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Efficacy and Safety of the Preserflo Microshunt With Mitomycin C for the Treatment of Open Angle Glaucoma

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Précis: The Preserflo Microshunt (PSM) is a safe and effective glaucoma microfiltering implant that significantly reduces the intraocular pressure (IOP), either alone or in combination with phacoemulsification, during the first year after surgery.

Purpose: The purpose of this study was to assess the safety and efficacy of the PSM for the treatment of open angle glaucoma with 0.2 mg/mL mitomycin C, either alone or in combination with cataract surgery.

Methods: A retrospective, open-label study of 64 eyes with primary open angle glaucoma that underwent PSM implantation and were followed up for at least 9 months. Success was defined as IOP 6–17 mm Hg and a reduction of at least 20%, complete without hypotensive medication, and qualified with medication. Safety was assessed by the incidence of adverse events. Secondary endpoints included mean hypotensive medications, visual acuity, and incidence of needling and surgical revision.

Results: A total of 51 eyes underwent PSM alone and 13 underwent PSM+phacoemulsification. In the overall population of the study, the mean IOP was significantly reduced from 22.03 ± 0.7 mm Hg at baseline to 12.7 ± 0.4 mm Hg at the final visit, $P < 0.0001$ (mean follow-up: 11 ± 1.4 mo). The IOP was significantly reduced in both groups ($P < 0.0001$). Ocular hypotensive medication was reduced significantly from 2.7 ± 0.7 to 0.2 ± 0.5 ($P < 0.0001$). No significant differences were found in IOP-lowering medication between groups (PSM alone, 0.2 ± 0.08; PSM+phacoemulsification, 0.1 ± 0.1; $P = 0.2$). At the final visit, 70.3% were considered as complete success and 12.5% as qualified success. The most common adverse event was clinical hypotony (7.8%) followed by hyphema (4.7%), and anterior chamber reformation (1.6%). Overall, 1.6% required needling and 15.6% surgical revision to restore the flow.

Conclusion: Glaucoma surgery with the PSM and mitomycin C was efficacious and safe in the short term, either alone or in combination with cataract surgery, and may be considered a surgical option for lowering IOP in primary open angle glaucoma.

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The reduction of the intraocular pressure (IOP) has been proven as the only valid treatment for glaucoma, which is the main cause for irreversible blindness worldwide.[1] In a recent study[2] carried out by the GBD 2019 Blindness and Vision Impairment Collaborators, among the global 33.6 million adults aged 50 years and older who were blind in 2020,[3] the second leading cause of blindness was glaucoma (3.6 million cases, ranging from 2.8 to 4.4), after cataracts. The study reported that glaucoma was also the fourth leading cause of moderate and severe vision impairment.

The actual gold standard for glaucoma surgery is trabeculectomy, described and applied since the mid-1960s, but new subconjunctival microfiltering tubes have been developed in recent years, aiming to reduce the high rate of adverse events (AEs) related with classic filtering surgery. One of them is the Preserflo Microshunt (PSM) (Santen Pharmaceutical Company Ltd, Osaka, Japan), an aqueous drainage shunt designed to be implanted "ab externo" to create a full-thickness fistula from the anterior chamber (AC) to a new space created underneath the complex conjunctiva-Tenon capsule.[4] The studies that have analyzed this device have shown different sample sizes (from 14 to 156 eyes) and follow-up times (1 wk–5 y).[5–21] In a recent major review, Bell et al[22] pointed out that the best available evidence regarding mitomycin C (MMC) dosing in combination with this device had been reported in the study carried out by Riss et al,[5] that compared 87 eyes with 2 concentrations of MMC (0.2 and 0.4 mg/mL) and locations (near and away from the limbus). The authors concluded that the trend was to increase the efficacy with higher concentrations of MMC placed close to the limbus. There have been other MMC regimes proposed (varying dose and/or time of exposure), however, up to date, there is no compelling evidence to support the superiority of 1 MMC protocol over another.[5] The review conducted by Bell et al[22] concluded that with PSM, the trend is to achieve higher rates of success with higher concentrations of MMC, increasing the rate of device-related AEs and reoperations as well. The clinical study with the longest follow-up has been carried out by Batlle et al,[9] reporting the outcomes of 23 patients with primary open angle glaucoma (POAG) 5 years after surgery using 0.4 mg/mL MMC for 3 minutes. The authors concluded that the reduction of the mean IOP and the number of hypotensive medications on the long term after

PSM implantation was sustained over time, with a low rate of postoperative complications and no long-term sight-threatening AEs.

The purpose of the present study was to assess the effectiveness and safety of the PSM implantation with 0.2 mg/mL MMC for 2 minutes in POAG patients.

METHODS

Study Design

This was a single-center, nonrandomized and single-arm study that retrospectively examined 64 eyes of 57 patients at the Oftalvist Clinic in Madrid, Spain. The patients underwent glaucoma surgery between October 2019 and April 2021. The study was approved by the Oftalvist Review Board and followed the tenets of the Declaration of Helsinki. All patients signed an informed consent after explaining the nature and possible consequences of the study.

Patients

POAG adult patients who were on maximum tolerable medical therapy and showed progressive visual loss were included in the study. The inclusion criteria were as follows: best-corrected visual acuity (BCVA) of 20/200 or better; uncontrolled glaucoma under maximum tolerated medication, IOP values ranging from 12 to 45 mm Hg, phakic or pseudophakic patients treated with intracapsular lens implantation and individuals who have shown rapid and significant loss of visual function (visual function index, mean deviation, and glaucoma progression analysis with the Humphrey Visual Field Analyzer; Carl Zeiss AG, Germany). Both eyes could be included at an interval of 1 month for uncomplicated cases. All patients included were submitted for PSM surgery with 0.2 mg/mL MMC for 2 minutes and a minimum follow-up of 9 months. The sample was divided into 2 subgroups, PSM alone or combined phacoemulsification-Preserflo (Phaco-PSM). PSM was implanted in 51 patients as a standalone procedure (79.6%), and 13 patients underwent combined surgery (20.3%). Table 1 shows the baseline characteristics of the overall population of the study and by subgroups (PSM and Phaco-PSM).

Exclusion criteria was considered: angle-closure, congenital, uveitic, or neovascular glaucoma elevated episcleral venous pressure, iridocorneal endothelial syndrome, epithelial downgrowth/ingrowth, Axenfeld-Rieger syndrome and pseudoexfoliation. Eyes with a history of previous filtering surgery (trabeculectomy, drainage devices) were only included when no signs of filtration were present at the slit-lamp examination (flat, vascularized bleb) and by anterior-segment optical coherence tomography (AS-OCT; Avanti Widefield, Optovue), by the presence of a uniform hyperreflective stromal pattern without microcysts and intrableb fluid cavity.

Surgical Procedure

The surgical procedure for PSM implantation has been previously described by our group.[13] In brief: "All surgeries were performed by the same surgeon (M.I.B.), with sub-Tenon anesthesia in the inferior-nasal quadrant. A traction suture on the superior cornea was used to expose the upper nasal conjunctiva to perform conjunctival peritomy and careful Tenon dissection over 2 clock hours, liberating all the attachments between the Tenon capsule and episclera and creating a posterior pocket between the superior and medial rectus muscles. A diathermy probe was applied to the sclera to control bleeding and to obtain a clear surgical field. MMC 0.2 mg/mL was used in all cases by introducing 3 soaked surgical sponges provided by the manufacturer under Tenon layer for 2 minutes, avoiding the limbus, and then gently washing with a balanced salt solution. A mark with trypan blue was placed with the tip of the caliper 3 mm away from the limbus, and a 1-mm-wide scleral preincision was created with a microknife until the tip was not visible. The scleral tunnel was created parallel to the surface of the sclera with a 25 G needle entering the AC at the trabecular meshwork. The PSM was then introduced into the tunnel until it reached the AC; its position was visually checked, ensuring that it was not too close to the iris or endothelium and was placed with the bevel facing up. A planar fixation structure resembling the fins of an arrow that seals the device in the pocket is located halfway down the tube, preventing leakage around the tube and the tube from migrating into the eye. The fins were placed at the end of the scleral tunnel to ensure that it was inside. Flow through the implant was confirmed by injecting balanced salt solution from the distal side of the tube with a 23 G cannula; a small air bubble advancing to the AC is usually observed, and drop-by-drop flow was confirmed from the end of the tube with a surgical sponge. Tenon layer was advanced before the conjunctiva to ensure that the implant was not caught in it, and then the conjunctiva was sutured watertight over Tenon layer with 10-0 nylon. A side-port incision was created at the end of the surgery to inject 0.1 mL of cefuroxime (1 mg/0.1 mL) into the

TABLE 1. Demographics and Baseline Characteristics

	Mean ± SD		
Variables	**Overall**	**PSM**	**PSM+Phaco**
Age (y)	73.44 ± 9.4	74 ± 1.3	70.9 ± 1.7
Male [n (%)]	32 (47)	27 (53)	5 (38)
Medicated IOP (mm Hg)	22.03 ± 6.3	22.5 ± 0.9	20.1 ± 1.3
IOP > 21 mm Hg [n (%)]	34 (53)	29 (57)	5 (38)
No. glaucoma medications	2.7 ± 0.7	2.8 ± 0.08	2.5 ± 0.2
Best-corrected visual acuity (Snellen decimal)	0.63 ± 0.3	0.61 ± 0.04	0.62 ± 0.09
Follow-up (mo)	11 ± 1.4	11 ± 0.2	11 ± 0.3
Spherical equivalent (D)	−0.62 ± 2.4	−0.5 ± 0.3	−1 ± 0.6
Central corneal thickness (μm)	509 ± 32.2	510.2 ± 4.9	506.9 ± 5.9
Visual function index (dB)	62.6 ± 27.7	62.5 ± 4.2	62.7 ± 9.1
Mean deviation (dB)	−13.49 ± 8.6	−13.6 ± 1.2	−13 ± 2.8

IOP indicates intraocular pressure; Phaco-PSM, combined surgery phacoemulsification-Preserflo Microshunt; PSM, Preserflo Microshunt as a standalone procedure.

TABLE 2. Proportion of Patients Who Were Classified as Complete (Without Medication) or Qualified (With Medication) Success Over the Course of the Study, Overall and by Groups of Standalone (PSM) or Combined Surgery (Phaco-PSM)

	Overall (%)		PSM (%)		Phaco+PSM (%)	
	Complete	Qualified	Complete	Qualified	Complete	Qualified
24 h	98.4	0	98.4	0	100	0
Week 1	96.8	0	96.8	0	100	0
Month 1	95.3	1.5	98	1.9	84.6	0
Month 3	93.7	6.2	86.7	3.7	92.3	7.6
Month 6	86.4	13.5	86.7	11.7	84.6	7.6
Final visit	70.3	12.5	71.6	11.3	53.8	7.6

Final visit (mean: 11 ± 1.4 mo).
Phaco-PSM indicates combined surgery phacoemulsification-Preserflo Microshunt; PSM, Preserflo Microshunt as a standalone procedure.

AC. For combined surgery, the surgical technique was the same and performed at the end of the phacoemulsification and intraocular lens implantation procedure."

Study Outcomes

The primary efficacy endpoint was the number of eyes that achieved complete success (IOP 6–17 mm Hg with at least 20% reduction without medication) and qualified success (IOP 6–17 mm Hg with at least 20% IOP reduction with medication). Patients with an IOP <6 mm Hg for >2 consecutive visits, those who required further glaucoma surgery or had surgery for complications were also considered as failure. The primary safety endpoint was the incidence of device-related and/or procedure-related AEs during the study (eg, hypotony, AC reformation, choroidal detachment, macular folds, prolonged inflammation, corneal decompensation, bleb leak, blebitis, endophthalmitis, malignant glaucoma, retinal detachment, perception loss). Secondary endpoints included the mean number of glaucoma medications, visual acuity, and the incidence of glaucoma reoperation (rate of needling, rate of open surgical revision, mean time for needling, and open surgical revision after surgery). IOP was measured using Goldmann applanation tonometry and BCVA using a standard decimal visual acuity chart. Ocular refraction and central corneal thickness were also reported.

Statistical Analysis

Statistical analysis was carried out using SPSS software (22.0 version; IBM Corp., Armonk, NY). Quantitative variables were shown as the mean ± SD, whereas qualitative variables were reported in terms of number and percentage. The normality distribution was checked by means of the Shapiro-Wilk test and the equal variance test by means of the Brown-Forsythe test. A *t* test was used to assess statistically significant differences between pre and postoperative outcomes. The statistical significance limit was set to a *P*-value <0.05 in all cases. Box plots and bar graphs were performed with Stata 17 (StataCorp LLC, College Station, TX).

RESULTS

Sixty-four eyes of 57 patients with POAG that underwent surgery between October 2019 and April 2021 were included. All eyes completed a minimum follow-up of 9 months (mean: 11 ± 1.4 mo, ranging from 9 to 12 mo). The demographic and baseline characteristics are shown in Table 1. The proportion male/female was 50.9%/49% ranging from 51 to 93 years. The mean medicated IOP was 22.03 ± 0.7 mm Hg, 28 eyes showed a preoperative IOP >21 mm Hg. The mean number of preoperative glaucoma medications was 2.7 ± 0.7 (ranging from 1 to 4).

The primary efficacy endpoint was to compute the number of eyes that achieved complete success (IOP 6–17 mm Hg and a reduction of at least 20% without

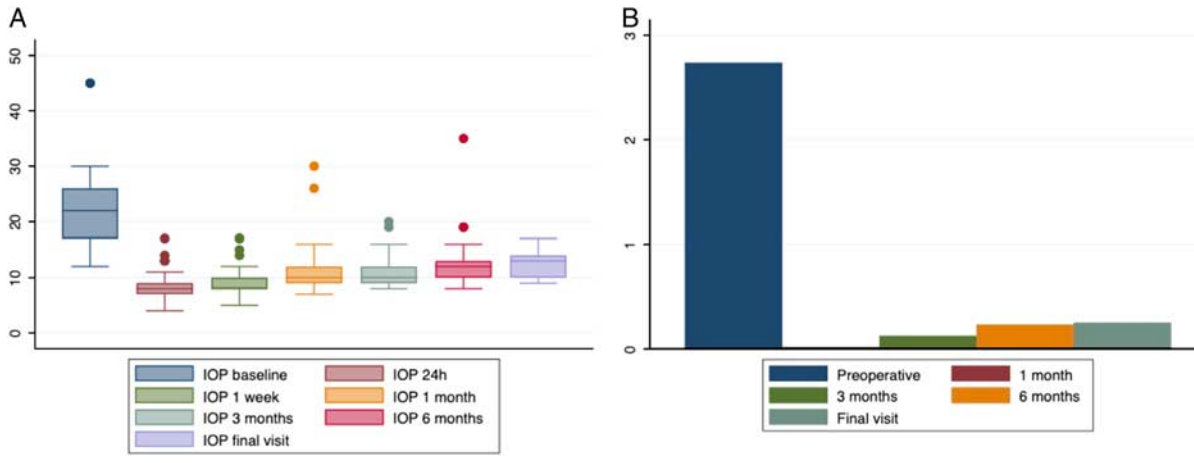

FIGURE 1. IOP (A) and number of ocular hypotensive medications (B) throughout the study. IOP indicates Overview of the mean intraocular pressure. Figure 1 can be viewed in color online at www.glaucomajournal.com.

TABLE 3. IOP (Mean ± SD) in the Overall Population of the Study and by Groups Over the Course of the Study

IOP (mm Hg)	Overall	PSM	Phaco-PSM
Preoperative	22.03 ± 0.7	22.5 ± 0.9	20.1 ± 1.3
24 h	8.3 ± 0.3	8.1 ± 0.2	8.9 ± 0.7
7 d	8.9 ± 0.3	8.7 ± 0.3	9.8 ± 0.6
1 mo	10.6 ± 0.4	10 ± 0.2	13 ± 1.8
3 mo	11.1 ± 0.3	11.2 ± 0.3	10.3 ± 0.4
6 mo	12.3 ± 0.4	12.6 ± 0.5	11.3 ± 0.5
Final visit	12.7 ± 0.4	12.8 ± 0.4	12.5 ± 0.6

The IOP reduction from baseline was significant ($P < 0.0001$) at all time points in the overall sample and by groups.

IOP indicates intraocular pressure; Phaco-PSM, combined surgery phacoemulsification-Preserflo Microshunt; PSM, Preserflo Microshunt as a standalone procedure.

medication) and qualified success (IOP 6–17 mm Hg and a reduction of at least 20% with medication). At the final visit, 45 eyes (70.3%) were considered as complete success and 8 eyes (12.5%) as qualified success. The mean IOP reduction at the final visit was −11.6 ± 6.2 mm Hg and the mean percentage of IOP reduction −46.9 ± 13.1%. Eight eyes (12.5%) were considered as qualified success. The mean IOP reduction in the overall population of the study at the final visit was −9.3 ± 6.5 mm Hg and mean percentage of IOP reduction, −38.7 ± 18.9%. Table 2 summarizes the proportion of patients classified as complete and qualified success in the overall population of the study and by groups (PSM vs. Phaco-PSM) over the course of the study. Overall, at the last follow-up visit the mean number of glaucoma medications had been reduced from 2.7 ± 0.7 to 0.19 ± 0.5 ($P < 0.0001$). Fifty-six eyes (87.5%) were medication free at the end of the study. No significant differences were found in IOP-lowering medication between groups (PSM alone, 0.2 ± 0.08; PSM+Phaco, 0.1 ± 0.1; $P = 0.2$). Figure 1 shows an overview of the mean IOP and number of hypotensive glaucoma medications throughout the study. Table 3 shows the mean IOP in the overall population of the study and by groups of standalone and combined surgery over the course of the study. The IOP was reduced significantly at all time points of the study ($P < 0.0001$), in the overall population and by groups. Mean Snellen decimal BCVA at the end of the study was 0.63 ± 0.29 (from 0.05 to 1.0), without statistically significant differences between presurgery and postsurgery values ($P = 0.4$).

TABLE 4. Summary of Procedure-related and/or Device-related Adverse Events

Adverse Event	n (%)	Time to Resolution (Mean ± SD) (d)
Clinical hypotony	5 (7.8)	33.0 ± 12.54
Anterior chamber reformation	1 (1.6)	
Choroidal detachment	5 (7.8)	
Macular folds	0	
IOP peak (< 1 mo)	2 (3)	11 ± 5.6
Bleb failure (> 1 mo)	8 (12.5)	85 ± 74
Prolonged inflammation	0	
Corneal decompensation	0	
Bleb leak	0	
Blebitis	0	
Endophthalmitis	0	
Malignant glaucoma	0	
Retinal detachment	0	
Perception loss	0	

IOP indicates intraocular pressure.

In relation to safety, Table 4 shows the device-related and/or procedure-related AEs. Overall, the most common non serious AE was hyphema (4.7%), solved without any further intervention. Serious AEs (situations that required further intervention), were the following: 1 patient that required needling (1.6%) due to the encapsulation of the bleb (Tenon cyst) 1 month after surgery, finally underwent surgical revision as well due to bleb fibrosis close to the final visit; 2 cases (3%) that showed IOP spike in the early postoperative period with a flat bleb at the slit lamp and absence of fluid assessed by AS-OCT, were treated with open surgical revision and 0.2 mg/mL MMC applied with sponges for 2 minutes; late fibrosis of the filtering bleb (> 1 mo) was reported in 12.5% of the patients and was managed with open surgical revision with MMC with the same concentration and methodology. The overall surgical revision of the implant (early and late), was reported in 15.6% of the total population of the study. This option was preferred to needling due to the deep position of the implant beneath the Tenon capsule. Clinical hypotony with choroidal detachment and a flat AC was reported in 7.8% of the patients, 1 case requiring AC reformation with viscoelastic (1.6%). Hypotony occurred usually in the first week and was resolved during the first month. There were no cases of late hypotony over the course of the study, or cases of visual loss due to hypotony maculopathy. No cases of bleb related events such as avascular blebs, bleb leaks, blebitis, endophthalmitis, tube migration, or perforation of the conjunctiva were reported. There were no cases of perception loss or malignant glaucoma in these series.

DISCUSSION

This retrospective study of 64 consecutive eyes with POAG analyzed the surgical success of the PSM implant combined with 0.2 mg/mL MMC for 2 minutes over a course of at least 9 months, with a mean follow-up of 11 months. The PSM significantly reduced the IOP during the course of the study ($P < 0.0001$) from 22.03 ± 0.7 mm Hg baseline to 12.7 ± 0.4 mm Hg at the last follow-up visit. The IOP reduction was also significant by groups (PSM alone or in combination with cataract surgery), $P < 0.0001$. In the overall population of the study, the mean number of glaucoma medications was reduced from 2.7 ± 0.7 baseline to 0.2 ± 0.5 at the last visit. Fifty-six eyes (87.5%) were medication free. No significant differences were found in the number of IOP-lowering medications between groups (PSM alone, 0.2 ± 0.08; PSM+Phaco, 0.1 ± 0.1; $P = 0.2$). The primary efficacy endpoint was the number of eyes that had achieved complete success (IOP of 6–17 mm Hg with at least 20% reduction without medication), and qualified success (the same criteria with medication). At the last follow-up visit, 70.3% eyes were considered as a complete success and 12.5% as a qualified success.

The results reported in the current study about efficacy are consistent with other clinical studies about PSM with concomitant use of MMC. Table 5 describes in detail those studies where this device was used, with information about the authors, year of publication, follow-up time, number of eyes, pre-IOP and post-IOP values, prenumber and postnumber of hypotensive medications, percentage of eyes free of medication, percentage of complete and qualified success, and

TABLE 5. Summary of Outcomes for Different Clinical Studies Using the PreserFlo Microshunt Device

References	Follow-up (mo)	Eyes	Pre-IOP	Post-IOP	Pre–No Medications	Post–No Medications	No. Eyes Medication Free (%)	Complete and Qualified Success (%)	Mitomycin C (Dose and Duration)
Riss et al[5]	12	23	23.8 ± 5.3	10.7 ± 2.8	2.4 ± 0.9	0.3 ± 0.8	64	73*	0.4 mg/mL† 2–3 min
		31	27.9 ± 6.7	13.3 ± 3.3	2.5 ± 1.4	0.5 ± 1.0	75	100*	0.2 mg/mL† 2–3 min
		33	25.4 ± 7.9	15.7 ± 4.6	2.9 ± 1.0	0.8 ± 1.3	87	100*	0.4 mg/mL‡ 2–3 min
Batlle et al[6]	36	22	23.8 ± 5.3	10.7 ± 3.5	2.4 ± 0.9	0.7 ± 1.1	64	63.6 and 95§	0.4 mg/mL 3 min
Schlenker et al[7]	12	156	21.4 ± NR	13.3 ± NR	3.4 ± NR	0.5 ± NR	74.8	76.9 and 92.5‖	0.2–0.5 mg/mL 2 min
Scheres et al[8]	24	14	20.1 ± 5.0	12.1 ± 3.5	2.3 ± 1.5	0.7 ± 1.1	64	49 and 79¶	0.2 mg/mL 3 min
Batlle et al[9]	60	18	23.8 ± 5.3	12.4 ± 6.5	2.4 ± 1.0	0.8 ± 1.3	61.1	56.5 and 26.1§	0.4 mg/mL 3 min
Ibarz-Barberá et al[10]	3	28	20.7 ± 6.3	10.9 ± 2	2.8 ± 0.7	0.6 ± 0.5	96	NR	0.2 mg/mL 2 min
Aghayeva et al[11]	1 wk	23	17 ± NR	7 ± NR	NR	NR	NR	NR	0.2 mg/mL 3 min
Quaranta et al[12]	12	31	24.12 ± 3.14	12.56 ± 2.64	3.29 ± 0.64	0.46 ± 0.77		67.74/67.74/45.16 and 93.54/90.32/48.38#	0.3 mg/mL 3 min
Ibarz-Barberá et al[13]	3	30	21.8 ± 5.2	10.9 ± 1.8	2.8 ± 0.7	0.6 ± 0.5	96	NR	0.2 mg/mL 2 min
Beckers et al[14]	24	81	21.7 ± 3.4	14.1 ± 3.2	2.1 ± 1.3	0.5 ± 0.9	73.8	78.3 and 21.7**	0.2–0.4 mg/mL 2–3 min
Pillunat et al[15]	6	26	15.9 ± NR	10.8 ± NR	4 ± NR	0 ± NR	100	100 and 90††	0.2 mg/mL 3 min
Martínez-de-la-Casa et al[16]	12	55	21.5 ± 3.3	14.6 ± 3.5	2.3 ± 0.5	0.2 ± 0.5	NR	62.1 and 82.8‡‡	0.2 mg/mL 2 min
Fea et al[17]	12	104	25.1 ± 6.5	14.1 ± 3.4	3.0 ± 1.0	0.77 ± 0.95	NR	26.0 and 58.7§§	0.2 mg/mL 3 min
Vastardis et al[18]	6	25	23.52 ± 5.78	11.56 ± 3.08	2.52 ± 0.91	0.04 ± 0.20	NR	48, 64, 68 and 68, 88, 92‖‖	0.2 mg/mL 3 min
Wagner et al[19]	6	35	18.0 ± NR	NR	2.0 ± NR	0.4 ± 0.8	NR	74.2 and 90.6	0.2 mg/mL 3 min
Baker et al[20]	12	395	21.1 ± 4.9	14.3 ± 4.3	3.1 ± 1.0	0.6 ± 1.1	65.5	65.1¶¶	0.2 mg/mL 2 min
Durr et al[21]	12	85	22.0 ± NR	13.0 ± NR	NR	NR	NR	61.0 and 79.7‖	0.2–0.5 mg/mL 2 min
This study	9–12	64	22.03 ± 6.38	12.92 ± 3.48	2.70 ± 0.72	0.19 ± 0.52	87.5	70.31 and 12.5	0.2 mg/mL 2 min

*IOP ≤ 18 mm Hg.

†Close to the limbus.

‡Deep in the pocket.

§Complete success requires all of the following: (1) IOP ≤ 21 mm Hg; (2) IOP reduction from baseline of ≥ 20%; (3) no reoperation for glaucoma (defined as requiring a procedure in an operating room); (4) no loss of light perception vision; (5) no chronic hypotony defined as IOP ≤ 5 mm Hg on 2 consecutive follow-up visits after 3 months; and (6) no use of supplemental glaucoma medication. Qualified success is the same as "complete success," but with use of supplemental glaucoma medication.

‖Upper IOP thresholds of 14 and 21 mm Hg for complete and qualified success with and without a 20% IOP reduction from baseline.

¶If success was achieved without medication, additional glaucoma surgery or other glaucoma therapy, it was considered a complete success and qualified success was obtained if target IOP was achieved without any additional glaucoma interventions, with or without IOP-lowering medication.

#Complete (ie, without medications) and qualified (ie, with or without medications) surgical success at 1 year was defined according to 3 IOP criteria: (1) IOP ≤ 17 and ≥ 6 mm Hg, with ≥ 20% IOP reduction from baseline (first criterion); (2) IOP ≤ 14 and ≥ 6 mm Hg, with ≥ 25% IOP reduction from baseline (second criterion); (3) IOP ≤ 12 and ≥ 6 mm Hg, with ≥ 30% IOP reduction from baseline (third criterion).

**Complete success (ie, supplemental glaucoma medications not required to maintain controlled levels of IOP) and qualified success (ie, requiring supplemental glaucoma medications to maintain controlled levels of IOP).

††Complete success was defined as mean diurnal IOP and peak diurnal IOP (a) ≤ 18 mm Hg for cases with mild glaucoma without threat of fixation and (b) mean diurnal IOP ≤ 14 mm Hg and peak IOP ≤ 18 mm Hg for cases with mild glaucoma with threat of fixation, moderate and advanced cases without clinical hypotony and the need of any IOP-lowering medication. Qualified success was defined with the same criteria but allowed for IOP-lowering medication.

‡‡Complete success was defined as a month-12 IOP ≤ 18 mm Hg and an IOP reduction ≥ 20% compared with baseline, without any hypotensive medication at month-12 visit. Qualified success was defined as a month-12 IOP ≤ 18 mm Hg and an IOP reduction ≥ 20% compared with baseline, with topical hypotensive medication at month-12 visit.

§§Complete success was defined as an IOP of 18 mm Hg or less, and an IOP reduction of 20% or more, without any hypotensive medication at the month-12 visit. Qualified success was defined as an IOP of 18 mm Hg or more and an IOP reduction of 20% or more with topical hypotensive medication at the month-12 visit.

‖‖Absolute success was regarded as the percentage of eyes achieving (a) 5 ≤ IOP ≤ 13 mm Hg, (b) 5 ≤ IOP ≤ 16 mm Hg, and (c) 5 ≤ IOP ≤ 21 mm Hg without additional medication or surgery and qualified success was regarded as the percentage of eyes achieving (a) IOP ≤ 13 mm Hg, (b) IOP ≤ 16 mm Hg, and (c) IOP ≤ 21 mm Hg with or without medication.

¶¶IOP ≥ 6 to ≤ 21 mm Hg and a ≥ 20% reduction in IOP from baseline on 2 consecutive follow-up visits after month 3, with or without glaucoma medications.

IOP indicates intraocular pressure; NR, not reported.

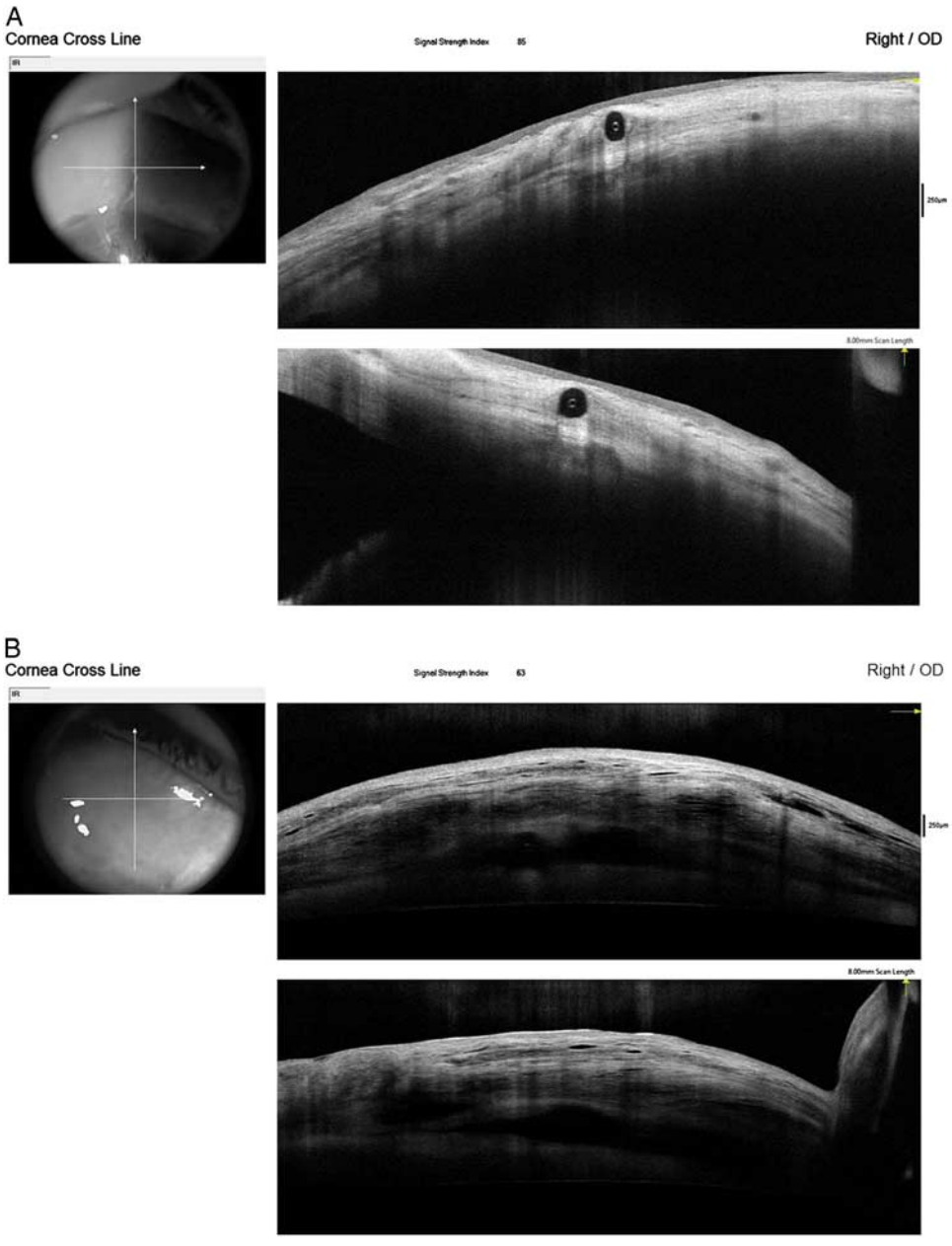

FIGURE 2. Anterior-segment optical coherence tomography of the bleb's morphology after PSM implantation. A, The hypereflective stroma that surrounds the tube means complete absence of fluid and fibrosis. B, The low reflectivity and multilayered stroma (stripping phenomena[24]) with an episcleral fluid cavity of low vertical diameter are typical features of the functioning filtering bleb after trabeculectomy.[25] PSM indicates Preserflo Microshunt. The intersection between the arrows indicates the spot where the AS-OCT is focused to obtain the image. The arrows can be rotated to obtain a cross section (white) or a longitudinal section (yellow). Figure 2 can be viewed in color online at www.glaucomajournal.com.

dose and time of MMC. Note that the definition of complete and qualified success may vary among the different studies (see footnote) and disables a direct comparison of the results in some cases. Despite this consideration, the success rates obtained in our study appear to be at least comparable to those reported in other studies with this device using the same concentration of MMC. The studies included in Table 5 show the outcomes for different sample sizes (from 14[8] to 381[20]), follow-up times (from 1 wk[11] to 5 y[9]) and concentration and time of application of MMC.

There is no clear consensus in the peer-reviewed literature on the most efficacious dose and time of MMC to be used during this surgery.[22] In our study, 0.2 mg/mL MMC was used for 2 minutes as it has been done in previous studies,[10–13,16,20] because the scientific evidence to strongly recommend the use of higher concentrations of MMC in populations of European descent is still scarce. Previously reported data from a multicenter study conducted across multiple European sites by multiple surgeons using 2 different concentrations of MMC (0.2 and 0.4 mg/mL)[14]

showed that postoperative IOP was similar between both subgroups at 1 and 2 years, however, there was a trend toward a greater IOP reduction with 0.4 mg/mL MMC compared with 0.2 mg/mL MMC after month 6 (the differences were significant only at 6 mo, probably because the study was not powered to assess the effects of different MMC concentrations). Interestingly, there was a significant difference in the medication reduction between groups, with 90.3% of patients in the 0.4 mg/mL MMC group free of medication at year 2 compared with 51,9% in the 0.2 mg/mL MMC group. The comparison of their results with the results of the current study shows that their percentage of complete success by subgroups of MMC concentration at 1 year (64% in the 0.2 mg/mL MMC group and 87.5% in the 0.4 mg/mL MMC group with 74,1% overall success[14]) was at least comparable to our results (complete success 70.3%). A deeper analysis between their subgroup of 32 patients with 0.2 mg/mL MMC and our 64 patients with the same concentration showed a higher success rate in our patients. The difference in demographics, varying surgical technique and postoperative management practices (as stated by the authors) in the multicenter study may have influenced the results, while the single-center, single-surgeon and common postoperative management method of the current study might have improved the surgical outcomes. In this sense, it is important to remark that the authors reported 3 out of 32 cases of surgical revision in the 0.2 mg/mL MMC group (9.3%), while in our series the percentage was higher (15.6%), due to early failure (3%) or late fibrosis (12.5%) of the filtering blebs. It is very likely that the rate of bleb fibrosis was actually comparable among their 0.2 mg/mL MMC subgroup of patients and ours, given that Preserflo provides a standardized flow rate of aqueous humor (theoretical and experimental resistance to flow = 1.3 mm Hg/μL/min, pressure drop 2.6 mm Hg[23]), but the way in which it was managed was probably different. In fact, 1 year after surgery they reported 0.9 mean number of medications versus 0.2 in our series, suggesting a probable trend toward the use of medication instead of surgical revision for the treatment of bleb failure in their study. In any case, the mean number of medications and the percentage of complete success at 1 year in their 0.4 mg/mL MMC subgroup (0.1% and 87.5%) was superior to our results (0.19 mean medication and 70.3% complete success), a superiority that follows the same trend reported by the authors with higher concentrations of MMC and supports the reliability of our results with 0.02% MMC.

The study with the longest follow-up (5 y) that analyzed 23 patients that underwent PSM implantation with 0.4 mg/mL MMC,[9] reported 82.6% overall success (IOP < 21 mm Hg with or without medication), 56.5% complete and 26.1% qualified success, suggesting that with a longer follow-up, the rate of bleb fibrosis increases despite the use of higher concentrations of MMC. The authors reported 8.7% surgical revision and needling at 5 years with 0.8 mean number of medications. In the current study, the percentage of surgical revision was higher (15.6%) and the mean number of medications lower (0.2) at 1 year, probably due to our tendency to surgically revise the fibrotic blebs to restore the flow and decrease the hypotensive medications. Even though the rate of fibrosis might have been lower in their patients due to the increase of the MMC concentration, the postoperative management of the bleb could have improved our results. In our opinion, one of the main advantages of PSM is the simplicity to surgically restore the flow in the same location, leaving other locations ("saving" conjunctiva) for potential further procedures. In our study, when bleb fibrosis was demonstrated clinically by the increase of the IOP in a patient with a flat bleb and by using AS-OCT, observing the absence of fluid around a superficial tube surrounded by hyperreflective tissue[10] (Fig. 2), surgical revision of the bleb was performed. The scar tissue formed around the implant that sometimes blocks the tube's lumen like the nest of a silkworm or, in other cases, an impermeable, thick, non-filtering membrane (excessive collagen deposition due to increased vertical shear stress in overpressured or too high blebs) that stops filtration, was removed. The implant was then checked for permeability and restoration of flow, and MMC 0.2 mg/mL was applied for 2 minutes. In any case, more evidence is required in this field since the possibility that more MMC is required in the mid-posterior part of the eye where the PSM drains and the Tenon capsule is thicker and more fibroblasts may reside,[10,14,26] is still not well known. Needling versus surgical revision is also another

TABLE 6. Hypotony Rates Reported in the Literature for the PSM

Implant	References	MMC (% and Method)	Hypotony (%)
Preserflo	Scheres et al[8]	0.02% sponges	39% (first week) Resolution 1 mo
Preserflo	Battle et al[9]	0.04% sponges	13% (3 first weeks)
Preserflo	Beckers et al[14]	0.02% sponges	0% (1 mo) 0% (2 y)
Preserflo	Beckers et al[14]	0.04% sponges	16.3% (1 mo) 0% (2 y)
Preserflo	Pillunat et al[15]	0.02% sponges+bevacizumab in the AC	69% (transient hypotony) 0% (long term)
Preserflo	Baker et al[20] (RCT)	0.02% sponges	28.9% (transient hypotony) 7.1% (long term)
Preserflo	Martínez-de-la-Casa et al[16]	0.02% sponges	Total: 1.7% (1 mo) PSM: 2.8% (1 mo) Combined: 0% (1 mo)
Preserflo	Ibarz et al[13]	0.02% sponges	11% 1 mo 0% 1–3 mo

AC indicates anterior chamber; MMC, mitomycin C; PSM, Preserflo Microshunt; RCT, randomized controlled trial.

TABLE 7. Overview of Some of the Studies That Report the Incidence of Hypotony With the XEN45 (XEN-GGM; Allergan Plc)

Implant and Technique	References	MMC (% and Method)	Hypotony (%)
XEN45 ab externo closed conjunctiva	Scheres et al[8]	0.02% injected	24% (first week)
XEN45 ab interno open conjunctiva	Dangda and colleagues[27,28]	0.02% injected (60 µg)	27% <5 mm Hg (transient hypotony)
XEN45 ab interno closed conjunctiva	Kim et al[29]	0.02% and 0.04% injected	66.7%–76.9%
XEN45 open vs. closed conjunctiva	Do et al[30]	0.02% injected (mean, 40 µg)	*Choroidal detachment:* Closed conjunctiva: 3.3% Open conjunctiva: 9.2%

"Ab interno": the implant is inserted through the anterior chamber. "Ab externo": the implant is inserted through the sclera. "Open conjunctiva": the conjunctiva is dissected to secure the implant's position beneath the Tenon capsule to decrease blockage, the implant can be insterted either "ab interno" or "ab externo." "Closed conjunctiva": there is no conjunctival dissection, the implant is always inserted "ab interno."

issue that needs further investigation, even though our results might suggest that open revision is more adequate due to the deep position of this device (a key for PSM success).

There is only one randomized controlled trial up to date that compares the effectiveness and safety of PSM versus the gold standard in glaucoma surgery, trabeculectomy.[20] Overall, 395 (Microshunt) and 132 (trabeculectomy) patients were randomized. At 1 year, the probability of success was lower in the PSM group (53.9%) compared with the trabeculectomy group (72.7%). Mean IOP decreased to 14.3 mm Hg in the Microshunt group versus 11.1 mm Hg in the trabeculectomy group. In the PSM group, complete success (IOP < 21 mm Hg) was achieved in 60.8% of the patients versus 68% after trabeculectomy. According to the authors, the 58 surgeons involved in the study had considerably greater experience with trabeculectomy compared with PSM, a fact that could explain the superior results achieved with trabeculectomy. In contrast, despite many of them where not experienced with Preserflo, and each of them might have performed hypothetically around 7 surgeries (this calculation was not described by the authors of the study), the mean IOP had still decreased significantly to 14.2 mm Hg on an average of 0.6 medications at year 1. In the current study, all the surgeries (65) were performed by the same surgeon that acquired experience with an initial learning curve of about 10 procedures. The experience acquired by the same surgeon over the course of the study might have improved the results compared with the multicenter study.

Regarding safety, the percentage of postoperative interventions and the incidence of hypotony reported in the randomized PSM versus trabeculectomy study discussed previously,[20] were higher in the trabeculectomy group (postoperative interventions: 67.4% trabeculectomy, 40.8% PSM; transient hypotony 49.6% trabeculectomy, 28.9% Microshunt; late hypotony occurring after 3 months 13.7% trabeculectomy, 6.1% PSM).

The incidence of early and especially late hypotony, reported by the authors seems to be higher compared with most of the studies published in the literature about this device (Table 6), including the current study (7.8% transient hypotony, 0% persistent hypotony). It is interesting to point out that the rate of hypotony reported in clinical studies ranges widely between 0% and 69%,[8,9,13–16,20] even though most of them report transient hypotony, with nearly no cases of persistent hypotony. Compared with its main competitor, XEN45 (XEN-GGM; Allergan Plc, Parsippany, NJ, EEUU), most studies have reported hypotony rates comparable to PSM (Table 7), despite resistance to flow is 3.4-fold higher through XEN45.[23] Interestingly, in the study conducted by Kim et al,[29] 63.2%–83.3% of the patients experienced hypotony, probably due to the high concentration of injected MMC used in the study (70% of the patients received an injection of 0.4 mg/mL without wash-out during an "ab interno"—closed conjunctiva technique). Regarding other filtering surgeries, Tables 8 and 9 show the hypotony rates reported by some studies about trabeculectomy, Express (Alcon, Fort Worth, TX, EEUU) and glaucoma drainage devices. In conclusion, most of the techniques that introduce a flow restrictive method (a valved mechanism, a ligature around the tube or the reduction of the luminal dimensions like the new microfiltering tubes), show a trend towards the reduction of persistent hypotony compared with trabeculectomy. PSM is one of them.

Another important issue related to the safety and efficacy of any filtering surgery is the type and technique of anesthesia. In the current study, the choice was to use anterior sub-Tenon anesthesia placed in the inferior-nasal quadrant, away from the

TABLE 8. Hypotony Rates Reported in Some Studies After Trabeculectomy and Express

Implant or Technique	References	MMC (% and Method)	Hypotony (%)
Trabeculectomy	Dangda and colleagues[27,28]	Not specified. Review article	35.6% anytime during follow-up (< 5 mm Hg)
Trabeculectomy	Gedde et al[31] TVT (5 y)	0.04% 4 min	31% persistent hypotony
Trabeculectomy	Baker et al[20]	0.02% sponges 2 min	49.6% transient hypotony 21.2% persistent hypotony
Express X-200	Bissig et al[32]	0.02% sponges 1 min	15% transient hypotony 8% flat anterior chamber
Express X-200	De Feo et al[24]	0.02% filter paper 3 min	32% transient hypotony at day 1 24.3% choroidal detachment
Express R50/T50/X50	Kanner et al[25]	0.04% 1–2 min	7.4% combined surgery (first week) 15.6% noncombined (first week)

Express indicates Express (Alcon); TVT, Tube Versus Trabeculectomy Study.

TABLE 9. Comparison of the Hypotony Rates Reported by Some Studies After Glaucoma Drainage Device Surgery

Implant or Technique	References	MMC	Flow Restriction Method	Hypotony
Baerveldt	Gedde et al[31] TVT (5 y)			13% persistent hypotony
Ahmed Versus Baerveldt	Ahmed Versus Baerveldt (5 y) Christakis et al[33]			*Flat anterior chamber:* Ahmed: 15% Baerveldt: 17% *Refractory hypotony:* Ahmed 1% Baerveldt 4%
Paul GI	Koh et al[34] (1 y)	14.9% used MMC	9.5% ligature 2.7% ligature and intraluminal tutor 14.9% intraluminal tutor	14.9% autolimited hypotony 9.5% hipotony requires intervention

MMC indicates mitomycin C; Paul GI, Paul Glaucoma Implant (Advanced Ophthalmic Innovations, Singapore); TVT, Tube Versus Trabeculectomy.

surgery site. This technique was first proposed by Ritch and Liebmann back in 1992 and its efficacy and patient satisfaction has been supported by many other studies.[35] Besides, among the anterior techniques (topical, subconjunctival, and sub-Tenon), the anterior sub-Tenon provides the higher amount of akinesia.[36] Even though some studies have reported the advantage of the anterior sub-Tenon technique on the site of surgery due to the atraumatic dissection of the Tenon capsule[37] others have proposed the opposite, an increased risk of bleeding and associated fibrosis.[38] In our opinion, the less the manipulation of the conjunctiva, the lower the inflammatory response will be, a main reason to locate the anesthesia away from the site of surgery.

Visual acuity after glaucoma surgery is an important issue related to the safety of the procedure. In the current study, there were no statistically significant differences in visual acuity between baseline and the last visit ($P = 0.4$), and no cases of device-related perception loss were reported. In a previous study published by our group,[13] a deep analysis of the visual, refractive and biometric effects of the PSM showed that the visual acuity decreased significantly on the first week and increased progressively to baseline at 3 months. Preserflo alone induced 0.3 D change of refractive sphere at 3 months, and induced a with-the-rule astigmatic shift with 0.4 D increase of the total corneal astigmatism versus 0.2 D in the combined Phaco-PSM group. An extensive review of the literature showed that both trabeculectomy and Preserflo induced a with-the-rule astigmatic shift, in the case of trabeculectomy around 1 versus 0.4 D in our series. The study concluded that the refractive changes induced by PSM were mild and transient, lower than trabeculectomy and comparable to deep sclerectomy. There was no data available in the literature for comparison with glaucoma drainage devices or XEN45.

A very relevant issue about safety with any new glaucoma implant is the loss of endothelial cells. The randomized controlled trial conducted by Baker et al[20] showed that the endothelial cell loss was comparable between both procedures at 1 year (−5.2% Preserflo, −6.9% trabeculectomy), being consistent with other reports of endothelial cell measurements after glaucoma surgery.[39] In a recent study published by our group,[40] the central endothelial cell density decreased significantly at 1 year—7.4%, and the mean monthly reduction of endothelial cell density, −14.6 cells/mm,^{2} was comparable to the Ahmed Valve placed in the ciliary sulcus. In the study, a shorter distance from the tip of the implant to the endothelium was reported to be a risk factor for endothelial cell loss. The tubes that were located further than 600 μm from the endothelium induced zero loss from the sixth month. Those results appeared to be at least comparable to those reported by Baker et al[20] with trabeculectomy and Preserflo.

We should consider 2 main limitations of this study: The follow-up time (mean: 11 ± 1.4 mo) supports the efficacy of the device on the first year but does not elucidate the further risk of fibrosis with this concentration of MMC. Another weakness of the study could be the inclusion criteria, all patients were diagnosed with POAG, so that the outcomes could not apply to other types of glaucoma.

In conclusion, the PSM alone or in combination with cataract surgery has demonstrated to be a safe and effective option to treat POAG patients. Further investigation is required to elucidate the optimal MMC concentration as well as the superiority of open surgical revision over needling to treat bleb failure.

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