THE EFFECT OF DIFFERENT DOSES OF SUBCONJUNCTIVAL BEVACIZUMAB ON THE RECURRENCE RATE OF EXCISED PRIMARY PTERYGIUM

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ABSTRACT

Purpose: To evaluate the safety of different doses of subconjunctival bevacizumab and their effects on the recurrence rate after primary pterygium excision.

Methods: This prospective randomized placebo-controlled clinical study was conducted on 59 eyes (59 patients). The visual acuity, refractive astigmatism, horizontal length of the pterygium, and recurrence risk factors were recorded. There were no statistically significant differences between the groups for age, sex, horizontal length of pterygium, preoperative visual acuity, astigmatism, and recurrence risk factors. The pterygium was excised from the conjunctival side and then peeled off the cornea. The bare sclera was covered with a rotational conjunctival flap from the superonasal area. After surgery, Group 1 (22 patients), Group 2 (17 patients) and Group 3 (20 patients) received 7.5 mg bevacizumab, 2.5 mg bevacizumab, and Balanced Salt Solution (BSS) subconjunctivally, respectively. Postoperatively, horizontal length of corneal epithelial defect, conjunctival congestion, and lacrimation were checked on the first and seventh day. The rate of recurrence (>1.5 mm fibrovascular overgrowth on the cornea) at month 6 was compared between the groups.

Results: There were no statistically significant differences between the groups for all measured variables except for moderate conjunctival congestion on the first postoperative day which was more common in the bevacizumab groups (P=0.002). Four eyes in Groups 1 (20%) and 2 (26.7%) and 3 in Group 3 (15.8%) experienced recurrence (p=0.73). All recurrences occurred at month 3 and subsequently thereafter.

Conclusions: In our study, perioperative injections of subconjunctival bevacizumab had no effect on primary pterygium recurrence and were not associated with any specific local complications.

KEYWORDS

Bevacizumab, Corneal Neovascularization, Pterygium.

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INTRODUCTION

Pterygium is a common ocular-surface disorder characterized by an excessive fibrovascular proliferation over the cornea. The pathogenesis of pterygia is not fully understood. Various factors including the environment, genetic components, antiapoptotic mechanisms, cytokines, growth factors, extracellular matrix remodeling, immunological mechanisms, and viral infections have been implicated as causative (1-3).

Treatment of a symptomtic pterygium is surgical excision. Pterygium excision is often combined with various adjunctive measures to prevent its recurrence. Among the medical methods employed, intraoperative and postoperative mitomycin C applications remain the most commonly used to prevent recurrence (1). Other medical alternative agents include 5-fluorouracil and daunorubicin (4-5). These agents have been shown to cause a reduction in the recurrence rate of pterygium, but they are potentially toxic to ocular tissues and have been associated with sight-threatening side effects like punctate epitheliopathy, bacterial superinfection, delayed-onset scleral melting, and endophthalmitis. Conjunctival autograft surgery is generally regarded as the procedure of choice for the treatment of pterygium because of its efficacy, low recurrence rate, and long-term safety (6-7).

The success of pterygium surgery is dependent on the degree of postoperative wound healing and the amount of scar tissue formation. Wound healing is the result of a sequence of several basic processes, including inflammation, cell proliferation, matrix formation and remodeling, angiogenesis, wound contraction, and epithelialization. With respect to the marked elevation of Vascular Endothelial Growth Factor (VEGF) in pterygia and the major role of VEGF in angiogenesis and fibroblast and inflammatory cell migration and proliferation,(8) VEGF blockade may result in the inhibition of new vessel formation and reduce recurrence after pterygium excision. Furthermore, an anti-VEGF approach might also offer a suitable antifibrotic therapy (9).

The available anti-VEGFs for clinical use are bevacizumab (Avastin, Genentech Inc./Roche), ranibizumab (Lucentis), and pegaptanib (Macugen). Bevacizumab is a recombinant, humanized monoclonal antibody against the soluble form of VEGF. It was the first anti-VEGF antibody to be approved by the U.S. Food and Drug Administration specifically for the treatment of some metastatic cancers. The ocular off-label administration of bevacizumab for the treatment of various neovascularizations has gained wide and rapid acceptance because of its safety, efficacy, and lower cost compared with other anti-VEGF drugs (10).

In our previous report (11), a single (1.25 mg) intraoperative subconjunctival bevacizumab administration had no effect on the recurrence rate of pterygium. Subconjunctival bevacizumab has been used in several human studies with doses up to 3 times the recommended intravitreal dose without serious systemic or local complications (12-13). The pharmacokinetics of subconjunctival anti-VEGF agents has not been elucidated and we do not know how long bevacizuamb would exert its effect on the conjunctival tissue. With respect to the abundant conjunctival vessels the half life of bevacizumab seems to be shorter than the intravitreal administration. The longest reported elimination half life of bevacizumab after a single intravitreal injection has been 9.8 days (14). Due to the lack of data about the half life of bevacizumab in conjunctival tissue and the extension of the pharmacological duration by 1 half-time (8 days to 11 days) after doubling the intravitreal dose (1.5 mg to 3 mg),(15) we performed this study to evaluate the effect of a 2.5 mg and a 7.5 mg dose of subconjunctival bevacizumab on the recurrence rate after primary pterygium excision. Since the tear levels of VEGF after pterygium excision increase postoperatively and peak on day 5 (16), the second injection in the group that received a total dose of 7.5 mg bevacizumab was delivered on day 4, one day before the peak level of VEGF in tear.

MATERIALS AND METHODS

This prospective randomized placebo-controlled clinical study was approved by the Ethics Com-

mittee of the Shiraz University of Medical Sciences. In this study, 59 eyes of 59 patients with primary pterygium were recruited. Informed consent was obtained from each participant. Patients referred to our center to receive treatment for their pterygium had a comprehensive eye examination and those who met the inclusion criteria were recruited. The inclusion criteria were primary pterygium with a decreased visual acuity secondary to the involvement of the visual axis or induced astigmatism, restricted ocular motility, cosmetic concerns, discomfort and irritation unresponsive to lubricants, or more than 3 mm horizontal extension of pterygium on the cornea. The exclusion criteria were glaucoma, nasolacrimal duct obstruction (regurgitation from lacrimal punctum), pregnancy, lactation, active ocular surface diseases or infections, autoimmune diseases, and any previous ocular surgery. The following conditions were regarded as risk factors for pterygium recurrence: age less than 30 years, inflamed pterygium, occupations with more than 5 hours of sun exposure per day, recurrent pterygium in the fellow eye, and arcus senilis (11).

All patients had a complete ophthalmological evaluation, which included best corrected visual acuity (LogMAR), manifest refraction, detailed slit lamp examination including horizontal length of pterygium in mm, and fundus examinations. By convention, cylinders are given as minus cylinders. The sample size was determined based on the result of our previous report,(11) in which the recurrence rate was 13.4% during 8 ± 1.4 months of follow up. We used Power SSC program version 1.00 Sample Size Calculator and Power Analysis [developed by F. Habibzadeh, MD, Shiraz NIOC Medical Education and Research Center, Shiraz, Iran]. With precision of 5%, a confidence level of 95%, and a consideration of finite population size, the sample size was 64. Considering the limitations of randomized clinical studies such as informed consent and inclusion and exclusion criteria, 59 patients were recruited. The subjects were randomized into 3 groups using Random Allocation Software version 1.0 [developed by M. Saghaei, MD, Department of Anesthesia, Isfahan University of Medical Sciences, Isfahan, Iran].

Group 1 received bevacizumab 5 mg/0.2 mL subconjunctivally at the end of surgery and 2.5 mg/0.1 mL on the fourth postoperative day (a total of 7.5 mg). In Groups 2 and 3, bevacizumab 2.5 mg/0.1 mL and 0.1 mL Balanced Salt Solution (BSS) were injected subconjunctivally at the end of surgery, respectively.

Postoperatively, patients were examined at 1 day, 1 week, 1 month, 3 months, and 6 months. On the first and seventh days after surgery, the following factors were evaluated: horizontal length of corneal epithelial defect in mm (as on of the factors for assessing the effect of bevacizumab on wound healing), conjunctival congestion, conjunctival flap status (retraction, melting, necrosis, or infection), corneal ulcers, corneal edema, anterior uveitis, and lacrimation. Since after pterygium excision nearly all patients have mild conjunctival congestion, conjunctival congestion was scored as either 1 for moderate or 2 for severe. Lacrimation was scored as either 0 (indicating absence of annoying lacrimation), or 1 (presence of lacrimation, so that the patient needs to wipe the eye). At the first month visit any remaining sutures were removed.

The prevalence of recurrence (defined as any fibrovascular growth of conjunctival tissue extending more than 1.5 mm across the limbus) (11, 17-18) was compared between the groups at the last visit, month 6.

Surgical Technique

All surgeries were performed under local anesthesia. To accomplish anesthesia, after instilling tetracaine eye drops, subconjunctival lidocaine / epinephrine was injected under the area of the pterygium and the injected lidocaine was directed to the area of further conjunctival flap in the superonasal quadrant using a cotton tip applicator. The pterygium was excised from the conjunctival side and then peeled off the cornea, which resulted in a smooth corneal bed. The bare sclera was covered by a pedunculated conjunctival flap without Tenon's capsule created from the adjacent superonasal conjunctiva and sutured using 8-0 Vicryl sutures. In order to prevent conjunctival flap traumatization and have the injected bevacizumab close to the operation site, subconjunctival bevacizumab or BSS were administered at the nasal side of the inferior fornix. After surgery, treatment with a topical antibiotic (0.5% chloram-

Table 1: *Demographic and Ocular Characteristics of Patients*

	Group 1	*Group 2*	*Group 3*	*Significance*
Number	22	15	20	
OD/OS	9/13	11/4	6/14	0.03
Age	41.95±12.01	45.86±16.07	43.50±12.33	0.68
Sex (M/F)	12/10	10/5	11/9	0.72
Daily sun exposure(hours)	4.67±3.57	5.00± 2.85	5.10±4.02	0.92
Horizontal size of Pterygium (mm)	3.00±1.19	3.56± 1.62	3.08±1.28	0.43
Preoperative vision (logMAR)	0.10±0.29	0.31± 0.53	0.17±0.31	0.27
Preoperative astigmatism (diopter)	-1.86±1.77	-1.75± 1.26	-1.68±2.33	0.95

Table 2: *Prevalence of Pterygium Recurrence Risk Factors in the Three Groups*

	Group 1	*Group 2*	*Group 3*	*Significance*
Inflamed Pterygium	3/22 (13.6%)	5/15 (33.3%)	4/20 (20%)	0.35
Occupations with >5 hours solar exposure per day	5/22 (22.7%)	7/15 (46.7%)	5/20 (25%)	0.24
Arcus senilis	2/22 (9.1%)	1/15 (6.7%)	2/20 (10%)	0.94
Age <30 years old	4/22 (18.2%)	2/15 (13.3%)	3/20 (15%)	0.91

phenicol, 4 times a day) and a corticosteroid (0.1% betamethasone, 4 times a day) was initiated. The medications were tapered over the course of 6 weeks. The second injection of bevacizumab (2.5 mg/0.1 mL) in Group 1 was administered at the nasal side of the inferior fornix on day 4 after surgery.

Statistical Analyses

All statistical analyses were done using SPSS program (version 16). Categorical data were compared between the three groups using the Chi-square test and numerical data were compared using the One-Way ANOVA test. Survival analysis and plot were used to follow the recurrence trend in each group. A value of $p < 0.05$ was considered statistically significant.

RESULTS

This study was conducted on a total of 59 eyes of 59 patients. Group 1 comprised of 22 eyes, Group 2 comprised of 17 eyes, and Group 3 comprised of 20 eyes. All patients completed the full course of postoperative visits except for 2 patients in Group 2 who were not able to be followed. Therefore, the statistical analysis was conducted on 57 eyes. There were no statistically significant differences between the 3 groups for age, sex, horizontal size of pterygium, duration of daily sun exposure, and preoperative visual acuity and refractive astigmatism (Table 1). There were no significant differences between groups in terms of recurrence risk factors (Table 2).

No difference between the groups was seen regarding the astigmatism at month 6, neither regarding conjunctival congestion, lacrimation, and horizontal length of corneal epithelial defect in mm on the first and seventh postoperative days. (Table 3), except for moderate conjunctival congestion on the first postoperative day which was more common in the bevacizumab groups (P=0.002). However, no cases of severe conjunctival congestion were seen on the first postoperative day in the bevacizumab groups. No local complications associated with the subconjunctival administration of bevacizumab were observed in the bevacizumab groups. No necrosis, ischemia, infection in the surgical bed area and conjunctival flaps, corneal edema, anterior uveitis, or conjunctival retraction and melting developed.

There were no statistically significant differences for recurrence rates between the groups (p=0.73). The rate of recurrence in Group 1 was 20% (4 eyes) and in Group 2 was 26.7%

Table 3: *Postoperative Course*

	Group 1	*Group 2*	*Group 3*	*Significance*
Recurrence (6 months)	4/20 (20%)	4/15 (26.7%)	3/19 (15.8%)	0.73
Horizontal length of corneal epithelial defect (mm)				
1st day	1.98±1.15	1.66±0.81	1.82±0.783	0.61
7th day	0.09±0.29	0.13±.35	0.04±0.09	0.61
Conjunctival congestion				
1st day				
Moderate	15/22 (68.18%)	9/15 (60%)	5/19 (26.31%)	0.002
Severe	0	0	4/19 (21.05%)	
7th day				
Moderate	7/22 (31.81%)	8/15 (53.33%)	6/20 (30%)	0.32
Severe	2/22 (9.09%)	0	2/20 (10%)	
Lacrimation				
1st day	17/22 (77.3%)	14/15 (93.3%)	15/19 (78.9%)	0.41
7th day	7/22 (31.8%)	5/15 (33.3%)	6/20 (30%)	0.97
Postoperative, 6 months, astigmatism (diopter)	-1.56±1.89	-1.47±1.13	-1.67±2.21	0.95

(4 eyes). Three patients in Group 3 (15.8%) experienced a recurrence. The presence and absence of recurrence are shown in *Figure 1*. The results of Kaplan- Meier survival curve are displayed in *Figure 2.* No patient in the 3 groups experienced recurrence during the first 3 postoperative months. There was no statistically significant difference among groups for recurrence during the 6 months follow up (p = 0.676).

DISCUSSION

A review of the literature shows that there are few reports on administering bevacizumab (intralesional injection or topical) to treat pterygia and that the reported results are controversial (12-13, 19-21). Although the case reports and case series have been in favor of bevacizumab, trails have shown no beneficial effect of bevacizumab on the recurrence rate of excised pterygium (12-13, 19). In our previous report, 30 patients with primary pterygium were randomized to subconjunctival bevacizumab (1.25 mg) or BSS (15 patients in each arm) immediately after primary pterygium excision combined with a rotational flap. 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 13.4% (p = 0.2). No serious ocular side effect was observed (11).

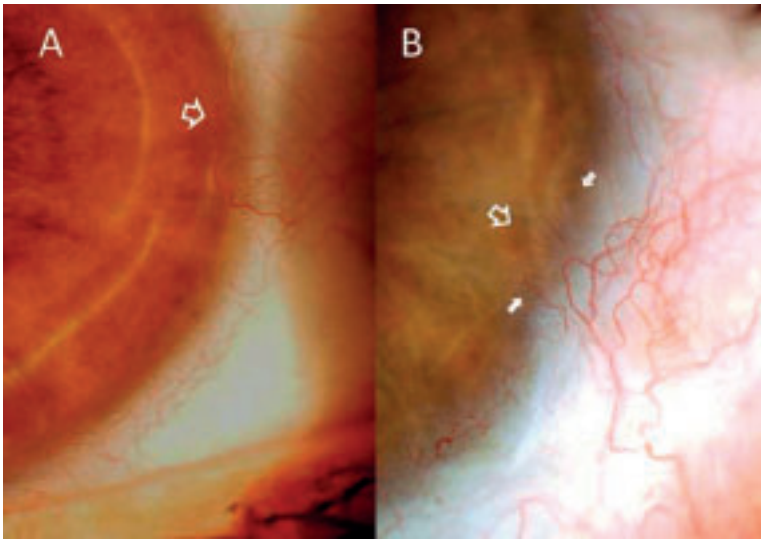

Fig. 1: A patient without recurrence (A), a patient with recurrence (>1.5 mm overgrowth of fibrovascular tissue over the cornea (B), the arrows, after primary pterygium excision.

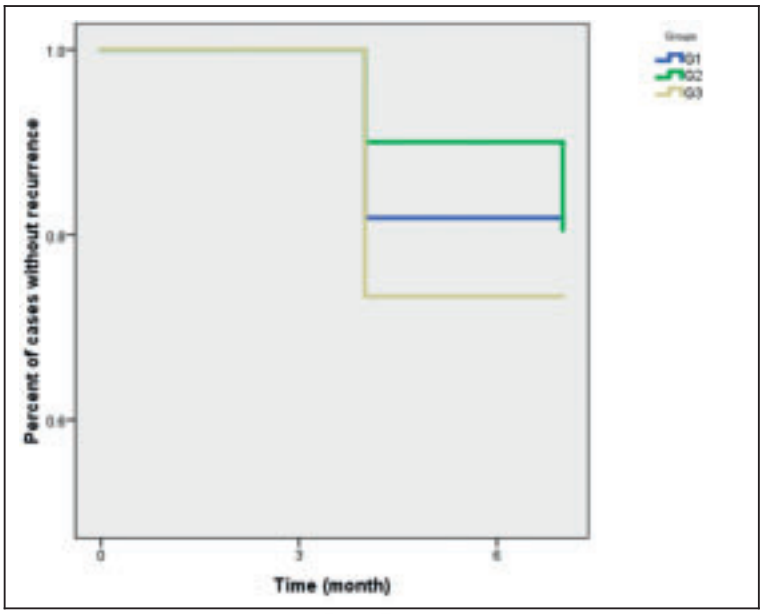

Fig. 2: Kaplan-Meier survival curve showing the percentage of success (lack of recurrence) among 3 groups, Group1 (7.5 mg bevacizumab), Group 2 (2.5 mg bevacizumab), and group 3 (Balanced Salt Solution).

The result of the present study is in accordance with the above mentioned study and Shenasi et al.'s report (19). In their study, 33 patients received 1.25 mg subconjunctival bevacizumab and another 33 patients had distilled water administered to them as control group immediately after primary pterygium excision by the bare sclera technique. The recurrence rate (defined as any fibrovascular growth crossing the limbus and extending over the cornea) was higher in the placebo group compared with the bevacizumab group (57.6% vs. 45.5%); however, this difference was not statistically significant (P =0.33). In our study 20% in Group 1, 26.7% in Group 2, and 15.8% in Group 3 had a recurrence (p= 0.73). The difference for the rate of recurrence between our study and theirs may be due to the criteria for defining the recurrence and technique of surgery. The reported recurrence rate after bare sclera technique has been around 40% (22-23).

In another prospective study, 80 patients with impending recurrent pterygium were randomized into 4 groups: 20 patients served as a control, and the other 60 patients served as treatment groups who either received a single subconjunctival injection of 1.25 mg, 2.5 mg, or 3.75 mg bevacizumab. The majority (83.75%) of patients had impending recurrence after primary pterygium excision. The remaining patients (16.25%) had had multiple surgeries for pterygium. The surgical methods used were not uniform among treatment groups, 72.50% had pterygium removal with conjunctival autograft, 26.25% had excision with amniotic membrane transplantation, and 1.25% had bare sclera technique employed. Three days after injection, the conjunctival injection decreased significantly in all treatment groups ($P < 0.01$). Four weeks after treatment, only patients in groups that received 2.5 and 3.75 mg bevacizumab showed a significant reduction in conjunctival vascularization ($P < 0.05$). The conjunctival hyperemia increased back to its preinjection states at later time points. During the 3 month follow-up, no significant difference was observed between the groups for the severity of impending recurrent pterygium ($P = 0.56$) (12). However, the difference in the nature of our study, which was a treatment for primary pterygium, to the above mentioned study, which was performed on recurrent impending pterygium, should be considered when comparing the results.

Although the results of subconjunctival bevacizumab reports have not been encouraging in reducing the recurrence rate, a few studies have reported some beneficial effect of topical bevacizumab. In a prospective randomized study (21), 26 patients with impending recurrent pterygium received eye drops containing bevacizumab (5 mg/mL) 2 times daily and betamethasone 4 times daily for 1 week and 28 patients were submitted to betamethasone alone four times daily for 1 week. The patients were followed for 3-6 months. All patients in both groups failed, but the mean duration for invasion of fibrovascular tissue over the cornea in the bevacizumab group was significantly long-

er than that for control group patients ($p < 0.01$). Although Leippi et al. (24) stated successful results for bevacizumab eyedrops (25 mg/mL, used 2-8 times per day for 5-24 weeks) after the excision of recurrent pterygia and conjunctival autograft in 5 eyes (4 patients), only 1 eye had no recurrence.

Many studies have demonstrated the safety of topical or subconjunctivally injected anti- VEGFs in treating corneal neovascularization, but minor complications including epitheliopathy,(25) and wound healing problems (26-27) have been reported. In this study, we did not observe any significant local complications after using subconjunctival bevacizumab. There were no statistically significant differences between groups for horizontal corneal epithelial defect on the first ($p=0.612$) and seventh ($p=0.614$) postoperative days. Although no difference was seen for lacrimation, the amount of conjunctival congestion was greater in the bevacizumab groups on the first postoperative day ($p=0.002$) which may be due to the acidic pH of bevacizumab (6.2). (28)

In this randomized clinical study there were no statistically significant differences in the patients' demographic data, and no beneficial effects of different doses of subconjunctival bevacizumab on preventing pterygium recurrence were observed. The absence of photographic documentation for detailed description of recurrence, and short follow up are limitations of the current study. As shown in the Kaplan-Meier Survival Curve all recurrences happened after the month 3 follow-up and subsequently thereafter. Some other reports also stated that the mean recurrence time after pterygium excision is 3-6 months and following patient more than 6 months may not change the results. (23),(29-31) Not receiving subconjunctival injections on the fourth day in Groups 2 and 3 might be another limitation of the present study, but the absence of any difference between groups for the evaluated measures on the seventh day may be a convincing reason that the second injections did not affect the result.

The failure of bevacizumab to reduce the recurrence of pterygium may be attributed to several reasons. It is possible that the dose used in our study was not enough to block VEGF effectively. There is also the possibility of a shorter half-life of the drug because of higher systemic absorption through abundant conjunctival vessels. Higher doses or topical administration of bevacizumab for several weeks may be needed in order to have a measurable effect. Furthermore, angiogenesis and recurrence in pterygium may be mediated through several factors other than VEGF cytokines such as basic fibroblast growth factor (bFGF), transforming growth factor-beta, and platelet-derived growth factor. Interventions targeted at these factors may be of more critical importance than VEGF.

In conclusion, this study found that different doses of subconjunctival bevacizumab were not associated with any local adverse effects; however, no significant reduction in the recurrence of primary pterygium was observed. This does not necessarily mean that bevacizumab has no place in the management of pterygium and therefore further studies involving the chronic administration of this drug are warranted.

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