



Efficacy and Safety of PreserFlo[®] MicroShunt After a Failed Trabeculectomy in Eyes with Primary Open-Angle Glaucoma: A Retrospective Study

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Received: April 13, 2021 / Accepted: May 27, 2021 / Published online: July 12, 2021
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ABSTRACT

Introduction: To evaluate the efficacy and safety of PreserFlo[®] MicroShunt in primary open angle glaucoma (POAG) eyes after a single failed trabeculectomy.

Methods: Retrospective review of POAG eyes with a failed trabeculectomy that underwent PreserFlo[®] MicroShunt implantation from March 2019 to November 2019, in two Italian glaucoma centers. Pre- and postoperative data were collected and compared.

Results: A total of 31 surgeries in 31 patients were reviewed. Mean preoperative IOP and mean preoperative number of medications were 24.12 ± 3.14 mmHg and 3.29 ± 0.64 , respectively, and decreased to 12.56 ± 2.64 mmHg

and 0.46 ± 0.77 at the 12-month postoperative follow-up visit ($p < 0.01$). The most frequent adverse events were transient hypotony (6 eyes, 19.3%) and choroidal effusion (3 eyes, 9.6%). In all cases spontaneous resolution was observed, with no intervention.

Conclusion: In POAG eyes with a single failed trabeculectomy, the PreserFlo[®] MicroShunt was safe and effective in reducing the IOP after a 12-month follow-up. The PreserFlo[®] MicroShunt may represent a viable choice as a second surgery.

Keywords: Glaucoma; MicroShunt; PreserFlo; Refractory glaucoma; Trabeculectomy

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Key Summary Points

Why carry out this study?

The optimal surgical management of eyes with primary open angle glaucoma after a failed trabeculectomy remains unknown. Available options include trabeculectomy revision or glaucoma drainage implant.

The PreserFlo[®] MicroShunt is a new surgical device implanted with a moderately invasive procedure.

The aim of the present study was to investigate the medium-term outcomes of PreserFlo[®] MicroShunt surgery in primary open-angle glaucoma eyes with a single failed trabeculectomy.

What was learned from the study?

The PreserFlo[®] MicroShunt is safe and effective in eyes with primary open angle glaucoma with a single failed trabeculectomy with a follow-up of 12 months. For this reason, it may be a viable choice as a second surgery in these eyes.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.14680986>.

INTRODUCTION

Trabeculectomy, introduced by Cairns in 1968 [1], is the gold standard technique for the surgical management of open-angle glaucoma [2]. Although trabeculectomy has been demonstrated to be effective in reducing the intraocular pressure (IOP) [3–6], its efficacy tends to

decrease over time, often requiring additional topical medical therapy.

When a trabeculectomy fails to achieve the target IOP despite a medical therapy, a second surgical intervention is needed. Available options in this case include revision of the previous trabeculectomy, a new trabeculectomy, or the use of a glaucoma drainage implant (GDI). Scarring processes, however, may have a detrimental effect on the revised trabeculectomy or the second trabeculectomy [7, 8]. In such cases, shunting the aqueous humor from the anterior chamber to the posterior subconjunctival space using a GDI may be advantageous, because the previously operated anterior conjunctiva is bypassed [9]. Unfortunately, this treatment strategy involves a considerably invasive procedure.

PreserFlo[®] MicroShunt (Santen, Osaka, Japan) is a new implantable device for IOP reduction in patients with open-angle glaucoma. The device is made of poly(styrene-*block*-isobutylene-*block*-styrene), a biocompatible, synthetic polymer also known as SIBS [10]. It is implanted *ab externo*, using a moderately invasive surgical approach. Mitomycin C (MMC) is also used during the implantation. The device redirects the aqueous humor posteriorly, and has been found to be effective at reducing IOP in initial non-comparative studies on glaucoma and ocular hypertensive eyes, with a low rate of complications, both in the short and in the long term [11–14]. As a result of the moderately invasive nature of the procedure compared to a trabeculectomy or a GDI, as well as the benefit of posterior aqueous humor redirection, the PreserFlo[®] MicroShunt may be a viable surgical option in eyes with a failed trabeculectomy.

The aim of the present study is to investigate the medium-term outcomes of PreserFlo[®] MicroShunt implantation in a group of primary open-angle glaucoma (POAG) eyes with a single failed trabeculectomy.

METHODS

A retrospective chart review was conducted of PreserFlo[®] MicroShunt interventions after a single failed trabeculectomy, performed in two

Italian glaucoma centers (IRCCS Policlinico San Matteo Foundation and Hospital, Pavia, Italy, and Centro Italiano Glaucoma, Milan, Italy), between March 2019 and November 2019. As the design of the study was retrospective in nature, no ethics committee approval was required.

Inclusion criteria were a previous diagnosis of POAG, a single failed trabeculectomy performed at least 6 months previously, IOP ≥ 21 mmHg despite maximum tolerated medical therapy, and follow-up of at least 12 months after Preserflo[®] Microshunt implantation. POAG was defined as the presence of ophthalmoscopically abnormal optic disk (diffuse or focal thinning of the neuro-retinal rim), open angle at gonioscopy (Shaffer grade III or IV) along with the presence of abnormal visual field (VF) consistent with glaucoma. Maximum tolerated medical therapy was defined as at least three drugs, administered as either fixed- or unfixed combinations. Eyes that had undergone previous intraocular surgeries, with the exception of trabeculectomy and/or uncomplicated phacoemulsification, were excluded from the study.

For study enrollment, a reliable VF had to be performed within the previous 2 months (24–2 SITA Standard program, Humphrey Visual Field Analyzer, Carl Zeiss Meditec, Dublin, CA, USA). The severity of VF damage was classified according to the Glaucoma Staging System 2 (GSS2) [15–17]. The GSS2 classifies VF test into seven stages, by considering VF mean deviation (MD) and pattern standard deviation (PSD) on a Cartesian plot [16]. The perimetric stages are identified by curvilinear lines inside the plot, and range from stage 0 (within normal limits) to stage 5 (severely affected). In comparison to other VF staging systems (The Advanced Glaucoma Intervention Study scoring system [18] and the Hodapp-Anderson-Parrish system [19]), the GSS2 has been demonstrated to be preferable for its ease of use for clinicians and researchers alike [20]. Furthermore, it has been used in a number of population-based studies and clinical trials [21–23].

Collected data included patient demographics, pre- and postsurgical IOP, number of glaucoma medications, and Snellen visual acuity.

Postoperative data were collected 1 day, 1 week, 1 month, 3 months, 6 months, and 12 months after Preserflo[®] MicroShunt implantation. Surgical notes were reviewed for intraoperative complications. Postoperative complications were collected from the patient charts, and included transient hypotony (defined as an IOP < 6 mmHg without choroidal effusion and spontaneous resolution by 15 days), choroidal effusion, hyphema, shallow anterior chamber, stent exposure, and endophthalmitis.

Complete (i.e., without medications) and qualified (i.e., with or without medications) surgical success at 1 year was defined according to three IOP criteria: 1. IOP ≤ 17 mmHg and ≥ 6 mmHg, with $\geq 20\%$ IOP reduction from baseline (first criterion); 2. IOP ≤ 14 mmHg and ≥ 6 mmHg, with $\geq 25\%$ IOP reduction from baseline (second criterion); 3. IOP ≤ 12 mmHg and ≥ 6 mmHg, with $\geq 30\%$ IOP reduction from baseline (third criterion).

The numbers of eyes requiring further surgical procedures in order to have the IOP controlled or the postoperative complications managed, following Preserflo[®] implantation, were reported. Data from these eyes were analyzed exclusively until the last follow-up available before the new intervention. Moreover, these eyes were considered as failures in the calculation of the 1-year success rates.

Surgical Technique

Careful conjunctival assessment was performed before surgery, aiming at identifying the best surgical site, i.e., temporally or nasally with respect to the previous trabeculectomy. Conjunctival mobility, fibrosis, and the presence of active inflammation were factors taken into account to evaluate where the PreserFlo could be implanted. A fornix-based sub-Tenon's flap was dissected over 90° to 120° , extending 8–10 mm posteriorly to the limbus. Three MMC-soaked sponges (0.3 mg/ml) were placed under the conjunctival flap for 3 min. After sponge removal, the tissue was meticulously rinsed with balanced salt solution. A reference point located 3 mm away from the surgical limbus was marked, and a shallow triangular

pocket was incised through the sclera, using a 1-mm-width pre-calibrated knife. A trans-scleral tunnel was then dissected with a 25G needle, extending from the apex of the pocket to the anterior chamber. The PreserFlo[®] implant was then inserted and its fins were firmly wedged into the previously dissected scleral pocket. Filtration through the device was confirmed by observing aqueous humor percolation from its distal end. Finally, the conjunctiva and Tenon's capsule were stitched to the limbus using 10.0 nylon sutures. Betamethasone eye drops were prescribed six times a day, and were gradually tapered over the following 4 months. Topical ofloxacin was administered four times a day for 15 days.

If needed, bleb needling was performed postoperatively at the slit-lamp using a 28G needle connected to a syringe, in order to penetrate the fibrous capsule around the distal end of the PreserFlo[®] MicroShunt, and thus restore aqueous humor flow through the device. Due attention was paid to avoid inadvertent perforation of the overlying conjunctiva and piercing subconjunctival blood vessels. In case of extensive scarring, a 0.1 ml solution containing an antimetabolite drug (50 mg/ml 5-fluorouracil (5FU) or 0.2 mg/ml MMC) was injected underneath the conjunctiva, at the end of the procedure. Following a negative or minimally positive Seidel test, the eye was patched with tobramycin antibiotic ointment until the next morning.

Statistical Analysis

Continuous variables were described as mean and standard deviation (SD). Categorical variables were reported as frequency and percentage. Continuous variables were tested for normality using the Shapiro–Wilk test. A non-parametric Wilcoxon signed rank test was used to compare baseline vs. postoperative data, as non-normal distribution of continuous variables was found. Taking into account the number of comparisons, a Bonferroni correction was applied.

Relationships between preoperative IOP, number of medications, time from previous

trabeculectomy, and 1-year follow-up IOP (outcome variable) were evaluated using univariate linear regression. Normal distribution of residuals was tested using the Shapiro–Wilk test, the Kolmogorov–Smirnov test, and the Anderson–Darling test, in addition to the visual inspection of the residual plot. Homogeneity of error variance was confirmed by examining the spread-location plot of residuals. One outlier was identified in the outcome variable (standardized residual > 3), and thus excluded from the analysis. All analyses were performed using R-project for Statistical Computing (R Core Team (2013), Vienna, Austria. <http://www.R-project.org/>).

RESULTS

Thirty-one pseudophakic eyes (31 patients) with a single failed trabeculectomy received PreserFlo[®] MicroShunt between March 2019 and November 2019 (Table 1), and were followed up for a mean of 13.35 ± 1.08 months. All patients were Caucasian, with a mean age of 67.98 ± 11.35 years. Trabeculectomy with MMC had been performed on average 32.77 ± 14.57 months before (range 7.7–66.0). According to the GSS2, VF before Preserflo[®] Microshunt implantation was classified as stage 2 in 3 eyes (9.68%), stage 3 in 23 eyes (74.19%), and stage 4 in 5 eyes (16.13%).

The PreserFlo[®] MicroShunt was positioned temporally with respect to the previous trabeculectomy, in 29 eyes (93.5%), and nasally in 2 eyes (6.4%). The mean preoperative and postoperative IOP and number of IOP-lowering medications are reported in Fig. 1. No relationship was found between the IOP at the 1-year follow-up visit and preoperative IOP ($p = 0.18$), number of IOP-lowering medications preoperatively ($p = 0.56$), and time from previous trabeculectomy ($p = 0.24$). Figure 2 shows a scatter plot of preoperative IOP versus 1-year follow-up IOP, taking into account the number of preoperative IOP-lowering medications.

Considering the success criteria at 1 year, 67.74%, 67.74%, and 45.16% of the eyes achieved complete success for the first (6–17 mmHg), second (6–14 mmHg), and third

Table 1 Patient characteristics

No. of eyes (patients)	31 (31)
Age in years, mean (SD)	67.98 (11.35)
Race	
White, <i>n</i> (%)	31 (100%)
Sex	
Men, <i>n</i> (%)	14 (45.1)
Women, <i>n</i> (%)	17 (54.8)
Eye	
Right, <i>n</i> (%)	17 (54.8)
Left, <i>n</i> (%)	14 (45.1)
Time from trabeculectomy (months)	
Mean (SD)	32.77 (14.57)
Minimum–maximum	7.7–66.0
IOP (mmHg), mean (SD)	24.8 (3.86)
Visual field MD (dB), mean (SD)	– 6.17 (1.88)
Visual field PSD (dB), mean (SD)	8.85 (2.12)
Stage of the disease (GSS2), <i>n</i> (%)	
Stage 2	3 (9.68)
Stage 3	23 (74.19)
Stage 4	5 (16.13)
Number of glaucoma medications (SD)	3.29 (0.64)
BCVA, decimal notation (SD)	0.57 (0.19)
Site of implantation	
Temporal <i>n</i> (%)	29 (93.5%)
Nasal <i>n</i> (%)	2 (6.4%)

SD standard deviation, *IOP* intraocular pressure, *MD* mean deviation, *PSD* pattern standard deviation, *GSS2* Glaucoma Staging System 2, *BCVA* best corrected visual acuity

(6–12 mmHg) criteria, respectively. Qualified success was achieved by 93.54%, 90.32%, and 48.38% of the eyes, when the respective success criteria were taken into account.

Of the 31 eyes undergoing surgery, 6 eyes (19.3%) returned to baseline visual acuity by

1 week, 6 eyes (19.3%) by 1 month, and 19 eyes (61.2%) by 3 months. None of the operated eyes experienced central visual acuity loss. One eye underwent one surgical revision of the Pre-serFlo® MicroShunt implant 4 months after the initial surgery because of uncontrolled IOP despite maximum tolerated medical therapy and bleb needling with antimetabolite.

The most frequent adverse event was transient hypotony (6 eyes, 19.3%). Choroidal effusion was documented in 3 eyes (9.6%); among them, one eye (3.2%) had shallow anterior chamber. Hyphema was reported in 1 eye (3.2%). All these complications resolved spontaneously. A total of 9 bleb needlings were performed in 6 eyes (19.3%). Three eyes (9.6%) received a single needling procedure, and 3 eyes (9.6%) received 2 needling procedures. Needling was augmented with 5FU in 2 eyes and with MMC in 1 eye. There was no case of stent exposure, hypotony maculopathy, persistent choroidal effusions, or endophthalmitis. No intraoperative complications were recorded.

DISCUSSION

The optimal surgical management of eyes with a failed trabeculectomy remains poorly defined. Trabeculectomy revision has been shown to be not particularly effective, likely because of the exaggerated healing response [8]. Conceptually, a GDI may have more chance of success, as it directs the aqueous humor posteriorly, away from perilimbal areas with extensive fibrosis.

The tube vs. trabeculectomy (TVT) study recruited patients with primary or secondary glaucoma and uncontrolled IOP (between 18 and 40 mmHg) who had previously undergone trabeculectomy or cataract extraction (mostly intra- and extracapsular techniques) [24]. A total of 212 eyes of 212 patients were enrolled in 17 centers, and randomized to Baerveldt GDI (350 mm², 107 eyes) or trabeculectomy plus MMC (0.4 mg/mL for 4 min, 105 eyes). Both interventions were similarly effective at reducing the IOP from 3 months postoperatively to the end of the follow-up, with a 5-year IOP of 14.4 ± 6.9 mmHg and 12.6 ± 5.9 mmHg in the tube and in the trabeculectomy group,

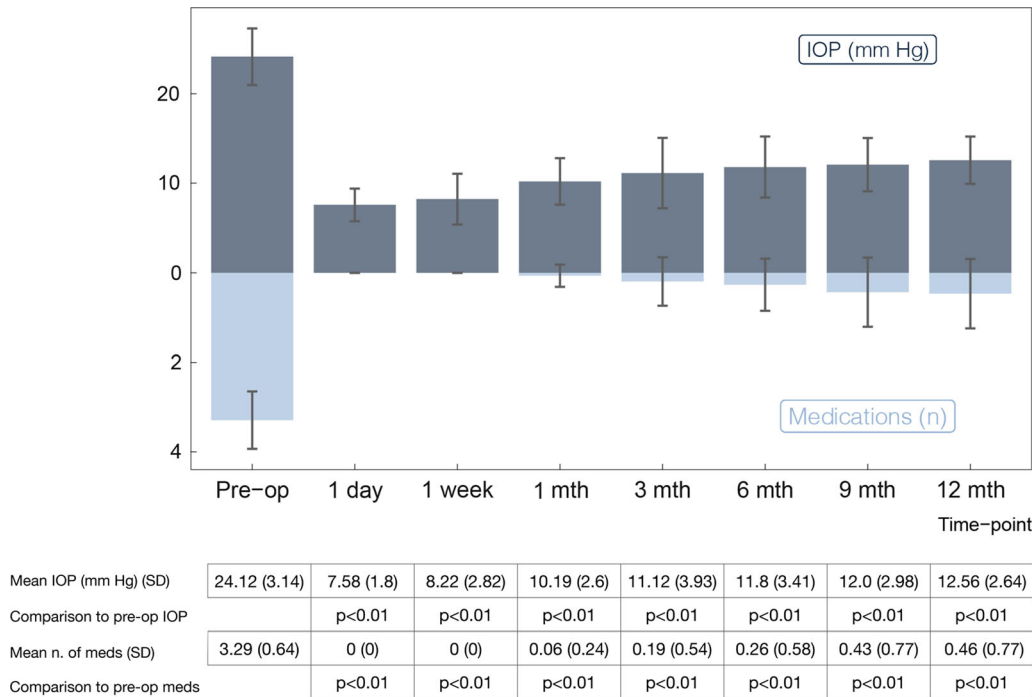


Fig. 1 Mean IOP and mean number of IOP-lowering medications throughout the study. Wilcoxon signed rank test was used to compare baseline vs. postoperative data.

IOP intraocular pressure, meds medications, SD standard deviation, mth month

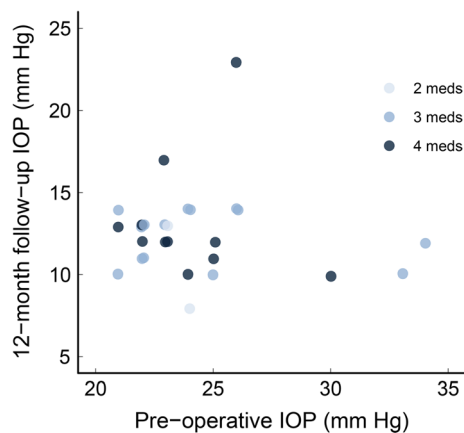


Fig. 2 Scatter plot of preoperative IOP versus IOP at 1-year follow-up, according to preoperative number of medications. Censored for reoperations ($n = 1$). IOP Intraocular pressure, meds medications

respectively ($p = 0.12$) [25]. The surgical safety profile was similar for both groups, with no difference in terms of number of serious complications over the entire follow-up [25]. The results of the TVT study supported the notion

that GDIs could be used earlier in the natural history of glaucoma, and not only in eyes that have already undergone glaucoma surgical procedures [26]. However, tube surgery remains particularly invasive, and may be associated with serious complications, such as hypotony, loss of central visual acuity, diplopia, corneal endothelial damage, and tube erosion [9, 25, 27]. In addition, a report by the American Academy of Ophthalmology has suggested that when a very low IOP is desired, a GDI may be a poor choice, because the IOP generally tends to settle at higher levels than after a trabeculectomy [28].

Nassiri et al. compared the efficacy and safety of a second trabeculectomy plus MMC vs. an Ahmed GDI in patients with a previous failed trabeculectomy [29]. At the 3-year follow-up visit, the IOP was reduced by 42.21% and 43.12% from baseline in the trabeculectomy and the GDI group, respectively ($p = 0.42$). The mean number of IOP-lowering medications at 3 years was 2.11 ± 1.73 and 2.20 ± 1.64 , respectively, in the trabeculectomy and in the

GDI group, with no between-group difference ($p = 0.82$). Although more eyes in the trabeculectomy group experienced postoperative complications (46.15% of the eyes in the trabeculectomy group vs. 30% of the eyes in the GDI group, $p = 0.03$), there was no significant difference in terms of number of complications, with the exception of wound leakage, occurring more frequently in eyes in the trabeculectomy group.

In our study, PreserFlo[®] MicroShunt was demonstrated to be effective at reducing IOP in eyes with POAG and a single failed trabeculectomy. Indeed, the IOP decreased significantly by 47.93% from baseline to the 1-year follow-up, and the mean number of medications also decreased significantly from 3.29 to 0.46. Relatively mild complications were encountered only at the postoperative period. The most frequent of these were transient hypotony and choroidal effusion. The IOP reduction and the decrease in the number of medications documented in our study were similar or better than those reported in both the TVT [25] and the Nassiri et al. [29] studies. Importantly, the safety profile of the procedure in our study was apparently better than the ones described in the TVT [25] and in the Nassiri et al. [29] trials. In the TVT study, serious complications (defined as ones requiring reoperation and/or causing loss of two or more Snellen lines) occurred in 22% and 20% of the enrolled eyes during the 5-year follow-up in the tube and in the trabeculectomy group, respectively ($p = 0.79$) [25]. Although the rate of serious complications in the study by Nassiri et al. was not reported, 7 eyes (10.7%) in the trabeculectomy group and 3 eyes (5%) in the Ahmed GDI group had more than one complication [29]. Moreover, at the end of the 3rd year of follow-up, 3 eyes (4.6%) in the trabeculectomy group and 2 eyes (3%) in the Ahmed GDI group had experienced loss of light perception. The comparison of our results with those of these studies, however, should be cautious, mainly because of the small sample size of our study and the relatively short-term follow-up.

In a recent study by Durr et al., the efficacy and safety of PreserFlo[®] MicroShunt were evaluated in 85 eyes with primary or secondary

glaucoma that had already undergone at least one surgical procedure (i.e., cyclophotocoagulation, trabecular bypass, trabeculectomy, GDI implant) [30]. At the 1-year follow-up visit, eyes implanted with PreserFlo[®] MicroShunt had a mean IOP of 13.5 mmHg with a mean of 0.9 medications (interquartile range 0–2). Sixty-one percent and 79.7% of the eyes achieved complete (without medications) and qualified (with medications) success, with failure being defined as IOP < 6 mmHg with vision loss, IOP > 17 mmHg, or IOP reduction < 20% from baseline. Needling plus MMC was performed in 11.8% of the eyes, and surgical bleb revision was undertaken in 4.7% of eyes ($n = 4$). The most frequent complications were choroidal effusion (11 eyes, 12.9%), shallow anterior chamber (8 eyes, 9.4%), hyphema (7 eyes, 8.2%), and hypotony maculopathy (3 eyes, 3.5%). A comparison of these results with ours is difficult, as we only enrolled patients with POAG and a single previous trabeculectomy. The IOP reduction after 1 year of follow-up in our study was similar and even better than the IOP reduction observed by Durr et al. [30]. Additionally, early hypotony was the most frequent complication in both studies. This adverse event may be relatively frequent with this type of surgery because of the lack of a valve mechanism embedded into the device.

Karimi et al. recently published a retrospective review of 17 eyes with primary or secondary glaucoma that underwent Xen[®] gel stent implantation after a failed trabeculectomy [31]. In this study, the IOP decreased from 21.5 ± 2.4 preoperatively to 13.6 ± 3.4 mmHg ($p < 0.05$) at 12 months (36.8% reduction from baseline), while the mean number of IOP-lowering medications decreased from 2.8 ± 0.6 to 1.0 ± 1.3 ($p < 0.05$). The most frequent complications were transient hypotony (23.5%), postoperative IOP spike (11.8%), and surgical failure (11.8%), requiring new interventions to control IOP. One eye (6%) lost one line, and 1 eye (6%) lost three lines of Snellen visual acuity by month 6. A mean of 2.4 bleb needlings/antimetabolite injections were required per eye to control the IOP. Because the Xen[®] gel stent and the PreserFlo[®] MicroShunt are different devices, with dissimilar design, and each requires a different

surgical technique, the results of our study are not comparable to the results by Karimi et al. [31].

Limitations of the current study include its retrospective design, the small sample size, and the medium-term follow-up. Moreover, our results may not be valid in eyes affected by other types of glaucoma than POAG.

CONCLUSION

The current study suggests that PreserFlo[®] MicroShunt in eyes with POAG and a single failed trabeculectomy is effective in reducing IOP after a follow-up of 12 months, with a favorable safety profile. As PreserFlo[®] MicroShunt surgery is less invasive in comparison to GDI surgery or trabeculectomy, it may represent a viable choice as a second surgery in these eyes. Further studies, with a greater sample size and a longer follow-up are warranted to confirm these first results. In addition, data about the comparative efficacy and safety of PreserFlo[®] versus other surgical options (e.g., second trabeculectomy, Xen or GDI implantation) in eyes with a failed trabeculectomy are needed.

ACKNOWLEDGEMENTS

Funding. Open access funding provided by Università degli Studi di Pavia within the CRUI-CARE Agreement. The contribution of the Fondazione Bietti in this study was supported by Ministry of Health and Fondazione Roma, Italy.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authors' Contributions. Conceptualization: Luciano Quaranta, Ivano Riva; Methodology: Luciano Quaranta, Ivano Riva, Roberto Carassa; Formal analysis and investigation: Eleonora

Micheletti, Luciano Quaranta, Ivano Riva; Writing—original draft preparation: Carlo Bruttini, Riccardo Fausto, Eleonora Micheletti, Ivano Riva; Writing—review and editing: Andreas Katsanos, Luciano Quaranta, Ivano Riva; Supervision: Luciano Quaranta, Ivano Riva.

Disclosures. Luciano Quaranta: Fee/Honoraria from Allergan, Bausch&Lomb, Novartis, Thea, Santen, Visufarma; Consultancy for Fidia-Sooft, Visufarma; Travel/Research grant from Allergan, Bausch&Lomb, Omikron, Novartis, Santen, SIFI. Roberto Carassa: Fee/Honoraria from Allergan, Fidia-Sooft, Omikron, Santen; Andreas Katsanos: Honoraria and congress expenses from Santen, Vianex, Zwitter; Research grant from Laboratoires Théa. Ivano Riva: Honoraria and congress expenses from Allergan, Santen, Visufarma, SIFI. Eleonora Micheletti, Carlo Bruttini and Riccardo Fausto declare that they have no conflict of interest.

Compliance with Ethics Guidelines. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. As the design of the study was retrospective in nature, no ethics committee approval was required.

Data Availability. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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