

Efficacy of autologous conjunctival flap on repairing the late-onset filtering bleb leakage

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Abstract

• **AIM:** To evaluate the effectiveness of autologous conjunctival flap surgery for repairing the late-onset filtering bleb leakage after trabeculectomy.

• **METHODS:** This study retrospectively reviewed 106 eyes from 106 patients with late-onset filtering bleb leakage after trabeculectomy who received autologous conjunctival flap surgery at the Zhongshan Ophthalmic Centre from 2005 to 2015. The basic information was recorded, and the interval time between trabeculectomy and autologous conjunctival flap surgery as well as related risk factors, intraocular pressure (IOP), anterior chamber depth (ACD) and best corrected visual acuity (BCVA) were analysed. Moreover, 41 patients who completed the 1-year follow up were analysed to determine the IOP and BCVA changes and long-term success rates.

• **RESULTS:** The 50 male and 56 female subjects (average age 39.13 ± 17.96 y) included 47 (44.34%) and 33 (31.13%) cases of primary open angle and primary angle-closure glaucoma. The mean interval between trabeculectomy and repair surgery was 60.60 ± 56.92 (3-264)mo. The mean mitomycin (MMC) concentration during trabeculectomy was 0.27 ± 0.04 (0.12-0.4) mg/mL in the fornix-based conjunctival flap group (68 patients) and 0.28 ± 0.04 (0.20-0.33) mg/mL in the limbal-based conjunctival flap group (11 patients). After bleb leakage, the patients' vision remained stable while the IOP decreased from 10.25 ± 4.76 (3-20.86) to 9.44 ± 4.33 (2-21) mm Hg ($P < 0.01$). In the 41 analysed patients, the IOP was controlled at 15.68 ± 5.11 (7-40) mm Hg in the 1st year after autologous conjunctival flap surgery and recurrence was not observed, for a long-term success rate of 100%.

• **CONCLUSION:** Autologous conjunctival flap repairing surgery is an effective technique for sealing filtering bleb

leakages and controlling IOP postoperatively.

• **KEYWORDS:** autologous conjunctival flap; filtering bleb leakage; trabeculectomy

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INTRODUCTION

Trabeculectomy is the most common filtering operation for glaucoma, and during this procedure, a piece of the trabecular meshwork to allow the aqueous humour to drain out of the anterior chamber and modulate the intraocular pressure (IOP) by a filtering bleb^[1], which represents the cardinal sign of a successful filtering glaucoma surgery^[2]. Filtering bleb leakage is a common postoperative complication after trabeculectomy, with risk factors that include surgically induced conjunctival trauma, inappropriate conjunctival closure hypotony, endophthalmitis and antifibrotic drug overuse, such as 5-fluorouracil (5-FU) and mitomycin (MMC) concentration, which bleb leaks in eyes treated with 5-FU or MMC may occur in 5% to 30% of patients^[3]. A Seidel sign which applies a fluorescein strip to the inferior tarsal conjunctiva or, very gently, directly to the bleb, will detect a leaking bleb. The main clinical manifestations are increased tearing, chronic low IOP, foreign body sensation and secondary endophthalmitis^[4]. Currently, the incidence of postoperative bleb leakage after trabeculectomy is variable in different studies and ranges from 0 to 56%^[5-6].

Clinically, the medical management to treat filtering bleb leakage after trabeculectomy includes pressure patching, bandage contact lens, fibrin tissue glue, cryopexy, thermal neodymium-doped yttrium aluminium garnet (Nd:YAG) lasers and cyanoacrylate glue^[7], which is determined by the types and severity of bleb leaks. In the early bleb leaks, if the leak is mild with an elevated bleb, a normal IOP and anterior chamber, it is permissible to observe the patient to allow time for the leak possibly to close spontaneously. If the leak is located in the centre of the conjunctival flap, the surgeon may close internally the undersurface of the conjunctiva with surgery. In the late bleb leaks, the repairing methods depend on several factors, such as the shape and feature of leaking

conjunctival bleb, IOP, anterior chamber, central vision *etc.* Many therapeutic modalities have been proposed to treat late leaks, including lubrication, pressure patching, a bandage contact lens, a glaucoma tamponade shield, a symblepharon ring, the injection of autologous blood cryopexy, thermal Nd:YAG laser, cyanoacrylate glue, and fibrin tissue glue^[8]. A variety of treatment options for the management of bleb leaks reflect the universality of the problems and the limitations of efficiency. However, obvious or large bleb leaks often require surgical repair, in which one of the most effective surgical methods is the autologous conjunctiva flap surgery^[9].

The autologous conjunctiva flap repairing surgery is a relatively simple method, especially for late-onset or severe leaking filtering bleb^[10]. Wilson and Kotas-Neumann^[11] firstly introduced four cases of autologous conjunctival flap after bleb excision, which only three cases had 2mo of follow up. Then Schnyder *et al*^[9] reported that free conjunctival flap was connected with the excision of the bleb in 16 cases of bleb leak, with 25% recurring within months. Many studies have focused on the conjunctival flap repair for bleb leakage after trabeculectomy to prove its efficacy, whereas the long-term success rate and IOP controllability are rarely reported.

In our study, we investigated 106 cases with filtering bleb leakage after trabeculectomy followed by autologous conjunctival flap repairing surgery and rigorously analysed the long-term postoperative success rates of 41 cases during the subsequent one year.

SUBJECTS AND METHODS

Clinical Data A retrospective study was conducted with 106 glaucoma patients who received filtering bleb leakage after trabeculectomy followed by autologous conjunctival flap surgery in the Zhongshan Ophthalmic Centre from 2005 to 2015. The recorded indexes included basic information, such as the patients' age, gender and eye, clinical features [*e.g.* glaucoma type, best corrected visual acuity (BCVA), IOP, and bleb characteristics] and the concentration, location, and time of the MMC application during the trabeculectomy. In all, 41 cases that completed the 1-year follow-up period and had complete follow-up materials were analysed to determine the IOP, BCVA and long-term success rates. The IOP was measured by the goldmann applanation tonometer, and the BCVA was expressed as decimal visual acuity with a test distance of 5 m. The anterior chamber depth (ACD) was acquired by the slitlamp; then under cobalt blue slitlamp illumination, a moistened sterile fluorescein strip was applied to the bleb surface. A leak was defined as a spontaneous faocal-point source of aqueous leakage from an area of interrupted conjunctival tissue occurring at least 3mo postoperatively. Diffuse transconjunctival aqueous flow, or "bleb sweat", did not qualify as a leak.

Our study was consistent with the tenets of the Declaration of Helsinki. All medical records were anonymous, and all information was used only for research purposes. All persons enrolled gave their informed consent prior to their inclusion in the study. The study was approved by the Investigational Review Board of Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China.

Inclusion and Exclusion Criteria The following characteristics were required for inclusion in our study: 1) diagnosed with glaucoma (congenital, juvenile, primary open angle glaucoma, primary angle-closure glaucoma, or secondary glaucoma); 2) filtering bleb leakage after trabeculectomy more than 3mo; 3) repair surgery with autogenous conjunctival flap without amniotic membrane or allogeneic sclera. The exclusion criteria were: 1) the early-onset filtering bleb after trabeculectomy less than 3mo; 2) the patients who have not completed all the follow-up on different timepoint postoperatively.

Surgical Technique All patients who accepted autologous conjunctival flap surgery in this study were treated with similar techniques by surgeons in the Department of Glaucoma. Conjunctival peritomy was performed from the temporal (Figure 1A) to the nasal side to relieve tension. The conjunctiva over the bleb was dissected, and a conjunctival flap was freed from scar tissue and episcleral attachments that extend approximately 1 or 2 clock hours at each side (Figure 1B). A cryopencil was used to damage the epithelium of the primary bleb (Figure 1C), and then a surgical beard blade was applied to 1 mm below the limbal location to remove the remaining epithelial cells (Figure 1D). The conjunctival flap was secured with 10-0 polygalactin sutures (Figure 1E, 1F), and a relief incision was used along the superior conjunctival fornix to ensure (Figure 1G) that the bleb was completely covered with a tightening-moderate state, which could facilitate the advancement of the conjunctiva (Figure 1H). The success of surgery was defined as negative Seidel's test and the well-healed bleb with a thin wall, and the failure of surgery was characterized as positive Seidel's test or a leaking filtering bleb.

Statistical Analysis The statistical analyses were performed with SPSS software (version 21.0, SPSS, Chicago, Illinois, USA), and *t*-tests were used to determine the statistical significance, with a *P* value <0.05 considered significant.

RESULTS

Clinical Data The study included 50 male subjects with 50 eyes (47.17%) and 56 female subjects with 56 eyes (52.83%). The average age was 39.13±17.96 years old, and the subjects included 5 children (1-13y; 4.72%), 59 youths (14-44y; 55.66%), 28 middle-aged individuals (45-59y; 26.42%) and 14 elderly individuals (60-77y; 13.21%). Fifty-six of the involved eyes (52.83%) were right eyes, and 50 were left eyes (47.17%). In addition, we reviewed 47 cases

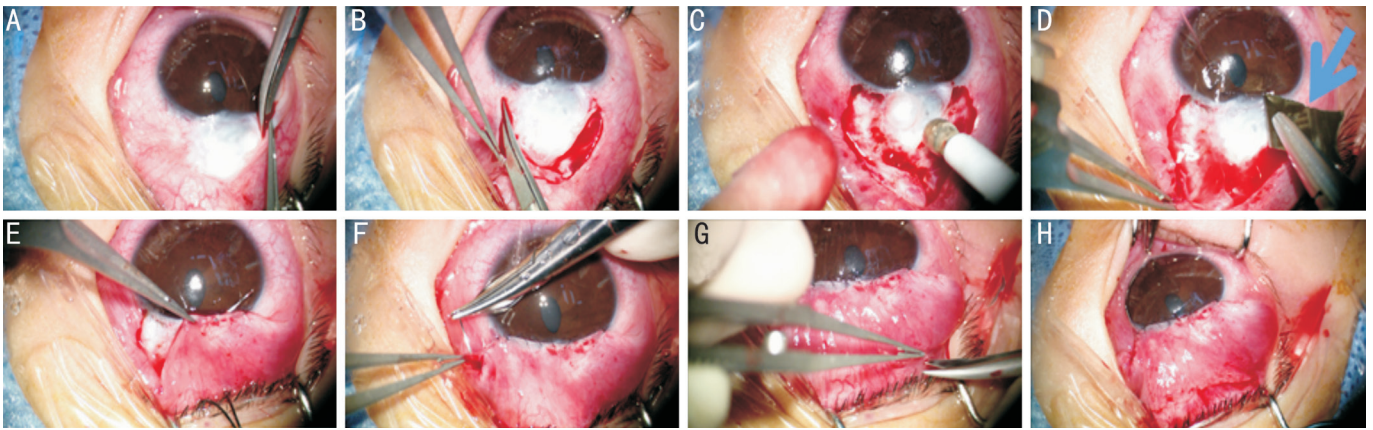


Figure 1 Intraoperative view A, B: Conjunctival peritomy performed from the temporal to the nasal side; C: Cryopencil used to freeze the epithelium of the primary bleb; D: Surgical beard blade inserted 1 mm below the limbal location to remove the remaining epithelial cells; E, F: Conjunctival flap secured with 10-0 polygalactin sutures; G: Relief incision along the superior conjunctival fornix; H: Postoperative ocular image.

Table 1 Mean concentration and time of MMC application during trabeculectomy with a fornix-based and limbal-based conjunctival flap

Type of flap	MMC		MMC Location (cases)		
	Concentration (mg/mL)	Time (min)	Beneath conjunctiva	Beneath sclera	Beneath conjunctiva and sclera
Fornix-based conjunctival flap	0.27±0.04 (0.12-0.4)	3.57±0.97 (2-5.5)	59 (86.76%)	3 (4.41%)	6 (8.82%)
Limbal-based conjunctival flap	0.28±0.04 (0.20-0.33)	3.27±0.96 (2-5)	10 (90.91%)	1 (9.09%)	0 (0)

MMC: Mitomycin.

(44.34%) of primary open angle glaucoma, 33 cases (31.13%) of primary angle-closure glaucoma, 11 cases (10.38%) of juvenile glaucoma, 10 cases (9.43%) of secondary glaucoma, 3 cases (2.83%) of congenital glaucoma and 2 cases (1.89%) of mixed glaucoma.

Mean Interval Between Trabeculectomy and Autologous Conjunctival Flap Surgery The mean interval between trabeculectomy and autologous conjunctival flap surgery was 60.60±56.92 (3-264)mo. For 11 cases (10.38%), the interval was more than 3mo and less than 6mo; for 9 cases (8.49%), the interval was between 6 to 12mo; and for 86 cases (81.13%), the interval was more than one year.

Related Risk Factors for Filtering Bleb Leakage MMC was administered to 79 patients (74.53%), and the mean concentration and time of MMC application for the trabeculectomy were 0.28±0.04 (0.12-0.4) mg/mL and 3.42±0.97 (2-5.5)min, respectively.

Among the patients, 68 (64.15%) treated with a fornix-based conjunctival flap were administered MMC, and the mean concentration and time were 0.27±0.04 (0.12-0.4) mg/mL and 3.57±0.97 (2-5.5)min, respectively. Of these cases, 59 were fitted with MMC sponges beneath the conjunctival flap, 6 cases were fitted with sponges under the conjunctival and sclera flap and 3 cases were fitted with sponges under the sclera flap. In 11 patients (10.38%) with a limbal-based conjunctival flap, the mean concentration of MMC was 0.28±0.04 (0.20-0.33) mg/mL and the time of MMC use was 3.27±0.96 (2-5)min; in addition,

10 of these cases were fitted with MMC sponges beneath the conjunctival flap and 1 case was fitted with a sponge under the sclera flap (Table 1). After trabeculectomy, 6 patients (5.66%) complained of the history of trauma, and another 123 patients (94.34%) had no other abnormal history.

Characteristics of the Filtering Bleb Leakage We investigated filtering bleb leakage before autologous conjunctival flap surgery. Fifty-one patients (48.11%) had a thin-walled bleb without obvious leakage, although leakage was induced with physical pressure on the trabeculectomy bleb, which resulted in a positive Seidel's test; 33 patients (31.13%) had obvious bleb leakage without a thin-walled bleb and a positive Seidel's test; 16 patients (15.09%) had a thin-walled bleb and obvious leakage tested by the fluorescein staining test. Two patients showed the leaking filtering bleb (1.89%) with infected history, which the bleb was leaking firstly, and then diagnosed as blebitis because of infection; after controlling the infection, the patients accepted the repairing surgery. Moreover, 4 patients (3.78%) showed localized filtering bleb adhesion as the contracted scar accompanied by leaking bleb. Thirty-four patients (32.07%) also had macular oedema, with 18 patients diagnosed by optical coherence tomography and 16 diagnosed via ophthalmofunduscopy.

IOP, BCVA and ACD After Trabeculectomy for Filtering Bleb Leakage and Autologous Conjunctival Flap Surgery We divided the shallow ACDs into three grades: Grade I (peripheral iris-cornea touch), Grade II (mid-iris to cornea

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Table 2 BCVA and ACD after trabeculectomy, during filtering bleb leakage and after autologous conjunctival flap surgery

Time point	BCVA	ACD		
		Grade I	Grade II	Grade III
1 st week after trabeculectomy	0.41±0.37 (0-1.5)	13 (12.26%)	2 (1.88%)	0 (0)
During leakage	0.39±0.40 (0-1.5) ^a	25 (23.58%)	20 (18.87%)	7 (6.60%)
1 st week after revision	0.36±0.34 (0-1.2) ^a	7 (5.34%)	0 (0)	0 (0)

^a $P>0.05$. BCVA: Best corrected visual acuity; ACD: Anterior chamber depth.

Table 3 IOP after trabeculectomy, during filtering bleb leakage and after autologous conjunctival flap surgery mean±SD (range)

Time point	1 st week after trabeculectomy	During leakage	After revision				
			1 st week	1 st month	3 rd month	6 th month	12 th month
IOP (mm Hg)	10.25±4.76 (3-20.86)	8.85±4.39 (2-21) ^b	13.95±5.79 (6-35) ^b	14.08±4.13 (6-30) ^a	15.20±4.58 (7-30) ^a	15.18±5.45 (7-40) ^a	15.68±5.11 (7-40) ^a

^a $P>0.05$; ^b $P<0.05$.

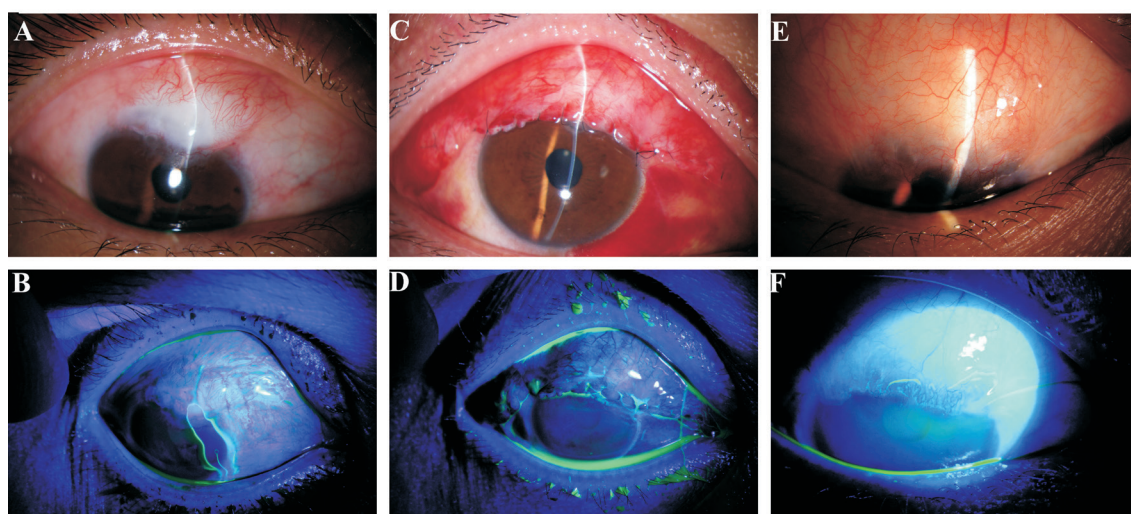


Figure 2 Therapeutic process of a case A, B: Leaking filtering bleb with a positive Seidel's test; C, D: The first week after the autologous conjunctival flap surgery; E, F: One year after autologous conjunctival flap surgery with a negative Seidel's test.

touch), and Grade III (central cornea-lens touch)^[12]. In the 1st week after trabeculectomy in 106 patients, 15 cases (14.15%) of a shallow ACD were observed, with 13 cases of Grade I and 2 cases of Grade II. The BCVA was 0.41±0.37 (0-1.5) (Table 2), and the IOP was 10.25±4.76 (3-20.86) mm Hg (Table 3).

For the cases exhibiting filtering bleb leakage, 52 (49.06%) out of 106 patients had a shallow ACD, with 25 cases of Grade I, 20 of Grade II, and 7 cases of Grade III. The BCVA changed to 0.39±0.40 (0-1.5), which indicated a minimal decrease and non-significant change ($P>0.05$) (Table 2). The IOP was clearly reduced to 8.85±4.39 (2-21) mm Hg ($P<0.01$), and 23 cases (17.56%) had an IOP lower than 6 mm Hg, 51 cases (46.56%) were between 6 and 10 mm Hg, and 32 cases (17.58%) were higher than 10 mm Hg (Table 3).

Within the first week after repair *via* autologous conjunctival flap surgery, only 7 cases (5.34%) had a shallow ACD of Grade I (Table 2), and the BCVA was 0.36±0.34 (0-1.2) ($P>0.05$) (Table 2), which was nearly equivalent to the preoperative BCVA. The IOP increased to 13.95±5.79 (1-35) mm Hg

compared with the pressure observed during bleb leakage ($P<0.001$) (Table 3).

Long-term Efficacy of Autologous Conjunctival Flap Surgery The 41 patients who completed the 1-year follow-up period and had complete follow-up materials showed nearly stable IOP levels postoperatively. In the 1st month, the IOP was 14.08±4.13 (6-30) mm Hg, and 2 of these cases were higher than 21 mm Hg and 5 were lower than 10 mm Hg. The IOP increased to 15.20±4.58 (7-30) mm Hg, with 4 cases of hypertension and 2 case of hypotension in the 3rd month. Then, the IOP reached a nearly stable level of 15.18±5.45 (7-40) mm Hg, with 7 cases of hypertension and 4 cases of hypotension in the 6th month. Finally, the IOP reached 15.68±5.11 (7-40) mm Hg, with 4 cases of hypertension and 2 cases of hypotension in the 12th month (Table 3).

None of the patients complained of the recurrence, and the success rate was 100%. Figure 2 shows a representative case of filtering bleb leakage. A raised, confined and white bleb, a shallow ACD, and near contact between the peripheral iris and the cornea endothelia are shown in Figure 2A and 2B; in this

case, the positive Seidel's test demonstrated obvious leakage. Images taken in the 1st week after autologous conjunctival flap surgery are shown in Figure 2C and 2D; in this case, the anterior chamber was deep. The bleb was dispersed and the Seidel's test was negative. After 1y, the filtering bleb did not leak and was flat without excessive scarring between the sclera lamella and bulbar conjunctiva, the conjunctiva had no obvious congestion, and the anterior chamber was deep (Figure 2E, 2F).

DISCUSSION

Late-onset filtering bleb leakage is a frequent complication of trabeculectomy that can occur from 3mo to years after surgery^[7,13]. Clinically, bleb leakage may be related to patent stitch tracts, deficient wound closure, surgically induced conjunctival trauma, or overuse of antifibrotic drugs, such as 5-FU and MMC^[14]. Differences in sample size, length of follow-up, definition of aqueous leakage, spontaneous or provoked leak detection, and filtering bleb location were reported to affect the leak rates^[3]. In our study, most patients with leaking blebs were administered MMC which these results are consistent with those of Henderson *et al*^[15], who found that 64% and 10% of the patients who received MMC were in the fornix-based group and the limbal-based group, respectively. The concentration and time of MMC administration in our study was in a normal range that has been widely applied clinically because wound healing modifying agents, such as 5-FU and MMC, can significantly enhance the success rate of glaucoma surgery^[13,16]. However, it is interesting to find that the youth age group had a higher tendency for bleb leak in our study, this is because the time and concentration of MMC used in trabeculectomy was higher than others' because of their faster proliferation of fibrous tissue, thus increased the risk of bleb leaking. MMC may represent a risk factor for filtering bleb leakage after trabeculectomy because it can damage fibroblasts and prevent them from secreting enough collagen to provide tensile strength to the bleb dome. Besides, 40% of eye exposed to MMC in the primary surgery still had leaked bleb, might because that their bleb were ultrafiltrative.

It is interesting to find that most patients showed a thin-walled bleb and no obvious leakage in our study, which matched with features "Late-onset leaks are typically associated with thin, cystic, avascular blebs"^[3]; moreover, many patients (26%) also had macular oedema, which can seriously threaten visual acuity. Such leakages should be treated as a serious problem because the more severe complications include macular oedema and flat chamber as well as corneal decompensation, choroidal effusion, suprachoroidal haemorrhage, and even endophthalmitis^[17]. As the clinical feature of bleb leaks was not obvious and may be easily missed by the clinician, it is important to inspect the bleb with fluorescein and cobalt blue illumination before measuring the IOP in eye postinfiltration

surgery, especially the region of transplant bleb tissue, to avoid the severe complications.

For late bleb leaks, many therapeutic modalities have been proposed to treat late leaks, including lubrication, pressure patching, a bandage contact lens, a glaucoma tamponade shield, a symblepharon ring, the injection of autograft blood cryopexy, thermal Nd:YAG laser, cyanoacrylate glue, and fibrin tissue glue^[8]. For large or obvious leaking blebs, surgical revision is considered a better choice^[4]. Although consensus on to management of bleb leakage has not been reached, our study's technique is similar to that described by Galin and Hung^[18]; moreover, some improvements have been made in which, the use of a cryopencil to injure the epithelium of the primary bleb can help connect the epithelium boundary between the filtering bleb and the conjunctiva after autologous conjunctival transplantation surgery; and a relief incision along the superior conjunctival fornix could relieve conjunctival tension and play a significant role by providing a space for a stable filtering bleb postoperatively.

Many studies have been conducted on filtering bleb revision surgery for late-onset leaking bleb after trabeculectomy, however, the evaluations of the success rate and long-term IOP controllability are seldom reported. Our study concluded that filtering bleb leak did not obviously affect visual acuity, while the IOP revealed a significant decrease. After repairing surgery, the ACD as well as the IOP was obviously improved which indicated that the aqueous fluid drainage channel was successfully built. All patients achieved adequate IOP control on 1st, 6th and 12th months on the follow-up, which the timepoint were according to Alwitry *et al*'s^[14] study, and this phenomenon also hinted that no further destruction of the conjunctiva was observed in this repairing surgery.

In anclusion, autologous conjunctival flap repairing surgery is effective for filtering bleb leakage after trabeculectomy because it can close the leak, maintain IOP, preserve vision and reduce postoperative complications.

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