

Interferon Alpha-2b Eye Drops Prevent Recurrence of Pterygium After the Bare Sclera Technique: A Single-Center, Sequential, and Controlled Study

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Purpose: To investigate the efficacy and safety of interferon (IFN) alpha-2b eye drops in preventing pterygium recurrence after the bare sclera technique.

Methods: Sixty eyes in 53 patients who underwent treatment for primary pterygium (the length of corneal invasion ranged from 2 to 4 mm) were enrolled in this prospective study. All patients were divided in chronological sequence into 2 groups. The control group included the first 30 eyes, whereas the treatment group included the next 30 eyes. After treatment with the bare sclera technique, levofloxacin and 0.1% fluorometholone eye drops were used 4 times a day for 3 months after surgical excision in both groups. In addition, IFN alpha-2b eye drops were applied in the treatment group 4 times a day for 3 months. Throughout an 18-month follow-up period, all patients in both groups were examined 1 day, 10 days, 1 month, 3 months, 6 months, 12 months, and 18 months after surgery. The main outcome measures were pterygium recurrence, conjunctival redness and thickness, and neovascularization and complications (ie, delayed conjunctival healing, persistent corneal epithelial defect, conjunctival granuloma, and scleral melting and necrosis).

Results: The recurrence rates in the control group and the treatment group at the end of the sixth month were 29.2% and 3.7%, respectively, and the rates were significantly different between the 2 groups ($P = 0.019$). Up to 12 months after surgeries, the recurrence rate was 33.3% in the control group and 7.4% in the treatment group, and the difference between the 2 groups was statistically significant ($P = 0.048$). The rates at the end of 18 months were the same. During

the follow-up period, no complications were observed except for 1 conjunctival granuloma (in the treatment group) and 2 corneal epithelial defects (one in the control group and the other in the treatment group).

Conclusions: Administration of IFN alpha-2b eye drops after the bare sclera technique appear safe and effective in reducing the recurrence of pterygium.

Key Words: pterygium, recurrence, IFN alpha-2b eye drops

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Pterygium is a common external eye disease associated with the growth of triangular fibrovascular tissue from the bulbar conjunctiva toward the cornea.^{1,2} Surgery is the main treatment for this condition, and recurrence is still one of the most common complications. Recurrent pterygium has features similar to those of primary pterygium histologically, yet proliferation of fibrovascular tissues tends to be more aggressive and prominent.³ In previous studies, a few mechanisms have been described that contribute to recurrent progression. It has been proven that chronic inflammation plays a major role in the recurrence of pterygium.² In addition, long-term ultraviolet exposure-mediated pterygium growth progression occurs by increasing secretion of cytokines, such as IL-2, IL-6, IL-8, and vascular endothelial growth factor (VEGF). All these cytokines initiate proliferation and migration of fibroblasts and vascular endothelial cells and stimulate an inflammatory reaction and angiogenesis.^{4,5} Most recently, pterygium progression was acknowledged as being similar to “tumor-like proliferation” rather than conjunctival degeneration.¹ In addition, several publications have observed a correlation between pterygium and ocular surface squamous neoplasia and have also found that human papillomavirus (HPV) infection was the common high-risk factor.^{4,6} Other authors also suggested that HPV and herpes simplex virus infections were related to primary and recurrent pterygium.^{5,6} Finally, an immune reaction has also been discovered to play a role in pathological progression of recurrent pterygium.^{7,8}

Surgical excision is the traditional treatment for pterygium^{3,9}; however, the bare sclera technique used alone is associated with a high recurrence rate (33%–45%),⁹ and

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multiple medical treatments are therefore necessary after surgery to prevent recurrence.

Interferons (IFNs) are cytokines secreted by cells in response to a variety of stressors, including infection and tumors.¹⁰ IFNs are classified into 2 types: type I includes 2 subtypes (IFN-alpha and IFN-beta), and type II mainly includes IFN-gamma.^{10,11} IFN alpha-2b is a recombinant biologic agent that has antiviral, antitumor, and antiangiogenic properties.¹² It has been used successfully in some systemic diseases, such as hematologic malignancies, leukemia, and viral hepatitis.^{10,12} IFN alpha-2b has topical uses for external eye disorders that encompass viral keratoconjunctivitis and ocular surface squamous neoplasia,^{13,14} Behcet uveitis,¹⁵ and vernal keratoconjunctivitis.¹⁶ Several studies have shown that as an antiproliferation agent, IFN alpha-2b eye drops were effective in preventing scarring of filtering blebs.^{17,18} We believe that this treatment may have promising clinical results in preventing pterygium recurrence via the same mechanism. The aim of our study is to explore the efficacy and safety of IFN alpha-2b eye drops for pterygium recurrence prevention after the bare sclera technique.

MATERIALS AND METHODS

Study Design

This is a single-center, sequential, and controlled clinical study. The study has been approved by the Ethics Committee of Beijing Tongren Hospital (review number: TREC2015-57), and it adhered to the principles of the Declaration of Helsinki. Preoperatively, the study patients were informed of the potential risks and available alternatives, and they provided written consent.

All participants met the following inclusion criteria: age >18 years, nasal and primary pterygium, and the head of pterygium invaded the cornea by 2 mm to 4 mm as measured by a slit-lamp biomicroscope. Exclusion criteria were patients with bilateral pterygium, ocular surface disorders (eg, meibomian gland dysfunction and dry eyes) combined with pterygium, and an external eye surgical history within the previous 6 months. Pregnant women were also excluded from the study.

Sixty eyes were divided into 2 chronological groups: the first 30 eyes were included in the control group (group I), and the other 30 eyes were included in the treatment group (group II). Postoperatively, all patients were treated with levofloxacin eye drops (Santen Pharmaceutical, Osaka, Japan) and 0.1% fluorometholone eye drops (Santen Pharmaceutical) 4 times a day for 3 months. In the treatment group, IFN alpha-2b eye drops (1 million IU/5 mL, Anke Biological Technology Company, Hefei, China) were applied 4 times a day for 3 months. All patients were asked to have checkups 1 day, 10 days, 1 month, 3 months, 6 months, 12 months, and 18 months after surgery.

Surgical Technique

The bare sclera technique was performed on both groups by the same surgeon (Doctor Hang Li from Beijing Tongren Hospital). After topical anesthesia with 0.5%

proparacaine hydrochloride eye drops, 2% lidocaine was injected beneath the body of pterygium to achieve local anesthesia. The pterygium was cut off from the limbus. The head of the pterygium was bluntly dissected from the cornea, and the body of the pterygium was separated and removed to approximately 1.5 mm in front of the plica semilunaris with scissors. The upper and lower margins of the conjunctiva were sutured 2 mm away from the limbus by a 10-0 nylon suture, exposing a small area of the rectangular bare sclera. Contact lenses were used to relieve the discomfort of patients until the sutures were removed 10 days after surgical excision.

Main Outcome Measures

Many objective variables, including age, sex, size, and grade of primary pterygium, were recorded before surgeries. The size of primary pterygium was defined as the horizontal distance from the apex of the pterygium head to the limbus. The grade was determined by the thickness of primary pterygium,¹⁹ which encompassed grade T1 (minimal elevation with definite confirmation of an episcleral vessel), grade T2 (moderate elevation, an episcleral vessel could be found in some of the elevated area), and grade T3 (marked elevation, an episcleral vessel could not be found). During the follow-ups, each patient was required to undergo vision acuity testing, intraocular pressure measurement, slit-lamp biomicroscope examination, and ocular surface photography. Recurrence, conjunctival redness and thickness, and neovascularization after surgical excision were examined and recorded by the slit-lamp biomicroscope photography system.

Table 1 shows the grades of pterygium recurrence. Recurrent pterygium was usually classified by morphology based on the previous pterygium recurrence grading system, which included grade 0 (normal conjunctiva), grade 1 (a few episcleral vessels without fibrous tissues), grade 2 (fibrovascular tissues, but not beyond the limbus), and grade 3 (fibrovascular tissues have invaded the cornea). Grade 0 and grade 1 were classified as no recurrence, whereas grade 2 and grade 3 were defined as recurrence. After surgery, conjunctival redness was graded as grade 1 (no redness or faint pinkish hue), grade 2 (scattered areas with moderate redness), and grade 3 (significant and diffuse redness).¹⁹ The grades of conjunctival thickness were similar to the grades of primary pterygium mentioned above. Neovascularization was measured as the length of the longest vessel to the limbus in recurrent pterygium. Complications were also observed and recorded in the follow-ups and included persistent corneal

TABLE 1. Standard Grading System of Recurrence of Pterygium

Grade	Description
0	Normal conjunctiva
1	A few episcleral vessels without fibrous tissues
2	Fibrovascular tissues not beyond the limbus
3	Fibrovascular tissues invading the cornea (>1.0 mm from the limbus)

TABLE 2. Preoperative Variable Analysis of the 2 Groups

	Group I	Group II	<i>P</i>
	n = 24	n = 27	
Age (mean ± SD)	55 ± 10	56 ± 8	0.123
Sex (male/female)	6/18	10/17	0.355
Pterygium size (mm) (mean ± SD)	2.96 ± 0.56	2.93 ± 0.59	0.706
Pterygium grade (T1/T2/T3)	3/11/10	3/13/11	0.696

TABLE 3. Recurrence Rate Analysis of the 2 Groups

Group		Recurrence (+),	Recurrence (-),	<i>P</i>
		n (%)	n (%)	
3 mo	Group I	3 (12.5)	21 (87.5)	0.331
	Group II	1 (3.7)	26 (97.3)	
6 mo	Group I	7 (29.2)	17 (70.8)	0.019
	Group II	1 (3.7)	26 (97.3)	
12 mo	Group I	8 (33.3)	16 (66.7)	0.048
	Group II	2 (7.4)	25 (92.6)	
18 mo	Group I	8 (33.3)	16 (66.7)	0.048
	Group II	2 (7.4)	25 (92.6)	

epithelial defects, delayed conjunctiva healing, conjunctival granuloma, scleral melting, and scleral necrosis.

Statistical Analyses

All data were analyzed using Statistical Package for the Social Sciences (SPSS, version 21.0; SPSS Inc, Chicago, IL), and *P* < 0.05 was defined as statistical significance. A χ^2 test was used to compare the recurrence rates of the 2 groups. Baseline data were evaluated by the independent sample *t* test

(age and pterygium size), χ^2 test (sex), or Fisher exact test (pterygium grade). The Mann–Whitney *U* test was applied to assess the data on conjunctival redness and thickness and neovascularization in the follow-ups.

RESULTS

There were 60 eyes of 53 patients included in our study from June 2016 to May 2017, and 51 eyes (24 in the control group and 27 in the treatment group) were followed up for more than 18 months. During the follow-up period, contact was lost for 6 patients (3 patients in the control group and 3 patients in the treatment group). In addition, 3 patients in the control group were excluded because they discontinued their eye drop usage, and 1 patient in the treatment group was excluded because she administered other eye drops after cataract surgery.

Table 2 shows the preoperative variables for the 2 groups. A total of 51 eyes of 43 patients were observed in our study, including 14 men and 29 women. The age of the patients ranged from 35 to 73 years, and the mean age was 56 ± 9 years. The size of primary pterygium varied from 2.12 to 3.90 mm. In the control group, there were 3, 11, and 10 primary pterygia of grades 1, 2, and 3, respectively. In the treatment group, there were 3, 13, and 11 primary pterygia of grades 1, 2, and 3, respectively. Overall, there was no significant difference between groups in patients’ age, sex, or primary pterygium size or grade (*P* > 0.05).

No recurrence was detected within 1 month in either group after surgery. Table 3 shows the recurrences of the 2 groups at postoperative months 3, 6, 12, and 18. At the third month after excision, 3 cases showed a grade 3 recurrence in the control group, whereas only one case in the treatment group exhibited a grade 3 recurrence, and this difference was not found to be statistically significant (*P* > 0.05). Figures 1 and 2 showed recurrent pterygia in the control group and the treatment group. At the sixth month, 7 cases (6 were grade 3,

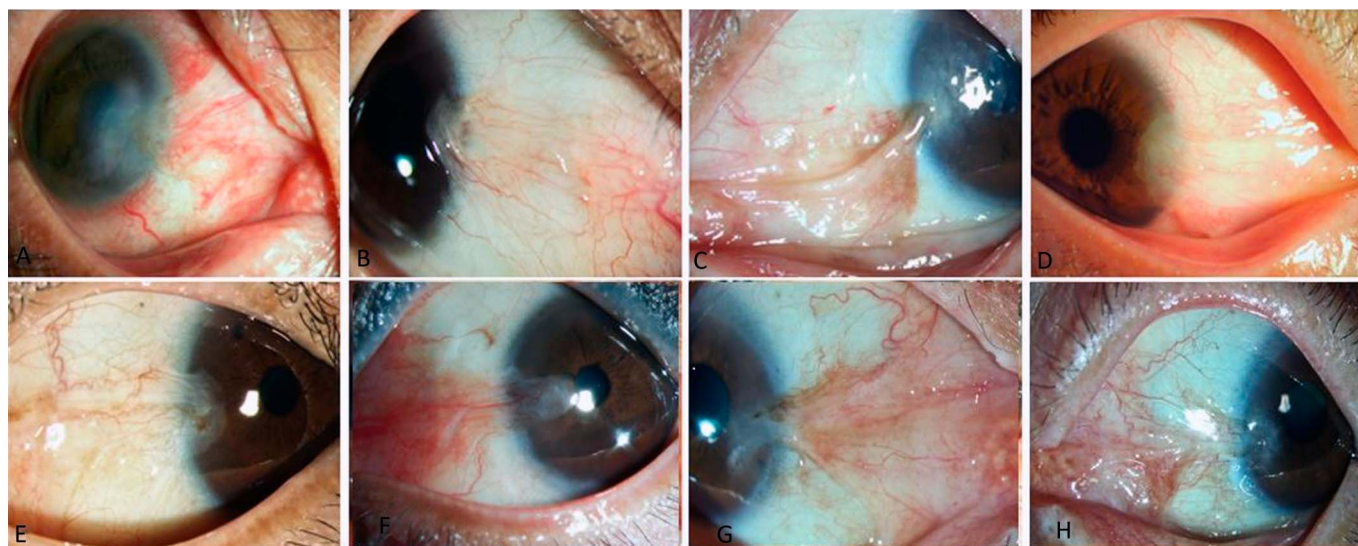
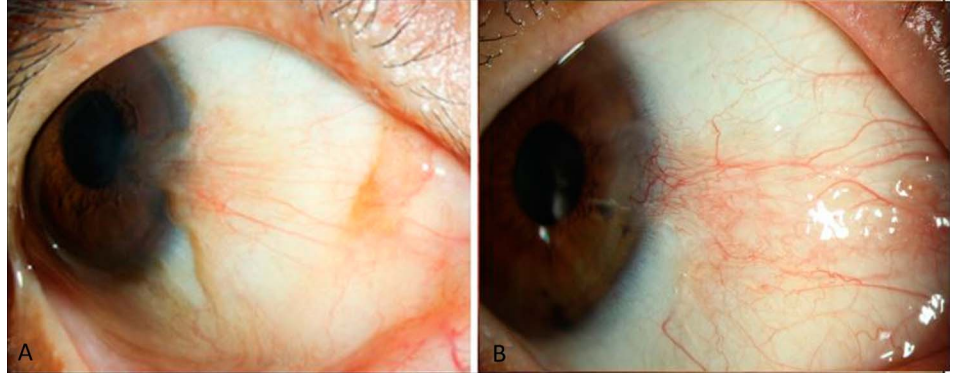


FIGURE 1. Photographs of the ocular surface in group I by slit lamp. The first 6 images (A–F) were recurrent pterygium of grade 3 after surgical excision, whereas the latter 2 images (G and H) were grade 2.

FIGURE 2. Photographs of the ocular surface in group II by slit lamp. A, Recurrent pterygium was grade 3. B, Recurrent pterygium was grade 2.



and 1 was grade 2) of recurrence occurred in the control group, whereas still only one case was identified as recurrence in the treatment group. The rates of recurrence in the control group and treatment group were 29.2% and 3.7%, respectively, and the difference between the 2 groups was statistically significant ($P = 0.019$). Up to the 12th month, 8 cases (6 were grade 3, and 2 were grade 2) in the control group and 2 cases (one was grade 3, and the other was grade 2) in the treatment group showed recurrence, and there was no increase at 18 months. The rates of the 2 groups were 33.3% and 7.4%, and the difference between the 2 groups was statistically significant ($P = 0.048$).

Figures 3 and 4 show the grades of conjunctival redness and thickness. Within 3 months, there was no statistically significant difference in conjunctival condition (redness and thickness) or the length of the new vessel. At the sixth month postoperatively, the length of the new vessel ranged from 0 to 4.59 mm, and a statistically significant difference between the 2 groups was noted for conjunctival redness ($P = 0.021$), conjunctival thickness ($P = 0.030$), and the length of the vascular tissues invading the cornea ($P = 0.041$).

During the follow-up period, no serious vision-threatening complications or systemic side effects were observed in any of the patients in our study. Other mild to moderate complications, including conjunctival granuloma and delayed conjunctival healing and scleral melting and necrosis and corneal epithelial defect, are recorded at every follow-up. Two cases (1 in the control group and 1 in the

treatment group) showed corneal epithelial point defects at the first month and recovered spontaneously by the third month. Only one conjunctival granuloma was recorded in the treatment group at the end of the first month. During the observational period, patients in the treatment group tolerated the eye drops well, and few ($n = 5$) had complaints about sensation of foreign bodies, irritation, and mild burning.

DISCUSSION

To date, this is the first controlled clinical study about the effect of IFN alpha-2b eye drops on prevention of pterygium recurrence. After 18 months of follow-up, we proved that IFN alpha-2b eye drops could extensively reduce the rate of pterygium recurrence after the bare sclera technique. Furthermore, we also demonstrated that the medication appeared to be safe and well tolerated.

Based on previous studies, a large number of surgical methods, especially graft techniques, have been developed to reduce the recurrence of pterygium.^{1,9} In addition, various adjuvant medications (antimetabolites and anti-VEGF antibodies) have been applied to reduce the recurrent rate after pterygium excision.^{1,2,10,20–34} Although mitomycin C and 5-Fluorouracil could reduce the recurrence rate to a large extent, the severe complications, such as scleral melting and necrosis and corneal perforation, have limited their clinical usage.^{22–28}

It has been established that IFN is characterized by its antiviral, anti-inflammatory, and immunomodulatory effects.

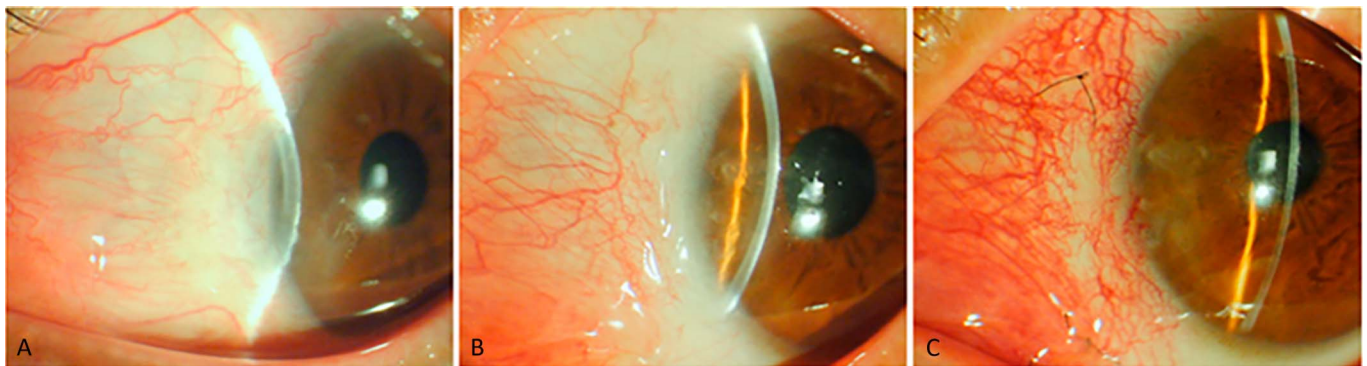


FIGURE 3. Slit-lamp photographs of redness scored as (A) grade 1: no redness or faint pinkish hue; (B) grade 2: scattered areas with moderate redness; and (C) grade 3: significant and diffuse redness.

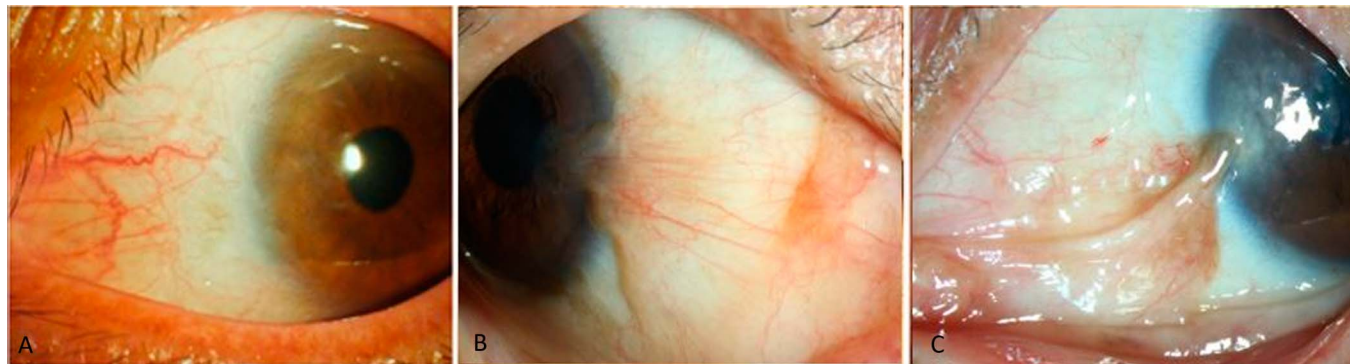


FIGURE 4. Ocular surface photographs of thickness scored as (A) grade T1: minimal elevation with definite confirmation of episcleral vessels; (B) grade T2: moderate elevation, episcleral vessels can be found through the elevated area; and (C) grade T3: marked elevation, episcleral vessels are completely covered by the elevated area.

Esquenazi³⁵ first reported that topical IFN alpha-2b drops could regress neovascularization significantly in the early stage of recurrent pterygium. Considering the multiple causes of pterygium recurrence mentioned above, previous studies have proven the effect of IFN on prevention of pterygium recurrence. Di Girolamo et al³⁶ stated that IFN-alpha serves as an anti-inflammatory and antiproliferative agent by inhibiting the mitogen-activated protein kinase (extracellular regulated protein kinases 1/2, c-Jun NH2-terminal Kin, and p38) pathway in cultivated pterygium epithelial cells to downregulate secretion of VEGF and inflammatory cytokines. Previous in vitro studies also demonstrated that human Tenon fibroblast cells were prone to Fas-mediated apoptosis after pretreatment with IFN-alpha and IFN-gamma, which could upregulate Fas, Fas-associated protein with a death domain, and caspase-8.³⁷ Some clinical studies have stated that IFN was effective in inhibiting proliferation of fibroblasts and treating early scarring of the filtering bleb.^{17,18} IFN can inhibit viral DNA replication to reduce recurrences caused by viral infection because HPV and herpes simplex virus have been found in cases of pterygium. Detorakis et al³⁸ proposed a “two-hit” theory for pterygium progression. The first hit is a damaging reaction mediated by ultraviolet exposure that causes genetic alteration or mutation, and the second hit is an oncogenic event mediated by viral infection in susceptible or compromised cells. According to the mechanism mentioned above, we inferred that IFN alpha-2b eye drops could be effective in preventing the recurrence of pterygium.

In our study, the recurrence rate ($n = 8$, 33.3%) after the bare sclera technique in the control group was similar to that observed in previous studies (33%–45%),⁹ whereas the rate in the treatment group was significantly decreased to 7.4% after surgery. The differences in the rate of recurrence between the control group and the treatment group were statistically significant at the sixth month ($P = 0.019$), the 12th month, and the 18th month ($P = 0.048$). The pterygium recurrences often occurred from the 3- to 6-month period in the study. At the end of the sixth month after surgery, another 4 cases recurred in the control group, whereas there was only one additional recurrence until the 18th month postoperatively. In the treatment group, 1 case recurred at the 12th month, and no more recurrent pterygium increase at the end of the 18th

month after surgery. In addition, the outcomes related to recurrence and severity also differed between the groups. Recurrent pterygium was more severe than the primary one in the control group in terms of size and thickness, whereas recurrent pterygium in the treatment group was smaller and thinner than the original. In addition to the low recurrence rate, there were no serious vision-threatening complications in the treatment group. Only one patient manifested conjunctival granuloma, which might have been caused by other factors (eg, the irregular conjunctival margin after excision, delayed conjunctival healing, and chronic inflammation). Few patients complained ($n = 5$) about eye drop irritation; however, to explore the tolerance of IFN alpha-2b eye drops, more normative scales should be applied to assess the patients' discomfort after surgery via outcomes such as eye pain, redness, and irritation.

In conclusion, IFN alpha-2b eye drops extensively reduced the recurrence of pterygium after the bare sclera technique and are well tolerated and appear safe. However, multicenter, randomized, and controlled studies are needed to validate our findings and determine the most effective timing and duration of topical IFN alpha-2b treatment. In addition, we will extend the follow-up time and use standard scales to observe the long-term safety and tolerance of IFN alpha-2b eye drops for preventing pterygium recurrence.

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