Evaluation of the additive effect of bevacizumab eye drops to mitomycin C in primary pterygium

Abstract

Purpose: To assess the additive effect of postoperative Bevacizumab eye drops to MMC augmented bare sclera in cases of primary pterygium concerning the safety and recurrence rate.

Patients and methods: This prospective randomized controlled study included 20 patients with bilateral primary pterygium. The right eye of each patient was treated by simple pterygium excision with bare sclera and MMC application followed by artificial tear eye drops for 4 weeks postoperative as placebo (group I included 20 eyes) and served as the control group. The left eye of each patient was treated by simple excision with bare sclera and MMC followed by topical Bevacizumab eye drops for 4 weeks postoperative (group II included 20 eyes). Both eyes were operated upon in the same session. All subjects were examined on days 1, 7, 14 and 30 and monthly for year to record any vascularization measured in mm or recurrence of pterygium measured horizontally from the limbus to its apex in the cornea.

Results: After 12 months of follow up, 3 eyes (15%) with recurrence were seen in group I which was not significantly different from group II with 2 eyes (10%). No corneal neovascularization in group II except in 5 eyes which of which only 1-2mm neovessels growth in 5 eyes and one eye more than 3mm and another eye 2-3mm however in group I no neovascularization in only 5 eyes with more than 3mm neovessels in 5 eyes, 5 eyes with neovessels 2-3mm and 7 eyes with 1-2mm neovessels. Total P-value concerning the presence and absence of vascularization between the two groups was 0.000805 which was highly significant.

Conclusion: Our study concluded that recurrence was not affected by the topical Bevacizumab with no statistically significant difference between the two groups; however, a statistically significant difference existed in the level of corneal neovascularization between the two groups suggesting that regression of neovessels is not a guarantee against recurrence of pterygium.

Keywords: primary pterygium, bevacizumab, mitomycin C

Abbreviations: VEGF, vascular endothelial growth factor; 5FU, 5 fluorouracil; MMC, mitomycin C; HTF’s, human tenon fibroblasts

Background

Simple excision of pterygium, although very simple, is associated with variable postoperative recurrence rate which is especially high with bare sclera technique.1-3 Recurrence of pterygium could be attributed to episcleral fibroblasts proliferation and neovascularization secondary to the traumatic and inflammatory processes following pterygium surgery. Histologically, pterygium comprises a highly developed vascular neoformation network that lies in a body of hypertrophic and elastic connective tissue and covered with an atrophic conjunctival epithelium. Several active angiogenic and epithelial growth factors have been shown to be drastically increased in pterygium tissue; the most crucial molecule among these factors is the vascular endothelial growth factor (VEGF). 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.4,5 Mutation in P53 gene on chromosome 17 with induced changes in the expression of Vascular Endothelium Growth Factor (VEGF) was suggested as a presumed etiology for pterygium recurrence.5

Several adjunctive agents have been tried to reduce the rate of recurrence, among them 5 Fluorouracil (5FU) and Mitomycin C (MMC) are still in use. MMC is an alkylating agent that acts by cross-linking the DNA of fibroblast and hence preventing it from proliferation and differentiation into myofibroblast in the episclera.6-7 Bevacizumab (Avastin; Genetech, San Fransisco, CA, USA) is a recombinant humanized monoclonal immunoglobulin G1 antibody that acts directly to inhibit VEGF. It was known to inhibit corneal neovascularization both in rat models and in humans.8,9 This study was conducted to assess the additive effect of postoperative Bevacizumab eye drops to MMC augmented bare sclera in cases of primary pterygium concerning the safety and recurrence rate.

Patients and methods

This prospective randomized controlled study included 20 patients with bilateral primary pterygium. Written consent was obtained from the patients and included an explanation of the study and agreement to have a photo of the eye area only taken. This study work follows the recommendations of the Ethics Committee of Zagazig university...
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(ZU-IRB) which conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). The sample size was calculated to be 40 eyes, the calculation was done using Epi-Info (Epidemiological Information Package) software version 6.1. The patients were selected from the patients attending the outpatient clinic of ophthalmology department of Zagazig University Hospital during the period from November 2013 to December 2014.

To ensure matching between the study groups, patients with bilateral pterygia only were included in the study and the right eye was randomly selected to be treated with MMC only while the left eye was randomly selected to be treated with both MMC and Bevacizumab. The right eye of each patient was treated by simple pterygium excision with bare sclera and MMC application followed by artificial tear eye drops for 4 weeks postoperative as placebo (group I included 20 eyes) and served as the control group. The left eye of each patient was treated by simple excision with bare sclera and MMC followed by topical Bevacizumab eye drops for 4 weeks postoperative (group II included 20 eyes). Both eyes were operated upon in the same session.

Preoperative assessment of the patients included complete history taking with special emphasis on previous ocular surgeries or systemic diseases especially connective tissue disorders. Complete ophthalmological examination including: visual Acuity, local slit lamp biomicroscopy with special stress on pterygium size and depth into the cornea and intraocular pressure measurement. Only patients with bilateral primary pterygium were enrolled in this study. Patients with previous pterygium or any other ocular surgeries, patients on ocular medications and patients with known connective tissue disorders were excluded from the study.

Surgical technique

Benoxinate Hcl 0.4% was instilled before surgery, lid speculum was inserted and 0.5 ml mixture of local anesthetic lidocaine HCL 20 mg/ml and epinephrine 0.0125 mg/ml was injected subconjunctivally in the pterygium area using a 25-gauge needle. Keratectomy was done with beaver No 15 blade and was started 1 mm in front of the apex of pterygium till the limbus where dissection and excision of the body was done. Tenon’s capsule was excised with cautery of the episcleral vessels. A cellulose sponge 3mm×4mm containing 0.2 mg/ml MMC was applied directly to the scleral bed for 2 minutes then irrigated with 30 ml of normal saline solution to clear MMC residues. Closure of the conjunctiva by 8/0 Vicryl sutures was done leaving 2-3 mm bare scleral area nasal to the limbus. The same technique was done in the second eye and patching of both eyes after the application of topical tobramycin and dexamethazone eye ointment (Tobradex®, Alcon Inc. USA).

Postoperative care

The right eye of each patient received topical tobramycin and dexamethazone (Tobradex®, Alcon Inc. USA) eye drops 4 times a day, topical tobramycin and dexamethazone (Tobradex®, Alcon Inc. USA) ointment at bed time and artificial tears eye drops 4 times a day for 4 weeks duration, the left eye received the same treatment as the right eye but instead of artificial tears Bevacizumab eye drops (10 mg/ml 1%) was used 4 times a day (in an identical bottle to the artificial tears eye drops bottle) for the same duration. The dose was calculated after Motarjemizadeh et al.\textsuperscript{10} who suggested that 10 mg/ml concentration of topical bevacizumab was a more effective dose for adjuvant pterygium therapy than 5 mg/ml dose. Bevacizumab was prepared and diluted with 0.9% normal saline under aseptic conditions and stored at 2-8°C as recommended by the manufacturer, the patients were instructed to dispose and change the eye drops bottle after one month and to place it in the refrigerator all the time.

All subjects were examined on days 1, 7, 14 and 30 and monthly for one year, in each visit slit lamp biomicroscopy was performed to record any neovascularization measured in mm or recurrence of pterygium measured horizontally from the limbus to its apex in the cornea, also any patient complaints were recorded especially those suggestive of any toxic systemic or ocular side effects as pain and burning sensation. The study was performed in a single-blinded way in which the patient did not know the type of eye drops used in each eye. The recurrence was defined as any new fibrovascular tissue growth observed on slit lamp examination beyond the limbus. Statistical analysis of the data was performed using the Z and Chi square tests.

Results

This study included 16 males (80%) and 4 females (20%). Age of the patients ranged from 39 to 68 years with a mean age of 53.6 years. According to the time spent outdoors in the patients, 6 patients (30%) were exposed to the sun for about 4-8 hours daily while the remaining 14 patients (70%) were exposed to more than 8 hours per day. Sixteen patients (80%) had their pterygium duration of more than 2 years and 4 patients (20%) had duration less than 2 years. All eyes had pterygium more than 2 mm invasion inside the cornea. The postoperative results after 12 months of follow up revealed that: In the first group, treated postoperatively by placebo eye drops, only 3 eyes (15%) showed recurrence and that was not significantly different from the bevacizumab group which showed 2 eyes with recurrence (10%). Table 1 shows the post-operative recurrence in the two groups.

Regarding corneal neovascularization, eyes were classified into 4 categories according to the extent of neovascular invasion beyond the limbus. The results are represented in Figure 1. Apart from the 1-2 mm corneal neovascularization category in which the control group had 7 eyes (35%) versus 5 eyes (25%) in the bevacizumab group, there were significant differences between the two studied groups in all other neovascularization categories. The total P-value concerning the presence and absence of vascularization was 0.000805 which is highly significant. There were no eyes with toxic side effects as pain or burning sensation in both groups. Figure 1 shows the postoperative neovascularization in the two groups.

![Figure 1 The incidence of neovascularization among the two groups.](Image)
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Table 1: The postoperative recurrence rate in the two groups

|               | Group 1 | Group 2 | P value |
|---------------|---------|---------|---------|
| Total         | 20      | 20      | 0.6353  |
| Recurrence: Number | 3      | 2       |         |
| Percentage    | 15%     | 10%     |         |

Discussion

Recurrence of pterygium following primary pterygium excision is a frustrating complication to both the patient and the surgeon. And it is associated with complications such as cosmetic problems, inflammatory changes, and oculomotor disorders or diplopia resulting from adhesion. Many wound modulating agents have been used in a trial to minimize recurrence, including irradiation, antimetabolites namely; 5-fluorouracil and mitomycin C. They all carried some complications such as scleral thinning, corneal damage and consequences of radiation exposure. It has been well-established that pterygium is composed of fibrovascular tissue and the pterygium formation and progression require neovascularization, suggesting that the vascular endothelial growth factor (VEGF) is involved in the pathogenesis of pterygia.11

With the emergence and availability of antivascular endothelial growth factors (anti-VEGF), they were suggested as a possible adjunctive therapy for pterygium excision by decreasing the vascularity of newly formed blood vessels, hence decreasing the recurrence rate.12,13 Intralesional injection of Bevacizumab was found by Fallah et al.14 to decrease pterygium size. Two separate studies conducted by El Shafie et al.15 and Singh et al.16 have concluded that preoperative administration of subconjunctival injection of Bevacizumab before the pterygium excision with conjunctival autograft is useful in the treatment of patients with primary pterygium without local or systemic adverse effects. Another study by Alhammami et al.17 concluded that subconjunctival Bevacizumab is of benefit in cases of recurrent pterygium. The subconjunctival injection carries the potential risk of systemic complications such as gastrointestinal perforation, hypertension, arteriolar hemorrhage, impaired wound healing, bleeding, endophthalmitis, and arterial thromboembolic events Therefore, it has been suggested that topical instillation is the best route of Bevacizumab administration because it provides both safety and efficacy.18,19

The dose of topical bevacizumab was debated by many authors. An in vitro study conducted by Park et al.20 found that both metabolic activity and viability of primary and recurrent pterygium human Tenon fibroblasts (HTF’s) are inhibited by bevacizumab in a dose-dependent manner, especially at concentrations greater than 7.5mg/ml. However, primary human HTF’s shows reduction in cellular density at a bevacizumab concentration of 5.0mg/ml. Motarjemizadeh et al.18 evaluated the impact of topical administration of Bevacizumab on pterygium recurrence, they found that subjects who had received placebo were about 5 times more likely to suffer from pterygium recurrence than patients who had been treated by 5mg/ml concentration of topical Bevacizumab. Moreover, no recurrences at all were observed in the patients receiving a concentration of 10 mg/ml suggesting that it is the optimum concentration needed to prevent recurrence.

On the other hand, Hwang and Choi,21 conducted a comparative study between topical 0.02% mitomycin C and 0.05% cyclosporine and topical 2.5% bevacizumab after surgery. They stated that lower recurrence rates were encountered in the mitomycin C and cyclosporine groups when compared to their control group, whereas the bevacizumab group showed no difference in the recurrence rate. Moreover, Razeghinejad and Banifatemi.22 found that Bevacizumab had no significant effect on the recurrence rate of pterygium Although reduction in the frequency of fibrovascular tissue crossing the limbus in the bevacizumab group to half that of the BSS group, the difference was not statistically significant. To our best knowledge, this is the first eye-to-eye study that evaluates the additive effect of Bevacizumab eye drops to the MMC in cases of primary pterygium regarding both recurrence and corneal neovascularization. The lack of a detectable intergroup difference may be due to small sample size. Furthermore, the delivered dose might have been too small to reach the desired concentration to inhibit a continuously generated pool of VEGF. Moreover, the presence of abundant conjunctival vessels increases the rate of systemic drug absorption and thus reducing the amount of locally available drug.

Conclusion

Our results showed that recurrence was not affected by the topical Bevacizumab with no statistically significant difference between our two groups, however, a statistically significant difference existed in the level of corneal neovascularization between the two groups suggesting that regression of neovessels is not a guarantee against recurrence of pterygium. Further studies are needed to evaluate the effectiveness of topical bevacizumab and other anti-VEGF in the prevention of recurrence of primary pterygia.

Acknowledgments

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Conflicts of interest

The authors declare that there is no conflict of interest.

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