Role of Anti VEGF Agent in Management of Primary Pterygium

Abhinav Singh¹, Sagarika Patyal³, Vinod K. Baranwal⁴, Gaurav Kapoor⁴
¹Military Hospital Dimapur, Nagaland, India; ²Centre for Sight New Delhi, India; ³Military Hospital Jhansi, Uttar Pradesh, India; ⁴Base Hospital Delhi Cantt (BHDC) & Army College of Medical Sciences (ACMS), Delhi Cantt., New Delhi, India

Objective: To assess the role of Anti VEGF agent in management of primary pterygium.

Study Design: Prospective Study.

Methodology: This prospective comparative study included twenty (20) eyes with primary nasal pterygium and off label use of a single dose of subconjunctival injection of Bevacizumab (0.05 ml, 1.25 mg) injected in the body of pterygium. The vascularity, thickness and size (in cm²) was recorded at baseline and 08 weeks after injection. The main outcome measures were the change in size, vascularity and thickness.

Result: There were 16 males (80%) and 04 females (20%), with a mean age of 41.5 yrs. There was no significant difference in the mean surface area of pterygium at different time intervals. However, the thickness and vascularity of the pterygium was significantly reduced. There was a significant difference in the pterygium grading by 2 masked observers at different times. At baseline, there were 14 (70%) grade II and 6 (30%) grade III pterygium. At 08 weeks post injection, there were 7 (35%) with grade I pterygium, 10 (50%) with grade II & 3 (15%) with grade III pterygium. No serious ocular or systemic side defects were observed.

Conclusion: Single dose subconjunctival injection of bevacizumab resulted in regression of pterygium thickness and vascularity. However, local injection of bevacizumab showed no significant difference in the size of the pterygium at the end of 08 weeks. The long term effect of anti VEGF agent in the management of primary pterygium requires further evaluation.

Keywords: Bevacizumab, Vascular Endothelial Growth Factor, Pterygium

Background

Pterygium is a common ocular surface disorder characterized by encroachment of a fleshy triangle of conjunctival tissue over the cornea. The pterygium is among the most common non infectious disorder encountered by an ophthalmologist. Pathogenesis of pterygium is not fully understood. Various studies have implicated the role of environmental factors such as UV rays, chronic irritation and chronic inflammation. Abnormal expression of tumor suppressor gene in pterygium epithelium suggests that mutations induced by ultraviolet radiation lead to limbal cell apoptosis and increase in growth factors as the earliest events in pterygium pathogenesis.

Among the growth factors known to be involved in pterygium pathogenesis is VEGF, which is known to be produced in response to several stimuli, including ultraviolet radiation. There is marked elevation of VEGF levels in pterygia compared with normal conjunctival samples. Although the pathogenesis of pterygium is still not fully understood, their formation and progression are known to depend upon neovascularization. The change in the angiogenic stimulator-inhibitor ratio leads to development of pterygium. Jim et al showed that pterygia tissue contains elevated levels of the VEGF and reduced levels of pigment epithelial derived factor. The growth inhibiting substance in the cornea act as a barrier to the limbal blood vessels and prevent them from entering the cornea. The role of VEGF is well established in the normal wound repair, because angiogenesis controlled mainly by VEGF is a key factor in the proliferative phase of wound healing by supplying oxygen and nutrients to support the process. VEGF is also required to facilitate the development of granulation tissue by means of increased vascular permeability that allows the deposition of fibrous substance and the migration of the inflammatory cells. Histopathologically, pterygium consist of atrophic conjunctival epithelium and a body of hypertrophied and elastotic degenerated connective tissue.

The recurrence rate after primary pterygium surgery is unacceptably elevated following simple excision. Therefore several methods, such as postoperative beta irradiation, conjunctival autograft transplantation and intraoperative application of MMC, Ologen implant are used to prevent recurrence following pterygium surgery.

Bevacizumab (Avastin, Gentech Inc., San Francisco, CA, USA) is a full length, humanized, monoclonal antibody, is pan VEGF inhibitor, i.e it acts against all types of VEGF produced in the body and neutralizes the biological activity of all types of VEGF. Bevacizumab is US-FDA approved for the treatment of metastatic colorectal carcinoma. Along with other anti-VEGF agents, it has been studied for various ophthalmic conditions associated with abnormal blood vessels proliferation. Bevacizumab has been used for choroidal neovascularization associated with age related macular degeneration (ARMD) and diabetic macular edema (DME). It is well tolerated when injected intraocularly and results in improvement in visual acuity, decreased central retinal thickness and reduction in the angiographic leakage.
No study has yet been reported or published using sub conjunctival injection of an anti VEGF, such as Bevacizumab, as an alternative treatment option for pterygium. It has been proved in the past, that the elevated levels of VEGF contribute to the development of fibrovascular proliferation. The aim of this study was to assess the role of Anti VEGF agent in management of pterygium. 

This outcomes of the study were:

a) Change in the pterygium in terms of thickness and vascularity till 08 weeks of follow up period.
b) Change in size of pterygium at 08 weeks.
c) Assess the post injection complications and adverse events.

**Methodology**

This off-label, single dose, interventional case series was conducted at Military Hospital, Dimapur, during July-September 2017. The ethical committee clearance, protocol, and informed consent were duly approved by the institution. A sample size of 20 patients, diagnosed as a case of primary nasal pterygium and only unilateral cases were included in the study. The measurement and grading was done based on the grading scheme proposed by Tan and coworkers in 1997 (Table 1). Grade II and Grade III were included in the study.

| Grade   | Description                                      | Grading Scheme |
|---------|--------------------------------------------------|----------------|
| Grade 1 | Atrophic                                         | Has clearly visible episcleral vessels under body of pterygium |
| Grade 2 | Intermediate                                     | Has partially visible episcleral vessels under body of pterygium |
| Grade 3 | Fleshy                                           | Has totally obscured episcleral vessels under body of pterygium |

This has been previously described and validated as a marker of severity of pterygium.

Exclusion criteria were mainly grade I pterygium, contraindication of bevacizumab (hypertension, previous myocardial infarction or stroke), previous ocular surgery, other ocular diseases, prior ocular trauma and prior ocular chemical injury.

All the eligible subjects were explained about the off-label use of the drug (anti VEGF). A comprehensive ocular examination was carried out for all patients and baseline parameters were obtained namely Snellen visual acuity, non contact tonometer, slit lamp examination and anterior segment photography using Carl Zeiss FF450 fundus camera with various magnifications.

The patients were asked to look in the extreme horizontal gaze to maximize the exposure of the pterygium and the dimensions of the pterygium were determined in the anterior segment photograp by measuring length in centimeter from base to apex (using caruncle as landmark) and width in centimeters at the base and the apical area.

The injection of anti VEGF was performed under direct visualization in minor OT using binocular microscope in 10x magnification by a single surgeon under sterile conditions.

All patients were instructed to instil eyedrops Moxifloxacin 0.5% 6 times one day prior to the intervention. In all patients, the injection of Anti VEGF was given in the body of pterygium in the minor operation theatre under complete aseptic conditions. Proparacaine 0.5% topical eye drops were instilled followed by scrubbing of eyelids by 10% povidone-iodine and conjunctiva was instilled with 5% povidone-iodine several minutes before the procedure. A sterile eyelid speculum was inserted. Topical proparacaine was instilled at the site of injection in the preferred site (in the body of the pterygium sub conjunctivally). Inj Anti VEGF was injected sub conjunctivally using a 30-guage needle at a dose of 1.25 mg in 0.05 ml.

Post-injection, a sterile cotton swab was placed at the site of injection to prevent reflux of drug. Topical antibiotic drop was instilled. Thereafter a sterile eye pad was placed that was removed 1 hour later. Patients were instructed to apply topical antibiotic drops 4 times a day for 5 days. Post injection follow-up included repeated clinical examination. Next day, at 04 weeks and at 08 weeks, patients were assessed for adverse events including sub conjunctival haemorrhage, corneal epithelial defects, post-injection inflammation and infection.

**Statistical Analysis**

Both descriptive and analytical approaches were used for data analysis. All numerical variables were compared using analysis of variance (ANOVA). Pairwise comparison was assessed using paired t-test for significant values. All statistical analysis was done using SPSS 16 version. A p value of less than or equal to 0.05 was considered statistically significant.

**Results**

Out of 20 patients, there were 16 males (80%) and 04 females (20%) with a mean age of 41.5 yrs (Chart 1). There was no significant difference in the mean surface area of pterygium at different time intervals (p > 0.05). At baseline, mean surface area was 1.30±0.2 cm². At 08 weeks, the mean surface area was 1.30±0.18 cm². However, the thickness and vascularity of the pterygium was significantly reduced. There was a significant difference in the pterygium grading by 2 masked observers at different times (p< 0.05). At baseline, there were 14 (70%) grade II and 6 (30%) grade III pterygium. At 08 weeks post injection, there were 7 (35%) with grade I pterygium, 10 (50%) with grade II & 3 (15%) with grade III pterygium (Table 2 & Chart 2).

| S.No. | Grade | Pre Injection | Post Injection |
|-------|-------|---------------|----------------|
| 1     | I     | -             | 7 (35%)        |
| 2     | II    | 14 (70%)      | 10 (50%)       |
| 3     | III   | 6 (30%)       | 3 (15%)        |

Thirteen (13) out of 20 patients (65%) developed subconjunctival haemorrhage, which resolved spontaneously after 2-3 weeks interval. There was no significant difference observed in mean IOP and BCVA. There was no episode of
ocular surface toxicity, corneal abrasions, epithelial defects, infection or uveitis during 08 weeks.

![Sex Distribution Chart](image)

**Chart 1**

**Comparison of Grading of Pterygium Pre and 08 Weeks Post Inj Anti VEGF**

| Grade | Pre Anti VEGF | Post Anti VEGF |
|-------|---------------|----------------|
| I     | 0             | 7              |
| II    | 14            | 10             |
| III   | 6             | 3              |

**Chart 2**

**Discussion**

The role of VEGF cannot be denied completely in direct or indirect pathogenesis of pterygium. A disturbance in the balance between angiogenic stimulators and antiangiogenic factors has been hypothesized in the formation and progression of pterygium.

There was no significant difference observed in the surface area before (1.30±0.2 cm²) and after (1.30±0.18 cm²) treatment with Anti VEGF. The drug was used mostly on grade II & III primary pterygia, these have thicker and greater amount of fibrovascular tissue. 07 out of 20 patients (35%) became grade I after intervention. There was no significant change in BCVA, IOP, local or systemic adverse effects observed during 08 weeks of Inj Anti VEGF. However, 13 out of 20 patients (65%) developed subconjunctival haemorrhage, which resolved spontaneously after 2-3 weeks interval, which can be considered as a minor complication of the procedure, no other complication was noted after the injection.

![Figure 1: Grade III pterygium before intervention.](image)

![Figure 2: Inj Bevacizumab 1.25mg (0.05ml).](image)

![Figure 3: Inj Bevacizumab](image)

![Figure 4: Same patient 08 weeks Post Bevacizumab](image)
Conclusion
Single dose of subconjunctival injection of bevacizumab resulted in regression of pterygium thickness and vascularity with no significant difference in the size of the pterygium at the end of 08 weeks. The limitations of this study was small sample size & short duration of follow-up. The results need to be validated to a larger group of population.

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Address for correspondence

Maj (Dr) Abhinav Singh DNB
Ground Floor, House No. 420
Sector 80, Mohali, Punjab 140308, India
Email id: docskool@gmail.com

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