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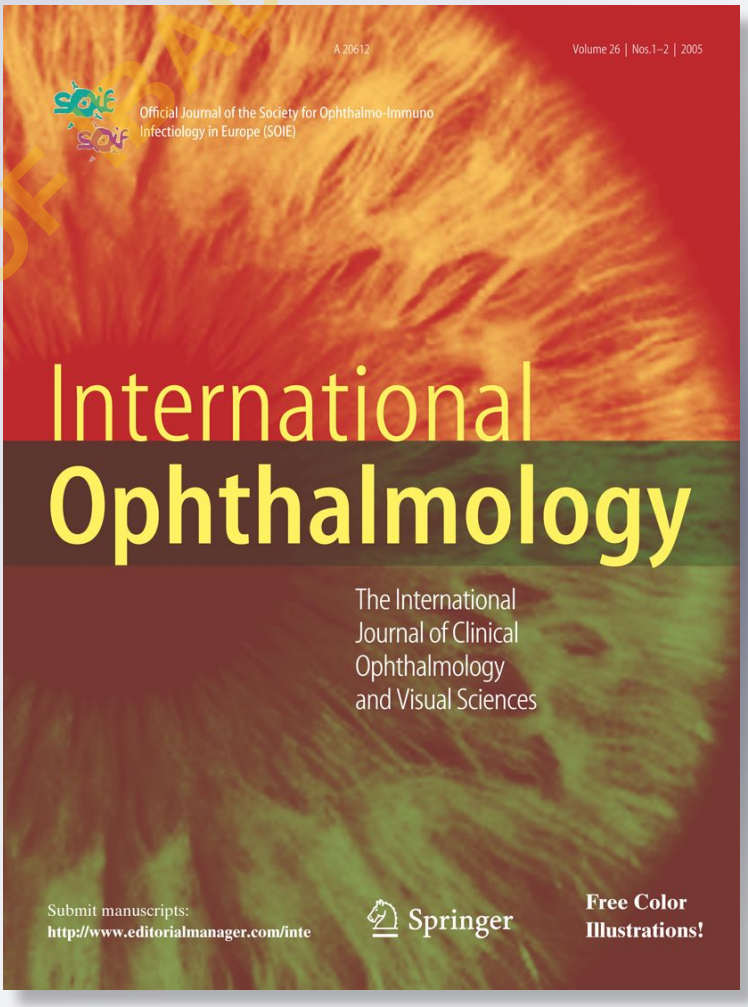

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Abstract To compare the efficacy of 5-fluorouracil (5-FU) with mitomycin C (MMC) in preventing pterygium recurrence when used as an adjuvant following pterygium excision with conjunctival autograft. Low-dose MMC combined with conjunctival autograft is an effective treatment for preventing recurrence following pterygium excision, but safety, cost, and availability limit its use in developing countries. There is a paucity of data on the efficacy of 5-FU when used in Africa as an adjuvant to conjunctival autograft following pterygium excision. This is a randomized controlled prospective trial using either 50 mg/ml 5-FU or 0.01% MMC. Eighty eyes of 80 subjects were studied. Forty-six subjects with a mean age 49.8 ± 13.8 years were treated with 5-FU (USD 13.0 per unit), while 34 patients with a mean age 51.9 ± 12.1 years were treated with MMC (USD 20.0 per unit). There was no significant difference in mean age between the two groups ($p = 0.48$). The ratio of male to female patients in both groups was similar at 0.92:1 for the 5-FU group and 1:1 for the MMC group ($p = 0.85$). Mean follow-up period was 35.2 ± 29.1 weeks. Recurrence rate in the 5-FU group was 8.7% compared to 11.8% in the MMC group (recurrence risk ratio = 0.71, 95% CI 0.17−3.1, $p = 0.7$). One patient from the MMC-treated group had corneoscleral melting. Other complications were mild and not sight threatening. In the prevention of pterygium recurrence, 5-FU appears to compare favorably with low-dose MMC when used as an adjuvant following pterygium excision and conjunctival autograft. Further studies are required to assess the long-term effect of using 5-FU in such cases.

Keywords Pterygium recurrence · 5-fluorouracil · Conjunctival autograft · Mitomycin C

Introduction

Pterygium is an elevated, superficial, external ocular degenerative lesion that usually forms over the perilimbal conjunctiva and sometimes extends onto the cornea. The etiology has been linked to ultraviolet exposure and chronic irritation by dust, wind, and other environmental factors [1]. When it is associated with ocular irritation, visual impairment, or cosmetic reasons, surgical excision may be considered using the most appropriate technique [2–4].

Both mitomycin C (MMC) and 5-fluorouracil (5-FU) have been shown to cause a reduction in the recurrence rate of pterygium, but both are potentially toxic to ocular tissues and have been associated with

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some complications [5]. Conjunctival autograft alone does not have some of the complications associated with 5-FU or MMC [6]. Studies that combined low-dose MMC with conjunctival autograft reported low recurrence and few complications when compared to either MMC or autograft alone [7, 8]. MMC is, however, expensive and not readily available in many developing countries. On the other hand, 5-FU is cheaper than MMC, is readily available, and is associated with fewer complications.

In a previous randomized controlled publication [9], we looked at the recurrence rate of pterygium treated with 5-FU compared with conjunctival autograft alone (as control). We found a recurrence rate of 11.4% in the 5-FU group compared to 12.4% in the control group. The main objective of this follow-up study is to compare the efficacy of 5-FU with that of MMC in preventing recurrence of pterygium when used as an adjuvant with conjunctival autograft.

Materials and methods

The randomized controlled prospective study was carried out at the Department of Ophthalmology, University College Hospital (UCH), Ibadan, Nigeria, between October 2006 and September 2008. Ethical permission was obtained from the UCH ethical committee, and full informed consent was obtained from all subjects.

Inclusion criteria included fleshy pterygium encroaching on the cornea of at least 2 mm and age >16 years. Selected patients were randomized into one of the two groups. One group had pterygium excision and conjunctival autograft with MMC, and the other group had pterygium excision and conjunctival autograft with 5-FU.

The sample size was calculated from estimation of proportions with an assumption of success of about 80% for 5-FU and 100% for MMC (alpha error = 0.05% and a power of 90%):

$$N = \frac{\mathrm{Za}/P_0(1-P_0) - \mathrm{Zb}/P_1(1-P_1)^2}{P_1 - P_0}$$
$$= 70 \text{ (or 35 per treatment group).}$$

The sample size was increased to 120, taking into consideration potential dropouts. Consenting adult subjects who met the selection criteria were randomized into two groups using a stratified sampling technique [9]. Small folded sheets of paper numbered 1−60 and 61−120 were kept in two separate envelopes to stratify for gender. Subjects who picked odd numbers were assigned to the 5-FU group, while those who picked even numbers were assigned to the MMC group. Patients with bilateral pterygium (seven subjects) had the worse eye randomized, while the contralateral eye was excluded from the study. Demographic information obtained from all subjects includes age, sex, occupation, laterality, location, morphology, size of the pterygium (measured with a slit-lamp from the limbus), and visual acuity.

At surgery, all patients received local anesthesia by local infiltration using subconjunctival 2% lidocaine HCL (lignocaine) with adrenaline 1:100,000. The head (apex) of the pterygium was excised from the cornea with a Bard Parker™ blade under microscope with subsequent blunt dissection from overlying conjunctiva and underlying sclera. The use of cautery was minimized. All surgical procedures were conducted and supervised by experienced surgeons (C.B., B.O., A.I., and O.O.).

Following initial pterygium excision, patients had the bare sclera area of the pterygium bed exposed to a 2 × 5 mm Weck-cel sponge soaked in 50 mg/ml of 5-FU for 5 min, during which there was intermittent wetting of the sponge every minute with a drop of 5-FU. At the end of 5 min, the sponge was removed and the eye was copiously irrigated with 30 ml saline. A conjunctival graft of a size equivalent to the sclera defect was excised from the ipsilateral pterygium-free superior (12 o'clock) bulbar conjunctiva, taking care to include limbal conjunctiva and 0.5 mm of clear cornea. This conjunctival graft was then sutured to the recipient bed with interrupted 8–0 vicryl sutures, taking care to ensure proper orientation of the ends of the graft (cornea end of the graft sutured to the recipient cornea). Patients in the MMC group had the same procedure as above but with 0.01% MMC (Biochem, Mumbai, India). A 2-mg vial was diluted using 5 ml water for injection, 0.5 ml of which was further diluted to make a 20 ml solution for direct application.

Postoperatively, both groups had instillation of chloramphenicol antibiotic ointment three times daily and dexamethasone (steroid) eyedrops four times daily for between 6 and 10 weeks, depending on duration of inflammation. They were also advised to wear dark

glasses to reduce exposure to sunlight and other environmental irritants.

Postoperative follow-up visits were at days 1, 7, 21, 30, 60, and 90 and every 3 months subsequently. Recurrence of pterygium was defined as any regrowth of fibrovascular tissue across the limbus observed with a slit-lamp. This assessment was done by an independent, blinded observer who was experienced in the assessment of pterygium. One patient from each treatment group was lost to follow-up before the second post-operative visit, and these patients were therefore excluded from further analysis. Other subjects were followed up for between 6 and 120 weeks (Fig. 1).

Data analysis was performed using Statistical Package for Social Sciences (SPSS) version 14. Pterygium recurrence and the complications arising from treatment were compared between the two groups of patients using frequency distribution tables. The difference in recurrence frequency between the two groups was evaluated using risk ratio and χ^2 test to determine the level of significance of any differences.

Results

A total of 80 eyes of 80 subjects were included in the study. Forty-six eyes were in the 5-FU group and 34 eyes were in the MMC group. The male:female ratio in the 5-FU group was 0.92:1, while in the MMC group it was 1:1. This difference was not statistically significant ($p = 0.85$). The mean age of the 5-FU-treated group was 49.8 ± 13.8 years, compared to 51.9 ± 12.1 years for the MMC-treated group ($p = 0.48$) (see Table 1).

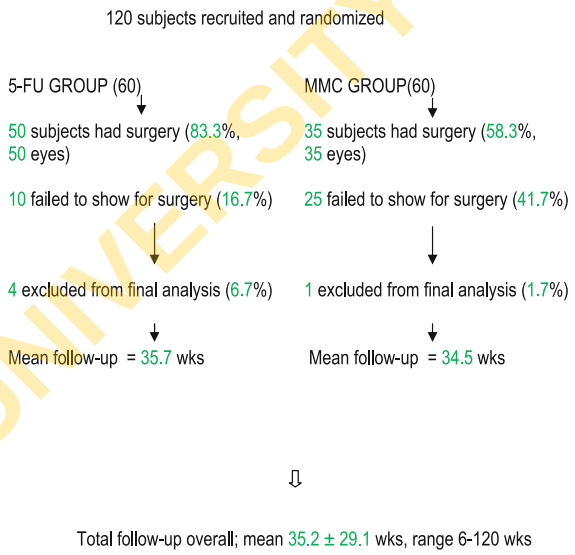

Fig. 1 Flow chart showing follow-up of pterygium treatment groups—5-FU plus autograft versus MMC plus autograft

Table 1 Characteristics of patients and pterygium treated with 5-FU plus conjunctiva autograft versus MMC plus autograft

	5-FU plus autograft		MMC plus autograft	
	No.	%	No.	%
Gender				
Female	24	58.5	17	41.5
Male	22	56.4	17	43.6
Age (years), $p = 0.48$				
Range	17–75		24–81	
Mean	49.8		51.9	
SD	13.8		12.1	
Pterygium morphology				
Fleshy	42	91.3	34	100.0
Atrophic	1	2.2	0	0.0
Inflamed	3	6.5	0	0.0
Pterygium location				
Nasal	43	93.5	31	91.2
Temporal	1	2.2	0	0.0
Nasal plus temporal	2	4.3	3	8.8
Size of pterygium from limbus (mm)				
Range	2–8		2–6	
Mean	3.4		3.3	
SD	1.3		1.2	
Total eyes	46	100.0	34	100.0

There were four cases of recurrence of the pterygium in each of the two treatment groups. Thus, the 5-FU group had a recurrence rate of 8.7%, compared to 11.8% in the MMC group. All recurrence occurred between 6 weeks and 6 months of follow-up. Two of the recurrences occurred within the first 2 months, while the other two occurred between the fourth and sixth month after surgery. Although 5-FU with conjunctival autograft appeared to have a lower recurrence of pterygium, this was not statistically significant (recurrence risk ratio = 0.71, 95% CI 0.17–3.1; $p = 0.7$ [Fisher's exact test]). One subject (in the MMC group) with both nasal and temporal pterygia had recurrence nasally. All the other recurrences were unilateral and nasal in location.

Table 2 Postoperative complications and pterygium recurrence following pterygium treatment with 5-FU and autograft versus MMC and autograft

	5-FU plus autograft		MMC plus autograft	
	($n = 46$)	%	($n = 34$)	%
Complication				
Sclera granuloma	3	6.5	1	2.9
Graft injection	3	6.5	1	2.9
Symblepharon	1	2.2	1	2.9
Corneoscleral melt/ necrosis	–		1	2.9
Conjunctiva cyst	–		1	2.9
Pterygium recurrence[a]	4	8.7	4	11.8
6 weeks	1	2.2	1	2.9
8 weeks	1	2.2	1	2.9
4 months	1	2.2	0	0.0
6 months	1	2.2	2	5.9

[a] Recurrence risk ratio = 0.71, 95% CI 0.17–3.1, $p = 0.7$ (Fisher's exact)

Stratified analysis of recurrence rate by surgeon showed no significant difference in recurrence rate between trainee (10.1%) and consultant surgeons (9.1%) ($p = 0.9$). Estimate of mean survival time using Kaplan–Meier survival analysis was 106.2 weeks for 5-FU and 88.4 weeks for MMC. The difference was not statistically significant ($p = 0.65$ using the log rank test). Mean follow-up period was 35.2 ± 29.1 weeks (Fig. 1). Only 56.3% of patients attended follow-up visits for 52 weeks or more.

The only sight-threatening complication was observed in the MMC group, in which corneoscleral melting was observed in a patient 2 weeks postoperatively. Other less severe complications included sclera granuloma at 6.5% in the 5-FU group and 2.9% in the MMC group, and symblepharon at 2.2% in the 5-FU group and 2.9% in the MMC group (see Table 2).

Discussion

In this study, the recurrence rate of pterygium following excision, conjunctival autograft, and 5-FU (50 mg/ml) is 8.7%. This is less than the recurrence rate of 11.8% noted in the MMC group, although the difference was not statistically significant. Treatment for pterygia using the bare sclera technique could be as high as 40% [2], hence the need for some form of adjunct treatment. Augmenting with conjuctival autograft is cheap, has few side-effects and may be associated with a reduction in the recurrence although there may be an increase in surgical time unless tissue glue is used. In our earlier report [9], the recurrence rate was 11.4% when pterygium excision was performed with 5-FU alone without conjunctival autograft and 12.1% when pterygium excision was combined with conjunctival autograft alone without any adjuvant. To our knowledge, there is no other published report on the combined effect of 5-FU with conjunctival autograft on prevention of recurrence of pterygium.

The recurrence rate of 11.8% that we observed in the MMC group (with conjunctival autograft) is higher than the 0% recurrence reported by Frucht-Perry et al. [7] and 1.5% reported by de la Hoz et al. [8], although the latter study used a higher concentration of MMC (0.02%). The recurrence rate (in the MMC group) in our study is, however, less than the 12.5% reported by Mutlu [10]. Our choice of 0.01% MMC (rather than 0.02% MMC, which was used in other studies) was to minimize the risk of complications arising as a result of higher dose-related MMC toxicity. It is probable that the lower concentration used may have reduced the overall effectiveness of MMC, thereby accounting for the higher recurrence rates observed in our study.

The only sight-threatening complication of corneoscleral melting and necrosis was observed in one of the subjects in the MMC plus conjunctival autograft treated group. It was fairly severe but no perforation occurred, and was managed conservatively using antibiotic lubricants, ascorbate and vitamin A supplements and tear substitutes. Sight was lost but the globe was salvaged. The occurrence of this complication was a surprise finding because most previously reported cases of corneoscleral melting had been reported with higher doses of MMC or when a low dose was used topically postoperatively [11]. However, corneoscleral melting following pterygium surgery with conjunctival autograft without MMC has been reported [12, 13]. Our report suggests that the sight-threatening complication of corneoscleral melting and necrosis could still occur even when low-dose MMC is combined with conjunctival autograft, presumably making it less safe than 5-FU. Furthermore, both MMC and 5-FU have been shown in experimental studies to have similar properties

of inhibiting the proliferation of normal Tenon's fibroblast cultures [14].

MMC is a chemotherapeutic agent (present in the culture filtrate of *Streptomycins caespitosus*). It acts by inhibiting DNA synthesis by cross-linkage to double-stranded DNA. It inhibits fibroblast proliferation and thus reduces scar formation (and pterygium recurrence when used in pterygium surgery) [15]. Adverse effects, which include corneoscleral melting, could be reduced when MMC is used in low doses and when it is combined with conjunctival autograft.

5-FU is a pyrimidine analog that inhibits fibroblast proliferation by competitive inhibition of thymidylate synthetase [16]. It was originally known for its widespread use as an anticancer drug. It has the ability to reduce fibroblast proliferation and subsequent scarring, thus its usefulness in preventing pterygium recurrence. It can be used topically with minimal risk of sight-threatening adverse effects. It is also relatively inexpensive and easy to administer [17].

We realize that our study may have some limitations. For example, even though we increased our sample size to reduce the effect of drop out, unfortunately 10 subjects earlier randomized to the 5-FU group and 25 subjects randomized to the MMC group, did not attend for surgery, thus reducing the number available for the study. Even postoperatively, only 56.3% of patients from either treatment group were available for review for up to 52 weeks. Inability to attend for follow-up is a common and major problem in many developing countries, partly due to transportation problems but also due to the reluctance of patients to attend unless they have problems. On the plus side, however, is the fact that both groups were properly randomized and comparable with little possibility of selection bias. Another potential limitation is the fact that surgery was performed by four different surgeons with the risk of possible inter-surgeon variation. To minimize this, the procedure was standardized, and all surgeons were conversant with the protocol before commencement of the study. There was also no statistically significant difference in recurrence rate of pterygium between trainee surgeons and consultant surgeons. Third, MMC was diluted manually using a 2-mg vial to make a 0.01% preparation, and hence potential measurement errors could have resulted in higher or lower dilution strengths than intended. A 0.02% rather than 0.01% MMC dilution should also have been used to make for easier comparison with older studies.

Although both MMC and 5-FU were found to be effective in preventing pterygium recurrence when combined with conjunctival autograft, MMC is not readily available, and it is more expensive when compared to 5-FU in developing countries. Thus, when effectiveness in preventing pterygium recurrence is added to cost and safety issues, 5-FU (combined with conjunctival autograft) would appear to compare favorably with low-dose MMC (combined with conjunctival autograft) for the treatment of pterygium in developing countries. We would, however, suggest further randomized controlled studies be performed, preferably using larger sample sizes with longer follow-up periods.

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Conflict of interest None of the authors have any proprietary interest, and there is no conflict of interest.

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