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Effect of Subconjunctival Injection of Bevacizumab in Preventing Recurrence of Pterygium before and after Surgical Removal

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ABSTRACT

Background: Recurrence, which is indicated by the expansion of fibrovascular tissue past the limbus and onto the cornea, is the main worry in pterygium surgery. Several techniques have been put forth to slow the pace of recurrence. Pterygium recurrences typically occur within the first three months following surgery.

Objective: To evaluate the efficacy of a protocol based on applying two 2.5 mg/ml bevacizumab injections, before and after surgery, as adjuvant therapy of surgical pterygium excision to assess its role in preventing the recurrence of pterygium.

Patients and Methods: A randomized control study was conducted on 84 patients. Complete ophthalmic examinations were performed on all patients, including the following: history, visual acuity, slit lamp examination, intraocular pressure (IOP) measurement, fundus examination, and Refraction by Auto refractometer.

Results: The recurrence rate was significantly lower in the group that underwent pre- and postoperative bevacizumab injection. Moreover, we observed improvements in dimensions and vascularization of pterygium one week after the first subconjunctival injection. In our study, there were some postoperative complications; most of them in the pretreated group were related to pterygium surgery, such as subconjunctival hemorrhage, photophobia, and conjunctival injection. All of these complications occurred in both groups, but with the use of bevacizumab the field was less vascular, and the subconjunctival hemorrhage was less remarkable in the pretreated group than in the control group.

Conclusion: Dimensions and vascularization of pterygium significantly decreased one week after the first subconjunctival bevacizumab injection. The recurrence rate was significantly decreased in the group that underwent pre- and postoperative bevacizumab injection.

Keywords: Subconjunctival Injection, Bevacizumab, Recurrence, Pterygium, Surgical Removal.

INTRODUCTION

Pterygium, which is characterised by fibrovascular conjunctival tissue spreading from the bulbar conjunctiva towards the cornea, is one of the most prevalent ocular surface illnesses. It restricts eye mobility, leads to dry eye, discomfort, a feeling of a foreign substance in the eye, and can even reduce visual acuity [(1)]. Although it seldom affects people under the age of twenty, it affects men more frequently than women [(2)].

The first time pterygia was shown to express vascular endothelial growth factor (VEGF) was in 2001[(3)]. VEGF levels in pterygia are greater than in normal conjunctiva [(4)].

This raises the possibility that pterygia sufferers may benefit from anti-VEGF medications. The Food and Drug Administration (FDA) has authorised bevacizumab, a recombinant humanised monoclonal antibody against VEGF, for the treatment of tumours. Numerous studies were conducted to evaluate the safety and effectiveness of bevacizumab in the treatment of pterygium, with contradictory results [(5)]. After pterygium excision, bevacizumab and other anti-VEGF medications were utilised either as a main therapy or an adjuvant therapy. Additionally, it has been used topically and subconjunctivally [(6)]. Anti-VEGF medications have been utilised to treat early recurrent pterygium as well as perioperative adjuvants [(7)].

Our aim in this study was to evaluate the efficacy of a protocol based on applying two 2.5 mg/ml bevacizumab injections, before and after surgery, as adjuvant therapy of surgical pterygium excision to assess its role in preventing the recurrence of pterygium.

PATIENTS AND METHODS

Type of study: A randomized controlled study.

Study settings: Suez Canal University Hospitals, Ophthalmology Department, Faculty of Medicine.

Study population: All patients who attended to Ophthalmic Outpatient Clinic and matched our inclusion criteria were enrolled in our study.

Inclusion criteria:

- Patients with primary pterygium.
- Age 18-70 years old.
- Both sex.
- Able to provide an informed consent and to complete the follow-up period.

Exclusion criteria:

- Congenital corneal diseases such as keratoconus patients, microcornea, and megalocornea.
- Patients with active ocular disease such as severe dry eye, corneal ulcer.
- Patients with corneal opacities and corneal dystrophies.
- History of ocular trauma or intraocular surgery.

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- Patients with any conjunctival neoplasms.
- Patients with collagen diseases.

Sample size:
The required sample size is 38 participants per group. After accounting for 10% non-response rate, 42 participants per group were required.

Methodology:
Complete ophthalmic examinations were performed on all patients, including the following:
History: Personal, ocular, and systemic history.

Examination:

- **Visual acuity:** uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA) using Landolt's chart.
- **Refraction:** For the purpose of determination of the degree of refraction, cycloplegic refraction was measured with an auto refractometer (NIDEK AR-600, Japan).
- **External eye examinations:** lids, orbit, lacrimal system, and ocular motility.
- **Slit-Lamp biomicroscopic examination** (Topcon -Japan)**:** a complete examination of the anterior segment performed for cornea, sclera, anterior chamber, iris, pupil, and lens.
- **Intraocular pressure measurement:** using Goldman applanation tonometer (Keeler, UK).

Fundus examination:

- Indirect ophthalmoscope (TOPCON ID-5).
- Volk's non-contact double aspheric biconvex lens (power: + 90).

Procedure:
The surgical technique for all patients in both groups featured: (1) Topical anaesthesia with eye drops, followed three minutes later by subconjunctival anaesthesia (lidocaine 2%) injection using an insulin syringe in the region around the pterygium (5 mm from the limbus. (2) Pterygium excision, beginning with the head and continuing with the body. (3) Exposition of a small, triangular-shaped bare scleral bed (with a base at the limbus level and 1mm-wide borders).

Patients were randomized into two groups:
Group A: 42 eyes received two subconjunctival bevacizumab injections (2.5 mg/0.1 ml), the first 7 days before pterygium excision and the second immediately after surgery. Bevacizumab injections for subconjunctival use were extracted from 100 mg commercially available vials. The first injection was performed at the level of the body of the pterygium, while the second injection was applied at the level of the apex and the margins of the excision triangle.
Group B: 42 eyes were enrolled in the control group and did not receive subconjunctival injections. Patients of both groups were treated with tobramycin and dexamethasone eye drops and lubricant eye drops three times daily for three weeks after surgery.
All patients were monitored for six months, to determine the recurrence frequency of pterygium among the study groups. Before the surgical excision on the seventh day, changes in vascularization and pterygia dimensions were assessed after the first injection. The pterygium's dimensions were calculated by dividing its area by its length in millimetres (from the base, which is regarded to be at the level of the caruncle, to the apex, which is considered to be at the most prominent position on the cornea) and width in millimetres at the base and apical regions [(8)].
We contrasted photographs obtained at the slit lamp at the registration visit with those taken seven days following the initial subconjunctival bevacizumab delivery in order to identify changes in vascularization after the first injection.

All images were graded for vascularization using the following system [(9)]: (1) Grade I (atrophic): distinct episcleral vessel underneath the pterygium body. (2) Grade II (intermediate): Under the pterygium's body, there are some visible episcleral vessels. (3) Grade III (fleshy): Under the pterygium's body, occluded episcleral vessels.
Follow-up visits were scheduled for one day, week, 1, 3, and 6 months. Recurrence was defined by the growth of fibrovascular tissue extending more than 1 mm across the limbus.

Ethical considerations:
The Local Research Committee, the Studies Committee, and the Research Ethics Committee of the Faculty of Medicine Suez Canal University all approved the study's protocol before it could be carried out. All patients provided written, voluntarily informed consent. The conduct of this study was governed by the Declaration of Helsinki, the World Medical Association's rule of ethics for human subjects research.

Statistical Analysis
Microsoft Excel software was used to code, input, and analyse historical data, critical clinical examinations, laboratory investigations, and outcome measurements. SPSS version 24.0 programme was then used to import the data and perform analysis. According to the type of data, qualitative were represented as number and percentage and were compared by Chi-square test (X^2), and quantitative continous group were represented by mean±SD and were compared by paired t-test. The p-value was set at <0.05 for outcomes that were significant and 0.01 for those that were highly significant.

RESULTS
Table 1 shows that there was no significant difference regarding age and sex distribution.

Table (1): Age and sex distribution between studied groups

			Group A	Group B	P-Value
Age			39.76±7.36	37.42±7.68	0.159
Sex	**Female**	N	21	18	
		%	50.0%	42.9%	
	Male	N	21	24	0.51
		%	50.0%	57.1%	
Total		N	42	42	
		%	100.0%	100.0%	

Table 2 shows no significant difference found between groups regarding side distribution.

Table (2): Side distribution between studied groups

			Group A	Group B	P-Value
Side	**Left**	N	19	20	
		%	45.2%	47.6%	
	Right	N	23	22	0.82
		%	54.8%	52.4%	
Total		N	42	42	
		%	100.0%	100.0%	

Table 3 shows that vascularity and dimensions significantly decreased from pre to post-injection.

Table (3): Vascularity and dimensions distribution pre and post-first bevacizumab injection in group A only

	Pre first injection	Post first injection	Paired t	P-Value
Pterygium vascularity	2.59±0.46	2.11±0.67	5.59	<0.01**
Pterygium dimensions	59.89±1.98 mm	57.17±1.99 mm	47.71 mm	<0.01**

**: Highly significant

Table 4 shows no significant difference between groups after first and third months, while after six months, group B was significantly associated with higher frequency of recurrence than group A.

Table (4): Recurrence distribution between studied groups

		Group A	Group B	P-Value
Recurrence after 1 month	N	0	2	0.15
	%	0.0%	4.8%	
Recurrence after 3 months	N	3	5	0.46
	%	7.1%	11.9%	
Recurrence after 6 months	N	4	11	0.046*
	%	9.5%	26.2%	

DISCUSSION

This study was intended to evaluate the efficacy of 2.5 mg/0.1 ml bevacizumab injections applied before and after pterygium excision surgery with bare sclera technique in preventing postoperative recurrence. The bare sclera technique has been chosen for this study because it is easy to perform and usually associated with higher recurrence rates, thus proving that surgery alone cannot be sufficient to prevent a recurrence. We chose not to administer any injection/placebo prior/after surgery in the control group since we intended to prevent any inflammatory response related to the injection that might influence the recurrence rate in this group. Furthermore, different excision techniques, even if featured with lower recurrence rate, may be associated with problems such as conjunctival graft edoema, graft necrosis, hematoma, tenon's pyogenic granuloma, corneoscleral dellen, epithelial inclusion cysts, donor site fibrosis (for conjunctival autografting and application of amniotic membrane, as well)[10].

Additionally, rotational conjunctival autografting is ineffective when there are significant scleral bare spots following excision [11]. The possibility of amniotic membrane contamination and subsequent failure is still there and cannot be disregarded in the context of amniotic membrane transplantation [12].

Additionally, the use of amniotic membranes is linked to increased prices and less availability. Adjunctive medications for pterygium excision include strategies to block the fibrovascular actions that are essential in recurrence. In order to avoid a recurrence of the pterygium, mitomycin C was applied to the scleral bed for three minutes [13]. The risks of this treatment, aside from the high expenses, include sclera ulcerations, necrotizing scleritis, perforation (more common in myopic eyes, maybe because the scleral walls are thinner), iridocyclitis, cataract, glaucoma, scleral calcification, and eye loss. This makes mitomycin C less completely safe and more challenging to give [14,15].

Over time, controlling recurring pterygium has proven to be safer and more efficient with the use of a single modest pre/intraoperative dose of mitomycin C. However, adverse effects including scleral thinning and delayed epithelization (>2 weeks) are still conceivable [16]. Additionally, if mitomycin C treatment is involved, melting of conjunctival or amniotic membrane transplant is still feasible, undermining the effectiveness of these procedures [17].

In earlier trials, bevacizumab subconjunctival treatment and surgical removal appeared to be well tolerated [18]. After several subconjunctival bevacizumab injections, there haven't even been any documented problems in our trial. Conjunctival hemorrhage and other minor adverse effects of bevacizumab subconjunctival injections have been documented, however due to the small sample sizes in

earlier trials, it is still unclear if these side effects are safe and whether they will last over the long term.

There is currently no agreement on the procedure that has to be followed, though. **Shenasi *et al.*** [19] did another trial testing subconjunctival bevacizumab injections following pterygium removal with bare sclera method. No notable side effects of bevacizumab have been seen throughout those investigations, however on that occasion, a single dose of a lower dosage of the drug was administered. According to **Razeghinejad *et al.*** [20], one intraoperative subconjunctival bevacizumab injection (1.25 mg/0.1 ml) did not change the recurrence rate.

It has been suggested to repeat the injection after the operation and use a higher dose of bevacizumab since a single low-dose bevacizumab injection, either preoperative or postoperative, showed no efficacy, likely because of the transient effects of anti-VEGF drugs related to their short half-life.

After a 1-year follow-up, the results of **Nava-Castañeda *et al.*** [21] study on the effectiveness of 2.5 mg/0.1 ml of conjunctival autograft and two subconjunctival bevacizumab injections (the first one right after surgery and the second one after 15 days) in minimising disease recurrence were good. Another investigation by **Ozsutcu *et al.*** [22] assessed the use of an intraoperative bevacizumab injection, with the precise dose linked with pterygium excision with rotating conjunctival flap followed by another injection after 1 week, reporting considerably less recurrence than rotational flap alone.

No side effects related to bevacizumab injection were observed in any previous study [23,24]. In our study, the recurrence rate was significantly lower in the group that underwent pre- and postoperative bevacizumab injection. Moreover, we observed improvements in dimensions and vascularization of pterygium one week after the first subconjunctival injection. Therefore, preoperative bevacizumab application may induce several morphological changes that facilitate the following surgical excision.

Even **Fallah *et al.*** [25] assessed the effectiveness of intralesional bevacizumab injection (2.5 mg/0.1 ml) in decreasing the size of pterygia and discovered that it was generally successful and well tolerated (mean decrease of lesion size was 3.97±3.84%). However, because the benefits of bevacizumab may be temporary, a second injection is necessary to terminate the acute fibrovascular phase, which starts right after surgery and may be the cause of the recurrence.

CONCLUSIONS

The subconjunctival administration of bevacizumab resulted in a significant reduction in both the dimensions and vascularization of pterygium after one week. Moreover, the group that received pre- and postoperative bevacizumab injections exhibited a significant reduction in the recurrence rate.

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Competing interests: Nil.

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