterygium in terms of recurrence prevention.

2. Materials and methods

Ninety-three patients with primary pterygium (47 women and 46 men) who underwent surgery were included. Indications for surgery were chronic irritation, cosmetic problems, and vision impairment.

At the initial visit all patients were examined, and the size and location of pterygia were defined. Pterygia were classified as atrophic type (type 1), noninflamed type (type 2), and inflamed type (type 3) according to clinical appearance. If the pterygium tissue was densely vascularized, hyperemic, and edematous, it was classified as inflamed. If the pterygium was less vascularized, nonedematous, and without edema, then it was classified as noninflamed. The atrophic type was defined as a pterygium with minimal vascularization, without hyperemia, and without edema.

Patients were divided into three groups based on treatment protocol (5-FU, MMC, and control). The same

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surgeon performed all surgeries. This study was approved by the institutional review board of the hospital, and it was in accordance with the principles of the Declaration of Helsinki. All patients gave informed consent before the study.

We used the technique defined previously by Altay et al. (8).

In the 5-FU group, 5-FU was applied intraoperatively to 29 eyes of 29 patients, including 13 women and 16 men. After cleaning the lids and conjunctiva with povidone-iodine solution, 0.4% benoxinate was dripped onto the conjunctiva for anesthesia. Lidocaine 2% was injected subconjunctivally under the body of the pterygium. The head of the pterygium was separated from the cornea with the help of two hooks. The corneal surface was flattened by using a number 15 scalpel. Following the excision of the head of the pterygium, minimal thermal coagulation was applied to the limbus. A 3 × 4 mm sponge soaked into 25 mg/mL 5-FU solution was then laid onto the scleral bed where the pterygium was excised. The conjunctiva and Tenon's capsule were covered over the sponge and kept in contact for 5 min. Extreme care was taken not to apply the antimetabolite agent on the cornea. After this period, the sponge was removed and the area was rinsed by using a 20 mL lactated-Ringer solution. Then conjunctiva was sutured with a 10/0 nylon stitch by leaving a 3 mm bare sclera next to the limbus. Following the application of antibiotic pomade, the eye was covered and the operation was completed (8).

In the MMC group, MMC was applied intraoperatively to 32 eyes of 32 patients, including 14 women and 18 men. Following pterygium excision, a sponge soaked into 0.02% MMC solution was applied onto the scleral bed where the pterygium was excised. The conjunctiva and Tenon's capsule were covered over the sponge and kept in contact for 5 min. After this period, the sponge was removed and the area was rinsed by using a 20 mL lactated-Ringer solution. The conjunctiva was then sutured with a 10/0 nylon stitch by leaving a 3 mm bare sclera next to the limbus. Following the application of antibiotic pomade, the eye was covered and the operation was completed (8).

In the control group, which included 20 women and 12 men, following excision of the head of the pterygium, the conjunctiva was sutured by leaving a 3 mm bare sclera next to the limbus. The procedure was finished by covering the eye after antibiotic pomade was applied.

Beginning from the first day after surgery, antibiotic drops were applied four times a day until complete epithelization. Topical steroid drops were also applied four times a day; they were gradually discontinued within 4 weeks by tapering the dose (8).

Patients were scheduled for follow-up visits on days 1, 3, 7, 15, and 30, and then monthly. At each visit patients were examined for the presence of corneal epithelial disorders, punctate keratitis, anterior chamber reaction, and recurrence. Patient complaints such as pain, irritation, watering, and photophobia were recorded. Recurrence was defined as the growth of fibrovascular tissue over the area of the previous pterygium, extending 1 mm or more onto the cornea (as observed with slit-lamp) by pulling of the conjunctiva (8).

Statistical analyses were performed using SPSS 15. The variables were investigated using visual and analytical methods (Shapiro–Wilk test) to determine whether or not they were normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed variables. Statistical evaluation was done by using one-way ANOVA, Student's t-test, and chi-square test. $P < 0.05$ was considered statistically significant.

3. Results

We compared age, size of pterygium, type of pterygium, and sex in patients with and without recurrence following surgery. The recurrence patients were younger when their mean age was compared with that of the other patients. The size of the pterygium was bigger in patients with recurrence. Recurrence in type 3 pterygia was higher than in type 2 ones, and there was no recurrence in type 1 pterygia. Recurrence rates of males and females were similar (Table 1).

The 5-FU group consisted of 29 patients, 13 women and 16 men, with a mean age of 45.44 (and a range of 24–73). The types of pterygium of these 29 patients were as follows: 1 atrophic (type 1), 20 noninflamed (type 2), and 8 inflamed (type 3) (Table 2).

The MMC group consisted of 32 patients, 14 women and 18 men, with a mean age of 47.71 (and a range of 18–73). The types of pterygium of these 32 patients were as follows: 3 atrophic (type 1), 20 noninflamed (type 2), and 9 inflamed (type 3) (Table 2).

The control group consisted of 32 patients, 20 women and 12 men, with a mean age of 48.65 (and a range of 25–80). The types of pterygium of these 32 patients were as follows: 2 atrophic (type 1), 19 noninflamed (type 2), and 11 inflamed (type 3) (Table 2).

There were no significant differences between the groups in terms of sex (chi-square, $P = 0.24$), type of pterygium (chi-square, $P = 0.85$), age (one-way ANOVA, $P = 0.61$), and age groups (chi-square, $P = 0.33$) as seen on Table 2.

In the 5-FU group, the mean size of the extension of the pterygium over the cornea was 3.15 mm (with a range of 2–4.5 mm); in the MMC group it was 3.20 mm (with a range of 2–5 mm); and it was 3.50 mm (with a range of 2.5–5 mm) in the control group. There was no significant difference among the groups in terms of pterygium size and recurrence rate.

Table 1. Factors affecting pterygium recurrence.

Factors	Recurrence		P
	Present	Absent	
Age (years; mean ± SD)	41.88 ± 11.13	50.71 ± 12.87	0.003*
Size of pterygium (mm; mean ± SD)	3.75 ± 0.72	3.12 ± 0.62	0.0001*
Types of pterygium			0.002**
Type 1 (%)	0 (0)	8	
Type 2 (%)	12 (20.7)	46	
Type 3 (%)	14 (51.9)	13	
Sex			0.94
Male (%)	13 (28.3)	33	
Female (%)	13 (27.7)	34	

*Statistically significant difference, Student's t-test.
**Statistically significant difference, chi-square.

Table 2. Patient mean ages, age groups, sex, and types of pterygia among the treatment groups.

Variables	Treatment groups		
	5-FU group n = 29	MMC group n = 32	Control group n = 32
Mean age (years)	45.44	47.71	48.65
Age groups			
10–20	1	0	0
21–30	0	5	2
31–40	7	6	5
41–50	13	9	9
51–60	7	5	8
>60	4	4	8
Sex			
Women	13	14	20
Men	16	18	12
Pterygium type			
Type 1	1	3	2
Type 2	20	20	19
Type 3	8	9	11

5-FU: 5-fluorouracil.
MMC: mitomycin C.

Twenty-nine patients in the 5-FU group were followed for an average of 14 months (with a range of 10–18 months) and 8 (27.6%) had a recurrence. Of these eight, the types of primary pterygia were type 2 in two and type 3 in six patients.

Thirty-two patients in the MMC group were followed for an average of 14 months (with a range of 12–18 months) and 4 (12.5%) had a recurrence. Of these four, the types of primary pterygia were type 2 in two and type 3 in two patients.

Thirty-two patients in the control group were followed for an average of 14 months (with a range of 12–17 months) and 14 (43.75%) had a recurrence. Of these fourteen, the types of primary pterygia were type 2 in eight and type 3 in six patients (Table 3).

The number of recurrences was lower in the 5-FU and MMC groups when compared with the controls (chi-square test, P = 0.04), but there was no significant difference between the 5 FU and MMC groups (Table 3). When we compared the recurrences between groups in terms of types of pterygia, significant differences were observed. However, this finding should be interpreted with caution, since chi-square results may be invalid because more than 20% of the cells, when comparing recurrences of type 3 pterygia among the groups, had an expected cell count of less than five.

The duration of recurrence in the MMC, 5-FU, and control groups was between 2.5 and 4 months, 2.5 and 5 months, and 2 and 4 months, respectively. There was no difference between the groups in terms of recurrence duration (one-way ANOVA, P = 0.30).

Comparisons of patient complaints following treatment among the groups are presented in Table 4. Pain and irritation symptoms were seen relatively more frequently in the 5-FU group (77.3%); however, this difference did not reach a statistical significance (P = 0.77). Pain and irritation were seen most commonly during the first 1–2 weeks following treatment.

The punctate epithelial staining rate of the cornea was significantly lower in the control group when compared with the 5-FU and MMC groups (P = 0.02).

The rate of photophobia was higher in the 5-FU group, but the difference was not significant (P = 0.06).

The rate of watering was not different among the groups (P = 0.08).

4. Discussion

Although the approach to mild symptoms can be conservative, the main treatment of pterygium is surgical excision. However, the major problem following surgery is the high recurrence rates (1–6).

Many factors such as type of pterygium, age of the patient, climatic characteristics, method of surgery, and the experience of the surgeon may affect the recurrence rates following surgery. Our study showed that pterygium recurrences were seen in younger patients, in patients with larger pterygia, and in patients with inflamed type pterygia.

Table 3. Recurrence rates and types of recurrent pterygia among the treatment groups.

	Recurrence rates in treatment groups		
	5-FU group n = 29	MMC group n = 32	Control group n = 32
Types of recurrence Pterygia	Numbers (Percentages)	Numbers (Percentages)	Numbers (Percentages)
Type 1	0/1 (0%)	0/3 (0%)	0/2 (0%)
Type 2*	2/20 (10%)	2/20 (10%)	8/19 (42.1%)
Type 3**	6/8 (75%)	2/9 (22.2%)	6/11 (54.5%)
Total*** ****	8/29 (27.6%)	4/32 (12.5%)	14/32 (43.75%)

* (P = 0.33, chi-square).
** (P = 0.08, chi-square); more than 20 % of cells in this subtable have an expected cell count of less than 5. The chi-square results may be invalid.
*** (P = 0.04, chi-square).
**** (P = 0.13, chi-square); a comparison between the 5-FU and MMC groups.

Table 4. Patient complaints during follow-up among the treatment groups.

Patient complaints	Treatment groups			
	5-FU (%)	MMC (%)	Control (%)	P
Pain and irritation	77.3	68	71	0.77
Punctate epithelial staining	35	20	4	0.02*
Photophobia	52	19	33.3	0.06
Watering	68	36.4	58.1	0.08

* Statistically significant difference, chi-square.

Every recurrence causes loss of conjunctival tissue, limits the movements of the extraocular muscles, or forms scar tissue, in addition to the occurrence of the same pathology. Therefore, the definitive therapy of pterygium by primary surgery is extremely important (5,9–14) When the surgical excision is applied alone for the treatment of primary or recurrent pterygium, it results in high recurrence rates, as reported in different studies (30%, 70%, and 80%) (9–11). Since the recurrence rates are high with surgical excision alone, today some specific techniques and adjunct treatments following surgery are used in order to decrease those rates. These include intraoperative and postoperative MMC, conjunctival autografting, and amnion membrane grafting (1–6,15).

Several studies are reported about the use of 5-FU and MMC in pterygium surgery with different results (9–11,14). Any direct comparison of clinical trials is difficult because of the variability of confounding factors such as differences in the dose and duration of application of the drugs, whether the pterygium is primary or secondary, type of pterygium, differences in the definition of recurrence, and differences in follow-up periods. In our study, we included only patients with primary pterygia.

MMC, a chemotherapeutic agent, acts by inhibiting DNA synthesis, mitosis, and protein synthesis. Its current application in pterygium surgery, glaucoma surgery, and corneal refractive surgery is on the rise because of its modulatory effects on wound healing (15).

The recurrence rates of pterygia with the use of intraoperative and postoperative mitomycin-C were between 0% and 38%. Complications such as scleral ulceration and thinning, delayed conjunctival epithelialization, iritis, corneoscleral and vitreoretinal toxicity, uveitis, and glaucoma were reported with MMC therapy (16–19).

Many studies compared intraoperative MMC and postoperative MMC application with bare sclera excision. The data from all studies indicate that the use of MMC reduces pterygium recurrence as compared with bare sclera excision for primary pterygia (20). One study (21) reported a 15.9% recurrence rate with intraoperative 0.02% MMC application for 5 min in the treatment of primary pterygia. Another study reported a 5.76% recurrence rate by using the same method (22). We found a 12.5% recurrence rate in our MMC group without any serious complications. The difference may be due to the type of pterygia in the studied patients.

The 5-FU is a pyrimidine analogue that inhibits DNA synthesis and is active on the synthesis phase of the cell cycle. Its ability to reduce fibroblastic proliferation and subsequent scarring has made it an important adjunct in ocular and periorbital surgeries (23). Studies showed that short-term application (for 5 min) of high doses of 5-FU was effective in inhibiting the long-term proliferation of Tenon's capsule fibroblasts (19,23). However, intraoperative application of low doses of 5-FU in primary pterygium surgery showed that it was inefficient in preventing recurrences. In that study, a low dose of 5-FU (10 mg/mL) solution was applied for 5 min (24). In our study, we applied 5-FU solution at a higher concentration (25 mg/mL) for 5 min intraoperatively. We found that the recurrence rate in the 5-FU group was 27.6%. This finding may be due to the higher concentrations of 5-FU in our study. Akarsu et al. studied intraoperative application of 5-FU (25 mg/mL, for 3 min) in primary pterygium surgery, and they found a 25% recurrence rate (25). Kareem et al. applied 50 mg/mL 5-FU solution for 3 min in primary pterygium and they found a 28% recurrence rate (26). These results are similar to ours.

Complaints such as pain and irritation, punctate epithelial staining, photophobia, and watering are documented in Table 3. Complaints were more common in the 5-FU group, but the disturbance did not last for a long time, and there were no serious ocular complications.

The intraoperative use of MMC and 5-FU has the advantage of direct monitoring of drug exposure when

compared with postoperative regimens, which require patient adherence. We applied sponges soaked with MMC and 5-FU directly onto the undersurface of the surrounding residual conjunctival bed, taking care not to spill any excess MMC and 5-FU onto the cornea and limbus; this may be the reason for the absence of serious complications. Altay et al. reported that intraoperative 5-FU and MMC had no pathologic effects on the neighboring conjunctiva; their effects were limited only to the area on which they were applied (8).

Our study and the other studies using intraoperative 0.02% MMC application for 5 min showed that MMC application was a safe and efficient way of preventing recurrences in pterygium surgery. Moreover, the recurrence rate with MMC was much lower than that with 5-FU (20,21,26).

We showed that pterygium type is important in pterygia recurrence rates. The inflamed type pterygium is more prone to recurrences following surgery. It may be useful to treat this type of pterygium with topical steroids and antiinflammatory agents prior to surgery. Younger patients and patients with larger pterygia are also more prone to recurrence.

In conclusion, single intraoperative applications of MMC and 5-FU are effective and safe for recurrence prevention in pterygium surgery. We think that MMC is more potent and it caused less complaints than 5-FU.

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