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20% ethanol assists the excision of primary pterygium

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20%乙醇辅助切除原发性翼状胬肉的疗效

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摘要

目的:介绍一种使用20%乙醇辅助切除原发性翼状胬肉的改良技术,并评估其手术效果。

方法:回顾性分析广西壮族自治区人民医院在2015-03/2016-02期间连续收治的病例,行翼状胬肉切除术。对原发性鼻侧翼状胬肉患者进行分析,最终共85例85眼符合纳入标准,其中44眼使用20%乙醇辅助翼状胬肉切除术(研究组),另外41眼未使用20%乙醇(对照组),随访期至少3mo。

结果:患者85例均无术中、术后并发症。研究组的角膜上皮平均愈合时间为2.84±0.43d,与对照组3.12±0.64d相比有差异(P<0.05)。两组患者术后3d内的症状(疼痛、刺激、异物感和溢泪)有显著性差异(P<0.05)。两组内术前和术后2wk,1,3mo之间的角膜内皮细胞形态改变无差异(P>0.05);两组间各对应时间点的角膜内皮细胞形态也均无差异(P>0.05)。两组间术前、术后2wk,1mo的最佳矫正视力(BCVA)无差异(P>0.05),但术后3mo的BCVA有差异(P<0.05)。

结论:20%乙醇辅助切除原发性翼状胬肉是一种简单、安全的方法,有助于在翼状胬肉和角膜之间建立一个清晰的分离平面。

关键词:翼状胬肉;乙醇;酒精;切除术;角膜内皮显微镜

Abstract

• AIM: To introduce a technique to improve the excision of primary pterygium and evaluate the surgical outcomes.

• METHODS: Recorded of consecutive cases were reviewed of pterygium patients treated with pterygium removal between March 2015 and February 2016 in People's Hospital of Guangxi Zhuang Autonomous Region, China. Primary nasal pterygium patients with at least 3mo follow-up periods were included. Finally, 85 patients (85 eyes) were investigated, 44 eyes were operated with 20% ethanol (the study group) and 41 eyes were operated without 20% ethanol (the control group).

• RESULTS: All of the 85 patients enrolled had no intraoperative and postoperative complications. The mean healing time of the corneal epithelium for the study group was statistically significant different of 2.84±0.43d compared with the control group of 3.12±0.64d (P<0.05). Overall, postoperative symptoms (pain, irritation, foreign body sensation and epiphora) were significantly different in postoperative 3d between the two groups (P<0.05). No statistically significant differences in corneal endothelium morphologies were found in two groups between preoperative and 2wk, 1 and 3mo postoperative, or between the two groups at any corresponding time point (all P>0.05). Between the two groups, there were no statistically significant differences in best-corrected visual acuity (BCVA) at preoperative, postoperative 2wk and 1mo (all P>0.05), but statistically significant difference was found in BCVA at the 3mo after surgery (P<0.05).

• CONCLUSION: The removal of primary pterygium with 20% ethanol is a simple and safe technique that helps to establish a clear separation plane between the pterygium and the underlying cornea.

• KEYWORDS: pterygium; ethanol; alcohol; excision; specular microscopy
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INTRODUCTION

Pterygium is a wedge-shaped ocular surface lesion that the abnormal fibrovascular growth of superficial conjunctival tissue extending onto the cornea[1]. Risk factors associated with primary pterygium included environmental factors such as ultraviolet exposure and dust or wind, genetic, lifestyle behaviors, immunological mechanisms and other factors[2-3]. The studies of pathogenesis indicate that pterygium is the result of the interaction of environmental and genetic factors; the genetic susceptible hosts exposure to the environmental conditions such as ultraviolet can cause oxidative DNA damage, cell proliferation, migration and angiogenesis, and ultimately lead to disease development[4].

Surgical excision is a logical treatment choice for pterygium, particularly for patients with recurrent inflammation, irritation, visual impairment, or unacceptable appearance. Due to simple excision is associated with high recurrence rates of 24%-89%[5], several adjuvant treatments are in use, such as conjunctival autografting, amniotic membrane transplantation, beta-irradiation, or mitomycin C[6-8]. At the same time, any remnant of the pterygium should be completely removed to prevent recurrences[9-10]. However, the pterygium head on the cornea often interferes with the excision of pterygium because of its tight adhesion to the cornea. Traditionally, firm attachment of the pterygium head on the cornea is removed by intensive mechanical scraping, which is associated with severe complications such as corneal perforation, irregular astigmatism and corneal scarring[3]. Therefore, to identify the plane between the pterygium and the underlying corneal during the pterygium surgery, and remove the pterygium tissue cleanly from the corneal surface while remaining a smooth surface of the underlying corneal without intensive corneal scraping is a problem needs to be solved. During these years, inspired by the use of ethanol in laser-assisted subepithelial keratectomy (LASEK), some researchers have carried out an effective method to apply 20% alcohol to the pterygium surgery to get over the difficulty on the complete removal of the pterygium head[3,11]. The main procedure is that, after anesthesia, a metal ring well was placed on the surface of the head of the pterygium as used in LASEK, two to four drops of ethanol 20% were applied inside the well and retained for 40-60s, and then a sponge was used to absorb the ethanol[12]. Following the profuse wash of Balanced Salt Solution (BSS) or not, the head of the pterygium was separated from the underlying cornea by blunt dissection. The practice described above provided us a way to deal with the head of the pterygium effectively. However, there is no consensus regarding the ideal treatment for the disease[13].

The purpose of this study is to introduce an improved technique to help remove the primary pterygium from the surface of the cornea and establish a smooth surface of the cornea without more scratching or polishing of the cornea, and to evaluate its outcomes.

SUBJECTS AND METHODS

This retrospective case series study conducted at the People's Hospital of Guangxi Zhuang Autonomous Region, China. The research followed the principles of the Declaration of Helsinki. The approval of local Ethics Committee was obtained. Records of consecutive patients suffering from nasal primary pterygium and treated with pterygium removal by one single surgeon (Chen Q) between March 2015 and February 2016 were examined. The data of the patients such as gender and age, grade and type of pterygium, method of surgery, duration of follow-up, pre- and postoperative complications and the recurrence of pterygium were taken from the medical records. Inclusion criteria: 1) a nasal primary pterygium and the pterygium invaded into the cornea from the limbus; 2) the follow-up periods were at least 3mo; 3) early postoperative symptoms and corneal epithelial healing time were noted; 4) the corneal specular microscopy was performed pre- and 2wk, 1mo and 3mo postoperative, and the corneal endothelium morphologies including endothelial cell density (ECD), coefficient of variation of cell size (CV), and percentage of hexagonal cells (HEX) were recorded; 5) the data of best-corrected visual acuity (BCVA) values at pre- and postoperative 2wk, 1mo and 3mo were noted. The BCVA values were obtained on a Snellen scale and then converted into logarithm of the minimum angle of resolution (LogMAR) values. Major systemic or ocular surface diseases and a history of ocular surgery, ocular glaucoma and trauma were accepted as exclusion criteria. Finally, 85 eyes (85 patients) were enrolled, and there were 44 eyes operated with 20% ethanol (the study group), the rest of 41 eyes operated without 20% ethanol (the control group).

Before the operation, according to the grading system proposed by Tan *et al*[14], the pterygium morphology was graded as grade 1 (atrophic), the episcleral vessels under the pterygium body are not fuzzy and can be clearly distinguished; grade 3 (fleshy), the episcleral vessels are completely obscured; or grade 2 (intermediate), all other pterygium not belonging to grades 1 or 3.

Surgical Technique The same surgeon (Chen Q) performed all operations under the operating microscope. A caliper was used to measure the length, and the area of the pterygium head was recorded. Because its shape is similar to a triangle, the area of the pterygium head = (length of limbus × length of the vertical line from the apex of pterygium head to

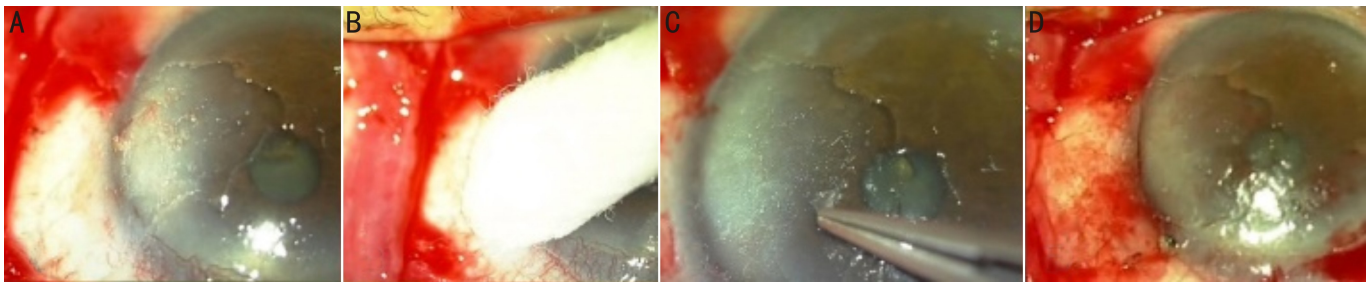

Figure 1 Surgical steps of using 20% ethanol in pterygium surgery A: The residual pterygium tissue on the corneal surface after blunt dissection of the pterygium head; B: After the excess alcohol in the sponge was absorbed, the sponge was placed on the surface of the residual abnormal scar tissue for 60s; C: The residual pterygium tissue was removed from the base with the ophthalmic forceps; D: The appearance of the corneal surface at the end of the procedure.

the limbus)/2. Standard preoperative sterile preparation was performed on the involved eye. Lidocaine hydrochloride 2 mL:40 mg was injected subconjunctival to the pterygium body for anesthesia following topical administration of 0.5% proparacaine hydrochloride (Alcaine; Alcon, Puurs, Belgium). Then, after the pterygium was cut between the head and the body with conjunctival scissors at the limbus, the pterygium head was gently isolated and excised from the corneal surface by blunt dissection. Before or after the pterygium body was removed, the residual pterygium leaving on the corneal surface was treated.

In the study group, a sponge was soaked with 20% alcohol, and the excess alcohol in the sponge was absorbed by the surgical towel, then the sponge was placed on the surface of the residual abnormal tissue on the cornea for 60s (Figures 1A, 1B). After that, the fibrovascular tissue was easily removed from the base with the ophthalmic forceps, and a surgical blade was used to scrap the corneal surface if necessary (Figure 1C). At the end of the operation, the corneal surface was clear and smooth (Figure 1D).

In the control group, according to the adhesion of the residual pterygium, blunt or sharp separation was used to polish the corneal surface until no pterygium tissue remained on the cornea.

Blunt and sharp dissection were performed to expose the pterygium body up to the semilunar fold, and this portion was excised 1 mm away from the lacrimal caruncle. Scrapping abnormal scar and Tenon capsule tissue on the wound bed to make the surface of the sclera smooth. And an electrocautery pen (YZ-II; Shanmu, Dalian, China) was used to control the bleeding when necessary. Finally, an additional 1.0 mm of length and width relative to the graft bed harvested from the inferior bulbar conjunctiva was transplanted to the bare sclera and welded directly using the electrocautery pen according to a study we performed before.

The eye was pressure patched with 0.3% tobramycin and 0.1% dexamethasone ophthalmic ointment (TobraDex; Alcon) for 24h to restrict the eyeball from blinking or movement.

Postoperative Follow-up Postoperatively, the corneal epithelial wounded area was observed by fluorescence staining and slit-lamp biomicroscopy examination was performed daily until the corneal epithelium was completely repaired. 0.3% tobramycin and 0.1% dexamethasone ophthalmic ointment (TobraDex; Alcon) were applied to the operated eye for 3-4d. After complete epithelialization of the cornea, the operated eye was not padded and patients were informed to use levofloxacin (Cravit; Santen, Jiangsu, Japan) and 0.02% fluorometholone (Santen) eye drops 6 times per day for 2wk and 4 times per day for the following 2wk.

Patients were then asked to return for follow-up at 2wk, 1mo and 3mo postoperative. Slit-lamp biomicroscopy, BCVA and intraocular pressure were performed at each visit, and specular microscopy was included from 2wk postoperatively when the corneal edema disappeared.

Symptoms were assessed daily within postoperative 3d. A 5-point scale developed by Lim-Bon-Siong *et al*[15] was used to evaluate and record the grading of patients' symptoms (pain, irritation, foreign body sensation and epiphora). It is a simple scale of 0-4: 1) 0: no symptom at all; 2) 1: presence of the symptom but easily tolerated; 3) 2: presence of the symptom causing some discomfort; 4) 3: presence of the symptom causing discomfort that interferes with usual activity or sleep; 5) 4: presence of the symptom that completely interferes with usual activity or sleep.

Side effects, complications and pterygium recurrence were recorded at follow-up. The grading system proposed by Prabhasawat *et al*[16] was applied to grade the recurrence. According to this system, grade 1 indicated the appearance of the surgical area was normal; grade 2 indicated fine episcleral vessels without fibrous tissue appeared in the operated site that extended to but didn't cross the limbus; grade 3 indicated a conjunctival recurrence that additional fibrovascular tissue appeared in the excised area but did not invade the cornea; and grade 4 indicated a corneal recurrence with fibrovascular tissue invading the cornea. If further growth of the recurrent pterygium was found during the follow-up, surgery was performed again.

Statistical Analysis Statistical analyses were carried out with SPSS software (version 26.0; SPSS, Chicago, USA). Analysis of variance, Student's t-test, Chi-square test and Fisher's exact test were used for statistical analyses. A P value less than 0.05 was considered statistically significant.

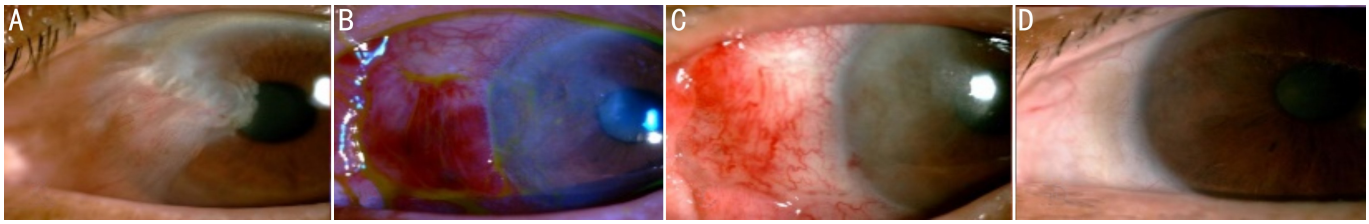

Figure 2 Preoperative and postoperative of a patient in the 20% ethanol group A: The preoperative appearance; B: The 3d postoperative after pterygium surgery; C: The 2wk postoperative after pterygium surgery; D: The 3mo postoperative after pterygium surgery.

Table 1 Patients' characteristics in the 20% ethanol and control groups

Parameters	20% ethanol group, $n=44$	control group, $n=41$	P
Age, y	57.95±10.59	54.66±10.51	0.154
Sex, n(%)			0.898
M	23 (52.3)	22 (53.7)	
F	21 (47.7)	19 (46.3)	
Area of the pterygium head, mm^2	8.59±1.42	8.40±1.40	0.538
MHT, d	2.84±0.43	3.12±0.64	0.019
Pterygium grade, n(%)			0.816
Grade 1	15 (34.1)	16 (39.0)	
Grade 2	24 (54.5)	22 (53.7)	
Grade 3	5 (11.4)	3 (7.3)	

MHT: Mean healing time of the corneal epithelium.

Table 2 Preoperative and postoperative cornea characteristics in the 20% ethanol and control groups mean±SD

Parameters	20% ethanol group, $n=44$	control group, $n=41$	P
ECD, cells/mm^2			
Preoperative	2833.32±380.73	2806.02±381.10	0.742
2wk postoperative	2836.88±377.79	2789.47±391.43	0.571
1mo postoperative	2818.29±391.87	2804.17±396.72	0.869
3mo postoperative	2811.46±376.98	2789.68±387.05	0.793
CV			
Preoperative	33.95±4.28	33.66±3.66	0.746
2wk postoperative	34.68±4.36	34.53±4.07	0.876
1mo postoperative	34.38±4.44	33.99±4.04	0.669
3mo postoperative	34.64±4.19	34.31±3.68	0.701
HEX			
Preoperative	56.36±6.94	55.12±6.56	0.400
2wk postoperative	54.70±7.52	56.32±8.29	0.350
1mo postoperative	56.39±7.28	54.85±7.53	0.343
3mo postoperative	56.50±6.69	56.20±7.46	0.843

ECD: Endothelial cell density; CV: Coefficient of variation of cell size; HEX: Percentage of hexagonal cells.

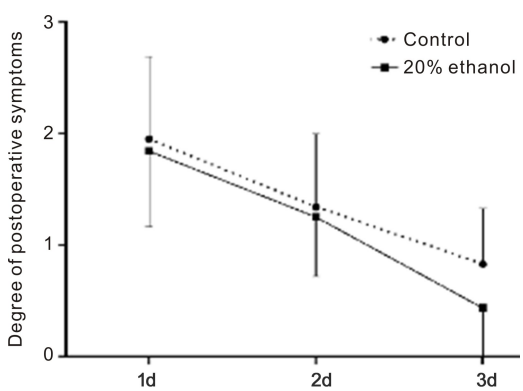

Figure 3 Five-point scale assessment of postoperative symptoms at 1, 2, 3d after pterygium surgery.

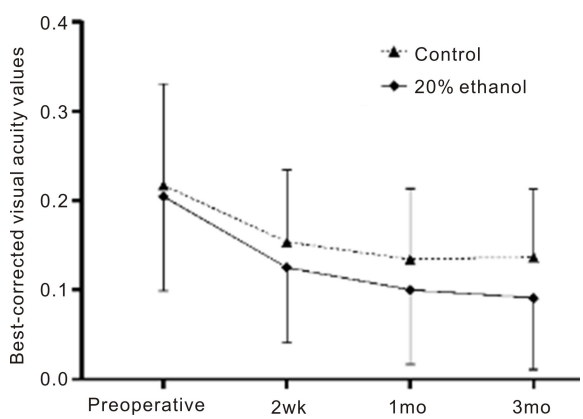

Figure 4 Best-corrected visual acuity values at preoperative and 2wk, 1 and 3mo postoperative.

RESULTS

Records were reviewed of all the patients with nasal primary pterygium who underwent pterygium surgery by one single surgeon between March 2015 and February 2016. There were 85 patients (85 eyes) included in the final analysis, 44 eyes operated with 20% ethanol (the study group) and 41 eyes operated without 20% ethanol (the control group).

Demographics and baseline characteristics are summarized in Tables. The study group consisted of 44 eyes (44 patients, 23 men and 21 women) with a mean age of 57.95±10.59 years, and the control group consisted of 41 eyes (41 patients, 22 men and 19 women) with a mean age of 54.66±10.51 years respectively. There was no statistically significant difference between the two groups in terms of gender, age or pterygium grades (Table 1). Also, with respect to the area of the pterygium head, the difference between the two groups was not significant (8.59±1.42 mm^2 *vs* 8.40±1.40 mm^2; P=0.538). In all eyes of the study group, the 20% alcohol technique for the separation of the pterygium head was successful. At the end of the operation, the corneas were clear and smooth without any residual pterygium tissue left on the cornea in all cases (Figure 1D). There were no intraoperative or postoperative complications detected in any eye. During follow-up periods of 3mo, only 1 case (2.3%) of recurrence was observed in the study group and 2 cases (4.9%) in the control group (P=0.607).

Figure 2 shows the preoperative appearance as well as the postoperative appearances of the patients in the study group. Interestingly, fluorescein staining showed that the mean healing time of the corneal epithelium for the study group was statistically shorter compared with the control group (2.84±0.43d *vs* 3.12±0.64d; P=0.019). Overall, postoperative symptoms scores were significantly different in postoperative 3d between the two groups (P=0.014); corresponding values at 1, 2 and 3d postoperative were 1.84±0.68, 1.25±0.53, 0.43±0.55 respectively in the study group, and 1.95±0.74, 1.34±0.66, 0.83±0.50 respectively in the control group (P=0.476, P=0.481, P=0.001, respectively; Figure 3). In general, there was no significant difference in BCVA values between the two groups (P=0.094); and when compared the values between the two groups at preoperative, 2wk and 1mo postoperative respectively, no significant statistical difference was found (0.20±0.11, 0.13±0.08, 0.10±0.08 in the study group *vs* 0.22±0.11, 0.15±0.08, 0.13±0.08 in the control group; P=0.600, P=0.113, P=0.057, respectively); but interestingly, there was statistical difference between the study group and the control group at the 3mo after operation (0.09±0.08 *vs* 0.14±0.08, P=0.009; Figure 4).

At baseline, mean ECD was 2833.32±380.73 cells/mm^2 in the study group and 2806.02±381.10 cells/mm^2 in the control group, respectively (P=0.742); corresponding values at 2wk, 1 and 3mo postoperative were 2836.88±377.79 cells/mm^2, 2818.29±391.87 cells/mm^2, 2811.46±376.98 cells/mm^2, and 2789.47±391.43 cells/mm^2, 2804.17±396.72 cells/mm^2, 2789.68±387.05 cells/mm^2, respectively. There were no significant between-group differences at any postoperative time point (P=0.571, P=0.869, P=0.793, respectively; Table 2, Figure 5). When the postoperative values at 2wk, 1 and 3mo were individually compared with the preoperative values, there were no statistically significant differences in each group (P=1.000, P=0.833, P=0.373, respectively in the study group; P=0.876, P=1.000, P=0.731, respectively in the control group). The mean preoperative CV was 33.95%±4.28% for the study group, and 33.66%±3.66% for the control group (P=0.746). Values were 34.68±4.36% at 2wk, 34.38±4.44% at 1mo, 34.64±4.19% at 3mo in the study group, and 34.53±4.07%, 33.99±4.04%, 34.31±3.68% in the control group at the corresponding time points (P=0.876, P=0.669, P=0.701, respectively; Table 2, Figure 6). Similar to the ECD, statistical analysis revealed insignificant differences between the preoperative CV and the values at all 3 postoperative time points in each group (all P>0.05). As concerning the HEX, it suggested statistical results similar to the ECD and CV (all P>0.05; Table 2, Figure 7).

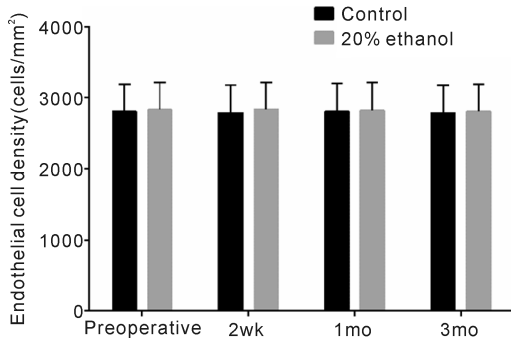

Figure 5 Endothelial cell density at preoperative, 2wk, 1 and 3mo postoperative.

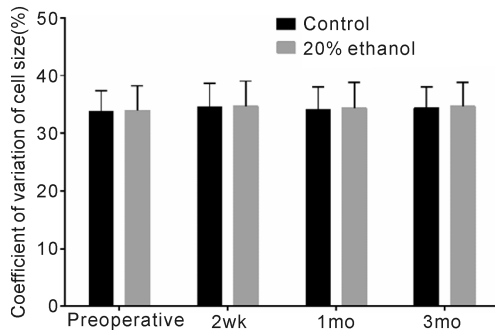

Figure 6 Coefficient of variation of cell size at preoperative, 2wk, 1 and 3mo postoperative.

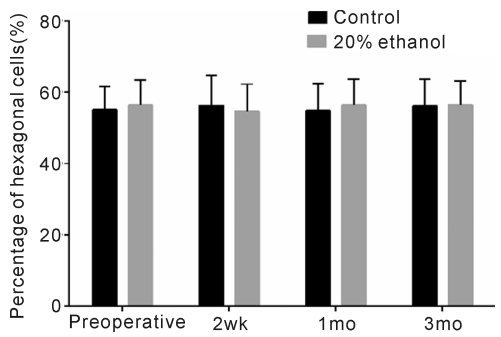

Figure 7 Percentage of hexagonal cells at preoperative, 2wk, 1 and 3mo postoperative.

DISCUSSION

To reduce the recurrence in pterygium excision, it is ophthalmologists' duty to excise the pterygium completely. Nevertheless, the pterygium head often firmly adheres to the surface of the cornea, which easily causes a rough corneal surface after the operation because of the persistent residual tissue. To overcome this difficulty and obtain a clear and smooth cornea, polishing with a surgical blade or a diamond burr was usually used[17]. However, this method tends to lead to scar formation[3], and the removal depth is not well controlled. Although a well-polished and smooth corneal surface can be obtained by using a diamond-tipped drill, the extra equipment increases the cost of the operation[3], that makes it hard to apply in underdeveloped areas; furthermore, the heat generated when it is used may cause thermal damage to the cornea[18-19].

For centuries, alcohol has been applied widely to clinical practice with its anti-microbial properties and it also induces apoptosis in a variety of tissues which made it used in some tumors treatment such as liver cancers[20]. It has been about a decade since ethanol was used in the cornea for excimer laser refractive surgery due to its rapid protein denaturation function. The treatment with 20% ethanol for 20-40s makes the separation of the epithelium and stroma between Bowman's layer or the basement membrane level without mechanical trauma on the stromal surface in LASEK[21]. So far, some studies have explored different dilutions of alcohol and their safety duration on cornea, and the results showed that alcohol with a concentration of less than 20% to stay on the cornea for less than a minute seemed safe[11]. It has been shown that postoperative wound healing was normal, most epithelial cells of the cornea were detected to be alive by vital staining after low-dose ethanol treatment[22]. Although LASEK has been performed increasingly in refractive surgery, no alcohol-induced complications were observed postoperatively[23]. In addition, it is known to cause rapid denaturation of proteins/peptides in tissues, including cytokines, enzymes and growth factors that may be involved in pterygium formation and recurrence after excision[21]. Inspired by all of these results, some researchers have applied 20% ethanol intraoperative in the pterygium removal surgery to separate the head of the pterygium from the underlying corneal surface by blunt dissection, and there were no intraoperative or postoperative complications detected due to alcohol[3,11].

These studies, therefore, prompted us to come up with the modified method by using a sponge soaked with 20% alcohol to cover the surface of the residual pterygial tissue rather than the metal well filled with 20% ethanol to put on the surface of the complete head of the pterygium that they described previously. In this way, the ethanol can be applied directly to the residual pterygium on the cornea, making it more effective. Furthermore, the process of absorbing excess alcohol from the sponge prevents it from spilling over into healthy tissues surrounding and causing unnecessary damage.

In this study, we found that the strong adhesions of the residual pterygium tissue could be released easily from the corneal surface and establish a clear separation plane between the pterygium and the underlying cornea in all eyes of the study group. Moreover, sponges are common and cheap in hospitals. According to our results, there was a significant statistical difference in the mean healing time of the corneal epithelium. This may be due to the mild degeneration of corneal surface tissue cells caused by our proposed technique, which did not result in prolonged postoperative corneal epithelial healing time. At the same time, some studies on the effect of dilute ethanol on corneal wound healing have suggested that ethanol treatment induces the expression of many growth factors and has some positive effect on corneal wound healing[21,24-25]. Besides, the mechanical force of excision of residual pterygium in the control group may have caused greater damage to the corneal surface to some extent or left a rough corneal surface, leading to prolonged healing time of corneal epithelium. These may also account for differences in symptom scores between the two groups on the third day after surgery. However, the difference in healing time of the corneal epithelium between the groups has minimum clinical importance, because it may be influenced by other factors, such as the application of corneal bandage lens and eye drops. Based on these results, we can infer that our proposed 20% ethanol method is to form a resection plane between the residual pterygium and cornea. This plane is helpful for blunt dissection and removal of residual pterygium from the cornea, leaving a clear smooth corneal surface. Moreover, the corneal endothelium morphologies turn out to be safe in the two groups during the postoperative follow-up examinations. And there was only one recurrence (2.1%) observed in the third month after the surgery, which is consistent with previous reports[26]. The limitation of our study is that the follow up of 3mo is a short period for recurrence. To get a definite conclusion, prospective randomized controlled studies, prospective comparative studies with other techniques, larger sample size and longer follow-up periods are needed. However, under the limitation of our study, using the technique we proposed made consistent results with other studies in the recurrence rates and turns out to be safe.

In conclusion, we proposed a safe, rapid, simple and cheap improved method to remove the firmly adhered residual pterygium easily from the corneal surface and obtain a clear and smooth corneal surface, which is conducive to the recovery of postoperative corneal surface.

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