



Intraoperative Application of 5-Fluorouracil and Mitomycin C in Primary Pterygium Surgery and its Effect on the Fibroblast Counts of Conjunctival Biopsies

Primer Pterijium Cerrahisinde İntrooperatif 5-Florourasil ve Mitomisin C Uygulaması ve Konjunktival Biyopsilerdeki Fibroblast Sayımına Etkileri

Pterijium Cerrahisinde İntrooperatif 5-Fu ve Mmc / Intraoperative 5-Fu and Mmc in Pterygium Surgery

Yesim Altay¹, Seza Petricli², Nagihan Ugurlu³

¹Ophthalmologist, Etimesgut State Hospital, ²Ophthalmologist, Sereflikochisar State Hospital, ³Ophthalmologist, Ataturk State Hospital, Ankara, Türkiye

Özet

Amaç: Primer pterijium cerrahisinden sonra nükslerin engellenmesi için intraoperatif 5-FU ve mitomisin C uygulamalarının etkinliğini belirlemek. **Gereç ve Yöntem:** Primer pterijium tanısı alan ellibir (51) hasta çalışma kapsamına alındı. 15 hastaya intraoperatif tek doz 25 mg/mL 5-FU 5 dakika; 20 hastaya %0,02lik mitomisin C 5 dakika uygularken 16 hastaya (kontrol grubu) sadece cerrahi eksizyon uygulandı. Post operatif 1,3,5,7, 15 ve 30. günlerde ve daha sonra her ay kontrol vizitleri yapıldı. Korneaskleral limbustan saydam korneaya doğru uzanan 1 mm lik fibrovasküler doku nüks olarak kabul edildi. Her gruptan operasyon esnasında ve postoperatif 3. ayda konjunktiva biyopsileri alındı. **Bulgular:** Ortalama 8 aylık takip süresi sonunda nüks oranları 5-FU, mitomisin C ve kontrol gruplarında sırasıyla %20, %15, %44 olarak saptandı. Sadece mitomisin C ve kontrol grupları arasındaki fark istatistiksel olarak anlamlı idi (Ki-kare, p=0.03). Konjunktiva biyopsilerinin patolojik incelemesinde fibroblast sayıları açısından fark saptanmadı. 5-FU ve mitomisin C gruplarında ciddi komplikasyon görülmedi. **Tartışma:** Nüksün önlenmesinde %0,02 lik mitomisin C 5 dakika süreyle uygulanması 5-FU uygulamasına göre daha etkili görünmektedir. Bu sonucu doğrulamak için daha büyük sayıda hastayı kapsayan çalışmalara ihtiyaç vardır.

Anahtar Kelimeler

5-Florourasil; Mitomisin C; Pterijium

Abstract

Aim: To determine the effectiveness of intraoperative 5-FU and mitomycin C application for prevention of recurrence after primary pterygium excision. **Material and Method:** We performed a prospective clinical trial of 51 patients with primary pterygia randomly assigned to a treatment group in which 15 patients received a single intraoperative application of 25mg/mL 5-FU for 5 minutes, 20 patients received a single intraoperative application of 0.02 % mitomycin C for 5 minutes and 16 patients underwent only surgical excision (control group). Follow-up visits were scheduled for postoperative days 1,3,7,15 and 30 and then every month. Recurrence was defined as 1 mm fibrovascular tissue over the corneal scleral limbus onto clear cornea in the area of previous pterygium excision. Conjunctival biopsies were taken preoperatively and at the third month postoperatively, in each group. **Results:** After mean follow up of 8 months, recurrence rates of surgical excision with 5-FU and mitomycin C and the control group were 20%, 15 %, and 44% of eyes, respectively. The only statistically significant difference was between mitomycin C and control groups (Chi-square; p=0.03). Pathologic examination of conjunctival biopsies did not show any difference in fibroblast counts. No serious complications were seen in 5-FU and mitomycin C groups. **Discussion:** Application of 0.02% mitomycin C for 5 minutes seems to be more effective than 5-FU for prevention of recurrence. A larger study population is needed to substantiate this result.

Keywords

5- Fluorouracil; Mitomycin C; Pterygium

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Corresponding Author: Yesim Altay, 48. Cadde Yonca Apt. No: 33/31 06520, Cukurambar, Ankara, Türkiye.

GSM: +905324902298 E-Mail: altayye@yahoo.com

Introduction

Pterygium is a fibrovascular growth extending from conjunctiva onto the cornea. It is believed that it is the result of ultraviolet injury to the subconjunctival connective tissue. Pterygium can cause chronic irritative symptoms, can impair vision by occluding the pupilla or by resulting in astigmatism, and can cause cosmetic problems [1,2].

Although many surgical techniques have developed for the treatment of pterygium, none of them is completely effective for the prevention of recurrences. Recurrence rates are between 24-89% following simple excision of pterygium [1-6]. Because of this high recurrence rates, the use of adjunct therapies such as beta radiation, antimetabolites like mitomycin-C, and 5-fluorouracil (5-FU), and conjunctiva autograft have been advocated. We planned this study to evaluate the efficacy of surgery with intraoperative 5-FU and mitomycin C application for the treatment of pterygium. The main objective of this study was to compare 5-FU and mitomycin C to simple excision in the treatment of pterygium, as well as complication rate and toxic effects of these drugs in ocular tissues.

Material and Method

Fifty-one patients (33 women and 18 men) who underwent surgery with the diagnosis of primary pterygium were included. Indications for surgery were chronic irritation, cosmetic problems, and impairment of vision by pterygium.

At the initial visit all patients were examined with biomicroscopy, and the size and localisation of pterygium were defined. Pterygia were classified as atrophic type (type1), non-inflamed type (type2), and inflamed type (type3) according to clinical appearances. Patients were divided into three groups by treatment protocol. The same surgeon did all surgeries. This study was approved by 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.

In the 5-FU group, 5-FU applied intraoperatively to 15 eyes of 15 patients including 11 women and 4 men. After cleaning the lids and conjunctiva by 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 pterygium was separated from the cornea by the help of two hooks. And corneal surface was flattened by using number 15 scalpel. Following the excision of the head of pterygium, minimal thermal coagulation was applied to limbus. And then a 3x4 mm sponge soaked into 25 mg/mL of 5-FU solution was laid onto the scleral bed where the pterygium was excised. The conjunctiva and tenon were covered over the sponge and kept in contact for 5 minutes. After this period the sponge was removed and the area was rinsed by using 20 cc lactated-Ringer solution. Then conjunctiva was sutured with 10/0 nylon stitch, by leaving a 3 mm bare sclera next to limbus. After applying antibiotic pomade, the eye was covered and the operation was completed.

In MMC group, MMC applied intraoperatively to 20 eyes of 20 patients including 12 women and 8 men. After cleaning the lids and conjunctiva by 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 pterygium was separated from the cornea by the help of two hooks. And corneal surface was flattened by us-

ing number 15 scalpel. Following the excision of the head of pterygium, minimal thermal coagulation was applied to limbus. And then a 3x4 mm sponge soaked into 0.02% MMC solution was laid onto the scleral bed where the pterygium was excised. The conjunctiva and tenon were covered over the sponge and kept in contact for 5 minutes. After this period the sponge was removed and the area was rinsed by using 20 cc lactated-Ringer solution. Then conjunctiva was sutured with 10/0 nylon stitch, by leaving a 3 mm bare sclera next to limbus. After applying antibiotic pomade, the eye was covered and the operation was completed.

In the control group, which included 10 women and 6 men, after the excision of the head of pterygium from 16 eyes, conjunctiva was sutured by leaving a 3mm bare sclera next to limbus. The procedure was finished by covering the eye after antibiotic pomade was applied.

Beginning from the first day following surgery, antibiotic drops were applied for four times a day until complete epithelization. And topical steroid drops were begun for four times a day, and then were ceased in four weeks by tapering the dose.

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

Conjunctival biopsies, 3x3 mm in size, from all patients in both study and control groups were excised intraoperatively from the conjunctiva next to the removed pterygium, and fixed with 10% formaldehyde solution. At the 3rd month follow-up visit, conjunctival biopsies from nasal conjunctiva of all patients were taken exactly in the same way.

Tissues embedded in parafine blocks were cut into a thickness of 5 microns, and the slides were stained with Hematoxyline-Eosin. The number of fibroblasts were counted in 10 microscopic area with 40x10 magnification, and then the mean numbers were calculated.

Statistical evaluation was done by using one-way ANOVA, and Chi-square tests, and by using SPSS 10.0 (Statistical Package for Social Sciences version 10.0, ®). P<0.05 was accepted for statistical significance.

Results

The 5-FU group consisted of 15 patients, 11 women and 4 men, with a mean age of 48.94 (range 30-73). Types of pterygium of these 15 patients were as follows; 3 atrophic (type 1), 7 non-inflamed (type 2), and 5 inflamed (type 3).

The MMC group consisted of 20 patients, 12 women and 8 men, with a mean age of 48.04 (range 32-70). Types of pterygium of these 20 patients were as follows; 3 atrophic (type 1), 12 non-inflamed (type 2), and 5 inflamed (type 3).

The control group consisted of 16 patients, 10 women and 6 men, with a mean age of 50.2 (range 25-80). Types of pterygium of these 16 patients were as follows; 2 atrophic (type 1), 9 noninflamed (type 2), and 5 inflamed (type 3). There were no significant differences between the groups in relation to gender (Chi-square, p=0,24), types of pterygium and age (one-way

Table 1. Patients' mean ages, gender, and types of pterygia among the treatment groups.

Variables	Treatment Groups		
	5-FU Group n=15	MMC Group n=20	Control Group n=16
Mean age (years)	48.94	48.04	50.02
Gender			
Women	11	12	10
Men	4	8	6
Type of Pterygium			
Type 1	3	3	2
Type 2	7	12	9
Type 3	5	5	5

ANOVA, p=0,62). Table 1.

In the 5-FU, the mean size of extension of pterygium over the cornea was 3,83 mm (range 2-7 mm), in the MMC, the mean size of extension of pterygium over the cornea was 3,50 mm (range 2-6 mm), whereas it was 3,20 mm (range 2-5 mm) in the control group. There was no significant difference among the groups in relation to the size of pterygium and the recurrence rates.

Fifteen patients in the 5-FU were followed for 9 months (range 4-13 months) and 3 (20%) had recurrence. Of these three, the types of primary pterygium were type 3 in two, and type 2 in one of the patients.

Twenty patients in the MMC group were followed for 12 months (range 5-14 months) and 3 (15%) had recurrence. Of these three, the types of primary pterygium were type 3.

Sixteen patients in the control group were followed for 7.1 months (range 2-11 months) and 7 (44%) had recurrence. Of these seven, the types of primary pterygium were type 3 in four, and type 2 in three of the patients. Table 2.

Table 2. Recurrence rates and types of recurrent pterygia among the treatment groups.

Variables	Treatment Groups		
	5-FU Group n=15	MMC Group n=20	Control Group n=16
Recurrence Rates (numbers/percentage)	3 (20%)	3 (15%)	7 (44%)
Types of Recurrent Pterygia			
Type 1	-	-	-
Type 2	1	-	3
Type 3	2	3	4

Although the number of recurrences were less in 5-FU group and MMC group when compared to the control group, The only significant difference was among the MMC and the control groups (Chi-square test, p=0,03).

Patients' complaints following treatment in the groups presented in Table 3. Pain and irritation symptoms were seen relatively more in 5-FU group (64%), however this difference was not reached a statistical significance (p=0,12). Pain and irritation were seen most commonly during the first 1-2 weeks after treatment. And at the end of 1 month these symptoms were present in only one patient in 5-FU group.

Punctate epithelial staining rate of cornea was significantly less

Table 3. Patients complaints during follow-up among the treatment groups.

Patients' Complaints	Treatment Groups			
	5-FU (%)	MMC (%)	Control (%)	P
Pain And Irritation	64	41	47	0.12
Punctate Epithelial Staining	57	43	9	0.04*
Fotophobia	85	43	37	0.01*
Watering	64	43	41	0.38

5-FU 5- fluorouracil
MMC mitomycin C
* Statistically significant difference, Chi-square.

in the control group when compared to 5-FU and MMC groups (p=0,04).

Rate of fotophobia was significantly higher in 5-FU group (p=0,01). Fotophobia was a common symptom in 5-FU group, and it lasted for 3 months in one of the patients.

Rate of watering was not different among the groups (p=0,38). There were no gender and age differences among the patients with recurrence and the patients without recurrence. However, the rate of type 3 pterygium was significantly higher among patients with recurrence when compared to patients without recurrence (p=0,03). Postoperative symptoms and signs were not different between the patients with recurrence and the patients without recurrence.

Pathologic examination of conjunctival biopsies which were excised during primary pterygium surgery showed that there were congestion, areas of epithelial thinning, and mononuclear cell infiltration of varying intensity. There was hyalinization under epithelium in the cut sections containing predominantly pterygium tissue. There were inflammatory cells predominantly in biopsies taken after 3 months following the primary surgery. The mean numbers of fibroblasts were 30.01 in the control group, 33.2 in MMC group, and 31.6 in 5-FU group at the beginning. And after three months, the mean counts of fibroblasts were 32.4; 25.8; and 28.2 in the control, MMC and 5-FU groups, respectively. When we compared the MMC and 5-FU groups and the control group, the mean count of fibroblasts were not different in biopsies taken during primary surgery and 3rd month postoperatively.

Discussion

Pterygium is a common disorder seen all over the world with a predominance in tropical and subtropical areas. The most accepted theory in the etiology of pterygium is the change in limbal cells due to long periods of exposure to ultraviolet (UV) light. It requires therapy because of minor cosmetical reasons to serious visual impairments. Approach to mild symptoms can be conservative, but the main treatment of pterygium is surgical excision. However, the major problem following surgery is the recurrence.

When the surgical excision is applied alone for the treatment of primary or recurrent pterygium, it results in high recurrence rates such as 30-70-80% [7-9]. Recurrence rates are higher among the younger patients. Many other factors such as the type of pterygium, climatic characteristics, method of surgery and the experience of the surgeon may affect the recurrence rates after surgery. Every recurrence causes loss of conjunctival tissue, limitation of the movements of extraocular muscles, or formation of scar tissue besides the occurrence of the same pathology. Therefore, the definitive therapy of pterygium by the

primary surgery is extremely important [5,10-12].

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 the rate of recurrence. Mitomycin C is a chemotherapeutic agent that acts by inhibiting DNA synthesis. Its use and application in ophthalmology has been increasing in recent years because of its modulatory effect on wound healing. Current application include pterygium surgery, glaucoma surgery, corneal refractive surgery. [13]

Recurrence rates by the use of intraoperative and postoperative mitomycin-C were between 0 to 38%. However, complications such as scleral ulceration and calcification, korneoscleral and vitreoretinal toxicity, uveitis, and glaucoma were reported with MMC therapy [14-17].

Young et al. [18] studied intraoperative 0.02% MMC application for 5 minutes in treatment of primary pterygium and reported 15.9% recurrence rate.

Akinci et al. [19] applied 0.02% MMC to 52 primary pterygium cases for 5 minutes, and reported 5.76% recurrence. We found 15% recurrence in our MMC group without any serious complications.

Fluorouracil is a pyrimidine analogue that was originally known for its widespread use as anti-cancer drug. The ability of 5-FU to reduce fibroblastic proliferation and subsequent scarring has made it an important adjunct in ocular and periorbital surgeries. It is used in dacryocystorhinostomy, pterygium surgery and in vitreoretinal surgery to prevent proliferative vitreoretinopathy [20].

Studies using human tenon capsule fibroblasts showed that short-term application (for 5 minutes) of high dose 5-FU was effective in inhibiting the long-term proliferation of tenon capsule fibroblasts [17,20].

A study investigating the low dose intraoperative application of 5-FU in primary pterygium surgery showed that it was inefficient in preventing recurrences. In this study, low dose 5-FU (10 mg/mL) solution was applied for 5 minutes. After a mean follow-up time of 12 months, the recurrence rate in 5-FU group was 60%, while it was 35% in the control group [21].

In our study, we applied 5-FU solution at a higher concentration (25mg/mL) for 5 minutes intraoperatively. We found the recurrence rate in 5-FU group as 20% which was less than the previous study. When we compared 5-FU and control groups, the difference in the recurrence rates was not significant. This finding can be due to small number of patients in our study. The complaints like burning, irritation, and photophobia were more common in our 5-FU group, but they were not disturbing for long period of time except one patient, and there was no serious ocular complication. Akarsu C. et al. [22] studied intraoperative application of 5-FU (25 mg/mL, for 3 minutes) in primary pterygium surgery, and they found 25% recurrence rate.

Several studies are reported about the use of 5-FU and MMC in pterygium surgery with different results. The differences may be related to;

1. Differences in the dose and period of application of the drugs,
2. Whether pterygium is primary or secondary,
3. Types of pterygium (atrophic, inflamed, non-inflamed)
4. Differences in the definition of recurrence,
5. Different follow-up periods.

We found that light microscopic evaluation of fibroblast counts in conjunctival biopsies taken intraoperatively and at the

third postoperative month revealed no significant differences among the groups. Our finding suggests that the effect of 5-FU and MMC was limited to the area to which it was applied, and it had no pathologic effect on the neighbouring conjunctiva. Cytotoxic effects of MMC and 5-FU were studied in the eyes of New Zealand white rabbits using light microscopy. The 5-FU treated eyes showed no microscopic evidence of toxicity. The authors concluded that there was a greater risk of toxic anterior segment effects when MMC was used as adjunctive therapy following pterygium surgery [23]. However, our study and two other studies using intraoperative 0.02% MMC application for 5 minutes showed that MMC application was a safe and efficient way of prevention of recurrences in pterygium surgery [18,19].

Competing interests

The authors declare that they have no competing interests.

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