Changes in ocular surface after withdrawal of anti-glaucoma medications following non-penetrating deep sclerectomy

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Purpose: To analyze the ocular surface changes in eyes after the withdrawal of anti-glaucomatous drugs when non-penetrating deep sclerectomy (NPDS) is performed. Methods: Thirty-one patients (33 eyes) diagnosed with glaucoma that underwent NPDS were included in this prospective study. The control group included 33 eyes. Four variables were studied using Keratograph 5M (K5M): ocular hyperemia (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 a Spectralis Fourier-domain optical coherence tomography (FD-OCT) instrument. Moreover, an evaluation of corneal and conjunctival staining was performed. In the glaucoma group, five visits were carried out: pre-surgery, 1 week after surgery, and 1 month, 3 months, and 6 months after surgery. In control groups, examinations were performed in only one visit. 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, eyes showed worse subjective data than healthy control subjects (P = 0.049). In this group, a significant improvement was observed in questionnaire responses (P < 0.001), LTMH-FD-OCT (P = 0.037), LTMH-KSM (P = 0.025), KSM-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 KSM LTMH, NI-BUT, corneal-conjunctival staining, nor in the most OH sector values at 6 months (P ≥ 0.62). Conclusion: A significant improvement in the ocular surface was observed 6 months after NPDS, suggesting that the withdrawal of the topical anti-glaucomatous treatment had a beneficial effect on the subjects.

Key words: Glaucoma, Keratograph, non-penetrating deep sclerectomy, ocular hyperemia, ocular surface disease

Primary open-angle glaucoma (POAG) is a chronic, progressive, and irreversible multifactorial optic neuropathy. Elevated intraocular pressure (IOP) is a major risk factor for the development and progression of glaucoma.[9] In most cases, the initial therapy consists of treatment using topical hypotensive drugs over long periods of time. Surgical treatment continues to play an important role when drugs fail and 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 and allow for 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 the risk of hypotony and other postoperative complications.[9] 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 comorbidity of glaucoma, OSD is influenced by the age, ethnicity, and 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 inferior quality of life in patients with glaucoma.[10,11]

Glaucoma treatments and OSD are correlated with the number of anti-glaucoma medications used, daily preservative concentration, the existence of PSO before glaucoma treatment, aging, and hormonal imbalances.[12] Although several...
publications describe changes in the ocular surface in patients with IOP-lowering eye drops.\textsuperscript{[12,18,20]} Few studies have evaluated these changes after trabeculectomy;\textsuperscript{[21,22]} to our knowledge, there are no current 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 impact of the withdrawal of anti-glaucomatous drugs. The OSD was also compared with healthy subjects (the control group).

Methods

For this prospective study, a total of 31 POAG patients (33 eyes) who underwent NPDS for uncontrolled IOP and notwithstanding medical treatment were consecutively recruited from the Glaucoma Unit for this study. Thirty-three eyes of 33 healthy volunteers, age- and sex-matched to the POAG group, were included as part of the control group.

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

The inclusion criteria for the POAG group stated that the participants must: be over 18 years of age, had been treated for a minimum of 6 months with topical hypotensive agents, had a clinical indication of NPDS, and a best-corrected visual acuity (BCVA) of >0.3 on the Snellen scale. Subjects were excluded from both groups if they had undergone ocular surgery within the last 6 months, used contact lenses, were diagnosed with ocular surface abnormalities, or had been diagnosed with dry eye disease (according to the diagnostic criteria established in the Dry Eye Workshop II (DEWS II)), or with any known systemic diseases associated with dry eye or secondary glaucoma.

All participants underwent a standard examination, including a general anamnesis, as well as treatment duration (time since the onset of the disease), total daily eye drops administered, 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). Daily preservative concentration was calculated according to the preservative concentration of each medication provided on the product data sheet (μg/μL). The latter was then multiplied by 7 because the average tear volume that remains in the eye following the instillation of a single drop is 7 μL.\textsuperscript{[23]} Finally, we multiplied the DPC by the number of daily eyedrops of 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 eyedrops were immediately discontinued after surgery, and patients were started on a combined treatment of tobramycin + dexamethasone (Tobradex®@, Alcon Cusi, Barcelona, Spain) five times a day in a descending pattern every week and ketorolac (Acular®, Allergan Pharmaceuticals Ireland, Westport, Ireland) twice a day for 2 months. All sutures were removed a month after surgery. No artificial tears or anti-glaucomatous drugs were prescribed within 6 months after NPDS.

In the glaucoma group, five visits were carried out: pre-surgery, 1 week after surgery, 1 month, 3 months, 6 six months after the surgical procedure. In the control group, examinations were performed in only one visit, and the same data was compared with the glaucoma group before and after surgery.

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 addition, a slit-lamp (SL) examination was performed.

Ocular surface disease index (OSDI) and National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25)

The OSDI has been reported to be reliable and effective in discriminating among stages of dry eye severity.\textsuperscript{[20]} It is composed of a 12-item questionnaire, divided into three subscales: the first one is related to visual function, the second one is associated with ocular symptoms, and the third one concerns environmental triggers.\textsuperscript{[21]}

Patients also answered the NEI VFQ-25 questionnaire. It 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 consists of 12 subscales that included questions on general health and general vision.

The algorithm has a scale ranging from 0 to 100, with higher scores representing a better visual function.\textsuperscript{[22]}

Questionnaires were administered to all subjects at the beginning of the session. In the POAG group, we repeated the questionnaires 6 months after surgery.

Oculus Keratograph 5M (KSM)

Oculus Keratograph 5M (KSM) (Oculus Optikgeräte GmbH, Wetzlar, Germany) is a device that consists of a keratometer and an optimized color 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).

The R-Scan system allowed us to perform automatic classification of conjunctival redness. After generating a keratograph image, five redness score (RS) areas were displayed on the computer screen.

Meibography was used to assess upper and lower eyelid version by using the meibography tool to generate IR images of tarsal conjunctiva. Manual grading of these images was performed using a meiboscore scale: graded from 0 to 3.\textsuperscript{[23]}

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 LTHM by using the method described by Arriola-Villalobos et al.\textsuperscript{[24]} In brief, the lower meniscus was imaged using the anterior segment lens and image capture software in the high-speed sclera mode by using a single vertical scan. For measurements, we used the caliper tool integrated into the device.
Slit-lamp examination and corneal-conjunctival staining
All subjects underwent a standard SL examination at A16 magnification. The cornea and the conjunctiva were stained using one drop of fluorescein to detect corneal and conjunctiva injury. Both were graded from 0 to 5 by using the Oxford scale.\(^{(24)}\)

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

The qualitative variables were described as percentages, and quantitative variables were described as 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.

A paired-sample \( t \) test was used for the comparative analysis of the repeated measurements taken from the POAG group; its corresponding non-parametric Wilcoxon test was used for non-normal datasets. All contrasts were bilateral with a significance level of 0.05.

For the comparative analysis of the different measurements between the POAG group and control group, 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.

**Results**
The data analysis was concluded from results taken from 33 eyes with POAG and 33 healthy control eyes. The mean age of the subjects was 75.33 ± 7.5 years in the POAG group and 72.91 ± 7.3 years in the control group \( (P = 0.188) \).

The mean duration of treatment from the start date was 108 ± 309 months.

Further, 87.87% of our patients received 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 eyedrops, benzalkonium chloride (BAK) being the most frequently used.

In the POAG group, 84.85% of patients were receiving prostaglandins. In the same line, 84.85% received \( \beta \)-blocker, 72.72% received carbonic anhydrase inhibitor, and 48.48% received \( \alpha \) adrenergic agonist. The mean of DPC and CPC

### Table 1: Clinical, demographic, and treatment data

| Parameters                          | POAG Group | Control group | \( P \) |
|-------------------------------------|------------|---------------|--------|
| Sex N (%)                           |            |               |        |
| Female                              | 18/33 (54.54%) | 17/33 (51.51%) | 0.624** |
| Male                                | 15/33 (45.45%) | 16/33 (48.48%) |       |
| Age (years±SD)                      | 75.33±7.5  | 72.91±7.3     | 0.188* |
| Treatment duration (months)         | Median±SD  | 108±309       |        |
| Minimum                             | 2          |               |        |
| Maximum                             | 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 (%)                  |            |               |        |
| Preservative-free                   | 0          |               |        |
| BAK                                 | 28 (84.85%)|               |        |
| PQ + BAK                            | 5 (15.15%) |               |        |
| Active ingredient n (%)             |            |               |        |
| Prostaglandin                       | 28 (84.85%)|               |        |
| \( \beta \)-blocker                 | 28 (84.85%)|               |        |
| CAI                                 | 24 (72.72%)|               |        |
| AAA                                 | 16 (48.48%)|               |        |
| DPC, µg/d                           | Mean±SD    | 1.89±0.88     |        |
| Minimum                             | 0.35       |               |        |
| Maximum                             | 3.5        |               |        |
| CPC, µg/d x treatment duration (days)| Mean±SD  | 1670.15±1973.48|        |
| Minimum                             | 53.20      |               |        |
| Maximum                             | 10482      |               |        |

SD: Standard deviation, *Student test; **Mann–Whitney test. AAA=\( \alpha \) adrenergic agonist; CAI=Carbonic anhydrase inhibitor; DPC=Daily preservative concentration; CPC=Cumulative preservative concentration
was 1.89 ± 0.88 and 1670.15 ± 1973.48, respectively. Table 1 summarizes the clinical, demographic, and therapy data.

In the POAG group, we found a significant improvement in OSDI and NEI-VFQ25 scores from pre-surgery time to 6 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 K5M-LTMH. 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 was observed 6 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 6 months (P = 0.062). Measurements of the K5M-LHTM were not different between groups before and after NPDS (P ≥ 0.15).

Before NPDS, the total and sector K5M-OH values in treated patients were significantly higher than in the control group (P ≤ 0.048). These differences disappeared in temporal sectors and the nasal-limbal sector (P ≥ 0.062) during the sixth-month postoperative visit. We observed a significant increase in total and sector values K5M-OH in the first week post-NPDS compared to the preoperative visit (P < 0.001); however, after 6 months, the total OH decreased significantly (P = 0.003). Fig. 1 shows an example of the evolution of OH.

In the POAG group, we detected a significant improvement in NI-BUT 3 months after NPDS (P ≤ 0.022); nevertheless, the average NI-BUT (NI-BUTav) was significantly higher than baseline values during the first week (P ≤ 0.048). Before surgery, NI-BUT measurements in glaucoma eyes were significantly lower than the control group (P ≤ 0.016); however, no substantial differences were observed in the sixth-month visit (P ≥ 0.104). Fig. 1 shows an example of the evolution of NI-BUT. Table 2 summarizes the results of questionnaires and ocular surface parameters measured.

Overall, the meibography image study showed no significant changes in the POAG group (P > 0.999). Significantly higher scores were found in treated subjects when compared to the control group before and after surgery (P ≤ 0.006). Table 3 shows the evolution of meibography.

We observed a significant decrease in corneal and conjunctival staining scores (Oxford) 6 months after NPDS (P < 0.001) in treated eyes. The percentages of eyes staining at different time intervals are shown in Table 4. Before surgery, 94% of POAG eyes were classified as Oxford ≥1; however, in the sixth-month visit, only 18% of the treated eyes had fluorescein corneal staining (P < 0.001). Similar findings were found in the conjunctival test. We observed that 97% of glaucoma eyes had positive conjunctival staining (Oxford ≥1) before surgery, but this percentage significantly decreased to 42% on the final visit (P < 0.001).

A significantly greater proportion of POAG patients showed at least some fluorescein staining before surgery compared to healthy control eyes (P < 0.001); however, no significant differences were observed during the last visit (P ≥ 0.254) [Table 4].
**Discussion**

The present study found that patients with glaucoma displayed significant improvement in OSD after NPDS. New non-invasive technologies such as K5M and FD-OCT can be useful tools in evaluating OSD in glaucomatous eyes.

POAG patients have already been participating in combined hypotensive drug treatment with preservatives. Corneal neurotoxicity and tear film disorder are examples of side effects that have been already described in patients. Therefore, the main idea of this study was to investigate the ocular surface changes after NPDS once anti-glaucoma eye drops were discontinued.

Portela et al. and Ling et al. have already described the worst scores in OSDI and NEI-VFQ25 questionnaires in glaucoma patients undergoing hypotensive treatment. Similarly, before surgery, our study showed significant differences in the median OSDI and NEI-VFQ25 scores between the POAG group and the healthy control group. However, to our knowledge, there is no previous information about such questionnaires after NPDS. In this current study, we observed a significant improvement in both tests during the sixth month after NPDS. Nevertheless, after surgery, we also discovered noteworthy differences between the two groups. This may be because 51.52% of patients had undergone anti-glaucomatous treatment in the contralateral eye (bilateral POAG).

Our findings support the literature evidence that POAG eyes had a higher prevalence of OSD. Before NPDS, treated eyes demonstrated worse objective data regarding OH, K5M-LTMH, NIBUT, meibography, FD-OCT-LTMH, and higher Oxford scores than controls. We documented a significant improvement in most of these parameters throughout the follow-up period. No significant differences were observed between groups in the following parameters: FD-OCT-LTMH, K5M-LTMH, NIBUT, corneal-conjunctival grading scale, and in most OH sectors values after 6 months. These findings demonstrate an improvement in OSD after NPDS due to discontinuing the treatment of anti-glaucomatous drops.

FD-OCT-LTMH measurements have been proposed as a good diagnostic method for OSD; showing low variability, good repeatability, and better reproducibility than the K5M-LTMH. This can explain the difference in LTMH measurements when using different devices. Therefore, these methods are not considered to be interchangeable.

Conjunctival hyperemia is a common side effect described after the use of most topical anti-glaucoma medications. Besides being a cosmetic problem, OH may lead to poor treatment adherence. Our results are consistent with previous studies, in that higher K5M-OH in the glaucoma group was observed. A significant increase in OH was detected in the first week after surgery. This may be due to the surgical procedure itself and/or to the postoperative treatment.

The OH-sector scores were gradually restored to the baseline level, with a significant improvement in most of the OH-sector values during the sixth month. Important group differences disappeared by the sixth month in all the sectors except for the nasal bulbar one. Pérez-Bartolomé et al. detected a greater impact of treatment burden on nasal hyperemia than on the temporal quadrant ones. This can 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.
Table 4: Corneal and conjunctival stain (Oxford scale) results

| Parameters                  | Control Group | POAG Group | POAG group pre-NPDS | NPDS and next visits*** |
|-----------------------------|---------------|------------|----------------------|-------------------------|
| Corneal staining oxford     | OXFORD 0      | 72.72%     | 72.72%               | <0.001                  |
|                             | OXFORD ≥1     | 21.21%     | 21.21%               | <0.001                  |
| Nasal conjunctival staining | OXFORD 0      | 97%        | 93.9%                | <0.001                  |
|                             | OXFORD ≥1     | 3%         | 3%                   | <0.001                  |
| Temporal conjunctival staining | OXFORD 0     | 6.6%       | 3%                   | <0.001                  |
|                             | OXFORD ≥1     | 93.9%      | 93.9%                | <0.001                  |

Previous studies have suggested that the mucin 5AC secreted by the goblet cell plays an important role in tear film stability and have reported toxic side effects of anti-glaucoma drugs on the conjunctiva, especially if preservatives are used.[12,37]

Moreover, the reduction in goblet cell density and mucin 5AC can be due to several glaucoma surgery factors such as the 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 postoperative topical medication,[39] as recently investigated by Zhong et al.[35] in their studies concerning the influence of trabeculectomy and phaco trabeculectomy on the ocular surface. According to previous reports, goblet cell density did not return to preoperative level after 3 months of cataract surgery,[39] the same occurred with mucin 5AC after phaco trabeculectomy.[36]

In line with these findings, we also found an improvement in NIBUTf and average values in the third month after NPDS; however, no significant differences were observed in the sixth month compared to healthy eyes.

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 may be a cause of dry eye by inducing meibomian gland loss, particularly when the bleb is avascular or contains numerous intraepithelial microcysts.[39]

In the present study, no significant changes were observed in the meibomian gland.

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 between groups in the final follow-up visit. The different bleb morphology in NPDS and trabeculectomy can explain our results. Oh et al.[40] also found that eyes that underwent trabeculectomy had significantly higher, broader, and lesser vascular blebs and more microcysts than eyes treated with NPDS.

Despite these significant findings, our study was subject to several limitations.

First, we were limited by our small sample size; despite this, we have been able to distinguish significant differences as it is the first study of its kind that uses non-invasive technologies to investigate OSD in glaucoma patients after NPDS.

Second, the clinical ophthalmological examinations were subjective, though they were performed by just one ophthalmologist to avoid possible bias, and the comparison of keratitis was done based on the already-published Oxford scale, thus yielding more reliable values.

Finally, post-surgical steroids could have improved the ocular surface, masking our results; nonetheless, the measurements of the third and sixth-month should not be influenced by the treatment because it should have already been completed at that stage.

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 K5M and FD-OCT, we report 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 questionnaires than before the participant had the surgery.

**Conclusion**

The current study demonstrates that the withdrawal of anti-glaucomatous topical treatment can improve the ocular surface 6 months after NPDS; however, further studies should be performed to corroborate our results.

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**Conflicts of interest**

There are no conflicts of interest.

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