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Risk factors for pterygium recurrence after surgical excision with combined conjunctival autograft (CAG) and intraoperative anti-metabolite use

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Abstract

Background: To identify the determinants of recurrence following primary pterygium excision combined with conjunctival autograft (CAG) and intraoperative use of Mitomycin C (MMC) or 5-Fluorouracil (5-FU).

Methods: A randomized controlled clinical trial comparing 5-FU (50 mg/ml) plus CAG versus MMC (0.01%) plus CAG in preventing recurrence of primary pterygium following excision.

Results: A total of 80 eyes of 80 subjects were studied, with 46 eyes in the 5-FU group and 34 eyes in the MMC group. The mean age was 50.7 ± 13.1 years with a male: female ratio of 0.95:1. Mean follow up period was 35.2 ± 29.1 weeks. The overall recurrence rate was 10%, with a rate of 8.7% in the 5-FU group and 11.8% in the MMC group. The mean age of the patients who had a recurrence was 38.1 ± 13.3 years compared to 52.1 ± 12.4 years in those without a recurrence (p = 0.003). The median size of the pterygium in patients who had a recurrence was 3.2mm, while the median size in patients who did not have a recurrence was 3.0mm (p = 0.8). Five (12.8%) males had a recurrence compared to three (7.3%) females (p = 0.48); while 10.5% of fleshy pterygia recurred compared to none (0%) of the non-fleshy pterygia (p = 1.00).

Conclusion: Younger age remains a risk factor for recurrence when both CAG and antimetabolites are combined in the treatment of pterygium, while the effect of gender, size and morphology of the pterygium may be diminished by such combination.

Keywords: *Pterygium, surgery, recurrence, risk factors.*

Résumé

Introduction: Pour identifier les déterminants de la récidive après l'excision de la ptérygoïde primaire combinée avec autogreffe conjonctivale (ACG) et l'utilisation peropératoire de la mitomycine C (MMC) ou le 5-fluorouracile (5-FU).

Méthodes: Un essai contrôlé randomisé clinique comparant le 5-FU (50 mg / ml) et de l'ACG par rapport MMC (0,01%) plus CAG dans la prévention des récidives de ptérygoïde primaire après l'excision.

Résultats: Un total de 80 yeux de 80 sujets ont été étudiés, avec 46 yeux dans le groupe 5-FU et 34 yeux dans le groupe de MMC.L'âge moyen était de 50,7 ± 13,1 ans avec un mâle : femelle rapport de 0.95:1. Moyenne suivi de période a été de 35,2 ± 29,1 semaines. Le taux global de récidive a été de 10 %, avec un taux de 8,7 % dans le groupe 5-FU et 11,8 % dans le groupe MMC. L'âge moyen des patients qui ont eu une récidive était de 38,1 ± 13,3 ans comparées à 52,1 ± 12,4 ans chez ceux sans récidive (P=0,003). La taille médiane de la ptérygoïde (la voile conjonctival chez les patients qui avaient une récurrence était 3,2 mm, tandis que la taille médiane chez les patients qui n'ont pas une réapparition à 3,0 mm (P= 0,8). Cinq (12,8 %) hommes avaient une réapparition comparativement à trois (7,3 %) femmes (P =0,48); alors que 10,5 % de charnue ptérygoïde réapparue comparativement à aucun (0 %) de ptérygoïdenon charnues (P =1,00).

Conclusion:Plus jeune âge demeure un facteur de risque de récidive lorsque les deux CAG et anti métabolites sont associés dans le traitement de ptérygoïde, tandis que l'effet du sexe, de la taille et de la morphologie de la ptérygoïde peut être diminué par une telle combinaison.

Introduction

The major marker for success in the treatment of ophthalmic pterygium is the absence of recurrence. Yet, recurrence is the commonest complication following pterygium excision [1,2]. Thus, there has been an evolution of different surgical techniques aimed at reducing the incidence of recurrence [3]. Recurrence rates in African populations range from <15% with the use of either 50mg/ml of 5-Fluorouracil (5-FU) alone or conjunctival autograft (CAG) alone to 40% with simple bare sclera excision [1,4]. The rate of recurrence after the bare sclera technique of pterygium excision alone is so high that it is no longer recommended or practiced without

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rate of 8.7% in the 5-FU group and 11.8% in the MMC group (recurrence risk ratio = 0.71, 95% Confidence Interval 0.17-3.1; p = 0.7 [Fisher's exact test]). All recurrences occurred between six weeks and six months of follow-up. One subject (in the MMC group) with both nasal and temporal pterygia had recurrence nasally. All the other recurrences were nasal in location.

The mean age of the patients who had a recurrence was 38.1 ± 13.3 years compared to 52.1 ± 12.4 years in those without a recurrence ($p = 0.003$; T test = – 3.02). Six (19.4%) of the patients aged below 50 years had a recurrence in contrast to two (4.1%) of those aged 50 years and above (RR 5.6, 95% C.I.= 1.1-30.0, P=0.05.) See Table 2.

The median size of the pterygium in patients who had a recurrence was 3.2mm, while the median size in patients who did not have a recurrence was 3.0mm ($p = 0.8$; Median test).

Table 2 shows further analysis comparing the recurrence rates with gender, pterygium morphology, location of pterygium, status of surgeon, and preoperative visual acuity.

Discussion

The pterygium recurrence rate in our study was relatively low and is within the range of recurrence rates (0 to 14.3%) reported by previous studies that combined intraoperative antimetabolites (mainly MMC) with CAG [6]. In addition, the recurrence rate of the 5FU group was similar to that of the MMC group.

The use of antimetabolites especially MMC and/or CAG in preventing pterygium recurrence is now widely accepted and commonly practiced [7,8]. However, in developing countries, like Nigeria, where MMC is relatively more expensive, 5FU with CAG is an effective alternative in preventing recurrence.

In our study, we found younger age to be a risk factor for recurrence following pterygium excision with combined adjuvant therapy. Specifically, patients aged 50 years and below were almost six times more likely to have a recurrence in spite of the use of both antimetabolite and CAG. This is similar to report of Young *et al* [9] who combined conjunctival rotational autograft with MMC and found the mean age of patients with recurrence to be significantly less than those without recurrence. Mutlu *et al* [10] made a similar observation in a similar study on recurrent pterygium. In addition, several studies, none of which involved combination of CAG with antimetabolite, reported that younger age was associated with higher risk of recurrence [2,3,11-22]. We think this finding may be related to reduced fibroblastic activity and slower healing process in older patients [23]. In addition, recent evidence suggests that mutations in K-RAS oncogene, which have been associated with pterygium recurrence, are more prevalent in younger patients [24].

On the contrary, in an earlier study, Tan *et al* [25] reported that although younger patients have higher recurrence rates, age was no longer a significant risk factor for recurrence after controlling for pterygium morphology. Their observation was in a group of patients who had pterygium excision using the bare sclera technique without any adjuvant treatment to prevent recurrence; a fact which makes it difficult to compare our study with theirs. Notwithstanding, it appears that the use of antimetabolite combined with CAG is essential in younger patients undergoing pterygium excision to reduce the risk of recurrence.

The morphology of the pterygium did not affect the recurrence rate in this study. This is at variance with the report of Tan *et al* [25]. Bearing in mind the dissimilarities in the surgical techniques used, a possible explanation for the difference between our finding and theirs is the fact that the vast majority of our subjects (95%) had fleshy pterygia while only four patients had non-fleshy pterygia.This makes it difficult to make definitive conclusions from our study even though the difference in the recurrence rates between the fleshy and non-fleshy pterygia was not statistically significant.Nonetheless, it is possible that the effect of morphology on recurrence may be modified or eliminated by the use of adjuvant therapy.

Even though those who had a recurrence had a slightly larger size of the primary pterygium, this difference was not statistically significant. Bahar *et al* [16] compared recurrence rate of extensive versus limited excision of primary pterygium and reported that larger pterygium size increased the risk of recurrence. Similarly, Yamada *et al* [22] in a comparative study of different β-irradiation doses found that smaller pterygia had lower risk of recurrence. Further studies are required to examine the effect of size of pterygium on recurrence following combination of CAG and antimetabolite.

We did not detect any association between gender and risk of recurrence in our study. Previous studies have reported that the female gender has a higher risk of pterygium recurrence [15,18,20]. While other reports stated that males have a higher recurrence rate [3,19]. None of these studies involved a combination of CAG and antimetabolite. It is

Table 1: Characteristics of pterygia excised with combined CAG* and intraoperative anti-metabolite use in 80 eyes.

Characteristic	Frequency	Percent (100%)
Operated eye		
Right	44	55.0
Left	36	45.0
Pterygium morphology		
Fleshy	76	95.0
Atrophic	1	1.3
Inflamed	3	3.7
Pterygium location		
Nasal	74	92.4
Temporal	1	1.3
Nasal & Temporal (double pterygium)	5	6.3
Preoperative Visual acuity		
≤ 6/18	70	87.5
6/24 – 6/60	4	5
5/60 – 3/60	4	5
< 3/60	2	2.5

**CAG – Conjunctival autograft*

in the MMC group were therefore included in the analysis of the factors associated with recurrence.

Data analysis was done using Statistical Package for Social Sciences (SPSS) version 19 and consisted of frequency distributions, χ^2, risk ratios (R.R.)with 95% confidence intervals (95%C.I.), Median test, and t-test. Statistical significance was inferred when $p \leq 0.05$. All tests were two-tailed.

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 mean age was 50.7 ± 13.1 years with a range of 17 – 81 years. The male: female ratio was 0.95:1. The mean size of the pterygia was 3.4 ± 1.3mm with a range of 2 -8 mm and median of 3 mm. Other clinical characteristics of the pterygia are presented in table 1. Ophthalmology residents performed 69 (86.3%) of the surgeries under close supervision by consultants, while consultants performed the rest (13.7%). The average follow up period was 35.2 ± 29.1 weeks with a range of six to 120 weeks.

Table 2: Comparison of recurrent rates with various clinical characteristics (N = 80 eyes)

Variable	Pterygium recurrence Yes n (%)	No n (%)	Relative risk (95% C.I.)	p value (Fisher's Exact test)
Age				
< 50 years	6 (19.4%)	25 (80.6%)	5.6 (1.1 -30.0)	0.05
≥ 50 years	2 (4.1%)	47 (95.9%)		
Gender				
Male	5 (12.8%)	34 (87.2%)	1.9 (0.4 – 8.4)	0.48
Female	3 (7.3%)	38 (92.7%)		
Morphology				
Fleshy	8 (10.5%)	68 (89.5%)		1.00
Not fleshy	0 (0.0%)	4 (100%)		
Location				
Double pterygium or temporal only	2 (40.0%)	3 (60.0%)	7.7 (1.1 – 55.2)	0.08
Nasal	6 (8.0%)	69 (92.0%)		
Surgeon status				
Consultant	1 (9.1%)	10 (90.9%)	0.9 (0.1 – 8.0)	1.00
Trainee	7 (10.1%)	62 (89.9%)		
*Preoperative VA**				
≥ 6/60	1 (16.7%)	5 (83.3%)	1.9 (0.2 – 18.8)	0.48
<6/60	7 (9.5%)	67 (90.5%)		

**VA – Visual acuity*

(1.7%) in the MMC group defaulted after the first postoperative visit and were excluded. Forty-six patients in the 5-FU group and thirty-four patients

There were eight cases of recurrence of the pterygium; four cases in each of the two treatment groups. The overall recurrence rate was 10%, with a

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necessary to further investigate the relationship between gender and recurrence in patients receiving combined adjuvant methods.

The location of the pterygium (nasal, temporal or double head) was not associated with recurrence in our study. This may be related to the small number of double head and temporal pterygia in our patients. In a study involving the use of β-irradiation, Wilder *et al* [26] observed that temporal primary pterygia were more likely to recur, although the number of temporal pterygia in their study was also small. In view of the fact that the proposed pathogenesis for pterygium formation favours the development of pterygium on the nasal aspect of the eye [27]; it would be expected for recurrence to be more prevalent nasally. Further studies on the effect of pterygium location on recurrence would elucidate this issue.

Severe preoperative visual impairment was also not associated with recurrence in this study. Bahar *et al* [16] reported that worse preoperative visual acuity was associated with recurrence. Pterygia may cause visual impairment by inducing astigmatism or by extending unto the central cornea. Thus, their finding could have been due to the confounding effect of size of the pterygia on recurrence.

The relatively low recurrence rate in the study, although desirable, influenced the strength of the comparisons and statistical analysis. This may have accounted for the statistical insignificance of some of the differences we observed in the comparisons. Multivariate analysis to further investigate the risk factors for recurrence would have been ideal; however, the few recurrences observed made the output of such analysis unreliable. A larger study is recommended in future.

Though the possibility of inter-surgeon variability may be considered a limitation of this study, in view of the fact that different surgeons performed the surgeries; pterygium excision is one of the commonest ophthalmic surgeries performed in our institution and all the surgeons were well versed in the procedure and used the same technique. There was also no statistically significant difference in the recurrence rate between residents and consultants in our study, although previous studies have shown that trainee surgeons or those with limited experience have higher recurrence rates [28,29].

The high dropout rate, short duration of follow up in some patients and the number of patients who failed to turn up for surgery after randomization are noteworthy limitations of our study.Poor follow up is a recurrent problem in the Nigerian setting especially because health care costs are borne entirely by the patients and follow up visits increase these out-of pocket expenses.

Understandably, apart from advising patients to wear sunglasses post-operatively, it is difficult to specifically control or evaluate their exposure to sunlight, wind and dust during the follow up period. Therefore, we could not evaluate the role of these environmental risk factors in our study.

In conclusion, younger age appears to remain a determinant of recurrence when both CAG and antimetabolites are combined in the treatment of pterygium. On the other hand, the effect of gender as well as morphology and size of the pterygium as risk factors for recurrence might be modified or eliminated by the combined use of antimetabolite and CAG. Young patients undergoing pterygium surgery should be appropriately counselled about the increased risk of recurrence and should be offered a combination of adjuvant methods to reduce the risk of failure of treatment. Further studies on the determinants of pterygium recurrence are necessary.

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problem and reports have shown that the disease and its associated fractures are among the important causes of morbidity and mortality affecting millions of people worldwide [2,3]. Osteoporosis is commoner in females than in males [4], evidence from a study indicated that one in three women and one in five men over the age of 50 years develop osteoporosis [4]. Reports indicate that the rate of osteoporotic fractures in African women is less than that for Caucasian populations [5, 6].

The measurement of BMD (the amount of mineralized tissue in a scanned area) is most commonly attained through dual-energy x-ray absorptiometry (DXA) . It is often used as an index of susceptibility to osteoporosis and it is determined by the peak bone mass (PBM) attained in early life as well as the rate of decrease in bone mass after the third decade of life [6,7].

The role of homocysteine a metabolite of the amino acid L-methionine, in the etiology of osteoporosis is not clearly understood. Available report has shown that it interfers with collagen cross-linking and this has been related to increased hip-fracture rate independent of BMD [8]. Osteoporosis is a common symptom of homocysteinuria [9], a rare autosomal recessive disease caused by mutation of the gene for methylenetetrahydrofolate reductase (MTHFR). The enzyme MTHFR is necessary for Hcy metabolism [10]. Study by Gjesdal *et al* [11] showed a 2.5-fold increase in fracture risk with Hcy levels >15 μmol/L. In the same study a positive linear relationship between Hcy levels and fracture risk was observed. Saito [12] reported that even mild hyperhomocysteinemia reduces bone quality and increases bone fragility in his study.

In addition to increased bone loss and fracture risk, elevated Hcy has also been linked to chronic inflammation [13]. In cultured cells, homocysteine has been shown to increase apoptosis of osteoblasts by increasing intracellular reactive oxygen species [14]. Vitamins B_6 , B_{12} and folate are necessary cofactors for the metabolism of homocysteine [15]. Decreased levels of these vitamins will invariably alter plasma homocysteine level.

Studies on homocysteine, B vitamins in relation to BMD in osteoporotic subjects in Nigeria are rare. This study was designed to evaluate plasma Hcy, B vitamins and bone mineral density in osteoporotic patients who may be at risk of bone fracture.

Materials and methods

Study subjects

Fifty osteoporotic patients (males and females) mean age of 57.0±1.9 years recruited for this study were patients with primary osteoporosis attending the General Out-Patient Clinic of the Department of Family Medicine, University College Hospital, Ibadan. The recruitement was based on BMD of T-Score below -2.5(<-2.5) using the Dual Energy X-ray Absorptiometry (DXA), EX-300 Densitometer (Osteosys, Poland)) . In accordance with WHO standard, the BMD of T-Score <1.0 (-0.9 to 4.5) of fifty apparently healthy volunteers (males and females) mean age of 54.8±0.9 years were included as controls. Patients with cardiovascular, renal, liver diseases and any other ailments that could affect the results of the study were excluded.

Ethical approval was obtained from the University College Hospital/University of Ibadan Ethical Review Committee. Written /oral informed consent was obtained from each subject. A structured questionnaire was used to obtain demographic information, medical history, family history, medication, smoking status, alcohol use, and menstrual status.

Anthropometric measurements

The weight of the participants without shoes was taken using Seca adult weighing scale. Height was measured using a meter rule calibrated on the wall. These measurements were used to calculate body mass index (BMI) W/H^2

Bone mineral density measurement

The Dual Energy X-ray Absorptiometry (DXA) supplied by the manufacturer (Osteosys, Poland) for scanning and analysis was employed. The BMD was measured at the distal radius of the forearm. Daily quality control was carried out to allow the densitometer to standardize and this was calibrated against a standard calibration block before measurement of the distal radius.

Sample collection

Five millimeters of fasting blood samples (10-12 hours) were collected by standard venipuncture without stasis and dispensed into Dipotassium Ethylene Diamine Tetra acetic acid (K_2EDTA) bottles and were placed immediately in ice pack in a dark container. The blood samples were spun at 3500 rpm for 10 minutes using MSE/Harrier centrifuge (UK) and the plasma was dispensed into clean plain containers and stored at -20°C until analyzed.

Determination of plasma total homocysteine

Plasma tHcy was estimated using an enzyme immunoassay (EIA) method [16]. (Kits were purchased from Axis® Homocysteine Scotland)