

## A Comparison Between Bevacizumab and Mitomycin C in Treatment of Primary Pterygium

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### ABSTRACT

**Background:** A pterygium is a fleshy, wing-shaped growth from the conjunctiva, crossing over the limbus onto the cornea. The tissue is fibrovascular and can occur over the nasal or temporal cornea. It can be a bilateral process and asymmetric with one eye affected by a larger pterygium than the other.

**Objective:** To compare between the effects of intraoperative subconjunctival injection of Bevacizumab (Avastin) and intraoperative topical Mitomycin C on the outcome of primary pterygium surgery as regard efficacy and complications.

**Methods:** Prospective, randomized, comparative clinical study was done on twenty eyes of twenty patients complaining of primary pterygium of variable duration that were surgically treated by simple excision. In addition to surgical excision, postoperative subconjunctival injection of bevacizumab was done for 10 eyes (group A), and postoperative application of mitomycin C (MMC) was done for 10 eyes (group B). The postoperative outcome was followed clinically for a minimum of 6 months and the main outcome criteria were recurrence rate and postoperative complications.

**Results:** A significant high recurrence rate was found in bevacizumab group (60%) in comparison to MMC group (10%). In group A subconjunctival hemorrhage was detected in 2 cases while no complications were detected in group B.

**Conclusion:** A single intraoperative subconjunctival injection of bevacizumab had decreased the recurrence rate after primary pterygium excision which seems to be marginally superior to bare sclera excision alone, but does not give a more desirable recurrence rate with insignificant complications as subconjunctival hemorrhage which resolved within 2 weeks.

**Keywords:** Pterygium, Bevacizumab, Mitomycin C.

### INTRODUCTION

A pterygium is a fleshy, wing-shaped growth from the conjunctiva, crossing over the limbus onto the cornea. The tissue is fibrovascular and can occur over the nasal or temporal cornea. It can be a bilateral process and asymmetric with one eye affected by a larger pterygium than the other. In addition, two pterygia can affect a single eye, one nasally and the other temporally. The pterygium consists of collagen tissue that is hyperplastic and denatured, marked by elastotic degeneration (degeneration of collagen fibers) <sup>(1)</sup>.

Pterygia can impair vision through altered tear film, induced astigmatism, photophobia, epiphora, and binocular diplopia due to contraction of the Tenon's capsule, which limits eye movements. Also pterygia can cause many symptoms such as eye irritation, foreign body sensation, and dryness. In mild climates, it is unusual for a pterygium to grow over the visual axis, but patients are often concerned about the cosmetic appearance of their eye. In potentially susceptible individuals, the pterygium can grow across the entire corneal surface, impairing vision <sup>(1)</sup>.

Inflammation and fibrovascular proliferation may be considered as important factors in occurrence. DNA damage has been reported to initiate pterygium development. Hereditary predisposition may be the underlying factor for pterygium occurrence. Ultra violet (UV) light has been shown to induce proinflammatory cytokines, chronic inflammatory cells, and growth

factors. It also may damage DNA in predisposed individuals. However, integration of factors associated with pterygium occurrence has not been reported <sup>(2)</sup>.

Despite evolutionary and modification of pterygium excision techniques, recurrence continues to be a limiting factor for success <sup>(3)</sup>.

The challenge continues to find an adjunctive agent with long-term safety and efficacy <sup>(4)</sup>.

Bevacizumab (Avastin) is a recombinant, humanized anti-VEGF monoclonal antibody. It was approved by the United States food and drug administration as a first line treatment for metastatic colorectal cancer in combination with chemotherapy <sup>(5)</sup>. It was used for treatment of neovascular age related macular degeneration, retinal vein occlusion, proliferative diabetic retinopathy, rubeosis iridis, neovascular glaucoma and other vision threatening diseases <sup>(6)</sup>.

### AIM OF THE WORK

To compare between the effects of intraoperative subconjunctival injection of Bevacizumab (Avastin) and intraoperative topical Mitomycin C on the outcome of primary pterygium surgery as regard efficacy and complications.

### PATIENT AND METHOD

Prospective, randomized, comparative clinical study was done on twenty eyes of twenty patients complaining of primary pterygium of variable duration

that were recruited from outpatient clinics of Ophthalmology Department of Al-Azhar University Hospitals. They were classified randomly into two groups:

Group (A): which received intraoperative subconjunctival injection of bevacizumab 1.25 mg (0.05 ml) after pterygium excision with bare sclera.

Group (B): which received intraoperative topical Mitomycin C 0.02% for duration of two minutes after pterygium excision with bare sclera.

**Inclusion Criteria:**

- Age (20-60) years.
- Patients with primary pterygium.

**Exclusion Criteria:**

- Patients with recurrent pterygia.
- Patients with ocular infection.
- Patients with corneal opacity preventing proper follow up.

**Preoperative Evaluation:**

- Assessment of uncorrected and best corrected visual acuity using Snellen’s chart.
- Fundus examination using indirect ophthalmoscope and assessment of intraocular pressure using applanation tonometry.
- Local examination of the primary pterygium as regards its degree and vascularity.

**Ethical consideration and Written informed consent: An approval of the study was obtained from Al-Azhar University academic and ethical committee.**

Every patient signed an informed written consent for acceptance of the operation.

A standardized surgical technique was performed for both groups. Instillation of only two drops of Benoxinate HCL 0.4% in the eye. The procedure was performed under peribulbar anesthesia in the form of mixture of 3 ml Debocaine 2.0% vial (Lidocaine HCL 20 mg/ml) for infiltration and nerve block, and 3 ml Marcaine (Bupivacaine HCL 0.5%). The bulbar conjunctiva at the edge of the scleral portion of the pterygium was incised with Wescott scissors and this portion was freed from the underlying sclera by blunt dissection.

The freed portion of the pterygium was then grasped with toothed forceps and torn from the cornea and a second forceps grasped the perilimbal tissue away to give counteraction.

Residual tissue is scraped from the corneal surface with beaver blade. Group (A) received subconjunctival injection of bevacizumab while group (B) received topical Mitomycin C for two minutes duration. Postoperative treatment was Tobramycin 0.3% drops and ointment five times daily for the drops and once at night for the ointment. Follow up was done for 6 months.

**Statistical analysis:**

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

**The following tests were done:**

- Independent-samples t-test of significance was used when comparing between two means.
- Chi-square (x<sup>2</sup>) test of significance was used in order to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following:
  - Probability (P-value)
  - P-value <0.05 was considered significant.
  - P-value <0.001 was considered as highly significant.
  - P-value >0.05 was considered insignificant.

**RESULTS**

There was no significant statistical difference between the two groups regarding age, sex and occupation (Table 1).

**Table (1): Comparison between the studied groups regarding demographic data**

Variables		Group A (N = 10)	Group B (N = 10)	P-value
Age (years)	< 30 years	2 (20%)	1 (10%)	0.82
	30 – 50 years	7 (70%)	8 (80%)	
	> 50 years	1 (10%)	1 (10%)	
Sex	Male	8 (80%)	7 (70%)	0.6
	Female	2 (20%)	3 (30%)	
Occupation	Outdoor	7 (70%)	6 (60%)	0.64
	Indoor	3 (30%)	4 (40%)	

This table shows no statistically significant difference (p-value > 0.05) between studied groups regarding demographic data.

As regard age, there were 2 patients (20%) < 30 years, 7 patients (70%) 30 – 50 years & 1 patient > 50 years in group A, while there were 1 patient (10%) < 30 years, 8 patients (80%) 30 – 50 years & 1 patient > 50 years in group B (p-value = 0.82).

Regarding sex, there were 8 males (80%) & 2 females (20%) in group A while there were 7 males (70%) & 3 females (30%) in group B (p-value = 0.6).

As regard occupation, there were 7 patients (70%) working outdoor and 3 patients (30%) working indoor in group A while there were 6 patients (60%) working outdoor and 4 patients (40%) working indoor in group B (p-value = 0.64).

**Table (2): Comparison between the studied groups as regard main complaints**

Variables		Group A (N = 10)	Group B (N = 10)	P-value
Main complain	Ocular irritation	3 (30%)	3 (30%)	0.93
	Irritation & cosmetic comp.	5 (50%)	4 (40%)	
	Cosmetic comp.	1 (10%)	2 (20%)	
	Irritation & visual disturbance	1 (10%)	1 (10%)	

This table shows no statistically significant difference (p-value > 0.05) between the studied groups as regard main complain.

In group A, ocular irritation was reported in 3 patients (30%), irritation and cosmetic comp. was reported in 5 patients (50%), cosmetic comp. was reported in 1 patient (10%) and irritation and visual disturbance was reported in 1 patient (10%).

In group B, ocular irritation was reported in 3 patients (30%), irritation and cosmetic comp. was reported in 4 patients (40%), cosmetic comp. was reported in 2 patients (20%) and irritation and visual disturbance was reported in 1 patient (10%).

Regarding the side of pterygium in the studied groups, all cases show only nasal type (Table 3).

**Table (3): Description of side of pterygium in studied groups**

Variables	Group A (N = 10)	Group B (N = 10)
Side of pterygium	100% Nasal	100% Nasal

This table shows that all studied patients (100%) in both groups had nasal side pterygium.

**Results of treatment:**

During the follow up period of this study, the recurrence occurred in 7 cases (35%) out of 20 cases of the study (Table 4 & 5). Recurrence was considered when a fibrovascular growth had occurred in the position of the previously excised pterygium crossing the limbus and extending onto the cornea for any distance.

**Table (4): Comparison between the studied groups as regard recurrence**

Variables		Group A (N = 10)	Group B (N = 10)	P-value
Recurrence	No	4 (40%)	9 (90%)	0.02**
	Yes	6 (60%)	1 (10%)	

\*\* : p-value < 0.05 is considered significant.

This table shows statistically significant difference (p-value < 0.05) between studied groups as regard recurrence. In group A, recurrence occurred in 6 cases (60%) while in group B it occurred only in 1 case (10%). Regarding the postoperative complications only two cases show postoperative complications (Table 5).

**Table (5): Comparison between the studied groups as regarding complications**

Variables		Group A (N = 10)	Group B (N = 10)	P-value
Complications	No	8 (80%)	10 (100%)	0.14
	Sub conj. Hemorrhage	2 (20%)	0 (0%)	

This table shows no statistically significant difference (p-value > 0.05) between both groups as regard complications. Sub-conjunctival hemorrhage occurred in 2 cases (20%) of group A while there were no complications in group B.



**Figure (1): A case of postoperative subconjunctival hemorrhage.**



**Figure (2a): A case of primary nasal pterygium**





**Figure (2b): The same case one month postoperative with bevacizumab injection**



**Figure (2c): The same case six months postoperative with recurrence**

## DISCUSSION

Regarding the ages of the patients of the present work; they ranged from 25-60 years old. The higher incidence was found to be in the age group of 30-50 years (75%). This may be due to maximum exposure to sun light and various irritants in this age, as pterygium is one of the sun related condition. This finding was in agreement with that was recorded by some previous studies e.g. **Bunga and Kotipalli** <sup>(7)</sup> who observed that the incidence of pterygium is higher in 3<sup>rd</sup> and 4<sup>th</sup> decades. The incidence is lower in 5<sup>th</sup> decade which is (10%). Cases reported below 20 years are 0%. 3<sup>rd</sup> & 4<sup>th</sup> decade persons are more active in outdoor work, so more exposure to the solar radiation. The lower incidence after 5<sup>th</sup> decade might because of inability to work and confined to home. **Chen** <sup>(8)</sup> found that the highest incidence (65.5%) in the age group 40-49 years.

Also in the present study, it was found that primary pterygia were common in males (75%) than females (25%) and the recurrence was more in males (40%, where 6 cases out of 15 male cases were recurred)

than females (20%, where one case out of five female cases were recurred).

These results were parallel to that found in other studies as **Bunga and Kotipalli** <sup>(7)</sup> who found that 70% of the affected patients were males while 30% were females. Also, in the study done by **Shenasi et al.** <sup>(9)</sup> there were 27 males (81.8%) and 6 females (18.2%) in their study group.

Regarding the occupation, in our study pterygia were more common in the outdoor than indoor patients (65%). Also recurrence was more in outdoor patients (71.4%) than indoor patients (28.6%).

In the study of **Bunga and Kotipalli** <sup>(7)</sup>, it was found that (76%) of the affected patients were in outdoor group, who are more exposed to sunny and dusty climate, while (24%) were indoor group.

Regarding the site of pterygium, in the present study all patients presented with nasal pterygium which was explained by the role of sun light. These findings were parallel to that of **Bunga and Kotipalli** <sup>(7)</sup> study in which 54 eyes (96.4%) of 56 eyes from 50 examined patients presented with nasal pterygia while (3.6%) presented with temporal pterygia.

Regarding the recurrence rate, in our study the pterygium recurred in 7 cases (35%) out of 20 cases. The recurrence in group (A) (bevacizumab group) occurred in 6 cases (60%) out of 10 cases. In group (B) (MM-C) the recurrence occurred in one case (10%) out of 10 cases. Recurrence was considered when a fibrovascular growth had occurred in the position of the previously excised pterygium crossing the limbus.

These results were parallel to that reported in other studies as **Kocabora et al.** <sup>(10)</sup> in which recurrence occurred in 10 cases (66.7%) out of 15 cases of (bevacizumab group), and in 4 cases (26.7%) out of 15 cases of (MM-C) group. Patients were followed up for 12 months after operation.

Also the recurrence rate in MMC group was comparable to that mentioned by **Panda et al.** <sup>(11)</sup> who recorded that (12%) recurrence rate in (MM-C) group after 7 months, where intraoperative (MM-C) was used in a concentration of 0.02% for 3 minutes.

This variability of the recurrence rate between studies may be due to differences in definition of recurrence, surgical technique, experience, patient demographics, racial and environmental factors.

Regarding the age of recurrence, the results of our work showed that the mean age of recurrence was  $33.75 \pm 3.6$  years and this was agreed with other studies that considered that young age as a risk factor for recurrence of pterygium as **Mastropasqua et al.** <sup>(12)</sup> who found that failure occurred only in young ages in (MM-C) treated

cases with a mean age about 31 years. Also **Panda *et al.*** <sup>(11)</sup> recorded that the age of recurrence ranged between of 22-27 years.

Regarding postoperative complications, in our study there were 2 cases out of 20 cases that showed postoperative complications (10%).

Complications observed in the bevacizumab group included 2 cases (20%) out of 10 cases that developed subconjunctival hemorrhage. These 2 cases improved after 2 weeks.

This was in agreement with the study of **Mak *et al.*** <sup>(13)</sup> who found that the most commonly detected complication with bevacizumab was subconjunctival hemorrhage which was self-limiting and may be related to the subconjunctival injection only.

Most studies concluded that anti-VEGF is safe and no systemic complications were detected <sup>(10)</sup>.

There were no complications observed in (MM-C) group which vary according to the concentration and the duration of application. With the most commonly used dose of 0.02% for 2 minutes, there were no severe complications detected <sup>(14)</sup>.

## CONCLUSION

In the present study, we concluded that a single intraoperative subconjunctival injection of bevacizumab decreased the recurrence rate after primary pterygium excision, which seems to be marginally superior to bare sclera excision alone, but does not give a more desirable recurrence rate with insignificant complications as subconjunctival hemorrhage which resolved within 2 weeks. On the other hand we concluded that intraoperative application of mitomycin C is effective in reducing the recurrence rate of primary pterygium after surgical excision. In our study there were no complications associated with (MM-C) use which were detected in other studies, so it should be used judiciously.

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