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Research Article

THE OUTCOME OF PREOPERATIVE SUBCONJUNCTIVAL BEVACIZUMAB INJECTION IN PTERYGIUM SURGERY

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A R T I C L E I N F O

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A B S T R A C T

Aim: to evaluate the safety and the efficacy of subconjunctival injection of bevacizumab (Avastin) for the management of primary pterygium and to estimate the recurrent rate of pterygium after surgery **Methods:** In this randomized prospective clinical study, the patients were randomized into two groups of 30 patients each. Study group received 1.25 mg/0.05 ml subconjunctival bevacizumab 1 week before pterygium surgery with conjunctivalautograft. Control group received 1.25 mg (0.05 ml) subconjunctival normal saline 1 week prior to pterygium surgery with conjunctivalautograft. Patients were followed up at day 1, day 7, 1 month and 3 months. The main outcome measures were morphology of pterygium after injection, intra-operative ease, recurrence of pterygia, and any complications. **Results**: After giving bevacizumab, there was statistically significant improvement in grade, color intensity, size of pterygium, and symptoms of patients. Intra-operatively, less bleeding was observed by the surgeon. No statistically significant difference regarding reduction in astigmatism, improvement of visual acuity, and complications were observed in two groups. Recurrence was noted in five patients (8.33%) in total study population at the end of 3 months. It was present in two patients (6.67%) in Group A and three patients (10%) in Group B. **Conclusion:** Single preoperative administration of subconjunctival injection bevacizumab given 1 week before the pterygiumexcision with conjunctivalautograft decreases the vascularity of newly formed blood vessels, hence decrease recurrence rate of pterygium .

INTRODUCTION

Pterygium, histopathologically characterized by elastotic degeneration of collagen and fibrovascular proliferation, is a very common conjunctival degenerative condition. Current treatment for pterygium focuses on surgical excision and prevention of recurrence. Conjunctivalautografting after pterygium excision is associated with very low rates of recurrence and complications when compared to other surgical techniques. The surgeon's skill and experience affect the recurrence rate, which varies between 2% and 39% with this technique[1,2]. In the literature, some medical approaches were also used intraoperatively and postoperatively to prevent the recurrence including adjunctive therapy with beta radiation, thiotepa, mitomycin C, 5-fluorouracil, and corticosteroids (triamcinolone) [3-7]. However, the value of such therapy is limited because of potential ocular side effects, such as increased intraocular pressure, secondary bacterial infection, scleral ulceration, poor epithelial healing, and superficial punctate keratitis. Several studies suggest that vascular endothelial growth factor (VEGF) plays an important role in the development of pterygium. Furthermore, VEGF has been identified in the epithelium of pterygium[8-12]. The overexpression of VEGF in pterygium tissue led us to consider to evaluate the role of anti-VEGF therapy, which could induce regression of blood vessels and hence retard progression of pterygium. Bevacizumab (Avastin; Roche, USA) is a recombinant humanized monoclonal antibody against VEGF that neutralizes all isoforms of human VEGF and inhibits VEGF-induced proliferation of endothelial cells[13,14]. Bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA, USA) is a recombinant, humanized anti-VEGF antibody that binds all VEGF isoforms and exerts a neutralizing effect by inhibiting the VEGF-receptor interaction. It has been suggested as a possible adjunctive therapy for pterygium excision that decreases the vascularity of newly formed blood vessels, hence decreasing the recurrence rate and appears to have a role in prevention of recurrence.[15] This study aimed to evaluate the effect of Subconjunctival injection of bevacizumab in a single dose followed by surgical excision of pterygium with conjunctivalautograft after 1 week.

Aims and Objectives

The study was conducted in the Department of Ophthalmology Government Medical College Anantnag to evaluate the safety and the efficacy of subconjunctival injection of bevacizumab (Avastin) for the management of primary pterygium and to estimate the recurrent rate of pterygium after surgery.

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METHODS

This prospective, comparative, randomized control study was conducted over a period of 18 months (from October 2020 to March 2022). Randomization was performed by simple randomization method using table of random number. A total of 60 eyes with primary pterygium of 60 patients were enrolled in this study. Each patient underwent a complete ocular examination including visual acuity, refraction, slit lamp biomicroscopy, fundoscopy and intraocular pressure (IOP) measurement, . Inclusion criteria were patients >18 years of age, patients with Grade II or III primary pterygium (according to Tan *et al*. grading scheme)[16] with the apex of the lesion past the limbus, patients willing to participate in the study, patients willing to follow-up. Exclusion criteria included patients with evidence of any ocular disease except refractive errors, prior ocular surgery in the past such as pterygium, squint, trabeculectomy surgery, administration of topical medications for pterygium, patients with recurrent pterygium, hypertrophied or atrophic pterygia, acute or inflamed pterygia, pseudo-pterygium, conjunctival intra epithelial neoplasia, history of glaucoma or ocular hypertension in the study eye, systemic conditions in which bevacizumab is contraindicated such as hypertension, proteinuria, bleeding tendencies, previous myocardial infarction or stroke, pregnant and lactating women, inability to follow-up for the duration of the study. The main outcome measures of this study are change in morphology of pterygium, evidence of any adverse events (evaluate safety and tolerability), and pterygium recurrence. Grading of each pterygium was done according to Tan *et al*.[16] grading scheme proposed in 1997 given as:

- Grade II: (Intermediate) has partially visible episcleral vessels under the body of pterygium
- Grade III: (Fleshy) has totally obscured episcleral vessels under the body of pterygium.

Grading of color intensity on scale of 0–4 was done according to Teng*et al*.,[17] (0 = unremarkable, 1 = trace, 2 = mild, 3 = moderate, 4 = diffuse).

After taking the written informed consent, patients were randomized into two groups of 30 eyes each, patient details were obtained and noted on predesigned proforma. One week preoperatively, Group A received subconjunctival bevacizumab (under topical proparacaine) in a dose of1.25 mg (0.05 ml) by 26-gauge needle into the body of pterygium by gently lifting with colibri forceps and Group B received subconjunctival normal saline 0.05 ml. After a week, examination of patient for size, vascularity, color intensity, and complications were recorded. This was followed by pterygium excision with conjunctival autografting in all the patients by a single surgeon to control for the surgeon bias. Complete sterilization and aseptic measures were taken during surgery. Peribulbaranesthesia using 2% xylocaine + adrenaline was injected. After opening the lids using a rigid speculum, 0.2–0.3 ml injection of 2% xylocaine was given at the site of the pterygium to raise it up to its attachment to the cornea. Using Crescent blade, the pterygium was shaved off the cornea starting 0.5 mm in front of its head. The pterygium attached with the conjunctiva was separated from the scleral surface with tenotomy scissor and excised leaving about 3–4 mm area of the bare sclera. After scrapping the episcleral tissue, the area of bare sclera then was measured horizontally and vertically. A free conjunctivalautograft was then taken from the superior limbal region= approximately 1 mm larger than the recipient site. Graft was then shifted to the recipient area and fixed with autologous blood. Any intraoperative complication was noted and was treated accordingly, and the patients were reassured. All cases were given dexamethasone + moxifloxacin eye drops postoperatively 4 times a day in the 1st week. Dexamethasone was tapered over 4 weeks and moxifloxacin was stopped after 2 weeks of the study. Carboxymethylcellulose (0.5%) eye drops 4 times a day for 2 months. Follow-up was done at day 1, 1 week, 1 month, and 3 months after the surgery. Symptoms such as pain, lacrimation and photophobia, grittiness, and redness were noted at each visit. Best-corrected visual acuity, refraction, clinical photographs, and slit lamp examination for any complications such as ischemia, necrosis, infection, graft dehiscence at surgical site were observed. Evidence of recurrence by appearance of surgical bed at 3 months was noted according to Prabhasawat's criteria[18] (Grade I: Normal appearance, Grade II: Fine episcleral vessels without corneal extension, Grade III: Episcleral vessels and fibrovascular tissue without corneal extension, Grade IV: Fibrovascular tissue extending past the limbus).

RESULTS

The age of the patients was between 18 and 64 years with a mean age of 37.33 years. Thirty-four patients (56.67%) were male while 26 patients (43.34%) were females. Male to female ratio was 1.34: 1. The ratio of the right and left eyes, gender distribution, age, range and size of pterygium were not statistically different between the two groups. The mean pterygium grade in Group A was 2.43 ± 0.09 preoperatively, which decreased to 2.13 ± 0.12 after bevacizumab injection (P = 0.001). The mean pterygiumcolor intensity in Group A was 3.13 ± 0.13 preoperatively, which decreased to 2.56 ± 0.15 after bevacizumab injection (P = 0.0007). No change was observed in size, grade, or color intensity of pterygia for 1 week in Group B . Postoperatively, In Group A, there was improvement of 1 line on Snellen's chart in 35% patients and improvement of two lines in 7.88%. Visual acuity remained same in 57.12% patients. In Group B, improvement of one line was there in 25.52%, and of two lines in 6.25%. Visual acuity remained same in 68.23% patients. No worsening was noted in any of the groups. Mean simK astigmatism decreased significantly after surgery in both groups. The "with the rule" astigmatism was found to be the most common type of astigmatism both before and after surgery (86.67%) in both the groups. The distribution of type of corneal astigmatism did not change by the surgery. Mean IOP did not change significantly in any group. In Group A, after injection, there was improvement in all symptoms (redness, irritation, pain, itching, watering, and photophobia) except mass and decreased vision. The change in symptoms after injection was statistically significant (P < 0.05). In Group B, after injection, no increase or decrease in symptoms was noted. These patients presented as increased redness after injection. There was an apparent subjective benefit in Group A in the form of lessbleeding due to less vascularized pterygium as compared to Group B pterygium. However, we did not quantify this effect. Patients were operated without any intra operative complications. Graft edema and congestion were present in 5.9% of patients in Group A and in 3.5% of patients in Group B on the first postoperative day. This was resolved in 1–2 weeks period. Recurrence was noted in five patients (8.33%) in the total study population at the end of 3 months. It was present in two

patients (6.67%) in Group A and three patients (10%) in Group B. There was no statistical difference between two groups ($P > 0.05$). There were 80% recurrences (four patients) below 50 years of age and only 20% recurrences (one patient) occurred above 50 years. Among all the patients in Group A, Grade II and III recurrence comprised 50% each. There was no Grade IVrecurrence seen. Among all the patients in Group B, Grade II and III recurrence comprised of 33.34% ($n = 1$) and 66.67% ($n = 2$), respectively. There was no Grade IV recurrence seen. 66.67% recurrences were seen in patients having Grade II pterygium, and 33.34% was seen in patients having Grade III pterygium. Similarly, 66.67% recurrences were in unilateral pterygium and 33.34% in bilateral pterygium.

DISCUSSION

The primary concern in pterygium surgery is recurrence, defined by regrowth of the fibrovascular tissue across the limbus and onto the cornea. In order to reduce the rate of recurrence, various modalities have been proposed. Generally, pterygium recurrences happen during the first 6 months after surgery. A number of factors such as the type of pterygium, age of the patient, environmental agents, and surgical technique may be responsible. In fact, the bare sclera technique, which involves excising the head and body of the pterygium while allowing the scleral bed to re-epithelialize, is usually associated with high recurrence rates (24–89%) [19]. The present aim of our study is to use anti-VEGF therapy in the treatment of pterygium in Indian patients. Because the anti-VEGF therapy induces the regression of blood vessels and decreases the size of pterygium. Blockade of VEGF can result in inhibition of new vessel formation. Hence, anti-VEGF has been suggested as possible adjunct therapy for pterygium excision that appears to play a role in prevention of recurrence. Since bevacizumab has a role in decreasing the size and vascularity of pterygium, it can be used preoperatively in highly vascular or large pterygium. Furthermore, it decreases the recurrence rate (though not statistically significant), it can be used in recurrent pterygium. The first study to demonstrate that increased VEGF level may play a role in pterygium development was reported in 2001 by Lee *et al*.[20] Thus, inhibiting VEGF by giving anti-VEGF like bevacizumab may reduce fibroblast proliferation and possibly recurrence, which forms the basis of our study. A recurrence rate of 8.3% was reported in our study after a period of 3 months. In Group A, bevacizumab in the concentration of 1.25 mg/0.05 ml was given. The optimal dosing for thesubconjunctival use of bevacizumab is still undetermined, but same concentration has been used in other studies.[21] There was statistically significant improvement with respect to meangrade of pterygium in Group A as compared to Group B in whichit remained unchanged. A study done by Felipe *et al*., showed similar improvement of mean grade at 2nd week postinjection.[22] They inferred that bevacizumab has potential to cause shrinkage and regression in the vascular caliber of pterygium blood vessels. The change of grade correlated with the change in colorintensity in Group A as bevacizumab cause shrinkage of vessels present in pterygium. Visual acuity remained same or improved postoperatively in both the groups. No worsening of vision was noted. There were five recurrences (8.33%) in our study. In Group A, there was recurrence in 6.67% of cases while in Group B, recurrence was observed in 10% cases. However, no statistically significant difference was observed. There was a shift of patients from worse to better vision, probablydue to a reduction in astigmatism. We observed that most of the recurrences (in four patients, 80%) were in age group <50 years and only one (20%) was inpatient of age >50 years. Our observation was consistent with the observation of Lewallen *et al*.,[23] Manning *et al*[24] and Figueiredo *et al*[25] who stated that most of the recurrences occurred in patients younger than 50 years in their study. Recent studies have shown that several factors, such as anti-apoptotic mechanisms, pro-inflammatory cytokines, growth factors, extracellular matrix remodeling, immunological mechanisms, viral infections and the genetic component may be involved in the pathogenesis of the disease.

CONCLUSION

Subconjunctival injection of bevacizumab at a dose of 1.25 mg (0.05 ml) 1 week before surgery of pterygium is safe and effective in terms of recurrence and the complication rate for the treatment of primary pterygium. Our study shows that single preoperative administration of subconjunctival injection of bevacizumab given 1 week before the pterygium excision with conjunctivalautograft is useful in the treatment of patients with primary pterygium without local or systemic adverse effects. It provides a promising approach in inducing regression in pterygium size, vascularity, and grade. Future we need to continue to follow-up our patients in a longer term to see if any differences are observed in the recurrence rate in the two groups in the long run.

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