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# Evaluation of ocular surface following PreserFlo Microshunt implantation: Functional outcomes and quality of life

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## Abstract

**Background:** This study aimed to evaluate the impact of PreserFlo Microshunt on the ocular surface, focusing on both objective and subjective parameters.

**Methods:** Prospective-observational study on 48 eyes undergoing PreserFlo Microshunt implantation, standalone or combined with phacoemulsification. At baseline, 1-month, 6-months and 12-months post-operative follow-ups, we performed Ocular Surface Disease Index (OSDI) questionnaire, Schirmer's test (ST), Tear-film break-up time (TBUT), fluoresceine staining (FS), tear osmolarity and minimum corneal epithelial thickness (Epi-$Thk_{MIN.}$) measurements.

**Results:** OSDI score improved from 37.43 ± 17.49 at baseline, to 24.13 ± 12.55 at 1-month ($p = 0.003$) and to 12.89 ± 8.54 and 13.09 ± 10.22 at 6-months and 12-months ($p < 0.0001$). TBUT and ST, in a similar way, non-significantly increased at 1-month, but then improved at 6-months and 12-months ($p < 0.05$ for both). Tear osmolarity significantly decreased from 308.2 ± 7.3 mOsm/L at baseline, to 303.3 ± 8.2 mOsm/L, 295.6.2 ± 7.0 mOsm/L and 297.6 ± 6.8 mOsm/L at 1-month, 6-months and 12-months ($p < 0.05$ for all). Epi-$Thk_{MIN}$ was stable when comparing baseline (44.9 ± 5.7 μm) and 1-month ($p = 0.28$), and successively increased in 6-months (47.8 ± 5.5 μm, $p = 0.02$) and 12-months (48.0 ± 3.6 μm, $p = 0.01$). In subgroup analysis, OSDI score and tear osmolarity were significantly higher at 1-month in combined group compared to standalone group ($p = 0.03$ and $p = 0.02$, respectively), but reaching comparable values in successive follow-ups. Further, Oxford scale grades for FS were significantly improved when comparing baseline–6-months and baseline–12-months.

Gloria Gambini and Matteo Mario Carlà contributed equally to this study.

**Conclusion:** PreserFlo implantation improved ocular surface subjective symptoms, increased TBUT and ST, and reduced FS, highlighting the potential benefits of this surgical intervention. Moreover, we reported significant improvements of tear osmolarity and corneal epithelium.

**KEYWORDS**

corneal epithelium, dry eye disease, ocular surface, PreserFlo Microshunt, tear osmolarity

## 1 | INTRODUCTION

Nowadays. the proper glaucoma management requires a multidisciplinary approach, not only limited to pure intraocular pressure (IOP) control but focusing also on patients' quality of life (QOL). Although effective, both preserved and preservative-free (PF) topical drugs determine conjunctival and corneal microstructure alterations, thus causing poor patient compliance, ocular discomfort, and generally a low QOL.[1,2] Moreover, different studies demonstrated that excipients and preservatives are primarily implicated as 'drivers' of chronic inflammation of the ocular surface, leading to instability of the precorneal tear film.[3,4] In vivo confocal microscopy showed that squamous metaplasia, inflammatory cell infiltrates (granulocytes, lymphocytes, Langerhans cells), dendritic cell activation, loss of goblet cells and stromal fibrosis are the most often seen changes in the conjunctival and corneal epithelium.[5] Therefore, the role of the ocular surface has become prominent, influencing the tolerability of glaucoma treatment.[6,7]

The gold standard trabeculectomy is able to reduce topical therapy burden but, on the other side, remains an invasive surgical technique the outcomes of which are greatly influenced by chronic ocular surface inflammation brought on by long-term pharmacological treatment. In fact, chronic inflammatory changes may affect the flow of aqueous humour (AH) through the bleb wall, with detrimental impact on the surgical result and increased risk of surgical failure.[8,9] Moreover, although uncommon, ocular surface problems including filamentary keratitis, dellen keratitis and corneal epithelial abnormalities can even follow a successful trabeculectomy, mainly due to the epithelial toxicity of antifibrotic drugs like 5-fluorouracil and mitomycin C (MMC).[10–12]

In recent years, glaucoma surgeons have begun to perform so-called minimally invasive glaucoma surgeries (MIGS), in an effort to lessen the invasiveness of traditional filtering surgery and the ocular surface toxicity associated with long-term anti-glaucoma pharmacological therapy.[13] Considering the benefits of minimal trauma, including no or little scleral dissection and minimal conjunctival manipulation, a good safety profile and a quicker recovery, MIGS may be a good option for patients with mild to moderate glaucoma or for those who are intolerant to standard medical therapy.[14]

In the group of the MIGS-plus (still requiring conjunctival opening), the 8.5-mm PreserFlo MicroShunt (Santen Pharmaceutical Co., Osaka, Japan), made by the biocompatible flexible polymer 'SIBS' (poly[styrene-blockisobutylene-block-styrene]) has shown significant and sustained IOP-lowering effects in several researches.[15–17] It is inserted via a 3-mm long scleral tract created with a 25G needle and implanted ab externo, with the goal of maintaining a continuous aqueous outflow through the tube's lumen to a posterior position at least 7-mm away from the limbus, behind Tenon's capsule.[18] This technique allows to create diffuse and posterior blebs with a repeatable morphology, similar to those described for functioning TB blebs.[19,20]

As of now, there are no reports in literature regarding the effects of this minimally invasive technique on ocular surface, including both post-operative adverse effects and QOL changes, as a consequence of drugs burden reduction. Starting from this assumption, the aim of this research is to evaluate the impact of PreserFlo MicroShunt implantation on the ocular surface, focusing on both objective parameters and subjective indexes.

## 2 | METHODS

In this prospective mono-centric observational analysis, we enrolled primary open-angle glaucoma (POAG) patients who underwent MicroShunt PreserFlo implantation at Fondazione Policlinico Universitario A. Gemelli – Rome between October 27, 2020, and December 20, 2021, and followed them in a 12-months follow up. The study was approved by the Catholic University of the Sacred Heart Ethical Committee in Rome, Italy, and followed the guidelines of the Declaration of Helsinki. All patients who were recruited provided signed, fully informed consent.

The presence of an open iridocorneal angle, evidence of glaucomatous optic nerve injury, and visual field (VF) deficits were all used to characterise primary open angle glaucoma (POAG). We determined the following

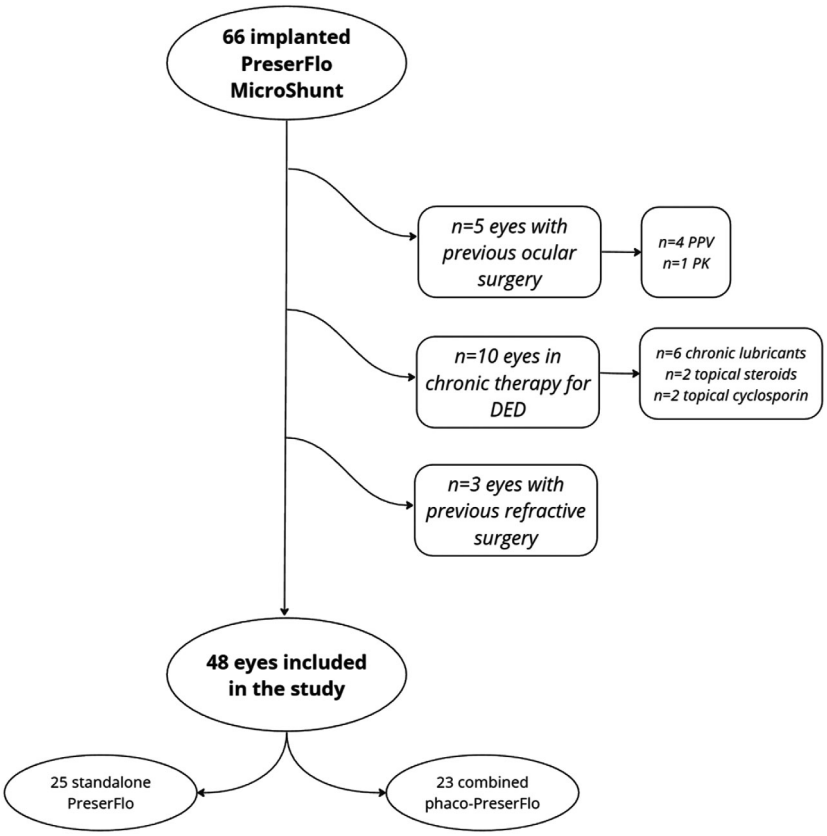


**FIGURE 1** Flow diagram detailing the initial cohort and the excluded patients, to define the final examined cohort.

inclusion criteria: POAG eyes with rapid and significant loss of visual function [mean deviation (MD), pattern standard deviation (PSD), visual function index (VFI), and glaucoma progression analysis (GPA)]; uncontrolled glaucoma on maximum tolerated topical medications with an intraocular pressure (IOP) of 12 to 45 mmHg; phakic or pseudophakic patients. In case of bilateral surgical indication, both eyes could be included if required, with surgeries at least 1 month apart.

Infectious keratitis, neovascular glaucoma, pigmentary glaucoma, allergic mucosal pathologies, pre-existing or concurrent corneal pathologies, history of prior ocular surgery with the exception of cataract phacoemulsification, and any patient who did not meet the inclusion criteria requirements were among the exclusion criteria. Moreover, subjects who were already using contact lenses, had undergone refractive surgery, were on chronic lubricants or were taking steroids or cyclosporin for the treatment of dry eyes were all excluded from the analysis.

Overall, 66 eyes underwent PreserFlo implantation during the study period, alone or combined with phacoemulsification. Forty-eight of them met all the inclusion and exclusion criteria. A flow diagram of the included eyes is available in Figure 1.

At the preoperative visit (baseline), all patient demographics (age, sex, date of surgery, laterality, and diagnosis), type of surgery (combined or stand-alone), and ocular parameters were gathered, including BCVA assessed with the Snellen chart, IOP at which the decision for surgery was made (measured with Goldmann applanation tonometer, GAT), and number of glaucoma medications. Additionally, data on individuals who had post-operative adverse effects was acquired. Surgery was performed after a significant period of topical therapy (35.5 ± 14.5 months) in all patients.

Post-operatively, at every follow-up, patients underwent a complete slit-lamp examination and three consecutive IOP measurements with GAT were performed, 5 minutes apart from each other, and an average value from the three was collected. Moreover, a complete set of examinations to assess ocular surface health was conducted at every follow-up. Patients were followed 1-month, 6-months and 12-months after surgery.

Surgical success was declared when patient's IOP reached values of 6–21 mmHg on two consecutive follow-up visits with a reduction of ≥20% in comparison to mean preoperative IOP in both visits. A complete success was intended for eyes which were not undergoing further medical therapies, although a qualified success was defined as eyes that had not failed but needed medical treatment to manage IOP. Patients requiring reoperation in the operating room, excluding bleb needling, were considered surgical failures. Moreover, failures were defined as patients with IOP outside of the target range or with

<20% IOP reduction from baseline on 2 consecutive follow-up visits after 3 months and not achieving at least 20% reduction below baseline in the last visit.

In a post-hoc analysis, eyes were split in two subgroups: standalone PreserFlo implantation versus combined phaco-PreserFlo procedure, in order to assess the role of combined cataract extraction on post-operative ocular surface parameters.

## 2.1 | Surgical procedure

All surgeries were performed by expert surgeons (S.R., T.C., A.S.) under peribulbar anaesthesia. A traction suture on the superior cornea was used to expose the upper nasal conjunctiva in order to perform conjunctival peritomy and careful Tenon dissection, in order to create a posterior pocket in the supero-nasal quadrant. To reduce bleeding and provide a clean surgical area, a diathermy probe was used on the sclera.

All patients were treated with Mitomycin C (MMC) 0.2 mg/mL by positioning three moist surgical sponges supplied by the manufacturer beneath Tenon's layer for 3 min, avoiding limbus, and then extensively rinsing with a balanced salt solution (BSS). At a distance of 3 mm from the limbus, a trypan blue imprint was made, and a 1-mm wide scleral pre-incision was made with a microknife. A 25-G needle was inserted into the anterior chamber at the trabecular meshwork to create a parallel scleral tunnel. After priming the PreserFlo MicroShunt with BSS to ensure its patency, it was placed with the bevel up in the conduit until it reached the AC, where it was visually inspected to ensure it was not too close to the iris or endothelium.

A planar attachment mechanism, resembling the fins of an arrow, is located halfway down the tube and prevents tube migration by securing the device in the pocket. Flow through the implant was verified using a surgical sponge to observe drop-by-drop flow from the extremity of the conduit. Tenon's layer was moved upstream of the conjunctiva to prevent the implant from becoming trapped, and the conjunctiva was then sutured impermeable using a 10–0 nylon fornix-based removable chain suture over Tenon's layer. In the case of combination surgery, the surgical approach did not change, and PreserFlo implantation was performed after phacoemulsification and IOL implantation.

In the post-operative period, patients received preservative-free topical dexamethasone 6 times a day for 4 weeks, with gradual tapering thereafter, and preservative-free topical ofloxacin, 4 times a day for a week.

## 2.2 | Ocular surface examinations

At baseline assessment and at every follow-up visit, the following parameters were collected.

### 2.2.1 | Subjective evaluation

Ocular surface disease index (OSDI) questionnaire was used, with scores ranging from 0 to 100. Higher scores on the OSDI indicate more subjective impairment and ocular surface disturbances.

### 2.2.2 | Objective evaluation

1. Schirmer's test (ST) without anaesthesia: after hooking the 5 mm folded end of an absorbent strip of paper over the lower lid's edge in the lateral lower conjunctival sac, the length of the strip's wetness after 5 min (with the eyes closed) was measured and recorded. We employed the Schirmer test tear strip, which consists of absorbent paper strips measuring 35 mm × 5 mm;
2. Tear film break-up time (TBUT): the time between the last complete blink and the first appearance of discontinuity of tear film or "dry" spot on the cornea under the cobalt blue filter of the slit lamp was measured using a fluorescein strip (Fluorets, Chauvin Pharmaceuticals, France) wetted with normal saline and administered with topical anaesthesia (Proparacaine HCl 0.5%, Sunways, IND). The average of two consecutive readings was calculated.
3. Fluoresceine staining (FS): the staining pattern was recorded in accordance to the Oxford Grading Scale and a numerical score (0–5) was assigned at every examination.[21]

**TABLE 1** Baseline demographic and clinical characteristics of the study population.

| | **Eyes ($n$ = 48)** |
|---|---|
| Study eye, RE, no (%) | 30 (63%) |
| Mean age, yrs | 72.2 ± 5.7 |
| Gender, male, no (%) | 20 (42%) |
| BCVA ± SD, decimals | 0.6 ± 0.3 |
| Mean IOP ± SD; mmHg | 22.0 ± 3.3 |
| Mean no. of IOP-lowering drugs ± SD | 2.8 ± 0.7 |
| Combined phaco-PreserFlo, no (%) | 23 (48%) |

Abbreviations: BCVA, best corrected visual acuity; IOP, intraocular pressure; RE, right eye.

**TABLE 2** Summary statistics of the OSDI, TBUT, Schirmer, tear osmolarity and minimum epithelial thickness (Epi-$Thk_{MIN}$) average by time in the entire cohort ($N = 48$). Results are expressed in mean ± standard deviation; CI (5th–95th percentile).

| | Baseline | 1-month | ΔBaseline-1-month *p*-value | 6-months | ΔBaseline-6-months *p*-value | 12-months | ΔBaseline-12-months *p*-value |
|---|---|---|---|---|---|---|---|
| OSDI Mean ± SD [95% CI] | 37.43 ± 17.49 [26.00–50.00] | 24.13 ± 12.55 [14.50–27.50] | **0.003** | 12.89 ± 8.54 [6.00–18.00] | **<0.0001** | 13.09 ± 10.22 [7.00–20.00] | **<0.0001** |
| TBUT (s) Mean ± SD [95% CI] | 7.51 ± 2.82 [6.00–10.00] | 7.68 ± 3.27 [5.00–11.00] | 0.35 | 8.97 ± 3.14 [6.00–11.00] | **<0.0001** | 9.31 ± 3.03 [7.00–11.00] | **<0.0001** |
| Schirmer (mm) Mean ± SD [95% CI] | 7.31 ± 2.27 [6.00–8.50] | 7.97 ± 2.35 [7.00–10.00] | 0.18 | 9.51 ± 2.77 [8.00–11.00] | **0.0005** | 9.83 ± 2.46 [8.00–11.00] | **0.0006** |
| Osmolarity (mOsm/L) Mean ± SD [95% CI] | 308.2 ± 7.3 [306.1, 310.3] | 303.3 ± 8.2 [300.9, 305.7] | **0.02** | 295.6.2 ± 7.0 [293.5, 297.6] | **<0.0001** | 297.6 ± 6.8 [295.6, 299.6] | **<0.0001** |
| Epi-$Thk_{MIN}$ (μm) Mean ± SD [95% CI] | 44.9 ± 5.7 [43.2, 46.5] | 46.5 ± 5.0 [45.0, 47.9] | 0.28 | 47.8 ± 5.5 [46.2, 49.4] | **0.02** | 48.0 ± 3.6 [46.9, 49.5] | **0.01** |

*Note*: Bold indicates significant values ($p < 0.05$).

Abbreviations: OSDI, ocular surface disease index score; TBUT, tear break up time.

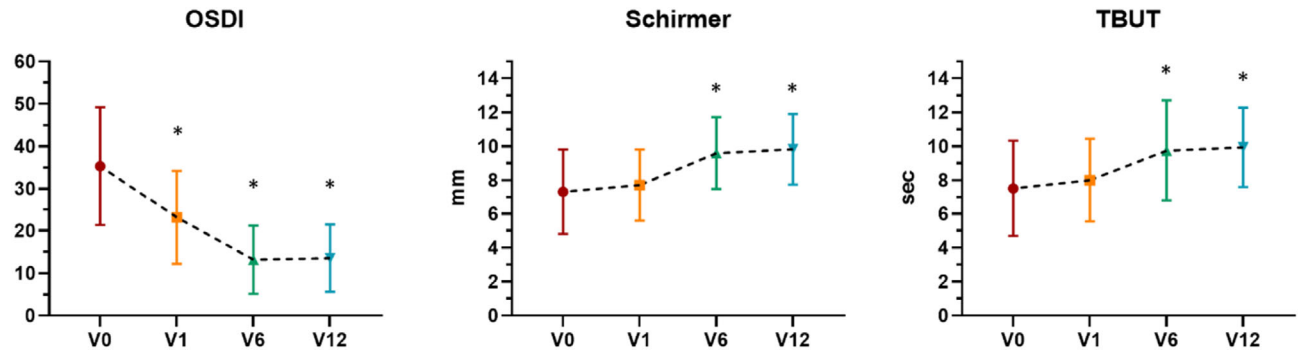


**FIGURE 2** Line charts showing subjective and objective ocular parameters variations at various follow up, in particular baseline, 1-month follow up, 6-month follow up and 12-month follow up in the entire cohort. OSDI, ocular surface disease index score; TBUT, tear break up time. Asterisks are for significant variations compared to baseline.

**TABLE 3** Comparison of frequency distribution in Oxford Scale evaluation at baseline visit, 1-month follow up, 6 and 12 months of follow-ups. Values are expressed as *N* (% of column).

| | | Baseline | | | | |
|---|---|---|---|---|---|---|
| **Oxford scale** | | **0** | **1** | **2** | **3** | ***p*-value** |
| 1-month | 0 | 12 (92%) | 8 (47%) | 4 (31%) | - | 0.08 |
| | 1 | 1 (8%) | 8 (47%) | 7 (54%) | 3 (60%) | |
| | 2 | - | 1 (6%) | 2 (15%) | 2 (40%) | |
| | 3 | - | - | - | - | |
| 6-months | 0 | 13 (100%) | 14 (82%) | 10 (77%) | 4 (80%) | **0.0003** |
| | 1 | - | 3 (18%) | 3 (23%) | 1 (20%) | |
| | 2 | - | - | - | - | |
| | 3 | - | - | - | - | |
| 12-months | 0 | 12 (92%) | 15 (88%) | 9 (69%) | 3 (60%) | **0.007** |
| | 1 | 1 (8%) | 2 (12%) | 3 (23%) | 2 (20%) | |
| | 2 | - | - | 1 (8%) | - | |
| | 3 | - | - | - | - | |

*Note*: Bold indicates significant values ($p < 0.05$).

Tear film osmolarity: performed under standard conditions via the TearLab® osmometer (CA, USA). After collecting a small tear sample, a disposable test card, thanks to a lab-on-a-chip system, is able to give osmolarity values (mOsm/L) with on-the-spot analysis.

Corneal epithelial thickness: corneal epithelial maps were performed using the MS-39 Anterior Segment-Optical Coherence Tomography (CSO, Firenze, Italy). Minimum epithelial thickness values (Epi-$Thk_{MIN}$) were collected at every follow-up.

## 2.3 | Statistical analysis

The statistical analysis was conducted using GraphPad PRISM Software, (Version 9.0; GraphPad, La Jolla, CA). Our sample's normality was determined using the Shapiro–Wilk test, and $p > 0.05$ was utilised to confirm the null hypothesis. We performed Analysis of Variance (ANOVA) for repeated measures and Dunnett's multiple comparison test with the Geisser–Greenhouse adjustment for matched pairs. To compare the difference between each pair of non-matched means, the Tukey test, which computes confidence intervals, was used. For contingency analysis, Chi-square and Fisher's exact tests were utilised. Oxford score was tested for level changes over time by the symmetry test (exact method). In addition, correlation studies were performed on continuous variables. The quantitative results were represented as the mean standard deviation, and a $p$ value <0.05 was deemed statistically significant. The 95% confidence interval (CI) of the mean was used.

# 3 | RESULTS

A total of 48 eyes were included in the study. The study population's mean age at the time of surgery was 72.2

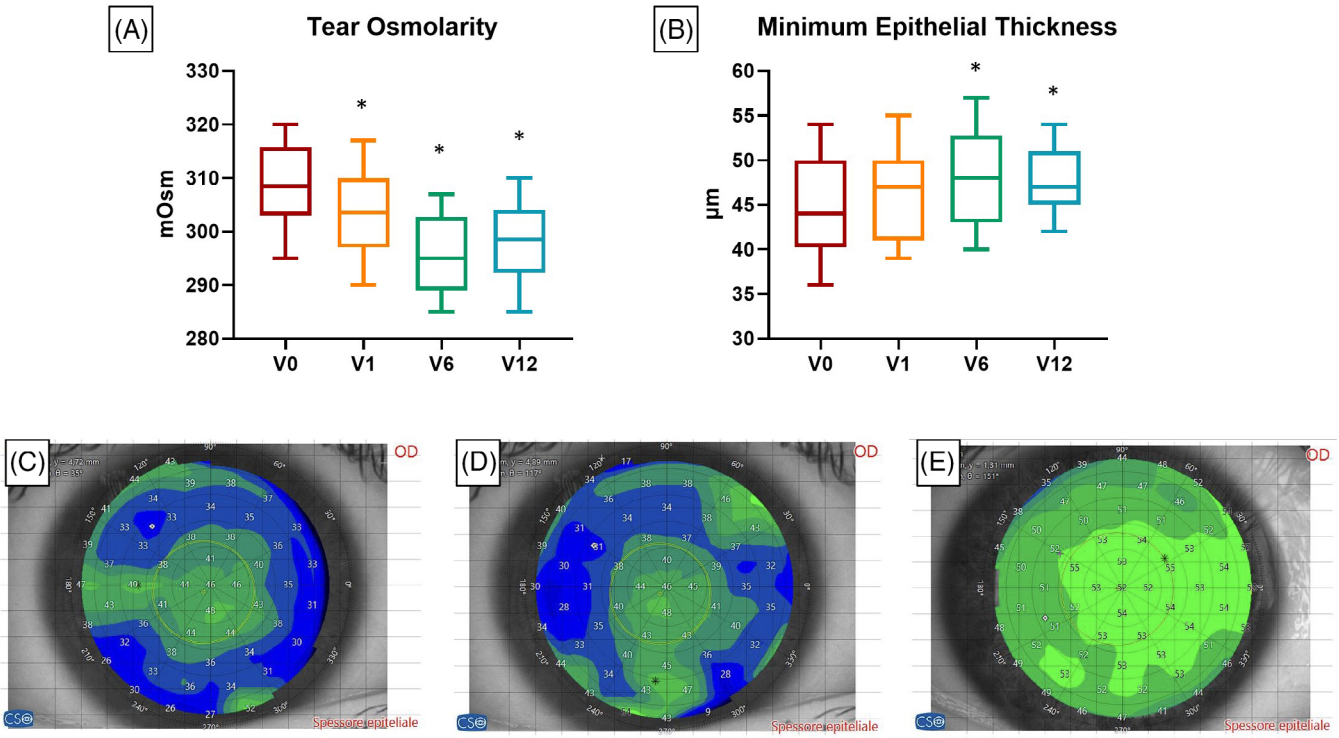


**FIGURE 3** Box and plot graphs showing variations of tear osmolarity (A) and minimum corneal epithelial thickness (B). Behind, MS39 AS-OCT scans of an eye showing significant improvement of the corneal epithelium when comparing baseline (C), one-month follow up (D) and six-months follow up (E). AS-OCT, anterior segment optical coherence tomography.

± 5.7 years; laterality (RE/LE) was 30/18; sex (M/F) was 20/28. Mean preoperative IOP treated with anti-glaucoma drugs was 22.0 ± 3.3 (range, 14–28 mmHg), on a mean number 2.8 ± 0.7 active principles; mean BCVA was 0.6 ± 0.3. A total of 25 patients (52%) were already pseudophakic, although 23 patients (48%) underwent combined surgery.

Demographic characteristics of the study cohort are visible in Table 1.

PreserFlo MicroShunt implantation reduced IOP to 11.3 ± 2.1 mmHg at 1-month, 12.9 ± 2.2 mmHg at 6-months and 14.1 ± 2.8 at 12-months. At every time intervals, the difference from baseline was substantial ($p < 0.0001$ at all follow ups). Complete surgical success rates were 62% and 56% at 6-months and 12-months, respectively. The probability of qualified success was 82% at 6-months and 79% at 12-months. Pairwise analyses of the IOP matched by age or sex did not show any statistical differences ($p = 0.58$ and $p = 0.47$, respectively), as well as combined cataract surgery ($p = 0.17$).

Eight eyes (17%) experienced early post-operative hypotony, which was self-limited and fully resolved in all instances at 1-month. One eye (2%) required anterior chamber reformation in the first postoperative week, although one incidence (2%) of choroidal effusion was detected, being successfully managed with conservative therapy and fully resolved in the first post-operative week. Two eyes (4%) required slit-lamp bleb needling during the follow-up period.

The mean number of medications significantly reduced to 0.5 ± 0.4 active principles at 6-months ($p < 0.0001$) and to 0.8 ± 0.5 at 12-months ($p = 0.0002$).

## 3.1 | Ocular surface results

A summary of ocular surface parameters at every follow-up is visible in Table 2.

### 3.1.1 | Subjective evaluation

OSDI score showed a significant decrease at all time-points. From 37.43 ± 17.49 at baseline, to 24.13 ± 12.55 at 1-month ($p = 0.003$) and to 12.89 ± 8.54 at 6-months ($p < 0.0001$). At 12-months, OSDI score stabilised at 13.09 ± 10.22 ($p = 0.76$ when compared to 6-months), with 92% of patients reporting a subjective improvement in ocular symptoms when compared to baseline. Notably, we found that the slight but not significant tendency of OSDI increase at the end of the follow up, correlated with the number of topical medication

needed to achieve target IOP at 12-months ($r = 0.21$, $p = 0.11$). [Figure 2] Furthermore, although at baseline we reported 21 cases (44%) of complaints regarding ocular symptoms which significantly affected QOL, at both 6-months and 12-months only 3 (6%) and 4 (8%) eyes reported impactful ocular symptoms, respectively.

### 3.1.2 | Objective tests

1. TBUT showed a non-significant tendency to increase at 1-month (7.68 ± 3.27 vs. 7.51 ± 2.82 s at baseline, $p = 0.35$). However, at both 6-months (8.97 ± 3.14 s) and 12-months (9.31 ± 3.03 s) a significant increase in TBUT was reported ($p < 0.0001$ in each follow-up when compared to baseline). [Figure 2]
2. Similar to TBUT, ST showed a gradual but not significant increase at 1-month (7.97 ± 2.35 vs. 7.31 ± 2.27 mm at baseline, $p = 0.18$). Successively, it significantly improved at both 6-months (9.51 ± 2.77 mm, $p = 0.0005$) and 12-months (9.83 ± 2.46 mm, $p = 0.0006$). [Figure 2]
3. The comparison of frequency distribution of Oxford scale grades between baseline – 1-month showed no statistical difference ($p = 0.08$). Conversely, the comparisons baseline – 6-months and baseline – 12-months showed a statistical difference of levels ($p = 0.0003$ and $p = 0.007$ at the two time points, respectively). [Table 3]

Tear osmolarity showed a significant decrease at all follow-up times: from 308.2 ± 7.3 mOsm/L at baseline, it decreased to 303.3 ± 8.2 mOsm/L, 295.6.2 ± 7.0 mOsm/L and 297.6 ± 6.8 mOsm/L at 1-month, 6-months and 12-months ($p = 0.02$, $p < 0.0001$ and $p < 0.0001$, respectively). [Figure 3] Correlation analysis showed a significant positive correlation between OSDI scores and tear osmolarity ($r = 0.48$, $p = 0.01$). Moreover, as expected, a significant correlation between reduction in tear osmolarity and reduction in the number of topical active principles was found when comparing baseline and 12-months ($r = 0.38$, $p = 0.02$).

The minimum corneal epithelial thickness was stable when comparing baseline (44.9 ± 5.7 μm) and 1-month (46.5 ± 5.0 μm, $p = 0.28$), and successively showed a significant increase in 6-months (47.8 ± 5.5 μm, $p = 0.02$), which was confirmed at 12-months (48.0 ± 3.6 μm, $p = 0.01$). Notably, at baseline, in 45 eyes (94%) the location of the minimum thickness zone was out of the central 3-mm, with 32 eyes (67%) showing the lower epithelial thickness in the inferior quadrant. At the end of the study period, 38 eyes (79%) had experienced an increase in epithelial thickness, with a mean gain of 4.4 ± 2.1 μm. [Figure 3].

**TABLE 4** Summary Statistics of the OSDI, TBUT, Schirmer, tear osmolarity and minimum epithelial thickness (Epi-$Thk_{MIN}$) at every follow up, divided into two subgroups: Standalone PreserFlo ($n = 25$) and combined phaco-PreserFlo ($n = 23$). Results are expressed in mean ± standard deviation. $p$-values indicate intergroup differences ($t$ tests).

| | OSDI | | | TBUT (s) | | | Schirmer (mm) | | | Osmolarity (mOsm/L) | | | Epi-$Thk_{MIN}$ (μm) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Standalone PreserFlo | Combined Phaco-PreserFlo | p | Standalone PreserFlo | Combined Phaco-PreserFlo | p | Standalone PreserFlo | Combined Phaco-PreserFlo | p | Standalone PreserFlo | Combined Phaco-PreserFlo | p | Standalone PreserFlo | Combined Phaco-PreserFlo | p |
| Baseline | 38.22 ± 16.19 | 36.47 ± 19.55 | 0.28 | 7.42 ± 2.95 | 7.87 ± 3.52 | 0.32 | 7.42 ± 2.77 | 7.28 ± 3.14 | 0.86 | 307.5 ± 7.9 | 308.9 ± 8.5 | 0.58 | 44.7 ± 5.5 | 45.2 ± 6.9 | 0.72 |
| 1-month | 21.05 ± 15.13 | 28.13 ± 13.65 | **0.03** | 7.96 ± 3.05 | 7.02 ± 2.82 | 0.18 | 8.38 ± 3.27 | 7.68 ± 2.99 | 0.15 | 301.3 ± 8.1 | 305.4 ± 7.9 | **0.02** | 46.7 ± 5.5 | 46.2 ± 6.9 | 0.48 |
| 6-months | 11.05 ± 8.13 | 13.82 ± 9.65 | 0.28 | 8.72 ± 3.25 | 9.27 ± 2.92 | 0.23 | 9.92 ± 3.13 | 9.18 ± 2.81 | 0.38 | 294.3 ± 6.8 | 296.8 ± 7.1 | 0.19 | 48.2 ± 4.9 | 47.2 ± 6.0 | 0.36 |
| 12-months | 12.71 ± 10.13 | 13.43 ± 10.65 | 0.32 | 9.42 ± 3.85 | 9.07 ± 3.11 | 0.29 | 10.02 ± 2.67 | 9.71 ± 2.26 | 0.45 | 296.7 ± 7.5 | 298.4 ± 7.0 | 0.20 | 47.7 ± 3.5 | 48.3 ± 3.9 | 0.22 |

*Note*: Bold indicates significant values ($p < 0.05$).
Abbreviations: OSDI, ocular surface disease index score; TBUT, tear break up time.

### 3.2 | Subgroup analysis

In the subgroup analysis, we divided the cohort in standalone PreserFlo group and combined phaco-PreserFlo group to assess the role of phacoemulsification-induced inflammation on ocular surface parameters. A summary of all parameters divided for each subgroup is visible in Table 4. No significant differences were found preoperatively for any of the parameters taken into consideration ($p > 0.05$ for all).

Interestingly, we found a significant difference between the two subgroups exclusively at 1-month. In particular, either OSDI score and tear osmolarity were significantly higher in the combined group when compared to the standalone group ($p = 0.03$ and $p = 0.02$, respectively). Nevertheless, both of them showed a significant decrease at 1-month, even in the phaco-PreserFlo group, when compared to baseline: OSDI decreased from $36.47 \pm 19.55$ to $28.13 \pm 13.65$ ($p = 0.01$), and tear osmolarity lowered from $308.9 \pm 8.5$ to $305.4 \pm 7.9$ ($p = 0.04$). TBUT and ST showed, in both groups, a non-significant tendency to increase at 1-month, when compared to baseline.

At successive follow ups, no significant differences were reported between the two groups. In both standalone and combined techniques, a significant improvement in all subjective and objective tests was reported. [Table 4].

## 4 | DISCUSSION

It is well recognised that topical glaucoma medications, whether preserved or preservative-free (PF), alter the ocular surface and adnexa, thus affecting patients' compliance and quality of life (QOL).[1,2] The number of IOP-lowering drugs was shown to be connected with the intensity of ocular surface disease (OSD) symptoms, and the use of benzalkonium chloride (BAK) containing eye drops was found to be correlated with corneal and conjunctival stains.[22,23] Excipients and preservatives are the main 'drivers' of chronic ocular surface inflammation, determining either hypersensitive reactions or, more frequently, a persistent cytotoxic response, which also results in squamous metaplasia, desquamation, keratinization, activation of dendritic cells, and loss of goblet cells.[24,25] Further, gold standard trabeculectomy, although significantly reducing topical therapy burden, has been associated with ocular surface impairment, either bleb- or MMC/5-FU-related.[11,12] In our study, we tried to assess the effect of a MIGS, PreserFlo MicroShunt, on ocular surface, in patients with prior topical therapy. Several parameters have been taken into account in order to highlight both structural and functional variations after surgery.

Evaluation of symptoms, such as the OSDI questionnaire, or clinical objective indicators, such as ocular surface staining, the Schirmer test, and TBUT, may help diagnose OSD.[26] Although the categorisation of dry eye is well defined, it is still challenging to interpret these tests when assessing other OSDs, particularly the adverse effects of eye drops or preservatives. In a recent study, the incidence of OSD among glaucomatous patients varied depending on the test type utilised, from 40% (corneal and conjunctival staining) to 67.5% (TBUT), with 60% of patients reporting symptoms.[27]

The main pathogenic component generating ocular surface inflammation, symptoms, and tissue damage in dry eye is currently thought to be tear osmolarity. In particular, studies on glaucoma patients under topical therapy showed a significant increase of tear osmolarity, with a mean of 308.8 mOsm/L, although the average tear osmolarity of healthy individuals is 302 mOsm/L.[28,29] Similarly, in our study, baseline average tear osmolarity was 308.2 mOsm/L, with 58% of patients having osmolarities greater than 308 mOsm/L (mild to moderate dry eye disease). Moreover, the quantity of preserved eye drop instillations was associated with tear osmolarity, with values >315 mOsm/L in patients who had two or more instillations of preserved eye drops. In fact, BAK is a quaternary ammonium that has been shown to work as a detergent on the tear film's lipid layer, decreasing stability and increasing evaporation rate and tear osmolarity in the process.[27] That being the case, tear osmolarity may be used to monitor OSD over time in glaucomatous patients, with reports claiming that osmolarity levels dramatically decrease after surgical treatment, in tandem with the cessation of topical therapies.[27,30] Consistently with these results, we reported a significant improvement in tear osmolarity after PreserFlo implantation, still maintained 1 year after surgery. At that time, only 3 eyes (6%) had a tear osmolarity higher than 308 mOsm/L, with significant clinical benefits.

Recent publications have examined the incidence of OSD in MMC-augmented trabeculectomy patients, along with post-operative complications such bleb-related endophthalmitis, avascularity, transconjunctival seeping, and delayed bleb leaks.[11,12,31,32] Therefore, any alteration to the conjunctiva's, eyelids', or cornea's typical architecture or functioning, may have the potential to cause the development of dry eye illness.[33] Moreover, MMC usage may contribute to the dysfunction of the ocular surface. The rapidly reproducing corneoscleral limbal cells are the focus of MMC's antimetabolite activity, which damages these cells and prevents an appropriate replacement of the corneal epithelium, which is typically replaced by stem cells every 3–7 days.[33,34] Nevertheless, a recent research revealed that patients under topical medications

had higher OSDI scores, osmolarity, and fluorescein stain grading, and lower Schirmer Test and TBUT, when compared to patients undergoing trabeculectomy. Moreover, OSDI and osmolarity in the trabeculectomy group were higher but much closer to the scores of healthy subjects, rather than the topical drugs group.[30] On the other side, TBUT in the trabeculectomy group was considerably lower, probably due to the presence of the bleb, which interrupts the ocular surface and affect the stability of the tear film, causing dysesthetic symptoms.[30] Neves et al. claimed that the higher filtering blebs are, and the closer they approach to the superior limbus, the more they affect the stability of the ocular surface, and Lee et al. demonstrated raised tear film osmolarity in almost 40% of post-trabeculectomy patients with increased bleb height.[35,36] On the other side, if a diffuse and flat bleb can be produced, ocular surface parameters are way similar to healthy subjects.[30] PreserFlo MicroShunt, being able to create a bleb 7-mm away from the limbus, may induce a lower impact on the stability of the tear film. In our research, we indeed reported significant improvements in both subjective and objective parameters, even when focusing on TBUT times, thus suggesting minor damage to the corneoscleral limbus microenvironment.

Studies with in vivo confocal microscopy (IVCM) showed that the conjunctiva of patients who underwent trabeculectomy was characterised by hyper-reflective cell borders and cytoplasm of corneal basal epithelial cells with diffuse hyper-reflective inflammatory cells (lymphocytes/granulocytes), confirming the presence of a persistent subclinical inflammatory process, which is anyway lower when compared to eyes under medical therapy.[25,37] On the other side, Baiocchi et al. showed that, after Xen 45 Gel Stent sub-conjunctival implantation, corneal basal epithelium had a regular shape and few hyper-reflective dots in the superficial layers could be found, with normo-reflective corneal sub-epithelial nerve plexus, validating the lower global rate of ocular surface inflammation in patients who underwent minimally invasive surgery. Moreover, they reported a substantial number of conjunctival inflammatory cells in eyes that had combined phacoemulsification together with Xen implantation.[25] From a clinical perspective, we wanted to analyse the effect of combined phacoemulsification, a proven driver of inflammation, on the variations of ocular parameters. As expected, in the combined procedure subgroup, we reported a slower improvement of ocular surface parameters, when compared to the standalone procedure. These findings suggest that cataract extraction, thus causing a migration of inflammatory cells on the ocular surface, affects the stability of the tear film and alters corneo-conjunctival microenvironment. Referring to subjective and objective parameters, either OSDI and tear osmolarity were higher in the combined group 1 month after surgery, but then became comparable between the two groups at 6-months and 12-months follow ups, upholding the trend towards the recovery of surface homeostasis following an initial phacoemulsification-induced pro-inflammatory phase.

In addition to classic aforementioned parameters, AS-OCT tomography has recently seen its role in the diagnosis of dry eye disease (DED). A recent study by Shousha et al. analysed the effects of DED on corneal epithelium, claiming that dryness of the surface results in an irregularity of the epithelium layer, which is translated into pain and discomfort driven by abundant corneal sensory neurons. Since the extent of this difference between DED patients and normal people was statistically significant, the role of the epithelium could become a criteria for DED diagnosis.[38] Additionally, similar to our findings, other studies reported that the peripheral corneal epithelium is more severely impacted by the DED-induced change in epithelial thickness than is the central epithelium.[39,40] In our study, we reported significant improvements in corneal epithelium thickness, particularly in the peripheral zone, during post-surgical follow-up, in line with the reduction of fluorescein staining, when compared to baseline values. These findings suggest that epithelial maps could become an important parameter to assess the evolution or restoration of surface abnormalities in patient undergoing glaucoma surgery.

It is important to acknowledge the limitations of this study. First, the study had a relatively short follow-up period, and long-term effects on tear stability and ocular surface health need to be investigated. Second, this study focused on a specific sample size of 48 eyes, and larger-scale studies, along with comparison with control groups or standard trabeculectomy groups, are warranted to validate the findings. Additionally, confounding factors such as height and extent of the bleb should be considered in future research. Furthermore, in future, we are keen on completing our findings adding both conjunctival and Meibomian gland disfunction parameters. In addition, an IVCM analysis after PreserFlo implantation could help to find confirmations, from a cellular point of view, of the lower grade of post-surgical inflammation of the ocular surface, when compared to classic trabeculectomy.

Consistently with our previous research in which we demonstrated the minimal effects of Preserflo Microshunt on anterior segment parameters,[41] in this study we highlighted the positive impact of this device in post-surgical ocular surface's health. The improved tear film stability, increased break-up time, and reduced fluorescein staining highlight the potential benefits of this surgical intervention, along with the significant effects on tear osmolarity and corneal epithelium. Further studies with

longer follow-up periods and larger sample sizes are recommended to corroborate these findings and explore the long-term impact of Preserflo Microshunt on the ocular surface.

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None.

## CONFLICT OF INTEREST STATEMENT
The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## ETHICS STATEMENT
Approved by Catholic University of the Sacred Heart Ethical Committee in Rome, Italy.

## INFORMED CONSENT STATEMENT
Written informed consent was obtained from all participants.

## CONSENT TO PUBLISH
The authors affirm that human research participants provided informed consent for publication of the images.

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