Subconjunctival bevacizumab injection on primary pterygium in Thammasat Hospital: a randomized controlled trial

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Purpose: To evaluate the reduction in horizontal dimension of primary pterygium after subconjunctival bevacizumab injection.

Materials and methods: Subjects with primary pterygium were randomized to study group (subconjunctival bevacizumab injection group) and control group. The inclusion criteria are 18 years or older subjects with primary pterygium less than 3 millimeters in horizontal dimension. The primary outcome is the reduction of horizontal dimension at 1 week, 1 month, 3 months and 6 months.

Results: Fifty-nine subjects with primary pterygium were enrolled in this study. The mean age is 56.25 years (± 12.90). Forty-seven subjects (79.70%) were female. Mean size reduction in the bevacizumab group was 0.517 mm. (± 0.301), 0.710 mm. (± 0.359), and 0.790 mm. (± 0.361) at 1 month, 3 months and 6 months respectively. Mean size reduction in the control group was -0.067 mm. (± 0.258), - 0.010 mm. (± 0.304) and -0.003 mm. (± 0.366) at 1 month, 3 months, and 6 months respectively. The P value of difference in pterygium size reduction between the bevacizumab group and control group is less than 0.001 at all visits.

Conclusion: The reduction of horizontal dimension in primary pterygium at 1 month, 3 months and 6 months is significantly greater in those who received subconjunctival bevacizumab injection compared to the control group.

Keywords: primary pterygium, size reduction, subconjunctival bevacizumab injection, randomized controlled trial

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Introduction

Pterygium is one of the most common degenerative conditions of the conjunctiva. The pathogenesis is associated with conjunctival inflammation and fibrovascular proliferation.[1]

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The treatment of pterygium includes nonsurgical and surgical management. Apart from lubrication, both anti-inflammatory and anti-fibrovascular agents may play an important role in nonsurgical modality. These anti-inflammatory agents include topical antihistamines, mast cell stabilizers and even corticosteroids. However, the anti-inflammatory agents have no evidence in reducing the pterygium size. Anti-fibrovascular agents are currently a relatively new modality for the

treatment of neovascular proliferation of retinal diseases although not yet approved by the United States Food and Drug Administration (FDA) for the treatment of pterygium.[2] Surgical excision still is the definite management of pterygium. In patients who do not meet the indication for surgery, there is no other treatment to reduce pterygium size. Several studies have shown that the vascular endothelial growth factor (VEGF) stimulates proliferating fibrovascular tissue in pterygium and anti-vascular endothelial growth factor (anti-VEGF) treatment may be effective in the inhibition of these proliferative processes.[3-5]

bevacizumab is a humanized anti-VEGF monoclonal IgG1 antibody. It acts by selectively inhibit the binding of VEGF to its cell receptors, leading to a reduction in vascular growth of tumor blood vessels and it has been approved by the FDA for the treatment of various types of cancers.[6, 7] bevacizumab injection is still off-label for treatment in almost all ocular diseases. However, preliminary studies suggest that bevacizumab may be effective in the treatment of ocular surface disease especially limiting the neovascularization and fibrovascular proliferation of pterygium.[8, 9]

This is the randomized controlled trial to study the effectiveness of subconjunctival bevacizumab injection in reduction of primary pterygium size.

Materials and methods

The study was approved by the Medical ethics Committee of Thammasat University (MTU-EC-OP-6-099/61), Pathum Thani, Thailand, and was conducted in accordance with the tenets of the Declaration of Helsinki. The study was conducted from 1st April, 2018 to 31th March 2019 in the Department of Ophthalmology, Thammasat Hospital.

Subjects 18 years or older with primary pterygium and horizontal dimension less than 3 millimeters were enrolled and randomized by a table of numbers.

The patients with recurrent pterygium, history of bevacizumab allergy, contraindications for bevacizumab use, pregnant or lactation period women were excluded.

Data regarding age, gender, occupation, underlying disease, drug history, best corrected visual acuity (BCVA) by Snellen chart and complete eye examination before and after treatment at 1 week, 1 month, 3 months and 6 months were recorded. The study protocol was performed with informed consent. The primary outcome of this study is to evaluate the efficacy of subconjunctival bevacizumab injection in decreasing the size of pterygium. The secondary outcome is to evaluate the adverse effects of subconjunctival bevacizumab injection. A p-value of less than 0.05 was considered statistically significant.

Study protocol

Sixty-two patients were enrolled in the study. Patients were randomized to two groups (1:1). Thirty-one eyes in 31 patients were enrolled in the study group and the same number of 31 eyes in 31 patients were enrolled in the control group.

In the study group, bevacizumab solution 100 mg/4 ml (Avastin^{R}) from Roche Thailand Ltd. was prepared by one pharmacist under sterile technique in negative pressure room. All of the patients in study group received a single subconjunctival injection of bevacizumab (2.5 mg/0.1 ml) using a 27-gauge needle injected to the head of pterygium by single blind ophthalmologist. If the patient had pterygium in both eyes or both quadrants of one eye, the biggest in horizontal diameter was selected. The patients in study group received 0.3% tobramycin with 0.1% dexamethasone eye drops (Tobradex^{R}) every four hours daily

for 1 week after subconjunctival injection of bevacizumab. The patients in control group received antihistamine eye drop (Hista-oph^{R}) four times a day and tears natural free eye drop (Alcon^{R}) every four hours for one week after enrollment. All patients were followed up at 1 week, 1 month, 3 months and 6 months. The tears natural free eye drop (Alcon^{R}) was prescribed during the follow up period in both groups.

Examiner was blinded to measure the pterygium size from the limbus to the apex of pterygium (not including the Stocker's line and subepithelial scar). bevacizumab related adverse effects were considered to present if the patients have gastrointestinal (GI) bleeding, central nervous system (CNS) bleeding, or wound healing problems. The data were collected by the co-author. Neither the co-author nor the examiner knows the intervention.

Statistical analysis

This study analyzed the data using excel tables (Microsoft Windows XP professional version 2002 service pack 3) and the statistical analysis was performed using SPSS software version 23.0 (IBM Inc, Chicago, IL). Demographic data are described using this program, as number (percentage), median (range), and mean ± standard deviation (SD). Chi-square/Fisher's exact test was employed to compare proportions between the study groups, independent-T test was used to compare the mean of the two groups and Mann Whitney U test was used for non-nominal distributions paired t-test or Wilcoxon Signed Ranks Test were used to compare the mean values in the group. All reported P values were 2-sides with $P<0.05$ set the threshold for statistical significance.

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Result

Two patients in the study group were lost to follow up due to transportation inconvenience and one patient in the control group was lost to follow up due to other systemic diseases. Finally, 29 patients (29 eyes) in the study group and 30 patients (30 eyes) in the control group had completed the study protocol.

According to Figure 1, the mean horizontal dimension of pterygium in the bevacizumab

Table 1: Patient characteristics

	Total (n = 59)		bevacizumab (n = 29)		Control (n = 30)	
	n	%	n	%	n	%
Sex						
Female	47	79.7%	25	86.2%	22	73.3%
Male	12	20.3%	4	13.8%	8	26.7%
Age						
<60	33	55.9%	16	55.2%	17	56.7%
≥60	26	44.1%	13	44.8%	13	43.3%
Mean±SD.	56.25	±12.90	57.17	±10.03	55.37	±15.29

Table 1: Patient characteristics (cont.)

	Total (n = 59)		bevacizumab (n = 29)		Control (n = 30)	
	n	%	n	%	n	%
Side						
Right eye	30	50.8%	15	51.7%	15	50.0%
Left eye	29	49.2%	14	48.3%	15	50.0%
Location (quadrant)						
Nasal	31	52.5%	15	51.7%	16	53.3%
Temporal	28	47.5%	14	48.3%	14	46.7%
Nationality						
Thai	58	98.3%	28	96.6%	30	100%
non Thai	1	1.7%	1	3.4%	0	0%
Occupation						
Outdoor	27	45.8%	14	48.3%	13	43.3%
Indoor	32	54.2%	15	51.7%	17	56.7%

The table 1 shows that there is no statistical difference in patient characteristics between study group and control group.

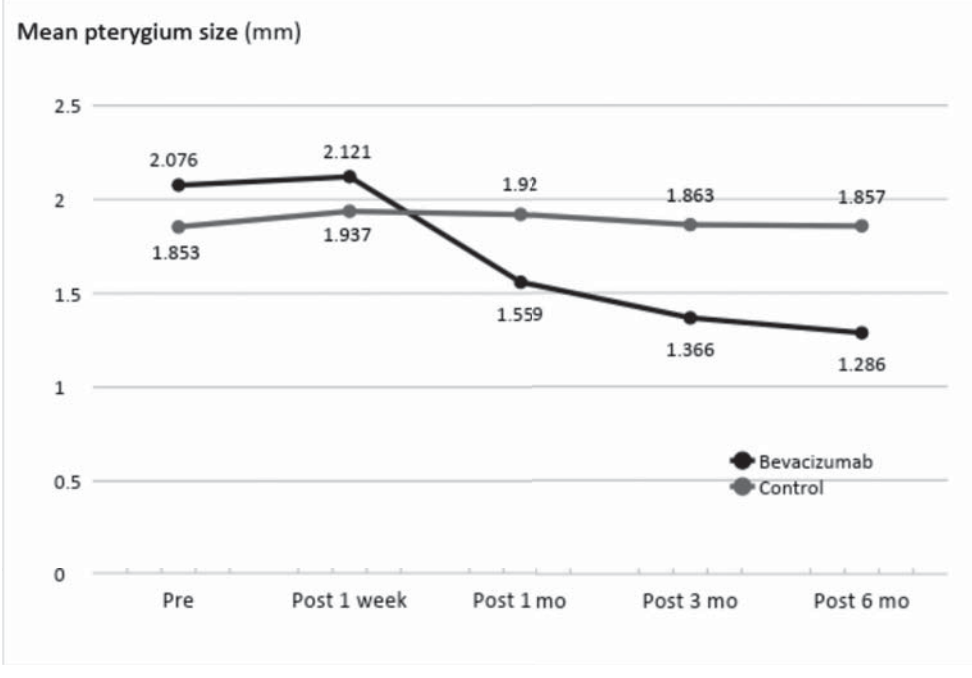

Figure 1: Pterygium dimension in bevacizumab group and control group

group were 2.076, 2.121, 1.559, 1.366 and 1.286 at pre-injection, 1 week post-injection, 1 month post-injection, 3 months post-injection and 6 months post-injection respectively.

The mean of dimension of pterygium in control group were 1.853, 1.937, 1.920, 1.863 and 1.857 at pre-treatment, 1week post-treatment, 1month post-treatment, 3 months post-treatment and 6 months post-treatment respectively.

Mean change of pterygium size reduction in the bevacizumab group were -0.045, 0.517, 0.710 and 0.790 mm at 1 week post-injection, 1 month post-injection, 3 months post-injection and 6 months post-injection respectively. Mean change of pterygium size reduction in the control group were -0.083, -0.067, -0.010 and -0.003 mm at 1 week post-treatment, 1 month post-treatment, 3 months post-treatment and 6 months post-treatment respectively. There was a statistically significant difference in pterygium size reduction between bevacizumab group and control group at all visits ($P < 0.001$). Eleven patients (37.9%) have subconjunctival hemorrhage after 1 week of bevacizumab injection. None had any systemic complications.

Table 2: The pterygium size and the reduction of pterygium size of pre-intervention and postintervention

	Total (n = 59)		bevacizumab (n = 29)		Control (n = 30)		P value
	Mean	**± S.D.**	**Mean**	**± S.D.**	**Mean**	**± S.D.**	
Pre inject	1.963	± 0.615	2.076	± 0.609	1.853	± 0.610	0.166 T
Post inject at 1 week	2.027	± 1.479	2.121	± 2.043	1.937	± 0.573	0.637 T
Post inject at 1 month	1.742	± 0.611	1.559	± 0.604	1.920	± 0.573	0.038* M
Post inject at 3 months	1.619	± 0.623	1.366	± 0.566	1.863	± 0.584	0.003* M
Post inject at 6 months	1.576	± 0.662	1.286	± 0.562	1.857	± 0.637	0.001* T
Difference							
Pre - 1 week	-0.064	± 1.330	-0.045	± 1.902	- 0.083	± 0.207	< 0.001* M
Pre - 1 month	0.220	± 0.405	0.517	± 0.301	- 0.067	± 0.258	< 0.001* T
Pre - 3 month	0.344	± 0.490	0.710	± 0.359	- 0.010	± 0.304	< 0.001* M
Pre - 6 month	0.386	± 0.538	0.790	± 0.361	- 0.003	± 0.366	< 0.001* T

M = P value from Mann-Whitney U-test, T= P value from Independent t-test

*The mean difference is significant at the 0.05 level.

Discussion

The regression of pterygium size in the bevacizumab injection group may be the effect of its anti-fibrovascular property. The first visit at 1 week after injection, there was a small progression of pterygium. The authors assume that this could be due to the inflammatory process after the injection before the anti-fibrovascular effect occurs after 1 month of injection. As expected, there was no regression of pterygium in the control group. In this study, there may be some biases such as the subconjunctival hemorrhage at 1 week after bevacizumab injection which can give the examiner the clue that these patients were in the study group. As the result of previous study, the subconjunctival hemorrhage usually disappears after 1 week.[9] The authors realize that the patient's awareness of sunlight avoidance

may be a confounding factor in our study. In the study group, patients may have avoided sunlight exposure which is the important protective behavioral factor of pterygium progression than those in the control group.

The pros of the study is the first assessor-blinded randomized controlled trial to study the effectiveness of subconjunctival bevacizumab injection in primary pterygium. Although there are many previous trials studying the same outcome but they were not well controlled and none of them were randomized.[10-12] The benefits of subconjunctival bevacizumab injection include its minimally invasive procedure, no operative room needed, short period of recovery and cost-effectiveness. It may be the new modality of primary pterygium management in the future. Nevertheless, the cons of our study include small sample size, lack of clinical information of pterygium (eg, atrophic type, fleshy type or thickness of pterygium), and short period of follow up time. There are many other anti-VEGF agents such as ranibizumab and aflibercept.[13, 14]

They may also have favorable effects in pterygium regression. The authors propose to the other future study to have a longer period of treatment and follow up, larger sample size, more variation of pterygium and using other interesting anti-VEGF agents. According to the study results, we found that there was no local and systemic adverse reaction except for subconjunctival hemorrhage which normally occurs in subconjunctival injection.

Conclusion

The reduction of horizontal dimension in primary pterygium is significantly greater in those who received subconjunctival bevacizumab injection. This local injection procedure has a low adverse event rate and can be used as an alternative treatment.

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