

Influence of pars plana vitrectomy on ocular surface using noninvasive Keratograph 5M

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Abstract

• **AIM:** To evaluate the influence of pars plana vitrectomy (PPV) on ocular surface using Keratograph 5M.

• **METHODS:** Totally 30 consecutive patients (30 eyes) undergoing primary 23-gauge PPV were recruited in the study. Ocular Surface Disease Index (OSDI) questionnaire was performed. Ocular surface parameters, including tear meniscus height (TMH), noninvasive tear break up time (NITBUT) and bulbar redness score were obtained preoperatively, in 1, 2, 4, 8 and 12wk postoperatively by Keratograph 5M. Correlations between all the clinical parameters were analyzed further.

• **RESULTS:** The percentages of both photophobia and gritty within 4wk after PPV were significantly higher than pre-operation, while they decreased to the preoperative levels in both 8wk and 12wk postoperatively. The percentage of sore eyes in the first week postoperatively was significantly higher than pre-operation, but there were no significant differences between the percentages of pre-operation and 2, 4, 8, and 12wk postoperatively. OSDI score increased significantly within 4wk postoperatively, but it returned to the preoperative level in 8 and 12wk. TMH increased with 2wk postoperatively, but there were no significant

differences compared with preoperation. Both NITBUT-first and NITBUT-average shortened significantly within 8 weeks postoperatively, but they gradually improved to the preoperative levels in 12wk. Bulbar redness score was significantly higher than the preoperative level within 4wk postoperatively, but it returned to the preoperative level in 8wk. NITBUT-first and NITBUT-average had a significant positive correlation at each visit. TMH had a significant positive correlation with NITBUT-average in the first week postoperatively.

• **CONCLUSION:** Keratograph 5M can provide a reliable noninvasive method to assess the influence of PPV on the ocular surface. PPV may cause various changes in both symptoms and signs of ocular surface damages at the early stage, while all these changes will return to preoperative levels gradually in 12wk postoperatively.

• **KEYWORDS:** Keratograph; ocular surface; tear film; pars plana vitrectomy; dry eye syndrome

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INTRODUCTION

Pars plana vitrectomy (PPV) was first introduced as a new treatment for vitreoretinal diseases by Robert Machemer in 1971. With the evolution and development of vitrectomy machines and related instruments, surgical techniques have been improved and the application of PPV has increased significantly in recent years. However, many patients undergoing PPV have complained of dry eye-related irritative symptoms postoperatively.

Dry eye syndrome is a multifactorial disease of tears and ocular surface due to tear deficiency and over evaporation, which can be caused by many complex factors, including inflammation, hyperosmolarity of tears, and neurosensory abnormalities, as well as unstable tear films^[1-2]. It leads to ocular discomfort and visual impairment, which can impact the quality of life greatly^[3]. Bulbar redness, or conjunctival hyperemia, is a

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non-specific ocular response due to multiple ocular surface disorders, including conjunctivitis, anterior eye inflammation, contact lens wear and dry eye syndrome. There are also many reports about the influence of surgical interventions on the ocular surface, such as corneal refractive surgery^[4], cataract surgery^[5] and glaucoma surgery^[6]. Evaluation of tear film and bulbar redness may help us to know the surgery-induced ocular surface changes and guide appropriate treatments. Nevertheless, the influence of PPV on ocular surface is poorly understood so far.

Traditional methods evaluating dry eye have been widely used in clinical practice, including Schirmer test and fluorescein tear breakup time (TBUT). However, these invasive examinations are subjective, difficult, and time-consuming, which need patients to cooperate very well. Additionally, these invasive examinations have been shown to have poor accuracy and reproducibility. The noninvasive Keratography 5M, advanced Placido topography, provides reliable objective measurements of ocular surface parameters including tear meniscus height (TMH), noninvasive TBUT (NITBUT), and bulbar redness score, with acceptable repeatability and reproducibility^[7-8]. It has been used in the evaluation of ocular surface in recent years, especially the diagnosis of dry eye. In this study, we used the Keratograph 5M (Oculus Optikgeräte GmbH, Wetzlar, Germany) to evaluate the changes of ocular surface after PPV, which is beneficial to manage PPV induced ocular surface damages.

SUBJECTS AND METHODS

Ethical Approval This prospective, descriptive study was approved by the Ethics Committee of the First Hospital Affiliated of Anhui Medical University and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Participants From April 2018 to October 2018, a total of 30 eyes from 30 consecutive patients who underwent primary 23-gauge PPV in our hospital were recruited. Their age ranged 43-75y with a mean of 59.33 ± 7.68 y. Half of them were male and the other half were female. All the patients were followed up for 3months. Exclusion criteria were: 1) age ≤ 18 or ≥ 75 y; 2) any eye diseases influencing ocular surface (e.g. keratoconjunctivitis, ectropion, hypophthalmos or glaucoma); 3) history of ocular injury or other ocular surgery within 6mo; 4) use of topical ocular medications influencing ocular surface within one week before the operation; 5) any other drugs used for postoperative complications during the follow-up period; 6) the follow-up period less than 3mo.

Surgical Techniques The three-port conventional 23-gauge PPV was done in all the 30 eyes by a single vitreoretinal surgeon under retrobulbar anesthesia induced with 0.1% ropivacaine hydrochloride. During the surgery, blood, anterior-

posterior traction, fibrovascular tissues and membranes were removed as completely and safely as possible. For the patients with macular hole, internal limiting membranes stained with indocyanine green were peeled to at least one disc diameter from the edge of the hole. Endolaser photocoagulation or retinal cryotherapy was done for sealing the retinal hole. Filtered air or silicone oil was used as intraocular tamponade if necessary. After removal of the cannula from the ports, sclerotomies were sutured with 8.0 absorbable sutures (VICRYLTM, W9560) and the ports were checked for leakages. After surgery, all the patients with intraocular air or silicone oil tamponade were instructed to maintain a prone position to achieve better effects. Additionally, all patients were given topical eye drops of tobramycin-dexamethasone (TobraDex, Alcon) and pranopfen (Pranopulin, Senju) four times daily for 1mo, and tropicamide-phenylephrine (Mydrin-P, Santen) was used twice daily for 2wk.

Ocular Surface Disease Index Questionnaire for Ocular Symptoms Subjective symptoms of ocular irritation were assessed by the 12-item OSID questionnaire. We modified the questionnaire by deleting the 4 and 5 items, which assess the existence of blurred and poor vision. Because it was difficult to distinguish the change of these symptoms caused by PPV alone or combined with PPV induced dry eye condition. OSDI score was calculated by the following formula: total points of all answered questions $\times 100$ / Total number of answered questions $\times 4$.

Keratography 5M Clinical examinations were all performed by the same ophthalmic technician using the Keratograph 5M under the manufacturer's instructions. All the ocular surface parameters were obtained preoperatively, 1, 2, 4, 8, and 12wk postoperatively. Additionally, all examinations were performed sequentially with 5min break as follows.

Tear Meniscus Height The subjects were instructed to look at a central target in the system and blink normally. The keratograph was set to "Tear film Scan (TF-Scan), tear meniscus" mode to capture an image of the ocular surface focused on the tear film following the manufacturer's instructions as previously reported^[9]. The central MH was measured manually by cursors provided by the system.

Noninvasive Tear Breakup Time Tear film stability was assessed in the "TF-Scan, NITBUT" mode. After manual focusing, the patients were asked to blink twice and then keep their eyes open as long as possible. At the same time, a video was recorded showing the presentation of tear film breakup over time. The NITBUT-first and NITBUT-average were generated automatically. The simultaneous time of the tear film starts to breakup was the NITBUT-first. NITBUT-average indicated the mean of all TBUTs occurring on the whole observed cornea.

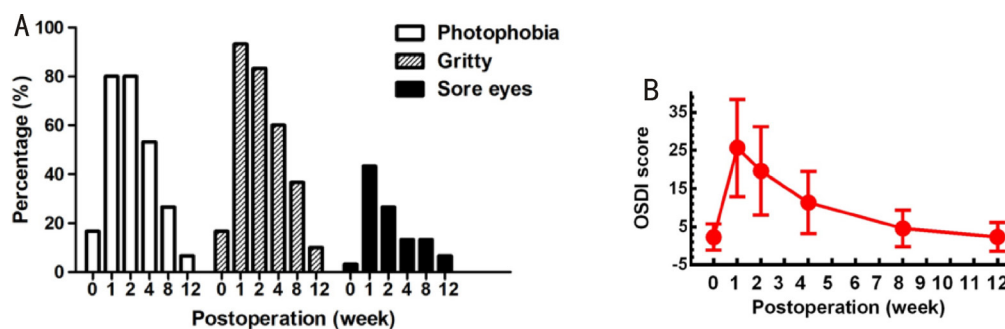


Figure 1 Changes of ocular surface symptoms and OSDI scores A: Changes in the distribution of photophobia, gritty and sore eyes; B: Change in OSDI score.

Table 1 Clinical parameters of preoperative and each visit postoperatively

mean±SD, n=30

Clinical parameters	Baseline	1wk	2wk	4wk	8wk	12wk
OSDI score	2.3±3.44	25.69±12.74	19.62±11.57	11.39±8.12	4.64±4.81	2.36±3.82
TMH (mm)	0.29±0.11	0.34±0.13	0.31±0.1	0.29±0.12	0.28±0.08	0.26±0.08
NITBUT-first (s)	12.11±3.28	4.58±1.7	6.52±2.58	8.86±2.82	10.65±2.8	12.46±3.11
NITBUT-average (s)	19.09±2.77	8.63±1.94	14.4±2.8	11.72±2.73	16.83±3.05	19.15±2.86
Bulbar redness score	1.66±0.5	2.69±0.74	2.24±0.67	1.98±0.65	1.71±0.47	1.57±0.43

OSDI: Ocular Surface Disease Index; TMH: Tear meniscus height; NITBUT: Noninvasive tear breakup time.

Bulbar Redness Bulbar redness was measured in the “R-Scan” mode. Subjects were instructed to focus on the light target. Then image of exposed bulbar conjunctiva was captured manually and the redness score was generated automatically. The score was calculated based on the area percentage ratio between blood vessels and the rest of the analyzed bulbar conjunctiva.

Statistical Analysis Statistical analysis was performed by SPSS 19.0 software. All values were expressed by mean±standard deviation (SD). The Kolmogorov-Smirnov test was applied to test the normality of the data. One-way analysis of variance and paired *t*-test were used for comparing differences in all variables. Chi-square test was used to analyze the percentages. Correlations between all variables were tested using Pearson’s correlation test. *P* values less than 0.01 were considered statistically significant.

RESULTS

Ocular Surface Symptoms and OSDI score Most patients complained of ocular surface discomfort after PPV, mainly including photophobia, gritty and sore eyes. Distributions of these symptoms during the follow-up were shown in Figure 1A. The percentages of either photophobia or gritty increased significantly at 1, 2, and 4wk postoperatively ($P<0.001$, <0.001 , 0.003 ; <0.001 , <0.001 , 0.001 , respectively), while they decreased to the preoperative levels in both 8 and 12wk postoperatively ($P=0.347$, 0.228 , 0.08 , 0.448 , respectively). The percentage of sore eyes in the first week

postoperatively was significantly higher than preoperation ($P<0.001$), but there were no significant differences between the percentages of pre-operation and 2, 4, 8, and 12wk postoperatively ($P=0.011$, 0.161 , 0.161 , 0.554 , respectively).

Table 1 showed the OSDI score at each visit and the change of OSDI score was shown in Figure 1B. Compared with the preoperative value, the OSDI scores were all significantly higher in 1, 2, and 4wk postoperatively ($P<0.001$, <0.001 , <0.001 , respectively), while they decreased to the preoperative level in 8 and 12wk postoperatively ($P=0.024$, 1 , respectively).

Ocular Surface Parameters Measured by Keratograph 5M

Table 1 summarized the ocular surface parameters at each visit, including TMH, NITBUT-first, NITBUT-average and bulbar redness score. In comparison with preoperative TMH, the values were higher within 2wk than preoperative, while there were no significant differences at every visit postoperatively ($P=0.012$, 0.336 , 0.665 , 0.508 , 0.088 , respectively). The change in TMH was shown in Figure 2A.

The change in NITBUT-first was shown in Figure 2B. NITBUT-first values in 1, 2, 4, and 8wk postoperatively were all significantly lower than preoperative (all $P<0.001$). However, there was no significant difference between the values in 12wk postoperatively and pre-operation ($P=0.172$). Similar to the changes in NITBUT-first and OSDI score, NITBUT-average was significantly shortened after PPV, but gradually improved as time passed (Figure 2C). The values in 1, 2, 4, and 8wk postoperatively were significantly lower

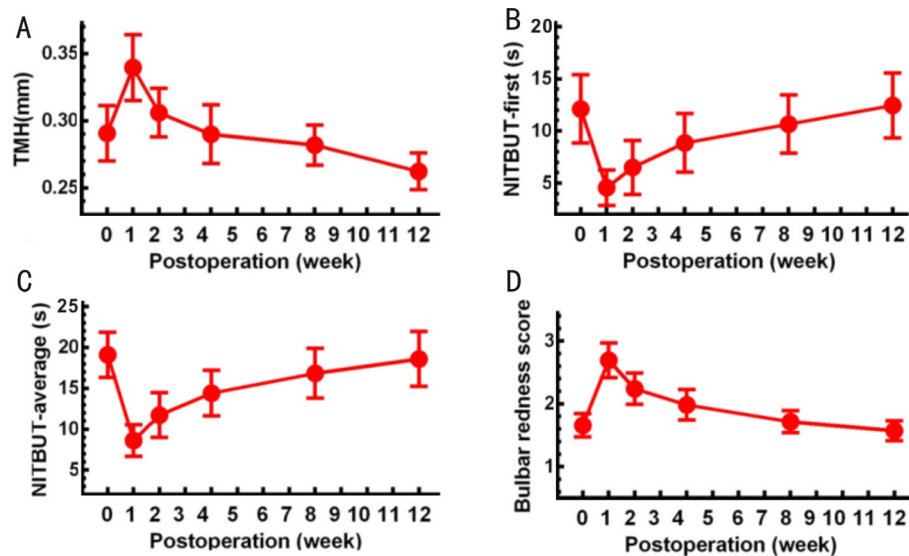


Figure 2 Changes of ocular surface parameters measured by Keratograph 5M A: Changes in TMH; B: Changes in NITBUT-first; C: Changes in NITBUT-average; D: Changes in bulbar redness.

than preoperative (all $P < 0.001$). However, the values were not significantly different between 12wk postoperatively and preoperative ($P = 0.781$). The change in the bulbar redness score was shown in Figure 2D. The score was significantly higher in 1, 2, and 4wk postoperatively than preoperative (all $P < 0.001$). However, compared to preoperative, there were no significant differences in both 8 and 12wk postoperatively ($P = 0.184$, 0.108 , respectively).

Correlations Between Clinical Parameters Correlations between all clinical parameters were analyzed. Significant positive correlation was found between NITBUT-first and NITBUT-average at each visit ($r = 0.548$, $P = 0.002$; $r = 0.586$, $P = 0.001$; $r = 0.58$, $P = 0.001$; $r = 0.587$, $P < 0.001$; $r = 0.634$, $P = 0.001$; $r = 0.584$, $P = 0.001$; respectively). In addition to this, we also found that TMH had a significant positive correlation with NITBUT-average ($r = 0.49$, $P = 0.006$) in the first week postoperatively.

DISCUSSION

Compared with other traditional methods, Oculus Keratograph is a noninvasive and objective method to assess the ocular surface, which is more likely to be applied in clinical practice with high practicability. Many studies reported that the stability of ocular surface was damaged after some surgery, causing dry eye related symptoms and signs, such as photorefractive keratectomy, laser in situ keratomileusis, and cataract surgery. In this study, we analyzed the changes of ocular surface after PPV *via* OSDI questionnaire, and measuring TMH, NITBUT and bulbar redness *via* keratograph 5M.

In the current study, we found many patients complained of eye discomfort, including photophobia and gritty, especially within 4wk postoperatively. Also, there were many patients complaining of sore eyes, especially in the first week. OSDI

questionnaire was used to assess symptoms of ocular surface subjectively in our study, which is one of the most commonly used questionnaires to assess dry eye. Our results showed that OSDI score increased significantly within 4wk after PPV, and it returned to preoperative level in 8 and 12wk postoperatively. This changing pattern corresponds with our clinical observation that few patients complain of eye discomfort after 4 weeks postoperatively. Tropicamide-phenylephrine (Mydrin-P, Santen) was provided for all patients routinely, which can lead to photophobia. Thus, the symptom of photophobia may be caused by both the PPV and Mydrin-P.

Schirmer test is a traditional method for detecting tear secretion, while it's an invasive operation which induces reflex tearing. A positive correlation between TMH and Schirmer test value has been reported^[10]. Thus, TMH can be considered as a noninvasive test for tear secretion and it's also a sensitive indicator of tear deficiency before dry eye appearance^[11]. Our study showed TMH increased 0.05 mm in 1wk and 0.02 mm in 2wk postoperatively which has little clinical significance, and there were no significant differences compared to preoperative. PPV induced stimulation of ocular surface may contribute to reflex tearing, such as surgical incisions, sutures, and bulbar conjunctival edema. Along with the incision healing, sutures absorption, conjunctival edema subsiding and trauma repair, tear secretion decreases and returns to the baseline level.

TBUT reflects the stability of tear film, which is an important index to evaluate dry eye^[12]. Fluorescein TBUT is widely used in clinical examination, while the fluorescein dye can destabilize the tear film and it has been reported that fluorescein BUT can be affected by the volume of fluorescein. Oculus Keratograph can detect the very early changes of the tear film and record very low NITBUT objectively with high

reliability and repeatability^[13-14]. Abdelfattah *et al*^[15] reported that NITBUT measured by Keratograph 4 can be substituted for the numerical fluorescein TBUT value. The present study recorded the changes of both NITBUT-first and NITBUT-average after PPV via Keratograph 5M. We found both of them were decreased significantly within 8wk postoperatively, especially in the first week, and recovered to the baseline levels gradually in 12wk postoperatively. Similar to our study, Servet *et al*^[16] reported that fluorescein TBUT impaired up to 1 month after phacoemulsification, followed by a recovering trend toward the preoperative level in 12wk. There was a significant positive correlation between NITBUT-first and NITBUT-average at each visit, demonstrating either of them can be used to evaluate tear film stability.

Golbet cells within conjunctival epithelium are special cells secreting mucins onto the ocular surface^[17]. Mucins secreted plays an important role in maintaining tear film stability, which can assist with removal of debris from the tear film and contribute to the hydrophilicity of tear film^[10-20]. Previous studies reported that the density of goblet cells didn't return to a preoperative level even at 3mo after cataract surgery^[21], but MUC5AC could recover to the preoperative level at 3mo after phacotrabeculectomy^[22]. Heimann *et al*^[23] reported that there was a significant decrease in MUC5AC positive goblet cells and distribution change of MUC1 in the conjunctival specimens of patients undergoing posterior segment surgery, which may contribute to the development of tear film instability and dry eye. The decrease in goblet cells has been reported to be correlated with the operative time of cataract surgery^[24]. Compared with cataract and glaucoma surgery, the operative time of PPV is longer, which may contribute to the decrease in goblet cells and tear film instability.

Operation induced damage to the cornea and conjunctiva destabilizes tear films. Intraoperative ocular surface manipulation, vigorous irrigation and microscopic light exposure were reported to be related to dry eye after cataract surgery^[25], which may be associated with reduced goblet cell density. Thus, we presumed that ocular surface damage during PPV contributed to the tear film instability. Additionally, surgical incisions, conjunctival sutures and edema lead to morphological changes of ocular surface, which may also affect tear distribution and leading to a decrease of tear film stability^[26]. In this study, we found there was moderate correlation between TMH and NITBUT-average just in the first week after PPV, demonstrating that the effect of surgery-induced reflex tearing on tear film instability was weak.

Benzalkonium chloride is the most common preservative used in eye drops. It can cause lots of ocular adverse effects, including dry eye, ocular inflammation, trabecular meshwork degeneration, and even optic nerve injury, which is associated

with its toxic effect^[27]. In our study, all three eye drops used postoperatively contained benzalkonium chloride which may also contribute to tear film instability and dry eye postoperatively. However, the influence of benzalkonium chloride on meibomian glands takes weeks. So, benzalkonium chloride may have little contribution to the tear film instability within 8wk postoperatively.

Bulbar redness is a common clinical sign after ophthalmic surgery, and it may reflect the response of ocular surface to pathogenic stimuli and the severity of inflammation. Fujita *et al*^[28] reported that IL-1 β , IL-6, and IL-8 increased significantly after PPV. Thus, inflammatory events of the ocular surface can be evaluated *via* detecting bulbar redness. In clinical practice, bulbar redness is mainly assessed by photographic scales, including Institute for Eye Research scale, the Efron scale, and the Validated Bulbar Redness grading scale^[29]. Unlike the image-based scales, Keratograph is the first commercially available device that can evaluate bulbar redness by analyzing the captured images automatically and objectively. Wu *et al*^[30] reported that its reproducibility was much higher than the other three image-based scales for evaluating bulbar redness. In our study, the bulbar redness score increased significantly within the 4wk postoperatively, but it recovered to the preoperative level in 8wk postoperatively. These results correspond with our clinical observation that most patients complain of eye discomfort within the 4wk after PPV, especially within the 2wk postoperatively. However, the sample size of this study is very small, which needs to be expanded. Also, another study on 25-gauge PPV without sutures needs to be carried out further to exclude the impact of sutures and PPV associated risk factors will be analyzed further to reduce ocular surface damage.

In conclusion, to the best of our knowledge, this is the first study to evaluate the ocular surface after PPV via noninvasive Keratograph, including tear film and bulbar redness. Our results demonstrated that PPV caused various changes in the symptoms and signs of ocular surface damage at an early stage, while these changes returned to preoperative levels gradually afterwards. This study can serve as a guide for further treatment of ocular surface after PPV^[31].

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