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Efficacy of Sub-Conjunctival Injection of Mitomycin C Versus Bevacizumab in Pterygium Treatment: Pakistani Population

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ABSTRACT

Background: Pterygium is a progressive fibrovascular tissue that affects the conjunctiva and cornea. The aim of the study was to compare the efficacy of Sub-conjunctival injection of Mitomycin C versus Bevacizumab in pterygium treatment focusing on their impact on recurrence rates to improve postoperative outcomes.

Methods: The Randomized clinical trial was conducted in the Ophthalmology department of Ziauddin University over 8 months. 54 patients aged above 18 with grade 2 or 3 pterygium were divided into 2 groups of 27. Group A received a Subconjunctival injection of Mitomycin C while Group B received Bevacizumab. Patients were monitored at 1st and 3rd week post injection followed by pterygium excision 1 month later. The postoperative follow-up was conducted at the 1st, 3rd, and 6th months to assess improvement in symptoms and recurrence. The data was analyzed using SPSS version 23; the Chi-square test and Paired T-test were applied with a significance level of $p < 0.05$.

Results: The study analyzed data from 54 patients with pterygium, having a mean age of 42.03±8.23 years, with a male-to-female ratio of 3:1. The common symptoms were Redness (40.74%), itching (27.8%), and decreased visual acuity (31.4%). Post-injection outcome in terms of pterygium vascularity and thickness was better in group B. The recurrence rates at the 6th-month post excision were 1 (7.4%) and 3 (18.5%) in group B.

Conclusion: Mitomycin C as an adjuvant treatment demonstrates superior efficacy in reducing pterygium recurrence and improving postoperative vision, compared to Bevacizumab.

Keywords: Pterygium, Mitomycin C, Bevacizumab.

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INTRODUCTION

Pterygium is a progressive fibrovascular conjunctival growth that potentially involves the cornea [1]. The prevalence of pterygium varies depending upon the geographic location, climate, and demographic factors [2]. Studies show that the global prevalence of pterygium ranges from 0.07% - 53% with higher rates in tropical and subtropical regions. The exact pathogenesis of pterygium is not fully understood, but it is believed to involve a combination of genetic, environmental, and ultraviolet (UV) light exposure factors [3]. Chronic exposure to ultraviolet B (UVB) is considered a significant risk factor [4]. It can damage the conjunctiva and promote the growth of abnormal tissue [5]. Environmental factors, such as dry, dusty, and windy conditions, also contribute to its development [6]. A pterygium most commonly occurs on the nasal side of the eye, often described as the corneal limbus, which is the border where the cornea meets with sclera [7]. Preventive measures such as wearing UV-protective sunglasses and reducing exposure to environmental irritants are often recommended[8]. Surgery for pterygium excision, which may involve the use of adjunctive treatments like Mitomycin C or conjunctival flaps and amniotic membrane, is typically indicated for progressive pterygium, chronic discomfort, visual impairment, and cosmetic purpose [9]. The use of intra-lesion injections of 5-fluorouracil (5-FU), Mitomycin C, Bevacizumab, and Ranibizumab for the treatment of pterygium is an emerging and innovative approach that reduces pterygium size, thickness, vascularity and recurrence [10]. Mitomycin C is an antimetabolite, used to inhibit cell growth and reduce the recurrence [11]. Bevacizumab is an anti-VEGF (vascular endothelial growth factor) medication. It works by reducing the growth of new blood vessels, which can be a characteristic of pterygium [12]. By reducing vascularization in the pterygium, Bevacizumab may help control its progression and size [13]. The study aimed to assess the efficacy of a sub-conjunctival injection of Mitomycin-C compared to Bevacizumab as an adjunct therapy following pterygium excision, in terms of recurrence.

METHODS

A randomized control trial study was conducted in the Ophthalmology department of Ziauddin University Hospital Karachi, over 8 months from 1st January to 31st August 2024. The ethical approval was obtained from the institutional ethical committee before initiating the study (7921023AKOPH/December 2023). The sample size was determined using the WHO sample size calculator, resulting in 54 patients divided into 2 groups of 27 through purposive sampling. Inclusion criteria included patients above 18 years and pterygium grades 2 and 3. Those with previous pterygium surgery or trauma, grade 1 pterygium, corneal opacity, lactating or pregnant females, and those with hypertensive, cardiac, or thromboembolic conditions were excluded. After obtaining informed consent, Group A received a Subconjunctival injection of Mitomycin-C, while Group B received a Subconjunctival injection of Bevacizumab. Both groups underwent adjunct surgical excision after the injection using the bare sclera technique. Patients were provided with information leaflets outlining the advantages and disadvantages of each drug to help them make an informed decision. The pre-operative assessment was performed by a single ophthalmologist and included evaluation of symptoms, clinical examination, baseline visual acuity, type of refractive error, best corrected visual acuity, and grading of pterygium type and size. Each pterygium was assessed and categorized based on thickness and vascularity of growth according to Tan and colleagues' grading system, introduced in 1997. The grading was determined by the visibility of the underlying episcleral blood vessels, a previously established and validated marker of severity. The pterygium was divided into three grades. Grade 1: (atrophic) exhibited visible episcleral vessels beneath the pterygium. Grade 2: (Intermediate) showed partially visible episcleral vessels. Grade 3: (Fleshy, Hypertrophic) had entirely obscured episcleral vessels. The pterygium size was assessed based on corneal involvement. Grade 1 extends up to the limbus, Grade 2 between the limbus and the pupillary margin, and Grade 3 extends across the pupillary margin [8].

Injections were administered in Operation Theater under topical anesthesia using Alcaine eye drops (proparacaine HCL). Group A received a 2mg/0.1 ml Subconjunctival injection of Mitomycin-C; while Group B received a 2.5mg/0.1 ml injection of Bevacizumab. During the procedure, patients were asked to look toward the temporal side to ensure adequate exposure for the injection. A 1ml syringe with a 29-gauge needle was used. Mitomycin C (MMC) was prepared in the operating theater during the procedure and Bevacizumab was provided by the pharmacy as pre-prepared sterilized injections. All patients were examined after 1st week and 3rd week of injection to assess improvements in symptoms and to examine any changes in vascularity, thickness, and the size of the pterygium growth. Surgical excision was performed 1 month after injection and patients were examined, the day after surgery, 3rd month, and 6th month. Data was entered and analyzed using SPSS version 23. Quantitative variables, including age, and recurrence rates were presented as mean ± standard deviation. Qualitative variables, like gender, occupation, pterygium grades, baseline visual acuity, refractive errors, location of pterygium, symptoms, and pterygium vascularity and thickness were presented as frequency and percentage.

RESULTS

In this study, the mean age of patients in both groups was 42.03± 8.23 years. The male-to-female ratio was found 3:1, with 41(76%) men and 13(24%) women, a significant difference attributed to a higher likelihood of men working outdoors. Patients presented with symptoms of ocular redness in 22(40.74%), itching and watering in 15 (27.8%), and decreased visual acuity in 17 (31.4%). Of all patients, 35(64.9%) worked outdoor, while 19(35.1%) stayed indoor. Pterygium was found in the right eye of 22(40.74%) patients, the left eye of 27 (50.0%), and in both eyes of 5(15.5%) patients. Baseline visual acuity was ≤ 6/18 in 34(63.0%) patients while remaining 20(37.0%) patients had >6/18. Refractive error was observed in the affected eye, Astigmatism in 24 patients (44.44%), Myopia in 6 (11.2%), Hypermetropia in 9(16.6%), and no refractive error in 15 patients (27.8%). Based on the size of Pterygium, 38 (70.4%) were grade 2 while 16 (29.6%) were Grade 3. Based on vascularity and thickness of pterygium, 34 (63.0%) were intermediate and 20 (37.0%) were hypertrophic. (Refer to table 1). Evaluation one week after surgery showed a reduction in vascularity, thickness, and astigmatism in both groups, with Group B demonstrating better outcomes than Group A (Figure 1).

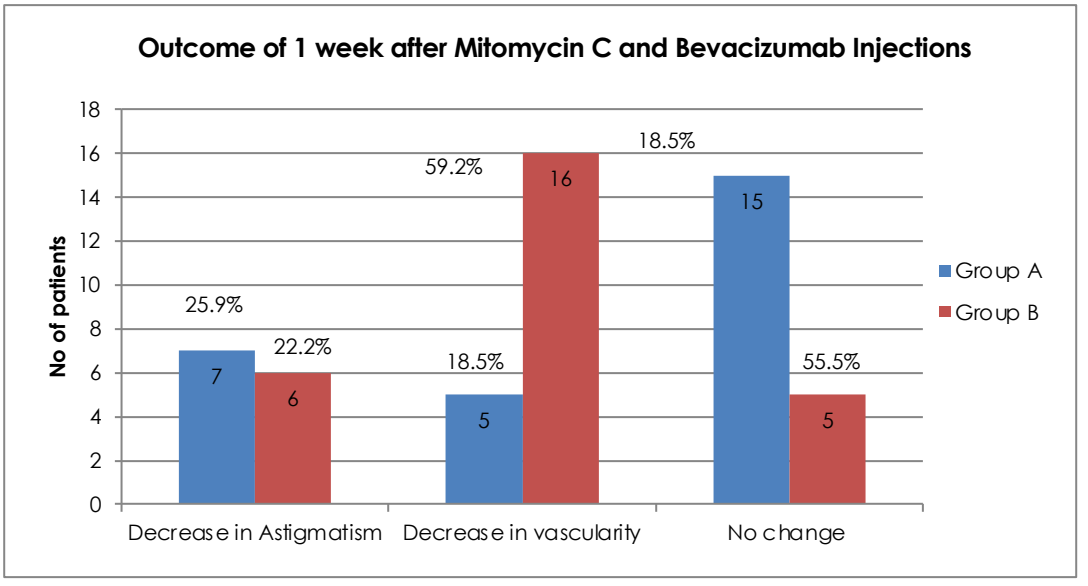

Figure -1: Comparison of Changes in Astigmatism and Vascularity for Week 1 In Both Mitomycin C and Bevacizumab Groups.

Age, Gender distribution, presence of symptoms, refractive error categories, and occupation were analyzed in association with pterygium grading using the Chi-square test, with significance indicated by a *p-value* < 0.05. Improvements in visual acuity, reduction in vascularity, and pterygium size and grading were analyzed through a Paired T-test with a *p-value* < 0.05. Comparison of outcome between the two treatments at each follow-up was analyzed through an Independent T-test.

Table 1: Baseline Demographic Characteristics and Pre-Operative Assessment of Study Participants.

Characteristics	Male	Female
Age		
≤ 40 years	14 (34.1%)	5 (38.4%)
> 40 years	27 (65.9%)	8 (61.6%)
Occupation		
Outdoor worker (35)	27 (65.9%)	8 (61.6%)
Indoor Worker (19)	14 (34.1%)	5 (38.4%)
Eye		

Left (22)	15 (36.6%)	7 (53.8%)
Right (27)	24 (58.5%)	3 (23.1%)
Both eye	2 (4.9%)	3 (23.1%)
Symptoms		
Redness	17 (41.5%)	5 (38.4%)
Itching	6 (14.6%)	2 (15.4%)
Watering	4 (9.8%)	3 (23.1%)
Decrease visual acuity	14 (34.1%)	3 (23.1%)
Visual Acuity		
≤ 6/18	27 (65.9%)	7 (53.8%)
> 6/18	14 (34.1%)	6 (46.2%)
Refractive Error		
Astigmatism	18 (43.9%)	6 (46.2%)
Myopia	3 (7.3%)	3 (23.1%)
Hypermetropia	8 (19.5%)	1 (7.7%)
No Refractive error	12 (29.3%)	3 (23.1%)
Pterygium Grade		
Grade 2 (38)	26 (63.4%)	12 (92.3%)
Grade 3 (16)	15 (36.6%)	1 (7.7%)
Pterygium Type		
Intermediate (34)	26 (63.4%)	8 (61.6%)
Hypertrophic (20)	15 (36.6%)	5 (38.4%)

The Pearson's Chi-square test shows significant correlations between pterygium grading and demographic variables; Age (p=0.020), gender (p=0.047), occupation (p=0.022), symptoms (p=0.033) and refractive error (p=0.002) (Table 2). However, visual acuity (p=0.088) was not statistically correlated, suggesting that certain factors were more predictive of pterygium severity than others.

Table 2: Pearson's Chi-Square Test Showing Correlation Between the Pterygium Grading and Demographic and Pre-Operative Clinical Presentation

Variables		Grade 2	Grade 3	Chi-square value	Df	P-value
Age	≤40	15 (27.8%)	4 (7.5%)	9.798	3	0.020
	>40	23 (42.4%)	12 (22.3%)			
Gender	Males	26 (63.4%)	15 (36.6%)	3.952	1	0.047
	Females	12 (92.3%)	1 (7.7%)			
Occupation	Indoor	14 (73.7%)	5 (26.3%)	5.246	1	0.022
	Outdoor	24 (68.6%)	11 (31.4%)			
Symptoms	Redness	9 (40.9%)	13 (59.1%)	6.844	2	0.033
	Itching	3 (42.9%)	4 (57.1%)			
	Watering	2 (28.6%)	5 (71.4%)			
	Decreased vision	5 (29.4%)	12 (70.6%)			
Visual acuity	≤ 6/18	22 (64.7%)	12 (35.3%)	9.593	5	0.088
	> 6/18	16 (80%)	4 (20%)			
Refractive error	Astigmatism	7 (29.2%)	17 (70.8%)	9.272	1	0.002
	Myopia	6 (100%)	0 (0%)			
	Hypermetropia	9 (90%)	1 (10%)			
	None	15 (100%)	0 (0%)			

The paired t-test was used to correlate pre- and post-treatment results for both groups (Table 3). Both groups showed a significant reduction in vascularity after the injection (p values < 0.050). Group A showed a more significant decrease in vascularity as compared to Group B. Post-surgery analysis showed a higher recurrence rate in Group B, 5 cases, as compared to 2 cases in Group A. Overall, Group B was more effective in initial symptom relief but experienced a higher recurrence rate post-surgery.

Table 3: Paired T-test showing the Pre- and Post-treatment Correlations

Variables	Group A			Group B		
Baseline vs post-injection	Mean change	df	p-value	Frequency	df	P-value
Vascularity	-6	26	0.001	-22	26	< 0.001
Astigmatism	-4	26	0.02	-3	26	0.05
Post-injection vs post-surgery	Mean change	df	p-value	Frequency	df	P-value
Astigmatism	-2	26	0.10	-1	26	0.20
Recurrences	2	26	0.02	5	26	0.01

Patients were analyzed using an Independent T-test at post-injection, 1 month, 3rd month, and 6th month post-surgery in terms of astigmatism and recurrence (Table 4). There was no significant difference in astigmatism between the groups after injection or at 1 month after surgery. However at the 3rd and 6th months, group A had significantly fewer cases of astigmatism (p= 0.020). Recurrence was absent in both groups at 1 month; however, by the 3rd and 6th month, Group B had significantly higher recurrence rates (p = 0.03). Overall, the findings suggest that Group B had better initial outcomes in vascularity while Group A achieved more significant long-term results with fewer cases of astigmatism and recurrence

Table 4: Comparison Between the Astigmatism and Recurrence Rates Between the Two Treatments at Different Points in Time.

Symptom	Time point	Frequency (Group A)	Frequency (Group B)	t- value	p-value
Vascularity	Post- Injection	21 (77.8%)	5 (18.5%)	6.42	<0.001
Astigmatism	Post-Injection	8 (29.6%)	9 (33.3%)	-0.39	0.700
	1-month post-surgery	6 (22.2%)	8 (29.6%)	-1.41	0.165
	3,6-month post-surgery	5 (18.5%)	9 (33.3%)	-2.44	0.02
Recurrence	1-month post-surgery	0	0	0.00	1.00
	3,6-month post-surgery	2 (7.4%)	5 (18.5%)	-2.28	0.03

DISCUSSION

Pterygium is an ocular surface disease characterized by invasive proliferation of fibrovascular tissue in the conjunctiva and cornea [14]. Various treatment modalities for pterygium management include vascular endothelial growth factors like Bevacizumab, Mitomycin C, 5 fluorouracil, and cyclosporine [15]. Mitomycin C and Bevacizumab are used in the management of pterygium, particularly during or before surgical procedures [16]. Both have potential side effects that require careful consideration [17]. Mitomycin C, while effective in reducing recurrence rate after surgery, leads to corneal epithelial defects, conjunctival inflammation, and delayed healing [18].

Subconjunctival Bevacizumab has better tolerance with some ocular side effects such as conjunctival hyperemia and blurred vision [19]. However, limited comprehensive research and data have prevented the establishment of a definitive treatment regimen, particularly in Pakistan, where few studies on this topic exist[20]. Due to insufficient comparative data, researches conducted on these medications individually were incorporated.

A meta-analysis focused on the efficacy and safety of using Bevacizumab injection with surgical excision on recurrence rate. Results showed that it signifi-

cantly reduced pterygium recurrence and improved visual outcome [20]. A study observed patients who received Bevacizumab before surgery had a significantly lower recurrence rate (6.7%) compared to those without the injection (40%) with a statistically significant difference (p=0.031) [21]. Another study reported that after Bevacizumab injection, there was a significant reduction in functional discomfort, and improvement in pterygium grade, with the highest success rate for recurrence after surgical excision [22]. A similar study was conducted where a single intraoperative application of 0.04% Mitomycin C, combined with bare sclera technique for pterygium excision resulted in minimal complication and 4% recurrence rate [23]. Another reported group A received monthly injections of 0.1 ml 5 fluorouracil for 3 months and group B received 0.1 ml injection Bevacizumab for the same duration. Improvement was observed in 21 patients (65.6%), while 2 patients (6.3%) in group B showed improvement [24]. A randomized controlled trial involving three treatments was conducted: group A treated with a pre-operative injection of 0.02% Mitomycin C and Group B with intraoperative Mitomycin C and pterygium excision with conjunctival graft. After 24 months of research, no significant difference in recurrence rate was found [25].

Our research compared the efficacy of Bevacizumab and Mitomycin C in preventing pterygium recurrences. Comparative investigation following intra-lesion injections of Mitomycin C in group A and Bevacizumab in group B showed that group B had a better outcome with a more significant decrease in vascularity and thickness of the lesion. The pterygium lesions were excised in both groups one month after intra-lesion injections. Post-operative follow-up at 3 and 6 months showed a greater recurrence rate in group B with 5 (18.5%) recurrences at both months as compared to 2 (7.4%) recurrences in group A.

CONCLUSION

In conclusion, both Mitomycin C and Bevacizumab effectively reduced pterygium recurrence, but have distinct side effects; regular follow-up is critical for managing adverse effects and optimizing outcomes in pterygium treatment.

LIST OF ABBREVIATIONS

None

CONFLICT OF INTEREST

None

FUNDINGS

None

ETHICAL APPROVAL

Taken from institutional ethical committee. 7921023AKOPH/December 2023.

AUTHORS CONTRIBUTIONS

AK was responsible for patient management and counseling. She analyzed and interpreted the patient's data and was a major contributor to writing the manuscript. **SS** Proofread the manuscript and did the data collection. **AF** was a contributor in writing the manuscript and conducted a Literature search. **AK** performed the Statistical analysis. **MS** did the literature search and references writing.

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