

## A Randomized Controlled Prospective Study to Assess the role of Subconjunctival Bevacizumab in Preventing Recurrence in Primary Pterygium Excision

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### **Abstract**

**Purpose:** To evaluate the safety and efficacy of subconjunctival bevacizumab on preventing the recurrence in primary pterygium excision

**Methods:** This randomized, placebo controlled clinical trial was conducted on 40 eyes of 40 patients attending the ophthalmology OPD, Rajindra Hospital Patiala, randomized to Group 1 (bevacizumab) 20 patients and Group 2 (balanced salt solution) 20 patients. Group 1 underwent pterygium excision and received a total of 0.5ml subconjunctival bevacizumab (2.5mg/0.1ml on the day of surgery). Group 2 received balanced salt solution in the same manner. Recurrence defined as any fibrovascular tissue crossing the limbus, and the number of patients with >1.5mm fibrovascular overgrowth on the cornea were compared between the study groups.

**Results:** There were no statistically significant differences between the groups for all measured variables except for the statistically significant rise in IOP in group 1 at the one week visit. Four patients in each group at the three- and six-month visits, respectively, had more than 1.5 mm fibrovascular tissue overgrowth on the cornea. Four eyes in group 1 and 2 experienced recurrence (p=1) at month 3 and thereafter.

**Conclusion:** Subconjunctival Bevacizumab had no significant effect on the recurrence rate of primary pterygium excision and was not associated with any adverse effects.

**Keywords:** Bevacizumab; Pterygium; Pterygium Recurrence; Neovascularisation

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### **I. Introduction**

A pterygium is a triangular 'wing-like' growth consisting of conjunctival epithelium and hypertrophied subconjunctival connective tissue that occurs nasally in the interpalpebral fissure, encroaching onto the cornea with unknown pathology.<sup>[1,2]</sup>

Pterygium may be defined as primary or recurrent, the latter may occur several weeks to months after excision of a primary pterygium. A pterygium consists of a 'head' at its apex, an avascular cap and body. Tan et al.<sup>[3]</sup> developed a simple clinical slit-lamp grading scale based on relative translucency of the body of the pterygium, which was predictive of recurrence. In this grading, T1 (atrophic) denotes a pterygium in which episcleral vessels underlying the body of the pterygium are unobscured and clearly distinguished. Grade T3 (fleshy) denotes a thick pterygium in which episcleral vessels underlying the body of the pterygium are totally obscured by fibrovascular tissue. Pterygia in which the episcleral vessel details are indistinctly seen or partially obscured are categorized as grade T2 (intermediate).

Pterygium occurs commonly in warm and dry climate with commonest age of onset appears to be in the 20s and 30s.<sup>[4,5,6,7]</sup>

The major environmental risk factor for the development of pterygium is exposure to UV light which is absorbed by the cornea and conjunctiva promoting cellular damage and subsequent cellular proliferation.<sup>[7-10]</sup> Another risk factors include genetic factors, dust, low humidity, and microtrauma from particulate matter, dry eyes and the human papilloma virus.<sup>[11-13]</sup>

Pterygium is characterized by abnormal subepithelial tissue containing altered collagen fibres hence described as "elastotic degeneration".<sup>[14-16]</sup>

A number of treatment methods have been described which includes adjunctive medical methods (mitomycin c, 5- fluorouracil, daunorubicin, thiotepa drops, and cyclosporine drops instillation), beta irradiation and surgical methods (conjunctival autograft, amniotic membrane grafts, conjunctival flaps, bare sclera technique, and excision with lamellar keratoplasty).<sup>[17]</sup> It has been well- established that pterygia are composed of proliferating fibrovascular tissue and the pterygium formation, and progression require neovascularization, many molecules regulate angiogenesis have been identified, suggesting that the vascular endothelial growth factor (VEGF) may be involved directly or indirectly in the pathogenesis of pterygia.<sup>[18]</sup> Various studies have shown that recurrence is high from 30% to 88% after simple excision in pterygium and in excision with bare sclera it may be 32%.<sup>[19]</sup> VEGF has been detected in increased amounts in pterygium epithelium, compared with normal conjunctiva by studies employing immunohistochemistry.<sup>[20]</sup>

Bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA, USA) is a recombinant, humanized anti-VEGF antibody that binds all VEGF isoforms and exerts a neutralizing effect by inhibiting the VEGF-receptor interaction. It has been suggested as a possible adjunctive therapy for pterygium excision that decreases the vascularity of newly formed blood vessels, hence decreasing the recurrence rate and appears to have a role in prevention of recurrence.<sup>[21]</sup> In this study we evaluated the effect of a 2.5 mg dose of subconjunctival bevacizumab on the recurrence rate of primary pterygium excision.

## **II. Methods**

This randomized, placebo-controlled clinical trial was conducted on the patients attending the ophthalmology OPD of Rajindra hospital Patiala from July 2015 to July 2016 with recurrent pterygium. Written informed consent was obtained from all patients and they were explained about the possible consequences. We interviewed the patient before hand to obtain information like personal data, contact number, any medical or ocular history, any history of drug allergy.

### **Inclusion Criteria**

1. Decreased visual acuity due to involvement of the visual axis
2. Discomfort and irritation unresponsive to lubricants
3. Restricted ocular motility
4. Cosmetic concerns
5. More than 3 mm extension of the pterygium over the cornea.

### **Exclusion Criteria**

1. Patients with dry eye syndrome
2. Patients with collagen vascular disease
3. Patients with pseudopterygium
4. Ocular surface disorders or infections
5. Previous ocular surgery
6. Allergy to Bevacizumab

All the patients underwent slit lamp examination to rule out any ocular surface disorder. Best corrected visual acuity (BCVA), manifest refraction and keratometry (Topcon Medical Systems, Inc.), IOP (measured by schiottz indentation tonometry), detailed slit lamp examination including horizontal length of the pterygium in mm, and fundus examinations was done. Routine investigations like blood pressure, random blood sugar was done to all the patients. Topical antibiotic was started prior to the day of surgery.

The following conditions were regarded as risk factors for recurrence: inflamed pterygium, occupations with considerable solar exposure, recurrent pterygium in the fellow eye, arcus senilis and age < 30 years.<sup>[22]</sup> We randomized the patients into 2 groups. Patients in group 1 (bevacizumab group) underwent pterygium excision with a rotational conjunctival flap, and received 2.5 mg subconjunctival bevacizumab ( 2.5 mg/0.1 ml on the day of surgery). Patients in group 2 also had pterygium excision and a rotational conjunctival flap but received 0.2 ml balanced salt solution (BSS) at the end of surgery but no more injections thereafter.

Post-excision, the patients were examined at day 1, week 1, and months 1, 3, and 6 by the same examiner who was blind to the groups (second author). In postoperative visits, the following factors were evaluated: horizontal dimension of the corneal epithelial defect in mm, conjunctival congestion, conjunctival flap status (retraction, melting, or infection), refraction, keratometry, IOP, and recurrence (defined as more than 1.5 mm of fibrovascular tissue overgrowth on the cornea and any fibrovascular tissue crossing the limbus).<sup>[22,23]</sup>

### **Surgical Technique**

The surgery was performed under local anaesthesia. To accomplish anaesthesia, after instilling paracaine eye drops, subconjunctival lignocaine/ epinephrine was injected under the area of the pterygium, and the injected lignocaine was directed to the area of conjunctival flap harvest in the superonasal quadrant using a cotton-tip applicator. The pterygium was excised from its conjunctival side, and the corneal component was peeled off. After excision of the pterygium, a pedunculated conjunctival flap devoid of Tenon's capsule was created from the adjacent superior conjunctiva and was placed over the bare sclera and sutured with 8-0 Vicryl sutures. At the end of the surgery, 0.5 ml bevacizumab (2.5 mg) or BSS was injected in the inferior fornix depending on randomization. Postoperatively, a topical antibiotic (1% moxifloxacin, four times daily), a corticosteroid (0.1% betamethasone, four times daily), and artificial tears (hydroxypropyl methylcellulose, four times daily) were initiated and tapered over the course of 4 weeks. All sutures were removed at the one month visit.

### III. Results

The study was conducted on 40 eyes of 40 patients with 20 eyes in each group. All patients completed the postoperative visits, except three who were lost to follow-up at month three and another subject at month six. There was no statistically significant difference between the study groups in terms of demographic data, operated eye, horizontal size of the pterygium, duration of daily sun exposure, preoperative BCVA, keratometric readings, corneal astigmatism, and IOP (Table 1). Regarding recurrence risk factors, there was also no significant difference between the study groups (Table 2).

As shown in Table 3 the recurrence rate of pterygium, changes in keratometry, corneal astigmatism, and conjunctival congestion in both groups revealed no statistically significant difference. Although no statistically significant difference was seen between groups for recurrence at all postoperative visits, the number of patients who had fibrovascular tissue crossing the limbus in group 2 was twice that of group 1 (7 versus 4 at three months and 8 versus 4 at six months). Locally, no necrosis, ischemia, infection in the surgical bed area, or conjunctival retraction and melting developed. Although baseline IOP was similar in both groups, patients in group 1 experienced a statistically significant rise at week one postoperatively (P=0.008). IOP returned to baseline levels in later visits with no intervention (Figure 1). The mean ± standard deviation of keratometric readings on the first postoperative month in group 1 was 42.95±12.08 mm which was not significantly different from that of group 2 (42.6±11.70 mm, P=0.080). Corresponding figures at the three and six monthly visits were also non-significant(P=0.591 & P=0.934 respectively). Post-operative corneal astigmatism also failed to reach a statistically significant difference.(P=0.836)

Table 1:

**Table 1.** Demographics and ocular characteristics of the study patients

	Group 1	Group 2	X <sup>2</sup>	p value
Number	20	20		
Gender (Female/Male)	9/11	10/10	1.82	0.178
Eye (Right/Left)	8/12	5/15	0.94	0.801
Age (Years)	40.71±7.06	43.45±9.38	0.01	0.913
Sun exposure per day (hours)	4.28±1.25	4.35±1.14	1.15	0.283
Horizontal pterygium size (mm)	2.95±1.10	2.65±1.23	0.16	0.689
Preoperative BCVA (logMAR)	0.09±.05	0.14±0.15	1.01	0.316
Preoperative corneal astigmatism (diopters)	2.15±1.14	1.45±1.00	1.17	0.280
Preoperative IOP (mmHg)	13.12±1.12	14.17±1.16	0.184	0.668

BCVA, best corrected visual acuity; IOP, intraocular pressure Values are presented in mean ± standard deviations

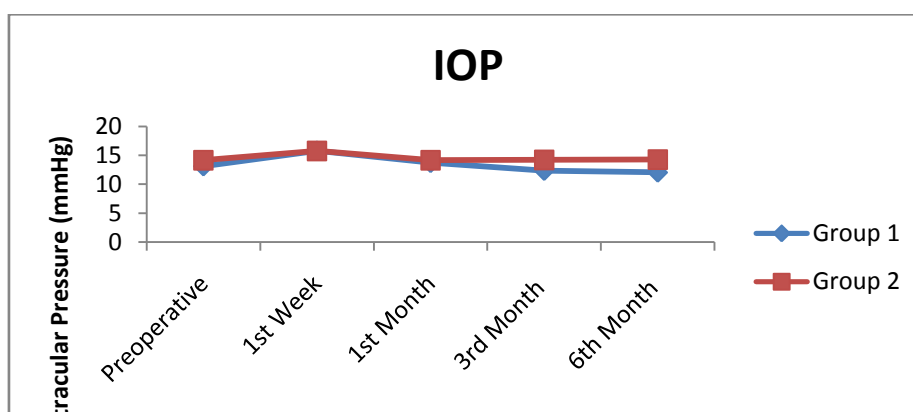
**Table 2.** Prevalence of risk factors for recurrence of pterygium in groups 1 and 2

	Group 1	Group 2	p value
Inflamed pterygium	2	3	1.00
Occupations with considerable solar exposure	5	5	1.00
Recurrent pterygium in fellow eye	0	2	0.481
Arcus senilis	2	2	1.00
Age <30 years	3	2	1.00
No risk factor	10	8	0.542

**Table 3.** Recurrence of pterygium and changes in keratometry, and corneal astigmatism over the postoperative course in groups 1 and 2

	Preoperative				Month 1				Month 3				Month 6			
	Group 1	Group 2	p value		Group 1	Group 2	X <sup>2</sup>	p value	Group 1	Group 2	X <sup>2</sup>	p value	Group 1	Group 2	X <sup>2</sup>	p value
Recurrence (any fibrovascular overgrowth on the corn)	--	--	-	--	1/20 (5%)	2/20 (10%)	0.59	0.561	3/19 (15.79%)	7/19 (36.84%)	1.477	0.148	4/18 (22.22%)	8/19 (42.10%)	1.713	0.095

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Recurrence (> 1.5 mm fibrovascular overgrowth on the cornea)	--	--	-	--	--	--	--	--	4/19 (21.05%)	4/19 (21.05%)	0	1.00	4/18 (22%)	4/19 (21.05%)	0.0	0.9
Keratometry (Mean ± SD)	42.45 ± 1.27 (2.52)	42.15 ± 10.74 (2.40)	0.8	0.932	42.95 ± 12.08 (2.70)	42.65 ± 1.70 (2.62)	0.080	0.937	44.05 ± 11.87 (2.65)	42.05 ± 11.44 (2.56)	0.542	0.591	42.25 ± 11.58 (2.59)	41.95 ± 11.28 (2.52)	0.083	0.934
Conjunctival congestion (Mean ± SD)					0.09 ± 0.23	0.24 ± 0.33	1.723	0.093	0.12 ± 0.24	0.19 ± 0.30	0.808	0.424	0.09 ± 0.24	0.22 ± 0.31	1.486	0.146
Corneal astigmatism (Mean ± SD)	2.25 ± 1.25	1.65 ± 0.82	1.798	0.080	1.15 ± 0.74	1.20 ± 0.77	0.209	0.836	1.25 ± 1.02	1.20 ± 0.95	0.161	0.873	1.55 ± 1.09	1.35 ± 0.99	0.605	0.549



#### IV. Discussion

The high rate of recurrence of pterygium post excision makes it a difficult task to manage. Since VEGF plays an important role in the pathogenesis of the pterygium, hence it was thought that Anti-VEGF could be beneficial. The present study was conducted to evaluate the safety and efficacy of subconjunctival bevacizumab on the recurrence rate of pterygia when used as an adjunct to primary excision and a rotational conjunctival flap. This is compatible with some other studies reporting no beneficial effect from bevacizumab administration on prevention of pterygium recurrence.

In the present study, all patients were followed for at least 6 months. Recurrence was defined as any fibrovascular growth of conjunctival tissue extending more than 1.5 mm across the limbus. The recurrence rate in both groups was similar and no serious ocular side effect was observed.

A study conducted at Ophthalmology Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt by Maha MS et al concluded that intraoperative subconjunctival bevacizumab following primary pterygium excision is not useful and possibly harmful hence larger studies are needed<sup>[24]</sup>

Another study by Razeghinejad M.R conducted at Department of Ophthalmology, Khalili Hospital, Shiraz University of Medical Sciences concluded that a single intraoperative subconjunctival bevacizumab injection had no effect on recurrence rate or early postoperative conjunctival erythema, lacrimation, photophobia or healing of corneal epithelial defects following pterygium excision.<sup>[25]</sup>

A study by Sonia D et al showed that Bevacizumab does not improve recurrence rates for pterygia when used as an adjunctive therapy postoperatively. It may even cause increased rates of recurrence, although further studies are needed before arriving at this conclusion.<sup>[26]</sup>

Another study conducted by Mohammad-Reza et al revealed that subconjunctival bevacizumab injections had no statistically but a probably clinically significant effect on the recurrence rate of pterygia.<sup>[27]</sup>

## V. Conclusion

In conclusion, this study found that although subconjunctival Bevacizumab was not associated with any local adverse effects but it failed to show any significant reduction in primary pterygium recurrence. The limited number of patients, lack of routine follow-up and the difficulty in measuring the size of pterygium before and after excision were the shortcomings of the study.

However, it does not imply that Bevacizumab has no role in the management of pterygium. Newer anti-angiogenic therapies will hopefully give better results in the future.

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