

Continuing Medical Education:

5-Fluorouracil vs avastin as adjunct to conjunctival autograft in the surgical treatment of pterygium

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Learning Objectives

Upon completion of this activity, participants will be able to:

1. Distinguish risk factors for pterygium
2. Evaluate the current management options for pterygium
3. Compare adjuvant treatment with 5-fluorouracil *vs* bevacizumab in the prevention of recurrence of pterygia
4. Assess the safety of 5-fluorouracil *vs* bevacizumab as adjuvant treatment of pterygia

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5-Fluorouracil vs avastin as adjunct to conjunctival autograft in the surgical treatment of pterygium

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Abstract

Background The use of adjunct antimetabolite therapy along with conjunctiva autograft has been shown to be effective in preventing pterygium recurrence. There has however been fewer reports on the effect of anti-vascular endothelial growth factor on pterygium recurrence.

Objective To compare 5-fluorouracil with conjunctival autograft with bevacizumab (avastin) used along with autograft in the surgical treatment of pterygium.

Methods A randomized controlled prospective study of outcome of pterygium treatment using 5-fluorouracil with conjunctiva autograft as adjuvant treatment compared avastin with conjunctiva autograft.

Results A total of 70 eyes of 70 patients were recruited into the study with a mean age of 51.49 (± 14.36) years. Thirty-five patients each were randomized into the 5-fluorouracil treatment group and into the avastin treatment group respectively. The mean follow-up was 18.35 months (18.44 for the 5-FU and 18.26 for the avastin group). Post operative, pterygium recurrence was observed in 1/27 (3.7%) eyes treated with 5-fluorouracil and 1/26 (3.9%) eyes of the avastin group. Both recurrences were observed at 1 year of follow-up and they were both female patients aged 46 and 52 years, respectively.

Conclusions Both 5-fluorouracil and avastin are comparably effective as adjunct to conjunctival autograft.

However, cost, availability, and convenience are other considerations with use of avastin.

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Introduction

Pterygium is an ocular surface degenerative lesion presenting as a wing shaped fibrovascular conjunctival growth. It is located at the interpalpebral region of the conjunctiva, mostly nasal and extends unto the cornea. Its prevalence has been reported to range from 0.3 to 29% and mainly found in the tropical region.^{1,2} The aetiopathogenesis of pterygium is not definite but various theories have been postulated. Exposure to ultraviolet light (mainly UVB) has been identified as a major risk factor for the development of pterygium.^{1,3} Other risk factors include chronic irritation from dust and wind.³ An individual with pterygium may present with visual disturbance due to its induction of astigmatism or by its growth extending on the cornea to occlude the visual axis. It may also cause ocular irritation and recurrent inflammation as well as being unsightly, cosmetically.

Conservative treatment using topical eye medications can be employed as a temporal relief measure for mild symptoms, such as foreign body sensation and inflammation. They include artificial tears, eye ointments for foreign body sensation and anti-inflammatory eye-drops for inflamed pterygia. The main stay of treatment of pterygium, however, is by surgical excision. In 1948, the bare sclera surgical technique was first fully described by D'Ombrian⁴ and this became the classical standard of treatment for many years. The aim of this technique is to ensure the complete removal of the head, neck, and body of the pterygium. This bare sclera technique has been plagued with a high-reported rate of recurrence; rates of up to 90% have been reported.⁵ In a bid to reduce the rate of recurrence, numerous

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adjunctive therapies have been developed especially over the last few decades.

Adjuvant treatment modalities are numerous in the present day surgical management of pterygium. Adjuvant surgical technique being employed in a bit to reduce recurrence include; lamellar keratoplasty, amniotic membrane transplantation, and conjunctival autograft.^{6,7} The lamellar keratoplasty is mainly indicated for recurrent pterygia with a scarred or thin cornea tissue. The conjunctival autograft treatment option is relatively popular and can be applied over the bare sclera either by a primary direct closure, a free conjunctival autograft⁸ or by a sliding conjunctival flap.⁹ Other adjuvant modalities include radiation therapy using beta-irradiation post-operatively, which is relatively safe, effective, and a satisfactory reduction of recurrence rate has been reported.^{10,11} Chemotherapy agents such as antimetabolite are also commonly used as adjuvant therapy; such as mitomycin C (MMC) and 5-fluorouracil (5-FU). These two antimetabolite are mainly applied over the bare sclera intraoperative, but can also be used as a preoperative intra-lesion injection or as a post-operative eye drop. The MMC has a stronger anti-proliferative effect owing to its action on both fibroblasts and vascular endothelial cell as against 5-FU which effect is mainly on the fibroblasts.¹² Although there is a significant reduction in the recurrence rate following these adjuvant therapies used separately or sometimes in combination, side effects from these treatment do occur. They include; punctate epitheliopathy, elevated intraocular pressure, and delayed onset sclera melting. These side effects has encouraged search for other safer modalities.

The use of alcohol (ethanol) and anti-vascular endothelial growth factors (anti-VEGF) has been recently introduced. Ethanol causes the denaturation of cytokines, growth factors, and enzymes involve in pterygium formation. A study comparing the use of ethanol and low-dose MMC as adjuvant therapy reported a lesser rate of recurrence and fewer post-operative complications in the ethanol group.¹³ The use of anti-VEGF has been encouraged by the demonstration of higher concentration of VEGF in pterygium tissue as compared with normal conjunctiva.¹⁴ Bevacizumab (avastin; Genentech Inc., San Francisco, CA, USA), an anti-VEGF, is a recombinant humanized murine monoclonal immunoglobulin G1. It inhibits the VEGF-A isoform, the main stimulant of angiogenesis. It is commonly used as an adjuvant for many neoplasms such as brain, lung, ovary, and breast cancers.¹⁵⁻¹⁸ It recently got approval by the Food and Drug Administration of the United State of America for intraocular use and its been used extensively for posterior segment vascular diseases and for corneal neovascularisation.¹⁹⁻²² A randomized clinical trial reported the use of subconjunctival bevacizumab injection

in conjunction with primary surgery and conjunctival autograft to be safe, well-tolerated, and capable of preventing recurrence when compared with the control.²³ Another randomized trial showed no statistically significant difference between the bevacizumab group and control, although recurrence rate was halved in the former.²⁴

The purpose of this study is to compare 5-FU with conjunctival autograft and bevacizumab (avastin) used along with autograft in the surgical treatment of pterygium.

Materials and methods

Study site

The study was carried out at the Department of Ophthalmology, University of Ibadan/University College Hospital, Ibadan, between October 2009 and December 2013.

Design

A randomized controlled and prospective study of outcome of pterygium treatment using 5-FU with conjunctiva autograft as adjuvant treatment compared with bevacizumab with conjunctiva autograft.

Ethical clearance

ethical clearance was obtained from the institutional ethical committee of the UI/UCH.

Selection of patients (inclusion/exclusion criteria)

The full procedure for selection and recruitment of patients for the study has been described elsewhere²⁵ but in brief, all patients seen with pterygium encroaching 2 mm or more into cornea (from the limbus) were selected and randomized into one of the two groups. Pterygia of size <2 mm into cornea as well as recurrent pterygium from previous surgery were excluded.

Sample size was calculated from estimation of proportions with assumption of success rate of about 80%²⁶ for 5-FU with autograft and expected success rate of 100% for bevacizumab with conjunctival autograft, alpha error, 0.05% and a power of 90%.

$$N = \frac{Z_a/P_0(1-P_0) - Z_b/P_1(1-P_1)^2}{P_1 - P_0} = 70 \text{ (or 35 per treatment group)}$$

Following adequate explanation and obtaining of consent, the subjects were randomized into their respective groups using a 'lucky dip' technique. Small-folded sheets of paper numbered 1-35 and 36-70 were kept in two separate envelopes (for male and female, respectively). Male and female patients who met the selection criteria were requested to pick one-folded sheet of paper from the

appropriate envelope as they presented consecutively to the clinic. Those who picked odd numbers were assigned to the 5-FU with conjunctiva autograph group, whereas even numbers were assigned to the bevacizumab with conjunctiva autograph group. For any patient with bilateral pterygia, the worse eye was randomized and the other eye excluded from the study. Information obtained from subjects using a structured questionnaire included age, sex, occupation, eye affected, location, morphology, size of pterygium from limbus (measured with a slit lamp), vision of eye to be operated, and information on previous pterygium surgery done.

All patients received subconjunctival 2% lignocaine with adrenaline, for local anaesthesia. Pterygium tissue was excised from the cornea with Bard-Parker blade under microscope with subsequently bluntly dissected from over lying conjunctiva and underlying sclera. The Tenon was then gently excised without damage to the rectus muscle. The use of cautery was minimized.

5-FU with conjunctiva autograph group

The 5-FU group after an initial pterygium excision had the bare scleral area of the pterygium bed exposed to a section of a 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 be removed and discarded and the eye copiously irrigated with 40–50 mls normal saline solution for about 1–2 min. A conjunctiva-free graft of a size equivalent to the scleral defect was excised from the pterygium-free superior 12:00 hours bulbar conjunctiva inclusive of limbal conjunctiva and 0.5 mm of clear cornea of the same eye. Thereafter the free graft was sutured to the recipient bed with 4–8 interrupted 8-0 vycril sutures taking care to ensure proper orientation of the ends of the graft (cornea end of the graft sutured to the recipient cornea).

Bevacizumab with conjunctiva graft procedure

This group had the bare scleral area of the pterygium bed covered with conjunctiva-free graft of a size equivalent to the scleral defect excised from the pterygium-free superior 12:00 hours bulbar conjunctiva inclusive of limbal conjunctiva and 0.5 mm of clear cornea of the same eye. The free graft was sutured to the recipient bed with 4–8 interrupted 8-0 vycril sutures taking care to ensure proper orientation of the ends of the graft (cornea end of the graft sutured to the recipient cornea). Thereafter a 0.05 ml of 0.5 mg bevacizumab subconjunctival injection was given adjacent to the graft.

Post operative, both groups had instillation of antibiotic ointment and dexamethasone (steroid) drops post-operatively for between 8 and 10 weeks, depending on duration of inflammation. Follow-up visits were at

post-operative days 1, 7, and 21, monthly for 2 months and every 3 months for between 1 and 2 years.

Recurrence of pterygium was defined as growth of fibrovascular tissue 1 mm or more into cornea as observed with a slit lamp.

Data analysis

All information was collected with the aid of a structured questionnaire and entered into a computer and analysed using Statistical Package for Social Sciences (IBM) for Windows, Version 19.0, IBM Corp (Armonk, NY, USA).

Seventeen (24.6%) of the patients comprising eight from 5-FU group and nine from the avastin group were lost to follow-up before the end of the study at 2 years and were excluded from the final analysis.

Results

A total of 70 eyes of 70 patients were recruited into the study with a mean age of 51.49 (± 14.36) years. Thirty-five of the patients each were randomized into the 5-FU treatment group and avastin treatment group, respectively. Table 1 show the age and gender distribution in the two groups. There was no statistical difference between the mean ages of the two groups.

In both groups >80% were nasal in location and >90% were large and fleshy in morphology as depicted in Table 2. The mean size in length of the pterygia for the 5-FU treatment group was 3.94 mm and for the avastin treatment group was 3.36 mm. There was no statistically difference between the two groups with a *P*-value of 0.11.

The mean follow-up was 18.35 months (18.44 for the 5-FU and 18.26 for the avastin group, respectively). Twenty-seven of the 5-FU and 26 of the avastin patients were followed up to 2 years. Post-operatively pterygium recurrence was observed in 1/27 (3.7%) eyes treated with 5-FU and 1/26 (3.9%) eye of the avastin group with a *P*-value of 0.32. Both recurrences were observed at 1 year of follow-up and they were both female patients aged 46 and 52 years, respectively. They were also both of the fleshy morphologic type. In this study complications such as granuloma formation, surface infection or sclera

Table 1 Demographic characteristics of the study population (*n* = 70)

| | 5-FU (n = 35) | Avastin (n = 35) | <i>P</i> -value |
|--------------------|-----------------------|------------------|-----------------|
| <i>Age (years)</i> | | | |
| Mean (\pm SD) | 52.00 (± 12.11) | 49.20 (14.13) | 0.38 |
| Range | 28–73 | 26–86 | |
| <i>Gender</i> | | | |
| Male | 16 | 21 | |
| Female | 19 | 14 | |

Table 2 Characteristics of operated pterygium

| | 5-FU (n = 35) | Avastin (n = 35) | P-value |
|--|--------------------|--------------------|---------|
| <i>Location</i> | | | |
| Nasal | 30 | 33 | |
| Temporal | 2 | 1 | |
| Both | 3 | 1 | |
| <i>Morphology</i> | | | |
| Fleshy | 32 | 33 | |
| Atrophic | 3 | 1 | |
| Inflamed | — | 1 | |
| <i>Size in mm (length from limbus)</i> | | | |
| Mean (\pm SD) | 3.88 (\pm 1.34) | 3.36 (\pm 1.58) | 0.11 |
| Range | 2–8.5 | 2–8 | |

necrosis were not observed. A total of 17 (eight of the 5-FU and nine of the avastin groups) were not analysed for recurrence because they were lost to follow-up in <1 year after surgery. Eleven of the 17 patients (64.7%) lost to follow-up were seen for at least 6 month post surgery.

Discussion

This study has observed the same successful rate of treatment (>96%) for the two groups which when compared, the rate of recurrence of pterygium in the avastin group of 3.9% is far less to a study conducted by Mohammad-Reza *et al*²⁴ which was 18.18%. In their study pterygium excision with conjunctiva autograft was also the baseline surgery with subsequent randomization into two groups of either bevacizumab subconjunctival injection or balance salt solution (BSS) injection intraoperatively. The rate of recurrence in the bevacizumab group was half that of the BSS group in their study, but this failed to reach statistically significant difference. Another study by Nava-Castaneda *et al*²³ reported no recurrence in the two groups that had subconjunctival bevacizumab injections after a 1 year follow-up period with recurrence only in the third group which had no injection given. This difference was statistically significant and they concluded that a single 2.5 mg/ml subconjunctival bevacizumab injection in conjunction with primary pterygium surgery accomplishing a conjunctival autograft procedure was safe, well-tolerated, and capable of preventing pterygium recurrences. Unlike the two studies mentioned above, our study compared bevacizumab and 5-FU with both having a baseline of pterygium excision with conjunctival autograft. The result showed a near 100% recurrence free rate in both studies comparable to the bevacizumab group of Nava-Castaneda *et al*²³ study, though they

used 2.5 mg/ml bevacizumab injection while we used 0.5 mg/ml bevacizumab injection.

This study also re-emphasized that combination of adjunct therapy is better than single adjunct therapy in reducing the rate of recurrence of pterygium. An earlier study by Bekibele *et al*²⁵ reported a success rate of bare sclera technique with intraoperative 5-FU group as 88.6% and conjunctival autograft group as 87.9%, respectively. A latter study which compared 5-FU with Mitomycin C as adjunct to conjunctival autograft also by Bekibele *et al*²⁷ reported recurrence rates of 8.7 and 11.8%, respectively. Whereas this current study which compared 5-FU and bevacizumab as adjuncts to conjunctival autograft reported a much higher success rate in preventing recurrence. 5-FU is relatively cheap and readily available while bevacizumab is more expensive and comes in higher concentrations that require dilution to desired concentrations with the possible risk of contamination and altered dosage. This, therefore, is the advantage 5-FU has over avastin in the management of pterygium in resource scarce settings.

A limitation of this study was that 17 (24.3%) of the subjects were lost to follow-up before the end of the study and were therefore not available for inclusion in the analysis of recurrence, their presence may have altered the success rate, however, they were evenly distributed between the groups and therefore not likely to bias the group comparison.

In conclusion, a single subconjunctival injection of 0.5 mg/ml bevacizumab intraoperatively with conjunctival autograft and 5-FU intraoperative use with conjunctival autograft have a very high success rate of prevention of pterygium recurrence close to 100%. Cost, convenience, and availability considered 5-FU would appear to have an advantage over bevacizumab. More studies are, however, needed to further explore the different effects between these drugs in preventing pterygium recurrence.

Summary

What was known before

- Reduced rate of recurrence: bevacizumab (avastin) has been reported to be an effective adjunct in pterygium management with reduced rate of recurrence as compared with placebo (balanced salt solution).

What this study adds

- Reduction of recurrence: 96% without recurrence at 2 year follow-up.
- Reduction in complication: no case of complications such as granuloma or infection.
- As effective as 5-fluorouracil: avastin effectiveness as an adjunct in pterygium autograft management is comparable with 5-fluorouracil outcome.

Conflict of interest

The authors declare no conflict of interest.

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5-Fluorouracil vs avastin as adjunct to conjunctival autograft in the surgical treatment of pterygium

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- You are evaluating a 52-year-old woman who complains of discomfort related to a 3.5-mm left-sided pterygium during the past year. She wants to know how this pterygium developed. Which of the following variables is the **most** established independent risk factor for pterygium?
 - Age older than 50 years
 - Female gender
 - Black race
 - Exposure to ultraviolet light
- You decide to proceed with treatment of this patient's pterygium. Which of the following statements regarding the management of pterygium is **most** accurate?
 - Surgery with the bare sclera technique alone is associated with recurrence rates of up to 90%
 - Patients with recurrent pterygia should not receive lamellar keratoplasty
 - Adjuvant radiotherapy does not reduce the risk for recurrence
 - 5-fluorouracil should be applied intraoperatively only
- You plan a conjunctival autograft procedure for this patient, along with intraoperative adjuvant therapy. What was the **major** outcome of the current study comparing 5-fluorouracil *vs* bevacizumab as adjuvant treatment?
 - 5-Fluorouracil was associated with lower rates of recurrence of pterygia
 - Bevacizumab was associated with lower rates of recurrence of pterygia
 - Recurrence of pterygia was rare and similar regardless of treatment with 5-fluorouracil or bevacizumab
 - Bevacizumab was associated with lower rates of recurrence of pterygia in the subgroup of patients with atrophic pterygia only

- What should you consider regarding the safety of 5-fluorouracil *vs* bevacizumab for adjuvant treatment of pterygia in the current study?
 - 5-fluorouracil was associated with higher rates of granuloma formation
 - Bevacizumab was associated with higher rates of infection
 - 5-fluorouracil was associated with higher rates of sclera necrosis
 - No major adverse events were reported in either adjuvant treatment group

Activity evaluation

1. The activity supported the learning objectives.

| | | | | |
|-------------------|---|---|---|----------------|
| Strongly disagree | | | | Strongly agree |
| 1 | 2 | 3 | 4 | 5 |

2. The material was organized clearly for learning to occur.

| | | | | |
|-------------------|---|---|---|----------------|
| Strongly disagree | | | | Strongly agree |
| 1 | 2 | 3 | 4 | 5 |

3. The content learned from this activity will impact my practice.

| | | | | |
|-------------------|---|---|---|----------------|
| Strongly disagree | | | | Strongly agree |
| 1 | 2 | 3 | 4 | 5 |

4. The activity was presented objectively and free of commercial bias.

| | | | | |
|-------------------|---|---|---|----------------|
| Strongly disagree | | | | Strongly agree |
| 1 | 2 | 3 | 4 | 5 |