



EFFECT OF TOPICAL BEVACIZUMAB ON RECURRENCE FOLLOWING PTERYGIUM SURGERY WITH CONJUNCTIVAL AUTOGRAFT

Dr. Muhammad Khizar Niazi^{1*}, Dr. Kashif Ali², Dr. Saad Mushtaq Malik³, Dr. Farooq Ahmed⁴, Dr. Hifza Masood⁵, Dr. Ifrah Idrees Lodhi⁶

¹FCPS (Ophthalmology), FCPS (Vitreoretina), FRCS Glasg (Ophthalmology), Medical Retina Fellowship (Birmingham, UK), Professor of Ophthalmology, CIMS Medical College Multan, NUMS, Pakistan

²MBBS, FCPS, CHPE, Associate Professor, CIMS Multan, NUMS, Pakistan

³MBBS, FCPS (Ophthalmology), CHPE (NUMS), Consultant Ophthalmologist & Assistant Professor of Ophthalmology, CIMS Medical College, Multan

⁴MBBS, FCPS, Senior Registrar CIMS Multan, NUMS Pakistan

⁵MBBS, FCPS, Registrar Ophthalmology, CMH and CIMS Multan

⁶MBBS, FCPS(I), Resident CMH Multan

***Corresponding author:** Muhammad Khizar Niazi

*Email: khizar_aleem@yahoo.com

Abstract

Objectives:

To determine the efficacy of topical bevacizumab in preventing the recurrence in patients undergoing pterygium surgery with conjunctival autograft.

Study Design: Randomized control trial

Place and duration of study: This study was conducted at the AFIO, MH, Rawalpindi, Pakistan from January 2023 to December 2023 over a period of 1 year.

Methods: A total of 80 patients aging between 20-30 years having Pterygium ≥ 2 mm as per diagnosed using slit lamp microscope and decided for surgery were added in the study through consecutive sampling and randomly distributed in to 2 equal groups including a Bevacizumab group and a Control group. All the patients in both groups underwent pterygium excision surgery through conjunctival autograft procedure. In bevacizumab group, patients received topical bevacizumab 5mg/ml administered in the operated eye at 6-hour intervals for the duration of 1 month. No such post-operative treatment was recommended in control group.

The primary outcome was defined as the number of eyes with the recurrence of the pterygium after 3 months of surgery

Results: Mean age of study population was 26.09 ± 2.7 years with age ranging between 20 to 30 years. Out of total patients 56.3% were males while 43.7% were females. Majority of the patients had Type III pterygium (80%) followed by Type II pterygium (20%). The results of study outcomes show that there was no difference between bevacizumab group and control group regarding recurrence of pterygium as per evaluated after 3 month post-operatively (10% Vs 7.5%, respectively, $p=0.692$).

Conclusion: Topical bevacizumab is not effective in preventing the recurrence in patients undergoing pterygium surgery with conjunctival autograft.

Keywords: Conjunctival autograft, Pterygium, Topical bevacizumab.

Introduction:

Pterygium is a frequent eye ailment reported at ophthalmic outpatient departments, for which the specific pathogenesis origin is yet unclear. The word “Pterygium” is derived from the Greek word "Pterygos," which means "wing," and is a common lesion of the ocular surface. With a wing-like appearance, the lesion is more common at the nasal limbus than the temporal.¹ Numerous plausible variables have been suggested for pterygium, such as exposure to UV radiation, sun exposure, humid and hot environment, genetic predispositions, persistent inflammation, and recently suggested some specific viruses. An underlying issue seems to be limbal cell deficiency, which triggers the release of growth factors that promote new blood vessel formation and cell proliferation. Pterygium was once thought to be a degenerative disorder, but it is now known that the condition is caused by aberrant growth and development of the epithelial cells at the corneo-scleral junction, which results in a fleshy growth on the surface of the cornea.^{1,2}

Various global studies have found the prevalence of pterygium to range widely from 0.7% to 31% and this prevalence rate varies based on the specific population examined. These studies indicate that males are approximately twice as likely to be affected by the condition compared to females. In tropical and subtropical areas, pterygium is more common. In a study conducted in Ethiopia, pterygium prevalence was mentioned to be higher in outdoor workers, widows, persons working under sun/wind exposure, alcohol users and with patients with severe blepharitis.³ Approximately 5.2% of people in India suffer from this illness.^{2,4} Although, detailed updated data not available, a recent study done in Pakistan at regional level shared the prevalence of up to 7.4%.⁵

Pterygium tends to progress gradually over time, with patients occasionally experiencing symptoms such as a gritty or scratchy sensation, discomfort or irritation, itchiness, and excessive tearing or watering of the affected eye. The diagnosis comprise of a comprehensive eye examination consisting of assessment of visual acuity, testing of the extraocular muscle movements and a thorough evaluation of the anterior segment of the eye. Additionally, a detailed refraction needs to be conducted to measure and document any astigmatism that may be present, including the type and degree of astigmatism. A study conducted by Khan B mentioned that pterygia exceeding 1.00 mm from the limbus induces astigmatism, and beyond this the size of pterygium directly correlate with higher amounts of induced astigmatism.^{6,7} The presence of dry eye should be evaluated and ruled out. The pterygium should be thoroughly assessed based on criteria including location on the eye, size of the growth, degree of visible blood vessel formation, how far it extends onto the cornea, and the area of corneal involvement or opacity caused by it. This evaluation can be initially performed using oblique illumination from a bright hand-held light source, and then confirmed and examined in greater detail utilizing slit-lamp biomicroscopy.⁶

There are many surgical removal treatments for primary pterygium including simple excision, conjunctival autograft and adjuvant treatment with antimetabolites such 5-Fluorouracil and Mitomycin C.⁸

Recurrence is the main complaint following the surgical excision as despite of employing numerous surgical methods, the recurrence reported in different studies ranges from 6.7% to 88%. Majority of recent research focuses on identifying preventative methods rather than the recurrence, which is thought to be due to fibroblast proliferation during the healing phase after conjunctival excision.⁹

The research done over this topic shares that due to its impact on endothelial proliferation, Vascular Endothelial Growth Factor (VEGF) may have a significant role in the formation of pterygium. Furthermore, while studying the pterygium, VEGF is found in epithelium, supporting its potential function in pathogenesis.¹⁰ A recombinant humanized monoclonal antibody against VEGF, bevacizumab neutralizes all types of human VEGF and prevents endothelial cell proliferation brought on by VEGF. It is said to have a role in the prevention of pterygium.¹¹

There is, however, variations in opinions shared by international literature regarding role of bevacizumab for preventing the recurrence of pterygium following excision through conjunctival autograft.

No study has been conducted in Pakistan on this important subject. This study was therefore planned to evaluate the role of topical bevacizumab on recurrence following pterygium surgery with conjunctival autograft. These results will help our ophthalmologists to establish evidence based treatment strategy for their patients undergoing pterygium surgery.

Methods:

This randomized control trial was conducted at the AFIO, MH, Rawalpindi, Pakistan from January 2023 to December 2023 over a period of 1 year.

Sample size was calculated using WHO calculator for hypothesis tests for two population proportions using following parameters:

alpha = 5% (two-sided), power = 90%

p1 (Recurrence of Grade 2-4 pterygium in bevacizumab group) =33%

p2 (Recurrence of Grade 2-4 pterygium in placebo group) = 90%.¹²

Estimated sample size: n1 =14, n2 =14

Patients reported with pterygium were gone through slit lamp examination for measuring the size and grading of pterygium. Corrected and uncorrected distance visual acuity was also measured.

A total of 80 patients aging between 20-30 years having pterygium ≥ 2 mm as per diagnosed using slit lamp microscope and decided for surgery were added in this study through consecutive sampling and randomly distributed in to 2 equal groups, a Bevacizumab group and a Control group through computer generated randomization.

Requirement of surgery was decided when there was recurrent episodes of eye irritation and discomfort for at least one month, necessitating surgical intervention for pterygium removal or the pterygium induced significant astigmatism in the patients warranting surgical removal of the pterygium as diagnosed through auto-refraction.

Exclusion criteria was set as patients with a history of chemical injury, patients having any corneal or ocular surface disease, patients with any history of traumatic injury and patients who had undergone pterygium surgery in the past.

All the patients in both groups underwent pterygium excision surgery through conjunctival autograft procedure. The surgical procedure was performed under topical anesthesia using 0.5% proparacaine hydrochloride eye drops. The head of the pterygium was detached from the cornea through blunt dissection utilizing a crescent knife. The body of the pterygium was then meticulously dissected and excised with Westcott scissors. Minimal cauterization was employed to achieve hemostasis, and the resulting defect was reconstructed by transplanting an autologous conjunctival graft harvested from the superior-temporal bulbar conjunctiva for both groups of patients and sutured using size 8/0 vicryl suture. Finally, the eyes were dressed with antibiotic ointment and a protective eye pad. All these procedures were conducted by the same surgeon.

Postoperatively, all patients were prescribed topical antibiotic eye drops (Moxifloxacin 2%, administered three times daily) for a duration of 15 days, as well as topical steroid eye drops (Fluorometholone 0.1%, administered three times daily) for one month.

In bevacizumab group, patients received additional topical bevacizumab 5mg/ml administered in the operated eye at 6-hour intervals for the duration of 1 month.

No such post-operative treatment was recommended in control group.

The primary outcome was defined as the number of eyes with the recurrence of the pterygium after 3 months of surgery (defined as a regrowth of the lesion extending 1mm or more onto the cornea from the limbus).

Corneal recurrence was referred to the regrowth of fibrovascular tissue encroaching onto the cornea, while conjunctival recurrence was characterized by the presence of recurrent blood vessels or fibrous tissue in the excised area without invading the cornea.

Approval of conducting the study was received from the ethical committee of the hospital.

The study purpose was explained and consent for participation was taken from the patients on written forms.

SPSS version 25 was used for the process of data analysis. Quantitative variables were calculated in form of mean and standard deviation. Qualitative variables were expressed in form of frequency and percentage. Chi-square test was employed to assess the statistical significance of differences among outcomes of the 2 groups keeping $p \leq 0.05$ as significant.

Results:

Mean age of patients was 26.09 ± 2.7 years (Range 20-30 years). Out of total patients 56.3% were males while 43.7% were females. The group wise details of demographics are given in Table-I.

Table-I: Demographics
n=80

Demographics		Bevacizumab group n=40	Control group n=40
Age (Mean±SD) years		26.3±2.4	25.88±2.95
Gender	Male n (%)	24 (60)	21 (52.5)
	Female n (%)	16 (40)	19 (47.5)

The details of clinical findings of patients shows that most of the patients had Type III pterygium in both the groups followed by Type II pterygium. The details of clinical findings are shown in Table-II.

Table-II: Clinical findings
n=80

Clinical findings		Bevacizumab group n=40	Control group n=40
Laterality	Right n (%)	21 (52.5)	20 (50)
	Left n (%)	19 (47.5)	20 (50)
Morphological type	III	33 (82.5)	31 (77.5)
	II	7 (17.5)	9 (22.5)
	I	0 (0)	0 (0)
IOP using GAT (Mean±SD) mmHg		15.21±5.42	14.69±6.43

The results of study outcomes show that there was no difference among the bevacizumab group and control group regarding recurrence of pterygium as per evaluated after 3 month post-operatively as shown in Table-III.

Table-III: Study outcomes n=80

Study outcomes		Bevacizumab group n=40	Control group n=40	p-value
Recurrence	Yes n (%)	4 (10)	3 (7.5)	0.692
	No n (%)	36 (90)	37 (92.5)	





Fig-I: Separation of pterygium body from overlying conjunctiva Fig-II: Separation of pterygium head from cornea

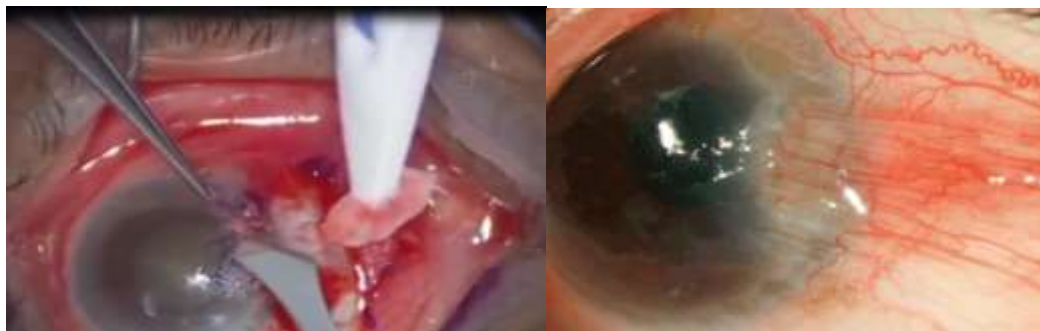


Fig-III: Removal of tissue from cornea Fig-IV: Recurrent pterygium

Discussion:

While various surgical procedures have been proposed to treat pterygia and to reduce the risk of recurrence, all those can potentially lead to several associated disadvantages. The application of Mitomycin C and 5-Fluorouracil, either before or after surgery, has remained an approach for preventing pterygium recurrence, however, this method has been linked to numerous potential complications. In modern ophthalmological practice, the use of conjunctival autografting has become a widespread approach for pterygium surgery, as it is considered a safe and efficacious surgical technique that also yields aesthetically pleasing outcomes. The risk of recurrence still persists in these cases, therefore, methods of preventing recurrence including the use of topical bevacizumab remain important.

In a study, Fallah et al. gave intralesional bevacizumab (2.5mg/0.1ml) injections to 17 pterygium patients. After 3 months, the vascularized corneal area was significantly decreased, there was also 4% statistically significant reduction in pterygium size.¹³

In a study evaluating topical bevacizumab (25mg/ml) eye drops used four times daily for three weeks in cases of impending pterygium recurrence, no recurrences were observed after one year of follow-up. Additionally, symptom resolution occurred with no local or systemic adverse effects reported. The findings suggested topical bevacizumab may effectively prevent recurrence in patients at high risk for pterygium regrowth.¹⁴

Dar MY studied the benefits of using bevacizumab subconjunctival injection 1.25 mg/0.05 ml one week prior to pterygium surgery. The results of this study showed the benefits in terms of improved grade, size and intensity of pterygium. However, no statistically significant difference was observed in the recurrent of pterygium in the study group and the placebo group (6.67% Vs 10%, $P > 0.05$).¹⁵

In another study, Fallah et al. studied the effect of topical bevacizumab for preventing recurrence in 54 patients undergoing pterygium surgery. Patients in both the groups, with topical bevacizumab or without it, had recurrence within 3-6 months, but bevacizumab delayed corneal invasion.¹⁶

Hwang S compared the efficacy of topical mitomycin C, cyclosporine, bevacizumab and a control group in preventing the recurrence after pterygium surgery. The study showed that after 6 months of follow up, no difference was recorded in the incidence of recurrence in between the bevacizumab 2.5% used for 3 months and the control group (41.7% Vs 45.5%, $=0.751$).¹⁷

Motarjemizadeh Q compared the efficacy of different concentration of topical bevacizumab and found that the dosage of 5mg/ml was significantly less effective than 10 mg/mL in preventing the recurrence of pterygium.¹⁸

Kasetsuwan N evaluated the efficacy of topical 0.05% bevacizumab as an adjunct after primary pterygium excision. A total of 22 patients were randomized to either receive bevacizumab or placebo. At 3 months follow up time, there was difference in conjunctival and overall recurrences rate but no significant difference in corneal recurrence was found between the 2 groups (8.33% in the bevacizumab group Vs 30% in placebo group (p=0.293).¹²

The Mean age of participants in our study was 26.09±2.7 years with age ranging between 20 to 30 years. The number of male patients was 45 (56.3%) while female patients were 35 (43.7%). Majority of the patients had Type III pterygium (80%) followed by Type II pterygium (20%). The results of this study outcomes show that there was no difference between bevacizumab group and control group regarding recurrence of pterygium as per evaluated after 3 month post-operatively (10% Vs 7.5%, respectively, p=0.692).

The results of our study are in line with the studies conducted by Dar MY, Hwang S, Motarjemizadeh Q and Kasetsuwan N and confirms that administration of topical bevacizumab 5mg/ml at 6 hours interval for one month doesn't help in preventing the recurrence in patients undergoing pterygium surgery with conjunctival autograft.^{12,15,17,18}

The limitations of this study includes the small sample size and short term follow up. Future studies with larger sample size and longer follow ups will add up to the use full data on this important subject.

Conclusion:

The results of this study share that topical bevacizumab application has no significant effect on the recurrence rate of pterygia. Future work on approaches like intra-operative or postoperative subconjunctival bevacizumab injections combined with topical treatment and targeting additional growth factors involved in pterygium pathogenesis may be useful in this regard.

Conflict of interest:

No

Disclaimer:

No

Acknowledgments:

The services of departmental staff in taking and maintaining the patient record are acknowledged.

References:

1. Celebi AR, Ozbey C, Mirza GE. The role of mast cells in vascularized recurrent pterygium. *Arq Bras Oftalmol.* 2014;77:285-7.
2. Rezvan F, Khabazkhoob M, Hooshmand E, Yekta A, Saatchi M, Hashemi H. Prevalence and risk factors of pterygium: a systematic review and meta-analysis. *Surv Ophthalmol.* 2018;63(5):719-735. doi: 10.1016/j.survophthal.2018.03.001.
3. Kassie Alemayehu T, Addis Y, Yenegeta Bizuneh Z, Mulusew Tegegne M, Alemayehu AM. Prevalence and Associated Factors of Pterygium Among Adults Living in Kolla Diba Town, Northwest Ethiopia. *Clin Ophthalmol.* 2020;14:245-255. doi: 10.2147/OPTH.S239982.
4. Gupta A, Maurya R P, Manisha, Kadir S M U, Patel A, Devi A, Patel E, et al. Recent update on pterygium. *IP Int J Ocul Oncol Oculoplasty.* 2022;8(2):95-108.
5. Haq I, Durra M, Tahir M. Prevalence of Pterygium among Welders in Okara District. *Ophthalmol Update.* 2020;18(2):25-27.
6. Sarkar P, Tripathy K. Pterygium. [Updated 2023 Aug 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK558907/>.
7. Khan B, Sohail A, Faridi TA, Jan U, Zahid F, Parveen I. Relation between different grades of pterygium and amount of induced corneal astigmatism: Different grades of pterygium. *Pak*

- Bio Med J. 2021;4(2):59-63. Available from: <https://www.pakistanbmj.com/journal/index.php/pbmj/article/view/74>.
8. Akbari M. Update on overview of pterygium and its surgical management. *J Popul Ther Clin Pharmacol.* 2022;29(4):e30–e45.
 9. Palewski M, Budnik A, Konopińska J. Evaluating the Efficacy and Safety of Different Pterygium Surgeries: A Review of the Literature. *Int J Environ Res Public Health.* 2022;19(18):11357. doi: 10.3390/ijerph191811357.
 10. Liu C, Song Y, Wang X, Lai Z, Li C, Wan P, et al. The Key Role of VEGF in the Cross Talk between Pterygium and Dry Eye and Its Clinical Significance. *Ophthalmic Res.* 2020;63(3):320-331. doi: 10.1159/000503636.
 11. Razeghinejad MR, Banifatemi M. Subconjunctival bevacizumab for primary pterygium excision; a randomized clinical trial. *J Ophthalmic Vis Res.* 2014;9:22-30
 12. Kasetsuwan N, Reinprayoon U, Satitpitakul V. Prevention of Recurrent Pterygium with Topical Bevacizumab 0.05% Eye drops: A Randomized Controlled Trial. *Clin Ther.* 2015;37:2347-51.
 13. Fallah Tafti MR, Khosravifard K, Mohammadpour M, Hashemian MN, Kiarudi MY. Efficacy of intralesional bevacizumab injection in decreasing pterygium size. *Cornea* 2011;30:127-9.
 14. Wu PC, Kuo HK, Tai MH, Shin SJ. Topical bevacizumab eyedrops for limbal- conjunctival neovascularization in impending recurrent pterygium. *Cornea.* 2009;28(1):103–4.
 15. Dar MY, Bhat MZ. The Outcome of Preoperative Subconjunctival Bevacizumab Injection In Pterygium Surgery. *Int J Curr Adv Res.* 2022;11(06):1123-6. DOI: <http://dx.doi.org/10.24327/ijcar.2022.1126.0251>.
 16. Fallah MR, Khosravi K, Hashemian MN, Beheshtnezhad AH, Rajabi MT, Gohari M. Efficacy of topical bevacizumab for inhibiting growth of impending recurrent pterygium. *Curr Eye Res* 2010;35:17-22.
 17. Hwang S, Choi S. A Comparative Study of Topical Mitomycin C, Cyclosporine, and Bevacizumab after Primary Pterygium Surgery. *Korean J Ophthalmol.* 2015 Dec;29(6):375-81. doi: 10.3341/kjo.2015.29.6.375.
 18. Motarjemizadeh Q, Aidenloo NS and Sepehri S. A comparative study of different concentrations of topical bevacizumab on the recurrence rate of excised primary pterygium: a short-term follow-up study. *Int Ophthalmol.* 2016;36:63–71.