Original Article

Preoperative Intralesional Bevacizumab Injection in Primary Pterygium in Tunisian Patients: A Randomized Controlled Prospective Study

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Abstract

Purpose: To assess the efficacy and safety of a single preoperative intralesional bevacizumab injection as an adjuvant treatment before primary pterygium surgery.

Methods: We conducted a randomized controlled interventional study from January 2019 to December 2020. The study included a total of 60 patients (60 eyes) with primary pterygium. We defined two groups of 30 patients each. Group A received an intralesional injection of bevacizumab (Avastin), 1 month before surgery (lesion excision and conjunctival autograft). Group B (control) had only the surgical treatment. Patients were followed up 7 days (D7), 1 month (M1), 3 months (M3), and 6 months (M6) postoperatively. Pre-, per-, and postoperatively, photographs of the lesions were taken, as well as a histopathological examination. The main outcome measures were the change in functional discomfort following intralesional bevacizumab injection and pterygium recurrence. Recurrence was defined as fibrovascular tissue growth invading the cornea. Therapeutic success was defined as the absence of pterygium recurrence in M6.

Results: The mean age of the 60 patients was 54.17 ± 10.53. After bevacizumab injection, the preoperative functional discomfort score decreased significantly ($P = 0.048$). There was a significant improvement in grade and color intensity ($P = 0.001$). We noted no local nor systemic complications after intralesional injection of bevacizumab. After pterygium excision, the success rate was statistically higher in Group A ($P = 0.047$). There was no significant difference in either final best-corrected spectral visual acuity or astigmatism between the two groups. We noted a statistically significant association between recurrence and color intensity ($P = 0.046$), vascular density ($P = 0.049$), and the degree of elastic tissue degeneration ($P = 0.040$).

Conclusion: A single preoperative subconjunctival injection of bevacizumab 1 month before surgery decreases the vascularity of newly formed blood vessels and hence may reduce the recurrence rate.

Keywords: Bevacizumab, Pterygium, Recurrence, Subconjunctival injection, Vascularity

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Introduction

Pterygium is a wing-shaped, proliferative, and invasive conjunctival degenerative condition involving most commonly the nasal part of the limbus.[1-4] It affects 0.3%–29% of people worldwide[5] and might lead to visual loss in case of extension to the corneal center or when associated with high astigmatism.

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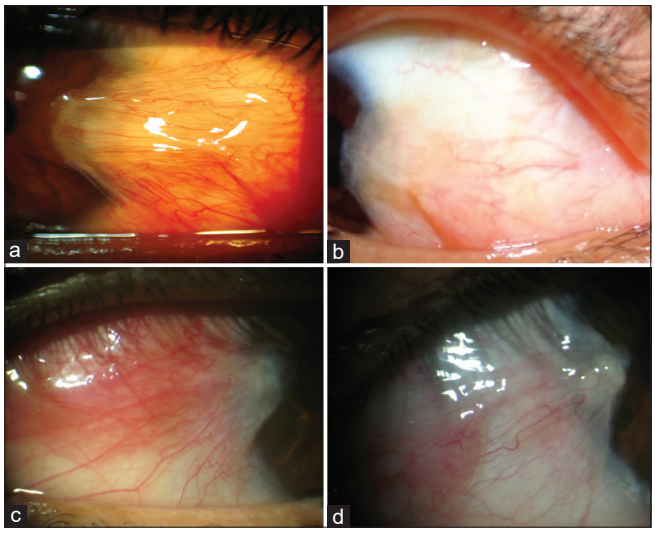

Figure 1: Representative images of pterygium before and after bevacizumab injection. (a and b) A 51-year-old male with a Stage 3, Grade 3 pterygium. (a) Pterygium before bevacizumab administration. (b) Pterygium image after 1 month from a single-dose subconjunctival injection of bevacizumab showing reduction in grade (Grade 1) and color intensity (trace). (c and d) A 37-year-old female with a Stage 2, Grade 3 pterygium. (c) Pterygium photograph at baseline. (d) Postinjection images showing reduction in grade (Grade 2) and color intensity (mild). As seen in the figures, the change in the size of the pterygium does not seem to be clinically significant after bevacizumab administration

The standard treatment of pterygium is surgical.[2-4] Any conservative treatment is mainly symptomatic and temporary, usually indicated for the early stages of the disease. Numerous surgical approaches have been attempted.[2-4,6] Currently, pterygium excision with conjunctival autograft represents the preferred surgical technique.[4]

Postoperative recurrence represents a major concern in pterygium management.[1-7] Thus, many authors recommend the use of adjunctive therapies including mitomycin C (MMC), 5-fluorouracil, topical cyclosporine, and beta irradiation to minimize the recurrence rate.[6,7]

Increased levels of pro-angiogenic growth factors, especially the vascular endothelial growth factor (VEGF), had been identified in the pterygium tissue.[4-8] Thus, anti-VEGF injections have been used by several authors.[5,8-17] It is suggested that anti-VEGF decreases the vascularity of newly formed blood vessels in pterygia, hence reducing the recurrence rate.[4,18]

Nevertheless, the role of anti-VEF in preventing pterygium recurrence is still controversial.[19] To address this point, we carried out a randomized controlled trial to investigate the clinical and histopathological effect of a single-dose preoperative subconjunctival injection of bevacizumab in the treatment of pterygium.

Methods

This prospective randomized controlled study adhered to the tenets of the Declaration of Helsinki. The study was approved by the Ethics Committee of Aziza Othmana Hospital and registered at the U.S. National Library of Medicine_ Clinicaltrials.gov with number: NCT05314673. Written informed consent was obtained from all participants.

The sample size in this study was calculated based on the recurrence rates after pterygium excision-conjunctival autograft with and without subconjunctival bevacizumab in the studies of Ozer *et al*.[2] and Singh *et al*.,[5] respectively. We used a statistical superiority design formula with a power of 0.8, a two-tailed significant level of 0.05, and a margin on a risk difference scale of 0.2. This indicated a sample size of 19 patients per group. Twenty percent of the sample size was added in anticipation of dropout patients.

We included 30 eyes of 30 patients in each group, hence a total of 60 eyes of 60 patients with primary pterygium between January 2019 and December 2020. We performed a simple randomization method using a table of random number. Group A received an intralesional injection of 0.05 ml (1.25 mg) of bevacizumab, 1 month before surgical treatment. Group B (control) had only the surgical treatment. Surgical treatment consisted of lesion excision and conjunctival autograft performed by a single surgeon.

Each patient underwent a complete ocular examination including best-corrected spectral visual acuity (BCSVA), refraction, slit-lamp biomicroscopy, intraocular pressure measurement, and fundoscopy.

We classified pterygium according to its stage (according to Vaniscotte *et al*.[20] classification; 1 = pterygium without extension beyond the limbus, 2 = pterygium slightly extending beyond the limbus, 3 = pterygium reaching the pupillary area, and 4 = pterygium invading the pupillary area), grade (according to Tan *et al*.[21] grading scheme; 1 = episcleral vessels underlying the body of the pterygium unobscured and distinguished, 2 = episcleral vessels are indistinctly seen or partially obscured, and 3 = episcleral vessels are totally obscured by fibrovascular tissue), and color intensity (according to Teng *et al*.;[22] 0 = unremarkable, 1 = trace, 2 = mild, 3 = moderate, and 4 = diffuse). We measured its corneal surface with ImageJ software.

We included patients over 18 years old having primary pterygium with surgical indications:

- Stages 2, 3, and 4
- Significant astigmatism >1.50 prism diopter
- Patients with significant functional signs: according to a discomfort score that we proposed.

Exclusion criteria were recurrent pterygium, suspected pterygium (sentinel vessels and resistant inflammation), and filtering surgery indication. Excluded were patients lost to follow-up or having a bevacizumab contraindication (hypertension, bleeding tendencies, previous myocardial infarction or stroke, and pregnant and lactating women).

Preoperative data gathered included basic demographic information (age and sex), medical and ophthalmological history, and involved eye (s).

We also assessed a "discomfort score" using subjective variables: (1) photophobia, (2) foreign body sensation, (3) ocular itching, (4) tearing, (5) ocular redness, and (6) visual blurring. Each variable was evaluated according to its severity from 0 to 10 (Visual Analog Scale). The discomfort score was evaluated in each visit.

Bevacizumab injections were given in the operating room. Topical anesthesia (oxybuprocaine hydrochloride 0.4%) and povidone-iodine (5% w/v, Bausch and Lomb, UK) eye drops were instilled in the eye 10 min prior to the injection. With a preloaded 1 ml syringe (containing 0.2 ml of 5 mg Avastin), 0.05 ml of Avastin (1.25 mg) was injected by a 26-gauge needle into the body of the pterygium. Formation of a bleb indicated intralesional injection of a drug. Postinjection, 1–2 drops of tobramycin were instilled topically and continued 4 times a day for 3 days.

One month from injection, examination of Group A patients was conducted for stage, grade, color intensity, size of pterygium evaluation, and complications screening.

All patients underwent pterygium excision with conjunctival autografting. All surgeries were performed by a single surgeon (M.H.). Strict aseptic measures were taken. After insertion of a lid speculum, 0.2–0.3 ml injection of 2% xylocaine was performed at the site of the pterygium to raise it up to its attachment to the cornea. Afterward, the pterygium was shaved off the cornea starting 0.5 mm in front of its head using a Crescent blade. The pterygium was cut near the limbus with Westcott scissors. The head of the pterygium was removed from the surface of the cornea. The pterygium attached with the conjunctiva was separated from the sclera with tenotomy scissor and excised leaving about 3–4 mm area of bare sclera. Following episcleral tissue scrapping, the size of the bare scleral area was measured horizontally and vertically with caliper. We did not use adjunctive MMC. Subsequently, a free conjunctival autograft was obtained from the superior limbal region of the same eye approximately 1 mm larger than the recipient site. Graft was then shifted to the recipient conjunctival edge and stitched limbus to limbus with interrupted 10/0 Vicryl suture. During the surgery, direct compression with sponges was applied to stop transient hemorrhages. When hemorrhages persisted, cautery was performed. At the end of the surgery, we did not use a bondage contact lens.

Any intraoperative complication was noted and treated accordingly. All patients received dexamethasone + tobramycin eye drops postoperatively 4 times a day in the 1st week. The eye drops were tapered over 4 weeks.

A histopathological examination of the excised pterygia tissue was performed. All specimens were fixed in 10% buffered formalin and were embedded in paraffin. Four-micrometer-thick sections were subsequently stained with hematoxylin and eosin (HE). The pathologist who interpreted HE-stained section results was blinded to the patients' group categories.

Blood vessel count was done on HE-stained sections as described by Mohamed *et al*.[18] It was expressed as the average number of vessels per high-power field (HPF) after observing 10 HPFs were excluded from the count of large vessels with thick muscular walls. The mean goblet cell and inflammatory cell counts were calculated using the same method.

Regarding hemorrhagic suffusion (extravasation of blood out of vessels) and elastic tissue degeneration, the average percentage of the area occupied by these lesions per HPF was determined.

Patients were examined 30 days before bevacizumab injection (D30), before surgery (day 0: D0), and then at D7, M1, M3, and M6 after surgery. We assessed recurrence at each visit.

Recurrence was classified according to Prabhasawat *et al*.[23] classification – Grade 1: normal appearance, Grade 2: some fine episcleral vessels in the excised area extending up to but not beyond the limbus and without any fibrous tissue, Grade 3: additional fibrous tissues that did not invade the cornea, and Grade 4: true recurrence with fibrovascular tissue invading the cornea.

Pterygium recurrence and discomfort score were considered the main outcomes. Recurrence was defined as Grade 4 of Prabhasawat *et al*. classification. Therapeutic success was defined as the absence of pterygium recurrence in M6.

Secondary efficiency outcome measures were mean changes from baseline in BCSVA (one Snellen line) and astigmatism, change in morphology of pterygium after injection, intraoperative ease, and evidence of any adverse events (safety and tolerability).

Statistical analysis was performed using IBM SPSS software (version 22.0; Statistical Package for Social Sciences Inc., Chicago, IL, USA). Independent *t*-tests were performed to make sure of group similarities at baseline; the assumptions of performing *t*-tests were met, and Chi-square tests were used for proportions. To study the correlation between two quantitative variables, we calculated the Pearson correlation coefficient *r*. If the application conditions were not satisfactory, the Spearman rank correlation coefficient was used. The significance level was set at 0.05 in all statistical tests. We completed a univariate study to identify the main risk factors for pterygium recurrence in our study.

Results

The mean age of the patients was 54.17 ± 10.53 years. The sex ratio (male/female) was 0.93. The two groups were comparable for the age and sex ratio ($P = 0.529$ and $P = 0.477$, respectively). All patients had no past medical history. All pterygia were on the nasal side.

Before bevacizumab injection, 50% of Group A and 56.7% of Group B had a Stage 3 pterygium without statistically significant difference ($P = 0.811$). The most frequent

grade was 3 (46.7% for Group A and 60% for Group B, $P = 0.672$). The pterygia coloration was moderate in 40% of Group A and diffuse in 47% of Group B. The mean discomfort score was 31.8 in Group A and 30.1 in Group B with no significant difference ($P = 0.332$). BCSVA averaged 20/32 for both the groups ($P = 0.944$). Mean astigmatism was −2.68 diopter (D) for Group A and −2.04 for Group B without significant difference ($P = 0.8$). The mean pterygium area measured with ImageJ software was 394.297 ± 209.59 mm^2 for Group A and 384.89 ± 183.59 mm^2 for Group B without significant difference between the two groups ($P = 0.854$) [Table 1].

One month after the bevacizumab injection in Group A, discomfort score decreased significantly to 22.46 ($P = 0.048$). There was also a decrease in grade level. Grade 1 became predominant (53.3%, $P = 0.001$). The color intensity improved to mild (53.3%, $P = 0.001$) [Figure 1a-d]. The pterygium stage did not significantly change ($P = 0.326$). The mean pterygium area became 404.5721 ± 172.566 mm^2 ($P = 0.141$). BCSVA and astigmatism remained unchanged ($P = 0.582$ and $P = 0.811$, respectively) [Table 2].

The discomfort score after surgery was significantly better in Group A in comparison with Group B on D7 and M1 ($P = 0.026$). The difference between the two groups was not statistically significant in M3 and M6 ($P = 0.207$ and $P = 0.850$, respectively) [Figure 2].

Therapeutic success was achieved in 96.7% of Group A and 80% of Group B [$P = 0.047$, Figure 3]. One patient in Group A and five patients in Group B (20%) had true pterygium recurrence (Grade 4 of Prabhasawat *et al*.[23] classification). It occurred between M3 and M6. Grade 3 recurrence was observed in one patient in Group A and three patients (10%) in Group B ($P = 0.133$). Grade 2 recurrence occurred in two patients from each group (6.7%) ($P = 1$).

In M1, astigmatism decreased more in Group A than in Group B without significant difference ($P = 0.295$). In M6, BCSVA improved similarly in both the groups (0.9 in Group A and 0.89 in Group B, $P = 0.851$). We noted no worsening in any of the groups [Table 3].

We conducted a histological comparison between the two groups. The injected pterygia sections showed a significant reduction of the vascular network [Figure 4a]. We observed more hemorrhagic suffusion in Group B (23.3%) than in Group A (3.3%) ($P = 0.01$).

Table 1: Demographic data and pterygium baseline characteristics within both the groups

	Group A, *n* (%)	Group B, *n* (%)	*P**
Mean age (years)	53.9	54.3	0.529
Sex ratio (male/female)	0.76	1.14	0.477
Stage			
Stage 2	2 (6.7)	1 (3.3)	0.811
Stage 3	15 (50)	17 (56.7)	
Stage 4	13 (43.3)	12 (40)	
Grade			0.672
Grade 1	8 (26.7)	7 (23.3)	
Grade 2	8 (26.7)	5 (16.7)	
Grade 3	14 (46.7)	18 (60)	
Color intensity			0.296
Trace	3 (10)	3 (10)	
Minimal	6 (20)	4 (13.3)	
Moderate	12 (40)	10 (33.3)	
Diffuse	9 (30)	13 (43.3)	
Mean pterygium area (ImageJ, mm^2)	394.297±209.59	384.89±183.59	0.854
Discomfort score	31.8	30.1	0.332

*Independent *t*-test was used to compare means and Pearson's Chi-squared test was performed to compare proportions

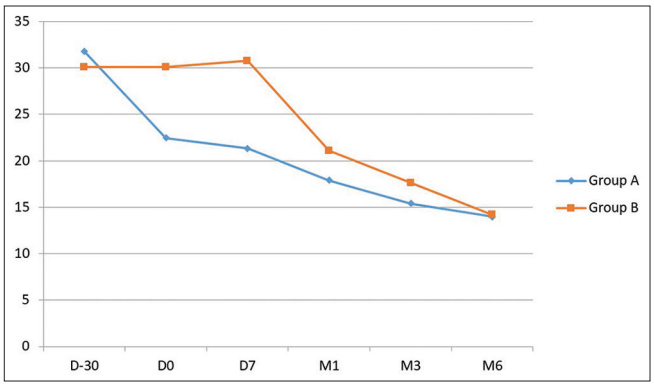

Figure 2: Discomfort score progression in the two groups

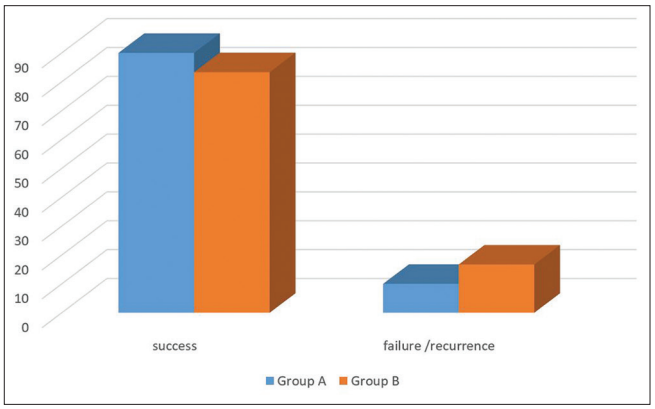

Figure 3: Postoperative success and failure rates in the two groups

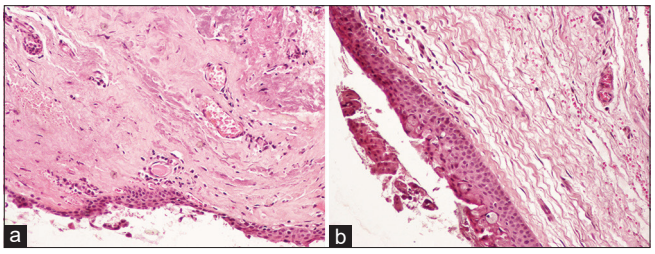

Figure 4: Changes in pterygium after Avastin injection: (a) Reduction of the vascular network; (b) Decreased number of goblet cells with less inflammatory cellular infiltration; hematoxylin and eosin stain, ×200

We also noted a lower number of goblet cells in the epithelium of pterygium in Group A with less inflammatory cellular infiltration without statistically significant difference ($P = 0.81$ and 0.06, respectively) [Figure 4b].

Besides, there were fewer areas of elastic tissue degeneration in the treated pterygia group without significant correlation ($P = 0.09$) [Table 4].

The main risk factors for pterygium recurrence in our study were the pterygium color intensity ($P = 0.046$), the vascular density of the excised tissue ($P = 0.049$), and the degree of elastic tissue degeneration ($P = 0.040$).

No serious ocular or systemic adverse events following intralesional bevacizumab injection were observed.

Postoperatively, there was only one case of graft necrosis in Group A which occurred on D15. Slit-lamp examination revealed a pale and avascular graft with a normal underlying sclera. The appearance of the graft did not change for the following 5 days. The graft was removed in the operative room, and a second superotemporal conjunctival autograft was performed. Postoperative first 6-month visits were unremarkable, and there were no signs of recurrence.

Discussion

The management of pterygium is still challenging due to the high rate of postoperative recurrence, especially in sunny countries like Tunisia.[4,5] Today, the excision of pterygium with conjunctival autograft remains the gold standard surgical technique to reduce this risk.[4] VEGF plays a major role in angiogenesis and inflammation and, thus, in the induction of recurrence after pterygium surgery [Table 5].[5,9-17] The present aim of our study was to evaluate the impact of preoperative bevacizumab injection on pterygium surgery outcomes 6 months postoperatively.

One month after the injection, there was no significant change in the pterygium stage ($P = 0.326$). To the best of our knowledge, no published study has investigated this parameter. One month seems a short time to induce regression or evolution and thus a change of the stage. However, we observed a significant improvement in the grade level and a reduction in the intensity of pterygium coloration. Our results are consistent with previous publications.[17,22,25] Indeed, bevacizumab would induce a decrease in vessel caliber and a reduction in the number of neovessels at the pterygial site thanks to its anti-angiogenic effect.[22,25] However, this impact was not stable during 6 months in the Besharati *et al*. series.[26]

Singh *et al*. noted a significant reduction in the pterygium area 1 week following bevacizumab injection.[5] Similarly, Besharati *et al*. obtained a decrease in measurements 3 months after the injection.[26] Fellah *et al*. reported that the anti-VEGF effect was temporary due to its limited half-life.[27] In our study, we observed a reduction of pterygium surface area, nonetheless not statistically significant ($P = 0.141$).

Table 2: Comparison of pterygium characteristics before and 1 month after bevacizumab injection (Group A)

	Baseline, *n* (%)	One month after bevacizumab injection, *n* (%)	*P**
Stage			
Stage 2	2 (6.7)	2 (6.7)	0.326
Stage 3	15 (50)	16 (53.3)	
Stage 4	13 (43)	12 (40)	
Grade			
Grade 1	8 (26.7)	16 (53.3)	0.001
Grade 2	8 (26.7)	12 (40)	
Grade 3	14 (46.7)	2 (6.7)	
Color intensity			
Trace	3 (10)	12 (40)	0.001
Mild	6 (20)	16 (53.3)	
Moderate	12 (40)	2 (6.7)	
Diffuse	9 (30)	0	
Mean pterygium area (ImageJ, mm^2)	394.297±209.59	404.572±172.566	0.141
Discomfort score	31.8	22.46	0.048

*Dependent *t*-test for paired samples was used to compare means and McNemar's Chi-squared test was performed to compare proportions

Table 3: Pre- and postoperative astigmatism and best-corrected spectral visual acuity within both the groups

	Group A	Group B	*P**
Astigmatism (DP)			
D30*	2.84	2.91	0.479
D0*	2.79	2.91	0.412
M1	1.32	1.45	0.295
M3	1.25	1.29	0.531
M6	1.26	1.28	0.506
BCSVA			
D30#	0.73	0.72	0.812
D0‡	0.74	0.72	0.793
M1	0.91	0.92	0.812
M3	0.89	0.88	0.843
M6	0.90	0.89	0.851

*Independent *t*-test was used to compare mean, #Baseline, ‡One month after intralesional bevacizumab injection (before surgery). BCSVA: Best-corrected spectral visual acuity, DP: Diopters

Table 4: Histological parameters within both the groups

	Group A	Group B	*P**
Mean vessel count	5.23±0.71	13.78±1.49	0.001
Mean goblet cell count	11.66±13.87	13.72±12.94	0.122
Mean inflammatory cellular infiltration count	11.98±5.20	15.17±9.23	0.068
Mean area of hemorrhagic suffusions (%)	4.6	25.8	0.001
Mean area of elastic tissue degeneration (%)	32.7	36.9	0.090

*Independent *t*-test was used to compare means and Pearson's Chi-squared test was performed to compare proportions

Table 5: Studies on adjuvant bevacizumab injection combined with pterygium surgery for primary pterygium

Study	Group	Number of patients (eyes)	Mean age	Surgical method	Beva dose (mg)	Follow-up (months)	Final number of patients	Recurrence	Complications
Razeghinejad, 2010[9]	Beva	17 (17)	41.7	RCF	1.25	7.7	15	2	7
	Control	21 (21)					15	2	10
Shenasi, 2011[10]	Beva	40 (40)	57.3	BST	1.25	9	33	15	19
	Control	40 (40)					33	19	21
Shahin, 2012[11]	Beva	20 (20)	58.1	LCA	1.25	6	20	4	0
	Control	21 (21)					21	2	0
Xu, 2013[24]	Beva	40 (40)	42.5	CLSCA	2.5	12	40	5	1
	Control	40 (40)					40	6	7
Ozsutcu, 2014[13]	Beva	30 (30)	42.02	RCF	2.5	9	30	3	0
	Control	60 (60)					60	12	0
Zhang, 2014[14]	Beva	34 (34)	49.95	CLSCA	2.5	6	34	0	N/A
	Control	32 (32)					32	4	N/A
Singh, 2015[5]	Beva	30 (30)	37.3	CAT	1.25	3	30	2	5
	Control	30 (30)					30	3	4
Nuzzi, 2017[17]	Beva	42 (42)	53.15	BST	2.5	6	42	3	0
	Control	41 (41)					41	10	0
Chen, 2019[15]	Beva	40 (50)	53.45	AMT	1.25	3	40	1	4
	Control	40 (50)					40	4	4
Yang, 2020[16]	Beva	53 (53)	64.3	LCA	1.25	12	53	1	N/A
	Control	48 (48)					48	4	N/A

AMT: Amniotic membrane transplantation, Beva: Bevacizumab, BST: Bare sclera technique, CAT: Conjunctival autograft transplantation, CLSCA: Corneal limbal stem cell autograft, LCA: Limbal-conjunctival autograft transplantation, N/A: Not available, RCF: Rotational conjunctival flap

Consistent with previous data,[5,9,25-27] we did not obtain any change in BCSVA. However, Sarac *et al*. reported an improvement 2 months after intralesional injection of bevacizumab.[28] As for astigmatism, we observed a modest improvement without significant difference. Sarac *et al*. and Razeghinejad *et al*. had similar results.[9,28] Singh *et al*., on the other hand, obtained no change.[5]

In our series, the discomfort score decreased significantly after injection ($P = 0.048$) in line with Sarac *et al*. series.[28] In the series of Teng, this decrease was temporary.[22] Enkvetchakul, however, found a nonsignificant reduction in the discomfort score.[25] Bevacizumab decreases inflammatory cells and pro-inflammatory cytokines flow in pterygium. It seems to reduce ocular functional discomfort.[8]

The study of histological sections found significant microscopic changes between the two groups. Indeed, the vascular network and hemorrhagic suffusion were significantly reduced in injected pterygia. The anti-angiogenic effect of anti-VEGF induces the regression of blood vessels and delays the progression of pterygium.[8,29]

The preinjected pterygia sections had an apparent decrease in the number of goblet cells in the epithelium with less inflammatory cellular infiltration without statistically significant difference. Alsmman *et al*. reported similar findings after bevacizumab and MMC injection.[29] According to Nuzzi *et al*., there was a positive correlation between the intensity of inflammation and the degree of pterygium vascularization.[17] Postoperatively, we obtained similar gain in BCSVA in both the groups. However, Sarac *et al*. reported a better improvement in BCSVA in patients with subconjunctival bevacizumab.[28] Astigmatism improved significantly in both the groups without statistically significant difference. This improvement was consistent with other studies.[5,28] The suppression of the mechanical effect caused by the fibrous tissue of the pterygium on the cornea induces the reduction of astigmatism. In addition, the excision of the pterygium reduces irritation and thus improves the quality of the tear film.

Similar to previous studies,[5,21,22] we obtained a significant decrease in ocular irritation postoperatively in Group A, as evidenced by the discomfort score that improved during subsequent controls. Bevacizumab induces involution of the vessels nourishing the pterygium, reducing their caliber and the subsequent inflammatory infiltrate. It decreases the redness and irritative signs.[17] However, this improvement was not permanent due to the short half-life of bevacizumab.[27] Further postoperative injections would have been required to maintain this beneficial effect on symptoms.[17]

VEGF is the most efficient pro-angiogenic factor with significant mitogenic effects on vascular endothelial cells.[8,27-29] Several studies showed overexpression of VEGF in endothelial and stromal cells in pterygial tissue.[8,23,29] As shown in Table 5, the efficiency of anti-VEGF as an adjunct therapy to prevent recurrence after pterygium surgery is still controversial. In our study, the recurrence rate was lower in the bevacizumab group, which is consistent with previous data[5,12-17] including a recent randomized controlled trial with a 12-month follow-up.[16] Conversely, other publications reported a lack of efficiency in this regard.[9-11]

Several factors could explain this result disparity. First, the follow-up period was different from one study to another. In ours, the follow-up period was relatively appropriate for assessing the risk of postoperative recurrence since most recurrences occur between M3 and M6 after surgery.[5] The second cause is the absence of a codified bevacizumab injection protocol, particularly regarding the administration time, the route, the dose, and the potential number of injections.

Bevacizumab is a short-lived drug. Its subconjunctival injection does not guarantee its effectiveness in inhibiting a continuous pool of VEGF contained in the pterygial tissue. Repeated injections may be necessary to optimize its effect on recurrence to the detriment of higher management cost.

Several other factors were controversial as to their correlation with a higher risk of recurrence of pterygium after excision including the grade,[30-32] the size,[33] the surface area,[29,34] the length and spread,[34] the vascularity index,[29,34] and the density of lymphatic tissue. Weinstein concluded that histology does not influence the recurrence rate.[35] The main risk factors for pterygium recurrence in our study were the pterygium color intensity ($P = 0.046$), the vascular density of the excised tissue ($P = 0.049$), and the degree of elastic tissue degeneration ($P = 0.040$).

The major limitation of this study was the short follow-up time. Further multicentric randomized studies testing the optimum time or dose of anti-VEGF injection with long-term follow-up are recommended.

As a result of this work, we recommend an intralesional injection of bevacizumab, especially for patients with a high functional discomfort score. The subconjunctival injection of bevacizumab is a harmless procedure without serious local or systemic side effects. It provides a promising approach in vascularity and grade regression and could reduce the risk of recurrence in the short-term. We also suggest a systematic histological examination of pterygia after surgery. Long-term monitoring is as well advisable to detect late recurrence.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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