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Evaluation of Adjunctive Subconjunctival Injection of Bevacizumab before Pterygium Surgery

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ABSTRACT

Background: Pterygium is a common ocular surface lesion involves the bulbar conjunctiva's fibrovascular expansion onto the cornea. The exact cause of pterygium remains unclear, however exposure to ultraviolet radiation is recognized as a significant contributing element. The development of pterygium is believed to involve vascular endothelial growth factor (VEGF). Bevacizumab, a monoclonal antibody, functions by attaching to and blocking VEGF.

Aim of study: This study aimed to assess the effectiveness and safety of preoperative subconjunctival bevacizumab for primary pterygium excision.

Patients and methods: This prospective study included 30 patients with primary pterygium attending the Ophthalmology Outpatient Clinic, Al-Azhar University Hospital, Assiut, Egypt. Patients were divided into two groups: Group "A" (15 patients) received subconjunctival injection of 2.5 mg bevacizumab 1 week before surgical excision of the pterygium with conjunctival autograft transplantation. Group "B" (15 patients) underwent pterygium excision with conjunctival autograft transplantation without injection of bevacizumab. Patients were followed up for 6 months.

Results: In group "A", 14 out of 15 patients (93.3%) showed no recurrence after bevacizumab injection and pterygium surgery. One patient (6.7%) had recurrence. In group "B", 6 out of 15 patients (40%) had recurrence after pterygium surgery without bevacizumab injection. The recurrence rate was significantly lower in the bevacizumab injection group compared to control group (p=0.031). No complications were observed with subconjunctival bevacizumab injection.

Conclusion: Subconjunctival injection of bevacizumab before surgical excision of primary pterygium is safe and effective in reducing the recurrence rate.

Keywords: Pterygium, Bevacizumab, Vascular endothelial growth factor, Recurrence.

INTRODUCTION

Pterygium refers to a wing-shaped encroachment of fibrovascular tissue from the bulbar conjunctiva onto the cornea [(1)]. This common ocular surface lesion can lead to chronic irritation, induced astigmatism, and visual deterioration [(2)]. Pterygium is estimated to affect over 200 million people worldwide, with prevalence varying based on geographic location and ultraviolet light exposure [(3, 4)]. Histologically, pterygium demonstrates elastotic degeneration of collagen and fibrovascular proliferation covered by conjunctival epithelium [(5, 6)].

Although the pathogenesis is not fully understood, ultraviolet radiation appears to be a major environmental trigger. Excessive UV exposure induces limbal stem cell damage and pro-inflammatory cytokine release leading to conjunctival overgrowth [(4)]. Hereditary factors also play a role, as pterygia demonstrate familial clustering in some populations [(7)].

Recent studies have provided evidence of viral infections and immunologic mechanisms to be contributing as well [(8)].

One promising anti-angiogenic drug is bevacizumab, a recombinant humanized monoclonal antibody that binds and inhibits all VEGF isoforms [(12)]. By blocking VEGF from binding receptors on vascular endothelium, bevacizumab can potentially inhibit neovascularization [(13)]. Studies have shown decreased VEGF levels and reduced proliferation after subconjunctival bevacizumab administration [(14)].

Given the role of VEGF in pterygium pathogenesis and the anti-VEGF properties of bevacizumab [(15)], we aimed to assess the effectiveness and safety profile of bevacizumab administered subconjunctivally before surgically removing primary pterygium.

PATIENTS & METHODS

This prospective comparative study was conducted at the Ophthalmology Clinic, Al-Azhar University Hospital in Assiut, Egypt. The study enrolled 30 patients with primary pterygium affecting the nasal limbus.

Inclusion criteria: Adults over 18 years old with primary nasal pterygium causing ocular irritation, induced astigmatism, or documented progression over 6 months.

Exclusion criteria: Patients with current ocular infections, prior pterygium surgery, pregnancy, hypertension and cardiac issues, or coagulopathy.

Patients were randomized into two equal groups: Group "A" (n=15) received subconjunctival injection of bevacizumab 1 week prior to pterygium excision with conjunctival autografting. Group "B" (n=15) underwent pterygium excision with conjunctival autografting alone without bevacizumab injection.

The subconjunctival injections were performed by an ophthalmologist using aseptic technique. Following the application of 0.5% proparacaine for local numbing, a 30 gauge needle was used to administer 0.1 mL (2.5 mg) of bevacizumab (Avastin) into the pterygium mass. One week later, pterygium surgeries on all patients were

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performed by the same surgeon. Under local anesthesia, the pterygium's leading edge was separated from the corneal surface, and the main mass was meticulously removed from the sclera. A conjunctival graft, harvested from the superotemporal section of the eye's surface, was then positioned and secured over the bare area with 8-0 vicryl stitches. Following the procedure, a regimen of antibiotic and steroid eye drops were prescribed for a duration of four weeks. Patient' progress was monitored at specific time frames: One day, one week, one month, three months, and six months post-surgery. A recurrence was identified by the presence of any new fibrovascular growth extending over the limbus onto the corneal area.

Outcome assessment:

The main outcome measured in this study was the six-month postoperative recurrence rate of pterygium in patients who received bevacizumab injections versus those in the control group. Pterygium recurrence was characterized by the emergence of fibrovascular tissue extending over the limbal boundary onto the clear cornea. Secondary outcomes evaluated included complications from injection or surgery such as infection, graft rejection, or wound dehiscence, visual acuity changes from preoperative to postoperative states, and patient-reported symptoms. Outcomes were measured by slit lamp examination at each follow-up visit.

Ethical Approval:

This research was conducted with the approval of Al-Azhar University's Ethics Committee and adhered to the Declaration of Helsinki principles. All participants provided written informed consents. The study's methods were ethically reviewed and monitored to ensure participant safety and compliance with international guidelines on human subject research.

Statistical analysis

Patient demographics and clinical characteristics were processed using IBM SPSS statistics version 20.0 (IBM Corp, Armonk, NY). Qualitative data, including gender, side of pterygium occurrence, and instances of recurrence, were reported as counts and proportions. Quantitative data such as the age of patients and the length of the follow-up period were presented as the mean and standard deviation (SD). For the assessment of differences in recurrence rates across the two cohorts, Fisher's exact test was employed. To evaluate the age and other continuous variables among the groups, we used the unpaired t-test. We considered a two-tailed p-value of less than 0.05 to be indicative of statistical significance in all tests conducted.

RESULTS

Table (1) showed the demographic details where males represented about 86.7% of group A and 80% of group B. The difference in the proportion of males between the two groups was not statistically significant (p-value of 0.624). Concerning age, group A spaned from 25 to 49, with an average age of 37.4 years and a standard deviation of 5.3.

Table (1): Demographic data

	Group A	Group B	P0value
Sex			
Male	13 (86.7%)	12 (80.0%)	0.624 Ns
Female	2 (13.3%)	3 (20.0%)	
Age			
Range	25 – 49	20 - 55	0.686 Ns
Mean ± SD	37.4 ± 5.3	38.3 ± 6.7	

Chi-square test used for relation between sex and groups independent t-test used for relation between age and groups Ns: No significant difference ($p>0.05$).

Table (2) presented a comparison of the pterygium recurrence rates between the two cohorts. After 6 months, merely 1 in 15 participants (6.7%) from the group treated with bevacizumab (Group A) experienced a recurrence. On the other hand, the recurrence was observed in 6 out of 15 subjects (40%) from the control group (Group B). The disparity in the rates of recurrence between the two groups was found to be statistically significant (p-value of 0.031).

Table 2 Recurrence

Recurrence	Group A	Group B	P. value
Yes	1 (6.7%)	6 (40.0%)	0.031*
No	14 (93.3%)	9 (60.0%)	

Chi-square test used for relation between recurrence and groups. *Significant difference ($p<0.05$).

Group A had a mix of bilateral and unilateral nasal pterygia, while all of Group B had unilateral nasal pterygia. Group A received Bevacizumab injections before surgery without any complications. After surgery, one patient in Group A and six in Group B experienced pterygium recurrence. All conjunctival autografts were successful with no graft failures or rejections.

Group A. Case No 1

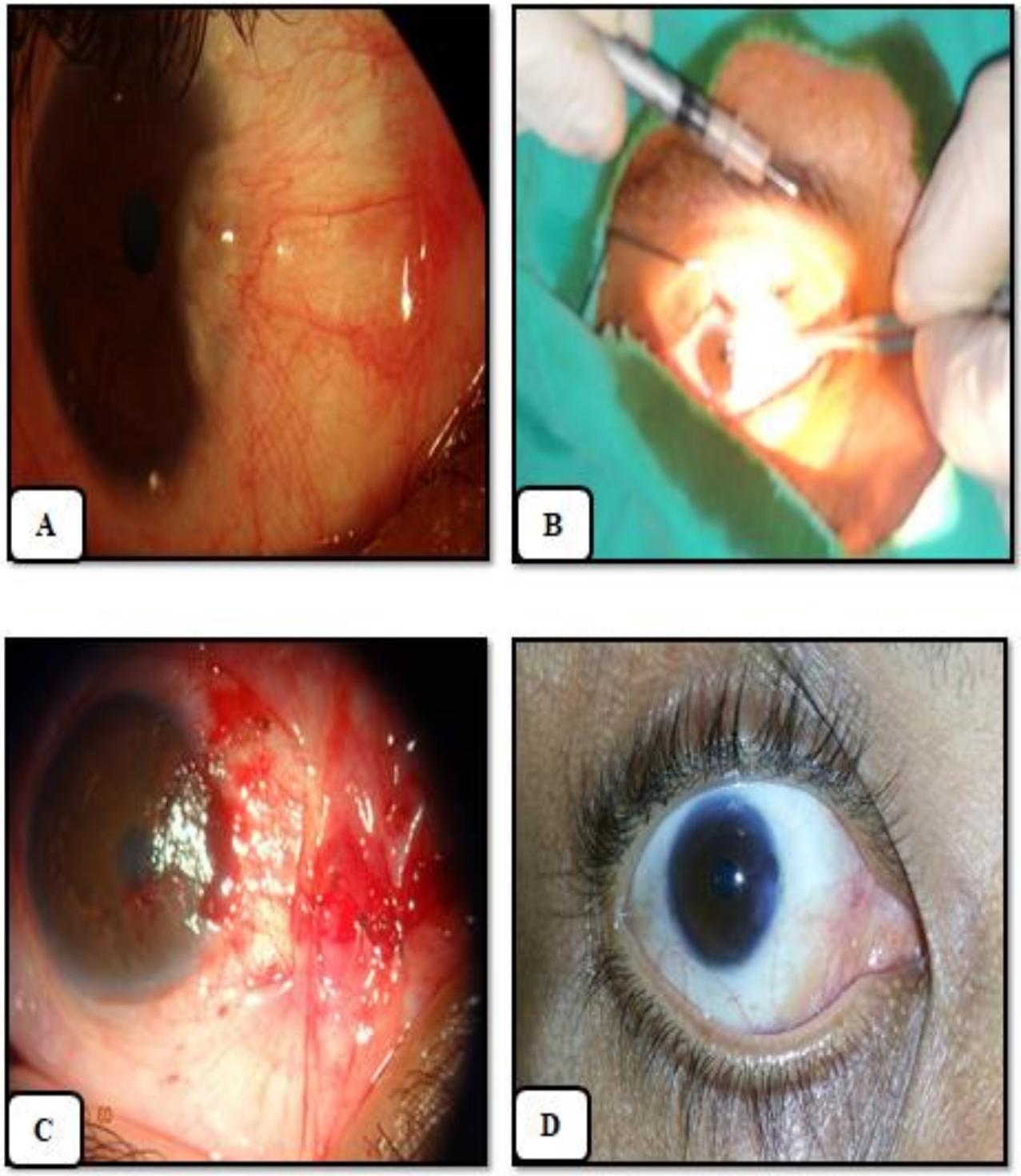


Figure (1): Progression of pterygium treatment in patient No (1) from group A:
a) Right pterygium before bevacizumab (Avastin) injection. .
b) During bevacizumab injection.
c) One day after surgical removal and conjunctival autograft transplantation**.**
d) 6 months post-surgery, no recurrence.

Group A. Case No 2

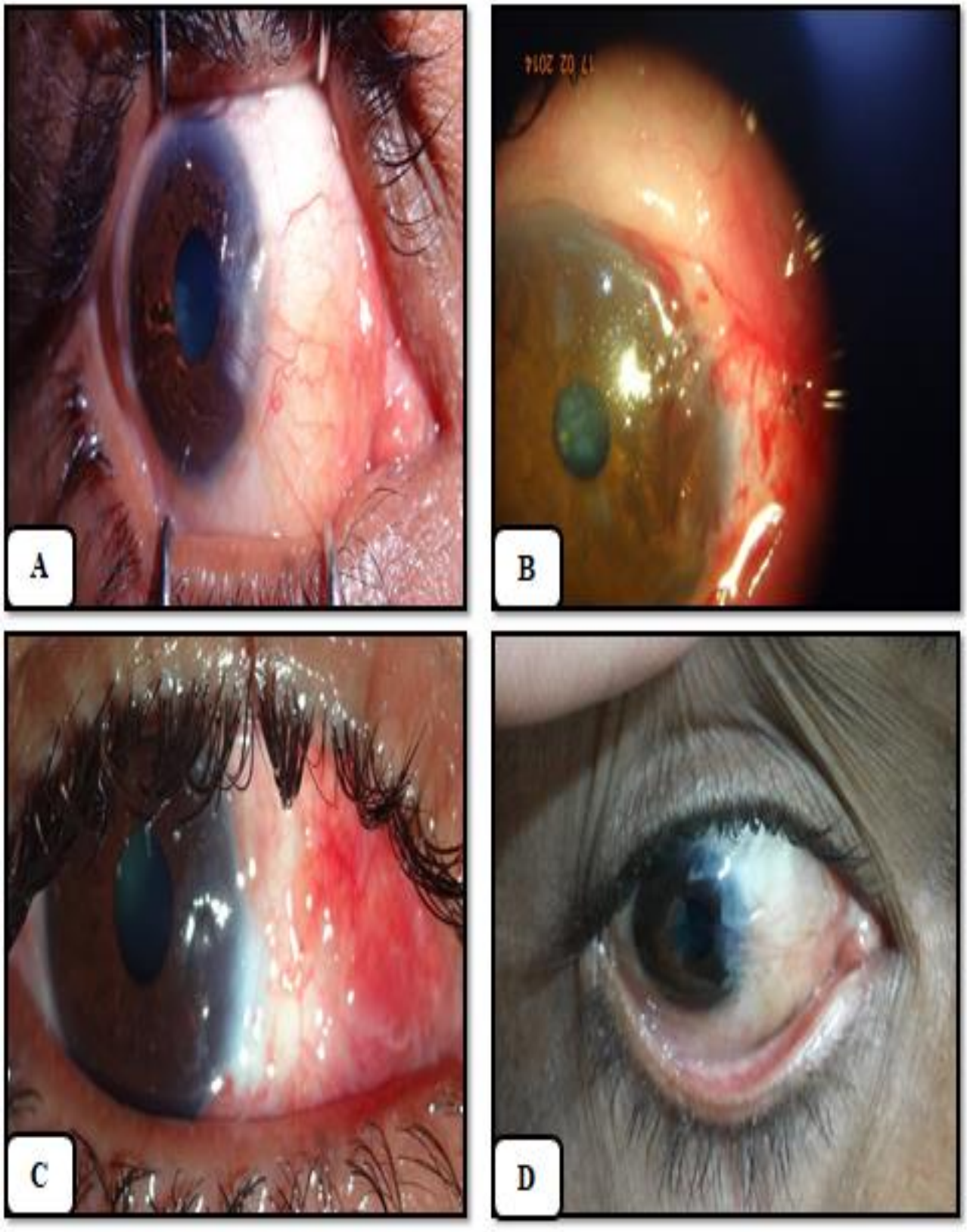
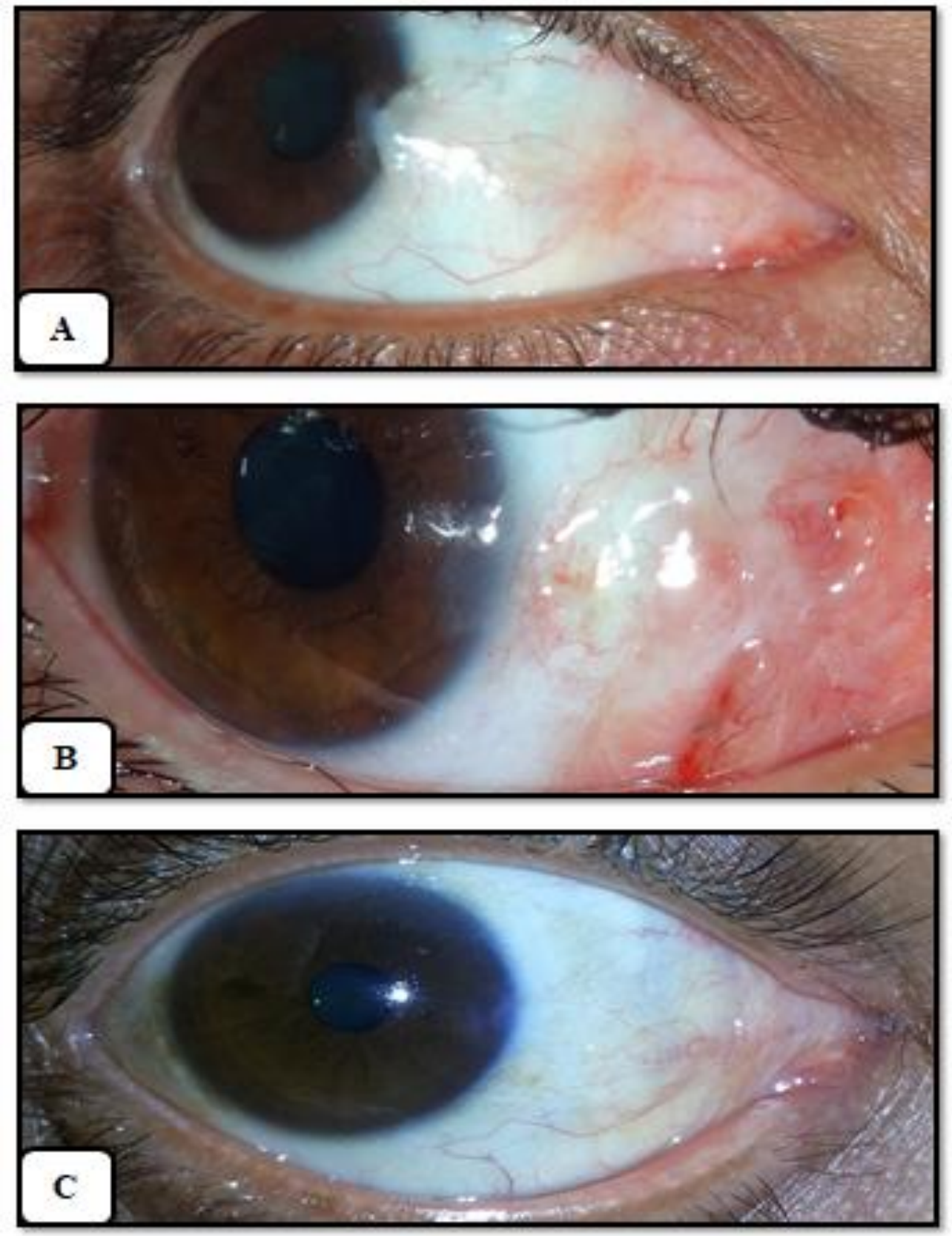


Figure (2): Progression of pterygium treatment in patient No (1) from group A:
a) Right pterygium before bevacizumab (Avastin) injection.
b) Post-surgery with conjunctival autograft (intraoperative).
c) One week after surgery and autograft.
d) Six months postoperative with bevacizumab injection, showing recurrence.

Group B. Case No 1

Figure (3): Right pterygium treatment phases in group B patient



a) Before surgery.
b) One week after surgical removal and conjunctival autograft transplantation.
c) Six months post-surgery with conjunctival autograft transplantation, no recurrence.

Group B. Case No 2

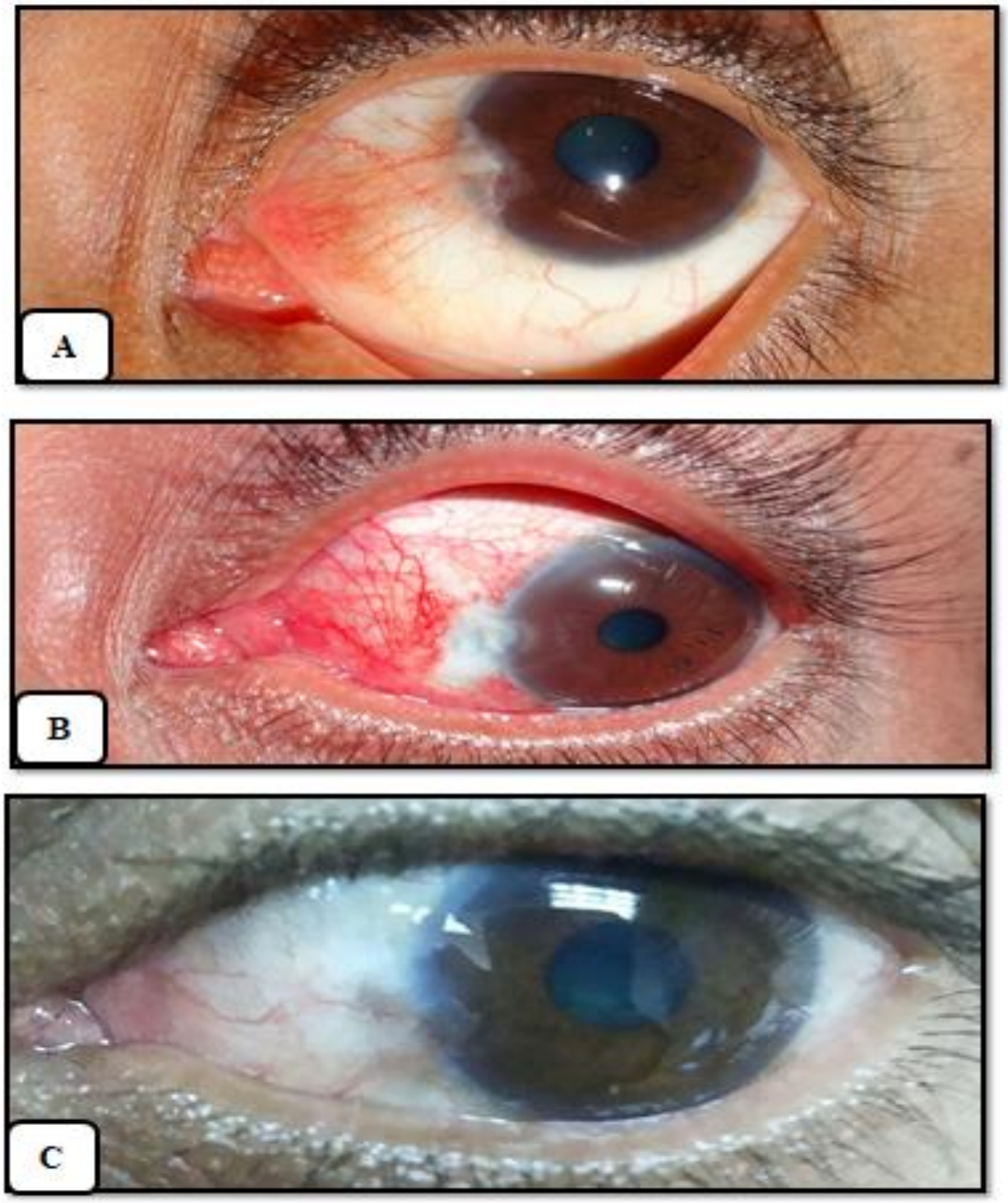


Figure (4): Lt pterygium treatment phases in a group B patient

a) Before surgery.
b) One week after surgical removal and conjunctival auto graft transplantation
c) Six months after surgery (Recurrent).

DISCUSSION

Our study investigated the effectiveness of preoperative intralesional bevacizumab (Avastin) injections combined with conjunctival autograft transplantation (Group A) compared to a control group that underwent pterygium surgery with conjunctival autograft transplantation but without bevacizumab treatment (Group B).

Within the scope of the study, we included 30 eyes from 30 different patients. It was observed that the patient age in group A varied between 25 and 49 years, with an average age of 37.4 ± 5.3 years. In contrast, group A's counterparts, group B, had an age range of 20 to 55 years and an average age of 38.3 ± 6.7 years. The higher prevalence of pterygium among these age brackets could be attributed to increased exposure to sunlight and environmental irritants, a notion supported by the findings of **Solomon *et al.*** [16] and **Prabhasawat *et al.*** [17].

Regarding gender predisposition, our study found 86.7% of group A and 80% of group B were male. This male predominance aligns with previous findings by **Tan *et al.*** [18, 19] that males have higher susceptibility, possibly related to more outdoor vocational exposure. This is further reinforced by studies from **Diaz *et al.*** [20] and **Karukonda** [21] indicating a greater pterygium occurrence in males, particularly those with outdoor occupations like farming. However, the influence of gender is complex, as other studies by **Peng and colleagues** [22] and **Nemesure *et al.*** [23] have found greater pterygium prevalence in females or no significant gender association, depending on population lifestyle and occupational factors. Nevertheless, our results do fit within the scope of research indicating a generally greater pterygium prevalence in males.

The correlation of pterygium with environmental factors such as UV light exposure, dry conditions, and exposure to elements like wind, dust, and heat has been well-documented, with **Ozkurt *et al.*** [24] highlighting these associations. Meanwhile, **Teng *et al.*** [25] proposed that immunologic and genetic factors also play roles in the pathogenesis of the condition [25], emphasizing the multifactorial nature of pterygium development, particularly among those with significant outdoor exposure.

Regarding the impact of bevacizumab on pterygium, several studies have shown varying results. Our study demonstrated a favorable tolerance to bevacizumab injections, with no complications during or post-injection in group A. The autografts were successfully integrated, and we observed only a single case of recurrence at the three-month follow-up, representing a recurrence rate of 6.7%. This is significantly lower than the 40.0% recurrence rate commonly reported in literature for procedures involving simple excision with a conjunctival autograft secured with sutures. The research by **Elnahas *et al.*** [26] focused on the impact of bevacizumab on pterygium recurrence post-surgery, with particular attention to the timing and dosing of bevacizumab injections. Their findings highlighted a notable decrease in recurrence when bevacizumab was administered both before and after excision using the bare sclera technique.

This contrasts with the findings of **Razeghinejad *et al.*** [27] who did not observe a significant change in recurrence rates following a single intraoperative bevacizumab injection at a lower dose. Their study suggests that the transient nature of anti-VEGF drugs may necessitate higher or multiple doses for effective prevention of recurrence. **Shenasi *et al.*** [28] echoed this sentiment, providing a single postoperative dose of bevacizumab and noting no significant long-term effects on recurrence prevention, despite an absence of notable adverse effects. Conversely, **Nava-Castañeda *et al.*** [29] documented a substantial reduction in recurrence with two doses of bevacizumab, when combined with conjunctival autograft. The dual-dose regimen, administered immediately after surgery and again after two weeks, proved effective over a one-year period [29]. **Ozsutcu *et al.*** [30] also reported positive outcomes with a similar strategy. An intraoperative bevacizumab dose supplemented by a follow-up injection one week later, in addition to pterygium excision and a rotational conjunctival flap, resulted in a significant drop in recurrence rates compared to the flap technique alone [30]. Furthermore, **Fallah *et al.*** [31] assessed the impact of an intralesional bevacizumab injection (2.5 mg/0.1 ml) and observed a mean reduction in lesion size, indicating the drug's potential efficacy and tolerability [31].

The work of **Teng *et al.*** [25] revealed that a single dose of bevacizumab led to almost total regression of irritation and hyperemia one week post-injection. However, by week seven, symptoms had returned to their pre-injection state, suggesting that the effects of the drug are not permanent. **Rashid *et al.*** [32] presented outcomes where subconjunctival bevacizumab administration effectively managed primary pterygium, reducing the mean surface area of the lesions without local or systemic adverse effects. **Mohammad *et al.*** [11] explored the clinical impact of subconjunctival bevacizumab in patients with primary and recurrent pterygium. The treatment resulted in a decrease in size, vascularity, thickness, and color intensity of the pterygium, affirming the drug's usefulness in managing these lesions without significant adverse effects. In a study by **Mandalos *et al.*** [33] the application of ranibizumab did not affect the histological appearance of primary pterygium, regardless the time between injection and surgical removal. **Galor *et al.*** [34] observed a 30% recurrence rate after administering subconjunctival ranibizumab in conjunction with primary pterygium surgery, suggesting a moderate level of effectiveness. **Lewallen** [35] described a low recurrence rate with conjunctival autografting. **Ashok and colleagues** [36] observed a recurrence rate of 5.7% in individuals who underwent pterygium excision followed

by conjunctival autografting, monitored over a period of six to twelve months.

These findings collectively suggest that while bevacizumab has shown promise in reducing recurrence rates in pterygium surgery, the degree of its effectiveness can vary. Some studies reported substantial benefits, while others suggested a more modest impact or no long-term benefits. The recurrence rates observed range widely from as low as 5.3% to 40%, dependent on the surgical techniques employed and the inclusion of bevacizumab in treatment protocols.

CONCLUSION

Pterygium, a prevalent condition affecting the surface of the eye, is prone to return after removal, particularly with the bare sclera method. Previous studies have suggested a role for vascular endothelial growth factor (VEGF) in the development of pterygium. Bevacizumab, an antibody that targets and neutralizes VEGF, has been shown in this research to significantly reduce the rate of pterygium recurrence when administered subconjunctivally before surgery compared to only using surgical excision and conjunctival autografting. The administration of bevacizumab was safely tolerated with no adverse effects noted. To validate the effectiveness of bevacizumab as an adjunctive treatment for primary pterygium, further extensive, randomized trials are necessary.

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