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ORIGINAL RESEARCH

Alterations in the Ocular Surface and Corneal Subbasal Nerve Plexus Following Various Retinal Surgical Procedures: A One-Year Confocal Microscopy Prospective Study

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Purpose: To evaluate the effects of retinal surgery on the ocular surface and corneal subbasal nerve plexus (SNP).

Methods: Ninety-eight patients undergoing 23-gauge pars plana vitrectomy for various vitreoretinal disorders were prospectively studied. We collected detailed operative and perioperative data, measuring dry eye syndrome (DED) severity and Ocular Surface Disease Index (OSDI) scores before surgery and at postoperative intervals. In vivo confocal microscopy (IVCM) quantified SNP and dendritic cell (DC) densities.

Results: Fifty-three patients were analyzed. Post-surgery, OSDI scores rose from a baseline of 5.5 ± 3.5 to 12.24 ± 6.5 at one month, later reducing to 7.8 ± 4.0 after a year. DED severity increased from 0.6 ± 0.6 initially to 1.6 ± 0.6 at three months, returning to near baseline (0.9 ± 0.6) one year after surgery. DC densities increased notably by the third (58.85 ± 75.6 cells/mm²) and ninth (59.95 ± 86 cells/mm²) postoperative months, especially in patients undergoing combined phacoemulsification, vitrectomy, and C3F8 gas tamponade. SNP parameters, particularly nerve fiber density and length, showed significant declines one month post-surgery, not recovering to baseline levels within a year. Fiber density dropped from 19.06 ± 8.3 fibers/mm² preoperatively to 4.68 ± 4.8 fibers/mm² at one month, partially recovering to 10.64 ± 8.2 fibers/mm² at twelve months. Fiber length decreased from 13.31 ± 3.2 mm/mm² to 6.86 ± 3.4 mm/mm² at one month, later improving to 9.81 ± 4.5 mm/mm² at twelve months, notably in patients with silicone oil (SiO2) tamponade.

Conclusion: Retinal surgery, especially when combined with phacoemulsification and C3F8 or SiO2 tamponade, significantly affects ocular surface integrity and SNP density, with these changes lasting up to a year. Expanded studies with more patients and longer follow-up, using finer 25- and 27-gauge vitrectomy tools, are recommended to confirm and extend these findings.

Keywords: corneal subbasal nerve plexus, ocular surface, retinal surgical procedures, confocal microscopy, dry eye syndrome after vitrectomy, intraocular surgery

Introduction

Internal vitreoretinal surgeries are critical for treating a range of retinal conditions, from retinal detachments (RD) and macular holes (MH) to complications of diabetic retinopathy (DR).[1] As these surgeries become more complex and frequent, there is an increased focus on the potential ocular surface complications they may entail, including postoperative dry eye, persistent corneal epithelial defects, and loss of endothelial cells.[2–8] These postoperative conditions not only impede the recovery of visual acuity but also diminish patient satisfaction and overall quality of life following surgery.[9]

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Significant advancements have been made in refining surgical techniques, including the development of more precise surgical instruments and the improvement of ocular irrigation solutions. However, corneal complications after vitreoretinal surgery continue to be reported, with reported incidence rates varying from 6% to 50.5%.[3–6] These complications arise from multiple factors, ranging from pre-existing conditions like dry eye disease (DED) to factors related to the surgical intervention itself, including the use of intraocular tamponades such as gas or silicone oil.[10,11] This diversity in causes underscores the importance of enhanced surgical techniques and postoperative care in reducing the prevalence and impact of corneal complications.

The corneal subbasal nerve plexus (SNP) is pivotal for ocular health, significantly affecting sensation and safeguarding the ocular surface.[12–14] Despite its importance, limited research has been conducted on the postoperative changes in the corneal SNP following vitreoretinal surgeries. In vivo confocal microscopy (IVCM) emerges as a cutting-edge imaging technique, providing non-invasive, high-resolution views of corneal cellular structures. By exploiting its capacity to examine cellular configurations, notably the corneal SNP, IVCM serves as a critical tool for identifying microstructural changes after surgery.[15] Yet, comprehensive insights into how advanced surgical methods, such as the 23-gauge pars plana vitrectomy (PPV) for vitreoretinal disorders, affect corneal nerve integrity are lacking. Our study aims to bridge this gap by exploring postoperative alterations in corneal nerve fibers, underscoring the need for thorough postoperative evaluations of the ocular surface to understand the full extent of surgical impacts.

Method

Participants

Between September 2010 and January 2012, a total of 98 consecutive patients diagnosed with retinal diseases and scheduled for vitreoretinal surgeries were recruited for this prospective study at the EYE & ENT Hospital of Fudan University. Each participant gave their informed consent after being thoroughly informed about the purpose of the study before inclusion. The study adhered strictly to the principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board and the Ethics Committee of the EYE & ENT Hospital (approval no. 2010-YS-015).

The inclusion criteria required individuals to be aged 18 years or older, have no history of prior ocular surgeries, eye trauma, or any conditions or drug histories that could influence corneal nerve health or visualization. Exclusion criteria included individuals with prior vitrectomy, corneal surgeries, or other ocular procedures, those undergoing systemic or ocular treatments that could affect corneal sensation or nerve structure, those with difficulties in obtaining clear IVCM images, or those with pre-existing corneal conditions that could degrade the quality of imaging. For inclusion in the final analysis, patients were required to attend at least one follow-up visit beyond the six-month postoperative assessment. Those who missed follow-up sessions at 6, 9, or 12 months, or had fewer than three follow-up examinations, were excluded from the final analysis.

Preoperative Examinations and Assessment of Ocular Surface Disease

Patients underwent standard ophthalmic evaluations prior to surgery. Assessments included best-corrected visual acuity (BCVA), spherical equivalent refraction (SER), and a non-contact intraocular pressure (IOP) measurement (Canon Full Auto Tonometer TX-F; Canon, Inc., Tokyo, Japan). Additionally, a comprehensive slit-lamp examination, inclusive of a fundus check, was conducted. To assess the ocular surface integrity, patients underwent three consecutive Tear break-up time (TBUT) tests, followed by a fluorescein staining test and a 5-minute Schirmer I test, all administered without anesthesia.

In preparation for the IVCM test, patients completed a Chinese translation of the Ocular Surface Disease Index (OSDI) questionnaire,[16] which evaluates the impact of DED on daily living. Subsequently, dry eye severity for each patient was classified according to the 2007 DEWS criteria.[17]

Surgical Technique

A singular vitreoretinal surgeon (R.J) performed all vitrectomy and phacovitrectomy procedures, utilizing a noncontact panoramic viewing system (RESIGHT 700; Carl Zeiss Meditec, AG, Germany). Patients received local anesthesia via a retrobulbar block technique. Combined phacoemulsification and 3-port conventional 23-gauge pars plana vitrectomy

were performed using the Constellation vision system (Alcon Laboratories, Fort Worth, TX) and, separately, a 23-Gauge transconjunctival sutureless vitrectomy was performed through Alcon's one-step system. For surgical access, the conjunctiva was displaced, and 30° angled incisions were made 3.5–4 mm away from the corneoscleral junction. These incisions were aligned parallel to the corneoscleral limbus using a unified 23-Gauge blade-trocar system. For cataract-afflicted patients, phacoemulsification was conducted with or without intraocular lens (IOL) implantation ahead of the core vitrectomy. During the surgery, the posterior hyaloid membrane was consistently removed and any remnant posterior vitreous was identified with triamcinolone acetonide (Xudong Haipu Pharmaceuticals, Co., Ltd., Shanghai, China). Perfluorocarbon liquid (PFCL) was employed for patients with RD to stabilize the retina for improved vitreous base trimming. For cases involving myopic foveoschisis (MF), macular hole (MH), and ERM, the internal limiting membrane (ILM) and epiretinal membrane (ERM) were stained using 0.3 mL BB dyd (Fluoron GmbH, Ulm, Germany), followed by a fluid-to-air exchange. The surgical conclusion involved the injection of pure air, an air-gas blend (C3F8), or Silicone oil (SiO2, Oxane 5700 cSt, Bausch and Lomb, Toulouse, France, in 7/50 eyes), dependent on the surgeon's judgment. Postoperative care included prescribing antibiotic and steroid eye drops, along with mydriatic eye drops, to be administered three times daily for a month. Intraocular pressure-modulating eye drops were also prescribed based on individual IOP readings.

Corneal Nerve Exploration via Confocal Microscopy

After preliminary clinical assessments, an in-depth examination of the central corneal SNP was conducted using IVCM with the Heidelberg Retina Tomograph III. With a specific focus on the corneal apex, established protocols guided the SNP assessment.[18–20] Each imaging session captured 100 frames at a rate of three frames per second, targeting the SNP layer. The evaluations were consistently executed by an adept investigator (Q.L W), ensuring the corneal apex's precise imaging by emphasizing patient eye alignment, thereby mitigating alignment-related variances.

For image selection, we systematically chose five images per eye, all from the central cornea, to represent the corneal SNP. These images were meticulously selected by two unbiased reviewers (Q.L W and X.J Z), prioritizing criteria such as clarity, optimal contrast, and the absence of motion artifacts. Using the cell count tool from Heidelberg, the density of dendritic cells (DCs), expressed as cells/mm², was manually derived by highlighting unique dendritiform structures present in the SNP layer. This quantification process encompassed all dendritic cells within the examined images, without differentiation between immature and mature DCs. To identify DCs, we utilized established morphological criteria, such as their dendritiform shape, branching patterns, and characteristic appearance within the SNP. These criteria were applied consistently by two independent reviewers (Q.L W and X.J Z), ensuring the accuracy and reliability of DC identification and quantification.

Evaluation Procedure for Subbasal Nerve Fibers

The ACCMetrics software (MA Dabbah, Manchester, UK)[21,22] served as our primary tool for image assessment, automatically generating a range of metrics. These metrics encompassed seven crucial parameters pertaining to the characteristics of corneal nerve fibers, spanning from density values to intricate structural attributes. Specifically, these parameters included:1. Corneal Nerve Fiber Density (CNFD): Representing the total presence of nerve fibers (number per mm²) within the SNP layer; 2.Corneal Nerve Branch Density (CNBD): CNBD quantifies the density of nerve axon branches (number per mm²) within the SNP layer;3.Corneal Nerve Fiber Length (CNFL): CNFL measures the length of nerve fibers (mm/mm²) within the SNP layer;4.Corneal Nerve Total Branch Density (CTBD): CTBD represents the overall density of nerve branches (total branches/mm²) within the SNP layer; 5.Corneal Nerve Fiber Area (CNFA): CNFA expresses the area occupied by nerve fibers (mm²/mm²) within the SNP layer;6.Corneal Nerve Fiber Width (CNFW): CNFW measures the width of nerve fibers (mm/mm²) within the SNP layer;7.Corneal Nerve Fractal Dimension (CNFrD): CNFrD, a dimensionless parameter, characterizes the complexity and irregularity of the corneal nerve fiber pattern within the SNP layer.

In the analytical phase, five selected images underwent meticulous evaluation by an expert assessor (Q.L W). The ensuing statistical analyses incorporated the mean values obtained from these images for each specified parameter.

Postoperative Follow-Up Procedures and Management

Scheduled postoperative follow-up visits were established at intervals of 1 week, 1, 3, 6, 9, and 12 months. During these scheduled visits, multiple assessments were undertaken, including: (1) BCVA; (2) comprehensive fundus examination; (3) IOP monitoring-with any patient recording an IOP exceeding 21 mmHg being prescribed pressure-lowering medications and receiving an additional appointment the succeeding week for reevaluation,(4) An encompassing ocular surface examination that included TBUT, corneal staining, Schirmer's test, DED severity grading, and the OSDI, and; (5). IVCM assessments at 1, 3-, 6-, 9-, and 12-months post-surgery.

Should complications arise, such as the detection of recurrent retinal detachment, the treating surgeon had the discretion to reintroduce C3F8 gas or alternatively perform a subsequent vitrectomy using SiO2, contingent on the patient's clinical presentation. For those manifesting sustained elevated IOP following SiO2 instillation, a proactive SiO2 extraction might be deemed necessary. All executed procedures and their subsequent outcomes were meticulously recorded within the patient's medical dossier.

Statistical Analysis

Statistical analyses were conducted using SPSS software (version 23.0, SPSS, Inc., Chicago, IL, USA). All data were presented in the format of mean ± standard deviation. Through the application of a repeated-measures ANOVA, comparisons were drawn between pre- and post-operative data, considering metrics such as OSDI score, DED severity, TBUT, Schirmer's test, DCs density, and IVCM SNP, all delineated by ACCMetrics. In instances where significant variances surfaced, post-hoc evaluations were carried out utilizing the Tukey's Honest Significant Difference (HSD) methodology. A threshold of p-value less than 0.05 was established for statistical relevance. For graphical representation of the shifts in the previously mentioned metrics, GraphPad Prism version 9.0.0 for Windows was employed. A mixed-effects model, designed for repeated measures, was invoked to assess the impact of various factors including patient age, gender, presence of retinal and systemic diseases, number of surgeries, and the duration of each surgery on surgery-induced changes in ocular surface evaluations, and on the densities of corneal SNP and DCs. This model was also leveraged for contrasting these changes among diverse groups, setting significance at correlations producing p-values below 0.05.

Results

The final analysis was conducted on a dataset of 53 eyes from 53 distinct patients. Of the 45 patients excluded from the final analysis, the data for 12 who had completed the 12-month follow-up were unavailable owing to a technical malfunction in the computer hardware. Additionally, 33 participants were excluded for not attending at least one follow-up visit after their six-month postoperative assessment. The adherence rates to the scheduled follow-ups at 1, 3, 6, 9, and 12 months were 96% (51/53), 91% (48/53), 72% (38/53), 49% (26/53), and 83% (44/53), respectively. The median age of our sample was 55.74±9.9 years, of which 33 were female. Out of these, 9 had a diagnosis of diabetes, 15 had hypertension, and 18 presented with high myopia. The retinal conditions diagnosed were as follows: MH (n=1), RD (n=35, 7 associated with MH), VH (vitreous hemorrhage, n=9; 7 due to branch retinal vein occlusion, 2 due to polypoid choroidal vasculopathy), ERM (n=5), ARN (acute retinal necrosis, n=2), and MF (n=1).

Patients were categorized into groups based on the type of tamponade used and the surgical procedures performed. Group 1 consisted of patients who underwent vitrectomy with air tamponade (Air), Group 2 with C3F8 tamponade (C3F8), Group 3 with SiO2 tamponade (SiO2), Group 4 underwent vitrectomy and phacoemulsification with C3F8 tamponade (Phaco+C3F8), Group 5 received vitrectomy, phacoemulsification, intraocular lens implantation, and C3F8 tamponade (Phaco+IOL+C3F8), and Group 6 underwent vitrectomy, phacoemulsification, and SiO2 tamponade (Phaco+SiO2). Table 1 and Table 2 provide an overview of the treatment groups SiO2 and Phaco+SiO2, respectively, including demographic and preoperative data. A notable difference in average age was observed among the groups, with Group 5 averaging 63.2 years and Group 3 at 50.7 years. The majority of patients in Groups 2, 4, and 5 underwent a single surgery, whereas some individuals in Group 6 experienced up to five surgeries. The longest average surgical duration was noted in Group 3 at 157.1 minutes, in contrast to Group 2's average of 58.5 minutes. Significant disparities in the number of surgeries and their durations were observed across the groups, with statistical significance (P<0.001).The findings of the postoperative OSDI

Table 1 Detailed Overview of Patient Treatment in SiO2 and Phaco+SiO2 Groups

Group/ Patients	Gender	Age	Conditions	Initial Treatment	Subsequent Treatments (Time Since 1st Surgery)	SiO2 Removal at 12-Month End
SiO2						
1	F	58	RD, HM	SiO2 injection	SiO2 removal (6 months)	Yes
2	M	51	ARN, HBP	SiO2 injection	SiO2 removal (8 months)	Yes
3	F	39	RD, HM	C3F8	SiO2 (1 month), Phaco+SiO2 (7 months)	No
4	M	49	RD, DM, HBP, HM	C3F8	SiO2 (3 months), SiO2 removal (8 months)	Yes
5	F	53	MH-RD, HM	SiO2 injection	Partial SiO2 removal (4 months)	No
6	M	50	MH-RD, HM	SiO2 injection	Phaco+SiO2 (8 months)	No
7	M	55	RD, HBP, HM	C3F8	SiO2 (3 weeks), Phaco+SiO2 (7 months)	No
Phaco+SiO2						
1	F	64	RD	C3F8	Phaco+SiO2 (1 month)	No
2	M	47	RD, DM, HM	Phaco+SiO2 injection	SiO2 removal (4 months)	Yes
3	M	47	RD, HBP, HM	Phaco+SiO2 injection	SiO2 removal due to emulsification (4 months)	Yes
4	F	56	MH-RD	Phaco+SiO2 injection	None	No
5	M	32	RD	C3F8	SiO2 (2 weeks), Phaco+SiO2 (4 months), SiO2 removal (9 months), SiO2 injection (10 months), SiO2 removal (12 months)	Yes
6	F	68	BRVO-VH, DM	Phaco+air	SiO2 (2 months), SiO2 removal (8 months)	Yes
7	F	71	MH-RD, HM	Phaco+SiO2 injection	SiO2 removal due to high IOP (12 months)	Yes
8	M	66	VH, DM, HBP	Phaco+SiO2 injection	SiO2 removal (8 months)	Yes
9	M	57	RD, HM	Phaco+SiO2 injection	SiO2 removal (9 months)	Yes
10	M	57	RD, DM	Phaco+SiO2 injection	None	No
11	F	49	ARN	Phaco+SiO2 injection	SiO2 removal (11 months)	Yes

Abbreviations: SiO2, Silicone oil; Phaco+SiO2, Phacoemulsification combined with silicone oil injection; RD, Retinal detachment; HM, High myopia; ARN, Acute retinal necrosis; HBP, High blood pressure; DM, Diabetes mellitus; MH-RD, Macular hole induced retinal detachment; BRVO-VH, Branch retinal vein occlusion-induced vitreous hemorrhage; VH, Vitreous hemorrhage.

Table 2 Overview of Preoperative Diagnoses and Patient Demographics Across Groups

Demographical Data	Group 1 (Air Tamponade)	Group 2 (C3F8 Tamponade)	Group 3 (Silicone Oil Tamponade)	Group 4 (Phaco, C3F8 Tamponade)	Group 5 (Phaco +IOL, C3F8 Tamponade)	Group 6 (Phaco, Silicone Oil Tamponade)	*P**
Eye(n)	9	12	7	9	5	11	
Age(years)	55. 6±9.3	54.4±10.3	50.7±6.0	62.7±6.5	63.2±5.2	55.8±11.5	0.020
Sex(female/male)	5/4	8/4	3/4	7/2	5/0	5/6	0.259
Number of surgeries(range)	1.2±0.4(1–2)	1±0(1)	2.3±0.8(1–3)	1±0(1)	1±0(1)	2±1.2(1–5)	0.000
Surgical Duration(minutes)	66.7±25.9	58.5±8.5	157.1±25.6	72.7±9.1	62.8±10.6	115.9±33.8	0.000
Diagnosis							
Retinal detachment (with/without macular hole)	0/1	1/11	2/4	4/4		2/6	
Macular hole	–	–	–	–	1	–	
Vitreous hemorrhage	3	–	–	1	3	2	
Epiretinal membrane	4	–	–	–	1	–	
Acute retinal necrosis	–	–	1	–	–	1	
Retinoschisis	1	–	–	–	–	–	
Systemic diseases							
Diabetes(n)	1	0	1	1	2	4	
Hypertension	2	2	3	4	2	2	
High myopia	4	0	6	4	0	4	

Notes: *Analysis conducted using a univariate analysis of variance (ANOVA), with statistical significance denoted as $P < 0.05$.

scores, DED severity, TBUT results, and Schirmer's test are detailed in Table 3 and the associated Figure 1. The OSDI scores significantly increased postoperatively, peaking at one month, then declined, approaching near-baseline values by the twelfth month (P<0.001). DED severity similarly escalated after surgery, reaching a maximum at three months and subsequently diminishing to baseline levels by the end of the year (P=0.005). TBUT results fluctuated marginally over the course of the year without showing statistical significance (P=0.144). Schirmer's test values initially decreased, registering the lowest at three months, but showed recovery in subsequent months.

Following the surgical intervention, significant changes in corneal SNP parameters and DCs density were recorded, as outlined in in Table 3, Figures 2, and 3. Specifically, there was a marked increase in DCs density from a pre-operative average of 19.46 cells/mm^2, peaking at 58.85 cells/mm^2 by the third month. However, this increased density subsided to 36.94 cells/mm^2 by the twelfth month (P=0.000). In contrast, CNFD showed a considerable decline from 19.06 nerves/mm^2 pre-surgery to 4.68 nerves/mm^2 in the first post-operative month. Notably, it rebounded to 10.64 nerves/mm^2 by the twelfth month (P=0.000). CNBD also saw a decline from a pre-surgical 27.20 axons/mm^2 to 5.90 axons/mm^2 in the first month, eventually recovering slightly to 14.73 axons/mm^2 by the twelfth month (P=0.001). CNFL declined from 13.31 mm/mm^2 pre-surgery to 6.86 mm/mm^2 in the first month but exhibited a gradual increase, reaching 9.81 mm/mm^2 by the end of the year (P=0.000). CTBD dropped from 45.20 branches/mm^2 to 20.57 branches/mm^2 in the first month and made a steady recovery, registering 32.49 branches/mm^2 by the twelfth month (P=0.001). Meanwhile, CNFA dropped to 0.0046 mm^2/mm^2 in the first month from 0.0065 mm^2/mm^2 pre-surgery and maintained relative consistency thereafter (P=0.038). CNFW witnessed a marginal fluctuation, with an increase from 0.0226 mm/mm^2 pre-surgery to 0.0248 mm/mm^2 in the first month, subsequently stabilizing by the twelfth month (P=0.001). In contrast, CNFrD initially decreased from 1.473 pre-surgery to 1.404 in the first month but saw a modest rise, settling at 1.433 by the twelfth month (P=0.004).

Employing a repeated measures mixed-effects model, it was discerned that factors such as patients' age, gender, retinal disease type, systemic disease presence, surgery number, duration, IOP, and the application of IOP-lowering medication bore no significant impact on post-surgical alterations in corneal SNP parameters and DCs density (all P>0.05). An anomaly was observed in CNFW, where patients with DM displayed a more significant post-surgical elevation compared to their non-DM counterparts (P=0.0177). No correlations were identified between ocular surface assessments and these parameters (all P>0.05), save for one: a notable positive correlation between post-surgical OSDI score shifts and patients' IOP (P=0.000).

In assessing post-operative alterations in DCs density, the Phaco+C3F8 group manifested the most pronounced increase, markedly surpassing the other five groups (all P<0.000). There were no discernible differences in post-operative

Table 3 Overview of Ocular Surface Assessment Parameters and Corneal Nerve Characteristics Before and After Surgery

Parameter	Before Surgery	After Surgery					*P**
		Month 1	Month 3	Month 6	Month 9	Month 12	
Eyes(n)	53	50	45	40	27	12	
OSDI score	5.5±3.5	12.24±6.5	11.2±4.9	8.90±4.5	9.2±3.9	7.8±4.0	0.000
DED severity	0.6±0.6	1.4±0.7	1.6±0.6	1.2±0.6	1.2±0.7	0.9±0.6	0.005
TBUT(s)	6.1±2.7	6.4±2.8	5.0±2.2	6.9±2.5	6.9±2.3	7.8±2.3	0.144
Schimer's test(mm)	10.21±5.4	8.75±4.3	7.38±3.4	10.36±5.0	9.52±4.1	12.05±5.0	0.033
DCs density(cells/mm2)	19.46±29.6	46.94±73.4	58.85±75.6	48.50±97.5	59.95±86	36.94±71.85	0.000
CNFD (number /mm^2)	19.06±8.3	4.68±4.8	6.23±6.3	8.57±7.3	8.05±7.1	10.64±8.2	0.000
CNBD (number/mm$^{2)}$	27.20±22.21	5.90±10.14	7.87±10.4	9.68±10.7	10.62±15.0	14.73±16.7	0.001
CNFL (mm/mm^2)	13.31±3.2	6.86±3.4	7.14±3.4	8.56±4.0	8.51±3.6	9.81±4.5	0.000
CTBD (total branches/mm^2)	45.20±29.5	20.57±21.9	21.34±18.9	25.78±20.1	28.32±19.2	32.49±29.7	0.001
CNFA (mm$^{2/}$ mm^2)	0.0065±0.002	0.0046±0.003	0.0049±0.003	0.0046±0.002	0.0048±0.002	0.0049±0.003	0.038
CNFW (mm$^/$ mm^2)	0.0226±0.002	0.0248±0.003	0.0242±0.003	0.0237±0.003	0.0243±0.004	0.0234±0.003	0.001
CNFrD	1.473±0.03	1.404±0.07	1.413±0.07	1.417±0.07	1.424±0.06	1.433±0.06	0.004

Notes: *Analysis conducted using a univariate analysis of variance (ANOVA), with statistical significance denoted as $P < 0.05$.
Abbreviations: DCs,dendriform cell density; CNFD, corneal nerve fiber density; CNBD, corneal nerve branch density; CNFL, corneal nerve fiber length; CTBD, corneal nerve total branch density; CNFA,corneal nerve fiber area; CNFW,corneal nerve fiber width; CNFrD, corneal nerve fractal dimension.

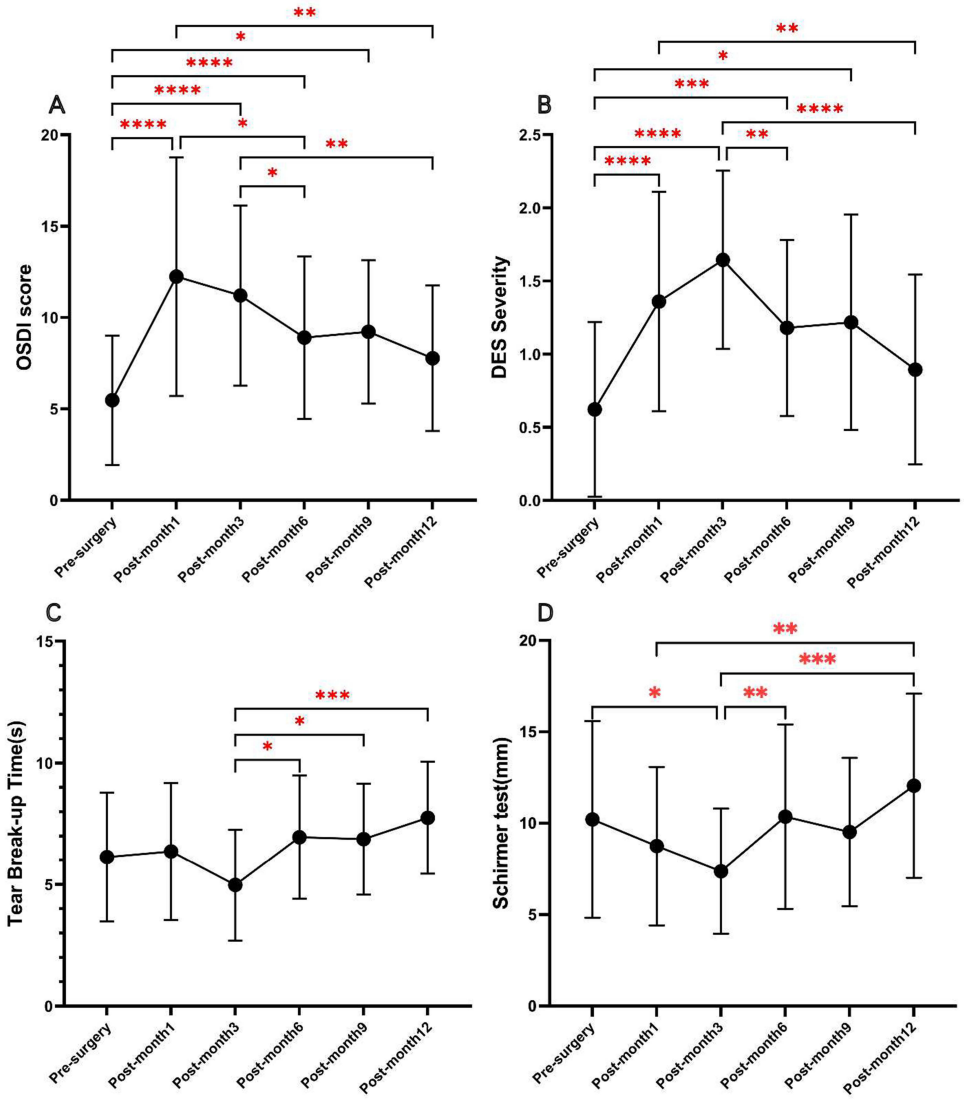

Figure 1 Longitudinal Analysis of Ocular Surface Parameters Post-Vitreoretinal Surgery. This figure depicts the trend changes in Ocular Surface Disease Index (OSDI) scores (**A**), Dry Eye Syndrome (DES) severity (**B**), Tear Break-up Time (TBUT) in seconds (**C**), and Schirmer Test results in millimeters (**D**) before and after vitreoretinal surgery. Differences over time were analyzed using repeated-measures ANOVA with Tukey's Honestly Significant Difference (HSD) test for post-hoc analysis. A p-value of less than 0.05 was considered statistically significant. Levels of significance are indicated by asterisks: *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

alterations for CNFD, CNBD, and CNFA across groups. The Phaco+SiO2 group evidenced significant reductions in CNFL and CTBD when juxtaposed with the Air group (P=0.0175, P=0.0491). In the domain of CNFW, both the C3F8 and Air groups portrayed notably larger CNFW values than other groups, achieving a significance level of P<0.05. Regarding CNFrD, the Phaco+SiO2 and SiO2 groups both recorded significant declines when juxtaposed with the Phaco +C3F8 group (P=0.0027, P=0.0125). In the context of DES severity, the C3F8+IOL+Phaco group exhibited heightened DES severity when contrasted with all five other groups, registering a significant variance. Similarly, the C3F8 group showcased an increased DES severity relative to the Phaco+SIO2 and SIO2 groups. Moreover, patients undergoing the Phaco+C3F8 procedure exhibited significantly elevated OSDI scores in comparison to those subjected to the Air procedure (P=0.0408).

Discussion

As advancements in intraocular surgeries, particularly vitrectomies, continue to develop, there's a growing concern about their impact on ocular surface health.[23–25] Such postoperative complications can significantly influence both a patient's

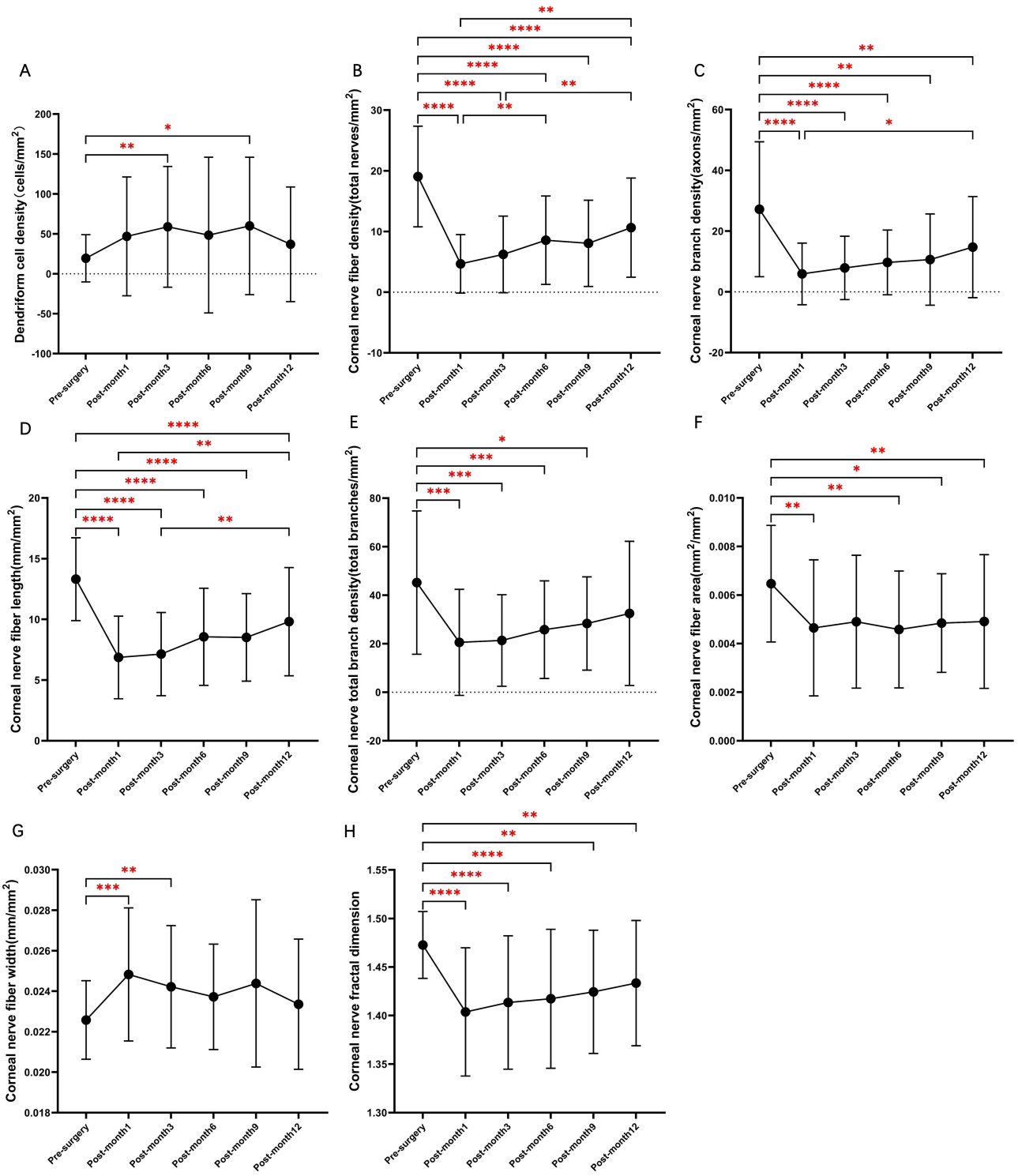

Figure 2 Assessment of Corneal Nerve Parameters and Dendriform Cell Density Post Surgery. The figure illustrates the changes over time in Dendriform Cell Density (**A**), Corneal Nerve Fiber Density (**B**), Corneal Nerve Branch Density (**C**), Corneal Nerve Fiber Length (**D**), Corneal Nerve Total Branch Density (**E**), Corneal Nerve Fiber Area (**F**), and Corneal Nerve Fiber Width (**G**), and Corneal Nerve Fiber Reflection (**H**) following surgical intervention. The data were analyzed using repeated-measures ANOVA with post-hoc Tukey's Honestly Significant Difference (HSD) test. Statistical significance is indicated by asterisks: *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

quality of life and their overall satisfaction with the procedure. This concern becomes even more pronounced within the aging population. They often grapple with retinal diseases that are further complicated by a myriad of systemic conditions. It is vital, therefore, to deeply understand the complex relationship between vitrectomy surgery and ocular

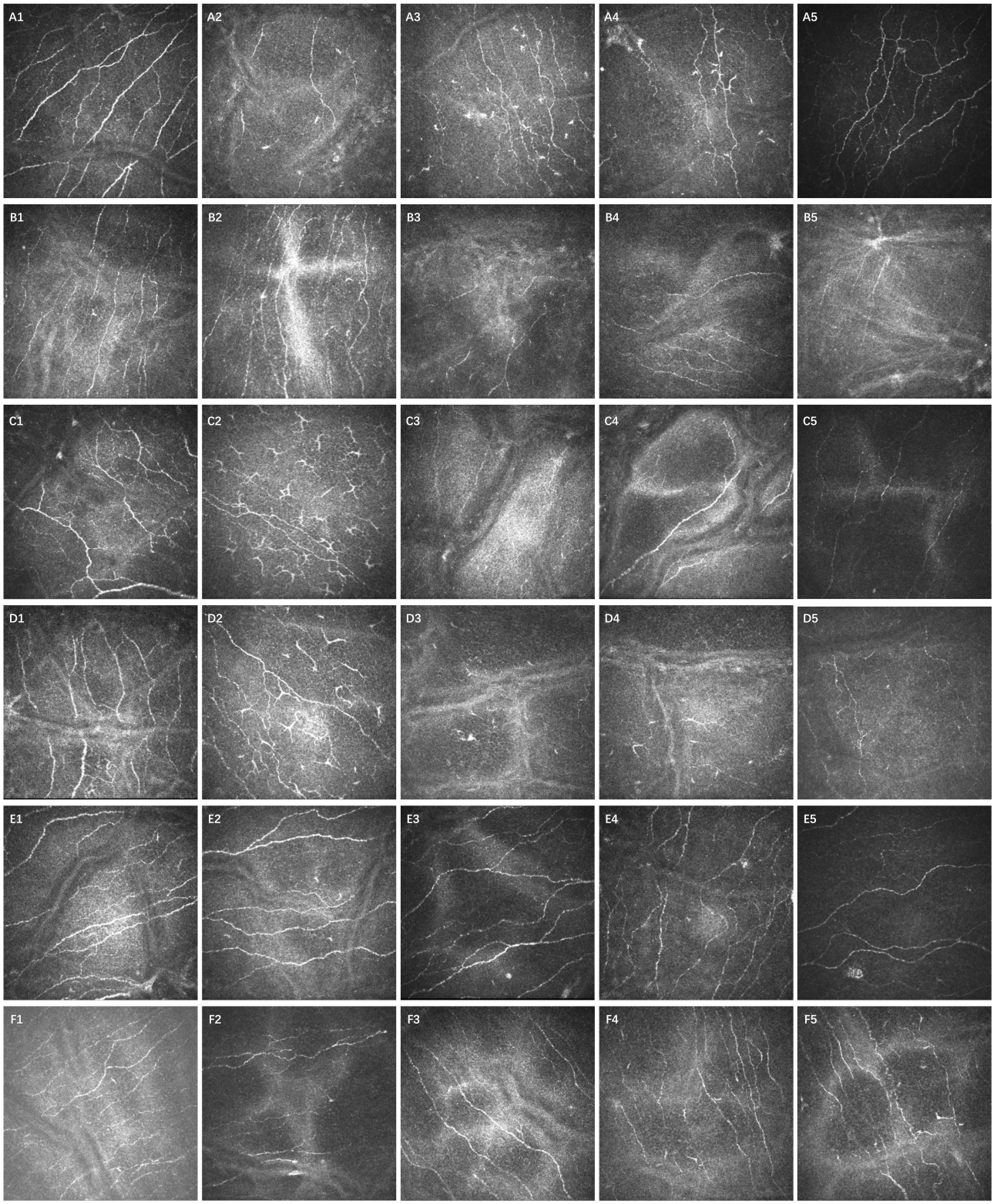

Figure 3 In Vivo Confocal Microscopy (IVCM) Images of Post-Vitrectomy Ocular Changes. The provided IVCM images capture the post-vitrectomy alterations in dendritic cells (DCs) and corneal subbasal nerve plexus (SNP) patterns in patients with retinal diseases under different vitrectomy procedures. Columns, sequentially from left to right, depict changes pre-surgery, and at 1, 3, 6, 9, and 12 months postoperative. **A1-A5** series corresponds to a 60-year-old male treated with vitrectomy and C3F8 tamponade for retinal detachment. **B1-B5** is from a 57-year-old female who underwent phacoemulsification, intraocular lens insertion, and vitrectomy with C3F8 tamponade for vitreous hemorrhage. **C1-C5** represents another 57-year-old female treated with phacoemulsification and vitrectomy using C3F8 for a macular hole-related retinal detachment. **D1-D5** captures the progression in a 47-year-old male post phacoemulsification and vitrectomy with SiO2 tamponade for retinal detachment. **E1-E5** documents a 50-year-old male treated with vitrectomy and SiO2 for a macular-related detachment. Lastly, **F1-F5** shows a 39-year-old female post vitrectomy with an air tamponade for an epiretinal membrane. The evident increase in DCs and corneal modifications emphasize the surgery's lasting influence on ocular health.

surface health, especially in this sensitive demographic. Our examination of 53 eyes from patients with vitreoretinal conditions provides insights into the consequences of diverse vitrectomy procedures, with an emphasis on ocular surface health and alterations in corneal SNP and DCs. A key feature of our study is the detailed examination of ocular surface parameters after vitrectomy, alongside alterations in corneal SNP and DCs, across different surgical techniques.

In clinical practice, numerous patients report experiencing eye irritation, sensations of foreign bodies, visual disruptions, and tear film dysfunction following vitrectomy surgery. Despite the prevalence of these complaints, there is a scarcity of literature that quantitatively assesses patients' experiences and grades the resultant ocular surface damage. The OSDI is a universally recognized and validated questionnaire specifically crafted to measure the severity of symptoms related to ocular surface diseases, notably dry eye.[16] The OSDI provides valuable insights into ocular discomfort and visual disturbances, rendering it indispensable for assessing post-surgical outcomes. Similarly, the DED severity grading allows for an objective evaluation of clinical manifestations associated with dry eye, such as tear film irregularities and ocular surface damage.[17]

In this study, the OSDI and DED severity grading were employed to thoroughly evaluate ocular surface health before and after vitrectomy, uncovering significant ocular alterations. Notably, a marked increase in OSDI scores was observed postoperatively, with the highest levels recorded in the first month after surgery before showing a decline. This discomfort is attributed not only to dry eye but also to factors including sensations at the surgical site, intraocular pressure (IOP) fluctuations, and the intrinsic trauma of the surgery. Similarly, DED severity showed a marked rise after surgery, reaching its peak in the third postoperative month.

Postoperative changes in ocular surface conditions can result from various surgical interventions, such as conjunctival and scleral incisions, suturing, prolonged light exposure, retinal laser therapy, and the use of preservative-containing eye drops. These interventions may lead to reductions in conjunctival goblet cell density and modifications in mucin composition, key elements in the onset of post-vitrectomy dry eye.[21,22] Liu BS et al have documented that individuals with pre-existing meibomian gland dysfunction might observe amplified symptoms immediately post-surgery, with a return to preoperative conditions after one month.[22] This underscores the importance of diligent monitoring of ocular surface health and management of dry eye symptoms, particularly in the first three months following surgery, to minimize negative effects on patients' visual outcomes and comfort.

DCs, pivotal in initiating immune responses, capture and present antigens to T cells in lymph nodes. An increase in corneal DCs is indicative of potential inflammatory reactions triggered by infections, injuries, surgical procedures, or various ocular conditions.[23] Our study observed a steady elevation in DC density, with significant peaks at the third and ninth months postoperatively. Analysis via mixed-effects models revealed that the group undergoing phacoemulsification with C3F8 tamponade (Phaco+C3F8) experienced the most substantial increase in DC density. The literature highlights C3F8's corneal toxicity, noting its detrimental effects on corneal endothelial cell proliferation and an increase in cell mortality rates.[24] Remarkably, patients undergoing vitrectomy combined with C3F8 tamponade reported up to 27.54 ± 10.57% corneal endothelium loss by six months, significantly exceeding losses in other groups.[25] The significant increase in DC density observed in the Phaco+C3F8 group in our study can be attributed to the combined stress of phacoemulsification and C3F8 injection, as well as extended gas-cornea contact post-phacoemulsification, especially when the lens barrier is compromised. These findings emphasize the need to recognize the potential inflammatory consequences of surgical procedures and the importance of modifying postoperative care to mitigate these effects.

The corneal SNP predominantly originates from the ophthalmic division of the trigeminal nerve. Entering the cornea through the long posterior ciliary nerves, it progresses across the horizontal meridian within the choroidal and suprachoroidal spaces, subsequently penetrating the peripheral cornea radially between the corneal epithelium and Bowman's layer. These nerve endings not only provide sensory feedback but also supply essential peptides vital for epithelial cell growth and function.[26,27] Damage or compression in the choroidal and suprachoroidal spaces may adversely affect the long posterior ciliary nerves, heightening the risk of neurotrophic corneal ulceration.[28] Bouheraoua et al noted a significant 74.3% decrease in subbasal nerve density and a 4.7% reduction in mean corneal sensitivity in RD patients six months post 360-degree laser retinopexy. There was also an observed decrease in postoperative corneal nerve density as total laser energy increased.[29] Similarly, Gian et al reported a reduction in corneal SNP six months post-PPV, even in patients who underwent fewer retinal laser treatments.[30] Our comprehensive study, spanning more visits and a longer duration than previously mentioned studies,

recorded pronounced post-vitrectomy declines in several corneal SNP parameters. The most significant drop was noted one month post-surgery, with values gradually recovering but failing to return to baseline by the end of the 12-month period. Intriguingly, our results highlighted that the combined Phaco+SiO2 procedure had a distinct impact on CNFL and CTBD compared to other surgical approaches. Moreover, both the combined Phaco+SiO2 method and standalone SiO2 injection resulted in significant CNFrD reductions post-surgery. These insights suggest that combining Phacoemulsification and SiO2 could cause more pronounced changes in the corneal SNP compared to other techniques. The reasons behind these alterations could be attributed to SiO2's inherent properties, heightened post-operative inflammation, changes in ocular surface dynamics post-surgery, or specific surgical techniques. Further investigation is essential to understand the exact factors influencing these post-operative shifts and to determine any long-term clinical consequences for patients' visual and ocular health.

This study is subject to several limitations. The modest sample size may not encompass the full demographic diversity of patients typically seen in vitreoretinal surgical procedures. Additionally, the relatively low follow-up rate could potentially diminish the persuasiveness of the results. Although advanced statistical methods, such as a repeated measures mixed-effects model, were utilized to validate our findings, further research with more extensive follow-up is warranted for substantiation. The predominance of RD cases within our cohort could result in a disproportionate representation of retinal pathologies, potentially introducing selection bias. Additionally, the low occurrence of systemic diseases such as diabetes mellitus in our cohort—a condition that independently affects the corneal epithelium and SNP—could introduce bias or limit the generalizability of our results. Certain surgical categories, such as patients undergoing phacoemulsification with intraocular lens implantation and C3F8 tamponade (Phaco+IOL+C3F8), were represented by only a few individuals, which limits the depth of analysis on the impact of combined surgeries on the corneal SNP. Moreover, the evolution of surgical practices during the study period presents a significant limitation; with the introduction of finer-gauge instrumentation such as 25–27 G, our results may not be indicative of the outcomes associated with these newer techniques. Future research should explore the comparative effects of different surgical gauges on the ocular surface and corneal nerve structures for up-to-date clinical relevance. Expanding the sample size, ensuring broader demographic representation, and prolonging follow-up periods would contribute to a more comprehensive understanding of the long-term effects of these surgical interventions.

Conclusions

In conclusion, our study highlights the significant changes to ocular surface health following vitrectomy. We found that different surgical techniques can lead to varying degrees of change, indicating the need for more focused attention on the relationship between vitrectomy and ocular surface health.To improve postoperative outcomes, we recommend personalized care protocols that consider the type of surgery each patient has undergone. Early and frequent monitoring after surgery is essential for identifying and managing any negative changes to the ocular surface. Educating patients about the importance of follow-up care and self-monitoring for symptoms is also crucial. Our research supports a collaborative approach to postoperative care, involving a team of specialists to create a comprehensive plan tailored to each patient's needs. Future studies should explore the mechanisms behind the changes observed in our study to develop specific interventions and guidelines that will minimize the adverse effects of surgery and improve patient satisfaction.

Data Sharing Statement

The data supporting the results of the current study can be found within the article.

Ethics Approval and Informed Consent

An approval from the Ethics Committee of the Institutional Review Board of the EYE & ENT Hospital was obtained. The study adhered to the ethical principles outlined in the Declaration of Helsinki. Written informed consent has been obtained from the patients to publish this paper.

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Disclosure

The authors declare no conflict of interest.

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