

**Research Article**

## THE EFFICACY OF AVASTIN ADJUNCTIVE TREATMENT VERSUS MITOMYCIN-C IN POST-OPERATIVE RECURRENCE OF PTERYGIUM

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### ABSTRACT

Pterygium is a common disease of the eye, especially in hot, dry areas near the equator. Pterygium is an overgrowth of fibro vascular tissue beyond the limbus of the cornea and several factors, including heredity, environmental factors such as dust, ultraviolet radiation involved in its creation. The purpose of the present study was to Comparison of intravenous and topical Mitomycin-c intraoperative use of Avastin in pterygium recurrence in patients admitted to the eye clinic of Hospital. In this study, 83 eyes of 81 patients with pterygium were divided into two groups, A and B. In group A, 47 eyes; in group B, 36 eyes underwent pterygium resection. In group A, local subconjunctival injection 0.1 cc Avastin (2.5 mg) and in group B, the applicator soaked in mitomycin-c 0.02% for 1 minute was used intraoperatively. Then about 6 month later, patients were evaluated in the final. The recurrence rate in group A, 23.4% in group B, 25% was observed that there was no significant difference between the two groups. Symptoms in patients complaining of foreign body, Avastin to 6.3% better than mitomycin-c acted. In effect, photophobia, red eye, eye discharge, eye dryness mitomycin respectively by 8%, 20.1%, 3.8% and 3.4% better results than Avastin has. It can also be noted that in our study, pterygium recurrence occurred in fewer employees and retirees. In this study, 20 eyes of 83 eyes had pterygium recurrent, that the recurrent rate was 24.1% than the recurrence rate of 30-70% of Bare-Sclera simple surgical technique. This difference does not show any remarkable results between two groups.

**Keyword:** Avastin, Mitomycin-c, Recurrent, Pterygium

### INTRODUCTION

Pterygium is a common eye disease in hot and dry area, especially in the eastern parts of Iran. It causes itchy eye, inflammation, and in advanced cases can affect vision.

Pterygium appears in the form of a thick triangular shaped lump of tissue in bulbar conjunctiva and extends over cornea. It is caused by elastotic degeneration of collagen and sub-epithelial fibro vascular tissue in conjunctiva. Pterygium causes damage to bowman layer and inflammatory changes (Ojaghi *et al.*, 2005).

Pterygium is seen in different geographical area, often in adults ages 20-40(Rouhani and Behzadi far, 2001). Significant causes of pterygium include prolonged exposure to ultra-violet light, irritants such as dust and wind, aging, K-ras system, tumor inhibitor genes such as P-63 and P-53, HPV-DNA, Defensin and Phospholipase D expression, as well as growth factor such as VEGF and bFGF (Efsthathios and Demetrios, 2009). Pterygium reoccurs in the first 3 months after surgery (Mehrtash, 2000). Its recurrence is much greater among people who live near the equator. Removal surgery is considered to be the main treatment for pterygium, but it is followed by recurrence of the disease. Surgery, thus, is used only in advanced cases. To solve the problem and to avoid the recurrence of pterygium, various methods have been developed and applied. The most is applying chemical substances in the area of surgery. Local administration of mitomycin and injectable Avastin during surgery is one of the latest methods which is of great importance due to its effectiveness and relinquish able side effects (Ojaghi *et al.*, 2005) and (Rouhani and Behzadi, 2001).

## **Research Article**

There is positive relationship between the occurrence of Pterygium and closeness to equator. Non-steroidal anti-inflammatory eye drop is used to treat inflammatory Pterygium and Pinguecula.

The indication for surgical intervention in Pterygium that attacks the optical area include: (1) pterygium removal and (2) avoiding the recurrence of pterygium. Nowadays new surgical methods include conjunctiva autograft transplantation, Amniotic membrane transplantation, chemical methods such as laser photocoagulation with Argon laser, photocoagulation with YAG laser, and other methods such as beta radiation therapy (Hashemi and Kheirkhah, 1999).

Rossana *et al.*, (2014) evaluated the clinical outcome(s) and complication(s) of subconjunctival bevacizumab treatment in patients with recurrent pterygium. All patients received one subconjunctival injection of 0.5 mL of bevacizumab (2.5 mg/0.1 mL). Their main outcome was the change in size and clinical appearance. The horizontal size of the pterygium (from limbus to apex) was recorded from baseline to 2 months after injection. Treatment-related complications and adverse events were reported (Iarissa and Anelise, 2014).

Ozsutcu *et al.*, (2014) studied the repeat of bevacizumab injection in rotational conjunctival flap surgery versus rotational conjunctival flap with adjunctive mitomycin-C (MMC) or rotational conjunctival flap alone. They concluded that Subconjunctival bevacizumab injection may decrease the recurrence rate of primary pterygium surgery with rotational conjunctival flap.

Administration of these two drugs has been studied separately. This study aims to evaluate and compare the application of mitomycin and avastin in treating the pterygium.

## **MATERIALS AND METHODS**

A random controlled clinical trial study was carried out in 2013 in Valiyeasr Hospital in Birjand. Subjects with primary pterygia bigger than 3mm that had undergone no pterygium surgery were included in the study. Subjects were under no administration prohibition of mitomycin and avastin. Those with rheumatic diseases, recurrent pterygium, and diabetic subjects were excluded.

### **Sampling**

The sample volume was determined using the following equation: the number of subjects in each group was estimated  $n=47.50$  subjects were studied in each group. This number was reduced in the second group, because some patients did not refer for follow-up visit in the 6th month.

Simple non-probability sampling was used to select the subjects among the candidates for pterygium surgery in Valiyeasr Hospital. The subjects, then, were divided into two groups (A and B) according to simple random sampling. Informed consent was obtained from all patients before enrolment. The surgery technique was as follows:

The conjunctiva was anesthetic by lidocaine 2% at a rate of 0.5 cc of subconjunctival injection. Firstly tried to detach pterygium by hook and in cases it is attached, the pterygium is pulled out with conjunctival forceps like pulling method. Cutting device is put tangent to the corneal lesion depth and the head is separated from adhesion. During this maneuver, keratectomy of surface layers of stroma is continue until deep transparent layers. Removing the head to Limbal of surgery continues to get to trunk of pterygium.

In small pterygium trunk progressively attacks the healthy conjunctiva and after removing the pterygium, which surrounding conjunctival should be cut. To avoid rupture and damage of healthy conjunctiva, using scissors the conjunctiva to separate it.

Finally the conjunctiva should be without any tension edges or avoiding of removing the surrounding healthy conjunctiva.. In cases of advanced, Hypertrophic pterygium with extensive subconjunctiva fibrosis avoided to cutting fibrous tissue which may damage the tendon of internal rectus muscle.

Pterygium is lifted free of the eye and cut away. If it is adherent, careful superficial dissection can be performed by forceps.

When using mitomycin 0.02%, first the applicator dipped in the drug is put on the surface of subconjunctival sclera. Then, the area is washed by Normal Saline serum and stitched by Silk 7<sup>0</sup>.

When using Avastin, 0.1cc Avastin 2.5 mg is injected in the subconjunctiva and the eye is patched with betamethasone and tetracycline cream for 24 hours.

**Research Article**

The patches are removed the day after the surgery. Postoperatively, patients were treated with Hydrocortisones for daily use for a month, Chloramphenicol 3 times per day for a week, artificial tears 3-4 times per day in case of dry eye, and Betamethasone drop 3 times per day for 6-8. In the follow-up visit at week 1 after the surgery stitches were removed. Follow-up visits were at months 1, 3, and 6.

A questionnaire was filled out for the subjects to obtain required information. Data were analyzed using SPSS software, Chi-square test, and T-test.

**Ethical considerations**

Informed consent was obtained from all patients after the nature and possible consequences of the study were explained. The study was approved by the Ethics Committee and received RCT code.

**RESULTS AND DISCUSSION**

**Results**

From among the 83 subjects participated in the study, 47 patients were undergone treatment with Avastin and 36 patients with mitomycin-c. Table 1 shows the distribution of the subjects according to age, gender, occupation, and the treatment method.

**Table 1: Distribution of the subjects according to demographical features**

Variable	Group	Frequency	Percentage
gender	male	37	44.6
	Female	46	55.4
age	40 and younger	23	27.7
	41-50	19	22.9
	51-60	24	28.9
	61 and older	17	20.5
occupation	Housewife	42	50.6
	Government employee/retired	14.5	12
	Self-employed	18.1	15
	Farmer and worker	16.9	14

According to the results shown in Table 1, higher frequency (24) belongs to the 51-60 age group and the lower frequency (17) belongs to the 60 and older age group.

**Table 2: Comparison of the frequency of pterygium recurrence in subjects according to the type of treatment**

type of treatment	Recurrence of pterygium	Total frequency (percentage)
avastin	36 (76.6)	11 (23.4)
Mitomycin-c	27 (75)	9 (25)
Total	63 (75.9)	20 (24.1)

P=0.87, df=1, X<sup>2</sup>=0.03

According to the results shown in Table 2, 11 patients treated with Avastin and 9 patients treated with mitomycin had recurrent pterygium. There was not any significant relationship between pterygium recurrence and the type of treatment (P=0.87).

**Research Article**

**Table 3: Distribution of subjects treated with Avastin according to demographical features**

Variable	Group	No Frequency (percentage)	Yes Frequency (percentage)	Statistical results
gender	male	18(78.3)	5(21.7)	P=0.79, df=1, X <sup>2</sup> =0.07
	Female	18(75)	6(25)	
occupation	Housewife	17(73.9)	6(26.1)	Fisher Exact Test=5.86 P=0.09
	Government employee/retired	9(100)	0	
	Self-employed	4(50)	4(50)	
	Farmer and worker	6(85.7)	1(14.3)	

As it is seen in Table 3, gender and occupation are not associated with the recurrence of pterygium in subjects treated with Avastin (P>0.05).

**Table 4: Distribution of subjects treated with mitomycin-c according to demographical features**

Variable	Group	No Frequency (percentage)	Yes Frequency (percentage)	Statistical results
gender	male	11(78.6)	3(21.4)	Fisher Exact Test P=1
	Female	16(7.727)	6(25)	
occupation	Housewife	14(73.7)	5(3.26)	Fisher Exact Test=0.98 P=1
	Government employee/retired	3(100)	0	
	Self-employed	5(71.4)	2(28.6)	
	Farmer and worker	5(714)	9(25)	

As table 4 shows, gender and occupation are not associated with the recurrence of pterygium in subjects treated with mitomycin-c (P>0.05).

**Table 5: Relative frequency of variables before surgery according to the type of treatment**

Variable		Avastin Frequency (percentage)	mitomycin Frequency (percentage)	X <sup>2</sup>	df	P
photophobia	Yes	37 (78.7)	27 (75)	0.16	1	0.69
	No	10(21.3)	9 (25)			
Red eye	Yes	43 (91.5)	34 (94.9)	0.36	1	0.55
	No	4(8.5)	2(5.6)			
Eye excretion	Yes	23(48.9)	24 (51.1)	0.36	1	0.55
	No	20(55.6)	16(44.4)			
Dry eye	Yes	40(85.1)	7(14.9)	1.34	1	0.25
	No	27(75)	9(25)			

As it is seen in table 5, there is no statistically meaningful difference between pre-operative fear of light, eye redness, eye excretion, eye dryness in subjects according to the type of treatment (P>0.05).

**Research Article**

**Table 6: Relative frequency of variables after surgery according to the type of treatment**

Variable		Avastin Frequency (percentage)	Mitomycin-c Frequency (percentage)	X <sup>2</sup>	df	P
Photophobia	Yes	9 (19.1)	4 (11.1)	0.99	1	0.32
	No	38(80.9)	32 (88.9)			
Red eye	Yes	25 (53.2)	12 (33.3)	3.25	1	0.07
	No	22(46.8)	24(66.7)			
Eye excretion	Yes	7(14.9)	4 (11.1)	0.25	1	0.61
	No	40(85.1)	32(88.9)			
Dry eye	Yes	16(34)	11(30.6)	0.11	1	0.74
	No	31(66)	25(69.4)			

As it is seen in table 6, there is no statistically meaningful difference between post-operative fear of light, eye redness, eye excretion, eye dryness in subjects according to the type of treatment (P>0.05).

**Discussion**

Though most of the subjects in this study are females, gender does not seem to be associated with the recurrence of pterygium. Mean age of subjects with recurrent pterygium treated by Avastin is significantly lower than subjects with no recurrent pterygium. Mean age of subjects treated by mitomycin show no relationship with recurrent of pterygium. It is in consistency with findings of Besharati *et al.*, (Besharati *et al.*, 2011). After the follow-up visits in the next 6 months after surgery, no significant difference was seen in the age groups. A notable result was related to the subject's occupation. 14.5% of patients were government employees and retired and 18.1% were self-employed with the lower level of recurrence. The highest level (67.5%) of recurrence was observed in farmers and workers.

Recurrence of pterygium was higher in female subjects (3.3%) than males ones. The recurrence in female patients treated with mitomycin- C was 5.9% higher than in male patients.

In patients treated by Avastin, those younger than 40 had the highest level of recurrence and 60 and older age group had the lowest level of recurrence. In patients treated by mitomycin-c, more recurrence cases was observed in those younger than 40. However, there was no significant difference among the age groups.

In patients treated by Avastin, government employees and retired patients had 0% of recurrence of pterygium. Self-employed subjects had the highest level of recurrence. In patients treated by mitomycin-c, lowest level of recurrence (0%) was observed in government employees and retired patients. Other groups show similar levels of recurrence.

25% recurrence was observed in the follow-up visits in the 6th month after surgery in patients who were treated by mitomycin-c 0.02% for 1 minute during the surgery. Rouhani *et al.*, (1995) reported 9.1% of recurrence in patients treated by mitomycin C 6.7% drops after surgery (Rouhani and Behzadi, 2001). As the time and the dosage of administration are two important factors in the efficacy of the drug, given smaller dose and shorter time of administration, the efficacy of the drugs reduces thus more recurrence rate. The bigger dose and the longer time of administration of the drug, the lower the percentage of recurrence of pterygium will be. The long-term side effects of administrating of bigger does for longer duration through surgery need to be considered as well. Therefore, administrating mitomycin-c 0.02% for 5 minutes reported to be promising. By comparing conjunctiva flap and mitomycin-c, Rouhani *et al.*, recurrence was 5.5% in mitomycin-c group and 35% in conjunctiva flap group (Rouhani and Sarifi, 1995). Omar *et al.*, (2012) assessed the efficacy and role of sub-conjunctival Bevacizumab in treatment of primary and recurrent pterygium. They found that sub-conjunctival injection is useful in management of patients with primary pterygium without local or systemic adverse effects (Rashid and Sarosh, 2012).

Khoshniyat *et al.*, found that bevacizumab injection is useful in reducing the photophobia symptoms, Chemosis (Conjunctivitis), and the size of pterygium in 6 months (Mustafa and emre, 2014). In this study there is no statistically significant difference between relative frequencies of pre-operative and post-

### Research Article

operative photophobia, eye redness, eye excretion, eye dryness ( $P > 0.05$ ). This can be due to using sponge dipped in mitomycin-c 0.02% for 1 minute over the sclera in subconjunctival area and washing with Normal saline serum. In addition, to avoid sclera exposure, conjunctiva was sutured by using Silk 7<sup>0</sup>. This can cause reduction in the above-mentioned effects. In general, in addressing the complaints about foreign body in the eye, Avastin showed a better efficacy than mitomycin-c. Subjects were photophobia pre-operatively which was improved after surgery. However Further study is required to determine whether mitomycin-c show a better efficacy in treating pterygium.

Ozsutucu *et al.*, (2014) studied showed the repeated bevacizumab injection in rotational conjunctival flap surgery versus rotational conjunctival flap with adjunctive mitomycin-c or rotational conjunctival flap alone. They concluded that Subconjunctival bevacizumab injection may decrease the recurrence rate of primary pterygium surgery with rotational conjunctival flap (Mustafa and Emre, 2014).

In a study to determine the efficacy and tolerability of topical bevacizumab as a postoperative adjunct in reduction of recurrence following primary pterygium surgery with conjunctival graft at a two year follow up, Sudhalkar *et al.*, (2012) found that topical bevacizumab is a potentially useful, convenient and safe therapy as an adjuvant to pterygium surgery (Sudhalkar, 2012).

Using the method of sunconjunctival injection of bevacizumab to treat pterygium, observed a reduction in the size of pterygium during the treatment (Besharati, 2011). Recent reports show that different Anti-VEGFs such as bevacizumab and ranibizumab have been used to treat pterygium (Ozgurhan *et al.*, 2013). New generations are on way and we should wait for their side effects to be identified through future researches.

One case of Melting sclera was seen in subjects treated by mitomycin-c. It was improved in 3 weeks after stopping administrating betamethasone drop and applying Vitamin A cream. In treating pterygium by Avastin, two cases of conjunctival suture were opened that improvement occurred after 3 weeks. So the judgment about the other influencing factors including tumor necrosis factors such as BFGF, TGF+ $\beta$ ,  $\alpha$ , and PDGF are effective in the recurrence of pterygium is optional (Kria *et al.*, 1990) and (Jin *et al.*, 2003).

### Conclusion

Post-operative general studies showed that Avastin causes less post-operative photophobia and eye redness than mitomycin-c. In addition, Avastin leads to less eye dryness after surgery than mitomycin-c.

With respect to the feeling of a foreign body in the eye, mitomycin-c showed more efficacies than Avastin. In general, both Avastin and mitomycin-c reduce the symptoms without any significant difference between Avastin and mitomycin.

### Suggestion

According to our findings, it may be suggested that Avastin be used for workers and farmers, for it is followed with a low level of recurrence. Mitomycin-c is suggested for patients from other occupational groups. It makes no difference in using Avastin or mitomycin-c for patients who are government employee or retired. Patient's job is the most important factor in addressing pterygium. Avoiding surgery is recommended for patients younger than 40. For patients older than 60 Avastine is suggested, for it is followed by lower rates of recurrence.

Longer administration of mitomycin C is also suggested.

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**Research Article**

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