Original Article

Sub-conjunctival injection of 5 Fluorouracil versus Bevacizumab in Treatment of Primary Pterygium

Shagufta Parveen[1], Saquib Naeem[2], Waqar Muzaffar[3], Muhammad Kamran Saeed[4], Zaheer-ud-Din Babar[5]
[1,3,4,5]Combined Military Hospital, CMH, Lahore. [2]Armed Forces Institute of Ophthalmology (AFIO), Rawalpindi

PJO – Official Journal of Ophthalmological Society of Pakistan
Volume2023;39(4):314-318.
Doi:10.36351/pjo.v39i4.1651

ABSTRACT

Purpose: To compare effectiveness and safety of 5 Fluorouracil versus Bevacizumab as sole therapy in the treatment of primary pterygium.

Study Design: Quasi-experimental study.

Place and Duration of Study: Combined Military Hospital Lahore, from January 2022 to January 2023.

Methods: A total of 64 patients were included and divided into 2 groups of 32 patients each. Group A patients received monthly injection of 0.1 ml, Fluorouracil (5FU) for 3 months while 3 injections of 0.1 ml Bevacizumab were administered in group B. Primary outcome measure was effectiveness (defined as improvement in Pterygium grade), at 4 weeks following the administration of last injection. Patients were examined for pterygium grading as well as any side effects of injections on each follow up visit. Data analysis was done by SPSS, Version 23.0.

Results: Mean age of patients in group A was of 33.53 ± 11.3 years versus 30.97 ± 12.6 years in group B with a range of 15–55 years. There were 45 (70.3%) males and 19 (29.7%) females. Improvement was seen in 21 patients (65.6%) in group A, as compared to only 2 (6.3%) in group B. There was a significant difference in pterygium improvement between the two groups ($p < 0.001$).

Conclusion: 5 Fluorouracil is more effective than Bevacizumab as sole therapy in treatment of primary pterygium but equally safe in terms of side effects.

Key Words: Bevacizumab, 5-Fluorouracil, Pterygium, Vascular Endothelial Growth Factor.

How to Cite this Article: Parveen S, Naeem S, Muzaffar W, Saeed MK Babar ZuD. Sub-conjunctival injection of 5 Fluorouracil versus Bevacizumab in Treatment of Primary Pterygium.

Correspondence: Shagufta Parveen
Combined Military Hospital, CMH, Lahore
Email: shagufta309@hotmail.com

Received: May 03, 2023
Accepted: August 19, 2023

INTRODUCTION

Pterygium is a conjunctival degeneration, presenting as growth of fibrovascular tissue and encroaching on to the cornea. There is elastotic degeneration of tissue in the subconjunctival region.[1,2] It usually involves nasal side of the bulbar conjunctiva and less commonly the temporal side.

The Greek word "pterygium" describes the shape of overgrowth, which resembles an insect wing.[3] Apart from the cosmetic concern to the patient, pterygium causes visual disturbance by encroachment on the visual axis, astigmatic effect, ocular inflammation and restriction of ocular movements.[3,4]

The exact pathophysiology of pterygium is not understood. However, known risk factors include exposure to ultraviolet-B radiation, inflammatory response, chemicals, trauma, dust and wind.[5] Prevalence of pterygium varies between 0.3 to 31 percent around the world, and is higher in men. Pterygium is typically seen in outdoor workers, welders, fishermen, farmers and landscape artists.[5] A strong association of sunlight exposure and pterygium

is supported by its higher prevalence in countries with hot climates.[6]

Apart from the environmental influences, contributory factors in the pathogenesis and progression of pterygium include fibrovascular proliferation, inflammation and an altered ratio of angiogenic stimulation-to-inhibition.[7]

Despite the fact that pterygium is a degenerative process, fibrovascular tissue proliferation is considered essential for its pathogenesis. Infact, angiogenesis and factors affecting angiogenesis such as: vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF- β), platelet-derived growth factor (PDGF), etc., are found in pterygium tissue.[5] Among these VEGF stains more intensively on pterygium immunohistochemistry studies in cases of primary and recurrent pterygia.[8]

While the mainstay of treatment for pterygium is surgical excision with conjunctival autograft, it is associated with high rate of recurrence, ranging from 10 to 80 percent, depending on the procedure used for excision.[9,10]

Newer strategies of preventing recurrence include adjunctive treatments with local administration of antimetabolites like 5-Fluourouracil, beta irradiation, mitomycin-C and anti-VEGF antibodies.[11] Bevacizumab has shown more precision in preventing recurrences, and is also associated with fewer side-effects.[8] In fact, use of Bevacizumab in the form of sub-conjunctival injection for the management of primary pterygium reduces the size of the lesion and improves visual function.[1]

5-fluourouracil (5-FU) is an antimetabolite that can be applied topically or injected for treatment of pterygium.[12] The recent use being more intralesional to mitigate the progression of primary and recurrent pterygium. This pyrimidine analogue works by interfering with the synthesis of RNA and DNA through the inhibition of enzyme thymidylate synthetase with consequent apoptosis of proliferating fibroblasts.[13]

The purpose of our study is to compare the effectiveness of 5-FU and Bevacizumab as the primary agents for the management of primary pterygium.

METHODS

This quasi-experimental study was carried out at Combined Military Hospital Lahore from January 2022 to January 2023 after approval from institutional review board (IRB Number 420/2022). Consecutive sampling was used for recruiting patients for this study. All the patients who presented with primary pterygium were recruited in the study. The minimum required sample size was 64, calculated by using WHO sample size calculator, where proportion of successful outcome in terms of vascularity grade was considered to be 50%, proportion of successful outcome in exposed group was considered to be 86.7%[3], with 80% study power, 95% level of confidence and 10% precision.

Patients between 15 to 55 years, who had primary pterygium with a grade of 2 or 3 (2 or more millimeter encroachment onto the cornea) were included in the study. Pterygium grading was done according to the following criteria: Grade 1 (Atrophic Pterygium with episcleral vessels clearly visible), Grade 2 (Intermediate Pterygium with episcleral vessels not clearly visualized), Grade 3 (Fleshy Pterygium, episcleral vessels were obscured).

Individuals who had recurrent pterygium, degenerative diseases of cornea, scarred or ectatic cornea, past history of chemical or mechanical ocular trauma or ocular surgery were excluded

Informed written consent was obtained from the patients. A detailed history was taken including medical history, presence of predisposing ocular conditions or recurrence. A thorough ocular examination that included slit lamp biomicroscopy to grade pterygium was performed. These patients were divided into 2 groups of 32 patients each.

Group A (5FU); Patients received 3 intralesional injections of 5FU on monthly basis.

Group B (AV); Patients received 3 injections of Bevacizumab on a monthly basis.

Both types of injections were administered in operation theater under aseptic conditions. Topical anesthesia was administered by instilling 2 drops of Proparacaine 0.5% into the conjunctival sac. One to two drops of 5% povidone iodine were instilled in conjunctival sac 5 minutes before injection. 0.1 ml of 5-FU (5 mg) in 1 ml insulin syringe was given intralesionally. After injection, 1 drop of Moxifloxacin was instilled. Moxifloxacin and Dexamethasone drops were given thrice daily for 5 days. Patients received a total of three injections on monthly basis. Similarly, patients in group B received 0.1 ml of a 2.5 mg/0.1 ml concentration of Bevacizumab sub-conjunctivally into

the body of the pterygium following administration of topical anesthetic (Proparacaine 0.5%) and 5% povidone iodine. Topical antibiotics (Moxifloxacin) and steroid drops (Dexamethasone drops) three times were used for 5 days after injection. These patients also had a total of three injections on monthly intervals. Follow-up was done at 1 week after administration of each injection to rule out any side effects. Final follow up was done after four weeks of administration of last injection in each group and effectiveness was determined in terms of improvement in the grade of pterygium ≥ 1 grade on slit lamp examination. Data was collected on a self-designed proforma.

Data was analyzed using SPSS version 23. Descriptive statistics for categorical data were presented as frequencies and percentages, while continuous data was presented as mean and standard deviation. The outcome variable, (successful treatment outcome), was binary in nature, it was compared between two study groups by using Chi-square test. Results were stratified for age and gender to rule out effect of potential confounders. Chi-square test was applied to assess significant differences. Significant associations were presented in terms of p-values. The p-value of ≤ 0.05 was considered significant.

RESULTS

Out of 64 patients included in the study, 45 (70.3%) were males and 19 (29.7%) were females, with mean age of 32.25 ± 11.98 years. Details are shown in table 1.

In group A, there were 32 participants, out of which 21 (65.6%) had a successful outcome whereas 11 (34.4%) achieved no effect. On the other hand, in group B, there were 32 participants, out of which only 2 (6.3%) had a positive outcome while remaining 30 (93.8%) achieved no effect. There was a significant difference in outcome when compared between the two groups (65.5% versus 6.3%, p-value < 0.001).

The results were stratified for age and gender to control the confounding effect. It was observed that there was no role of gender or age in achieving positive treatment outcome among group A and group B as shown in table 2.

Patients in both groups were followed for complications. It was observed that 3/32 (9.3%) patients in group A developed complication of punctate epithelial keratitis, whereas in group B, 2/32 (6.2%) developed sub-conjunctival hemorrhage. The complication rates are compared in figure 2.

Table 1: *Demographic details of study participants (n = 64).*

Sr. No.	Characteristics	Overall (n = 64)	Group A (n = 32)	Group B (n = 32)
1.	Mean age in years (mean ± SD)	32.25 ± 11.98	33.53 ± 11.3	30.97 ± 12.6
2.	Minimum age in years	15	17	15
3.	Maximum age in years	54	52	54
4.	Age range	39	35	39
	Gender			
5.	• Male	45 (70.3%)	21 (65.6%)	24 (75.0%)
	• Female	19 (29.7%)	11 (34.4%)	8 (25.0%)

DISCUSSION

Pterygium remains one of the most common ocular surface disorders despite extensive research in prevention and treatment of this disease. In addition to being a cosmetic nuisance, it may lead to chronic ocular surface inflammation, corneal scarring, irregular astigmatism and restricted ocular motility.[14] Due to its high prevalence in regions close to the equator and particularly in people who have chronic exposure to UV radiation, ultraviolet light is considered to be a predisposing factor.[15] Although the exact etiology of pterygium is uncertain, other environmental factors such as, dryness, genetic and immunological factors are known to contribute to its occurrence.[16]

Table 2: *Stratification of results by age and gender.*

		Outcome	Group A (n = 32)	p	Group B (n = 32)	p
Age	15-35 years	Successful outcome	12 (66.7%)	0.888	1 (5.3%)	0.780
		Unsuccessful outcome	6 (33.3%)		18 (94.7%)	
	36-55 years	Successful outcome	9 (64.3%)		1 (7.7%)	
		Unsuccessful outcome	5 (35.7%)		12 (92.3%)	
Gender	Male	Successful outcome	13 (61.9%)	0.540	2 (8.3%)	0.399
		Unsuccessful outcome	8 (38.1%)		22 (91.7%)	
	Female	Successful outcome	8 (72.7%)		0 (0.0%)	
		Unsuccessful outcome	3 (27.3%)		8 (100%)	

5-FU being an anti-proliferative and anti-fibroblastic agent was initially used as an anticancer drug. As fibroblast proliferation was found to be the underlying etiology of pterygium, it is rational to use 5FU as an adjuvant for treatment of primary as well as recurrent pterygia. Similarly, pterygium formation and progression has also demonstrated underlying angiogenesis. The use of Bevacizumab is poorly understood in inhibiting pterygium growth but its antiangiogenic nature is believed to play a key role.

5-FUhas long been utilized in pterygium as an adjuvant to prevent recurrence.[18,19] However, use of 5FU as sole therapy to halt progression and recurrence of pterygium is relatively recent. Said et al. reported that intralesional 5FU could halt pterygium progression; avoiding need for surgery.[10] Our study also demonstrated effectiveness in terms of reducing vascularity and thickness. However, our study included primary pterygium cases as opposed to recurrent pterygium patients recruited by Said et al. Khan et al, also demonstrated that intralesional 5FU was effective in improving cosmetic appearance of pterygium as was our inference from the current study.[13]

Role of Anti-VEGF agents has been documented as primary therapy, as well as chemoadjuvant, in treatment for early recurrent pterygium. Studies have shown the effectiveness of intralesional injection of Bevacizumab in impending recurrence.[20] However, recurrence was not an outcome measure in our study. In accordance with our finding, a study conducted by Terek et al, also revealed the beneficial effect of single intralesional injection of Avastin on pterygium vascular pattern.[7]

A meta-analysis performed by Hu et al, indicated that there was a higher risk of developing sub-conjunctival hemorrhage in Bevacizumab group.[21] Similar trend was seen in our study, as 2 patients in Bevacizumab group developed sub conjunctival hemorrhage as opposed to none in 5FU group.

Epithelial keratopathy is a known adverse effect of 5-FU as it leads to inhibition of mitosis of corneal epithelium.[2] Although, the study conducted by Shah et al, had demonstrated no such adverse effect, our study revealed 3 cases of punctate epithelial keratitis in 5FU group but no such event was seen in Bevacizumab group.[3]

Our study demonstrated the superior efficacy of 5FU as sole therapy in improving the clinical appearance of primary pterygium as compared to Bevacizumab, as reduction in grade of pterygium was seen in 21 (65.6%) patients in 5FU group versus only 2 patients (6.3%) in Bevacizumab group. However, since no other known study comparing the efficacy of the two treatment modalities is available, further studies are recommended to reach a definitive conclusion.

It was a pilot study with small sample size and limited follow up period as its limitations. Further studies are encouraged on large data sets to determine significance of our findings.

CONCLUSION

Use of 5-FU in treatment of primary pterygium is more effective but equally safe when compared to Bevacizumab.

Conflict of Interest: Authors declared no conflict of interest.

Ethical Approval: The study was approved by the Institutional review board/Ethical review board **(CMH/420-2022).**

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Authors' Designation and Contribution

Shagufta Parveen; Assistant Professor: *Concepts, Design, Literature Search, Data Acquisition, Data Analysis, Statistical Analysis, Manuscript Preparation, Manuscript Editing, Manuscript Review.*

Saquib Naeem; Professor: *Concepts, Design, Literature Search, Data Analysis, Statistical Analysis, Manuscript Editing, Manuscript Review.*

Waqar Muzaffar; Professor: *Concepts, Design, Data Acquisition, Data Analysis, Statistical Analysis, Manuscript Editing, Manuscript Review.*

Muhammad Kamran Saeed; Professor: *Concepts, Design, Data Acquisition, Data Analysis, Manuscript Preparation, Manuscript Editing, Manuscript Review.*

Zaheer-ud-Din Babar; Associate Professor: *Concepts, Design, Data Acquisition, Data Analysis, Statistical Analysis, Manuscript Editing, Manuscript Review.*