Changes in Ocular Surface Disease Evaluated after Nonpenetrating Deep Sclerectomy

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Abstract

Objective: To analyse the ocular surface changes in eyes after the withdraw of anti-glaucomatous drugs when non-penetrating deep sclerectomy (NPDS) is performed.

Methods: 31 patients (33 eyes) diagnosed of glaucoma that underwent NPDS, were included in this prospective study. Control group included 33 eyes of 33 age and sex-matched volunteers. Five variables were studied with Keratograph 5M (K5M): ocular hyperaemia (OH), non-invasive tear film break-up time (NI-BUT), lower tear meniscus height (LTMH) and meibography. LTMH was also measured using the anterior segment module of Spectralis Fourier-Domain Optical Coherence Tomography (FD-OCT). Also, an evaluation of corneal and conjunctival staining was performed.

In addition, patients were asked to answer two questionnaires: Ocular Surface Disease Index (OSDI) and National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) before and 6-months after surgery.

Results: Before NPDS, treated eyes, showed worse objective data than healthy controls ($p \leq 0.049$). In this group, a significant improvement was observed in the questionnaires ($p < 0.001$), LTMH FD-OCT ($p = 0.037$) and LTMH K5M ($p = 0.025$), K5M OH ($p = 0.003$), NI-BUT ($p = 0.022$) and conjunctival and corneal staining ($p < 0.001$). No significant differences were observed between groups in FD-OCT and K5M LTMH, NI-BUT, corneal-conjunctival staining and in the most OH sector values at 6 months ($p \geq 0.62$).

Conclusion: A significant improvement in the ocular surface was observed 6 months after NPDS, suggesting that the withdrawn of the topical anti-glaucomatous treatment has a beneficial effect.

1. Introduction

Primary open-angle glaucoma (POAG) is a chronic, progressive, and irreversible multifactorial optic neuropathy that is characterized by changes in visual field and in optic nerve (ON) head (1, 2). Elevated intraocular pressure (IOP) is a major risk factor for the development and progression of glaucoma. (3)

Nowadays, the only strategy that has reliably demonstrated preservation of visual function is the reduction of IOP. In most cases, the initial therapy is medical treatment with topical hypotensive drugs that are maintained for long periods of time. Surgical and laser treatment continue to play an important role in the treatment of these patients when drugs fail (contraindications, side effects, lack of compliance...), the target pressure cannot be achieved or glaucoma progression is detected. (4, 5)

In terms of surgical treatments, trabeculectomy and non-penetrating deep sclerectomy (NPDS) procedures reduce IOP allowing aqueous humor drainage into the subconjunctival space. Among the advantages of NPDS, it is worth mentioning that the progressive filtration of aqueous humor from the anterior chamber to the subconjunctival space reduces postoperative complications (6).

The term ocular surface disease (OSD) includes a wide spectrum of conditions such as dry eye syndrome (DES), anterior blepharitis, meibomian gland dysfunction (MGD), conjunctivitis and keratitis (7).

A higher prevalence of OSD has been described in glaucoma patients and has multifactorial etiology. As a comorbidity of glaucoma, OSD is influenced by the age, ethnicity, sex of the patient and chronic use of topical anti-glaucomatous drugs (8, 9). Furthermore, OSD has been responsible for poor adherence to treatment and a worse quality of life in glaucoma patients (10, 11).

Although there are several publications that describe changes in the ocular surface in patients with IOP lowering eye drops (8, 12–16), there are few studies that evaluate these changes after trabeculectomy (17, 18); and, to our knowledge there are no studies evaluating the changes observed in the ocular surface after NPDS.

Therefore, the purpose of this study is to evaluate the changes in OSD in patients with glaucoma after NPDS and the withdrawn of antiglaucomatous drugs. The OSD was also compared with healthy subjects (control group).

2. Materials And Methods

For this prospective study, a total of 31 POAG patients (33 eyes) who underwent NPDS for uncontrolled intraocular pressure (IOP) despite medical treatment, were consecutively recruited from the Glaucoma Unit (Hospital Universitario Ramón y Cajal, Madrid, Spain). 33 eyes of 33 healthy volunteers, age and sex-matched to the POAG group, were included as a control group.

The study was approved by the Clinical Research Ethics Committee of Ramon y Cajal Hospital (CEIC), and conducted in accordance with the principles of the Declaration of Helsinki. Before recruitment, written informed consent was obtained from each participant.

Inclusion criteria in POAG group were: age over 18 years, a minimum of six-month treatment period with topical hypotensive agents, clinical indication of NPDS, and best-corrected visual acuity (BCVA) > 0.3 in the Snellen scale. Subjects were excluded in both groups if they had undergone ocular surgery (cataract, glaucoma, refractive, ocular surface surgery) within the last six months, use of contact lenses, ocular surface abnormalities (conjunctival chalasis, conjunctival scars and corneal irregularities), diagnosis of dry eye disease (according to the diagnostic criteria established in the Dry Eye WorkShop II (DEWS II) (19), known systemic diseases associated with dry eye (Sjögren's syndrome, rheumatoid arthritis, lupus erythematosus ...) or diagnosis of secondary glaucoma (congenital, traumatic, steroidal, uveitic).

All participants underwent a standard examination including a general anamnesis, sex and medical history data, recording the age of each patient. Treatment duration (time since the onset of the disease), total daily eye drops, total daily eye drops with preservatives, type of active principles as well as the type of preservative (polyquaternium or benzalkonium chloride), daily preservative concentration (DPC) and cumulative preservative concentration (CPC) were recorded. Daily preservative concentration was calculated regarding the preservative concentration on each medication, provided in the product data sheet ($\mu\text{g}/\mu\text{L}$). The latter is then multiplied by 7, as the average tear volume ($7 \mu\text{L}$) remaining in the eye following the instillation of a single drop (12). Finally, we multiply the DPC by the number of daily eye drops for each drug. In the case of patients with polytherapy, the following DPCs for each drug were added. Cumulative preservative concentration was determined as the product of DPC plus treatment duration (in days).

Anti-glaucoma eye drops were immediately removed after surgery, and patients started a combined treatment Tobramycin + dexamethasone (Tobradex™, Alcon Cusi, Barcelona, Spain) five times daily, in a descending pattern every week and Ketorolac (Acular™, Allergan Pharmaceuticals Ireland, Westport, Ireland) twice a day for two months. All sutures were removed a month after surgery. No artificial tears or anti-glaucomatous drugs were prescribed within six months after NPDS.

OSD indicators were recorded in the following order by the same examiner: Ocular Surface Disease Index (OSDI) and National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25); K5M and FD- OCT using the anterior segment module. In a separate room, slit-lamp (SL) examination was performed. Both areas presented similar environmental conditions heating to a temperature of $21-25^{\circ}\text{C}$ with a weak source of ambient light, and with no ventilation ducts over the equipment being used. The schedule in which the different explorations were made was from 8 to 15 hours.

2.1. Ocular Surface Disease Index (OSDI) and National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25)

All patients included in both groups answered two questionnaires: OSDI and NEI VFQ-25.

The OSDI has been reported to be reliable and effective to discriminate among stages of dry eye severity (20) and was validated in Brazil by Prigol et al. (21). It is composed of a 12-item questionnaire that is divided into 3 subscales: the first one is related to visual function (questions 1 to 5), the second one is associated with ocular symptoms (questions 6 to 9) and the third one regards environmental triggers (questions 10 to 12). All items of the OSDI questionnaire were scored from 0 to 4-point Likert scale (0 to 4 corresponding to: none of the times, some of the times, half of the time, most of the time, and all of the time, respectively). This total score was recorded for each participant. The impact of dry eye was then assessed categorically as normal (scores of 0–12), mild (scores of 13–22), moderate (scores of 23–32), or severe (scores of 33–50), as previously described (15).

Patients also answered to the NEI VFQ-25 questionnaire, which was validated in Brazil by Simao et al. (22). NEI VFQ 25 measures the dimensions of self-reported vision-targeted health status, which concerns above all persons who have chronic eye diseases. We used the version that is most commonly used in studies including glaucoma patients. It consists of 12 subscales as follows: general health; general vision; difficulties with distance-vision activity; vision-specific role difficulties; peripheral; difficulties with near-vision activities; colour vision; vision-related dependency; mental health; social function; ocular pain; and driving difficulties. Each subscale consists of a minimum of one item and a maximum of four items. The algorithm has a scale ranging from 0 to 100, with higher scores representing a better visual function.

OSDI and NEI VFQ 25 were administered to all subjects at the beginning of the session. In POAG group, we repeated the questionnaires six months after surgery.

2.2. Oculus Keratograph 5M (K5M)

Oculus Keratograph 5M (K5M) (Oculus Optikgerate GmbH, Wetzlar, Germany) is a device that consists of a keratometer and an optimized colour camera. The TF-Scan module was used to record non-invasive tear film break-up time (NI-BUT) and to measure low tear meniscus height (LTHM), through infrared lighting. The instrument was aligned at the pupil centre and NI-BUT measurements started when the patient blinked. The device shows two NI-BUT values: the first break-up time (NIBUTf) and average (NIBUTav). For LTHM measurements, the scan was taken below the corneal vertex, centered on the inferior cornea and lower eyelid. We used the integrated calliper tool provided by the device.

Through the R-Scan system, K5M allows us to perform an automatic classification of conjunctival redness. The patients were required to stare straight ahead and focus on the fixation mark inside the camera, so that the entire corneal area appeared in the center of the image. After generating a keratograph image, five redness scores (RS) (accurate to within 0.1 unit) are displayed on the computer screen. These scores (nasal limbal, temporal limbal, nasal bulbar, temporal bulbar and global) appear along with the total area analyzed (mm^2).

Meibography was assessed with upper and lower eyelid eversion using the meibography tool to generate IR images of tarsal conjunctiva. Manual grading of these images was performed using a meiboscore scale: grades from 0 to 3; being, no loss of meibomian glands: grade 0; loss of less than 1/3 of the total meibomian gland area: grade 1; loss of 1/3 to 2/3 of the total area: grade 2 and loss more than 2/3 of the area grade 3 (23).

2.3 Spectralis Fourier-domain optical coherence tomography (FD-OCT)

The anterior segment module of Spectralis Fourier-domain optical coherence tomography (Heidelberg Engineering GmbH, Heidelberg, Germany) was used to measure LTMH using the method described by Arriola-Villalobos et al. (24). Briefly, the lower meniscus was imaged using the anterior segment lens with the image capture software in the sclera mode, high speed, and single vertical scan. The scan was taken below the corneal vertex, centered on the inferior cornea and lower eyelid. The corneal vertex was determined by the position of specular reflection. The patient was asked to blink normally during the imaging procedure while looking straight at a fixation target. Images were captured within the first second immediately after the blink. For LTMH measurements on the images, we used the calliper tool provided by the gadget.

2.4. Slit-lamp examination and corneal-conjunctival staining

All subjects underwent a standard slit-lamp (SL) examination at A16 magnification in the second office. The cornea and the conjunctiva were stained using one fluorescein drop (Minims-fluorescein sodium 2.0%; Chauvin Pharmaceuticals Ltd., Surrey, UK) to detect corneal and conjunctiva injury. Both were graded from zero to five using the Oxford scale (0 = no staining; I = minimum; II = mild; III = moderate; IV = marked; V = severe) (25).

2.5. Statistical analysis

All statistical tests were performed using IBM SPSS version 15.0 (SPAA Inc., Chicago, IL.)

The qualitative variables were described in percentages, and quantitative variables were described with means and standard deviations or median, maximum, and minimum depending on their distributional characteristics in both groups. Kolmogorov-Smirnov test was used to assess the normal distribution of data.

Paired sample T-test was used for the comparative analysis on the repeated measurements in POAG group or its corresponding non-parametric Wilcoxon test for non-normal data. All contrasts were bilateral with a significance level of 0.05.

For the comparative analysis of the different measurements between POAG group and controls, the Student's T test for independent samples or its corresponding non-parametric U of Mann-Whitney test was used. All contrasts were bilateral with a significance level of 0.05.

3. Results

The data analysed derived from 33 eyes with POAG and 33 healthy control eyes. Mean age was 75.33 ± 7.5 years in POAG group and 72.91 ± 7.3 years in controls ($p = 0.188$).

The mean duration of treatment from the start date was 108 ± 309 months. 87.87% of our patients were receiving three or more drops per day, while 66.67% received three or more preservative drops per day. 100% of our patients used at least one drop of preservative, being benzalkonium chloride (BAK) the most frequently used.

In the POAG group, 84,85% of patients were receiving **prostaglandines**. In the same line, 84,85% received **β -Blocker**, 72,72% **carbonic anhydrase inhibitor**, and 48,48% **α adrenergic agonist**. The mean of DPC and CPC was 1.89 ± 0.88 and 1670.15 ± 1973.48 , respectively. Table 1 summarizes clinical, demographic and therapy data.

Table 1
Clinical, demographic and treatment data.

Parameters	POAG GROUP	CONTROL GROUP	P value
SEX N (%)			p = 0.624**
Female	18/33 (54.54%)	17/33 (51.51%)	
Male	15/33 (45.45%)	16/33 (48.48 %)	
AGE (years +/- SD)	75.33 ± 7.5	72.91 ± 7.3	p = 0.188*
Treatment duration (months)			
Median +/- SD	108 ± 309		
Minimum	2		
Maximun	1792		
DAILY EYEDROPS N (%)			
1	3 (9,09%)		
2	1 (3,03%)		
≥ 3	29 (87,87%)		
DAILY EYEDROPS WITH PRESERVATIVES N (%)			
1	4 (12,12%)		
2	7 (21,21%)		
≥ 3	22 (66,67%)		
PRESERVATIVE N (%)	0		
Preservative-free	28 (84,85%)		
BAK	5 (15,15%)		
PQ + BAK			
ACTIVE INGREDIENT N (%)			
Prostaglandine	28 (84,85%)		
β-Blocker	28 (84,85%)		
CAI	24 (72,72%)		
AAA	16 (48,48%)		
DPC, µg/d			
Mean +/- SD	1,89 ± 0,88		
Minimum	0,35		
Maximun	3,5		
CPC, µg/d x treatment duration (days)			
Mean +/- SD	1670,15 ± 1973,48		
Minimum	53,20		
Maximun	10482		
SD: standard deviation, *t Student test; ** Mann- Whitney test.			
AAA = α adrenergic agonist; CAI = carbonic anhydrase inhibitor; DPC = daily preservative concentration; CPC: cumulative preservative concentration.			

In POAG group, we found a significant improvement in OSDI and NEI-VFQ25 scores from pre-surgery time to six months after NPDS (24.33 ± 7.7 vs 15.06 ± 6.93, p < 0.001 and 61.78 ± 13.20 vs 74.42 ± 11.97, p < 0.001; respectively).

Treated subjects demonstrated a significant increase in the mean LTMH measured by K5M. This improvement is significant from the third postoperative month when compared with baseline values (p ≤ 0.025). When comparing the LTMH by FD-OCT, the improvement is observed six months after NPDS (p =

0.037). Before surgery, mean FD-OCT LTMH measurements in POAG eyes were significantly lower than control eyes ($p = 0.043$); however, no significant differences were observed after six months ($p = 0.062$). Measurements of the LTM by the K5M were not different between groups before and after NPDS ($p \geq 0.15$).

Before NPDS, the total and sector K5M-OH values in treated patients were significantly higher than in control group ($p \leq 0.048$). These differences disappeared in the sixth month postoperative visit in temporal sectors and in the nasal-limbal sector ($p \geq 0.062$). We observed a significant increase in total and sector values K5M-OH in the first week post-NPDS compared to preoperative visit ($p < 0.001$); however, after six months, the total OH decreased significantly ($p = 0.003$). Figure 1 shows an example of the evolution of OH in one of our patients.

In POAG group, we detected a significant improvement in NI-BUTf three months after NPDS ($p \leq 0.022$); nevertheless, the average NI-BUT (NI-BUTav) was significantly higher than baseline values during the first week ($p \leq 0.048$). Before surgery, NI-BUT measurements in glaucoma eyes were significantly lower than controls ($p \leq 0.016$); but no significant differences were observed in the sixth month visit ($p \geq 0.104$). Figure 2 shows an example of the evolution of NI-BUT in one of our patients. Table 2 summarizes the results of questionnaires (OSDI and NEI VQF25) and ocular surface parameters measured preoperatively, in the first week, first month, third and sixth month, after surgery in POAG and control group. Figure 3 shows the evolution of the OS parameters in the POAG group.

Table 2
Questionnaires (OSDI and NEI VQF25) and ocular surface parameters measured preoperatively (Mean $\pm$ SD)

Parametres	GLAUCOMA GROUP						CONTROL GROUP					
	Pre-NPDS	1 week	p	1 month	p	3 months	p	6 months	p	Controls	Baseline versus controls	6 months versus controls
OSDI (unit)	24.33 $\pm$ 7.7							15.06 $\pm$ 6.93	$p < 0.001^*$	6.24 $\pm$ 3.345	$p < 0.001^*$	$p < 0.001^*$
NEI VQF25 (unit)	61.78 $\pm$ 13.20							74.42 $\pm$ 11.97	$p < 0.001^*$	84.73 $\pm$ 10.1	$p < 0.001^*$	$p < 0.001^*$
LTM FD-OCT (μ m)	258.85 $\pm$ 52.82	282.65 $\pm$ 55.18	$p = 0.081^*$	277.35 $\pm$ 57.44	$p = 0.208^*$	281.19 $\pm$ 60.33	$p = 0.157^*$	296.19 $\pm$ 64.64	$p = 0.037^*$	289.04 $\pm$ 51.95	$p = 0.043^*$	$p = 0.062^*$
LTM K5M (mm)	0.301 $\pm$ 0.1	0.421 $\pm$ 0.17	$p < 0.001^*$	0.341 $\pm$ 0.02	$p = 0.053^*$	0.364 $\pm$ 0.11	$p = 0.01^*$	0.352 $\pm$ 0.15	$p = 0.025^*$	0.321 $\pm$ 0.06	$p = 0.356^*$	$p = 0.150^*$
TOH K5M (score)	2.06 $\pm$ 0.66	2.71 $\pm$ 0.79	$p < 0.001^*$	1.90 $\pm$ 0.70	$p = 0.076^*$	1.85 $\pm$ 0.60	$p = 0.063^*$	1.69 $\pm$ 0.61	$p = 0.003^*$	1.42 $\pm$ 0.41	$p < 0.001^*$	$p = 0.039^*$
NBH K5M (score)	2.20 $\pm$ 0.66	2.86 $\pm$ 0.80	$p < 0.001^*$	2.13 $\pm$ 0.75	$p = 0.538^*$	2.02 $\pm$ 0.67	$p = 0.139^*$	1.83 $\pm$ 0.65	$p = 0.014^*$	1.54 $\pm$ 0.42	$p < 0.001^*$	$p = 0.039^*$
NLH K5M (score)	1.85 $\pm$ 0.65	2.51 $\pm$ 0.86	$p < 0.001^*$	1.52 $\pm$ 0.64	$p = 0.538^*$	1.59 $\pm$ 0.66	$p = 0.457^*$	1.52 $\pm$ 0.66	$p = 0.021^*$	1.05 $\pm$ 0.43	$p = 0.001^*$	$p = 0.062^*$
TBH K5M (score)	1.92 $\pm$ 0.65	2.62 $\pm$ 0.83	$p < 0.001^*$	1.81 $\pm$ 0.63	$p = 0.220^*$	1.77 $\pm$ 0.68	$p = 0.212^*$	1.67 $\pm$ 0.64	$p = 0.052^*$	1.43 $\pm$ 0.39	$p < 0.001^*$	$p = 0.068^*$
TLH K5M (score)	1.55 $\pm$ 0.66	2.3 $\pm$ 0.89	$p < 0.001^*$	1.42 $\pm$ 0.72	$p = 0.289^*$	1.27 $\pm$ 0.54	$p = 0.016^*$	1.23 $\pm$ 0.57	$p = 0.010^*$	1.1 $\pm$ 0.4	$p = 0.048^*$	$p = 0.236^*$
NIBUTf K5M (s)	5.96 $\pm$ 4.15	5.96 $\pm$ 4.92	$p = 0.999^*$	8.07 $\pm$ 5.61	$p = 0.100^*$	9.16 $\pm$ 6.70	$p = 0.014^*$	8.47 $\pm$ 5.19	$p = 0.022^*$	8.87 $\pm$ 5.29	$p = 0.016^*$	$p = 0.760^*$
NIBUTav K5M (s)	10.28 $\pm$ 5.83	12.84 $\pm$ 5.76	$p = 0.048^*$	14.92 $\pm$ 4.53	$p = 0.001^*$	16.53 $\pm$ 4.38	$p < 0.001^*$	15.72 $\pm$ 3.99	$p < 0.001^*$	13.81 $\pm$ 5.31	$p = 0.013^*$	$p = 0.104^*$
OSDI: Ocular Surface Disease Index; NEI VFQ 25: National Eye Institute Visual Functioning Questionnaire; LTM Lower tear meniscus height; TOH: total ocular hyperemia; NBH: nasal bulbar hyperemia; NLH: nasal limbal hyperemia; TBH: temporal bulbar hyperemia; TLH: temporal limbal hyperemia; NIBUTf: First non-invasive tear film break-up time; NIBUTav: Non-invasive tear film break-up time average. * t Student test												

Overall, meibography image study showed no significant changes in POAG group ($p > 0.999$). Significant higher scores were found in treated subjects when compared to control group, before and after surgery ($p \leq 0.006$). Both, Table 3 and Fig. 4 show the evolution of meibography throughout the visits.

We observed a significant decrease in corneal and conjunctival staining scores (Oxford scale) six months after NPDS ($p < 0.001$) in treated eyes. The percentages of eyes showing corneal and conjunctival staining at different time intervals are shown in Table 4. Before surgery, 94% of POAG eyes (31 eyes) were classified as Oxford ≥ 1 ; however, in the sixth month visit, only 18% of the treated eyes (six eyes) had fluorescein corneal staining ($p < 0.001$). Similar findings were found in conjunctival test. We observed that 97% of glaucoma eyes (32 eyes) had positive conjunctival staining (Oxford score ≥ 1) before surgery; but this percentage significantly decreased to 42% (14 eyes) on the last visit ($p < 0.001$).

Table 3 Meibography measured with K5M. JENVIS grading scale.

Parameters	SUPERIOR MEIBOGRAPHY K5M JENVIS SCALE					INFERIOR MEIBOGRAPHY K5M JENVIS SCALE				
	Pre-NPDS	3 months	6 months	Control	P value POAG-control before and 6 months	Pre-NPDS	3 months	6 months	Control	P value POAG-control before and 6 months
GRADE 0	3.03%	3.03%	3.03%	39.39%		12.12%	15.2%	24.2%	48.48%	
GRADE 1	39.39%	39.39%	39.39%	57.58%		63.64%	36.4%	60.6%	45.45%	
GRADE 2	48.48%	48.48%	48.48%	3.03%		18.18%	42.45%	15.2%	6.06%	
GRADE 3	9.09%	9.09%	9.09%	0%		6.06%	6.1%	0%	0%	
P value		p>0.999***	p>0.999***		p<0.001**		p>0.999***	p>0.999***		P=0.006**

** Mann- Whitney test.; ***Wilcoxon test;

A significantly greater proportion of POAG patients showed at least some fluorescein corneal and conjunctival staining before surgery compared to healthy control eyes ($p < 0.001$); however, no significant differences were observed during the last visit ($p \geq 0.254$) (Table 4). Figure 5 shows the improvement of conjunctival and corneal staining in the POAG group throughout the visits.

Table 4 Corneal and conjunctival stain (Oxford scale) results.

Parameters		CORNEAL STAINING OXFORD					NASAL CONJUNCTIVAL STAINING OXFORD					TEMPORAL CONJUNCTIVAL		
		Pre-NPDS	1 week	1 month	3 months	6 months	Pre-NPDS	1 week	1 month	3 months	6 months	Pre-NPDS	1 week	1 month
POAG GROUP	OXFORD 0	6.1%					3%					3%		
	OXFORD ≥ 1	93.9%	0%	27.3%	45.5%	81.82%	97%	0%	3%	15.2%	57.6%	97%	0%	6.
			100%	72.7%	54.5%	18,18%		100%	97%	84.8%	42.4%		100%	9.
P value POAG group pre-NPDS and next visits***			p=0.157	p=0.02	p<0.001	p<0.001		p=0.317	p>0.999	p=0.102	p<0.001		p=0.317	p=0.
CONTROL GROUP	OXFORD 0	72.72%				72.72%	78.79%				78.79%	78.79%		
	OXFORD ≥ 1	27.27%				27.27%	21.21%				21.21%	21.21%		
P value POAG-control **		p<0.001				p=0.254	p<0.001				p=0.66	p<0.001		

** Mann- Whitney test.; ***Wilcoxon test;

4. Discussion

The present study has found that patients with glaucoma had a significant improvement in OSD after NPDS. New non-invasive technologies such as K5M and FD-OCT could be useful tools to objectively study different parameters of the ocular surface that could help us to evaluate the OSD in glaucomatous eyes.

In this prospective study, all POAG patients were already in a combined hypotensive drug treatment with preservatives. Corneal neurotoxicity and tear film disorder are examples of side effects that have been already described in patients with glaucoma (26–28) due to the chronic use of IOP-lowering therapies. Therefore, the main idea of this study was to investigate the ocular surface changes after NPDS once anti-glaucoma eye drops were removed.

Portela et al.(29) and Ling et al.(30) have already described worst scores in OSDI and NEI-VQF25 questionnaires in glaucoma patients with hypotensive treatment. Similarly, before surgery, our study showed significant differences in the median OSDI and NEI-VFQ25 scores between POAG group and healthy controls. However, to our knowledge, there is no previous information about these questionnaires after NPDS. In the current study, we have observed a

significant improvement in both tests during the sixth month after NPDS. Nevertheless, after surgery, we also found significant differences between groups. This may be due to the fact that 51.52% of patients have anti-glaucomatous treatment in the contralateral eye (bilateral POAG).

Our findings support literature evidence (11, 29, 31–33), and the present study found that POAG eyes had a higher prevalence of OSD criteria than the healthy controls. Before NPDS, treated eyes, showed worse objective data regarding OH, LTMH, NIBUT and meibography evaluated by the Keratography 5M, worse FD-OCT LTMH and higher Oxford scores on ophthalmologic examination than the healthy controls. However, we document a significant improvement in most of these parameters throughout the follow-up period. No significant differences were observed between the groups in the following parameters: FD-OCT LTMH, K5M LTMH, NIBUT (f and av values), corneal-conjunctival staining grades and in most OH sectors values six months after surgery. These findings could demonstrate an improvement in OSD after NPDS due to anti-glaucomatous drops withdrawn.

LTMH can be measured with both modern devices (FD-OCT and K5M) reducing the interpretation bias of subjective assessments. FD-OCT LTMH measurements have been proposed as a good diagnostic method for OSD; showing low variability (34) good repeatability (35, 36) and a better reproducibility than the K5M (24). This could explain the difference in LTMH measurements when using the different devices. Therefore, these methods are not considered to be interchangeable.

Conjunctival hyperaemia is a common side effect described after the use of most topical anti-glaucoma medications (12, 31). Besides being a cosmetic problem, ocular hyperaemia may lead to poor treatment adherence. In recent studies, the Keratography 5M emerged as a reliable method to consistently score bulbar redness (12, 31, 37). Previous studies (12, 31) have already described the relationship between conjunctival hyperaemia and anti-glaucoma medication using K5M. Our results are consistent with previous studies, we observed higher K5M OH in the glaucoma group. In our prospective study, a significant increase of OH was observed in the first week after surgery. It could be due to the surgical procedure itself and/or to the postoperative treatment with anti-inflammatory drops. The OH-sector scores were gradually restored to the baseline level, observing a significant improvement in most of OH-sectors values during the sixth month. Significant group differences, disappeared by the sixth month in all the sectors except for the nasal bulbar one. Pérez-Bartolomé et al. (31) detected a greater impact of treatment burden on nasal hyperaemia scores than on the temporal quadrant ones. It could be explained by a longer contact time of the tear film in the nasal area, due to the normal spreading of the tear film across the ocular surface until it reaches the lacrimal punctum.

Previous studies have suggested that goblet cell secreting mucin 5AC, plays an important role in tear film stability (38) and several studies have reported toxic side effects for anti-glaucoma drugs on the conjunctiva, especially if preservatives are used (12, 39, 40). Moreover, the reduction in goblet cell density and mucin 5AC could also be due to several glaucoma surgery factors such as: toxicity of MMC used during the surgery, damage of the conjunctival nerves and the limbus stem cells, inflammation or mechanical trauma produced by the surgery and post-operative topical medication (41–43). Zhong et al. (35) have recently investigated the influence of trabeculectomy and phacotrabeculectomy on the ocular surface in a 3-month retrospective study using Oculus Keratograph. They observed that both, NIBUTf and NIBUTav values, tended to improve in the first and third month after surgery; recovering baseline in the third month postoperatively. According to previous reports, goblet cell density did not return to preoperative level after three months cataract surgery (44), the same happened with mucin 5AC after phacotrabeculectomy (41). They propose that the improvement of the NI-BUT is related to the recovery of the levels of goblet cell density and mucin 5AC. In line with these findings, we also found NIBUTf and average values improvement in the third month after NPDS; additionally, not significant differences were observed in the sixth month compared to healthy eyes. Taking into account these results, parameters of ocular surface could not return to preoperative levels until three months post-NPDS.

Recent studies have suggested that trabeculectomy filtering bleb is a determining factor in the state of the ocular surface for at least half a year. It could cause dry eye by inducing meibomian gland loss, particularly when the bleb is avascular or contains numerous intraepithelial microcysts (45, 46). According to previous research, trabeculectomy filtering bleb morphology also affects tear film (46, 47) indicating that the higher filtering bleb would decrease TBUT and increase the corneal staining.

In the present study, no significant changes were observed in meibomian gland six months after NPDS. Furthermore, we documented a significant reduction in the percentage of glaucoma eyes with Oxford ≥ 1 in the third month postoperatively, and no differences were recorded in corneal and conjunctival staining between groups in the last follow up visit. The different bleb morphology in NPDS and trabeculectomy could explain our results. (48, 49). Oh and colleagues found that eyes that underwent trabeculectomy had significantly higher, broader and lesser vascular blebs than eyes treated with deep sclerectomy. Also, eyes treated with trabeculectomy were more likely to show microcysts. Longer-term follow-up studies will be necessary to determine if deep sclerectomy bleb could cause more meibomian gland loss degrees.

Despite the significant findings, our study is subject to a number of limitations. First of all, the small sample size; which however has been enough to find significant differences, being the first study that uses non-invasive technologies (Keratograph and FD-OCT) to investigate OSD in glaucoma patients after NPDS. Second, the clinical ophthalmology examinations (corneal and conjunctival staining) are subjective, however, they were performed by just one ophthalmologist to avoid possible bias, and the comparison of keratitis was done using the Oxford scale, already published, obtaining therefore more reliable values. Finally, post-surgical steroids could improve ocular surface masking our results, nonetheless, the measurements of the third and sixth month should not be influenced by the treatment since it had already been completed.

In conclusion, although the association between anti-glaucoma eye drops and OSD has been extensively explored, to the best of our knowledge, this is the first study to compare different ocular surface parameters before and after NPDS. In addition, based on the objective parameters measured by Keratographs 5M and FD-OCT, we have reported a significant improvement of different variables such as OH-sectors, NI-BUT and LHTM after NPDS; as well as, lower corneal-conjunctival fluorescein staining and better total scores on the OSDI and NEI-VFQ25 questionnaires than before surgery.

The current study demonstrates that the withdrawn of anti-glaucomatous topical treatment could improve the ocular surface six months after NPDS. In addition, NPDS may be considered as a good as surgical technique to restore the ocular surface, however further studies should be performed to corroborate

our results.

Abbreviations

BAK	Benzalkonium chloride
CPC	Cumulative preservative concentration
DES	Dry eye syndrome
DPC	Daily preservative concentration
FD-OCT	Fourier-domain optical coherence tomography
IOP	Intraocular pressure
K5M	Keratograph 5M
LTMH	Lower tear meniscus height
MGD	Meibomian gland dysfunction
NBH	Nasal bulbar hyperemia
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire
NI-BUT	Non-invasive tear film break-up time
NIBUTav	Non-invasive tear film break-up time average
NIBUTf	First non-invasive tear film break-up time
NLH	Nasal limbal hyperemia
NPDS	Nonpenetrating deep sclerectomy
OH	Ocular hyperemia
ON	Optic nerve
OSD	Ocular Surface Disease
OSDI	Ocular Surface Disease Index
POAG	Primary Open Angle Glaucoma
PQ	Polyquaternium
QoL	Quality of life
SL	Slit lamp
RS	Redness scores
TLH	Temporal limbal hyperemia
TBH	Temporal bulbar hyperemia
TBUT	Tear film breakup time
TOH	Total ocular hyperemia
VA	Visual acuity

Declarations

5. Disclosure/Conflicts of Interest

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PRÉCIS

The present study found that patients with anti-glaucomatous drugs had a significant improvement in ocular surface parameters, measured with K5M and FD-OCT, after non-penetrating deep sclerectomy.

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Figures

Figure 1. Ocular hyperaemia: A: Pre-surgery; B: 1 week; C: 1 month; D: 3 months; E: 6 months

Figure 1

Ocular hyperaemia: A: Pre-surgery; B: 1 week; C: 1 month; D: 3 months; E: 6 months

Figure 2. NIBUT: A: Pre-surgery; B: 1 week; C: 1 month; D: 3 months; E: 6 months

Figure 2

NIBUT: A: Pre-surgery; B: 1 week; C: 1 month; D: 3 months; E: 6 months

OCULAR SURFACE PARAMETERS IN POAG GROUP

Figure 3: Ocular surface parameters measured in POAG Group. LHTM Lower tear meniscus height; TOH: total ocular hyperemia; NBH: nasal bulbar hyperemia; NLH: nasal limbal hyperemia; TBH: temporal bulbar hyperemia; TLH: temporal limbal hyperemia; NIBUTf: First non-invasive tear film break-up time; NIBUTav: Non-invasive tear film break-up time average

Figure 3

Ocular surface parameters measured in POAG group.

Figure 4: Meibography K5M Jenvis scale in POAG group

Figure 4

A: Meibography K5M JENVIS scale in POAG group. B: Corneal and conjunctival staining Oxford scale in POAG group.

Figure 5: Corneal and conjunctival staining Oxford scale in POAG group

Figure 5

Corneal and conjunctival staining Oxford scale in POAG group.