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ROLE OF TOPICAL BEVACIZUMAB IN PREVENTION OF PTERYGIUM RECURRENCE AFTER SURGERY

Emad A. Saliem*[1], MD and Ahmed G. Elmahdy[2], MD.

[1]Department of Ophthalmology, Faculty of Medicine, Al-Azhar University, Asyut, Egypt.
[2]Department of Ophthalmology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.

***Corresponding Author: Emad A. Saliem**

Department of Ophthalmology, Faculty of Medicine, Al-Azhar University, Asyut, Egypt.

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ABSTRACT

Background: To evaluate the efficacy and tolerability of topical Bevacizumab 0.05% for treatment of 1ry pterygium and to detect the rate of recurrence after excision. **Patients and Methods:** This study included sixty eyes of 60 patients (37 males and 23 females) with primary pterygia. Thirty patients were considered as a control group (group A), received only topical antibiotic and steroid treatment for 1 month after pterygium excision with bare sclera technique, while the remaining thirty patient (group B) had received additional topical Bevacizumab 0.05% instillation for one month postoperatively. All patients were followed up for 6 months. During this period, the main outcome measures were corneal neovascularization, pterygium recurrence, and other postoperative complications. **Results:** The postoperative results revealed that after 6 months of follow-up: in (group A) there were 4 eyes (13.33%) showed recurrence which was not statistically significance different from group B which recorded 2 eyes recurrence (6.66%) P=0.4511 (>0.05). There were corneal neovascularization in 23 eyes (76.66%) in group A which was statistically significance different from group B which were 10 eyes (33.33%) P=0.018 (<0.05). **Conclusion:** Topical Bevacizumab for 1 month after surgical excision of pterygium with bare sclera technique is well tolerated and effective to prevent vascularization and reducing the recurrence rate after pterygium excision as it reduces the vascular element of the pterygium.

KEYWORDS: Bevacizumab, pterygium.

INTRODUCTION

A pterygium is a triangular fibrovascular subepithelial ingrowth of degenerative bulbar conjunctival tissue over the limbus onto the cornea.[1] The pathogenesis of pterygium is not definitely known. Various studies have implicated environmental factors, such as ultraviolet light, chronic irritation, and inflammation.[2]

Recent studies suggest that vascular endothelial growth factor (VEGF) plays an important role in the pathogenesis of a pterygium.[3,4] The over expression of VEGF in pterygium tissue should be in consideration to evaluate the role of anti-VEGF therapy, which could induce regression of blood vessels and hence retard progression of pterygium.[5,6]

The standard treatment for pterygium was surgical excision with bare sclera technique which was associated with a high recurrence rate. Therefore adjuvant treatment options are used to reduce this recurrence, such as the use of beta radiation, conjunctiva autograft, amniotic membrane grafting and mitomycin C.[7]

Pterygium recurrence is one of the challenging problem facing ophthalmologists due to multiple factors related to vascular component of the pterygium and corneal stem cells activity. The recurrence of pterygium could occur due to fibroblast proliferation and corneal neovascularization as parts of healing process following conjunctiva excision.[8]

Corneal neovascularization secondary to the traumatic and inflammatory process following pterygium surgery is one of the triggering factors for pterygium recurrence. Another hypothesis is that loss of limbal stem cell barrier function allows conjunctiva to grow over cornea. Therefore adjuvant treatment aims at inhibiting the fibroblast proliferation or covering the bare sclera with a tissue of similar properties.[9]

Vascular endothelial growth factor (VGEF) is an angiogenic factor in the cornea and is considered the trigger factor for corneal neovascularization and hence pterygium recurrence.[10]

Bevacizumab (Avastin) is a full-length, humanized, monoclonal antibody, it binds to and neutralizes the biologic activity of all types of human VEGF, so it prevents interaction with its receptors on the surface of endothelial cells.[11]

Several studies stated that the use of topical or subconjunctival Bevacizumab as an off-label treatment may be useful in the management of patients with primary and recurrent pterygium without significant local or systemic adverse effects.[12,13]

The recurrence of pterygium was evidenced by fibrovascular tissue growth onto the cornea across the limbus.[14]

The present study evaluated the effect of topical Bevacizumab on postoperative recurrence after pterygium surgery with bare sclera technique.

PATIENTS AND METHODS

The prospective randomized comparative study was performed at AL-AZHAR University Hospitals, AL-AZHAR University, and included 60 eyes of 60 patients with primary pterygium for first time. Written consent was obtained from the patients and included an explanation of the study and agreement to have a photo of the eye area only taken. All cases were subjected to

(I) History of systemic diseases.
(II) Visual acuity.
(III) Intraocular pressure measurement.
(IV) Local slit lamp ophthalmic examination for cornea and conjunctiva.
(V) All operations were performed in operating room under an operating microscope. The pterygium surgery was performed by using bare sclera technique. The pterygium was grasped at the limbus and avulsed from the corneal surface with a muscle hook. Westcott scissors were used to remove the pterygium body, and the corneal and sclera surfaces were polished with a 15 Bard-Parker blade and to control bleeding minimal cauterization may be needed. The eye was covered with an eye patch after administration of topical antibiotic & steroid drops and ointment. A therapeutic contact lens was applied after surgery until corneal re-epithelialization was completed. Postoperatively all cases were divided randomly into two equal groups. **Group A** which included (30 eyes of 30 patients) was treated with antibiotic & steroid eye drops and ointment, four times daily for 2 weeks. **Group B** (30 eyes of 30 patients) were received additional 5 mg/ml topical Bevacizumab four times daily for one month postoperatively. These drops were prepared from the commercial Bevacizumab solution under sterile conditions and stored in sterile vials at +4°C for 48h. Patients were examined on the first postoperative week, 1st, 3rd, and 6th months after surgery for postoperative complications and recurrence rates. Follow-up of cases weekly up to 6 months was performed recording corneal neovascularization from the limbus and pterygium recurrence, also patient complaint from any toxic side effects as pain and burning sensation.

Exclusion criteria included patients with previous pterygium surgery, ocular surface diseases (e.g. blepharitis, Sjögren syndrome and dry eye disease), eyelid diseases and any condition for which Bevacizumab is contraindicated (allergy to Bevacizumab, pregnant and lactating females, hypertension, bleeding tendencies and previous myocardial infarction or stroke).

The pterygia were classified into grades 1, 2 and 3 based on slit lamp evaluation

Grade 1 (atrophic) had clearly visible episcleral vessels under the body of the pterygium.
Grade 2 (intermediate) had partially visible episcleral vessels under the body
of the pterygium.
Grade 3 (fleshy) had totally obscured episcleral vessels underlying the body
of the pterygium.

STATISTICAL ANALYSIS

Both descriptive and analytic approaches were used in the data analysis. Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS version 10). Chi-square was used to determine the association between grades and time intervals. A (P) value less than 0.05 was considered statistically significant.

RESULT

The demographic data of patients in group A revealed that 17 patients (56.66%) were male and that 13 patients (43.33%) were female. Age of the patients ranged from 32 to 69 years with a mean age of 50.3±11.6 years.. Group B revealed that 20 patients (66.7%) were male and that 10 patients (33.3%) were female. Age of the patients ranged from29 to 72 years with a mean age of 48.6±9.8 year.

20 patients (33.3%) in grade 1, 32 patients (53.4%) in grade 2, and 8 patients (13.3%) in grade 3. There were no statistically significant differences regarding the age, sex, laterality and the length of pterygium. No intraoperative complications were recorded with significant improvement of corneal clearance in all patients.

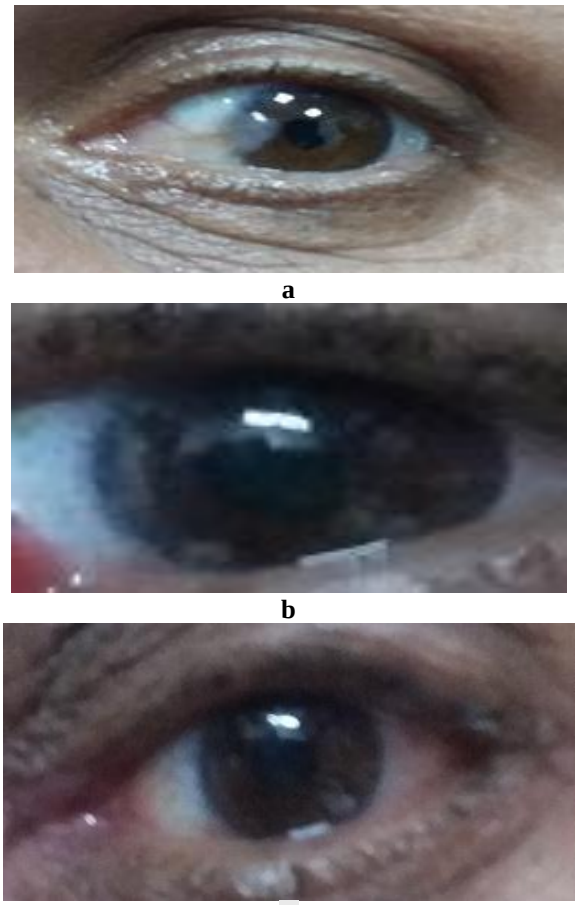
The postoperative results revealed that after 6 months of follow-up: in group A treated postoperatively by antibiotic and steroid, among the 30 eyes there were 4 eyes (13.33%) showed recurrence which had no statistically significance different from group B which recorded 2 eyes (6.66%) P=0.4511 (>0.05).

Regarding to corneal neovascularization, in group A, there was corneal neovascularization in 23 eyes (76.66%) including the recurrent 4 eyes which had statistically significant different from group B which was 10 eyes (33.33%) P=0.018 (<0.05), and no corneal neovascularization in group A in 7 eyes (23.33%) which had statistically highly different from the group B in 20 eyes (66.6%) P<0.0001 (<0.05).

Total P value concerning the presence and absence of vascularization between the two groups was P<0001 (<0.001) which was highly significant (Table 1), (Figures 1,2,3). there were no eyes recorded any toxic side effects as pain ,and burning sensation.

Table. 1: the rate of pterygium recurrence and corneal neovascularization.

parameter	Group A		Group B		P value
	NO	%	NO	%	
PTREGIUM RECURANCE	4	13.33	2	6.6	0.4511
No corneal vascularization	7	23.33	20	66.66	<0.001
Corneal vascularization	23	76.66	10	33.33	0.018

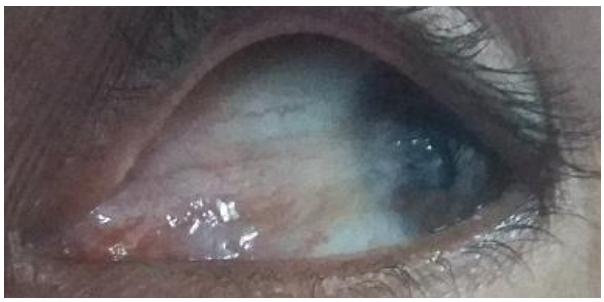


a

b

C

Figure 1: Grade 2 primary pterygium in a 43-yrs-old female patient. (a) The preoperative view. (b&c) The postoperative view 3&6 months after pterygium surgery without Bevacizumab.



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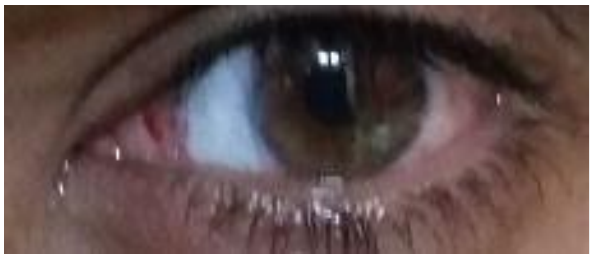
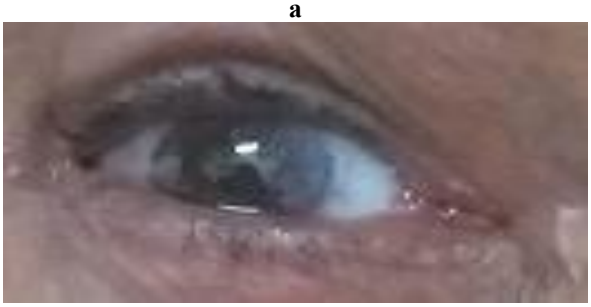


b

Figure 2: Grade 2 primary pterygium in a 32-yrs-old male patient. (a) The preoperative view. (b) The postoperative view 3 months after pterygium surgery with topical instillation of Bevacizumab.

a



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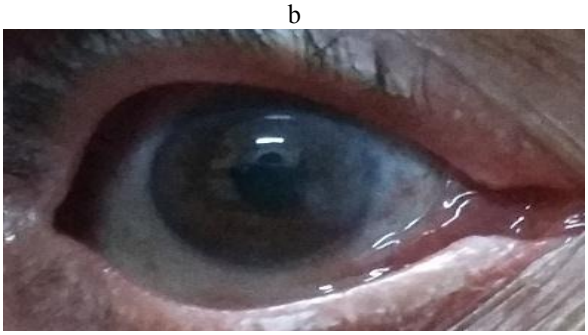

C

Figure 3: Grade 3 primary pterygium in a 49-yrs-old female patient. (a) The preoperative view. (b&c) The postoperative view 3&6 months after pterygium surgery with topical instillation of Bevacizumab.

DISCUSSION

Pterygium is a proliferative disease with corneo-conjunctival fibrovascular growth onto the cornea.[15] Surgery has been considered as a main treatment for primary pterygium.[16] However, complications such as recurrence following the surgery may occur.[17] Substances such as mitomycin C and 5-FU are recommended to decrease the chance of recurrence; however, their usage is associated with undesirable complications such as infection and scleral necrosis.[18]

Vascular endothelial growth factor (VGEF) is an angiogenic factor in the cornea and is considered the trigger factor for corneal neovascularization and hence pterygium recurrence. The use of topical or sub conjunctiva Bevacizumab which is an anti (VEGF) is relatively safe and well tolerated in pterygium surgery in prevention of recurrence.[19]

In this study, the postoperative results revealed that after 6 months of follow-up: in group A, among the 30 eyes there were 4 eyes (13.33%) showed recurrence which had no statistically significant different from group B which recorded 2 eyes (6.66%) P=0.4511 (>0.05). but there was a high statistically significant concerning the presence and absence of vascularization between the two groups was P<0001 (<0.001).

Also, **Ozgurhan et al**[20], did not find statistically significant deference in the recurrence rate, he applied topical Bevacizumab as adjunctive therapy 1 month after conjunctival autograft surgery for recurrent pterygia and found that the drug was safe and effective only to prevent corneal neovascularization.

In contrast with **Wu et al**[21], they reported having success with topical Bevacizumab in a patient suffering from impending recurrent pterygium.

Also, **Fallah and coauthors**[22] reported that short term use of topical Bevacizumab was effective in delaying of recurrence of impending pterygia in a study including 54 patients. However, the use of mitomycin C in their study might be an additive factor in the inhibition of recurrence.

This study demonstrated the high efficacy of topical Bevacizumab 5 mg/ml in minimizing corneal neovascularization, that is in agreement with many studies such as the **Kim et al**.[23]

In another study by **Manzano et al**,[24] the effect of topical Bevacizumab on experimental corneal neovascularization in rats was studied. They reported that topical administration of Bevacizumab had decreased corneal neovascularization by 40% following chemical injury.

In this study, No local irritation, allergic reaction, or surface epitheliopathy was observed. This is in contrast with a 60% rate of spontaneous loss of epithelial integrity as recently reported by **Kim et al**[23], this might occur due to the use of topical Bevacizumab at a higher concentration (1.25%) twice daily for a much longer period (3 months), and adverse effects generally appeared during the 2nd month of treatment. This suggests that the duration of treatment may well determine the safety of topical Bevacizumab.

CONCLUSION

Topical Bevacizumab for 1 month after surgical excision of pterygium with bare sclera technique is well tolerated and effective to prevent corneal and conjunctival neovascularization and reducing the recurrence rate after pterygium excision.

REFERENCES

1. Kaniski JJ, Clinical Ophthalmology. (7th edition) Butterworth-Heinemann Ltd Publisher, 2010; 96.
2. Di Girolamo N, Chui J, Coroneo MT et al. role of cytokines, growth factors, and matrix metalloproteinases. Prog Retina Eye Res., 2004; 23: 195-228.
3. Liang K, Jiang Z, Zhao B, et al., The expression of vascular endothelial growth factor in mast cells promotes the neovascularization of human pterygia. Br J Ophthalmol, 2012; 96(9): 1246–51.
4. Aspiotis M, Tsanou E, Gorezis S, et al., Angiogenesis in pterygium: study of microvessel density, vascular endothelial growth factor, and thrombospondin-1. Eye, 2007; 21(8): 1095–101.
5. Ranieri G, Patruno R, Ruggieri E, et al., Vascular-endothelial growth factor (VEGF) as a target of Bevacizumab in cancer: from the biology of the clinic. Curr Med Chem. 2006; 13(16): 1845–57.
6. Ferrara N, Hillan KJ and Novotny W., Bevacizumab (Avastin), a humanized anti-VEGF monoclonal antibody for cancer therapy. Biochem Biophys Res Commun, 2005; 333(2): 328–35.
7. Bazzazi N, Ramezani A and Rabiee MA., A comparative study of conjunctival autograft and minimally invasive pterygium surgery in primary pterygia. Pak J Biol Sci., 2010; 13: 409-12.
8. Kamil Z, Bokhari SA and Rizvi F., Comparison of Conjunctival Autograft and Intra-Operative Application of Mitomycin-C in Treatment of Primary Pterygium. Pak J Ophthalmol, 2011; 27: 221-5.
9. Bekibele CO, Ashaye A, Olusanya B, et al., 5-Fluorouracil versus mitomycin C as adjuncts to conjunctival autograft in preventing pterygium recurrence. Int Ophthalmol, 2012; 32: 3-8.
10. Hu Q, Qiao Y, Nie X, et al., Bevacizumab in the treatment of pterygium: a meta-analysis. Cornea, 2014; 33: 154-60.
11. Hurwitz H, Fehrenbacher L, Novotny W, et al., Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med., 2004; 350: 2335-42.

12. Razeghinejad MR, Hosseini H, Ahmadi F, et al., Preliminary results of subconjunctival Bevacizumab in primary pterygium excision. Ophthalmic Res., 2010; 43: 134-8
13. Lekhanont K, Patarakittam T, Thongphiew P, et al., Randomized controlled trial of subconjunctival Bevacizumab injection in impending recurrent pterygium: a pilot study. Cornea, 2012; 31: 155-61.
14. Chowers I, Pèer J, Zamir E, et al., Proliferative activity and p53 expression in primary and recurrent pterygia. Ophthalmology, 2001; 108: 985-8.
15. Chui J, Coroneo MT, Tat LT, et al., Ophthalmic pterygium: a stem cell disorder with premalignant features. Am J Pathol, 2011; 178: 817-27.
16. Karukonda SR, Thompson HW, Beuerman RW, et al., Cell cycle kinetics in pterygium at three latitudes. Br J Ophthalmol, 1995; 79: 313- 7.
17. Ozdemir O, Altintas O, Altintas L, et al., Comparison of the effects of subconjunctival and topical anti VEGF therapy (Bevacizumab) on experimental corneal neovascularization. Arq Bras Oftalmol., 2014; 77: 209-13.
18. Young AL, Leung GY, Wong AK, et al., A randomized trial comparing 0.02% mitomycin C and limbal conjunctival autograft after excision of primary pterygium. Br J Ophthalmol, 2004; 88: 995-7.
19. Gebhardt M, Mentlein R, Schaudig U, et al Differential expression of vascular endothelial growth factor implies the limbal origin of pterygia. Ophthalmology, 2005; 112(6): 1023–30.
20. Ozgurhan EB, Agca A, Kara N, et al Topical application of Bevacizumab as an adjunct to recurrent pterygium surgery. Cornea, 2013; 32(6): 835–8.
21. Wu PC, Kuo HK, Tai MH, et al., Topical Bevacizumab eyedrops for limbal-conjunctival neovascularization in impending recurrent pterygium. Cornea, 2009; 28(1): 103–4.
22. Fallah MR, Khosravi K, Hashemian MN, et al., Efficacy of topical Bevacizumab for inhibiting growth of impending recurrent pterygium. Curr Eye Res., 2010; 35(1): 17–22.
23. Kim SW, Ha BJ, Kim EK, et al., The effect of topical Bevacizumab on corneal neovascularization. Ophthalmology, 2008; 115: e33-8.
24. Manzano RP, Peyman GA, Khan P, et al., Inhibition of experimental corneal neovascularization by Bevacizumab (Avastin) Br J Ophthalmol, 2007; 91(6): 804–7.