

# Influence of glaucoma surgery on the ocular surface using oculus keratograph

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## Abstract

**Purpose** To investigate the influence of trabeculectomy and phacotrabeculectomy on the ocular surface.

**Design** Retrospective, case–control study.

**Methods** Eighty-one samples without dry eyes were recruited and divided into three groups, including phacoemulsification group ( $N = 30$ ) as control group, trabeculectomy group ( $N = 27$ ) and phacotrabeculectomy group ( $N = 24$ ) as study groups. Ocular surface parameters, including noninvasive keratograph first (NifBUT) and average (NiaBUT) tear film breakup time, tear meniscus height (TMH) and corneal fluorescein stain (CFS), were estimated preoperatively, at 3 days, 1 month and 3 months postoperatively using oculus keratograph.

**Results** No significant difference was observed in ocular surface parameters at baseline among three groups ( $p > 0.05$ ). The magnitude of NifBUT and

NiaBUT was reduced at 3 days and 1 month postoperatively in phacotrabeculectomy group, but greater than that in the other two groups (All  $p < 0.001$ ). In all the groups, both the NifBUT and NiaBUT tended to recover at 1 and 3 months postoperatively, whereas both of them did not recover to baseline at 3 months postoperatively in trabeculectomy (NifBUT,  $p = 0.001$ ; NiaBUT,  $p < 0.001$ ) and phacotrabeculectomy group (NifBUT,  $p < 0.001$ ; NiaBUT,  $p = 0.020$ ). TMH was raised at 3 days postoperatively and restored to the baseline level at 1 and 3 months postoperatively for three groups ( $p > 0.05$ ). CFS was elevated at 3 days postoperatively and different in recovery at 1 and 3 months postoperatively for three groups.

**Conclusions** The influence of phacotrabeculectomy on ocular surface is worse than that of trabeculectomy for the short run and is not distinct different for a long time.

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**Keywords** Glaucoma · Dry eye · Ocular surface · Breakup time · Oculus keratograph

## Introduction

Glaucoma is an irreversible blindness disease, causes optic nerve atrophy and vision loss. Antiglaucoma eye drop and trabeculectomy reducing the intraocular pressure (IOP) are the main therapeutic methods for

glaucoma. Unfortunately, prolonged eye drop treatment causes ocular surface damage. Consequently, when the treatment compliance of prolonged eye drop is severe or its effect is bad, trabeculectomy is another appropriate choice.

Dry eye is a multifactorial disease characterized by aqueous deficiency and/or over evaporation. The instability of tear film or ocular surface damage is resulted in poor vision. Dry eye syndrome (DES) could be lead to by many complex factors, including age, hormonal changes, environmental factors, topical medications, systemic diseases and drugs, autoimmune diseases, meibomian gland dysfunction [1] and ocular surgery, some of the underlying mechanism remains to be studied. Previously, researches have indicated that the more stable the tear film is, the better the contrast sensitivity would be [2], and the severe DES [3] could cause worse functional visual acuity and deteriorated quality of life [4]. Therefore, in order to improve the visual quality and patient satisfaction, the stability of tear film should be concerned in clinical practice.

As compared to the traditional examination of ocular surface, oculus keratograph is a kind of noninvasive, objective and comprehensive examination or diagnostic method which is convenient and with good repeatability. In addition, ocular keratograph can assess much more ocular surface parameters including noninvasive first breakup time (NifBUT), noninvasive average breakup time (NiaBUT), tear meniscus height (TMH), lid margin analysis, corneal staining and meibomian gland loss.

Appropriate management of ocular surface has become a new challenge in glaucoma care for a long time. There are many reports about the influence of trabeculectomy or cataract surgery on the ocular surface [5–7]. Nevertheless, few studies have compared the influence of different anti-glaucoma surgery on the ocular surface. Hence, the purpose of this study was to compare the influence of trabeculectomy and phacotrabeculectomy on the ocular surface.

## Methods

### Study design and participants

This study was abided by the Declaration of Helsinki for human research and approved by the institutional

ethical committees of the Department of Ophthalmology, Wuhan General Hospital of Liberation Army, Southern Medical University, China. Before the study, written informed consent was taken from each patient.

From June 2016 to March 2017, 81 eyes of 62 patients were recruited and divided into three groups according to different surgical procedures, including phacoemulsification group (30 eyes of 18 cataract patients) as control group, trabeculectomy group (27 eyes of 23 glaucoma patients) and phacotrabeculectomy group (24 eyes of 21 glaucoma patients) as study groups. Preoperatively, all patients underwent full ophthalmological examination, including slit lamp, anterior chamber depth, central corneal thickness, gonioscopy, fundus examination, and the glaucoma patients accepted Humphrey field analyzer 24-2 and 10-2. Exclusion criteria for patients were as follows: (i) ocular injury, infection, ocular surgery and using contact lens; (ii) using for topical medications of preservative Benzalkonium eye drop and systemic drugs; (iii) other ocular surface diseases (pterygia, allergies, blepharitis, lacrimal dust obstruction and so on); (iv) dry eye disease according to the Japanese dry eye diagnostic criteria [8].

Parameters including NifBUT, NiaBUT, TMH and CFS were measured and recorded preoperatively, 3 days, 1 month and 3 months postoperatively by ocular keratograph (Wetzlar, Germany). All the checks were completed in dark room with 25 °C constant temperature and 30% humidity by one operator. The CFS was inspected with one drop of 1% fluorescein dye instilled according to the method used by Toda and Tsubota [9]. Two eyes of each patient were examined three times at 10 min intervals, and the average data of the right eye were used for further analysis.

### Cataract and glaucoma surgery

Phacoemulsification was completed by one surgeon (Lei Yang), phacotrabeculectomy and trabeculectomy were accomplished by another surgeon (Wenqian Zhang).

3.2 mm clear corneal incision was main incision, 1 mm the side puncture made at a 45° angle from the main incision, the phacoemulsification time was controlled in 3 min and a posterior chamber intraocular lens was inserted. 0.5% proparacaine hydrochloride (Alcaine company) was topical anesthesia.

Compound topical (Santen Pharmaceutical Company) was used to dilate the pupils before cataract surgery. 1% prednisolone acetate (Allergan Pharmaceuticals Ireland) six times for the first day postoperatively and four times for 2 weeks.

Phacotrabeculectomy was performed under local anesthesia with 3 ml of 2% lidocaine retrobulbar injection. A fornix-based conjunctival flap and a 3 × 4 mm rectangular limbal-based scleral flap were formed in the superior area. A sponge soaked in a 0.3 mg/ml solution of 5-fluorouracil was applied under the conjunctival flap and scleral flap for 3 min and the area was irrigated thoroughly with 500 ml physiological saline. Then, 11 o'clock position phacoemulsification and intraocular lens implantation were performed. After end of cataract surgery, we continued trabeculectomy and removed trabecular and peripheral iris tissue. The scleral flap and conjunctival wound were sutured with 10-0 nylon (alcon.USA). Patient instilled 1% prednisolone acetate eye drops four times daily for 1 month postoperatively. In all cases, intraoperative complication did not happen.

### Statistical analyses

All the analyses were performed with SPSS software (IBM, Somers, NY, version 23.0). Each value was presented as the mean ± standard deviation (SD). For three groups baseline comparison, the Chi-square test was used for the comparison of categorical variables for gender, and analysis of variance (ANOVA) was adopted to compare continuous variables for parameters of ocular surface, IOP, operative time and age. The repeat measurement analysis of variance (repeat measurement ANOVA) was used to compare within-group continuous variable.  $p < 0.05$  at two tails was considered statistically significant.

## Results

### Demographic and clinical characteristics of participants

Four participants excluded for follow-up failure, leaving a final subjects of 81 (cataract, 30; glaucoma, 51) completed the follow-up visits. At baseline, no significant differences were found in terms of gender, composition of glaucoma and parameters of ocular

surface (all  $p$  values  $> 0.05$ ), whereas, significant differences of age, IOP and operation time were found among three groups (Table 1).

As shown in Table 2, the ocular surface, including NifBUT, NiaBUT, TMH and CFS were become bad at 3 days postoperatively among three groups (all  $p$  values  $< 0.001$ ). All these parameters of ocular surface were gradually improved as time passed. Phacoemulsification group restored to baseline at 1 and 3 months postoperatively (all  $p$  values  $> 0.05$ , except CFS  $p < 0.001$  in 1 month). Parameters of ocular surface as well as IOP for trabeculectomy group and phacotrabeculectomy group had statistically significant difference after surgery (all  $p$  values  $< 0.001$ , except TMH).

### Noninvasive keratograph tear film breakup time

Change in NifBUT value in the phacotrabeculectomy group was statistically significantly different from that in the control group after surgery ( $p < 0.05$ , respectively). Change in NifBUT value in the trabeculectomy group was not significantly different from that in the control group at 3 days and 1 month postoperatively ( $p = 0.734$ ,  $p = 0.226$ , respectively) but was statistically significantly different at 3 months postoperatively ( $p < 0.05$ ). Change in NifBUT value was significantly different between the two study groups at 3 days and 1 month postoperatively ( $p < 0.001$ , respectively) but was not significantly different at 3 months postoperatively ( $p = 0.271$ ) (Fig. 1).

NiaBUT rangeability was more obvious than NifBUT. Change in NiaBUT value in the phacotrabeculectomy group was significantly different from that in the control group at 3 days and 1 month postoperatively ( $p < 0.001$ , respectively) and was not significantly different at 3 months postoperatively ( $p = 0.655$ ). Change in NiaBUT value in the trabeculectomy group was not significantly different from that in the control group after surgery ( $p = 0.974$ ,  $p = 0.829$ ,  $p = 0.668$ , respectively). Change in NiaBUT value was significantly different between the two study groups at 3 days and 1 month postoperatively ( $p < 0.001$ , respectively) but was not significantly different at 3 months postoperatively ( $p = 0.976$ ) (Fig. 2).

**Table 1** Demographic and clinical characteristics (mean  $\pm$  SD) at baseline for three groups

Parameters	Phacoemulsification $N = 30$	Trabeculectomy $N = 27$	Phacotrabeculectomy $N = 24$	$p$ value
Age (years)	66.77 $\pm$ 3.56	52.19 $\pm$ 3.28	53.25 $\pm$ 3.40	< 0.001
Gender	17M/13F	16M/11F	13M/11F	0.935
PACG/POAG		21/6	19/5	0.588
IOP (mmHg)	12.80 $\pm$ 1.42	27.85 $\pm$ 2.30	27.25 $\pm$ 2.07	< 0.001
Operation time (min)	14.07 $\pm$ 1.70	32.26 $\pm$ 4.10	51.38 $\pm$ 4.08	< 0.001
NifBUT (s)	14.17 $\pm$ 1.24	14.19 $\pm$ 1.68	13.82 $\pm$ 1.11	0.557
NiaBUT (s)	16.76 $\pm$ 0.98	17.57 $\pm$ 2.08	17.24 $\pm$ 1.39	0.143
TMH (mm)	0.27 $\pm$ 0.01	0.28 $\pm$ 0.02	0.28 $\pm$ 0.01	0.781
Corneal staining score	0.42 $\pm$ 0.12	0.43 $\pm$ 0.13	0.44 $\pm$ 0.13	0.834

$p < 0.05$  was considered to be statistically significant

PACG primary angle closure glaucoma, POAG primary open angle glaucoma, IOP intraocular pressure, NifBUT noninvasive keratograph first tear film breakup time, NiaBUT noninvasive keratograph average tear film breakup time, TMH tear meniscus height

### Tear meniscus height

Change in TMH value in the phacotrabeculectomy group was not significantly different from that in the control group at 3 days, 1 month and 3 months postoperatively ( $p = 0.531$ ,  $p = 0.866$ ,  $p = 0.680$ , respectively). Change in TMH value in the trabeculectomy group was not significantly different from that in the control group after surgery ( $p = 0.718$ ,  $p = 0.938$ ,  $p = 0.646$ , respectively). Change in TMH value was not significantly different between the two study groups after surgery ( $p = 0.787$ ,  $p = 0.927$ ,  $p = 0.974$ , respectively) (Fig. 3).

### Corneal fluorescein stain

Change in CFS value in the phacotrabeculectomy group was not significantly different from that in the control group at 3 days postoperatively ( $p = 0.051$ ) and was significantly different at 1 and 3 months postoperatively ( $p < 0.05$ ). Change in CFS value in the trabeculectomy group was not significantly different from that in the control group at 3 days, 1 month and 3 months postoperatively ( $p = 0.141$ ,  $p = 0.214$ ,  $p = 0.065$ , respectively). Change in CFS value was not significantly different between the two study groups at 3 days and 1 month postoperatively ( $p = 0.601$ ,  $p = 0.141$ , respectively) but was significantly different at 3 months postoperatively ( $p < 0.05$ ) (Fig. 4).

### Discussion

DES frequently occurs after surgery, patient maybe experience serious irritation symptoms. Some literature [10, 11] reported that the stability of ocular surface was observed by BUT and CFS after surgery. Consistent with previous reports, we found obviously a decreased value of BUT and increased value of CSF after surgery. Generally, dry eye after surgery may happen in patients being suffered from an increase in preexisting dry eye, or experiencing surgically-induced dry eye. We analyzed the influence of surgery on the ocular surface and its time course in our research.

During operation process, patients suffered from vigorous irrigation of the cornea intraoperatively, ocular surface manipulation and exposure to light of microscope were reported to experience postoperative dry eye [12, 13], and this might be associated with the reduction in the number of goblet cell. Recent evidence has suggested that goblet cell secreting mucin 5AC plays important role in tear film stability [14]. However, we speculated that a longer operation may cause more decrease in the goblet cell and the stability of tear film. At the same time, according to previous reports that goblet cell density did not return to preoperative level at 3 months after cataract surgery [15] and the mucin 5AC could restore to baseline at 3 months after phacotrabeculectomy [16], the recovery of goblet cell and mucin may be not necessarily

**Table 2** Mean ( $\pm$  SD) of IOP and ocular surface parameters measured preoperatively and at 3 days, 1 month and 3 months after surgery for three groups

Parameters	Baseline	3 days	1 month	3 months	<i>p</i> value			
					Overall	Baseline versus 3 days	Baseline versus 1 month	Baseline versus 3 months
<b>Phacoemulsification</b>								
IOP (mmHg)	12.80 $\pm$ 1.42	12.77 $\pm$ 1.29	12.70 $\pm$ 1.24	13.17 $\pm$ 1.46	0.567	0.922	0.732	0.392
NifBUT (s)	14.17 $\pm$ 1.24	12.57 $\pm$ 1.79	13.48 $\pm$ 1.21	13.91 $\pm$ 1.28	< 0.001	< 0.001	0.005	0.209
NiaBUT (s)	16.76 $\pm$ 0.98	15.46 $\pm$ 1.55	16.04 $\pm$ 1.58	16.40 $\pm$ 1.29	< 0.001	< 0.001	0.029	0.168
TMH (mm)	0.27 $\pm$ 0.01	0.30 $\pm$ 0.02	0.27 $\pm$ 0.01	0.28 $\pm$ 0.01	< 0.001	< 0.001	0.923	0.358
Corneal staining score	0.42 $\pm$ 0.12	0.69 $\pm$ 0.21	0.58 $\pm$ 0.13	0.43 $\pm$ 0.12	< 0.001	< 0.001	< 0.001	0.444
<b>Trabeculectomy</b>								
IOP (mmHg)	27.85 $\pm$ 2.30	12.93 $\pm$ 1.62	13.48 $\pm$ 1.78	14.07 $\pm$ 1.67	< 0.001	< 0.001	< 0.001	< 0.001
NifBUT (s)	14.19 $\pm$ 1.68	12.42 $\pm$ 1.78	13.03 $\pm$ 1.48	13.23 $\pm$ 1.22	< 0.001	< 0.001	< 0.001	0.001
NiaBUT (s)	17.57 $\pm$ 2.08	15.48 $\pm$ 1.86	15.95 $\pm$ 1.67	16.19 $\pm$ 1.47	< 0.001	< 0.001	< 0.001	< 0.001
TMH (mm)	0.28 $\pm$ 0.02	0.30 $\pm$ 0.01	0.27 $\pm$ 0.02	0.27 $\pm$ 0.02	< 0.001	< 0.001	0.327	0.814
Corneal staining score	0.43 $\pm$ 0.13	0.77 $\pm$ 0.18	0.63 $\pm$ 0.15	0.50 $\pm$ 0.14	< 0.001	< 0.001	< 0.001	0.002
<b>Phacotrabeculectomy</b>								
IOP (mmHg)	27.25 $\pm$ 2.07	13.04 $\pm$ 2.10	13.25 $\pm$ 1.80	13.29 $\pm$ 1.83	< 0.001	< 0.001	< 0.001	< 0.001
NifBUT (s)	13.82 $\pm$ 1.11	10.13 $\pm$ 1.48	11.05 $\pm$ 1.51	12.83 $\pm$ 1.26	< 0.001	< 0.001	< 0.001	< 0.001
NiaBUT (s)	17.24 $\pm$ 1.39	12.59 $\pm$ 1.96	13.45 $\pm$ 1.44	16.18 $\pm$ 2.63	< 0.001	< 0.001	< 0.001	0.020
TMH (mm)	0.28 $\pm$ 0.01	0.31 $\pm$ 0.02	0.27 $\pm$ 0.01	0.27 $\pm$ 0.02	< 0.001	< 0.001	0.216	0.528
Corneal staining score	0.44 $\pm$ 0.13	0.80 $\pm$ 0.22	0.70 $\pm$ 0.19	0.64 $\pm$ 0.17	< 0.001	< 0.001	< 0.001	< 0.001

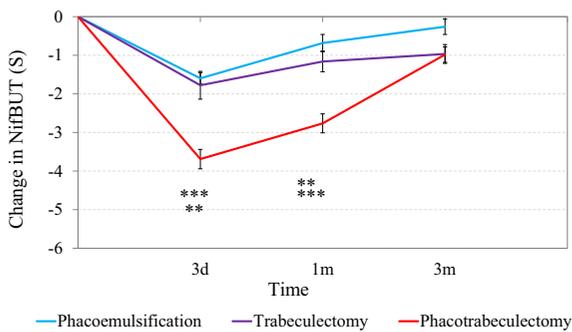
Continuous values were analyzed by ANOVA.  $p < 0.05$  was considered to be statistically significant

*IOP* intraocular pressure, *NifBUT* noninvasive keratograph first tear film breakup time, *NiaBUT* noninvasive keratograph average tear film breakup time, *TMH* tear meniscus height

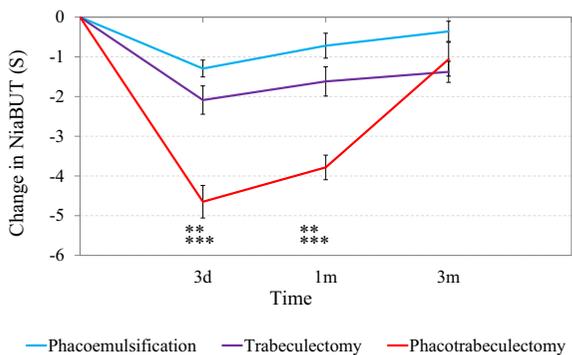
synchronous which needed to be clarified in a further study.

Corneal incision damages intact cornea innervations. In normal condition, cornea is innervated by the ciliary

nerve of the branch of the trigeminal nerve, which deliver signals to brain, and then stimulate lacrimal gland to secrete tears [17]. Corneal surgery procedures disrupt the normal organization of corneal nerve and result in

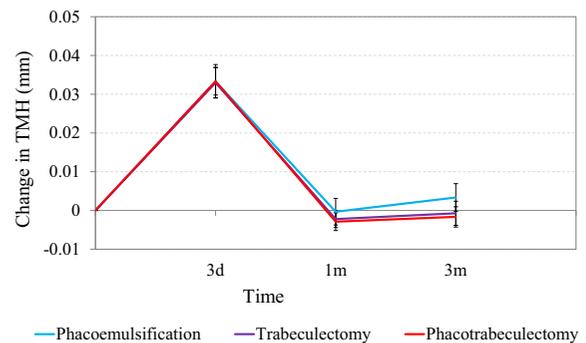


**Fig. 1** Change in noninvasive keratograph first tear film breakup time (NifBUT) in three groups. Change value represented difference value between postoperative and preoperative. Significance was evaluated by repeated measures analysis of variance (ANOVA),  $p < 0.05$  was considered statistically significant. \*Significant difference between phacoemulsification group and trabeculectomy group. \*\*Significant difference between phacoemulsification group and phacotrabeculectomy group. \*\*\*Significant difference between trabeculectomy group and phacotrabeculectomy group

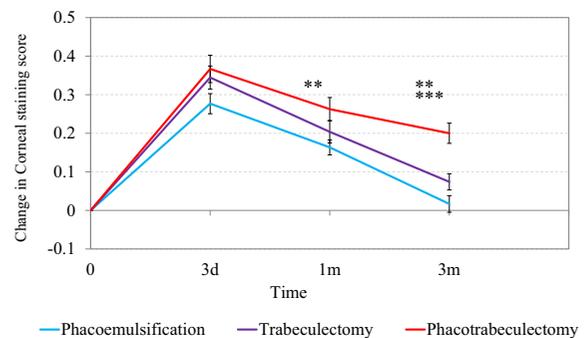


**Fig. 2** Change in noninvasive keratograph average tear film breakup time (NiaBUT) in three groups. Change value represented difference value between postoperative and preoperative. Significance was evaluated by repeated measures analysis of variance (ANOVA),  $p < 0.05$  was considered statistically significant. \*Significant difference between phacoemulsification group and trabeculectomy group. \*\*Significant difference between phacoemulsification group and phacotrabeculectomy group. \*\*\*Significant difference between trabeculectomy group and phacotrabeculectomy group

reduction for number of blinking and secretion of tears. In addition, corneal incision prompts inflammatory mediator release [18], especially, IL-8, IL-6, TNF- $\alpha$  and IFN- $\gamma$  which may weaken corneal sensitivity [19], destroy corneal nerve action and lead to deteriorate tear film stability. The recovery of corneal nerve is completed approximately at 1 month postoperatively. These explain why dry eye test values are prominent early after surgery



**Fig. 3** Change in tear meniscus height (TMH) in three groups. Change value represented difference value between postoperative and preoperative. Significance was evaluated by repeated measures analysis of variance (ANOVA),  $p < 0.05$  was considered statistically significant



**Fig. 4** Change in corneal fluorescein stain (CFS) in three groups. Change value represented difference value between postoperative and preoperative. Significance was evaluated by repeated measures analysis of variance (ANOVA),  $p < 0.05$  was considered statistically significant. \*Significant difference between phacoemulsification group and trabeculectomy group. \*\*Significant difference between phacoemulsification group and phacotrabeculectomy group. \*\*\*Significant difference between trabeculectomy group and phacotrabeculectomy group

and improve thereafter. In accordance with these opinions [15], we observed that the influence of phacoemulsification on ocular surface was largely eliminated over time and was also restored to normal values at 1 month postoperatively.

Filtering bleb could influence the ocular surface at least half a year. For some subjects [7] accepted trabeculectomy at least 6 months, small filtering bleb still obstructed ocular surface by aggravating fluorescein staining, shorting BUT. Filtering bleb morphology effects tear film according to previous research [20] which indicated that the higher filtering bleb would decrease BUT and increase the corneal staining,

whereas the extent of filtering bleb was not related to the tear film stability. Moreover, filtering bleb could cause dry eye by inducing meibomian gland loss [21], which could decrease meibum secreting and prevent tear evaporation [22].

In our study, phacotrabeculectomy has corneal incision, filtering bleb and the longest exposure time in three groups, which could induce more decrease in BUT and increase in CFS than the other two groups in the early postoperative period. As time passed, the influence of corneal incision and exposure to light of microscope on ocular surface might be eliminated gradually, thus the dry eye test values restored partially. So we found that the change of parameters of ocular surface has the same tendency at 1 month postoperatively in the two study groups. Parameters of ocular surface did not return to preoperative levels at 3 months after glaucoma surgery, filtering bleb may play an important role.

Misuse of eye drops was identified as a major pathogenic factor for DES [23]. The use of topical medication containing preservative benzalkonium chloride (BAK) antiglaucoma eye drops, topical anesthesia and antiproliferative agents (5-fluorouracil, mitomycin C) can cause tear film instability and lead to dry eye [24]. However, some eye drops such as antibiotics, 1% prednisolone and artificial tears of 0.15% zinc-hyaluronate [25] could improve ocular surface environment and accelerate tear film recovery. In order to eliminate interference of eye drops, we minimize the use of topical drugs without affecting the operation in advance. Li et al. [23] reported that the dry eye appeared at 1 week, was peaked at 1 month, and partially recovered at 3 months postoperatively, and values of BUT and CFS were significantly decreased with a slightly improved thereafter which were still lower than baseline at 3 months postoperatively. This finding was different from our results, which may be related to the abuse of preservative drugs before and after surgery. Consisted with some studies [5, 26], in this study, parameters of ocular surface in patients who did not instill any preservatives eye drops postoperatively, returned to baseline after 3 months postoperatively.

In addition to surgery and topical eye drops, the biggest risk factor for influence of tear film stability was the history of ocular surface disease [27] which was considered in the exclusion criteria of our subject. Moreover, demographics factors including age, gender and race [28] could also influence ocular surface. In this study, all recruited patients were Chinese with

no significant difference in the ratio of female/male, whereas the onset age of senile cataract was older than glaucoma. Nevertheless, the baseline ocular surface parameter was not significantly different among three groups, which, to our best knowledge, could improve the accuracy of the experiment results.

Comparing to conventional approach, ocular keratograph is a noninvasive, convenient and diagnostic method with good repeatability which could be used to measure tear film breakup time without using fluorescein sodium. Moreover, when compared to the fluorescein sodium tear film breakup time (TBUT), the ocular keratograph can record small breakup time that our eyes could not see [29]. In this study, the variation trend of NifBUT was found the same as NiaBUT, which made our conclusions more persuasive.

Although we have shown novel findings in our study, some limitations can't be ignored. Firstly, the sample size is small and the follow-up period is relatively short, these could be influenced our findings in part. In addition, only four parameters of ocular surface were measured, because prolonged examination may cause patient uncomfortable. Other observation index, such as MGD and tear film osmolarity, may reflect the function of ocular surface [30], which need to be investigated in further study. At last, glaucoma surgery including EXPRESS mini-shunt or Ahmed implantation may has different influences on tear film which also needed further study.

In conclusion, the influence of phacotrabeculectomy on ocular surface is worse than that of trabeculectomy for the short run and is not distinct different for a long time. In addition, the stability of tear film did not fully recovered after glaucoma surgery but fully restored at 1 month after cataract surgery. In order to improve visual function and quality of life for patients, phacotrabeculectomy combined with proper treatment of artificial tears was recommended.

#### Compliance with ethical standards

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

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