



# Efficacy of bevacizumab injection after pterygium excision and limbal conjunctival autograft with limbal fixation suture

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## Abstract

**Purpose** To determine the efficacy of subconjunctival bevacizumab injection after pterygium excision with limbal conjunctival autograft and limbal fixation suture.

**Methods** This retrospective study included a total of 150 eyes of 150 patients with primary pterygium who received three different procedures after pterygium excision, i.e., 49 eyes with limbal conjunctival graft (group A), 48 eyes with limbal conjunctival autograft with limbal fixation suture (group B), and 53 eyes with limbal conjunctival autograft with limbal fixation suture followed by bevacizumab injection (group C). Image analysis was performed using preoperative anterior segment photographs to measure parameters including relative length, relative width, relative area, and vascularity index of pterygium. Recurrence of pterygium was determined at 1 year after surgery, and outcomes were compared between the 3 groups. Risk factors related to recurrence were evaluated using univariate and multivariate analyses.

**Results** Recurrence rates after 1 year were 18.4% (9/49), 8.3% (4/48), and 1.9% (1/53) in groups A, B, and C, respectively ( $P = 0.004$ ). Multivariate analysis showed that patients in group C had significantly reduced risk of recurrence compared with those in group A ( $P = 0.009$ ), whereas the risk of recurrence was not significantly different between groups A and B ( $P = 0.227$ ) and groups B and C ( $P = 0.068$ ), respectively. Among various parameters, higher vascularity index had significant correlation with increased risk of recurrence ( $P = 0.008$ ).

**Conclusions** Bevacizumab injection after limbal conjunctival autograft and limbal fixation suture may effectively reduce recurrence after pterygium excision. The vascularity of pterygium was associated with a higher risk of recurrence.

**Keywords** Bevacizumab · Limbal conjunctival autograft · Pterygium · Recurrence · Vascularity

## Introduction

Pterygium is a wing-shaped fibrovascular tissue overgrowth of conjunctiva that involves the corneal surface [1–4]. It can cause cosmetic problems or serious visual impairment by involving

the visual axis or inducing significant astigmatism. In these cases, surgical treatment is indicated [1–4]. However, simple excision of pterygium is associated with a high rate of recurrence [5, 6]. Various adaptations of the surgical technique, such as amniotic membrane transplantation, anterior lamellar keratoplasty, conjunctival and/or limbal autograft, and the application of antimetabolites have been introduced to avoid recurrence [5, 7–12]. However, it is almost impossible to entirely eliminate recurrence, which still remains a great challenge [5, 13].

Previously, we reported that limbal conjunctival autograft transplantation with limbal fixation sutures could be effective in reducing recurrence after pterygium excision [12]. As angiogenesis of the pterygium tissue may reflect its proliferative activity associated with recurrence, reduction of angiogenesis and fibroblast proliferation by anti-vascular endothelial growth factor (VEGF) injection appears to be an intriguing option for preventing recurrence [14–16]. Therefore, in addition to the limbal conjunctival autograft and limbal fixation

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suture, we postulated that postoperative anti-VEGF injection may reduce the risk of pterygium recurrence by reducing angiogenesis and fibroblast proliferation.

In the present study, we evaluated the efficacy of bevacizumab injection, an anti-VEGF agent, after pterygium excision and limbal conjunctival autograft with limbal fixation suture. We also determined the risk factors associated with pterygium recurrence after surgery.

## Methods

### Ethics statement

This study was approved by the Institutional Review Board of Kangwon National University Hospital and adhered to the tenets of the Declaration of Helsinki.

### Study participants

This retrospective study included 150 eyes of 150 consecutive patients who underwent pterygium excision and limbal conjunctival autograft at the Kangwon National University Hospital between February 2014 and May 2018, and were followed up for at least 1 year after surgery. After pterygium excision, each patient received one of the following three procedures: (1) limbal conjunctival autograft only (group A), (2) limbal conjunctival autograft with limbal fixation suture (group B), and (3) limbal conjunctival autograft with limbal fixation suture followed by bevacizumab injection at 1 week after surgery (group C). Exclusion criteria included previous pterygium excision, history of ocular surgery, history of ocular trauma, connective tissue disorders, systemic vasculitis, glaucoma, and diabetes mellitus [17, 18].

### Surgical procedure

In all groups, pterygium excision and limbal conjunctival autograft were performed under topical anesthesia using 0.5% proparacaine hydrochloride (Alcaine®; Norvatis, Basel, Switzerland) as previously described [7, 12]. All surgeries were performed by one surgeon (S.B.H.). Briefly, the pterygial body was excised using a Westcott scissor, and the head was separated with a disposable Beaver Blade (Beaver Visitec International, Waltham, MA, USA). Subconjunctival fibrovascular tissue was thoroughly dissected. An autologous limbal conjunctival graft harvested from the superotemporal bulbar conjunctiva was placed onto the site where the pterygium had been removed, and then was secured to the adjacent conjunctiva with interrupted 8-0 polyglactin sutures (Vicryl; Ethicon) sutures in all patients. In group A, no additional procedure was done.

In groups B and C, the limbal margin of the graft was fixed at the donor limbus with a long circumferential interrupted 10-0 nylon suture. This suture was removed 1 week after surgery.

In group C, subconjunctival bevacizumab injection was also performed at the superior, inferior, and nasal area adjacent to the graft (1.25 mg/0.05 ml to each area) immediately after removal of the 10-0 nylon suture.

Postoperatively, topical levofloxacin 0.5% and prednisolone acetate 1% were applied 4 times a day for 1 month.

### Image analyses

Anterior segment photographs (ASP) of the pterygium were taken preoperatively at  $\times 10$  magnification using a Haag-Streit BM 900 slit-lamp microscope (HAAG STREIT AG, Bern, Switzerland) in combination with a digital camera (Canon EOS 20D; Canon, Tokyo, Japan) as previously described [17–19]. Slit beam lighting with maximum width (30 mm) and 4 mm height of the beam at a 45° oblique angle was used for anterior segment photography. The photographs were saved as a JPG file format (2544  $\times$  1696 pixels, RGB) [17–19].

Image analysis using preoperative ASPs was performed as previously described [17, 18]. Briefly, the length, width, and area of the region of the cornea covered by pterygium were calculated using the ImageJ software (ver. 1.48, National Institutes of Health, Bethesda, MD, USA). The relative length (RL) of pterygium (involving the cornea) was calculated by dividing the length of pterygium, defined as the distance of the horizontal line from the edge of pterygium head to the corneal limbus, by horizontal corneal diameter. The relative width (RW) of pterygium was calculated by dividing the width of pterygium, which was determined as the distance between the two points where pterygium intersects the corneal limbus, by vertical corneal diameter. The relative area (RA) of pterygium was calculated by dividing the area of the cornea involved by pterygium by the area of the whole cornea [17, 18].

Vascularity index (VI) of the pterygium involving the cornea was determined using an in-house software that uses the contrast-limited adaptive histogram equalization (CLAHE) algorithm which automatically extracts vasculature and scores the degree of vascularity in numeric values ranging from 0 to 100 [17–19]. Briefly, the color image was converted to a gray scale image, and contrast was enhanced using the CLAHE algorithm. The image was then thresholded and divided into background and red vessels, and VI was calculated as the ratio of the number of pixels identified as vessels to the total number of pixels in each region [19, 20]. The region of pterygium involving the cornea was manually marked as the region of interest (ROI) from an ASP, and VI was automatically calculated by the software. Measurement using the CLAHE algorithm was done by one ophthalmologist (HKY) who was masked to the patient information.

## Main outcome measures

Recurrence rates at 1 year after pterygium excision were compared among the three groups. Recurrence was defined as the presence of fibrovascular tissue over the corneal limbus onto the cornea at the area of prior pterygium excision [21, 22]. Factors associated with recurrence including age, sex, type of surgery (group), and image parameters of pterygium, such as RL, RW, RA, and VI, were determined.

## Statistical analysis

Statistical analysis was performed using the SPSS software version 20.0 (SPSS, Inc., Chicago, IL, USA). All continuous variables were expressed as mean  $\pm$  standard deviation (SD). Recurrence rates were compared among the three groups using one-way analysis of variance (ANOVA). Univariate analysis and multivariate analysis using binary logistic regression analysis were performed to determine risk factors of recurrence. *P* values of  $<0.05$  were considered statistically significant.

## Results

The study population comprised of 90 men (60.0%) and 60 women (40.0%), and the average age was  $64.9 \pm 11.2$  years (range, 37–88 years).

In comparison of the three groups, there were no significant differences in age ( $P=0.728$ ) and sex ( $P=0.913$ ). Image parameters of pterygium were not significantly different among the three groups including VI ( $P=0.155$ ), RL ( $P=0.352$ ), RW ( $P=0.276$ ), and RA ( $P=0.103$ ) (Table 1).

Recurrence of pterygium within 1 year was found in 9 cases (18.4%) in group A (detected at 4 months in three, at 6 months in five, and at 9 months in one case), 4 cases (8.3%) in group B (detected at 6 months in two and at 9 months in two cases), and 1 case (1.9%) in group C (detected at 6 months), which was significantly different among the three groups ( $P=0.004$ ). There was a significant difference in recurrence rates between groups A and C ( $P=0.006$ ), although no significant differences was found between groups A and B ( $P=0.233$ ) and between groups B and C ( $P=0.188$ ), respectively (Table 2). Complications such as cysts, graft retraction or dehiscence, ischemia, avascular bed, persistent epithelial defect, or scleral melting were not found in any patient.

Univariate analysis showed that higher VI had significant association with increased risk of recurrence ( $P=0.026$ ). However, age, sex, RL, RW, and RA had no significant association with the risk of recurrence (Table 3).

In multivariate analysis, the type of surgery (group) ( $P=0.025$ ) and VI ( $P=0.008$ ) were significantly related to recurrence, whereas the associations between recurrence and age ( $P=0.073$ ), RL ( $P=0.791$ ), RW ( $P=0.784$ ), or RA ( $P=0.872$ ) were not significant. Patients in group C showed a 0.049-fold (95% CI, 0.005–0.466) decreased risk of recurrence compared with those in group A ( $P=0.009$ ), whereas there was no significant difference in recurrence rates between groups A and B ( $P=0.227$ ), and groups B and C ( $P=0.068$ ), respectively. Higher VI had a 1.089-fold (95% CI, 1.023–1.160) increased risk of recurrence ( $P=0.008$ ) (Table 4).

## Discussion

In the present study, we evaluated the efficacy of subconjunctival bevacizumab injection after pterygium

**Table 1** Comparison of clinical characteristics between the three groups

| Variables                 | Group A ( <i>N</i> =49) | Group B ( <i>N</i> =48) | Group C ( <i>N</i> =53) | <i>P</i> value     |
|---------------------------|-------------------------|-------------------------|-------------------------|--------------------|
| Age (y)                   | 65.9 $\pm$ 11.1         | 64.3 $\pm$ 12.7         | 64.3 $\pm$ 9.0          | 0.728*             |
| Sex (M:F)                 | 59%:41% (29:20)         | 58%:42% (28:20)         | 62%:38% (33:20)         | 0.913 <sup>†</sup> |
| Vascularity index (VI, %) | 25.6 $\pm$ 11.0         | 21.9 $\pm$ 11.9         | 26.4 $\pm$ 13.6         | 0.155*             |
| Relative length (RL, %)   | 25.8 $\pm$ 9.8          | 23.2 $\pm$ 9.4          | 23.9 $\pm$ 8.8          | 0.352*             |
| Relative width (RW, %)    | 48.5 $\pm$ 11.2         | 45.1 $\pm$ 10.2         | 47.1 $\pm$ 10.3         | 0.276*             |
| Relative area (RA, %)     | 12.4 $\pm$ 5.7          | 10.3 $\pm$ 6.0          | 10.2 $\pm$ 5.4          | 0.103*             |

All data are expressed as mean  $\pm$  SD or percentage, as appropriate

y, year; M, male; F, female;

Group A, limbal conjunctival autograft after pterygium excision.

Group B, limbal conjunctival autograft with limbal fixation suture after pterygium excision.

Group C, limbal conjunctival autograft with limbal fixation suture followed by bevacizumab injection after pterygium excision.

\**P* value was calculated using one-way analysis of variance (ANOVA)

<sup>†</sup> *P* value was calculated using Pearson's chi-square test

**Table 2** Comparison of recurrence rates among the three groups

|               | Group A (N = 49) | Group B (N = 48) | Group C (N = 53) | P value       | Pair-wise differences                                                              |
|---------------|------------------|------------------|------------------|---------------|------------------------------------------------------------------------------------|
| Recurrence    | 9 (18.4%)        | 4 (8.3%)         | 1 (1.9%)         | <i>0.004*</i> | 0.233 <sup>†</sup> (Group B vs Group A)                                            |
| No recurrence | 40 (81.6%)       | 44 (91.7%)       | 52 (98.1%)       |               | 0.006 <sup>†</sup> (Group C vs Group A)<br>0.188 <sup>†</sup> (Group C vs Group B) |

Group A, limbal conjunctival autograft after pterygium excision.

Group B, limbal conjunctival autograft and limbal fixation suture after pterygium excision.

Group C, limbal conjunctival autograft and limbal fixation suture followed by bevacizumab injection after pterygium excision.

Recurrence, cases with recurrence at postoperative 1 year.

No recurrence, cases without recurrence at postoperative 1 year

\**P* value was calculated using linear-by-linear association among the three groups; <sup>†</sup>*P* value was calculated using Fisher's exact test

Statistically significant factors are expressed in italics

excision and limbal conjunctival autograft with limbal fixation suture (group C), by comparing the outcomes of pterygium excision and limbal conjunctival autograft with limbal fixation suture (group B), and pterygium excision with limbal conjunctival autograft alone (group A). Subconjunctival bevacizumab injection after limbal conjunctival autograft with limbal fixation suture significantly reduced recurrence after pterygium excision. We also determined that higher vascularity of pterygium was associated with a higher risk of recurrence at 1 year after surgery [18], because prior studies showed that almost all recurrences occur within a year [23, 24].

We used the ImageJ software for the determination of RL, RW, and RA, which has been proved to be reliable for quantification of length, width, and area of pterygium involving the cornea [17, 18]. An in-house software using CLAHE algorithm applied for the measurement of VI was also found to be suitable for the quantification of conjunctival vascularization using ASPs in our prior studies [17–20].

The results of the present study suggest that subconjunctival injection of an anti-VEGF agent,

bevacizumab, following limbal conjunctival autograft with limbal fixation suture (group C) may decrease the risk of recurrence compared with limbal conjunctival autograft alone after pterygium excision (group A). However, simply adding a limbal fixation suture after limbal conjunctival autograft did not reduce the risk of recurrence (group B vs group A). These results indicate that vascularity of the pterygium has significant association with recurrence, which is in accordance with our previous study [18].

High VEGF levels are detected in pterygial tissue, which is known to play an important role in the progression of pterygium by mediating angiogenesis and fibrovascular proliferation [25–27]. Thus, it can be postulated that increased vascularity indicates active fibrovascular proliferation and abundant production of VEGF and VEGF receptors (VEGFR), which raises the risk of recurrence after pterygium excision [18]. Gumus et al. [28] revealed that overexpression of VEGFR represents the clinical aggressiveness of pterygium and may have a predictive value for recurrence. Detorakis et al. [29] also demonstrated that VEGF-A expression had significant

**Table 3** Univariate analysis of potential risk factors for pterygium recurrence

| Variables                 | Recurrence (n = 14) | No recurrence (n = 136) | P value            |
|---------------------------|---------------------|-------------------------|--------------------|
| Age (y)                   | 61.9 ± 10.3         | 65.2 ± 11.2             | 0.280*             |
| Sex (M:F)                 | 9 (64%):5 (36%)     | 81 (60%):55 (40%)       | 0.783 <sup>†</sup> |
| Vascularity index (VI, %) | 31.6 ± 13.2         | 23.9 ± 12.1             | 0.026*             |
| Relative length (RL, %)   | 28.4 ± 9.5          | 23.9 ± 9.2              | 0.107*             |
| Relative width (RW, %)    | 50.5 ± 10.3         | 46.5 ± 10.6             | 0.191*             |
| Relative area (RA, %)     | 13.5 ± 6.4          | 10.7 ± 5.7              | 0.132*             |

All data are expressed as mean ± SD or percentage, as appropriate

y, year; M, male; F, female;

Recurrence, cases with recurrence at postoperative 1 year

No recurrence, cases without recurrence at postoperative 1 year

\**P* value was calculated using Student's *t* test

<sup>†</sup>*P* value was calculated using Pearson's chi-square test

**Table 4** Multivariate analysis of potential risk factors for pterygium recurrence

| Variables              | Odds ratio (95% CI) | <i>P</i> value* |
|------------------------|---------------------|-----------------|
| Age                    | 0.444 (0.896–1.005) | 0.073           |
| Group                  |                     | 0.025           |
| Group B vs Group A     | 0.444 (0.119–1.656) | 0.227           |
| Group C vs Group A     | 0.049 (0.005–0.466) | 0.009           |
| Group C vs Group B     | 0.111 (0.011–1.173) | 0.068           |
| Vascularity index (VI) | 1.089 (1.023–1.160) | 0.008           |
| Relative length (RL)   | 1.106 (0.902–1.145) | 0.791           |
| Relative width (RW)    | 1.103 (0.923–1.112) | 0.784           |
| Relative area (RA)     | 0.984 (0.813–1.192) | 0.872           |

CI, confidence interval

Group A, limbal conjunctival autograft after pterygium excision.

Group B, limbal conjunctival autograft with limbal fixation suture after pterygium excision.

Group C, limbal conjunctival autograft with limbal fixation suture followed by bevacizumab injection after pterygium excision.

\**P* value by multiple logistic regression analysis

Statistically significant factors are expressed in italics

association with the aggressiveness and postoperative recurrence of pterygium. Lin et al. [30] showed that lymphatic microvessel density was associated with the time to recurrence after pterygium excision. The findings of Tan et al. [31] that fleshy pterygia had a higher risk of recurrence than atrophic ones also support our assumption.

The results of the present study suggest that postoperative injection of anti-VEGF agents may reduce the risk of recurrence after pterygium excision, presumably by decreasing fibrovascular proliferation and vascular regeneration via inhibition of the activity of VEGF. Previous studies showed the efficacy of topical or subconjunctival bevacizumab therapy in preventing neovascularization [16, 32]. Topical bevacizumab therapy for 1 month after surgical excision of recurrent pterygium was effective to prevent neovascularization [16]. Subconjunctival bevacizumab injection was effective in preventing recurrences after primary pterygium surgery [33], as well as in reducing the size of recurrent pterygium [34]. Recent meta-analysis studies concluded that adjuvant treatment using bevacizumab showed a statistically significant decrease in recurrence rates after pterygium surgery [35, 36]. However, several other reports suggested that subconjunctival bevacizumab injection may have no effect on reducing pterygium recurrence [37–39]. Further prospective studies with larger population are necessary to determine the effect of subconjunctival anti-VEGF injection on postoperative pterygium recurrence.

Limbal conjunctival autograft is known to reduce the risk of recurrence compared with simple removal of pterygium [5, 10]. Our previous study suggested that a limbal fixation suture

combined with limbal conjunctival autograft could be more effective in reducing the risk of recurrence after pterygium excision compared with limbal conjunctival autograft alone without limbal fixation suture [12]. In this study, a lower recurrence rate was found in patients with limbal fixation suture and limbal conjunctival autograft (group B) than those with limbal conjunctival autograft alone (group A), although the difference was not statistically significant in multivariate analysis. Meanwhile, addition of postoperative subconjunctival bevacizumab injection together with limbal fixation suture (group C) significantly decreased the risk of recurrence compared with limbal conjunctival autograft alone (group A). Therefore, we believe that subconjunctival bevacizumab injection after limbal conjunctival autograft with limbal fixation suture could be the most effective method for preventing recurrence after pterygium excision as for now.

This study has the following limitations: First, the mean age of 64.9 years in the study participants is relatively old. Only two patients (1.3%) are  $\leq 40$  years old, and 15 (10%) are  $\leq 50$  years old, which may cause bias in the evaluation of the effect of age on recurrence. As young age is suggested to be a risk factor of recurrence [40–45], further studies including sufficient number of patients with younger age would be necessary. Second, there is no guideline regarding the time point, dosage, route of administration, or frequency of treatment with anti-VEGF agents. In this study, we performed anti-VEGF injection at the same time as we removed the limbal fixation suture at 1 week after pterygium excision [12]. Although anti-VEGF injection of 3.75 mg (1.25 mg each for superior, inferior, and nasal areas) at 1 week after surgery was effective in the present study, the optimal time and dosage of injection, as well as the indication, still remains uncertain. Previous studies evaluated the effect of anti-VEGF injection using various dosages, time points, and routes of administration. Singh et al. [46] showed that a single administration of 1.25 mg/0.05 mL subconjunctival bevacizumab 1 week prior to surgery decreased the vascularity of neovascularization. However, 1.25 mg/0.1 mL subconjunctival bevacizumab injected immediately after surgery did not significantly prevent recurrence [37], while twice the larger dose of 2.5 mg/0.1 mL subconjunctival bevacizumab injection immediately after surgery effectively prevented pterygium recurrence [33]. A total of 7.5 mg bevacizumab (5 mg/0.2 mL on the day of surgery and 2.5 mg/0.1 mL on the fourth day after surgery) injection caused no adverse effect on early postoperative wound healing [47], although there was no significant effect on recurrence [39]. Meanwhile, in recurrent cases, triple injections of 2.5 mg/0.1 mL subconjunctival bevacizumab with a 2-week interval in the area of recurrent pterygium have been suggested to be effective [34]. Not only injection but also topical bevacizumab (5 mg/mL or 25 mg/mL) has shown to be effective for preventing neovascularization after pterygium excision or delaying recurrence of impending recurrent

pterygium [16, 48, 49]. Up to now, there is no consensus on the indications that justify the use of anti-VEGF agents and the standard dose or frequency according to risk factors of recurrence. Therefore, we believe that prospective trials with a larger population should be performed to evaluate the efficacy of anti-VEGF therapy, and establish indications and standard treatment regimens including dosage, time point, and route of administration. Third, image analysis of anterior segment photographs can only measure vascularity of the ocular surface level. Although vascularity of the pterygial surface is conceivably correlated with vascularity of the total pterygium tissue, surface vascularity would have limited value for representing the whole vascularity of a pterygium. Thus, future studies using tools such as optical coherence tomography angiography for more precise quantification of vascularity of the total pterygial tissue would be helpful.

In conclusion, this study demonstrated that higher vascularization was associated with an increased risk of recurrence after pterygium excision. Subconjunctival injection of bevacizumab after pterygium excision and limbal conjunctival autograft with limbal fixation suture may be effective for preventing pterygium recurrence.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was not required for this type of study.

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