Subconjunctival Bevacizumab for Primary Pterygium Excision; a Randomized Clinical Trial

Mohammad-Reza Razeghinejad, MD; Mohammad Banifatemi, MD
Poostchi Ophthalmology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Purpose: To evaluate the safety of local bevacizumab and its effect on recurrence of primary pterygium excision.

Methods: This randomized, placebo-controlled clinical trial was conducted on 44 eyes of 44 patients randomized to Group 1 (bevacizumab) and Group 2 (balanced salt solution). Group 1 underwent pterygium excision with a rotational conjunctival flap and received a total of 7.5 mg subconjunctival bevacizumab (5 mg/0.2 mL on the day of surgery and 2.5 mg/0.1 mL on the fourth day after 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 >1.5 mm fibrovascular overgrowth on the cornea were compared between the study groups.

Results: There was no statistically significant difference between the study groups in terms of demographics, pterygium size, daily sun exposure, preoperative visual acuity, keratomeric readings, corneal astigmatism, or IOP (P>0.05). Three and 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 (P=1 and 0.62, respectively). At the three-month visit, 3 patients in Group 1 versus 7 patients in Group 2 (P=0.13), and at the six-month visit 4 patients in Group 1 versus 8 patients in Group 2 (P=0.17) had fibrovascular tissue crossing the limbus. Patients in Group 1 experienced a statistically significant rise in IOP at the one-week visit (P=0.007).

Conclusion: Bevacizumab had no significant effect on the recurrence rate of pterygium. Although the frequency of fibrovascular tissue crossing the limbus in the bevacizumab group was half that of the BSS group, the difference failed to reach a statistically significant level.

Keywords: Angiogenesis; Bevacizumab; Pterygium; Pterygium Recurrence

INTRODUCTION

Pterygium is a degenerative fibrovascular proliferation of conjunctival tissue over the cornea. It usually invades the nasal limbus and spreads along the interpalpebral fissure. Pterygium affects 0.3 to 29% of the population worldwide and may necessitate surgical removal. Postoperative recurrence is not uncommon. Various adjunctive measures, including medications (mitomycin C, 5-fluorouracil, corticosteroids and daunorubicin) and beta irradiation have been used to prevent the recurrence of pterygia. However, these methods are associated with
side effects, such as punctate epitheliopathy, bacterial superinfection, delayed-onset scleral melting, and elevation of intraocular pressure (IOP). Considering potential complications of these agents, safer adjuvants have been pursued.

The abundant expression of the vascular endothelial growth factor (VEGF) in pterygia suggests that anti-VEGF therapy may induce regression of blood vessels in pterygia or prevent its recurrence after excision.\(^7\) Bevacizumab (Avastin; Genentech Inc., San Francisco, California, USA) a recombinant humanized murine monoclonal immunoglobulin G1 (IgG1), inhibits the VEGF-A isoform, the main stimulant of angiogenesis. This antibody is now widely used as an adjuvant for many neoplasms such as brain, lung, kidney, ovary, and breast cancers.\(^8\)\(^-\)\(^13\) Although not FDA approved for intraocular use, it is used extensively for posterior segment vascular diseases and more recently for corneal neovascularization.\(^14\)\(^-\)\(^21\)

In our previous report,\(^22\) a single (1.25 mg) subconjunctival bevacizumab administration at the end of operation had no effect on the recurrence rate of pterygia. In several human studies, bevacizumab has been used subconjunctivally with doses up to 3 times the recommended intravitreal dose without serious systemic or local side effects.\(^23\)\(^-\)\(^24\) We do not know how long bevacizumab may exert its effect on the conjunctival tissue, because the pharmacokinetics of subconjunctival bevacizumab has not been elucidated. Because of the abundance of conjunctival vessels, the half-life of subconjunctival bevacizumab seems to be shorter than that of intravitreal administration. The longest reported elimination half-life of bevacizumab after a single intravitreal injection has been 9.8 days.\(^25\) It has been shown that doubling the dose of intravitreal bevacizumab (from 1.5 mg to 3 mg) extends the pharmacological duration of bevacizumab by 1 half-time (8 to 11 days).\(^26\) Due to the lack of data about the half-life of bevacizumab in the conjunctiva and the aforementioned data on the pharmacokinetics of intravitreal bevacizumab, we performed this study to evaluate the effect of a 5 mg dose of subconjunctival bevacizumab on the recurrence rate of primary pterygium excision. The second injection (2.5 mg) was delivered on the fourth postoperative day summing to a total dose of 7.5 mg bevacizumab; this was based on the fact that tear levels of VEGF following pterygium excision peak on the fifth postoperative day.\(^27\)

The results of studies on the effect of bevacizumab on recurrence rates have been mixed. Although some studies have shown a beneficial effect from bevacizumab in terms of reducing recurrence,\(^28\)\(^,\)\(^29\) the majority did not.\(^22\)\(^,\)\(^30\)\(^-\)\(^31\) The majority of these studies are limited to case reports or case series. In this randomized placebo-controlled clinical trial we report the results of subconjunctival bevacizumab on the recurrence rate of pterygia following primary excision.

**METHODS**

This randomized, placebo-controlled clinical trial was approved by the Ethics Committee of the Shiraz University of Medical Sciences, and written informed consent was obtained from all patients. The research followed the tenets of the Declaration of Helsinki. Indications for pterygium surgery included decreased visual acuity due to involvement of the visual axis or induced astigmatism, discomfort and irritation unresponsive to lubricants, restricted ocular motility, cosmetic concerns, or more than 3 mm extension of the pterygium over the cornea. Patients with glaucoma, regurgitation from the lacrimal puncta (indicating nasolacrimal duct obstruction), diabetes mellitus, pregnancy, lactation, ocular surface disorders or infections, autoimmune diseases, and previous ocular surgery were excluded from the study.\(^22\)

We recorded all participants’ demographic data, average duration of daily sun exposure, best corrected visual acuity (BCVA), manifest refraction and keratometry (Topcon RM-A2000, Topcon Medical Systems, Inc.), IOP (measured by a calibrated Goldmann applanation tonometer), detailed slit lamp examination including horizontal length of the pterygium in mm, and fundus examinations. 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.22

Patients were randomized to 2 groups using Random Allocation Software version 1.0 (provided by M. Saghaei, MD., Department of Anesthesia, Isfahan University of Medical Sciences, Isfahan, Iran). To generate a random sequence, an equal size was selected in the setting of blocks. Patients in group 1 (bevacizumab group) underwent pterygium excision with a rotational conjunctival flap, and received a total of 7.5 mg subconjunctival bevacizumab (5 mg/0.2 ml on the day of surgery and 2.5 mg/0.1 ml on the fourth day after 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.

All procedures were performed by the first author. Postoperatively, 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 graft 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).22, 32

Surgical Technique
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 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, 0.2 ml bevacizumab (5 mg) or BSS was injected in the inferior fornix depending on randomization. The second injection of bevacizumab (2.5mg/0.1 ml) in group 1 was administered on day 4 after surgery. Postoperatively, a topical antibiotic (0.5% chloramphenicol, 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.

Statistical Analysis
All statistical analyses were performed using the SPSS program version 16 (SPSS, Inc, Chicago, Illinois, USA). Categorical data were compared between the study groups using Chi-square and Fisher’s Exact Tests; numerical data were compared using an independent-T test. The General Linear Model Repeated Measures procedure was used for analysis of variances when the same measurement was made several times in each group. P values less than 0.05 were considered as statistically significant.

RESULTS
A total of 44 eyes of 44 patients were enrolled including 22 eyes in each group. All patients completed the postoperative visits, except two 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, kerometric 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 spherical equivalent 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
Locally, no necrosis, ischemia, infection in the surgical bed area, or conjunctival retraction and melting developed. However, conjunctival cysts were detected in two patients (one in each group) at the three-month visit, and these were excised. Although baseline IOP was similar in both groups, patients in group 1 experienced a statistically significant rise at week one postoperatively (P=0.007). IOP returned to baseline levels in later visits with no intervention (Figure 1). The mean ± standard deviation of horizontal dimension of corneal epithelial defects on the first postoperative

the limbus in group 2 was twice that of group 1 (7 versus 3 at three months and 8 versus 4 at six months).

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the limbus in group 2 was twice that of group 1 (7 versus 3 at three months and 8 versus 4 at six months).

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day in group 1 was 1.98±1.1 mm which was not significantly different from that of group 2 (1.83±0.80 mm, P=0.64). Corresponding figures at the first-week visit were 0.09±0.29 and 0.04±0.0 mm, respectively (P=0.45). Subconjunctival hemorrhage on the first postoperative day was seen in 16 (72.7%) and 10 (47.6%) eyes in groups 1 and 2, respectively (P=0.09). At week 1, and months 1 and 3, corresponding figures were 7 (31.8%) versus 11 (52.4%) (P=0.17), 1 (5%) versus 2 (9.5%) (P=1.0), and 1 (5%) versus 1 (4.8%) (P=1.0) in groups 1 and 2, respectively.

**DISCUSSION**

The current study was designed to evaluate the safety of bevacizumab and its effect on recurrence rate of pterygia when used as an adjunct to primary excision and a rotational conjunctival flap. Statistically, no beneficial effect was observed from 7.5 mg subconjunctival bevacizumab on preventing the recurrence of pterygium. This is compatible with some other studies reporting no beneficial effect from bevacizumab administration on prevention of pterygium recurrence.22,28,29,31,33 In our previous report,30 patients with primary pterygia were randomized to subconjunctival bevacizumab (1.25 mg) or BSS (15 patients in each arm) immediately after primary pterygium excision combined with a rotational conjunctival flap. In the current 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. Fallah et al28 evaluated the effect of topical bevacizumab in 54 patients undergoing pterygium surgery using the bare sclera technique with mitomycin C who had been diagnosed with impending recurrent pterygium. Of the 54 patients, 26 received topical bevacizumab eye drops (5mg/ml) twice daily and betamethasone 4 times daily for one week, and betamethasone alone was administered to the remainder of the patients, who were followed for 3-6 months. All patients in both groups failed; however the interval to invasion of fibrovascular tissue over the cornea was significantly longer in the bevacizumab group. They concluded that topical bevacizumab together with betamethasone drops can cause a delay in progression, especially when administered earlier than 30 days following pterygium excision. In our patients, the rate of fibrovascular tissue crossing the limbus in group 1 was half of that of group 2 at months 3 and 6, which seems to be clinically important although not statistically significant.

In a study, pterygia were excised using the bare sclera technique and 33 patients received 1.25 mg subconjunctival bevacizumab and another 33 subjects had distilled water administered to them as the control group intraoperatively. The control group experienced higher recurrence rate (defined as any fibrovascular growth crossing the limbus and extending over the cornea) as compared to the bevacizumab group; however, this difference was not statistically significant.34 The difference in the recurrence rate between our study and theirs may be due to both recurrence definition criteria and surgical technique. The reported recurrence rate after bare sclera technique has been around 40%.35-36 In contrast to the above mentioned studies, four others have reported success for treatment of pterygium recurrence with administration of topical bevacizumab.37-40 Wu et al administered
topical bevacizumab (25mg/ml, 4 times a day for 3 weeks) to a patient with an impending recurrent pterygium and noted prominent regression of vessels after treatment. Leippi et al. stated that the use of bevacizumab eye drops prevents the recurrence of pterygium. Five eyes (4 patients) were treated with topical bevacizumab eye drops (25mg/ml) 2 to 8 times per day for 5 to 24 weeks as an adjunct to excision of recurrent pterygium and conjunctival autograft, and were followed from 3 to 14 months. No pterygium recurrence was detected in one eye while others experienced different stages of recurrence. Fallah et al administered intralesional injections of bevacizumab (2.5mg/0.1 ml) to 17 patients with pterygia (14 subjects with primary and 3 with recurrent lesions). The size of vascularized cornea showed a statistically significant decrease at the end of the 3-month follow-up period. Although a statistically significant decrease in pterygium size (4%) was also observed, it did not seem to be clinically important. Mansour also reported prompt regression of conjunctival microvessels in the pterygial bed one week after a single subconjunctival injection of bevacizumab in two cases with an inflamed residual bed unresponsive to topical anti-inflammatory therapy

Potential side-effects of topical and subconjunctival anti-VEGF agents are still being evaluated. In a prospective study by Kim et al topical bevacizumab (12.5 mg/ml) was used twice day for three months in seven patients with corneal vascularization. It was found that while corneal blood vessels regressed in seven of ten treated eyes, 6 eyes developed epithelial defects during the second month of treatment. In one patient, the epitheliopathy progressed to stromal thinning resulting in a descemetocele. Another report described a 75-year-old man with a history of an idiopathic corneal melting who was treated with topical bevacizumab (25 mg/ml, four times a day for one month), which caused marked regression of the blood vessels. He also used it for six weeks after corneal transplant surgery. The patient was found to develop recurrent stromal melting in the the donor necessitating repeat corneal transplantation and a Gunderson flap. In our study, the mean horizontal dimension of the corneal epithelial defect at week one in group 1 (0.09 mm) was twice that of group 2 (0.04 mm), however the difference was not statistically significant. This difference may be due to a negative effect of bevacizumab on wound healing.

An intravitreal injection of anti-VEGF agents causes a predictable and probably volume-related rise in IOP, although there are reports of persistent IOP elevation. In volume-related IOP elevation, a very rapid decrease in IOP over a short period occurs. Persistent IOP elevation ranging from 8 to 35 mmHg in magnitude has been observed in patients who received intravitreal anti-VEGF injections. Possible mechanisms contributing to sustained IOP elevation following intravitreal injection are inflammation, drug-induced trabeculitis, uveitis, endophthalmitis, and undetectable low-grade inflammation. It is also possible that anti-VEGF agents may cause IOP elevation
by decreasing the physiological function of the trabecular meshwork. Since the mode of injection was subconjunctival in our study and because intraocular inflammation was not detected in any patient, the possible mechanism seems to be trabeculitis or a decrease in physiologic trabecular meshwork function.

In our study, there were no statistically significant difference in patients’ demographic data, and subconjunctival bevacizumab had no beneficial effect on the recurrence rate of pterygium. The relatively short follow-up, and lack of treatment with subconjunctival BSS on the fourth day could be limitations of the current study. However, the commonly reported mean recurrence time after pterygium excision is 3–6 months. Conducting a prospective, randomized clinical trial strengthens the credibility of the results. In addition, the absence of any difference between groups for the evaluated outcome measures (except IOP on the seventh day) is a convincing argument that BSS does not affect the result.

In summary, this study revealed that subconjunctival bevacizumab injections had no statistically but a probably clinically significant effect on the recurrence rate of pterygia. Various cytokines and growth factors have been investigated for their role in the pathogenesis of pterygia. Given the complex pathogenesis of pterygia, an isolated approach to treatment leaves other factors unattended. Addressing other factors such as basic fibroblast growth factor, transforming growth factor-beta, and platelet derived growth factor which seem to play a greater role in pterygium recurrence may be of greater importance than VEGF. The efficacy of topical bevacizumab after intraoperative injection or more postoperative subconjunctival injections combined with topical treatment targeting other growth factors involved in pterygium pathogenesis can be investigated in future studies.

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Conflicts of Interest

None.

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