Effectiveness of Sub-Conjunctival Bevacizumab After Pterygium Excision at Armed Forces Institute of Opthalmology

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ABSTRACT

Objective: To determine the effectiveness of sub-conjunctival Bevacizumab after pterygium excision.
Study Design: Quasi-experimental study.
Place and Duration of Study: Armed Forces Institute of Ophthalmology Rawalpindi Pakistan, from Aug 2019 to Jan 2020.
Methodology: Thirty-six patients were included and divided into two groups. In group A (n=18), pterygium excision with conjunctival auto-graft was followed by injection of 0.3ml of 7.5mg of Bevacizumab. Patients of Group B (n=18) did not receive any Bevacizumab. All the patients were followed up after 7 days, two weeks, 4weeks and 24 weeks after the start of management. The visual analog score was used for pain assessment, Snellen chart for visual acuity and intraocular pressure was measured with applanation tonometry.
Results: After six months the recurrence rate was less in Group-A (n=3, 16.6%, *p*=0.005) than Group-B (n=4, 22.2%, *p*=0.01) The recurred pterygium size was also greater in Group-B (mean=0.27 ± 0.28mm, *p*=0.006) than Group-A (mean=0.11 ± 0.21mm, *p*=0.006). Patients of Group-A experienced less pain post-surgery. The intraocular pressures were same in both the groups. Visual acuity improvement was seen in the Group-A (n=11, 61%, *p*=0.008)) than group B (n=4.22%, *p*=0.008).
Conclusion: Administration of Bevacizumab under the conjunctiva after pterygium excision may be useful in averting lesion relapse, less post-op pain, and improved visual acuity.

Keywords: Cornea, Immuno-modulators, Pterygium recurrence, Pterygium surgery, Sub-conjunctival bevacizumab.

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INTRODUCTION

Pterygium is a triangular fibro-vascular degenerative growth of the bulbar conjunctiva which grows over the cornea in the interpalpebral fissure, either temporally or nasally. It may arise due to degeneration of subconjunctival connective tissue or from the limbal epithelial basal cells. It is one of the causes of dry and irritated eyes due to disruption of the tear film.[1,2] As the growth crosses the limbus and comes above the cornea, it tugs the corneal surface leading to astigmatism and visual disturbance. In Pakistan, due to the dry climate and extreme heat and dust storms during summers in most provinces, people are more subjected to having pterygium and dry eyes. Presently, it is believed that pterygium most commonly affects individuals exposed to the outdoor environment, particularly in tropical and subtropical countries. Therefore, exposure to dry, dusty, windy, and sunny weather is blamed as being the risk factor.[3] Since it occurs due to hot and humid climates, people exposed to sunlight during outdoor activities, such as sailors, skiers and sports people, usually develop it. Other factors may be genetics, tumour suppressor gene *p*53, male gender preponderance or a deficiency of limbal stem cells leading to conjunctivalization of the cornea.[2]

The prevalence of pterygium ranges from 0.7% to 31% in various studies conducted worldwide.[4] Surgery is the mainstay of treatment which has proven to give better results and improves the visual disturbances to the maximum. It is usually performed under local anaesthetic infiltration. Nevertheless, post-operative pain and discomfort become the patient's primary concern for the next 36–48 hours after the anaesthetic effect wears off, contributing to patient dissatisfaction. Therefore, Anaesthetic agents, bandage contact lenses, NSAIDs and opioids have been used postoperatively to reduce pain and discomfort.[5,6] In such scenarios, avoidance of recurrence is a favourable desire of both patients and surgeons. It is reported that the odds of recurrence of pterygium after excision is 50% in the first four months and 97% within the first year.[7] Anti VEGF Agents have been proven to have a beneficial effect in controlling the growth of pterygium.[6] Theory behind this is that VEGF overexpression plays a role in developing the pterygium. Therefore, anti VEGF seems to halt the process. Bevacizumab is a monoclonal antibody derivative which has shown some good results in

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controlling dry eye conditions.[8,9] In our study, we aimed to assess the effectiveness of sub conjunctival Bevacizumab after pterygium excision.

METHODOLOGY

The study was conducted at the Armed Forces Institute of Ophthalmology Rawalpindi Pakistan, from August 2019 to January 2020. It was a quasi experimental study approved by the Ethics Committee of the institute (vide certificate 187/ERC/AFIO dated 6th Jan 2017), and informed written consent was taken from all patients.

Inclusion Criteria: Patients aged 30 to 67 years irrespective of gender or ethnicity, having pterygium Grade 2-4 were included in the study.

Exclusion Criteria: Patients with prior pterygium surgery, recurrent pterygium and pterygium undergoing treatment with 5 Fluorouracil were excluded from the study.

The sampling technique was consecutive sampling. The sample size was calculated using a WHO calculator with a 5% significance level. The power of the study was 0.8, and the effect size was 1.989.[10]

Patients were divided into groups A and B of 18 patients each. The same surgeon operated on all patients. A proforma was used to record the personal profile of the patient and initial ocular examination, including visual acuity using Snellen's chart, intraocular pressure using applanation tonometry, and detailed slit-lamp anterior and posterior segment examination of both eyes.

Out of 36 patients, 18 patients (50%) were assigned to Group-A, in whom pterygium excision with conjunctival autograft was followed by injection of a total dosage of 0.3ml of 7.5mg of Bevacizumab to determine if it was effective at this dose as per selected study criteria. This was carried out as intraoperative subconjunctival administration of 0.2ml of 5mg Bevacizumab post pterygium excision at the lesional site followed by 0.1 ml of 2.5mg after three weeks to the same patient. The remaining 18 patients (50%) were assigned to Group-B who did not receive any Bevacizumab after pterygium excision and conjunctival autograft. All the patients were reviewed at 7 days, two weeks, 4weeks and 24 weeks after the beginning of management. Only topical lubricants were used during the follow-up period, and no steroids were administered to any patient. After the surgery, postoperative pain was assessed using a visual analogue scale VAS (0-10), as shown in the Figure.

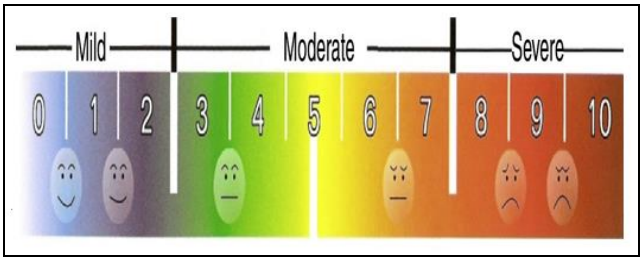

Figure: Visual analogue scale (VAS).

A score of 0 signified no pain, and 10 signified worst pain. Recurrence was seen as the reappearance of a fibrovascular encroachment, crossing the thalamus onto the cornea. Pterygium size was determined in millimetres by gauging the length (from the level of the caruncola to the most protuberant corneal surface) and width at the corneal base and apical areas. Changes in vascularization were assessed by comparing the first slit lamp pictures of patients taken with those taken one week after the first subconjunctival Bevacizumab injection. Applanation tonometry was used to determine the intraocular pressure. While visual acuity was assessed by Snellen chart at 6 feet and compared with pre-op visual acuity.

Statistical Package for Social Sciences (SPSS) version 24.0 was used for the data analysis. An independent sample t-test was applied to compare means in the data. In addition, the chi-square test was used to compare categorical variables. The *p*-value lower than or up to 0.05 was considered as significant.

RESULTS

Thirty-six eyes of 36 patients with pterygium grades 2 to 4 were studied. Two groups were made by convenience sampling, each having 18 patients (50%) from ages 32 years to 67 years and were divided into the groups irrespective of their gender. Group A (mean age = 42.17 ± 9.3 years) intraoperatively received 0.2ml of 5mg Bevacizumab followed by 0.1ml of 2.5mg after three weeks, while the Group-B (mean age = 50.06 ± 11.4 years) did not, with females (n=14, 39%) and males (n=22, 61%) in the total sample. All patients were followed up at 7days, two weeks, 4 weeks and 24 weeks after the start of management to assess the recurrence of the pterygium and any other parameters that had developed throughout the treatment.

The recurrence rate in our study sample was less in Group-A (n=3, 16.6%, *p*=0.005) as compared to

Group-B (n=4, 22.2%, *p*=0.01). The recurred pterygium size measured using a slit lamp after six months was greater in Group-B (Mean = 0.27 ± 0.28 mm, *p*=0.006) than the Group-A (Mean = 0.11 ± 0.21 mm, *p*=0.006). The sample measured the greatest size of recurred pterygium was measured as 0.7 mm in the sample.

VAS scale was used to assess the degree of pain post-surgery. Patients specified their pain intensity by indicating 0 being the mild pain to 10 being severe pain. Patients of the Bevacizumab group experienced significantly lesser pain post-surgery than the other group, as shown in the Table.

Table: Mean post-op pain based on VAS score

Groups	Mean Post-op Pain Vas Score	*p*-value
A (Bevacizumab Administered)	1.72 ± 0.75	0.025
B (No Bevacizumab Administered)	2.67 ± 1.30	

Intraocular pressure was measured in all the patients preoperatively and postoperatively with applanation tonometry. The intraocular pressures measured preoperatively and postoperatively showed no change in both groups. While visual acuity improved in more patients in the Group-A (n=11, 61%, *p*=0.008)) than Group-B (n=4. 22%, *p*=0.008).

DISCUSSION

Pterygium recurrence has always been a concern for both the surgeon and the patient. It is believed that pterygium recurrence is caused by trauma that is accidentally done during surgery leading to post-operative inflammation, which causes activation and proliferation of sub-conjunctival fibroblasts and vascular cells.[11,12] Our study concluded significantly low recurrence in Group-A due to Bevacizumab , contrary to the work done by Liu *et al*,[11] in their meta-analysis done in 2017 found no difference in the recurrence with or without Bevacizumab.

They had studied nine studies with regards to the Bevacizumab efficacy and concluded that the short term effects of Bevacizumab are not significant enough to comment on the recurrence of pterygium because of several reasons like the route of administration, category of pterygium, surgical procedure, patient's age, environmental factors etc. as they all have an impact on pterygium relapse.[12] This was further supported by Park *et al*.[13]

Later the updated meta-analysis done by Sun *et al,*[14] negated the earlier results, proposing data like our study. They included eighteen random controlled trials in their meta-analysis and found that the joint estimation found a statistically significant effect of Bevacizumab on pterygium relapse. (RR=0.74, *p*=0.03). Subgroup evaluation results also supported that Bevacizumab was beneficial.[15] We were further supported by Yang *et al*,[16] who highlighted the comparison of various surgical techniques for the pterygium excision and found that adjuvant Bevacizumab helped decrease the recurrence rate. They studied in retrospect limbal conjunctival graft (Group A), limbal conjunctival autograft with limbal fixation suture (Group B), and limbal conjunctival autograft with limbal fixation suture followed by Bevacizumab injection and found recurrence rates after one year were 18.4%, 8.3%, and 1.9% in groups A, B, and C, respectively (*p*=0.004). The reason here was explained by Kim *et al,*[17] by proposing that Bevacizumab helps inhibit the migration of fibroblasts by Bevacizumab induced down regulation of MP-13.

Furthermore, single-dose preoperatively or intraoperatively did not show any changes documented in the literature, as highlighted by Nuzzi *et al*.[18] Hence we administered an extra dose after three weeks. Hu *et al,*[19] concluded that intralesional Bevacizumab injection (2.5mg/0.1ml) reduces the size of pterygia (mean decrease of lesion size was 3.97 ± 3.84%). However, they also highlighted that Bevacizumab effects might be temporary; a second injection is required to inhibit the acute fibrovascular phase that occurs in the immediate post-operative time leading to the recurrence onset. Regarding the pterygia grading size measurements, Hu *et al*,[19] described that only corneal encroachment by fibrovascular covering the excision area and invading the cornea (grade 4) was a recurrence.

In both cases, the IOP measured in our study before and after the surgery were alike in the sample. This reflected that no complications like changes in the intraocular pressure are accepted when Bevacizumab is administered. The literature reviews also revealed no complications associated with Bevacizumab administration post-surgery.[20] Pain and discomfort are significant causes of patient dissatisfaction post-surgery. Tafti *et al,*[20] demonstrated that significant post-operative pain occurs in almost 60% of the patients, mainly on the first post-operative day and slightly less on the second post-op day. Multiple analgesic techniques have been employed, including topical anaesthetics, NSAIDs and opioids. However, long-term use of these medications may slow the epithelial healing leading to keratitis; subepithelial infiltrates and thinning. Though the pain reduction is reported to be

efficient, prolonged use may lead to complications, as mentioned. Bevacizumab has been mentioned in the literature regarding halting the production of metalloproteinases and other inflammatory pathways activation. Hence leads to decreased inflammation and revascularization, which helps early healing and decreases painful experiences post-surgery.[21]

CONCLUSION

The use of sub-conjunctival Bevacizumab following pterygium excision may help prevent pterygium recurrence. No untoward side effects due to Bevacizumab were seen in our study, indicating the relative safety of the administered dose. This treatment protocol is recommended at other centres for comparative outcomes.

Conflict of Interest: None.

Author's Contribution

ZA: Conception of main topic, design of study, research and data compilation and statics, OZ: Overall supervision and final approval of the publishable version, AA Critical review of the intellectual content and correction, QUA: Full assistance in research and data compilation.

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